DIECKMANN CYCLIZATIONS USING SOLID-SUPPORTS AND HALOGENATION OF POLY(*P*-METHYLSTYRENE)

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ABSTRACT

Dieckmann cyclization is one of the most successful methods for the formation of compounds which contain rings of carbon atoms. Dieckmann discovered this process in 1894 and used it for the preparation of compounds containing five and six carbon atoms in a ring. The purpose of the present work was to prepare rings containing five and fifteen carbon atoms through Dieckmann cyclization of non-ring compounds having two different reactive groups at the ends (known as unsymmetrical diesters). The cyclization reactions were carried out in solution as well as inside swollen polystyrene (plastic) supports where one end of the diester was bound to the support. The yields were good using much higher concentrations of reactants than reported in the literature. The Dieckmann cyclization of unsymmetrical diesters can result in two products, but previously only one had been obtained. Both have been observed in this research, and 81 % of the product that had never been observed before was obtained from one reaction. The attempts at Dieckmann cyclization of unsymmetrical diesters to form rings of fifteen carbon atoms failed in solution as well as on the polymer supports because the esters reacted in a different way. Although the cyclization reactions in solutions worked at 25 ^{o}C, the cyclization reactions of polymer supported esters were effective only at temperatures higher than 100 ^{o}C, because the chemical compound used to effect cyclization could not penetrate the swollen plastic at lower temperature.

Polymers constructed of networks of long carbon chains and having reactive chemical groups attached to them are important for the preparation of polymeric reagents and catalysts. An inexpensive, safe, new method to prepare such polymers was developed in our laboratory. The substitution of a hydrogen atom of a close relative of polystyrene

with a chlorine or bromine atom was carried out with commercial laundry bleach. Sometimes the reaction was aided by a catalyst which disperses the bleach into both water and oily organic solvents. The extent of substitution of chlorine or bromine in the polymer was determined by analyses using infrared light and using radio waves in a magnetic field.

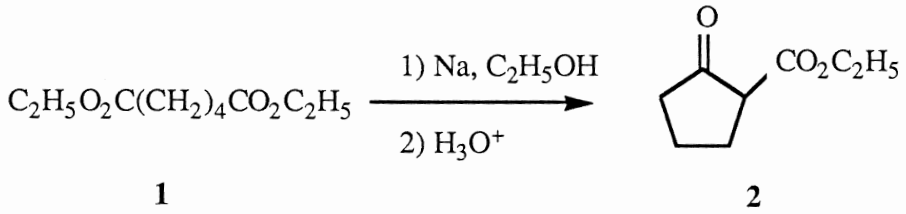
CHAPTER I

INTRODUCTION

DIECKMANN CYCLIZATION

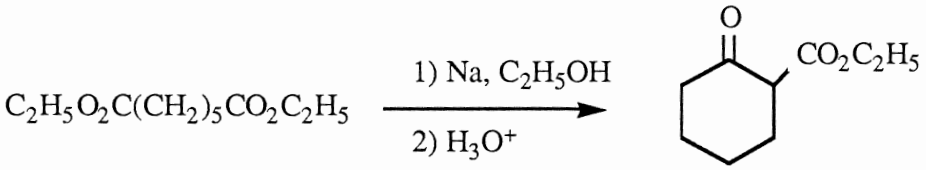
The importance of five- and six-membered ring ketones among organic compounds has made Dieckmann cyclization a central ring-forming reaction in organic chemistry. The importance of the Dieckmann reaction is further enhanced by the alkylation-decarboxylation sequence leading to a virtually limitless variety of α-substituted cyclopentanones and cyclohexanones. Any additional flexibility that serves to broaden the scope of the Dieckmann reaction will be valuable, since this reaction is an important component of synthetic design.[1] The successful synthesis of carbocyclic compounds from open chain precursors is dependent upon the competitive interplay of a number of factors, among the most important of which is ring size. Entropy effects dictate a decreased rate of closure with increasing probability of separation of the terminal C-α and C-ω carbons. On the other hand, the net enthalpy due to bond distances, bond angles, torsional effects, and van der Waals forces as the atoms in the chain assume the cyclic transition state is a complex function of ring size. The sum of the enthalpy contributions affords maximum rates of formation for five- and six-membered carbocycles and minimum rates for nine- and ten-membered rings.[2]

Dieckmann[3] discovered in 1894 that heating an adipic or pimelic ester with sodium and a trace of alcohol led to formation of a cyclopentanone or a cyclohexanone as shown below (eq. 1 and 2). The Dieckmann reaction has proved useful for the preparation of a variety of carboxylic and hetrocyclic ketones and has been extended to the synthesis of seven- and eight-membered and larger rings.



$C_2H_5O_2C(CH_2)_4CO_2C_2H_5$ [1]

1 **2**

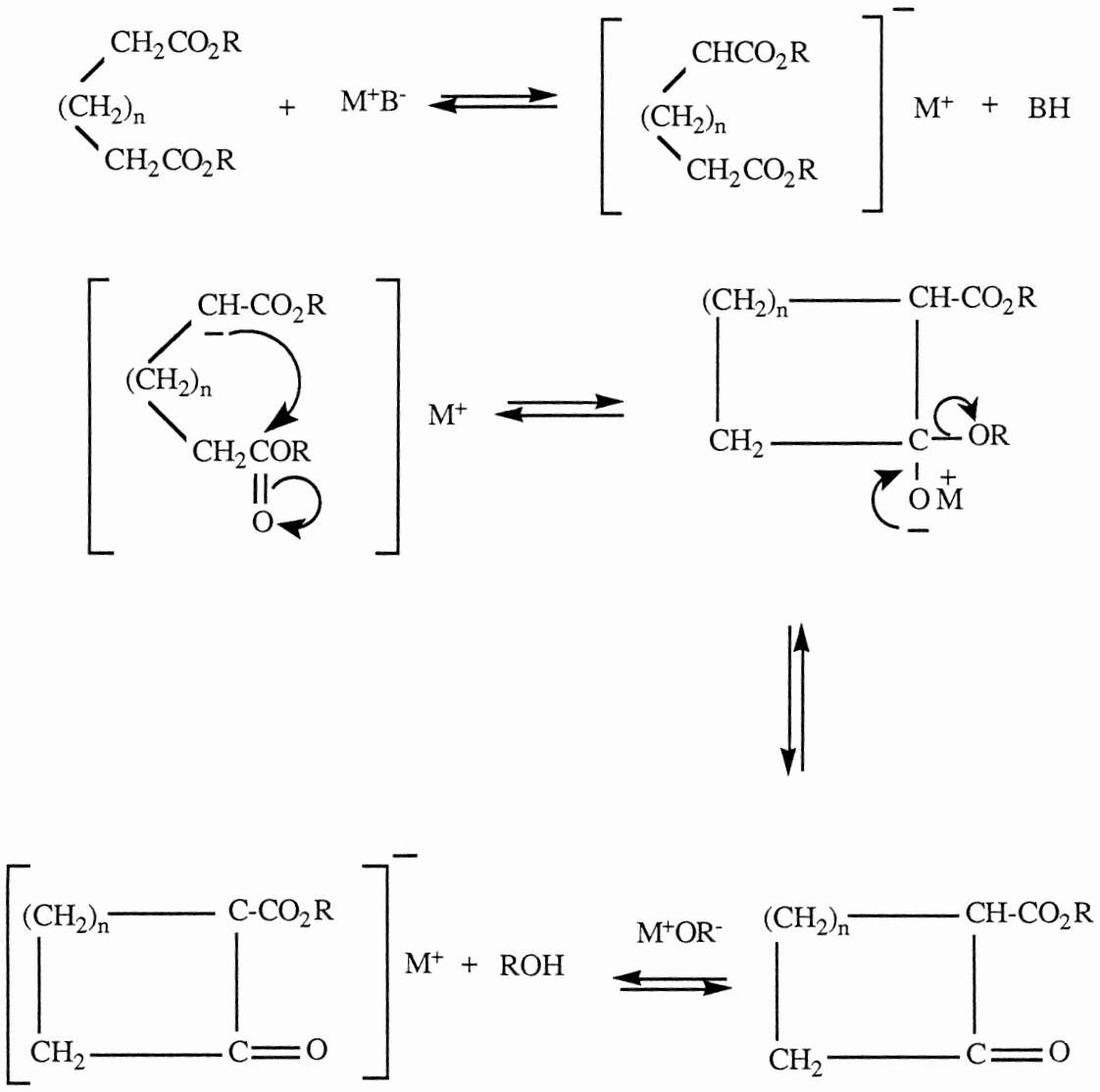


$C_2H_5O_2C(CH_2)_5CO_2C_2H_5$ [2]

3 **4**

The mechanism of the Dieckmann reaction as described by Schaeffer and Bloomfield[1] is shown in Scheme I. The first step is the rapid reversible removal of the proton from the carbon α to one of the ester carbonyls to form the enolate ion, which is stabilized by delocalization of the charge between the α-carbon and the carbonyl oxygen. The second step involves the addition of the enolate to the ester to form a tetrahedral intermediate. Formation of the β-keto ester occurs in the third step by loss of alkoxide. Removal of the acidic proton from the β-keto ester in the fourth step actually provides the driving force for the reaction.

Scheme I. Mechanism of Dieckmann Cyclization

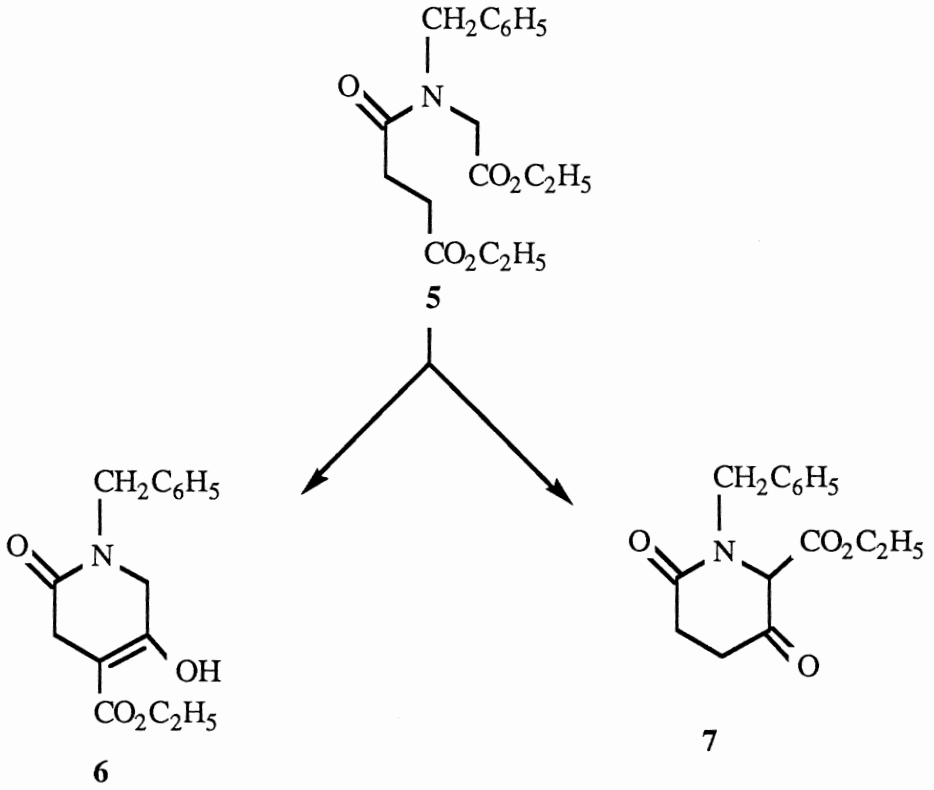


Cyclization of unsymmetrical diesters can result in two possible monomeric carbocycles. Therefore, in the past[1,4] almost always symmetrical diesters have been used to avoid the problem of separation of two cyclic monomeric β-keto esters at the end of the reaction. In general only one product will be formed from an unsymmetrical diester if the reaction is carried out under equilibrating conditions and if the alternative product cannot form a stabilized enolate anion.[1,5]

A dependence on solvent has been reported by Carrick and Fry[6] in their determination of the ^{14}C isotope effect (intramolecular) in the Dieckmann cyclization of diethyl *o*-phenylenediacetate-1-^{14}C, with a value of 1.6±0.5 % observed with sodium in toluene and 5.6±0.7 % found with sodium ethoxide in ethanol. From their ^{14}C labeled studies they concluded that the rate determining step in the Dieckmann reaction involves both labeled positions in carbon-carbon bond formation. However, an intermolecular isotope effect of 8.5 % is observed with both diethyl *o*-phenylenediacetate-1-^{14}C and diethyl *o*-phenylenediacetate-2-^{14}C with sodium ethoxide in ethanol.

Dieckmann cyclization is regioselective when one of the two ester groups has a methine α-carbon or when, in the presence of an appropriate base, the acidity of the two α-methylene groups or the stability of the two possible cyclized products is different.[1,7] Just recently regioselectivity in the Dieckmann cyclization was observed using different bases.[8] Dieckmann cyclization of ethyl N-benzyl-N-[(ethoxycarbonyl)methyl] succinamate (**5**) with sodium ethoxide gave regioselectively ethyl 1-benzyl-2,5-dioxo-4-piperidinecarboxylate (**6**) in 80 % yield, whereas under non-equilibrating conditions (potassium *t*-butoxide, toluene) the regioisomer ethyl 1-benzyl-3,6-dioxo-2-piperidinecarboxylate (**7**) was isolated as the main product (ratio **7**:**6** = 3:2, 84 % overall yield) (eq. 3). Using potassium hydride as a base in THF the ratio was 6:1, but the yield decreased to 60 %. It was expected that a kinetically controlled condensation would favor formation of **7** owing to the predictably higher acidity of the methylene protons adjacent to the nitrogen atom. When keto ester **7** was subjected to equilibrating conditions (sodium

ethoxide in refluxing ethanol) it was converted to **6**, the most stable of the two regioisomeric keto esters.

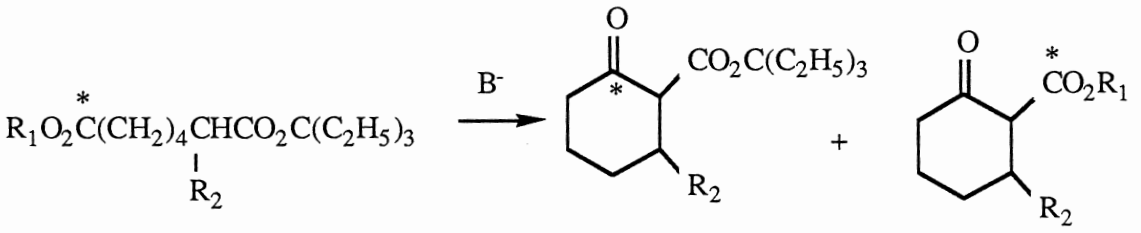


[3]

In their study of application of solid phase synthesis to cyclization Crowley and Rapoport[9] have followed the Hauser[10] results and have isolated the products from the essentially regiospecific closure of unsubstituted and 3-ethyl-substituted 1-triethylcarbinyl-7-aralkyl pimelates-7-^{14}C (**8**) to triethylcarbinyl 2-oxocyclohexanecarboxylate-2-^{14}C (**9**) using potassium triethylcarbinolate (4.5 molar equivalent of base) in refluxing toluene (Scheme II). Apparently the attack of the enolate anion on the carbonyl carbon of the triethylcarbinyl ester was hindered. However, the closure of dialkyl 3-alkyladipates, pimelates, and suberates in the opposite direction is well documented.[1, 11] From cyclizations of the unsubstituted benzyl triethylcarbinyl pimelate (**8b**) and of 7-benzyl

1-triethylcarbinyl 3-ethyl pimelate (**8d**) with potassium triethylcarbinolate Crowley and Rapoport[2] reported a mixture of triethylcarbinyl and benzyl β-keto esters, which they could not separate by column chromatography, and established the presence of less than 1 % (NMR analyses) of benzyl ester in both cases. They also found that replacement of the triethylcarbinyl ester by the ethyl ester in **8a** and **8b** yields β-keto esters with the label extensively scrambled. This scrambling results from intervention of kinetically competitive transesterification of the original diester prior to cyclization with potassium triethylcarbinolate. However, to our knowledge there are no examples of product control leading to both possible isomeric β-keto esters via Dieckmann cyclization from the same unsymmetrical diester.

Scheme II. Unidirectional Dieckmann Cyclization

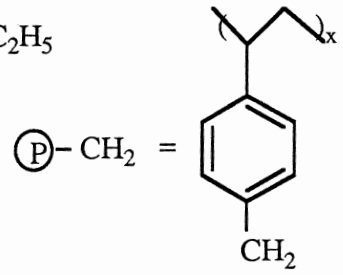


8a: R_1 = Ⓟ–CH_2, $R_2 = H$ **9a**: $R_2 = H$ **10a**: $R_1 = CH_2C_6H_5$, $R_2 = H$

8b: $R_1 = CH_2C_6H_5$, $R_2 = H$ **9b**: $R_2 = C_2H_5$ **10b**: $R_1 = CH_2C_6H_5$, $R_2 = C_2H_5$

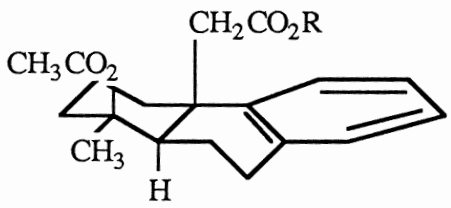
8c: R_1 = Ⓟ–CH_2, $R_2 = C_2H_5$

8d: $R_1 = CH_2C_6H_5$, $R_2 = C_2H_5$



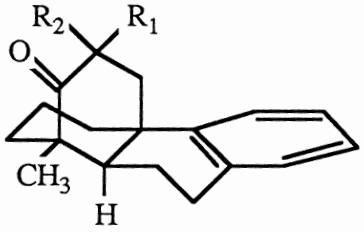
Hauser and Chambers[10] have developed a general method for the synthesis of trialkylacetic acids involving the alkylation of enolates of dialkylacetic esters using sodium amide or potassium amide, and the triethylcarbinyl ester, which hindered the usual attack of the amide ion at the carbonyl carbon so as to permit the preferential ionization of its α-hydrogen as required for the alkylation.

Ghosh and coworkers[12] have reported Dieckmann cyclization of the diester [(±)-methyl-20-methoxycarbonylpodocarpa-8,11,13-trien-19-oate] (**11a**) in aqueous methanolic potassium and sodium hydroxides. The diester **11a** (1 mmol) on refluxing for 5-6 h with 1 % aqueous methanolic (1:9) KOH (10 mmol), gave a crystalline epimeric mixture of the β-keto esters **12** and **13** in 85 % yield (95:5 from ^{1}H NMR) along with 13 % of the half-ester acid **11b**. Repeating the reaction with aqueous methanolic sodium hydroxide under identical conditions gave a mixture of the β-keto esters **12** and **13** in 50 % yield, and the unreacted diester **11a** along with the half-ester acid **11b** in a ratio of 65:35 (50 %). However, attempted cyclization of the diester (**11a**) under Dieckmann conditions employing bases such as NaOMe-MeOH, NaOMe-benzene or NaH-benzene were uniformly unsuccessful, and in every case the starting material was recovered. The diester **11a** with refluxing potassium methoxide in methanol for 6 h or potassium *t*-butoxide in benzene for 15 h resulted in an isolated yield of 80 to 85 % of β-keto esters **12** and **13** (80:20). On the other hand, with 2-5 % of dimethylformamide in an excess of refluxing 1 % methanolic sodium methoxide for 5-6 h, the β-keto esters **12** and **13** were formed in 70-75 % yield (GLC). The various bases employed so far for such cyclizations are alkoxides, alkali metal hydrides, or alkali metals in anhydrous media. However, not much information is available on the effect of the cation and solvent used for such cyclizations.[1,13,14]



11a : $R = CH_3$

11b : $R = H$

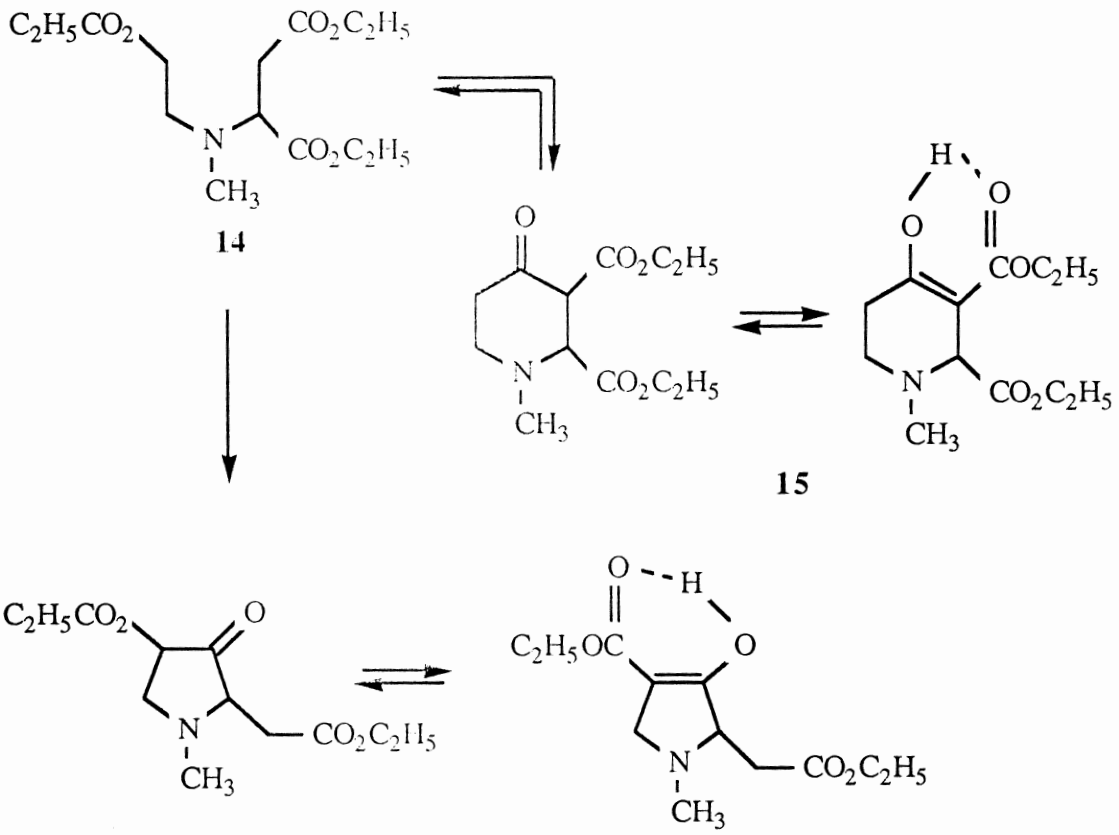


12 : $R_1 = H$; $R_2 = CO_2CH_3$

13 : $R_1 = CO_2CH_3$; $R_2 = H$

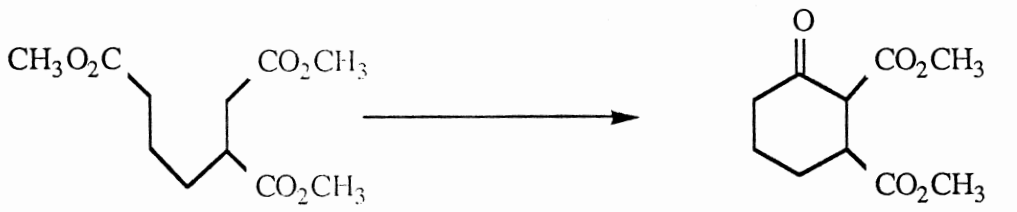
Augustine, Zelanski and Malarek[15a] have studied the regiochemistry of ring closure in the Dieckmann cyclization of an amino triester (Scheme III). They found that the cyclization of diethyl N-(2-carbethoxyethyl)-N-methylaspartate (**14**), using sodium hydride in benzene, sodium in toluene, or sodium ethoxide in ethanol, gave only the six-membered cyclized product, 1-methyl-2,3-dicarbethoxy-4-piperidone (**15**). Under these conditions five-membered ring formation was expected. However, only starting material (**14**) and product (**15**) were observed, with the yield of **15** being much lower than that obtained with sodium hydride even when longer reaction times were used. Under irreversible conditions (potassium *t*-butoxide in toluene at -20 ^{o}C) 1-methyl-2-carbethoxymethyl-4-carbethoxy-3-pyrrolidinone (**16**) was the primary product. The results show that the ring closure can be under kinetic or thermodynamic control, with the abstraction of the most acidic proton in aprotic media being responsible for the formation of the six-membered ring while equilibration in protic media would lead to the more stable cyclopentanone.[15a]

Scheme III. Dieckmann Cyclization of an Amino Triester **14**

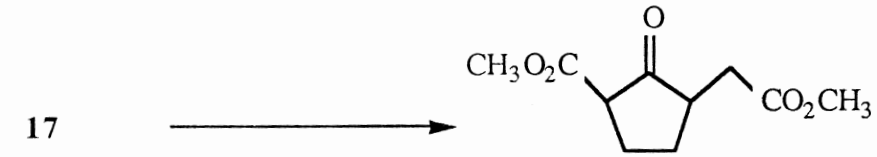


Clark-Lewis and Mortimer[16] studied the competition between the formation of five- and six-membered rings containing a heteroatom (eq. 6). They stated that only the pyrrolidinone **21** was formed on cyclization of the triester **20** with sodium in benzene followed by decarboxylation. This contradicts what has been found on cyclization of **17** in which the six-membered ring (**18**) is favored under these conditions (eq. 4). It is possible that, in non-polar media under conditions which would permit the equilibration of the anions, six-membered ring (**18**) is favored because of an intramolecular stabilization of the product enolate. Such stabilization could be expected to be more important in non-polar media than in polar solvents, but in the sodium ethoxide-ethanol reaction, the most stable

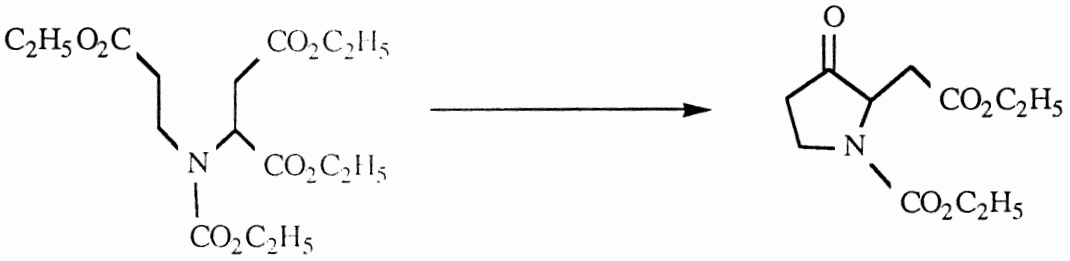
isomer (**19**) is the one formed (eq. 5). In the heterocyclic series, the same compound (**21**) is formed from **20** under both conditions; so little can be said about the relative stabilities. In the carboxylic series, the cyclopentanone is expected to be more stable, but this is in contrast to the results obtained by competitive cyclization of dimethyl adipate and dimethyl pimelate.[15b] It is evident that there is no single explanation for the results found in these reactions, and intramolecular and intermolecular solvation as well as proton acidities and anion stabilities all play an important role.[15a]



17 **18** [4]



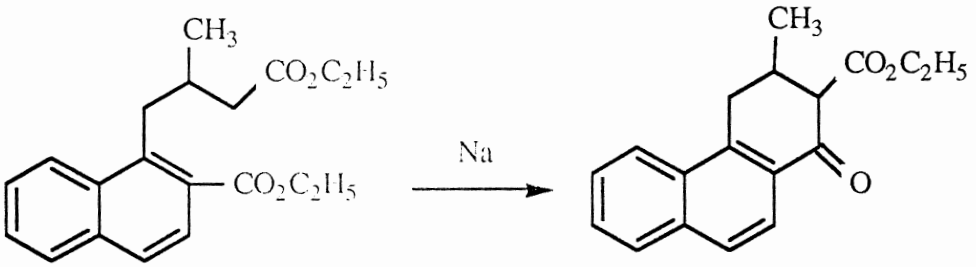
17 **19** [5]



20 **21** [6]

Very few mixed diesters have been cyclized. These fall into two classes, substituted benzoic esters[17] and diesters of which one carbonyl is lactonized.[18]

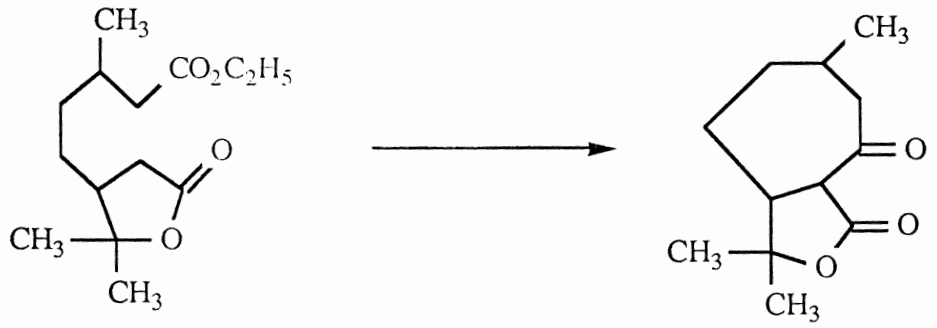
In the case of substituted benzoic esters, the diester **22** dissolved in benzene was heated with finely divided sodium on a steam bath to effect the Dieckmann cyclization to give the β-keto ester **23** (eq. 7).[17]



[7]

22 **23**

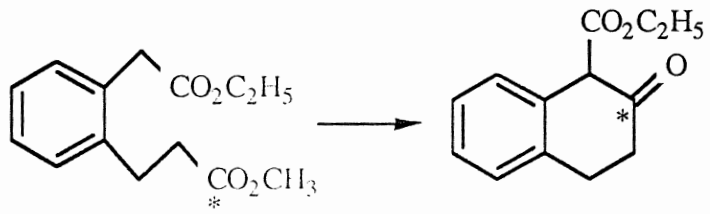
Lactone **24** in the presence of potassium *t*-butoxide in boiling xylene under high dilution gave bicyclic lactone **25** (eq. 8) (71 %).[18]



[8]

24 **25**

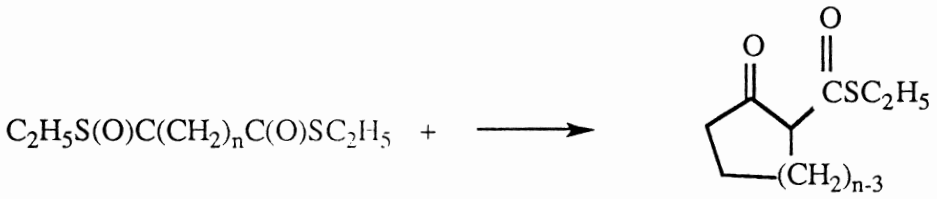
In another example,[19] employing a methyl ethyl diester the acidity of the benzylic proton, as well as thermodynamic preference, led to a single product (e.g., **26-27**) (eq. 9).



[9]

26 **27**

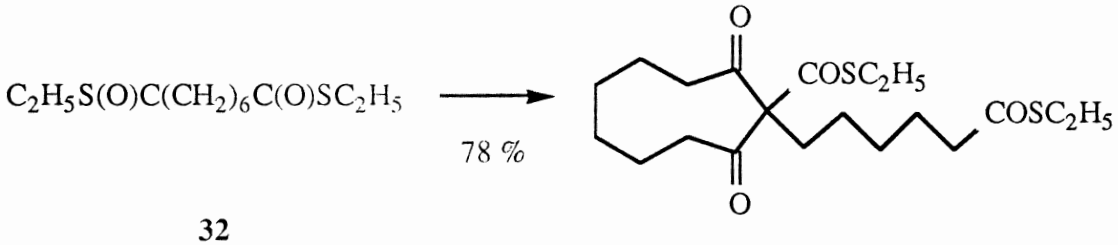
Numerous Dieckmann cyclizations to form the medium and large rings from precursors other than usual symmetrical diesters have been reported. Recently a dithiol ester version of the Dieckmann cyclization which proceeds at room temperature has been reported by Liu and Lai.[20] They obtained smooth conversion of adipic dithiol ester (**28**) to a 5-membered cyclic β-keto ester (**29**, 91 %) in 2 h when treated with 1.3 equivalents of sodium hydride and a catalytic amount (0.1 equivalent) of ethylene glycol in 1,2-dimethoxyethane. The corresponding pimelic dithiol ester (**30**) also was cyclized to a six-membered β-keto thiol ester (**31**) in 86 % yield (eq. 10). However, the same reaction conditions failed to induce seven-membered ring formation from suberic dithiol ester (**32**), and when the reaction mixture was brought to reflux, a 78 % yield of the dimeric compound **33** was isolated (eq. 11).



[10]

28 : n = 4 **29** : n = 4

30 : n = 5 **31** : n = 5

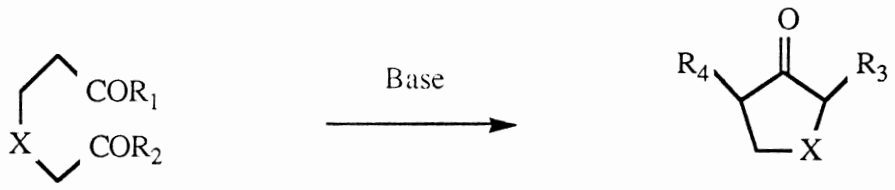


[11]

32 **33**

However, the cyclization of unsymmetrical diesters forms two isomeric β-keto esters.[1, 21-23] Yamada and co-workers[7] have described a regioselective cyclization of the half thiol diester **34a** by treatment with 1.5 equiv of lithium diisopropylamide in THF (0.1 M solution of **34a**) at -30 ^{O}C for 3 h to give an isolated 74 % yield of the β-keto ester **35a** . Also the half-thiol diesters (**34b-d**), cyclized smoothly with sodium hydride at room temperature giving the corresponding β-keto esters (**35b-d**) (Scheme IV).

Scheme IV. Dieckmann Cyclization of Unsymmetrical Diesters



34 **35**

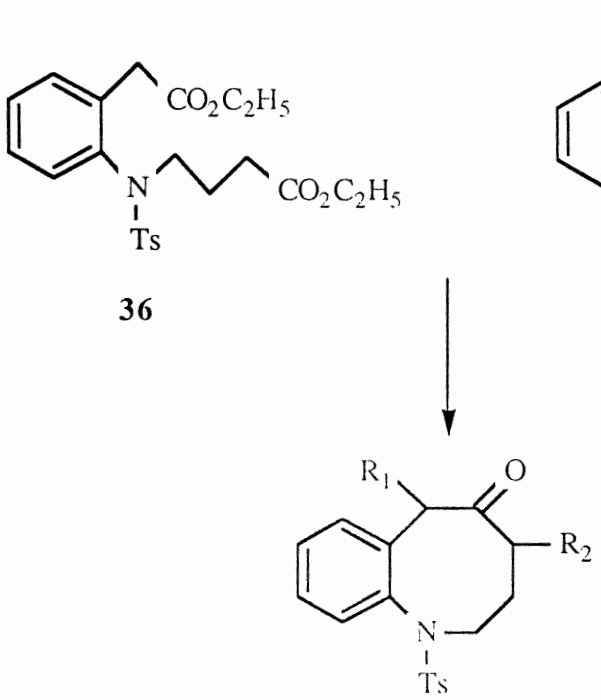
34	X	R_1	R_2
a:	CH_2	SC_2H_5	OC_2H_5
b:	S	SC_2H_5	OCH_3
c:	S	OC_2H_5	SC_2H_5
d:	$NCO_2C_2H_5$	SC_2H_5	OC_2H_5

35	X	R_3	R_4	% yield
a:	CH_2	$CO_2C_2H_5$	H	74
b:	S	CO_2CH_3	H	74
c:	S	H	$CO_2C_2H_5$	70
d:	$NCO_2C_2H_5$	$CO_2C_2H_5$	H	77

Most Dieckmann cyclizations employ symmetrical diesters and alkoxide bases. Some of the selected examples in the following section show the use of other reagents and diesters for the preparation of small, medium, and large rings in high yields. Conditions that utilize new solvents and bases are likely to be needed for Dieckmann cyclizations on polymer-supports.

Dispersed potassium[24] in toluene has been used for Dieckmann cyclization of diethyl adipate at room temperature to give ethyl 2-oxocyclopentanecarboxylate in 83 % isolated yield. Following the same process, diethyl pimelate, adiponitrile and pimelonitrile yield ethyl 2-oxocyclohexanecarboxylate (75 %), 2-cyanocyclopentanone (82 %) and 2-cyanocyclohexanone (75 %). In contrast, diethyl suberate, azelate and sebacate were recovered unaffected after several hours in the presence of the reagent.

Nomura and co-workers[13] have prepared tetrahydro-1-benzazocin-5(6*H*)-ones (**39-43**) by the Dieckmann condensation of the diesters **36** and **37** and the cyano ester **38** by using sodium-potassium alloy as the base (eq. 12).



36

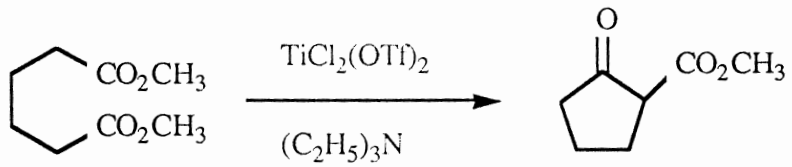
37 : R = $CO_2C_2H_5$

38 : R = CN

[12]

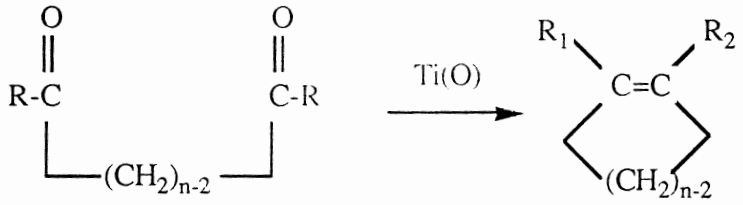
Reactant	Product	R_1	R_2	% yield
36	**39**	H	$CO_2C_2H_5$	29
36	**40**	$CO_2C_2H_5$	H	30
37	**41**	CH_3	CO_2CH_3	26
37	**42**	CH_3	$CO_2C_2H_5$	29
38	**43**	CH_2	CN	46

Recently new methods for the Claisen and the Dieckmann cyclization have been reported for diesters effected by dichloro-bis (triflouromethanesulfonato) titanium (IV) = (titanium (IV) bistriflate) in the presence of triethylamine.[25] Dimethyl adipate (**44**) with 1.5 equiv. of titanium (IV) bistriflate and 2.2 equiv. of triethylamine in the presence of 4 Å molecular sieves gave methyl 2-cyclopentanonecarboxylate (**45**) in 80 % isolated yield (eq. 13). Dimethyl pimelate **44** under the same reaction conditions in 10 h gave 51 % yield of methyl 2-cyclohexanonecarboxylate.



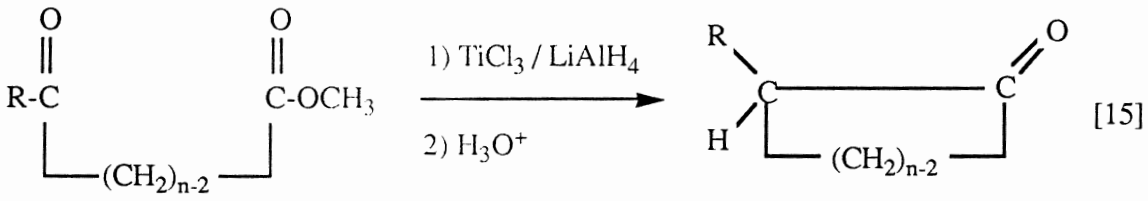
44 **45** [13]

McMurry and co-workers reported a new and general method for the synthesis of cycloalkanes.[26-28] Treatment of diketones or keto aldehydes with an activated Ti(O) reagent, prepared by reduction of $TiCl_3$ with a Zn-Cu couple, effects an intramolecular coupling reaction leading to the cycloalkene. The reaction (eq.14) gives high yields on all ring sizes four through seventeen.



[14]

The basic idea for cycloalkane preparation was also applied to substrates of higher oxidation state such as keto esters for the synthesis of cycloalkanones by titanium induced cyclization (eq.15). The substrate (**46a-d**) dissolved in 20 mL of dimethoxyethane was added to a refluxing black slurry of titanium coupling reagent, prepared by reduction of $TiCl_3$ with $LiAlH_4$, over a 24 h period via syringe pump, and the reaction mixture was refluxed for an additional 3 h to give 45-63 % isolated yields. Rings of size four through fourteen were successfully prepared in synthetically useful yields, although the medium sized rings, eight through eleven, showed a decrease in yield (50 %, 8-,9-,10-membered) compared with both smaller (80 and 82 %, 6-, and 7-membered) and larger rings (63 and 60 %, 12-, and 13-membered).[26]



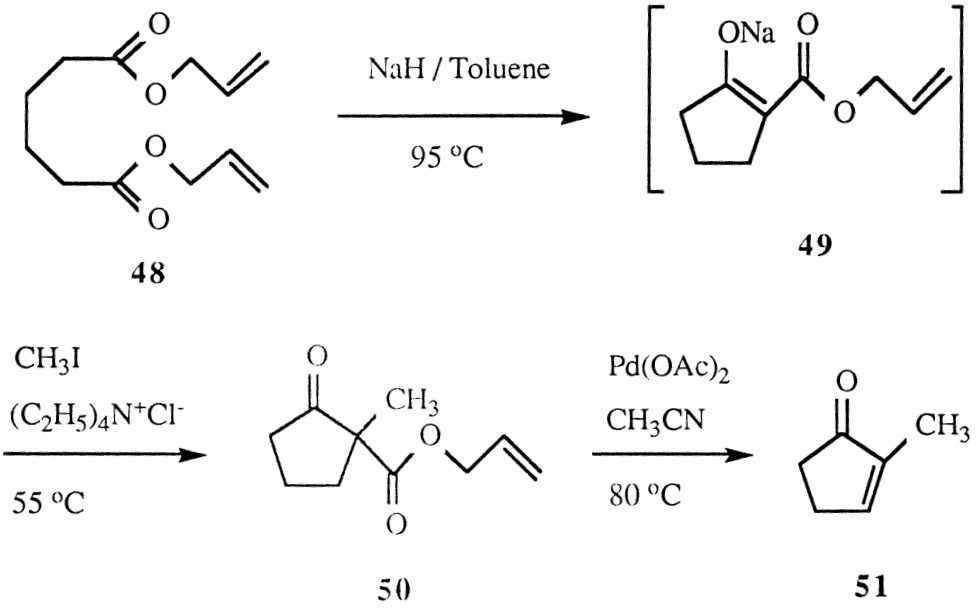
[15]

46			**47**		
46	R	n	**47**	Ring size	% yield
a	CH_3	8	**a**	10	50
b	C_2H_5	9	**b**	11	45
c	C_2H_5	10	**c**	12	63
d	CH_3	11	**d**	13	60

The intramolecular version of alkylation of malonic ester derivatives with alkyl halides has been used for the synthesis of small and common carbocyclic rings. The 7-, 8, 12-, 13-, 17-, and 21-membered rings were obtained in 68, 22, 32, 52, 62, and 55 % isolated yields respectively along with 14-42 % of dimeric rings under high dilution reaction conditions.[29]

2-Methyl-2-cyclopentenone (**51**), an important starting material for many natural product syntheses, has been prepared by the method of Scheme V in 75 % yield.[30] As shown in the following scheme, the Dieckmann cyclization of diallyl adipate (**48**), followed by methylation gives allyl 2-methyl-2-cyclopentanonecarboxylate (**50**) in 87 % yield. Then **50** is subjected to the palladium-catalyzed decarboxylation-dehydrogenation to give **51** in 75 % isolated yield.

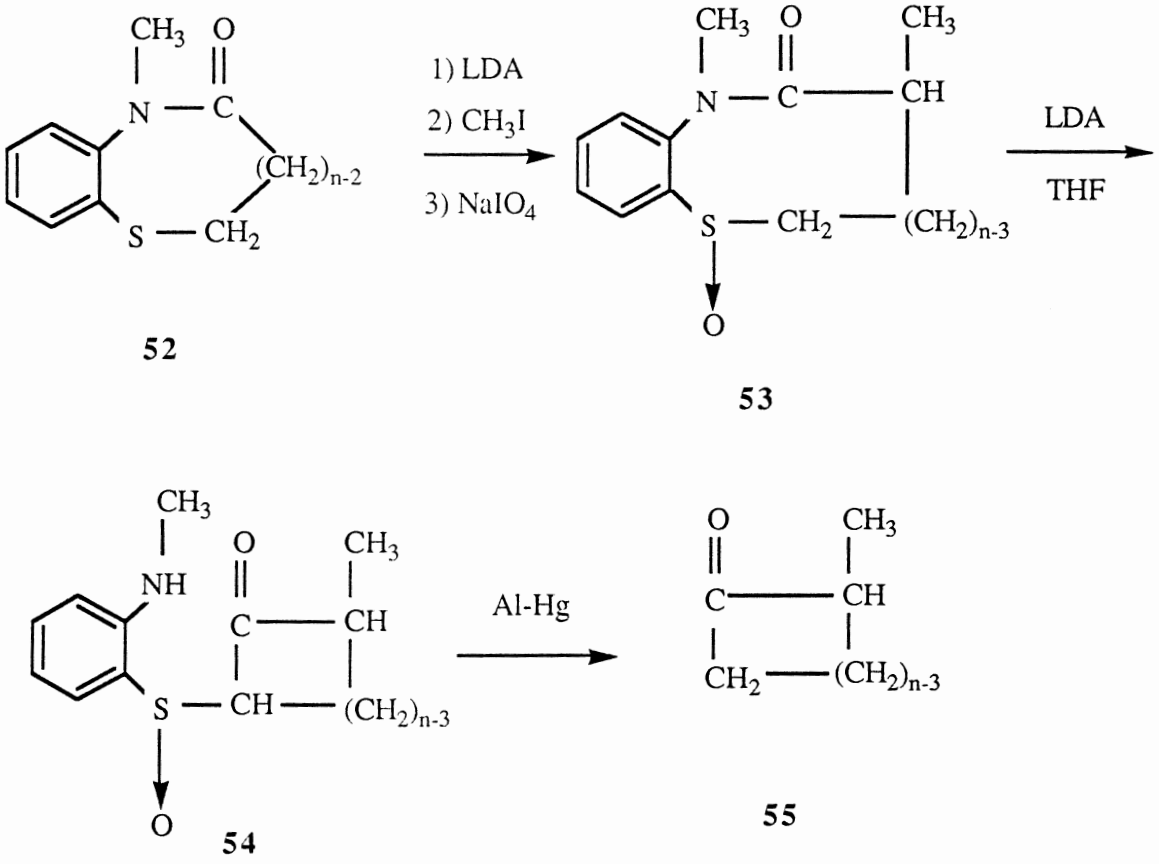
Scheme V : Synthesis of 2-Methyl-2-Cyclopentenone (**51**)



48 **49** **50** **51**

Ohtsuka and Oishi[31] have reported an effective method for the formation of medium ring ketones (8-12 membered), based on the intramolecular cyclization of large ring lactam sulfoxides or sulfones in 63-97 % yields as outlined below in Scheme VI. The entropy effect inherent to the cyclization is minimized when both reaction sites are forced to come close. The 8-membered ketone, has a 12-membered lactam sulfide **52** as an intermediate, which can be prepared easily, since large ring sulfides are known to be prepared in high yields.[32] Base induced intramolecular cyclization of **53** proceeds through a lower energy 6-membered transition state to give **54**, which is converted to the desired medium ring ketones (**55a-e**) through reductive desulfurization of **54** in high yields.

Scheme VI : Formation of Medium Ring Ketones

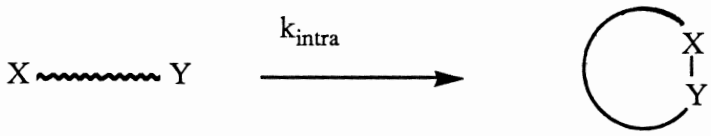


52 **53** **54** **55**

52	**55** (% yield)*
a: n = 8	**a**: 65
b: n = 9	**b**: 63
c: n =10	**c**: 74
d: n = 11	**d**: 97
e: n = 12	**e**: 69

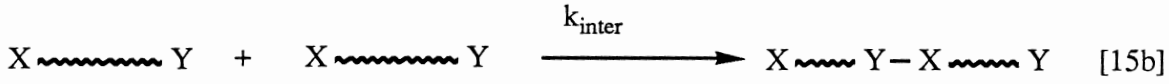
* Overall yields from the lactam sulfoxides **53**.

Cyclization reactions are usually accompanied by formation of the dimers and oligomers due to the competition between unimolecular and bimolecular cyclizations as observed by Crowley and Rapoport,[33] and Leonard and Schimelpfenig[34] in the formation of medium and large rings. Ring formation by an intramolecular reaction implies the use of a bifunctional substrate as the starting material. This is shown schematically in eq 15a where x and y are reactive functional groups at the end of a chain undergoing closure.



[15a]

The cyclization reaction suffers from the competition of a polymerization reaction through head-to-tail condensation (eq 15b). If the latter process is bimolecular, the intermolecular reaction is second order whereas cyclization is first order.



[15b]

The extents of formation of dimers and oligomers depend upon the relative rates of unimolecular and bimolecular condensation.[35, 36] Polymerization is negligible when the initial substrate concentration is much smaller than the effective molarity (EM), which is defined as k_{intra} / k_{inter} and represents the reactant concentration at which the rate of cyclization equals the rate of polymerization.[37]

$$d[\text{cyclic monomer}]/d[\text{dimer}] = k_{intra}[\text{diester}]/k_{inter}[\text{diester}]^2$$

$$EM = [\text{diester}] \text{ at which } d[\text{monomer}]/d[\text{dimer}] = 1$$

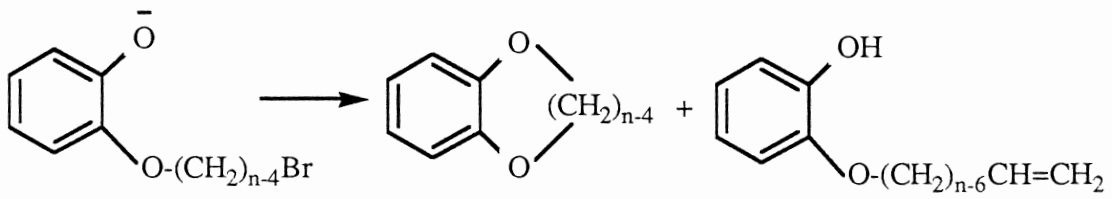
$$\text{i.e; } EM = k_{intra}/k_{inter}$$

The observation that cyclization rates have a first order dependence while polymerization has a second order dependence upon concentration led Ruggli[38] and Ziegler, Eberle and Ohlinger[39] to introduce the high dilution principle into cyclization reactions. The cyclization reactions carried out under high dilution conditions reduced the bimolecular collisions leading to dimerization and oligomerization relative to ring closure. Leonard and Schimelpfenig[34] have examined Dieckmann cyclizations of α,ω-diesters with potassium *t*-butoxide in boiling xylene under high dilution conditions and found that the conditions employed are useful for obtaining the cyclic 14- and 15-membered monoketones and the 18-, 20-, 22-, and 24-membered diketones. However, 0 % or negligible yields of 9-, 10-, 11-, and 12-membered monoketones were obtained. Transannular steric repulsion suppresses the closure of the medium size rings, and intermolecular condensation followed by intramolecular cyclization of the longer chains resulted in diketone formation.

Blomquist, Prager and Wolinsky[40] have provided a method for the reduction of dimeric diketones to monoketones, so the dimeric products may be considered to be precursors of large ring carbocycles.

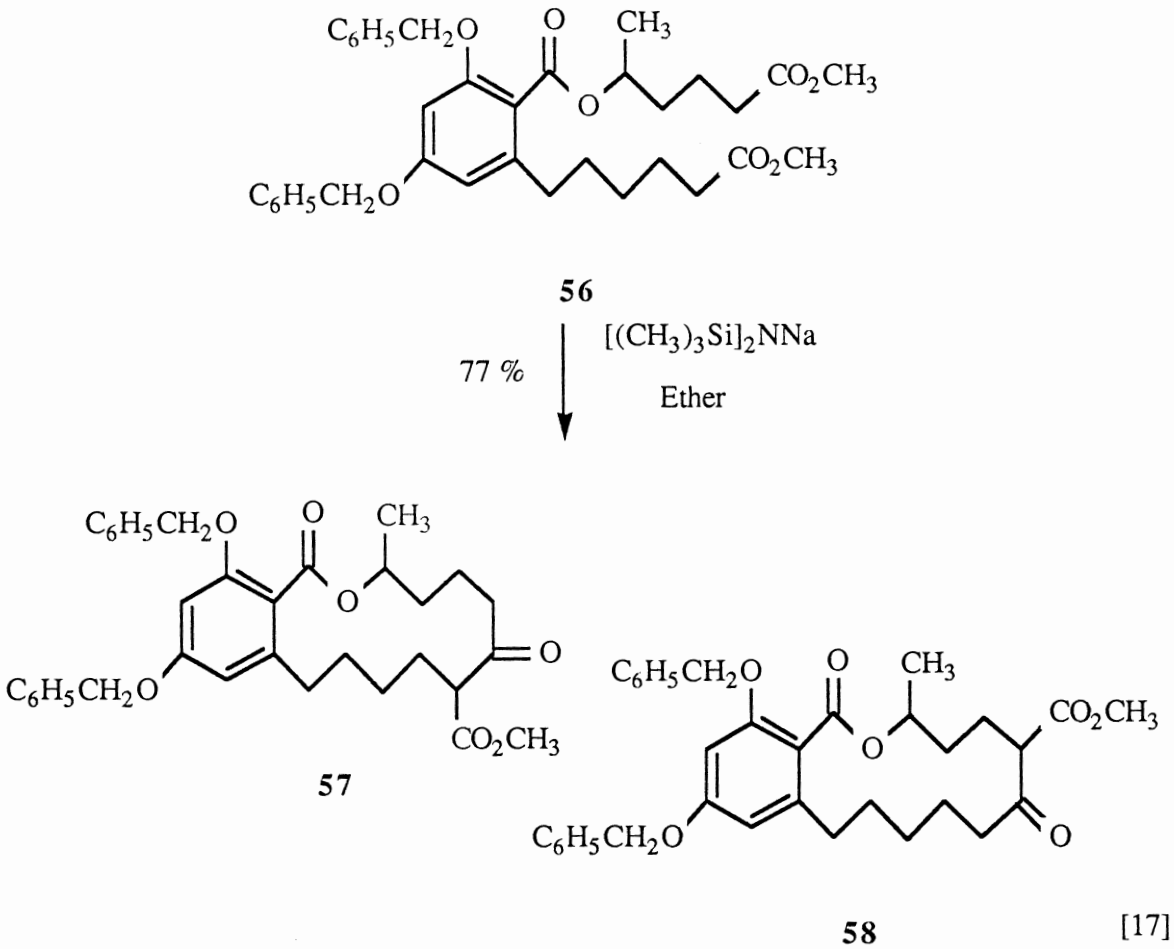
Cort, Mandolini and Masci[41] have discussed intramolecular β-elimination competing with ring formation from *o*-(ω-bromoalkoxy)phenoxides over a wide range of ring sizes (eq. 16). They also calculated rate constants and effective molarities for intramolecularly assisted elimination reactions occuring through 7-, 8-, 9-, 10-, and 14-membered cyclic

transition states. A comparison is carried out with the competing intramolecular substitution reactions leading to ring formation.



[16]

The reaction conditions successfully used by Leonard and Schimelpfenig[34] for the cyclization of alkanedioic esters, potassium *t*-butoxide in refluxing xylene, did not work for the cyclization of 4-carbomethoxy-1-methylbutyl 2,4-bis(benzyloxy)-6-(5-carbomethoxypentyl)benzoate (**56**).[42] The dibenzyl ether was completely destroyed due to the prolonged basic treatment lowering the yield of the desired cyclization product. The problem was solved by substituting sodium bis(trimethylsilyl)amide for potassium *t*-butoxide. Sodium bis(trimethylsilyl)amide is a strong base, and soluble in non-polar organic solvents such as ether.[43] This later property permitted Hurd and Shah[42] to have a homogeneous reaction at moderate temperatures, and allowed the Dieckmann cyclization to proceed smoothly in good yields to give a mixture of two β-keto esters **57** and **58** (eq. 17). No attempt was made to separate this mixture, since the two isomers were equally useful in the synthesis of R, S-zearolanone. Dieckmann cyclization of a model diester, dimethyl hexadecanedioate was attempted also, which under conditions of high dilution in a refluxing ether solution of sodium bis(trimethylsilyl)amide gave methyl 2-cyclopentadecanonecarboxylate in 64 % yield, which was an improvement over the 48 % yield of cyclopentadecanone obtained with potassium *t*-butoxide in refluxing xylene.[34]



[17]

Various reactions can destroy the starting diester. They include ether formation, E2 elimination and pyrolytic cracking of the alkoxy function. Together with hydrolysis, they constitute the source of carboxylic acid mixtures. Transesterification of ester starting materials can also take place. Bunnet, Robinson and Pennington,[44] Goering, Rubin and Newman,[45] and Barthel[46] report S_N2 ether formation from ester by alkoxide. Hauser and Chambers[10] reported olefin formation during ester hydrolysis to be a major side reaction in the case of tertiary alkyl esters of stronger acids.

The critical parameter to be adjusted in a high dilution cyclization is the rate of feed of the bifunctional reactant into the reaction medium. The concentration of the reactant must

be low enough to favor the intramolecular reaction. The usefulness of many macrocyclization procedures is often hampered by the exceedingly low rates of feed required to cyclize a synthetically significant amount of material.

A further technique, restriction of the mobility of the reacting termini by absorption on a metal surface such as sodium, which effects cyclization, was introduced by Stoll and Rouve[47] in the acyloin reaction, and applied effectively by Hansley[48] and by Prelog, Frenkiel, Kobelt, and Barman[49] for the preparation of nine- and ten-membered carbocycles.

Successful Dieckmann reactions require: (1) The cyclization of an enolate should be the fastest reaction taking place; (2) Competitive polymerization should be prevented by high dilution,[50] immobilization,[4] or some other technique; (3) Closure should lead to a single or predominant carbocycle, easily separable from other products. Solid phase synthesis[51-53] appeared to be a technique for the development of a cyclization method which meets a number of these criteria.

Solid-Phase Synthesis

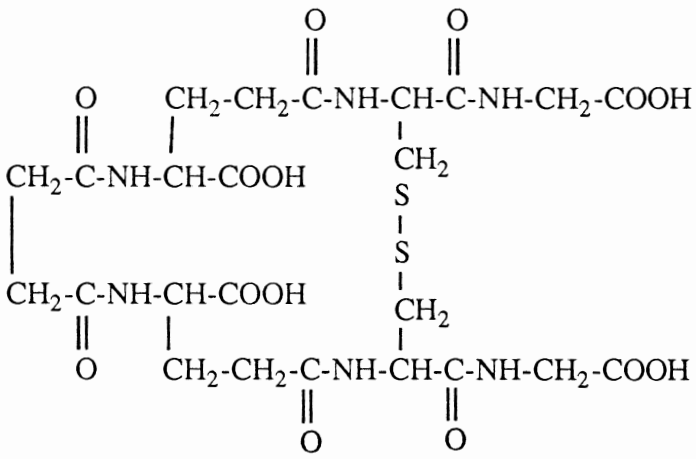
The literature of solid-phase peptide synthesis is very extensive. It has been reviewed by Merrifield[51,54-55] and by Stewart and Young.[56] In the Merrifield approach, which is the most popular one, the first step is conversion of chloromethylated 1 % cross-linked polystyrene to resin bound N-protected amino acid ester. The standard protecting group for α-amino functions is the Boc group, which is cleaved in the next step, and next Boc-amino acid is then coupled to the amino acyl resin. Following completion of assembly of the desired blocked peptide on the resin, the peptide resin is treated with anhydrous HF to cleave the benzyl ester linking the peptide to the resin in order to liberate the free peptide. All the reactions using polymers as supports have been carried out in solvent swollen gels, which allows all reagents to penetrate readily through the polymer beads and also allows

the finished products to diffuse out of the swollen polymer. In most of the syntheses a minimum amount of solvent has been used to swell the polymer to a gel.

After the original report[57] of solid phase peptide synthesis, parallel activity developed in the application of resin attachment to non-peptide organic synthetic objectives. It was reasoned that polymer-bound reactants could be converted to products with two major advantages over solution chemistry. One of these is the ease of purification afforded by the method, the dominant thrust behind its widespread utilization in peptide synthesis. The other objective rested on the premise that resin-bound species would not likely react with one another, thus attaining effectively high dilution on the solid phase support.[9] Both peptide and nonpeptide methodology have been the subject of many recent reviews.[58]

The cyclic analogue **59** of oxidized glutathione (GSSG)[59] with restricted conformation has been synthesized on an aminomethyl copoly(styrene-1 % divinylbenzene) resin in quantitative yield. The GSSG **59** was synthesized in different steps. First the tripeptide resin was synthesized from Boc-glycyl-4-(oxymethyl)phenylacetamidomethyl-resin (Boc-Gly-OCH_2-Pam-Res) by normal stepwise solid-phase peptide synthesis using the preformed symmetric anhydrides of the Boc-amino acids. The N^{α}-protecting groups were removed by treatment with 50 % trifluoroacetic acid in CH_2Cl_2. After neutralization with 5 % diisopropylethylamine in CH_2Cl_2, the peptide was reacted with exactly 0.5 molar equiv of succinic anhydride in DMF. The carbonyl groups so generated on one-half of the peptide chains in the polymer were then coupled to the N^{α}-amino groups on the remaining unreacted peptide chains, by using a dicyclohexylcarbodiimide / *N*-hydroxybenzotriazole coupling method in DMF. After the cleavage with HF and reduction at pH 8.5 with dithiothreitol, the succinyl hexapeptide was then oxidized in air in 0.1 M NH_4OAc buffer, pH 8.2.[59] This is a very good example of a solid support synthesis, which shows the site-site interaction (reaction of two polymer-bound species with one another) between peptide chains on the same resin bead. In the early period of resin supported synthesis it was often assumed that functional sites on low-cross-linked polystyrene-divinylbenzene copolymer

beads were isolated and that their reactions were analogous to reactions in solution at high dilution.[56,60-63] It has become more and more clear, however, that site isolation in such system is usually a kinetic phenomenon and that site-site interaction can readily occur.



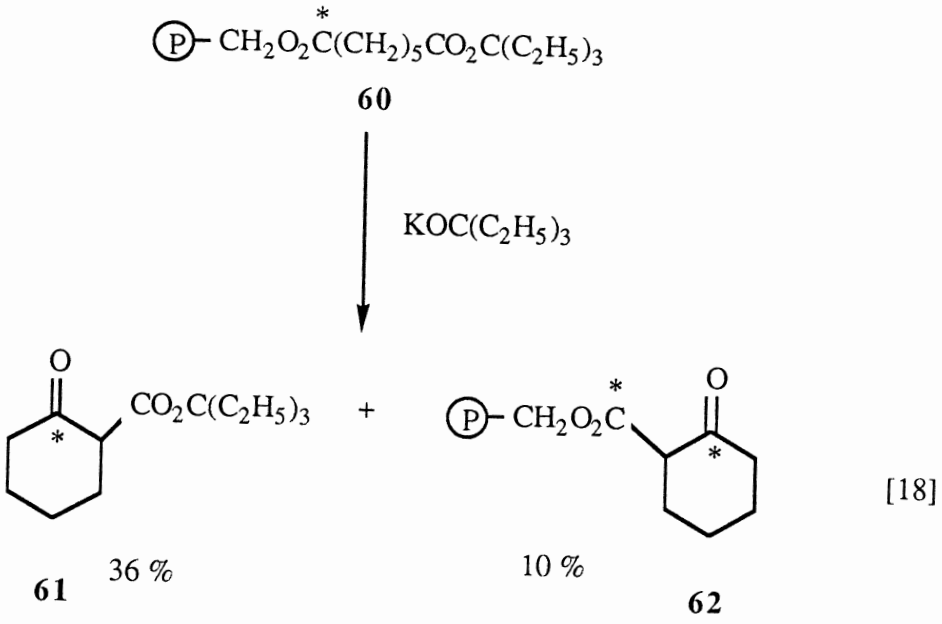
59

Solid supports have also been used to prepare 13-membered ring lactones. A 2 % cross-linked polystyrene support was used to immobilize 12-hydroxydodecanoic thiol ester for lactonization at much higher concentrations than those used in the high dilution syntheses. Reactant concentrations in typical high dilution reactions are 1-10 mM, and the large volume of solvent required makes the high dilution synthesis impractical for all but small scale reactions. The polymer-supported 12-hydroxydodecanoic thiol ester swollen in dichloromethane was cyclized to 12-dodecanolide (13 %) along with 19 % of the corresponding diolide. Under similar conditions, 0.01 M model thiol ester in solution gave < 2 % each of monolide and diolide. However, using acetonitrile as solvent, 0.01 M model thiol ester gave 26 % and 35 % yields of monolide and diolide.[64]

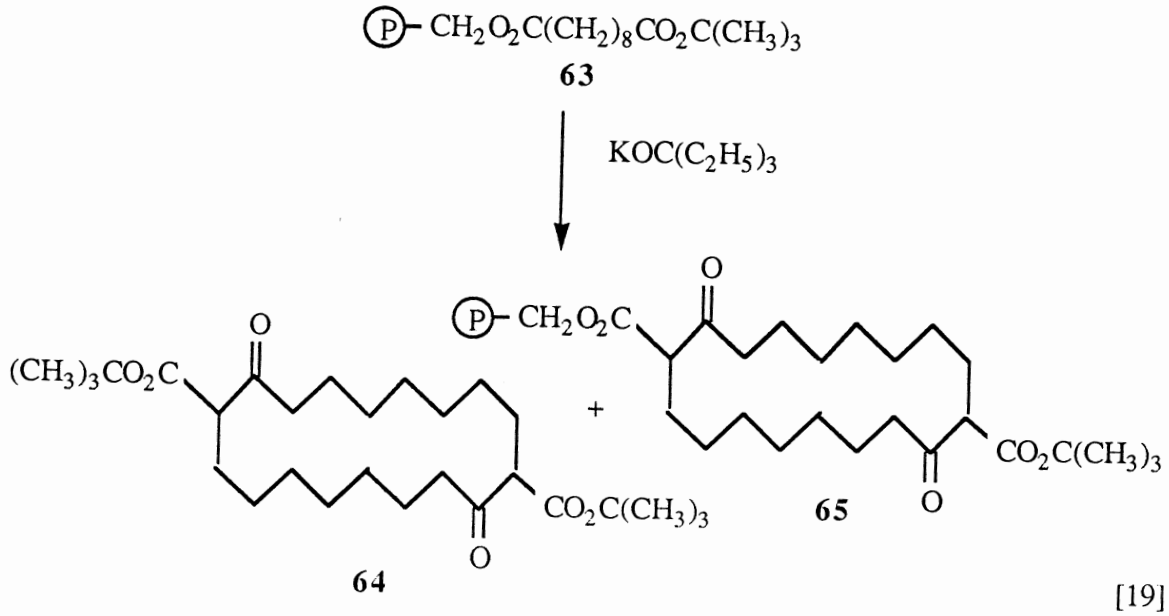
Polymers are widely used as supports for chemical reagents.[58b,65,66] The steric and polar microenvironments of the bound reagents are expected to be different from the

ones encountered by the low molecular weight analogues (unbound substrates). This influence of the polymer-backbone can lead to different reaction paths in the heterogeneous medium.[67,68]

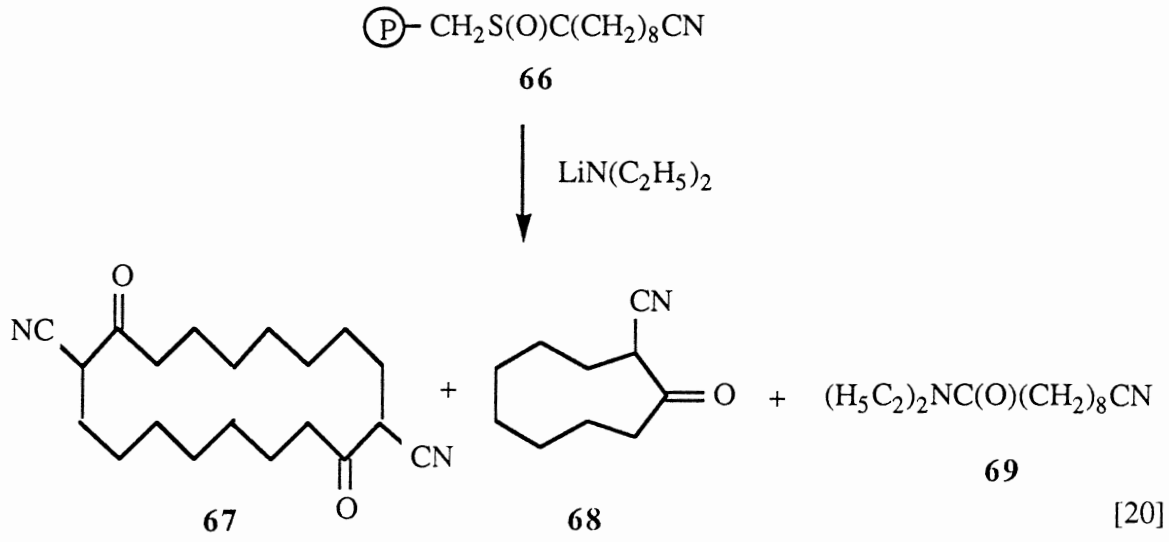
Dieckmann cyclizations of polymer-bound diesters have been investigated previously by Crowley and Rapoport.[2,9,69] They obtained acceptable yields of six-membered β-keto esters, but valiant attempts to synthesize the nine-membered β-keto ester failed. Crowley and Rapoport described an interesting application of a unidirectional Dieckmann cyclization of polymer-bound benzyl triethylcarbinyl pimelate for the synthesis of specifically radio labeled cyclohexanone derivatives.[2] Extensive ^{14}C isotopic labeling experiments with benzyl alkyl pimelates and the corresponding (polystyrylmethyl) alkyl pimelates **60** established that only reactions of the highly hindered *t*-butyl and triethylcarbinyl esters with potassium triethylcarbinolate as base avoid extensive scrambling of the labeled carbonyl carbon atoms and competing transesterification reactions during Dieckmann cyclization. The example that gave the least scrambling of the label is shown in equation 18. The reactions were carried out by adding the 2 % cross-linked resin, DF 0.021-0.045 (DF = fraction of polymer repeat units functionalized), to a refluxing solution of 4.5 molar equivalents of base in toluene and cooling the reaction mixture after 1.5-5 minutes. The autocleaved keto ester **61** showed essentially all keto ^{14}C label, while the ^{14}C in the resin retained keto ester **62** was almost completely scrambled by an intraresin reaction. Less hindered bases and mixed diesters led to scrambling in the autocleaved keto ester also, and to somewhat lower overall yields. The polymer-bound pimelic esters provided improved yields over solution cyclizations, which were attributed to greater ease of product purification, and enabled easy isolation of the product of unidirectional cyclization of mixed diesters.[2]


P- CH2O2C(CH2)5CO2C(C2H5)3
60
KOC(C2H5)3
CO2C(C2H5)3
+
P- CH2O2C
61
36 %
10 %
62

[18]


P- CH2O2C(CH2)8CO2C(CH3)3
63
KOC(C2H5)3
P- CH2O2C
(CH3)3CO2C
+
CO2C(CH3)3
CO2C(CH3)3
64
65

[19]



[20]

Attempted nine-membered keto ester syntheses produced small amounts of both autocleaved and resin retained cyclodimers, **64** and **65** (eq. 19).[69] Treatment of an analogous 9-cyanononanoic thiolester resin **66** with lithium diethylamide gave 5 % of 2-cyanocyclononanone (**68**), 10 % of cyclodimer **67**, and 40 % of the cleaved cyanoamide **69** (eq. 20). A more hindered base, lithium bis(triethylsilyl)amide, gave 19 % yield of cyclodimer **67** and 75 % cleavage of the uncyclized starting material from the resin. The predominant dimerizations are due to the failure of the resin to separate polymer-bound ester enolates and α-cyanocarbananions from other polymer-bound esters.[70]

Numerous experiments have demonstrated that polymer chains in 1-2 % cross-linked polystyrene are highly flexible.[69,71] For synthetic purposes, however, site isolation can be achieved if polymer-chain motion is slow enough to retard interchain reactions more than it retards the desired reaction.[72] Kraus and Patchornik[73] avoided self-condensation of polymer-bound ester enolates and achieved acylation and alkylations of the enolates in low yields at 0-25 °C. Crowley and Rapoport[33] did not obtain nine-membered rings by Dieckmann cyclization with diesters bound to highly flexible 2 % cross-linked polystyrene, and obtained dimers and oligomers. They reduced the loading of polymer-species to 0.1

mmol of ester / g of dry polymer in their attempts to prevent polymer-polymer reactions, but never tried to reduce polymer-chain mobility by use of more highly cross-linked polymer. We selected the Dieckmann cyclization[3] of α,ω-dicarboxylic esters as the reaction with which we could test the efficiency of highly cross-linked resin-bound esters. Successful cyclizations could extend the range of solid-phase reaction conditions to include enolate condensations at high temperatures. The aim of site-isolation syntheses is to prevent reaction of two polymer-bound species with one another and thereby promote reaction of the polymer-bound species with a reagent in solution or intramolecular reaction of the polymer-bound species. The polymer-polymer reactions can be prevented only if the network is rigid enough to isolate reactive sites from one another.[74] Chain mobility in cross-linked polystyrene decreases as the degree of cross-linking increases and as the swelling of the polymer decreases.[69,71] Most attempts at site isolation syntheses have employed conditions of high polymer chain mobility, lightly cross-linked (1-4 % divinylbenzene) polystyrenes and good swelling solvents.[2,33,74-77]

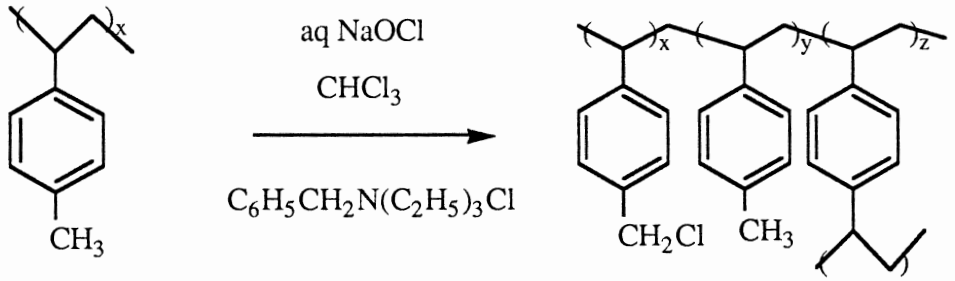
Reagents supported on solvent-swollen, cross-linked polystyrene are less mobile than reagents in solution. As a result, the rate of reaction between two polymer-supported species can be retarded relative to the rate of intramolecular reaction of polymer-supported species with a soluble reagent.[70] The objective of this study was to prepare small and large rings by Dieckmann cyclization of diesters bound to highly cross-linked polystyrene. Dieckmann cyclization of diesters covalently bound to 6 % cross-linked copolymers containing 10 % vinyl benzyl chloride (VBC), and to 10 % cross-linked, 10 % VBC resins, and Dieckmann cyclizations in solution were examined at much higher concentrations and with different bases than those reported in the literature.

Halogenation of Poly(*p*-Methylstyrene)

Cross-linked chloromethylated polystyrenes (**71**) are key intermediates in the preparation of anion-exchange resins,[78] supports for solid-phase peptide synthesis,[57] and supports for polymeric reagents and catalysts.[79] The currently available methods for preparation of chloromethyl-substituted polystyrenes have severe limitations. Lewis acid catalyzed chloromethylation is most often performed with the carcinogenic chloromethyl methyl ether and its unavoidable contaminant, the far more potent carcinogen bis(chloromethyl) ether.[80] Methods are available to generate chloromethyl methyl ether *in situ*,[81] and alternative less volatile chloromethyl ethers of unknown toxicity have been used to lessen the hazard.[82] The other major route to chloromethyl-substituted polystyrene is copolymerization of (chloromethyl)styrenes, available as a 70 / 30 *meta/para* mixture at a high price.[83]

Mohanraj and Ford[84] discovered a third method that is cheap and safe, phase-transfer-catalyzed chlorination of poly(*p*-methylstyrene) (**70**) with commercial aqueous sodium hypochlorite bleach solutions (eq 21). The method was based on the findings of Hamilton and co-workers[85] who selectively monochlorinated toluene with hypochlorite and a phase-transfer catalyst. Conversions up to 20 % of methyl to chloromethyl groups were achieved with no detectable formation of dichloromethyl groups in the poly(*p*-methylstyrene) (**70**). Conversions up to 61 % of methyl to chloromethyl groups also were achieved with ≤ 4.4 % concomitant formation of dichloromethyl groups. The method also was applied to soluble, 1 % cross-linked, and 20 % cross-linked poly(*p*-methylstyrene) (**70**). The chlorination reactions were carried out by treating a dissolved or swollen polymer in a halogenated solvent with an excess of either laundry bleach (3.5 % sodium hypochlorite) or swimming pool bleach (9.4 % sodium hypochlorite) and a phase-transfer catalyst. The degree of chlorination was determined by comparing the peak areas due to the unreacted methyl carbons at 21.1 ppm, the

chloromethyl carbons at 46.1 ppm, and the dichloromethyl carbons at 71.7 ppm in 75 MHz ^{13}C NMR spectra. ^{13}C NMR analyses were performed with full ^{1}H decoupling and peak areas were corrected for nuclear Overhauser enhancement factors (NOE), 1.674 and 1.816 for the methyl and chloromethyl carbon peaks in a 1 % cross-linked gel polymer.[84]



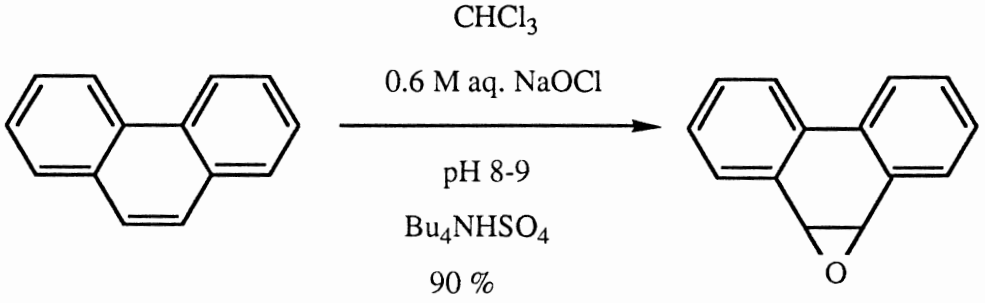
[21]

70 **71**

Hamilton and co-workers reported that a number of arene oxides can be prepared in high yields by direct oxidation of arenes by the hypochlorite-PTC method, such as by reacting for few hours at room temperature a solution of the arene in chloroform or dichloromethane with aqueous commercial bleach (adjusted to pH 8-9) in the presence of a catalyst such as tetrabutylammonium hydrogen sulphate as shown below in equation 22.[86,87] Although arene oxide was the major product in most cases, some arenes give mainly chlorinated products under the oxidation conditions employed. Observation of the chlorinated products led them to study the chlorination of toluene to α-chlorotoluene, anisole to ring chlorinated anisoles, and alkenes to a complex mixture of chlorinated and oxidized products, including the epoxide with sodium hypochlorite in the presence of a phase-transfer catalyst. The reaction of toluene dissolved in dichloromethane with an excess of commercial bleach (adjusted to pH 8-9) in the presence of tetrabutylammonium hydrogen sulphate resulted into an overall 94 % conversion of toluene in 4 h to the

following products: benzyl chloride (64 %), benzal chloride (11 %), benzoic acid (1 %), cresols (0.8 %), benzaldehyde (0.7 %), benzyl alcohol (0.6 %), *p*- and *m*-chlorotoluenes (0.5 %), and *o*-chlorotoluene (0.4 %). In control experiments in the absence of a phase-transfer catalyst but with all other conditions the same, 95 % of the toluene initially present is recovered unchanged.

Salt addition to the reaction mixture shows that addition of sodium chloride to the sodium hypochlorite solution or the use of commercial bleach (1.2 M Cl^-) enhances the rate of the reaction. Sodium nitrate has a similar effect. Such ions are known to cause salting out of the organic compounds from the aqueous phase, which is observed in anion extractions involving quaternary ammonium salts, and are known to enhance the decomposition of hypochlorite at the pH used in the reaction. The PTC chlorination and epoxidation are proposed to proceed by a free-radical mechanism involving chlorine monoxide (Cl_2O) and the chloroxy radical ($ClO^{\cdot}$) as the hydrogen abstracting species.[86]



[22]

Hanzlik and co-workers[88] have investigated the primary and secondary kinetic deuterium isotope effects in the chlorination of $PhCH_3$, $PhCH_2D$, $PhCHD_2$, and $PhCD_3$ in a two-phase system of hypochlorite / CH_2Cl_2 with a phase-transfer catalyst. From the relative rate constants for all possible H- and D-abstractions, on the basis of the deuterium content of the benzyl chlorides, the primary and secondary kinetic deuterium isotope effects

were found to be 5.90 ± 0.41 and 1.03 ± 0.02, respectively. The values of secondary and primary kinetic deuterium isotope effects for the bromination of toluene with N-bromosuccinimide were also studied and were not significantly different from those for chlorination.

A number of organic reactions proceed via the attack of anions on water-insoluble substrates. To accelerate such reactions and thus allow them to be run under mild conditions has been a traditional goal in organic chemistry. The uses of dipolar aprotic solvents,[89] macrocyclic crown ethers,[90-92] and macrobicyclic polyethers (cryptands)[93-95] have been significant advances in mild reaction conditions. In late 1960's[96] a new general technique was developed, phase-transfer catalysis (PTC). PTC has the advantage of being simple and economical and so met with immediate success in industrial applications. Reactions are conducted in a two-phase system consisting of mutually insoluble aqueous and organic layers. Ionic reagents (salts, bases, or acids) are dissolved in the aqueous phase, and the substrate in the organic phase for liquid-liquid PTC. Alternatively, ionic reagents can be used in the solid state as a suspension in the organic medium (solid-liquid PTC). The transport of the anions from the aqueous or solid phase to the organic one, in which the reaction occurs, is promoted by catalytic amounts of lipophilic agents, usually quaternary onium salts.

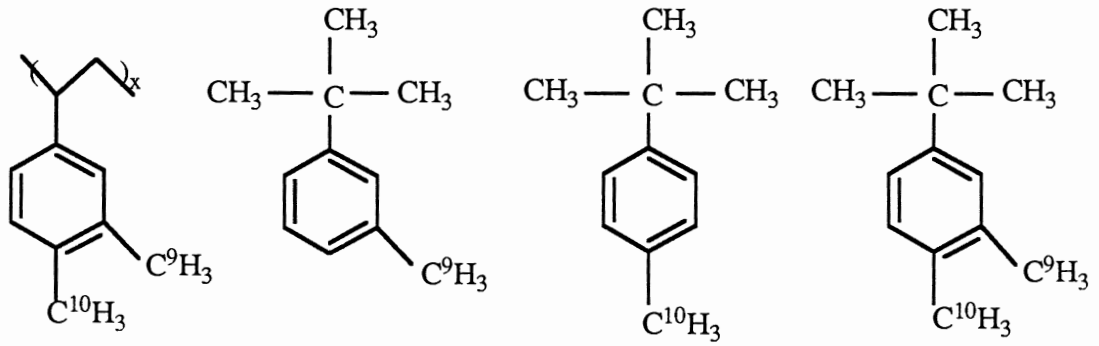
An ideal solvent for PTC must be aprotic and immiscible with water to avoid strong interactions with the ion pairs and thus poor reactivity. Furthermore, it must be chemically stable under the reaction conditions. From this point of view, some chlorinated solvents, such as chlorobenzene and dichloromethane, appear to be particularly favoured. However chloroform reacts with bases such as hydroxide ion.

Extraction constants for phase transfer catalysts from water into organic solvents are often determined at constant ionic strength of the aqueous phase. However, as the concentration of inorganic salts increases, a salt effect is observed leading to the transfer of organic salts from the aqueous phase into the organic phase. For example, the extraction

constants of tetra-*n*-butylammonium chloride and tetra-*n*-butylammonium bromide in water-dichloromethane increase by a factor of 1000 if 2 mol / L of potassium carbonate is added. Bicarbonate and carbonate anions are not extracted under these conditions. A similar salt effect arises from 50 % aqueous NaOH used in many PTC reactions for the generation of carbanions and carbenes. This allows the use of quaternary salts which normally show an unfavourable partition coefficient with respect to the organic phase, such as benzyltriethylammonium chloride.[97]

Salvadori and co-workers[98] have reported the benzylic radical bromination of atactic and isotactic poly(3,4-dimethylstyrenes) (**72**) using either the N-bromosuccinimide-benzoyl peroxide or the bromine-potassium carbonate-light systems. Brominated and unbrominated polymers were studied by ^{13}C NMR spectroscopy. A remarkable difference in the chemical reactivity of the methyl groups in positions 3 and 4 of the benzene ring between atactic and isotactic poly(3,4-dimethylstyrene) (**72**) was observed. In the case of atactic poly(3,4-dimethylstyrene), using the same molar ratio between the brominating agent and methyl groups (1:1) yields the monobromination of both methyl groups, whereas an estimated ^{13}C NMR analysis of the peaks for isotactic brominated poly(3,4-dimethylstyrene) showed that only about 20 % of the polymer structural units show bromination at the methyl groups in both the 3 and 4 positions and about 80 % are brominated only on the methyl group in the 4 position. These results suggest a conformational control by the polymer main chain of the chemical reactivity of the two methyl groups on the benzene ring. To assign the chemical shifts of C^9 and C^{10} in the polymer (**72**), longitudinal relaxation time (T_1) measurements were performed on 1-*t*-butyl-3,4-dimethylbenzene (**75**). A longer relaxation time for C^9 with respect to C^{10} was in fact expected, because of the anisotropic tumbling of the molecule.[82] The results obtained were T_1 = 5.80 s (C^{10}, 19.6 ppm) and T_1 = 6.8 s (C^9, 20.1 ppm). The chemical shifts were assigned using 1-*t*-butyl-3-methylbenzene (**73**) and 1-*t*-butyl-4-methylbenzene

(**74**) as model compounds, and the chemical shift of C^{10} was observed at a higher field of about 0.4-0.6 ppm with respect to the chemical shift of C^{9}.

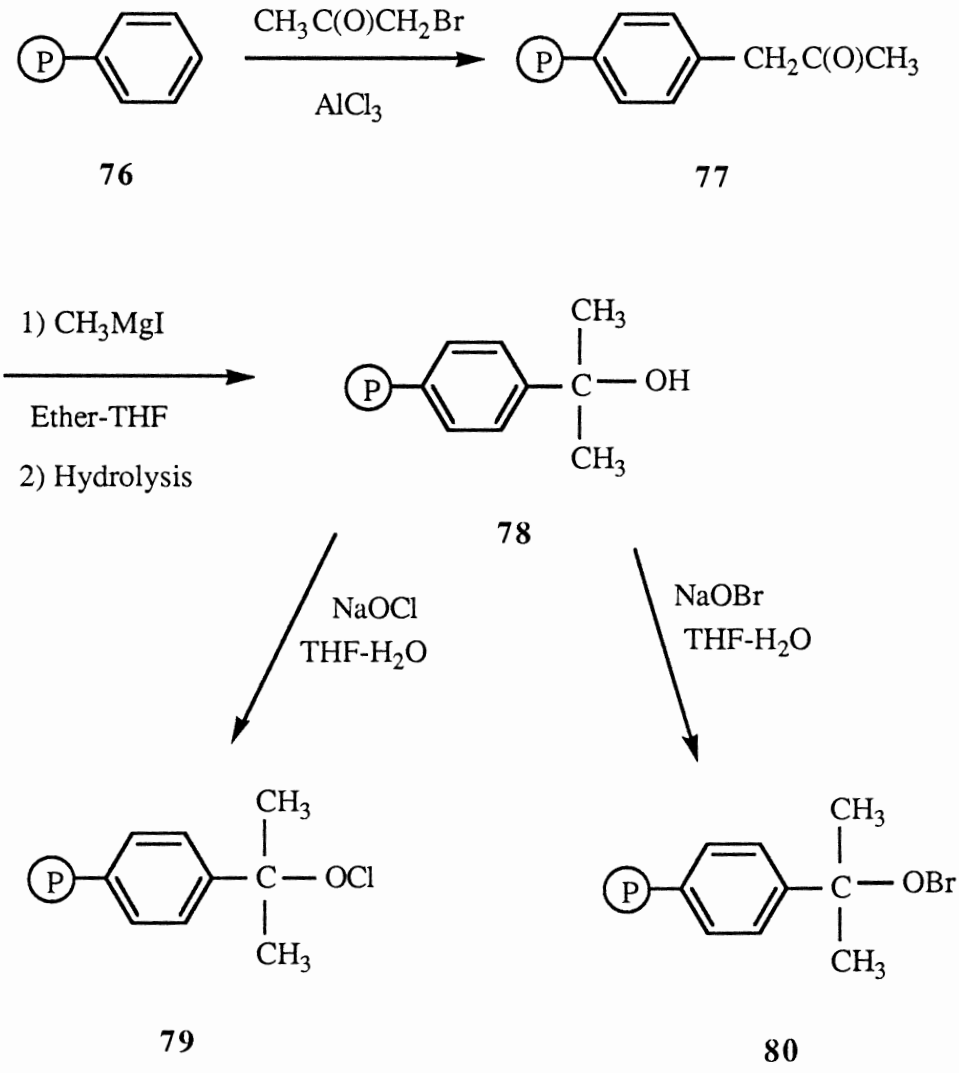


72 **73** **74** **75**

Sreekumar and Pillai[99] have prepared polymer-supported hypohalites as solid-phase oxidizing and halogenating reagents, and used them for the oxidation of primary and secondary alcohols. The preparation of these reagents involved a three step reaction using 2 % cross-linked polystyrene (**76**) as shown in Scheme VII. A ketone functional group was introduced into the polymer **76** by a Friedel-Crafts reaction with bromoacetone. The keto group was then converted to a tertiary alcohol (**78**) by a Grignard reaction with methylmagnesium iodide, and **78** upon treatment with hypohalites gave polymer-bound cumyl hypochlorite **79** and hypobromite **80**. The hypohalite contents were estimated iodometrically and verified by elemental analysis. Halogen contents used in the study were in the range of 0.6 to 2.4 mmol of chlorine or bromine per gram of the resin. The polymer-supported hypohalites (**79** and **80**) were found to be recyclable without any loss in capacity in one step by treating with the sodium hypochlorite in a THF-H_2O mixture. These polymer-supported hypohalites (**79** and **80**) were found to oxidize primary and secondary alcohols to their corresponding aldehydes and ketones in isolated yields from 80

to 98 %. The oxidation conditions involve stirring of the alcohol with a two fold molar excess of the hypochlorite function in the resin in solvents such as chloroform or dichloromethane at 50 ^{o}C to 60 ^{o}C for 40 to 44 h. The polymer-supported hypohalites (**79** and **80**) were also found to be suitable for halogenation of carbonyl compounds and amides.

Scheme VII. Preparation of Polymer-Supported Hypohalites



76 **77** **78** **79** **80**

Lee and Freedman[100] reported oxidation of alcohols and amines with aqueous NaOCl in the presence of a phase-transfer catalyst. Aryl carbinols are smoothly converted to carbonyl compounds by stirring at room temperature with an excess of 10 % aqueous NaOCl (commercial swimming pool bleach) in a dichloromethane solution of substrate containing 5 % tetra-*n*-butylammonium bisulphate as phase-transfer catalyst. However, in the absence of a phase-transfer catalyst little or no reaction occurred and alcohols were recovered unchanged. An unexpected specific solvent effect was also observed. Benzene, carbon tetrachloride, chloroform and dichloromethane served as good solvents for oxidation reactions, but ethyl acetate significantly increased the rate of reaction. *p*-Methylbenzyl alcohol in dichloromethane gave 78 % aldehyde in 83 minutes with 18 % unreacted alcohol, and in ethyl acetate the reaction was over in 30 minutes to give quantitatively the corresponding aldehyde. Similar reactions of primary amines containing a monosubstituted α-carbon gives predominantly nitriles with minor amounts of aldehydes.

In another study[101] primary alcohols were selectively and quantitatively oxidized to aldehydes in a few minutes at 0 ^{o}C in dichloromethane-0.35 M aqueous NaOCl in the presence of a catalytic amount of 4-methoxy-2,2,6,6-tetramethylpiperidine-1-oxyl. The addition of 0.10 mol equiv of KBr and buffering of the aqueous solution at pH 8.6 with sodium bicarbonate were also important. Secondary alcohols were converted to ketones. Further oxidation of aldehydes to carboxylic acids was slow. However, the aldehydes can be converted to the carboxylic acids in few minutes under the same reaction conditions by addition of catalytic amounts of phase-transfer catalyst.

Mn(III) tetraarylporphyrins catalyze epoxidation of olefins by NaOCl under phase-transfer conditions, the reaction rates increase by addition of a molar excess of pyridines or N-alkylimidazoles, which behave as axial ligand on the complex metals.[102] However Montanari and co-workers[103] found that very efficient epoxidation catalysts are easily obtained when a pyridine function or an N-alkylimidazole is anchored to the porphyrin ring

by an aliphatic chain. Under aqueous-organic two phase conditions, reaction rates become extremely fast when the pH of the aqueous NaOCl is lowered from 12.7 to about 9.5. Cyclooctene and *cis*-stilbene epoxidations were carried out in dichloromethane-water with 3.5 M NaOCl (pH 12.7), 0.005 molar equiv. of Mn(III) porphyrin, 0.012 molar equiv. of a phase-transfer catalyst (Aliquat 336) at 25 ^{o}C. At pH 12.7 the addition of a phase-transfer catalyst noticeably affected the reaction rates, especially at higher conversions (an increase from 20 % to 75 % conversion in 120 minutes), but the influence of the phase transfer catalyst was very small at pH 9.5 (84 to 100 % conversions in 7 minutes)

Attachment of the First Amino Acid to the Chlorinated Poly(*p*-Methylstyrene) (**71**)

One important use of the chlorinated poly(*p*-methylstyrene) (**71**) is solid phase peptide syntheses. A suitable insoluble support and a satisfactory means of attaching the first amino acid to it are of critical importance for successful solid phase peptide synthesis.[104]

Slow resin attachment reactions may be anticipated in solid phase peptide synthesis when either the entering Boc-amino acid or the N-terminal residue on the peptide-resin is sterically hindered. Among naturally occuring amino acids, those with β-branching, such as valine, isoleucine, and threonine give problems. Among unnatural amino acids, N-alkyl or α-alkyl amino acids are particularly slow to react. With these residues, coupling reactions may need to be prolonged for many hours and repeated in order to effect complete coupling.[105]

The original Merrifield method[106] for the preparation of polymer-bound amino acid ester involved heating the triethylamine salt of a Boc-amino acid in ethanol with the chloromethyl resin. The reaction was quite slow and also resulted in formation of quaternary ammonium groups on the polymer. Using chloromethyl resin containing

approximately 0.7 mmol Cl / g, which is a desirable degree of substitution, amino acid degree of substitution typically is in the range of 0.2 to 0.4 mmol / g, which is satisfactory for most syntheses of average size peptides. The attachment is faster if the triethylamine is replaced by 2 mmol of KF per mmol of Boc-amino acid, ethanol is replaced by DMF,[107] and the reaction is carried out with stirring for 24 h at 50 ^{o}C. Short peptides containing 5-10 amino acids may be synthesized on resins with a higher degree of amino acid substitution with apparently satisfactory results, but for synthesis of long peptides, the degree of substitution should be 0.2-0.3 mmol / g.[108] More complete substitution of Cl groups on the resin may be obtained by use of the cesium salt of the Boc-amino acid,[109] which will minimize the possibility of undesirable side reactions later during the synthesis due to remaining unreacted chloromethyl groups on the resin.

The goal of this research was to find efficient methods for chlorination and bromination of the methyl groups of poly(*p*-methylstyrene) and to prepare partially chloromethylated resins for use in the peptide synthesis. It has been demonstrated that the methyl groups of 1 % cross-linked poly(*p*-methylstyrene) can be chlorinated with and without a phase-transfer catalyst. Also, chloromethyl contents suitable for use of the 1 % cross-linked gel resin for solid phase peptide synthesis and for most polymer-supported reagents and catalysts can be achieved.

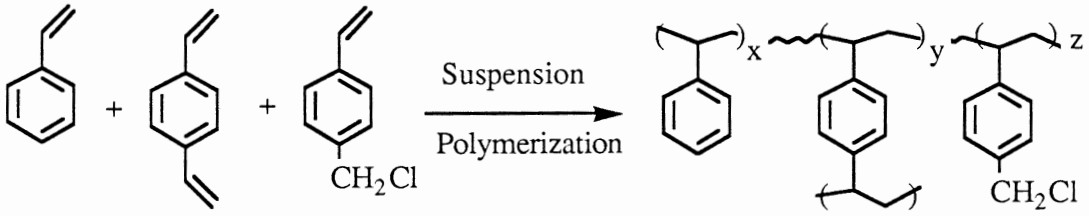
CHAPTER II

RESULTS AND DISCUSSION OF

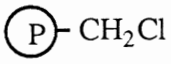
DIECKMANN CYCLIZATION

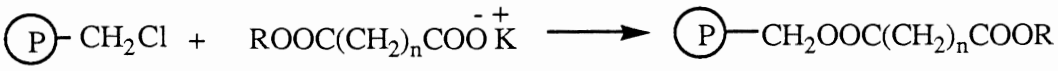
Dieckmann cyclization is one of the most general methods for preparing five- and six-membered rings.[1] It has been extended to the preparation of medium and large size rings, which are formed in competition with formation of oligomers. Polymerization can be limited by use of the high dilution method or immobilization of the reactant diester. Solid phase synthesis is one promising immobilization method. Earlier reports[2,3,9,69] have appeared of the solid phase cyclization of pimelates, unidirectional Dieckmann cyclizations and solid-phase organic synthesis. Formation of nine- and ten-membered rings was attempted by Crowley and Rapoport,[69] using highly flexible 2 % cross-linked polystyrene. They obtained dimers and oligomers but no medium sized rings. They reduced the loading of polymer-bound diester to 0.1 mmol of ester per g of dry polymer in their attempts to prevent polymer-polymer reactions, but never tried to reduce polymer chain mobility by use of more highly cross-linked polymer. Stimulated by these observations we attempted to synthesize small and large size rings by the Dieckmann cyclization of diesters bound to highly cross-linked polystyrenes at much higher concentrations than are used in high dilution cyclizations.[34] Dieckmann cyclizations of dioates covalently bonded to resins as well as in solutions have been examined. The plan of our solid-phase synthesis is outlined in Scheme VIII.

Scheme VIII. Solid-Phase Synthesis

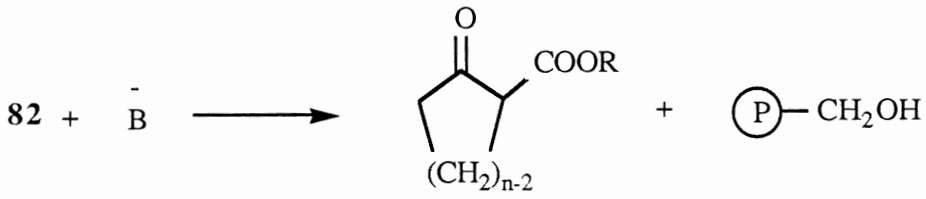


81

81 = 



81 **82**



83 **95**

Polystyrene (**81**) Cross-Linked with 6 % and 10 % Divinylbenzene (DVB)

The 6 % and 10 % DVB cross-linked polystyrenes (**81**) were prepared by suspension polymerization, using azobis(isobutyronitrile) (AIBN) as the free radical initiator.[83] The less reactive second double bond in DVB, does not react completely under the usual suspension polymerization conditions for 36 h at 70 ^{o}C, according to CPMAS ^{13}C NMR spectroscopic results, but it has been found that all vinyl groups cannot be consumed completely even at 135 ^{o}C.[110] To consume most of the second double bonds of DVB, after 7 h of heating at 70 ^{o}C, the temperature of the reaction mixture was raised to 95 ^{o}C for another 30 h. The degree of functionalization (DF) and percent ring substitution in the polymer were calculated from the weights of the monomers used in the polymerization. For Dieckmann cyclization 60/100 and 100/200 mesh fractions of beads were used.

Formation of Adipic Acid Monotriethylcarbinyl Ester (**88**)

As shown in Scheme IX, the starting material used for the preparation of adipic acid monotriethylcarbinyl ester (**88**) was adipic acid monomethyl ester (**84**). Monoester **84** was smoothly converted to its acid chloride **85,** which in turn was treated with 3-ethyl-3-pentanol (triethylcarbinol) (**86**) and pyridine in diethyl ether as shown in Table I to prepare methyl trethylcarbinyl adipate (**87**). The highest yield of the mixed diester **87** obtained was 54 % when a mixture of the acid chloride **85**, triethylcarbinol (**86**) and pyridine in diethyl ether was stirred for 18 h at room temperature. However, even after 24 h stirring at room temperature acid chloride **85** furnished only 43 % of the mixed diester **87**. From these observations, it was concluded that a higher boiling ether might help to increase yield of the mixed diester **87**. Therefore, in another attempt esterification was carried out in tetrahydrofuran (THF). The acid chloride **85** was added to a refluxing solution of pyridine

and triethylcarbinol (**86**) in THF, and 1 h reflux resulted in a 50 % yield of the mixed diester **87**, which was used without further purification. (TLC developed in 10 % ethyl acetate in petroleum ether showed a minor impurity with low R_f). Esterification of the acid chloride **85** was also attempted with triethylcarbinol (**86**) using no solvent. The mixture of acid chloride **85** and triethylcarbinol (**86**) was heated to 65 ^{o}C, where a vigorous evolution of gas was observed, and the temperature of the reaction mixture was raised to 110 ^{o}C. The evolution of the gas ceased after five minutes, so heating was discontinued and reaction mixture was stirred at room temperature for 2 h. Vacuum distillation of the product mixture resulted in adipic acid monomethyl ester (**84**) (97%) and 3-chloro-3-ethyl pentane (63 %). In another attempt acid chloride **85** dissolved in 20 mL of toluene was cooled to 0 ^{o}C and was stirred with potassium triethylcarbinolate at 0 ^{o}C for 2 h. GLC analysis of the product revealed a mixture 10 % triethylcarbinol and 48 % methyl triethylcarbinyl adipate (**87**) (% by peak area).

Scheme IX. Formation of Adipic Acid Monotriethylcarbinyl Ester (**88**)

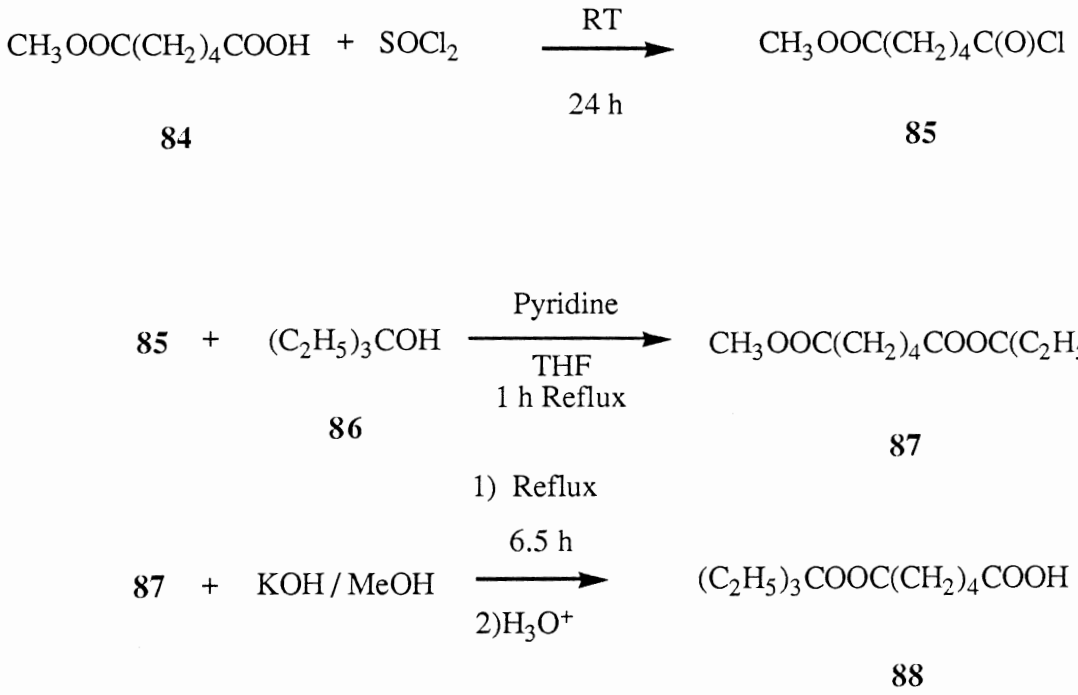


Table I. Formation of Methyl Triethyl-carbinyl Adipate (**87**)

85 mmol	**86** mmol	pyridine mmol	diethyl ether mL	time h	**87** % yield[a]
5.2	5.2	5.2	20	2	18[b]
72.0	72.0	72.0	25	6	41
151.7	151.7	151.8	50	4	32
266.0	170.5	266.0	70	18	54
292.5	292.5	292.5	50	24	43
310.0	310.0	310.0	130[c]	1	50

[a] Vacuum distilled. [b] Flash chromatographed. [c] Tetrahydrofuran.

Following Scheme IX, selective hydrolysis of the methyl ester of the mixed diester **87** was carried out with potassium hydroxide in methanol to prepare adipic acid monotriethylcarbinyl ester (**88**). Experiments 9 and 10 in Table II showed hydrolysis of the methyl triethylcarbinyl adipate (**87**) with 2.5 M KOH in methanol, to 78 % and 90 % of adipic acid monotriethylcarbinyl ester (**88**), which appeared to be pure by TLC and IR. However, in the final experiment the product contained adipic acid along with the hydrolyzed monoacid monoester **88**. The adipic acid was precipitated out by dissolving the mixture in diethyl ether, and 85 % (isolated) of adipic acid monotriethylcarbinyl ester (**88**) was recovered. In another attempt, the reaction mixture was refluxed with 2 M KOH in methanol, to give 54 % of monoacid monoester **88** (experiment 4, Table II). On 13 g scale using 2 M KOH in methanol 86 % of monoacid monoester **88** resulted (experiment 5, Table II). Although TLC of the product showed the presence of a minor amount of starting

material **87**, it was used in the synthesis without further purification. Hydrolyses carried out with different concentrations of KOH in methanol as well as in glyme, at different temperatures for different lengths of time, resulted in the recovery of the starting material **87** or in partial hydrolysis (Table II).

Table II. Selective Hydrolysis of Methyl Ester in the Mixed Diester **87**

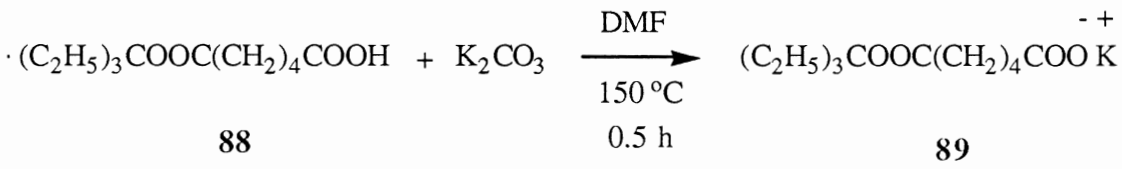
Expt.	mixed diester **87** mmol	KOH/MeOH mmol (M)	time h	**88** % yield
1	7.8	8.1[a]	1	no reaction
2	3.9	7.2 (3.6)	1	41[b]
3	7.8	14.4 (3.6)	2	68[b]
4	3.9	20.0 (2.0)	2	54[c]
5	50.4	200.0 (2.0)	2	86[d]
6	29.2	60.4 (3.0)	2	52[e]
7	31.2	62.3 (2.0)	2	74[e]
8	38.8	77.2 (2.0)	4.25	96[d]
9	19.4	51.0 (2.5)	6.5	78[f]
10	15.5	51.0 (2.5)	6.5	90[f]
11	58.2	153.0 (2.5)	5 min	85[f]

[a] Reaction was caried out in diglyme, using no methanol. [b] GLC analyses (% by peak area). [c] Flash chromatographed. [d] TLC showed presence of starting material **87**. [e] Based on consumed starting material **87**. [f] Isolated yield.

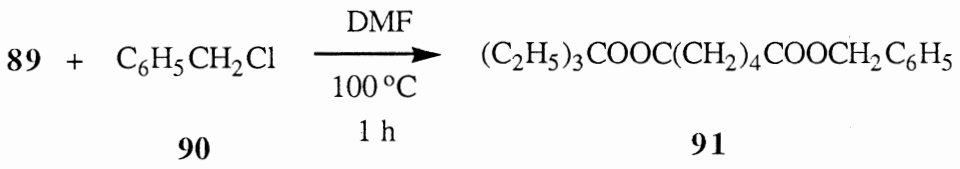
Benzyl Triethylcarbinyl Adipate (**91**)

Following Scheme X, benzyl triethylcarbinyl adipate (**91**) was synthesized from adipic acid monotriethylcarbinyl ester (**88**) and benzyl chloride (**90**). The potassium salt of monoacid **88** was formed by heating powdered potassium carbonate in DMF for 15 minutes with stirring in a 150 ^{O}C oil bath. Dissolution of the potassium carbonate indicated completion of the reaction, but all reactions were stirred for 30 minutes. In the final experiment (Table III) the benzyl chloride (**90**) was added in a refluxing solution of potassium salt of adipic acid monotriethylcarbinyl ester (**88**) and was refluxed for 1 h to give 84 % of benzyl triethylcarbinyl adipate (**91**). However, the same reaction at 100 ^{O}C for 1 h gave 58 % of the mixed diester **91**, along with dibenzyl adipate (**92**) (16 %), and adipic acid (**93**) (2 %). In an attempt to prepare diester **91**, the potassium salt **89** of monoacid monoester **88** was cooled to room temperature. The clear yellow solution of the potassium salt **89** in DMF started getting turbid below 70 ^{O}C and precipitated at room temperature. Benzyl chloride (**90**) was added at room temperature and the reaction mixture was stirred for 2.25 h. Progress of the reaction was monitored by TLC analysis of aliquots. After stirring at room temperature no product was detected, so the mixture was stirred at 60 ^{O}C for 1.5 h and then at 95 ^{O}C for 1 h. When the temperature was increased to 95 ^{O}C, reaction occured spontaneously, which was observed easily from color change, mud color to light yellow. So all of the benzyl ester preparations were carried out in a 95-100 ^{O}C oil bath (experiments 1-4, Table III).

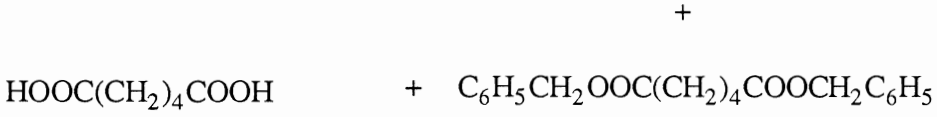
Scheme X. Formation of Benzyl Triethylcarbinyl Adipate (**91**) and Triethylcarbinyl (4-polystyrylmethyl) Adipate (**94**)



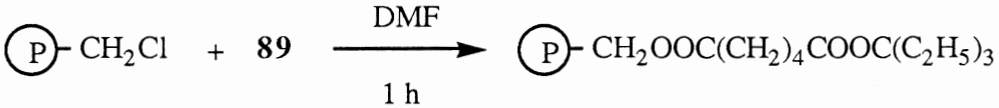
88 **89**



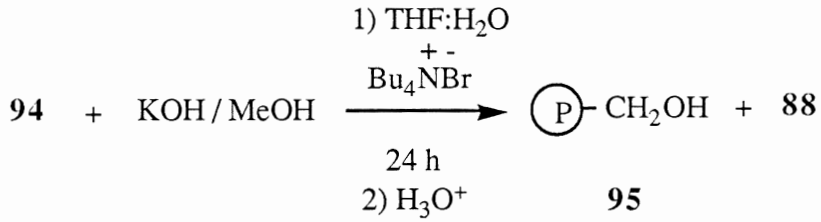
90 **91**



93 **92**



81 **94**



95

Triethylcarbinyl (4-polystyrylmethyl) adipate (**94**) was prepared using three kinds of polymers as shown in the Table IV. In experiments 1-6 the polymer used contained 10 % DVB and 25 % VBC (**81**), and polymer-bound ester **94** was prepared by a modified method of Crowley and Rapoport.[2] In all the experiments adipic acid monotriethylcarbinyl ester (**88**) was converted to its potassium salt **89** by heating a solution of **88** in DMF with powdered potassium carbonate in a 150 ^{o}C oil bath for 30 min, as described earlier. After cooling to room temperature chloromethylated polystyrene **81** was added to the solution of **89** in DMF. The reaction mixture was heated in a 150 ^{o}C oil bath for 1 h to afford 64-91 % conversions of chloromethylated polystyrene **81** to polymer-bound ester **94**. IR of the polymer-bound esters showed complete loss of -CH_2Cl peak at 1265 cm^{-1}. However, elemental analyses of the polymers in experiments 7 and 8 showed 0.39 % Cl (0.12 mmol / g) and 0.78 % Cl (0.22 mmol / g), and 63 % and 70 % conversions of chloromethyl groups to polymer-bound ester **94** respectively were found by hydrolysis of the polymer-bound ester **94**. According to Crowley and Rapoport[2] the reaction mixture should be heated for 10 h at 150 ^{o}C for essentially complete conversion of chloromethyl groups in 2 % cross-linked polymer. However, for the synthesis of large size rings through Dieckmann cyclization our aim was only partial conversion of chloromethyl groups in a highly cross-linked polymer.

Table III. Formation of Benzyl Triethyl-carbinyl Adipate (**91**)

88 mmol	benzyl chloride (**90**) mmol	DMF mL	**91** % yield
12.0	12.0	25	92[a]
13.8	13.8	16	81[b]
14.0	14.0	20	58[c]
12.3	14.0	10	96[d]
14.8	14.8	20	84[e]

[a] TLC showed a minor fast moving spot. [b] TLC showed one spot; 10 % of **88** was also recovered. [c] Flash chromatographed, dibenzyl adipate (**92**) (16 %), adipic acid (**93**) (2 %). [d] TLC showed one spot. [e] Flash chromatographed.

To find percent conversion and loading of the polymer-bound ester **94** (Table IV), samples used later in cyclization reactions were subjected to hydrolysis in THF:MeOH:H_2O (9:1:1) with KOH (overall concentration of KOH 0.3 M), in the presence of a phase transfer catalyst, tetra *n*-butylammonium bromide. After refluxing for 24 h, reaction mixtures were acidified and the resulting product, adipic acid monotriethylcarbinyl ester (**88**), was characterized by TLC, IR and ^{1}H NMR.

Table IV. Formation of Triethylcarbinyl

(4-Polystyrylmethyl) Adipate (**94**)

Ⓟ-CH_2Cl **81**, mmol	DVB/VBC % contents	**88** mmol	DMF mL	% conv.[a]	product **93** mmol / g[a]
3.28	10/25	3.36	15[b]	c	
3.28	10/25	3.36	30	d	
6.56	10/25	6.72	60	64	0.86
6.56	10/25	6.72	60	91[e]	
9.31	10/25	9.55	120	46	0.77
49.36	10/25	46.31	100	50	0.72
6.60	6/10	6.00	40	63	0.40
6.60	10/10	6.02	30	70	0.42

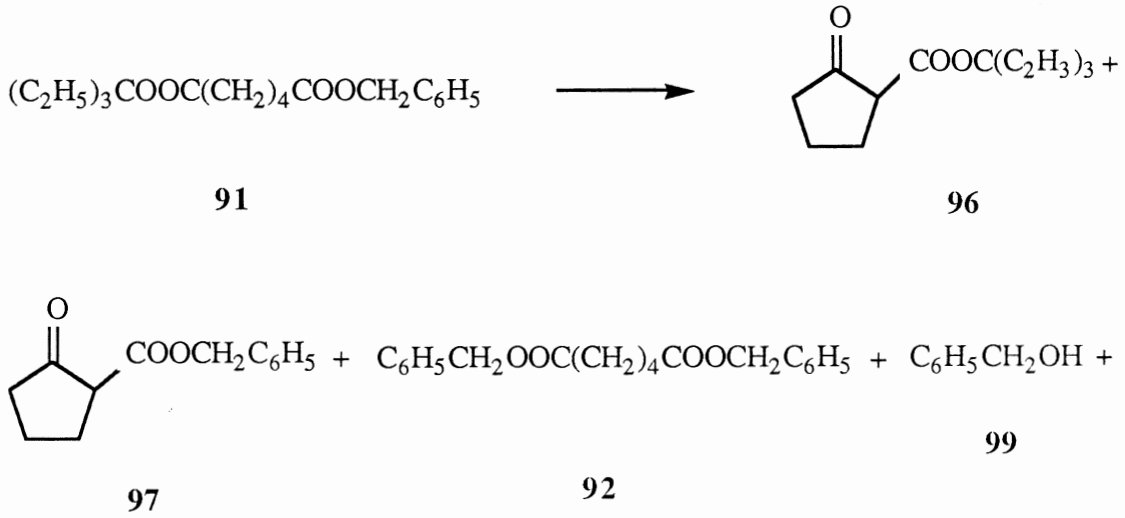
[a] % conversion of Ⓟ-CH_2Cl (**81**) to polymer-bound ester **94** and mmol/g calculated from hydrolyses of **94**. [b] Instead of DMF, *o*-dichlorobenzene was used as a solvent. [c] IR showed incomplete conversion by residual -CH_2Cl peak. [d] IR showed complete conversion by absence of -CH_2Cl peak. [e] Calculated from weight gain in the polymer.

Dieckmann Cyclization Reactions in Solution

To find the best base-solvent system for the Dieckmann cyclization of the polymer-bound mixed diesters (**94**), benzyl triethylcarbinyl adipate (**91**) was used as a model compound. All of the cyclization reactions were run at room temperature and always base was added to a solution of the mixed diester **91**. The reactions were carried out at 0.11 M to 2.6 M concentrations of the mixed diesters, much higher than reported in the literature.[1,4] As shown in Scheme XI cyclization of **91** in solution reactions could lead to one or two cyclized products, triethylcarbinyl 2-cyclopentanonecarboxylate (**96**) and benzyl 2-cyclopentanonecarboxylate (**97**). With the choice of a proper base the mixed diester **91** could be cyclized selectively to **96** or **97**. Using alkoxide bases such as potassium triethylcarbinolate and potassium *t*-butoxide, **91** cyclizes selectively to give **96** (48-75 % flash chromatographed, Table V). However, using lithium bis(trimethylsilyl)amide in THF at room temperature the cyclization of the mixed diester **91** resulted in benzyl 2-cyclopentanonecarboxylate (**97**) regioselectively (Table VI). Toluene as a solvent (experiment 4), gave a mixture of 55 % **97** and 24 % **96** by ^{1}H NMR analysis.

Scheme XI. Dieckmann Cyclization Reactions

a) in Solution



b) in Polymer-Bound Ester **94**

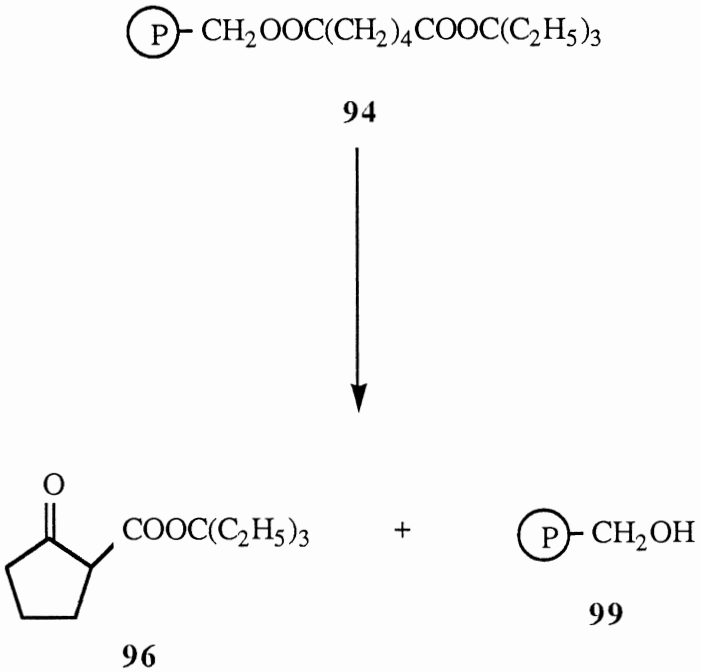


Table V. Dieckmann Cyclization of Benzyl Triethyl-carbinyl Adipate (**91**) with Alkoxide Bases

91 mmol	base	mmol base	solvent	concn of **91**, M	time h	% yield[a] **96**
3.88[b]	$(C_2H_5)_3COK$	7.75	-	2.60	16	48
3.00	$(C_2H_5)_3COK$	6.05	DMF	0.11	21	53
1.51	$(C_2H_5)_3COK$	3.02	DMF	0.15	10	75[c]
1.50	$(C_2H_5)_3COK$	3.00	toluene	0.15	2	80[c]
1.50	$(C_2H_5)_3COK$	3.00	toluene	0.15	2	80[c]
3.00	$(CH_3)_3COK$	6.00	DMF	0.12	0.25	75
0.77	$(CH_3)_3COK$	1.55	DMF	0.12	5	70
0.60	$(CH_3)_3COK$	1.21	DMF	0.12	0.83	92[c]
1.03	$(CH_3)_3COK$	2.07	THF	0.11	1.33	64

[a] Flash chromatographed, unless noted as TLC only. [b] Methyl triethylcarbinyl adipate (**87**). [c] TLC showed **96** as the major product.

Table VI. Dieckmann Cyclization of Benzyl Triethylcarbinyl Adipate (**91**) with $[(CH_3)_3Si]_2NLi$

91 mmol	base mmol	solvent	concn of **91**, M	time h	% yield[a] **96**	**97**
0.94	1.88	THF	0.12	1	6	81
5.23	15.00	THF	0.09	0.25	-	38
0.90	1.80	THF	0.15	0.25	16	64
1.50	3.00	toluene	0.13	4.75	24	55
1.51	1.51	THF	0.15	17[b]	-	72[c]

[a] Flash chromatographed, unless noted as TLC only. Mixture compositions were determined by ^1H NMR analysis. [b] 25 °C for 4.5 h and refluxed overnight. [c] TLC showed **97** as the major product.

Dieckmann cyclization reactions were also attempted with sodium hydride and potassium hydride as bases. Hydride bases were not soluble in THF or DMF, but when they were present in the form of fine suspension, cyclization reactions went at room temperature (Table VII, except experiments 1 and 2). Sodium hydride (NaH) used was crystalline (97 %) as well as 80 % by weight in mineral oil. Using crystalline NaH in refluxing THF for 7 h **91** did not cyclize. However, heating the reaction mixture at 100 ^{o}C in DMF for 4 h resulted in a yield of 53 % of **96**. Experiments 3 and 4 in the Table VII showed cyclization reactions using NaH (80 % by weight in mineral oil). The reaction mixtures containing diester **91**, sodium hydride and THF or DMF were stirred at room temperature for 17 h and 18 h respectively and were monitored by taking aliquots. The products after extraction with diethyl ether and hexane were subjected to flash chromatography to yield the cyclized product **96** (26 %) and (37 %) respectively.

Using potassium hydride (KH) (35 % by weight in mineral oil) in THF at room temperature for 0.58 h gave **96** in a yield of 70 %. Dibenzo-18-crown-6 in THF and 18-crown-6 in DMF were used to enhance the solubility of KH, which could make it a more powerful base. Use of dibenzo-18-crown-6 increased the yield from 70 % to 75 %. However, dibenzo-18-crown-6 was not soluble in THF. The use of 18-crown-6, which was soluble in THF, led to decrease in the yield (experiments 7 and 8 in Table VII). The crown ethers were used to increase the solubility of the base in the medium, and to increase the likelihood that base would diffuse into the polymer beads to help cyclization of the polymer-bound esters, as discussed in a later section.

Table VII. Dieckmann Cyclization of Benzyl Triethylcarbinyl Adipate (**91**) with Hydride Bases

Expt.	**91**	base	mmol base	solvent	concn of **91**, M	time h	% yield of **96**[a]
1	1.21	NaH[b]	4.20	THF	0.09	7[c]	No reaction
2	1.22	NaH[b]	3.33	DMF	0.12	4[d]	53[e]
3	1.66	NaH	3.30	THF	0.17	17	26
4	0.70	NaH	1.40	DMF	0.06	18	37
5	0.62	KH	excess	THF	0.12	0.58	70
6	0.68	KH[f]	4.53	THF	0.05	1	75
7	0.34	KH[g]	0.67	DMF	0.08	0.5	34
8	0.72	KH[g]	1.33	DMF	0.10	1	27

[a] Flash chromatographed. [b] Sodium hydride (crystalline, 97 %). [c] Refluxed, [d] 25 °C for 2.5 h (no reaction), 60 °C for 2.75 h (no reaction), 100 °C for 4 h. [e] TLC showed a mixture; major product was **96**. [f] Potassium hydride with dibenzo-18-crown-6. [g] Potassium hydride with 18-crown-6.

A series of other bases were used in different solvents at room temperature. Besides alkoxides, hydrides and lithium bis(trimethylsilyl)amide, the only other successful base was potassium triphenylmethide. One hour stirring at room temperature in THF, and flash chromatography of the product mixture gave 44 % of the cyclized product **96** and 3 % of **97**, along with benzyl alcohol (**99**) (55 %), dibenzyl ether (**98**) (17 %) and adipic acid triethylcarbinyl ester (**88**) (6 %). Formation of dibenzyl ether showed that the benzyloxy anion attacked the benzyl -CH_2 carbon of the benzyl ester, resulting in dibenzyl ether (**98**) and adipic acid triethylcarbinyl ester (**88**)

Dieckmann Cyclizations of Triethylcarbinyl (4-Polystyrylmethyl) Adipate (**94**)

Dieckmann cyclizations of polymer-bound ester **94** were attempted with alkoxide bases and in different solvents at room temperature as well as at high temperatures. Table VIII reports cyclizations to five membered rings using alkoxide bases with all three kinds of polymers. Before addition of base the polymers were allowed to swell completely by heating in THF or DMF with a 80 ^{o}C or 150 ^{o}C oil bath for 5 minutes. Base was added using a syringe. When the base was added to a swollen polymer at 150 ^{o}C, the polymer turned red color at once and then gradually turned from red to yellow. Experiments 6 to 10 in Table VIII report the cyclization of polymer-bound ester **94** (10 % DVB, 25 % VBC polymer) with potassium *t*-butoxide, using THF and DMF as a solvents. The highest yield of the cyclized product **96** obtained was in DMF at 130 ^{o}C. The product was extracted with petroleum ether to yield 75 % of the cyclized product **96** which appeared to be pure by TLC, IR, ^{13}C NMR, ^{1}H NMR, elemental analysis and mass spectrum. Experiments 1 to 7 (Table VIII) report attempted cyclizations of polymer-bound ester **94** with potassium triethylcarbinolate in toluene. The highest yield of triethylcarbinyl 2-cyclopentanonecarboxylate (**96**) obtained was 44 % (flash chromatographed).

No reaction of polymer-bound ester **94** at room temperature was observed in DMF or in toluene. The IR spectra of the recovered polymers were the same as that of the starting polymer **94**. The polymers after prolonged heating with bases showed the same IR spectra as the starting materials (polymer-bound ester **94**) (experiments 1-5 except 3, Table VIII). In experiment 3 the spectrum of recovered polymer was different from that of the starting material. Therefore, after the cyclization reaction, the dried polymer was swollen in dichloromethane and HBr gas was bubbled through it for 2 h. It resulted in a pale yellow oily product whose IR, ^{13}C NMR and ^{1}H NMR spectra were very complex, and I could not assign the structure. IR of the residual polymer after cleavage with HBr showed that there was still some polymer-bound ester left even after 2 h of treatment with HBr in dichloromethane. To obtain the resin retained keto ester it was cleaved from the support under acidic conditions (HBr/CH_2Cl_2) since alkaline hydrolysis might cause Claisen reversal. Due to the complex nature of the recovered material after HBr treatment, no attempt was made to complete the cleavage.

A series of other cyclization reactions were attempted using potassium *t*-butoxide and potassium triethylcarbinolate in toluene as bases at different temperatures under different conditions. Results are in Table VIII. In the final four experiments two different kinds of polymer-bound esters **94** (0.42 mmol / g of the dry polymer), 6 % DVB and 10 % VBC polymer (experiment 11-13, Table VIII) and 10 % DVB and 10 % VBC polymer (experiment 14, Table VIII) had been used. Duplicate experiments 12 and 13 confirm the reproducibility of the results. The IR spectra of the residual polymers showed 100 % conversion of the polymer-bound ester **94** by absence of ester carbonyl group.

Dieckmann cyclization reactions of the polymer-bound ester **94** were attempted with other bases. High temperatures were required in the case of lithium bis(trimethylsilyl)amide and potassium hydride. The only other successful base besides alkoxide bases was potassium hydride in DMF. Potassium hydride suspended in DMF was added to a preswollen polymer at room temperature and the reaction mixture was

heated for 1.5 h in a 150 ^{o}C oil bath. Flash chromatography gave **96** in a 22 % yield. Lithium bis(trimethylsilyl)amide showed some reaction at 80 ^{o}C and 150 ^{o}C, but the product mixture could not be separated by flash chromatography due to very close R_f values. In solution reactions using lithium bis(trimethylsilyl)amide as a base, benzyl triethylcarbinyl adipate (**91**) produced benzyl 2-cyclopentanonecarboxylate (**97**) (Table VI). Therefore, residual polymers were checked for the polymer-bound cyclized product. In one case after heating for 4 h at 80 ^{o}C, the IR spectrum of the residual polymer was the same as that of the starting polymer **94**, but in another attempt after heating for 16 h at 80 ^{o}C the IR spectrum of the residual polymer was somewhat different from that of **94**. No attempt was made to hydrolyze and identify the polymer-bound material. Use of potassium triphenylmethide and lithium triphenylmethide did give some reaction at room temperature as well as at higher temperatures, but the products were not identified.

Table VIII. Dieckmann Cyclizations of Polymer-Bound Ester **94** with Alkoxide Bases

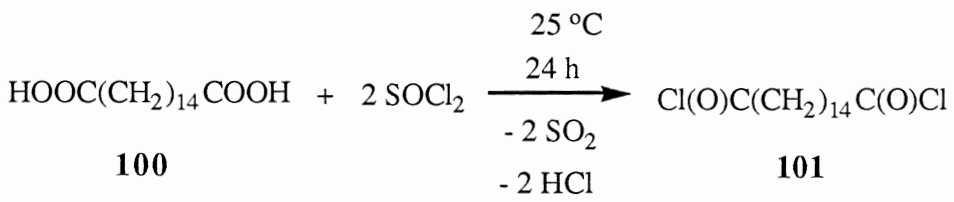
Expt.	**94** mmol	base	mmol base	Solvent	concn. of **94**, M[a]	temp.[b] °C	time h	% yield of **96**
1	2.16	$(C_2H_5)_3COK$	4.3	DMF	0.11	24	24	24[c]
2	0.86	$(C_2H_5)_3COK$	1.9	DMF	0.08	100	18	22[d]
3	2.32	$(C_2H_5)_3COK$	4.6	DMF	0.15	150	2.5	44[e]
4	1.44	$(C_2H_5)_3COK$	3.0	DMF	0.22	25	24	
						150	3	32[d]
5	1.44	$(C_2H_5)_3COK$	2.9	toluene	0.15	24	6	
						60	10[c]	
6	1.44	$(CH_3)_3COK$	3.0	THF	0.29	80	2	17[d]
7	1.44	$(CH_3)_3COK$	3.0	DMF	0.29	100	0.75	64[f]
8	1.44	$(CH_3)_3COK$	3.0	DMF	0.36	100	0.13	18[f]
9	1.44	$(CH_3)_3COK$	3.0	DMF	0.29	130	0.25	75[f]
10	1.44	$(CH_3)_3COK$	3.0	DMF	0.21	150	0.5	40[d]
11	0.84	$(C_2H_5)_3COK$	2.5	DMF	0.17	130	0.25	77[e]
12	0.84	$(CH_3)_3COK$	2.0	DMF	0.21	150	0.25	80[f]
13	0.84	$(CH_3)_3COK$	2.0	DMF	0.21	150	0.25	80[f]
14	0.84	$(C_2H_5)_3COK$	2.0	DMF	0.22	150	0.25	75[e]

[a] The concn of **94** is the overall concn of the polymer-bound ester groups in the reaction mixture. [b] Temperature of the oil bath. [c] With 18-crown-6, TLC showed a mixture of spots with minor cyclized product **96**. [d] TLC showed **96** as major product. [e] Flash chromatographed. [f] Product was not chromatographed; TLC showed one spot.

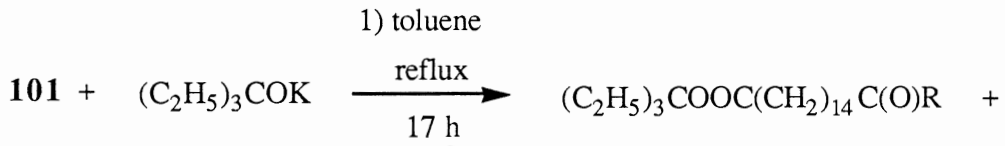
Formation of Hexadecanedioic Acid Mono-triethylcarbinyl Ester (**102b**)

The key intermediate desired for the synthesis of the 15-membered ring, hexadecanedioic acid monotriethylcarbinyl ester (**102b**), was prepared in 38 % yield as shown in Scheme XII. This method was developed due to difficulties in the preparation of **102b** from hexadecanedioic acid (**100**), using the method developed in the preparation of 5-membered rings (Scheme V). The method of Scheme V, a) selective hydrolysis of dimethyl hexadecanedioate (**108**) to hexadecanedioic acid monomethyl ester (**110**), and b) selective hydrolysis of the methyl ester of methyl triethylcarbinyl hexadecanedioate (**112**) to hexadecanedioic acid monotriethylcarbinyl ester (**102b**), resulted in a low yield. A critical factor in the selective hydrolysis of the methyl triethylcarbinyl adipate (**87**) is the hydrolysis of the triethylcarbinyl ester during acidic workup. In the process of optimizing the hydrolysis conditions, the hydrolysis products were analyzed by GLC, which in the early attempts showed presence of triethylcarbinol in the product mixture. To find the factor responsible for the hydrolysis of triethylcarbinyl ester, two reactions were run. One mixture, after refluxing for 2 h with 2 M KOH in methanol and acidification with 18 % aqueous HCl at 0 ^{o}C, showed triethylcarbinol (GC retention time 0.89 min, 32 % by peak area). The other mixture after 3 h reflux with the base was acidified with glacial acetic acid at 0 ^{o}C. GLC analysis of the product showed 12 % triethylcarbinol by peak area. The formation of 32 % triethylcarbinol showed that triethylcarbinyl ester is hydrolysed by concd HCl. Analysis of the diester **87** proved that it was stable in the injection port at 300 ^{o}C. The best conditions to minimize or eliminate the cleavage of triethylcarbinyl ester proved to be acidification to pH 2-3 with 1 N HCl using a pH meter, and that method was used for acidification of all reaction mixtures containing triethylcarbinyl ester.

Scheme XII. Formation of Hexadecanedioic Acid Monotriethylcarbinyl Ester (**102b**)

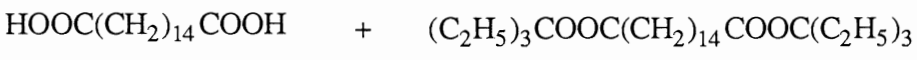


100 **101**



102a : R = Cl

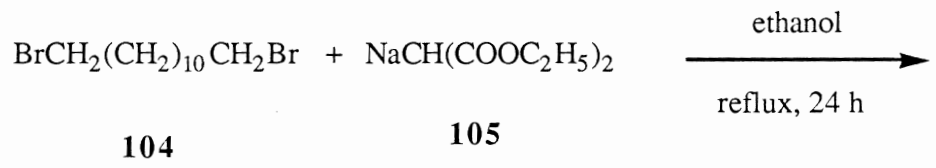
102b : R = OH



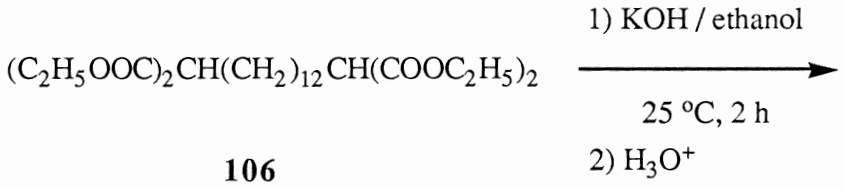
100 **103**

Hexadecanedioic acid (**100**) was prepared using Chuit's[111] method, by refluxing 1,12-dibromododecane (**104**) with the sodium salt of diethyl malonate **105** as shown in Scheme XIII.

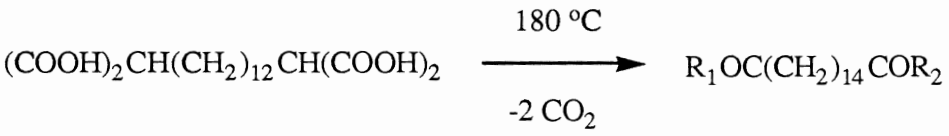
Scheme XIII. Synthesis of Hexadecanedioic Acid (**100**)



104 **105**



106



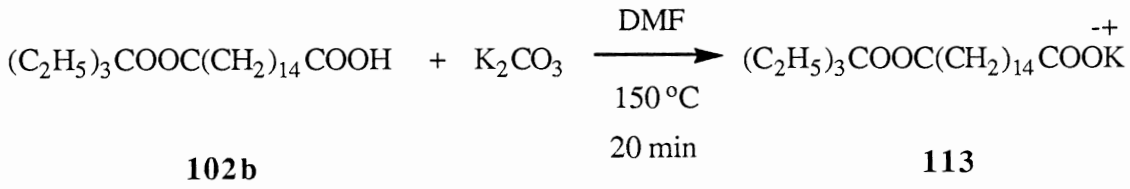
107

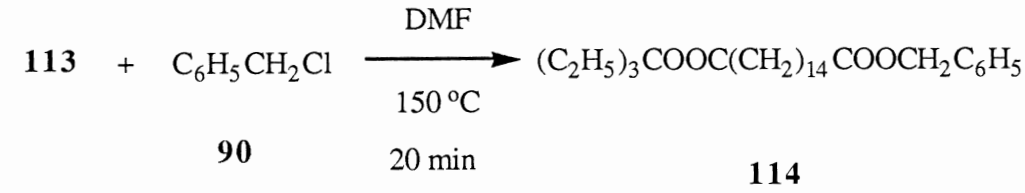
	R_1	R_2
100	OH	OH
108	OCH_3	OCH_3
109	OC_2H_5	OC_2H_5
110	OCH_3	OH
111	OC_2H_5	OH
112	OCH_3	$OC(C_2H_5)_3$

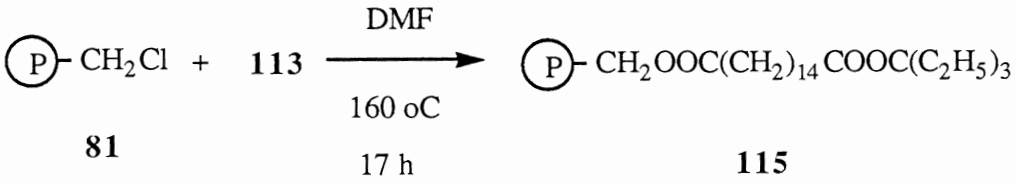
Formation of Benzyl Triethylcarbinyl Hexadecanedioate (**114**) and Triethylcarbinyl (4-Polystyrylmethyl) Hexadecanedioate (**115**)

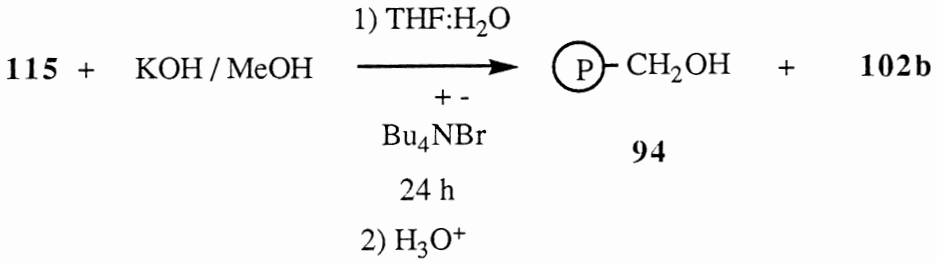
For formation of the mixed diester **114** and polymer-bound ester **115**, hexadecanedioic acid monotriethylcarbinyl ester (**102b**) was converted to its potassium salt **113** in DMF by heating it with powdered potassium carbonate (Scheme XIV). Benzyl triethylcarbinyl hexadecanedioate (**114**) was obtained in 94 % yield in 20 minutes. However, for the synthesis of polymer-bound ester **115**, a solution of potassium salt **113** with the chloromethyl polymer **81** (DF = 0.07) in DMF was refluxed at 160 ^{o}C for 17 h. It was found from the recovery of hexadecanedioic acid monotriethylcarbinyl ester (**102b**) from the hydrolysis of the polymer-bound ester **115** that 48 % of the chloromethyl groups had been converted to polymer-bound ester **115**. IR analysis of the polymer-bound ester **115** showed a weak peak at 1270 cm^{-1} due to the residual chloromethyl groups. Elemental analysis showed 0.5 % Cl (0.14 meq / g of the dry polymer), but residual chloromethyl groups could not be detected from ^{13}C NMR analysis of the polymer-bound ester **115**.

Scheme XIV. Formation of Benzyl Triethylcarbinyl Hexadecanedioate (**114**) and Triethylcarbinyl (4-Polystyrylmethyl) Hexadecanedioate (**115**)









Attempted Dieckmann Cyclizations of Benzyl Triethyl-carbinyl Hexadecanedioate (**114**)

Before trying cyclization of polymer-bound ester **115** to prepare cyclopentadecanone (**116**), cyclizations of benzyl triethylcarbinyl hexadecanedioate (**114**) were attempted by adding base directly to a solution of the mixed diester **114** at room temperature. Also the cyclization reactions were attempted by adding a solution of the mixed diester **114** to a refluxing solution of the base using a syringe pump. All attempts at Dieckmann cyclization of the mixed diester **114** to the 15-membered ring with alkoxide bases and with lithium bis(trimethylsilyl)amide resulted in mixtures of starting mixed diester **114**, di(triethylcarbinyl) hexadecanedioate (**103**), benzyl alcohol (**99**), hexadecanedioic acid monotriethylcarbinyl ester (**102b**), and hexadecanedioic acid (**100**), as shown by TLC, and flash chromatography in some cases.

In another two cyclization attempts using potassium triethylcarbinolate in toluene, the products were flash chromatographed, which gave 24 % and 40 % di(triethylcarbinyl) hexadecanedioate (**103**) due to transesterification of benzyl triethylcarbinyl hexadecanedioate (**114**). Along with **103**, benzyl alcohol (**99**) and starting material **114** were also recovered. However, using DMF as a solvent with potassium triethylcarbinolate the product mixture showed a major spot due to hexadecanedioic acid monotriethylcarbinyl ester (**102b**) on TLC plate along with number of other spots. Cyclization reactions with potassium *t*-butoxide mainly resulted in a mixture of compounds shown by TLC with monoacid monoester **102b** as the major one. Similarly cyclization attempts with lithium bis(trimethylsilyl)amide were unsuccessful, showing a number of spots on TLC plates.

When the mixed diester **114** dissolved in DMF was added through a syringe pump at a rate of 0.1 mL / min to a refluxing solution of the base in DMF, the reaction mixture turned dark orange color. The product in turn was refluxed with 3 N HCl in ethanol. TLC (developed in 5 % EtOAc in petroleum ether) showed three major spots with R_f 0.87, 0.53

and 0.06 with two minor spots. The R_f of the mixed diester **114** was 0.53 and of cyclopentadecanone (**116**) was 0.50. However, when cyclization of the mixed diester **114** was carried out in toluene, it resulted in a light yellow solid. TLC (developed in 5 % EtOAc in petroleum ether) showed no cyclized product with two major spots, R_f 0.43 and 0.14 [hexadecanedioic acid monotriethylcarbinyl ester (**102b**)]. The addition of the mixed diester **114** to a refluxing solution of potassium *t*-butoxide through a syringe pump at a rate of 0.1 mL / h over a period of 2 h, and then 3 h additional reflux resulted in a white solid [major component hexadecanedioic acid (**100**) shown by TLC].

Dieckmann Cyclizations of Diethyl Hexadecanedioate (**109**)

Synthesis of cyclopentadecanone (**116**) by Dieckmann cyclization was attempted with different diesters. Table IX shows attempts with diethyl hexadecanedioate (**109**). A modified procedure of Leonard and Schimelpfenig[34] resulted in mixtures of products difficult to separate by flash chromatography. All of the product mixtures were hydrolyzed and decarboxylated with 10 % HCl in ethanol, and were subjected to GLC analysis using cycloheptanone as an internal standard. In one case (experiment 2, Table IX), the product mixture was flash chromatographed. A mixture of fast moving material gave a yellow oil which solidified upon sitting, smelled like musk, and was analyzed by GLC to reveal 39 % of cyclopentadecanone (**116**). No transesterification products were detected. However, starting diethyl hexadecanedioate (**109**) was detected also by GLC. Additional 3 h reflux after complete addition of the diethyl ester **109** improved the yield of **116** from 2 % to 14 % (experiments 3 and 4, Table IX).

Addition time versus addition rate was also investigated (experiments 6 and 7, Table IX). In experiment 6 the diethyl ester **109** addition was completed in 4 h at a rate of 2.7 mL / h, which with an additional 1 h reflux showed a 13 % yield of **116** along with 12 % diethyl ester **109**. Using the same solvent the addition time was increased to 9 h

(experiment 7) at a rate of 2.5 mL / minute with an additional 2 h reflux. The results were the same as in experiment 6. This showed that not the addition time but the addition rate was responsible for the cyclopentadecanone (**116**) formation in xylenes as a solvent.

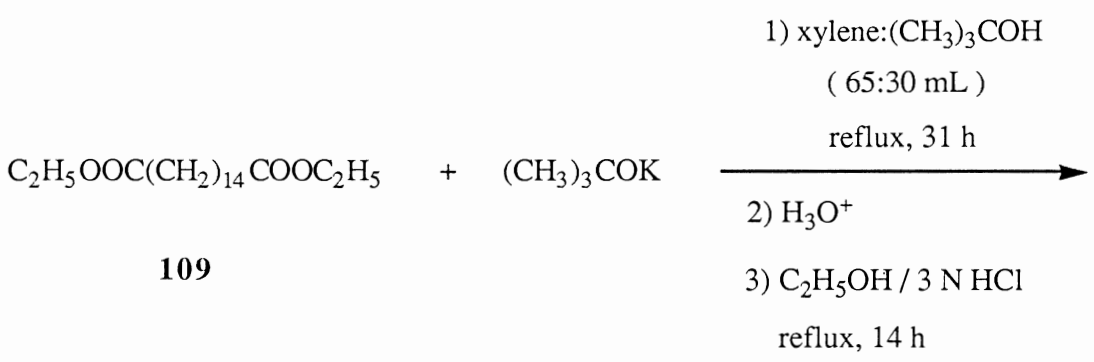
Table IX. Dieckmann Cyclizations of Diethyl Hexadecanedioate (**109**)

Expt.	**109** mmol	base	mmol base	solvent	concn of **109**	time[a] h	**116** % yield[b]	**109** % recovd.[b]
1	15.9	$(CH_3)_3COK$	76.4	xylenes	0.08	2	3	
2	6.4	$(CH_3)_3COK$	30.6	xylenes	0.08	25	39	
3	0.6	$(C_2H_5)_3COK$	3.0	THF	0.03	4.75	14	46
4	0.6	$(C_2H_5)_3COK$	3.0	THF	0.03	1.75	2	28
5	0.6	$(C_2H_5)_3COK$	3.0	toluene	0.03	3	4	24
6	0.6	$(C_2H_5)_3COK$	3.0	xylenes	0.03	5	13	12
7	1.5	$(C_2H_5)_3COK$	7.3	xylenes	0.03	11	13	13
8	0.6	$(C_2H_5)_3COK$	3.5	xylenes	0.001	27.5		73
9	0.6	$[(CH_3)_3Si]_2NLi$	1.2	xylenes	0.03	2	3	
10	0.6	$[(CH_3)_3Si]_2NLi$	1.2	xylenes	0.03	2	4	
11	0.6	$[(CH_3)_3Si]_2NLi$	1.2	THF	0.03	2	5	
12	3.3	NaH	6.5	xylenes	0.06	20		96

[a] The total time includes addition of the diethyl ester **109** and additional reflux time.

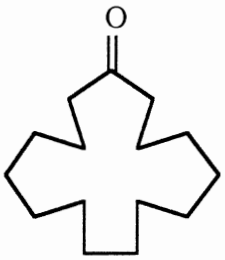
[b] GLC analysis.

At high dilution (0.001 M, experiment 8), there was no cyclized product **116**. With 0.03 M **109** 13 % of cyclopentadecanone (**116**) was formed (experiments 6 and 7). Cyclization of diethyl ester **109** with lithium bis(trimethylsilyl)amide showed only 3 to 5 % formation of cyclopentadecanone (**116**) with no starting material **109** detected by GLC analysis (experiments 9-11, Table IX). In all three cases the base was freshly prepared and was added to a refluxing solution of the diethyl ester **109** at a rate of 0.1 mL / minute over a period of 2 h. TLC of the reaction products showed a number of spots, with very close R_f values. A cyclization attempt with sodium hydride showed no reaction with 96 % recovery of the diethyl ester **109**. An attempt to cyclize dimethyl hexadecanedioate (**108**) with addition of potassium *t*-butoxide in xylene using syringe pump, resulted in 82 % yield of hexadecanedioic acid (**100**). Attempted cyclization of di(triethylcarbinyl) hexadecanedioate (**103**) with potassium triethylcarbinolate in toluene resulted in recovery of the starting material.



$C_2H_5OOC(CH_2)_{14}COOC_2H_5$ + $(CH_3)_3COK$

109



116

[23]

Attempted Dieckmann Cyclization of

Polymer-Bound Ester **115**

The cyclization reactions of triethylcarbinyl (4-polystyrylmethyl)hexadecanadioate (**115**) (10 % DVB 10 % VBC polymer) (DF = 0.035) were tried at room temperature as well as at higher temperature with potassium triethylcarbinolate and potassium *t*-butoxide in different solvents using 0.01 to 0.06 M final concentration of the polymer-bound ester **115** in the reaction mixture. The cyclization attempts mostly resulted in transesterification to give di(triethylcarbinyl) hexadecanedioate (**103**) and hydrolysis to give hexadecanoic acid monotriethylcarbinyl ester (**102b**). The observation of the same results in the cyclization of the polymer-bound ester **115** as in solution cyclization reactions of benzyl triethylcarbinyl hexadecanedioate (**114**) showed that the long chain mixed diesters were more prone to transesterification and hydrolysis than to enolization and cyclization.

Discussion

The most successful Dieckmann cyclizations of benzyl triethylcarbinyl adipate (**91**) and of triethylcarbinyl (4-polystyrylmethyl) adipate (**94**) are listed in Table X. The polymeric benzyl ester in cyclization reactions provided the advantage of isolation of products by simple filtration (experiments 7, 8, 9, 12, and 13, Table VIII). The cyclized product was extracted from the filtrate with diethyl ether or petroleum ether, and pure product was isolated by drying and evaporating the solvent. The Dieckmann cyclization of a mixed diester in solution may produce a mixture of two β-keto esters, whose separation by some conventional method becomes necessary. When a non-polymeric benzyl ester (**91**) was used, the separation of the two β-keto esters, triethylcarbinyl 2-cyclopentanonecarboxylate (**96**) and benzyl 2-cyclopentanonecarboxylate (**97**) was achieved by flash chromatography.

If polymer-bound ester **94** cyclizes both ways, one product will be cleaved from the polymer support and the other will be bound to the polymer. After recovering one product by simple filtration, the other can be cleaved from the polymer by HBr treatment. If the cyclization reaction forms the triethylcarbinyl ester selectively, the byproduct polymer can be separated by filtration. From solution cyclizations of the mixed diester **91**, chromatographic purification of product is required. The purification of the mixture of the two β-keto esters was difficult by chromatography, because of very close R_f values. The time consumed to obtain the two cyclized products is almost same in solid phase and solution reactions, but if the cyclization results in one product, then certainly polymer-bound materials are far better than their solution analogues.

Another important factor, which could make the solid support preferable is the use of higher concentrations than in solution reactions. As reported in experiment 8, Table VIII, up to 0.36 M polymer-bound ester **94** has been used in the cyclization reactions. Such high diester concentrations fail to give decent yields of cyclization in solution to medium

and large rings. Despite the advantages of using polymer-bound esters, temperatures of more than 100 ^{o} C are required for the cyclization reactions, which makes them unsuitable for the heat sensitive materials. The alkoxide base has low affinity for polystyrene, and at lower temperatures cannot diffuse into the polymer. Formation of a small amount of enolate may make the inner microenvironment of the polymer matrix more favorable for the alkoxide base, so that diffusion of base into the polymer is an autocatalytic process, causing the enolization and cyclization. The difficulty of diffusion of the alkoxide bases at lower temperatures can be observed visually also. The polymer-bound ester changes from light yellow to dark brown color at once upon enolization and cyclization, and it changes back to light yellow upon acidification during the workup.

Regioselectivity in Dieckmann cyclization has been well documented in the literature, and variously substituted starting materials have been used. According to Crowley and Rapoport,[33] unidirectional cyclization can be achieved by the use of one ester which is much more hindered than the other. They obtained unidirectional cyclization of mixed diesters, unsubstituted **8b** and 3-ethyl substituted **8d,** to **9a** and **9b** (Scheme II) with potassium triethylcarbinolate in toluene. The bulky triethylcarbinyl group forced the cyclization to be regiospecific. By using the highly hindered triethylcarbinyl group Dieckmann cyclization of the mixed diester **91** was also effected regiospecifically by attack of the enolate of the triethylcarbinyl ester at the carbonyl carbon of the benzyl ester.

Table X. Dieckmann Cyclizations in Solution and in Polymer

91 mmol	base	mmol base	solvent	concn of **91**, M	time min	**96** % yield[a]	**97** % yield[a]
3.00[b]	$(CH_3)_3COK$	6.00	DMF	0.12	15	75	-
1.03[b]	$(CH_3)_3COK$	2.07	THF	0.11	80	64	-
0.62[b]	KH	excess	THF	0.12	35	70	-
0.68[b]	KH	4.53[c]	THF	0.05	60	75	-
1.22[b]	NaH	3.33	DMF	0.12	240	53	-
0.94[b]	$[(CH_3)_3Si]_2NLi$	1.88	THF	0.12	60	6	81
0.84[d]	$(CH_3)_3COK$	2.50	DMF	0.21	15	80[e]	-
0.84[f]	$(C_2H_5)_3COK$	2.00	DMF	0.22	15	75	-
1.44[g]	$(CH_3)_3COK$	3.00	DMF	0.29	15	75[e]	-

[a] Flash chromatographed. [b] Benzyl triethylcarbinyl adipate (**91**). [c] With dibenzo-18-crown-6. [d] Polymer-bound ester **94** (6 % DVB, 10 % VBC polymer, at 150 °C). [e] Isolated pure. [f] Polymer-bound ester **94** (10 % DVB, 10 % VBC polymer, at 150 °C). [g] Polymer-bound ester **94** (10 % DVB, 25 % VBC polymer, at 130 °C).

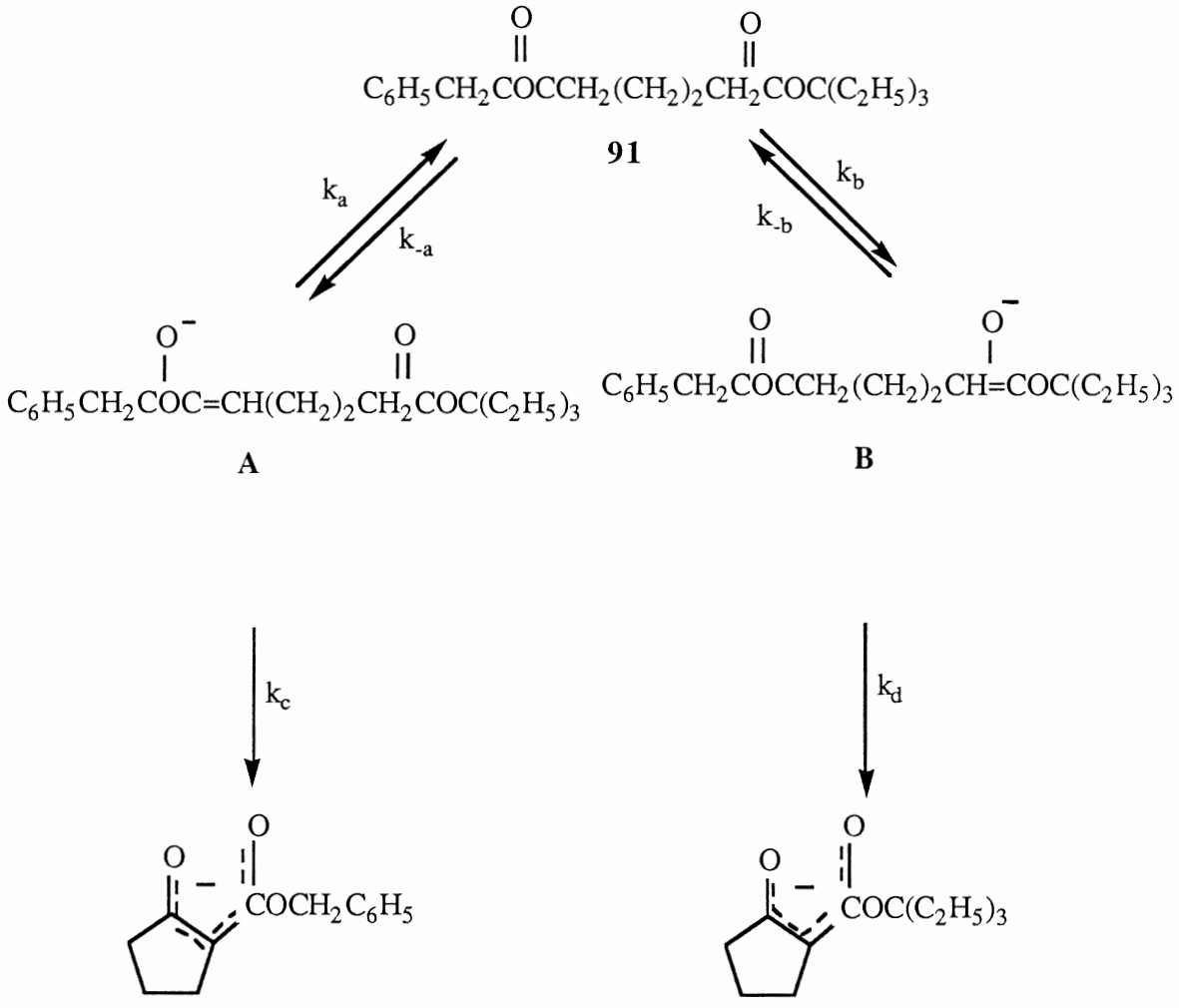
Our results (Table V, VI and VII) show the preparation of cyclopentanones by Dieckmann cyclization of mixed diesters at higher concentrations and much milder conditions (room temperature) in higher yields. Earlier, cyclization reactions of mixed pimelic diesters to cyclohexanones have been carried out by adding the mixed diester to a refluxing solution of 4.5 equiv of potassium triethylcarbinolate in toluene.[33]

Using polymer-bound esters for the synthesis of small size rings simplified the isolation of the products (experiments 8, 9,12 and 13, Table VIII), but higher temperatures were required to effect the cyclization. However, the attempts at Dieckmann cyclizations to prepare large size rings using polymer-bound ester were unsuccessful, due to intervention of transesterification reactions. This suggests further modifications of the solid phase method will be required to achieve the synthesis of large size rings.

We found that using lithium bis(trimethylsilyl)amide as a base in THF or toluene resulted in unusual regioselectivity of cyclization of mixed diester **91** to give benzyl 2-cyclopentanonecarboxylate (**97**) (81 %) and triethylcarbinyl 2-cyclopentanonecarboxylate (**96**) (6 %, Table X). The driving force for the reaction is the formation of the stable enolate of a 2-alkoxylcarbonylcyclopentanone (Scheme XV). With an alkoxide base the formation of ester enolate **A** and **B** is easily reversible, and product formation is governed by the relative energies of the transition states leading to cyclic products. The lithium bis(trimethylsilyl)amide is a strong base, and in an aprotic solvent favors the conditions of kinetic control of enolate **A** formation, in which deprotonation is rapid and irreversible. Thus the product distribution using lithium bis(trimethylsilyl)amide reflects the relative rates of formation of enolates **A** and **B**. Potassium hydride gives the same major product as the potassium tertiary alkoxides, which suggests thermodynamic control of enolate formation with rate-limiting cyclization. Most likely the reaction of solid potassium hydride with ester is slow, so that proton transfers from ester to enolate effectively equilibrate enolates **A** and **B**. Potassium as the cation may also favor easier equilibration of enolates than lithium as the cation. Using lithium triphenylmethide, the products were 44 % of **96**

and 3% of **97**, which indicates incomplete equilibration of enolates **A** and **B** during the time required for cyclization. No other bases with lithium as cation were investigated. For future research this could be another field of exploration to determine the selectivity of the bases with specific cations.

Scheme XV. Mechanism of Dieckmann Cyclization



Ethyl esters are used more frequently in the Dieckmann cyclization than any others. Increasing the size and complexity of the alkoxy group appears to lower the yield. With adipic esters the following conversions have been obtained, methyl 81 %, isobutyl 61 %, benzyl 57 %.[1] When diethyl hexadecanedioate (**109**) was used in solution, using modified conditions of Leonard and Schimelpfenig,[34] we obtained the cyclization product. Attempted cyclization of di(triethylcarbinyl) hexadecanedioate (**103**) failed, and diester **103** was recovered. However, dimethyl hexadecanedioate (**108**), which was thought to be an easier case to cyclize than the diethyl analogue **109**, also failed. Prolonged treatment with potassium *t*-butoxide resulted in complete hydrolysis of the dimethyl ester and hexadecanedioic acid (82 %) (**100**) was recovered at the end of the reaction.

Conclusions

Dieckmann cyclizations of benzyl triethylcarbinyl adipate (**91**) to triethylcarbinyl 2-cyclopentanonecarboxylate (**96**) were carried out in 48 % to 75 % isolated yields using alkoxide and hydride bases. Using lithium bis(trimethylsilyl)amide as a base in THF or toluene resulted in unusual regioselectivity of cyclization of mixed diester **91** to give benzyl 2-cyclopentanonecarboxylate (**97**) (81 %) and triethylcarbinyl 2-cyclopentanonecarboxylate (**96**) (6 %).

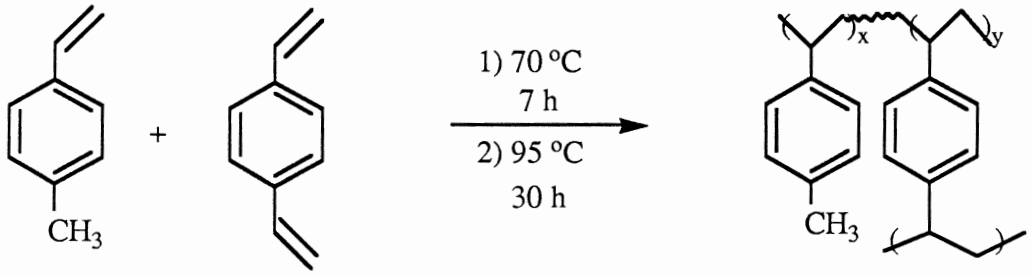
Dieckmann cyclizations of triethylcarbinyl (4-polystyrylmethyl)adipate (**94**) using potassium triethylcarbinolate and potassium *t*-butoxide to form the triethylcarbinyl 2-cyclopentanonecarboxylate (**96**) were effective only at 100 ^{o}C to 150 ^{o}C and gave 64 % to 80 % isolated yields of **96**. The goal of this research was to extend the polymer-bound Dieckmann method to synthesize medium and large rings. Attempts to synthesize a 15-membered ring by Dieckmann cyclization in solution and on polymer-supports gave as the major products the transesterified ester di(triethylcarbinyl) hexadecanedioate (**103**) and the triethylcarbinyl half ester **102b**. Perhaps there were no cyclization reactions because the

two heavy ends of the mixed diester **114** could not attain the conformation required for cyclization. Clearly transesterification of the benzyl ester was faster than cyclization. Ethyl esters are used more frequently in the Dieckmann cyclization than any others. The only successful Dieckmann cyclization to prepare 15-membered ring was of diethyl ester **109** using alkoxide bases. A high dilution procedure gave cyclopentadecanone (**116**) in 39 % yield. The success with diethyl hexadecanedioate (**109**) showed that for the cyclization of long chain compounds we need a diester which does not hydrolyze or transesterify but does enolize and cyclize quickly. To use the polymers as supports for the synthesis of medium and large rings, further modification of the polymer-support will be required and our results suggest that the necessary changes will involve decreasing the tranesterification and hydrolysis of the polymer-bound material or to use better reactions than Dieckmann involving other reagents and materials.

CHAPTER III

CHLORINATION AND BROMINATION OF POLY(*P*-METHYLSTYRENE)

p-Methylstyrene was copolymerized in suspension with 1 % divinylbenzene to copolymer **70** by a method identical with one used for cross-linked polystyrenes (eq. 24).[83]

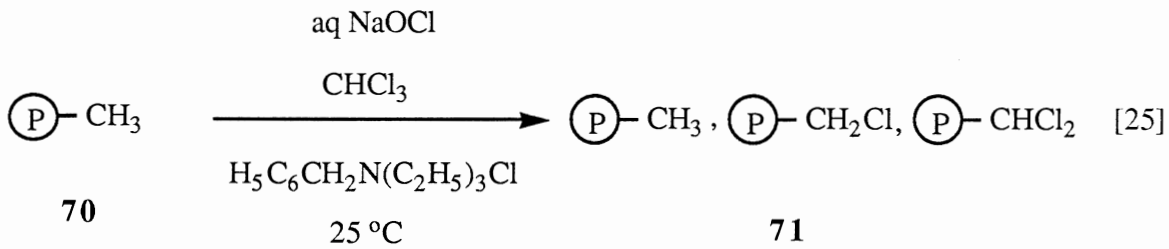


[24]

70 = (P)– CH_3

The polymer **70** was swollen in a minimum amount of chloroform and treated at room temperature with different amounts and concentrations of laundry bleach at pH 8.4 (2.61 %-5.23 % sodium hypochlorite by weight) and of freshly prepared sodium hypochlorite (3.83 % by weight) in the presence of the phase transfer catalyst (PTC)

benzyltriethylammonium chloride (eq. 25). For analysis of the degree of chlorination of **71** the peak areas due to the unreacted methyl carbons at 21.1 ppm, the chloromethyl carbons at 46.1 ppm and the dichloromethyl carbons at 71.7 ppm were compared in 75 MHz ^{13}C NMR spectra. Results are reported in Table XI. The chlorinated poly(*p*-methylstyrene) (**71**) samples used as standards were analyzed by ^{13}C NMR and elemental analyses earlier by Mohanraj.[84]



[25]

71 = P-CH_2Cl

The chlorinated polymers were analyzed quantitatively by IR spectroscopy for -CH_2Cl groups (1265 cm^{-1} peak). The peak at 1110 cm^{-1} was used as standard. As illustrated in Figure 1, the Beer's law plot of percent conversion of methyl to chloromethyl groups versus the absorbance ratio of peaks at 1215 and 1110 cm^{-1} from IR spectra showed a good correlation (r = 1.00). From the slope of the line in Figure 1, a K value of 0.248 was obtained. A modified Beer's law equation used for the plot was

$$DF = K A_s / A_{ref}$$

where A_s = absorbance for -CH_2Cl groups (1265 cm^{-1} peak), A_{ref} = absorbance at 1110 cm^{-1} used as reference, and DF = degree of functionalization. A correlation coefficient of r = 1.00 showed that along with primary methods (^{13}C NMR and elemental analyses), the secondary IR method can also be used for quantitative analysis of

TABLE XI. Reactions of Poly(*p*-Methylstyrene) (**70**)

with NaOCl Solutions at Room Temperature

Expt.	reactant polym[a] **70** mmol	NaOCl mmol	NaOCl Wt. % in water	time min	PTC[b] mol %	pH Initial	pH Final	product DF[c]	product (mmol Cl / g) IR	NMR	elem. anal.
1	416.5	904.0	5.23	120	9.8	8.4	-	0.61[g]	5.7	4.5	5.1
2	8.3	7.5	5.23	30	-	8.4	-	0.25	2.0	-	-
3	16.7	21.6	5.00	63	1.0	8.4	9.1	0.17	1.4	-	-
4	16.7	21.6	5.00	60	1.5	8.4	9.2	0.14	1.2	-	-
5	16.7	21.6	5.00	41	1.0	8.4	9.1	0.14	1.2	-	-
6	8.3	7.5	3.50	100	1.0	8.3	8.7	0.21	1.7	-	-
7	16.7	7.5	3.50	240	0.5	8.4	9.0	0.08	0.7	-	0.64
8	16.7	15.0	3.50	200	1.0	8.4	9.1	0.06	0.5	-	0.46
9	8.3	15.0	2.61	180	2.0	8.4	-	0.64[g]	5.7	4.8	-
10	8.3	7.5	2.61	90	2.0	8.4	-	0.60	4.3	3.8	4.3

Table XI (Continued)

Expt.	reactant polym[a] **70** mmol	NaOCl mmol	NaOCl wt. % in water	time min	PTC[b] mol %	pH initial	pH final	product DF[c]	product (mmol Cl / g) IR	NMR	elem. anal.
11	8.3	7.5	2.61	15	1.0	8.4	8.2	0.13	1.1	-	-
12	8.3	7.5	2.61	210	1.0	8.1	-	0.04	0.4	-	-
13	8.3	5.1	3.83	450	1.0	8.4	8.4	0.24	1.9	-	-
14	8.3	6.2	3.83	450	-	8.4	5.9	0.09	0.7	-	-
15	845	1078	5.00	570	2.0	8.4	-	0.15	1.2	-	-
16[d]	845	359	5.00	96	1.0	8.4	-	0.27	2.0	2.1	2.4
17	787[e]	575	5.00	186	-	8.4	9.1	0.03	0.3	-	-
18[f]	787[e]	539	5.00	240	1.0	8.4	10.3	0.10	0.9	-	-

[a] 1% Cross-linked poly(*p*-methylstyrene) (**70**) (8.3 mmol of repeat units per g), swollen in minimum amount of the chloroform. [b] Phase transfer catalyst (benzyltriethylammonium chloride), mol % based on polymer repeat units. [c] Degree of functionalization, calculated from IR analyses unless reported otherwise. [d] Polymer **15** was subjected to chlorination again to get the required DF (0.27). [e] Linear poly(*p*-methylstyrene) (8.5 mmol of repeat units per g). [f] Polymer **17** was subjected to chlorination again to get the required DF (0.10). [g] $-CHCl_2$ groups determined from NMR analysis (Expt. 1, 7 %, Expt. 9, 15 %).

percent conversion of methyl to chloromethyl groups, at least when $A_s/A_{ref} \leq 1.5$. Data points at $A_s/A_{ref} > 2$ are scattered.

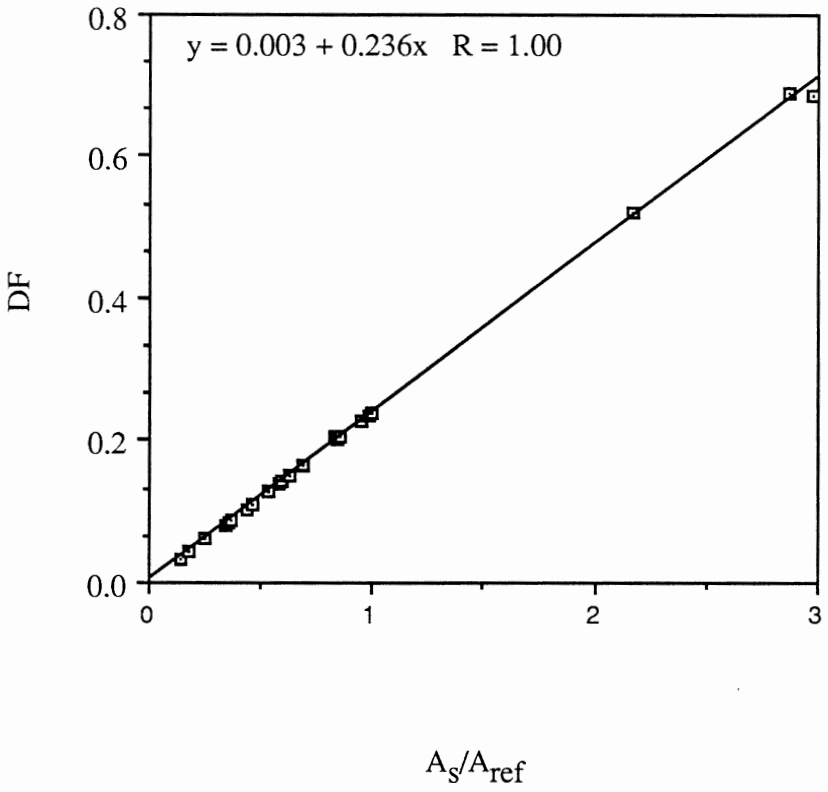


Figure 1. Quantitative IR analysis of chlorinated poly(*p*-methylstyrene) (**71**).

The IR and ^{13}C NMR analyses in Table XI showed that methyl groups of 1 % cross-linked poly(*p*-methylstyrene) (**70**) can be chlorinated with and without a phase transfer catalyst with success. Chloromethyl contents suitable for use of the 1 % cross-linked gel resins for solid-phase peptide synthesis can be achieved with no detectable dichloromethyl groups by reaction with 2.61, 3.50 and 3.83 % sodium hypochlorite (laundry bleach and sodium hypochlorite freshly prepared from sodium hydroxide and chlorine) (experiments

12, 7, 8 and 14) in the presence of a PTC. No chlorination of poly(*p*-methylstyrene) (**70**) was observed with a 2.61 weight percent solution of NaOCl at pH 8.4 when no PTC was used even after 7 h of stirring at room temperature. However, the same reaction with 2 and 1 mole % of PTC in 1.5 and 0.25 h respectively at room temperature resulted in 60 % and 13 % conversion of methyl into chloromethyl groups (experiments 10 and 11). High conversions of 66 % and 75 % of methyl into chloromethyl groups (experiments 1 and 9) with 5.23 and 2.61 weight percent NaOCl solution were accompanied by 7 % and 15 % dichloromethyl groups (from ^{13}C NMR analyses). Using freshly prepared NaOCl, 3.83 % by weight sodium hypochlorite, chlorination of methyl groups of poly(*p*-methylstyrene) (**70**) gave up to 24 % conversion of methyl into chloromethyl groups (experiment 13) in the presence of a phase transfer catalyst. The same reaction, in the absence of phase transfer catalyst (experiment 14) resulted in 4 % conversion. The final four experiments showed that 1 % cross-linked (experiments 15 and 16) as well as linear poly(*p*-methylstyrene) (**70**) (experiments 17 and 18) can be converted to the desired percent of chlorinated poly(*p*-methylstyrene) (**71**), by subjecting again the less chlorinated polymer to chlorination at pH 8.4 with no formation of dichloromethyl groups.

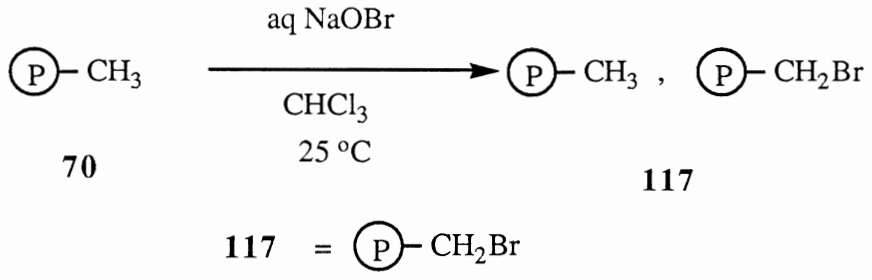
The polymer swollen in chloroform was also treated with freshly prepared aqueous sodium hypobromite [7.8 %-3.11 % by weight, (6.55 M in hypobromite, 1.36 M in bromide and 0.2 M in bromate)[114] eq 26]. Table XII shows conversions of methyl to bromomethyl groups of 1 % cross-linked poly(*p*-methylstyrene) (**70**), using no phase transfer catalyst (experiments 1, 2 and 3). The degree of bromination in the brominated poly(*p*-methylstyrene) (**117**) was also determined from the peak areas due to the unreacted methyl carbons at 21.1 ppm and the bromomethyl carbon at 34.4 ppm in 75 MHz ^{13}C NMR spectra. Results reported in Table XII show that up to 38 % conversion of methyl to bromomethyl groups was obtained in 2 h at room temperature without any dibromomethyl group formation detectable by ^{13}C NMR analysis.

TABLE XII. Reactions of Poly(*p*-methylstyrene) (**70**)

with NaOBr Solutions at Room Temperature

Expt.	polym[a]	NaOBr	NaOBr	time	pH		product	product (mmol Br / g)	
	70 mmol	mmol	% by Wt.	min	initial	final	DF[b]	NMR	elem. anal.
1	8.3	17.0	7.8	4	8.5	4.3	0.15	1.13	0.93 (7.4 %)
2	8.3	8.5	5.2	6	8.5	4.1	0.18	1.34	0.90 (7.2 %)
3	8.3	8.5	3.1	120	8.5	4.1	0.37	2.54	2.50 (19.7 %)
4	8.3	11.2[c]	-	120	-	-	0.18	1.33	1.82 (14.5 %)

[a] 1% Cross-linked poly (*p*-methylstyrene) (**70**) (8.3 mmol of repeat units per g) swollen in chloroform. [b] Degree of functionalization, calculated from NMR analyses ((P)-$\underline{C}H_2Br$, 34.4 ppm). [c] Bromine in CCl_4 and deionized water (12:20 mL).



[26]

Formation of (Polystyrylmethyl)trimethylammonium Chloride (**118**)

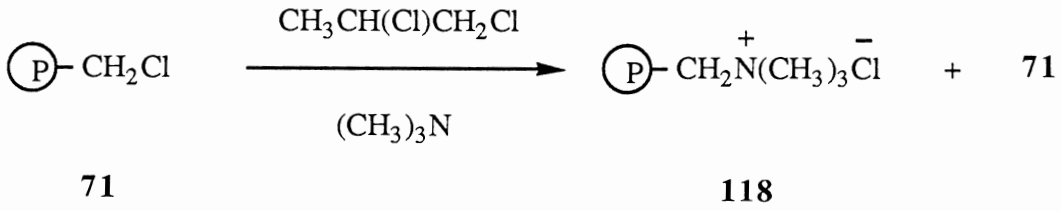
Some of the chlorinated poly(*p*-methylstyrenes) (**71**) were converted to (polystyrylmethyl)trimethylammonium chloride (**118**) anion-exchange resins with trimethylamine at room temperature as shown in Scheme XVI, and conversions up to 56 % of chloromethyl groups to ammonium sites were obtained (Table XIII). However, an attempt at using an aqueous solution of trimethylamine (25 weight % in water) (experiment 1), gave only 10 % conversion. Anion-exchange capacity was determined by the Volhard titration method,[115] which agreed with elemental analyses. Maybe higher than 56 % conversions of chlorinated poly(*p*-methylstyrenes) (**71**) could be obtained at longer reaction times or at higher temperatures under pressure, but no higher conversion reaction was attempted in the present study. The anion-exchange reactions were carried out at room temperature using a dry ice condenser. The constant condensation of trimethylamine cools the reaction mixture. The actual temperature in the reaction flask was not measured, but it was lower than room temperature (25 ^{o}C). This lowering in temperature could be responsible for low conversions. Therefore, higher conversions might be attained by heating the reaction flask, or running the reaction at higher temperature under pressure.

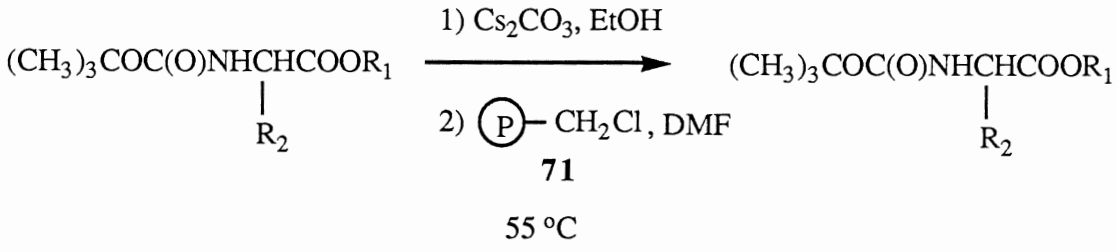
TABLE XIII. Formation of (Polystyrylmethyl)-trimethylammonium Chloride (**118**)

Expt.[a]	polym. **71** mmol	$CH_3CH(Cl)CH_2Cl$ mL	$(CH_3)_3N$ mmol	time h	product DF	% conv.	AEC[b] mmol / g	elem. anal. % N (mmol / g)	% Cl (mmol/g)
1	13.5	15.0	173.2[c]	8.8	0.06	10	0.44	-	-
7	0.7	5.0	107.5	5.0	0.04	45	0.21	0.44 (0.31)	1.8 (0.51)
16	4.0	10.0	215.1	5.0	0.13	47	0.97	1.4 (0.97)	5.3 (1.50)
10	3.0	3.0	107.5	5.0	0.28	48	1.90	2.7 (1.96)	11.5 (3.24)
1	13.6	15.0	204.3	2.0	0.33	56	2.40	3.4 (2.4)	12.9 (3.63)
1	13.5	15.0	441.0	5.5	0.33	56	2.40	3.3 (2.4)	13.2 (3.72)

[a] Product from Table XI. [b] Determined by Volhard titration. [c] 25 weight % in water.

Scheme XVI. Reactions of Chlorinated Poly(*p*-Methylstyrene) (**71**)





119 R_1 = H, R_2 = $CH_2C_6H_5$

120 R_1 = H, R_2 = $CH(CH_3)_2$

121 R_1 = Cs, R_2 = $CH_2C_6H_5$

122 R_1 = Cs, R_2 = $CH(CH_3)_2$

123 R_1 = P-CH_2, R_2 = $CH_2C_6H_5$

124 R_1 = P-CH_2, R_2 = $CH(CH_3)_2$

Formation of Polymer-Bound Boc-Amino Acid Esters (**123** and **124**)

In solid-phase peptide synthesis[51,52] the most widely used starting material is an N-protected amino acid bound via a benzyl ester linkage to an insoluble copolymer of styrene and divinylbenzene. The reaction of chloromethylated polystyrene-*co*-1%-divinylbenzene

resin with the cesium salts of N-protected amino acids proceeds fast and without side reactions to give N-protected amino acyl resin esters free of quaternary ammonium sites or reactive chloride. In the present study reactions of chlorinated poly(*p*-methylstyrenes) (**71**) with cesium salts of Boc-L-phenylalanine (**119**) and Boc-L-valine (**120**) were studied for conversion of the chloromethylated polymer **71** to amino acid esters (**123** and **124**, Scheme XVI) suitable for solid-phase synthesis.[51,52] To check the feasability and coupling of the chloromethylated polymer **71** prepared by the new and cheap method,[84] reactions of cesium salts of protected amino acids, phenylalanine (**119**) and valine (**120**) were explored. Slow coupling reactions were anticipated in solid phase peptide synthesis[105] when the entering Boc-amino acid was sterically hindered. Among naturally occuring amino acids, those with β-branching, such as valine, isoleucine and threonine gave problems.[105] As shown in Table XIV, the cesium salts of Boc-L-phenylalanine **121** and Boc-L-valine **122** gave 65 % to 76 % conversions (Table XIV) of chloromethyl groups to polymer-bound amino acid esters (**123** and **124**). Gisin,[109] using 1.2 mols of the cesium salt of Boc-L-valine (**122**) per mol of chloromethyl groups in the polymer in DMF at room temperature in 20 h in a sealed vessel, converted 94 % of the chloromethyl groups to polymer-bound amino acid esters **124**. When the temperature was raised to 50 ^{o}C, esterification with cesium salt of Boc-L-valine **122** was complete in less than 12 h. Similarly, in 16 h at room temperature in a sealed vessel using 1 equivalent of the cesium salt of Boc-L-phenylalanine (**121**), 85 % conversion of chloromethyl groups to polymer-bound amino acid ester **123** was obtained. The reactions reported in Table XIV were carried out in DMF at 55 ^{o}C under inert atmosphere. Conversions were fair (65-76 %) with unreacted chloromethyl groups left in the polymer (Table XIV). The unreacted chloromethyl groups were analyzed by boiling the resin in pyridine and titrating the resulting chloride ion in excess nitric acid by a modified Volhard method.[115]

TABLE XIV. Attachment of the Cesium Salts of Boc-Amino Acids to Chlorinated Poly(*p*-Methylstyrene) (**71**)[a]

Expt.[b]	polym. **71**, mmol of $-CH_2Cl$	DMF mL	amino acid	Cs salt mmol	time h	product DF	% conv.[c]	amino acid[d] mmol / g	residual $-CH_2Cl$ groups mmol / g[c]
8	0.46	5	Boc-L-Phe	0.5	21.5	0.05	75	0.43	0.12
16	1.05	3	Boc-L-Phe	1.0	23.0	0.22	65	1.83	0.73
7	0.35	5	Boc-L-Val	0.3	39.0	0.07	66	0.63	0.24
16	2.10	8	Boc-L-Val	2.4	26.0	0.23	76	1.85	0.50

[a] All mixtures were heated with a 55 ^{o}C oil bath. [b] Product from Table XI. [c] From residual Cl analyses by Volhard titration. [d] Bound to the polymer; determined from Cl analyses. [e] Analyzed by the modified Volhard method after refluxing the polymer with pyridine.

In the first experiment (Table XIV), using 1 equivalent of cesium salt of Boc-L-phenylalanine **121** resulted in a 75 % conversion of chloromethyl groups to polymer-bound amino acid ester **123**. However, in another reaction on a different polymer (experiment 2), using 0.95 equivalent of cesium salt resulted in a decreased conversion (65 %). This suggests that by using an excess (as used by Gisin[109]) of the cesium salt of Boc-amino acid, quantitative conversion of the chloromethyl groups to the polymer-bound amino acid esters could be obtained. The same results were obtained with the cesium salt of Boc-L-valine **122** (Table XIV).

Discussion

The chlorination and bromination reactions with NaOCl and NaOBr were not protected from the light. Hamilton and co-workers,[85] reported that light appears to speed up the analogous chlorination of toluene. As noted in this research and earlier,[85] the chlorination reaction only proceeded rapidly when the pH of the aqueous hypochlorite solution was between 8 and 9. Under these conditions significant amounts of HOCl are present to allow chlorine monoxide (Cl_2O) formation, as shown in Scheme XVII.[112,113] Hamilton and co-workers,[85] studied a range of pH values and found that the optimum pH was 7.5-9.0 for the formation of benzyl chloride from toluene. At lower pH the amount of nuclear chlorination increases, and at higher pH the reaction slows down.

Commercial bleach (0.55 M in hypochlorite, 1.2 M in chloride, 0.01 M in chlorite, and 0.3 M in chlorate) has been used for the chlorination of methyl to chloromethyl groups of poly(*p*-methylstyrene) (**70**). The freshly prepared sodium hypochlorite (experiments 13 and 14, Table XI), also showed chlorination with and without PTC. As reported in Table XI an increase in pH was observed at the end of the chlorination reactions. This is probably due to the formation of sodium hydroxide (Scheme XVII).

Mechanism of Chlorination of Poly(*p*-Methylstyrene) (**70**)

Hamilton and co-workers[85,86] proposed that the chlorination of hydrocarbons using NaOCl proceeds by a free radical mechanism with the chloroxy radical ($ClO^{\cdot}$) as an important chain carrying species, as shown in Scheme XVII. The $ClO^{\cdot}$ radical abstracts a hydrogen from the methyl group of the poly(*p*-methylstyrene) (**70**) and Cl_2O donates a chlorine atom to the benzylic radical in the propagation steps proposed by Hamilton and co-workers.[85]

Scheme XVII. Mechanism of Chlorination

Generation of Cl_2O

$$HCl + NaOCl \longrightarrow HOCl + NaCl$$

$$HOCl + ClO^- \longrightarrow Cl_2O + \overline{O}H$$

Generation of $ClO^{\cdot}$

$$Cl_2O \longrightarrow Cl^{\cdot} + ClO^{\cdot}$$

$$Cl^{\cdot} + ClO^- \longrightarrow Cl^- + ClO^{\cdot}$$

Propagation

$$\text{(P)}\text{-}CH_3 + ClO^{\cdot} \longrightarrow \text{(P)}\text{-}CH_2^{\cdot} + HOCl$$

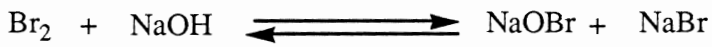
$$\text{(P)}\text{-}CH_2^{\cdot} + Cl_2O \longrightarrow \text{(P)}\text{-}CH_2Cl + ClO^{\cdot}$$

All bromination reactions were carried out without a phase transfer catalyst, and in light. The bromination reaction in the dark with and without PTC was not studied. The decrease in pH at the end of the reaction indicates that the bromination mechanism is different from the chlorination mechanism. It may proceed by the mechanism of Scheme

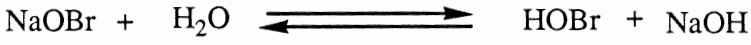
XVIII via abstraction of a benzylic hydrogen atom with a bromine atom instead of bromoxy radical (BrO˙). The formation of HBr could be responsible for decrease in pH. The bromine atom may be produced by the photolytic cleavage of bromine. On acidification of the NaOBr solution at -15 ^{o}C, it is not clear which species in the hypobromite solution is producing bromine. A reddish color appears in the solution upon acidification of the cold solution of NaOBr, which is a clear indication of Br_2 formation. The bromination of methyl to bromomethyl groups of 1 % cross-linked poly(*p*-methylstyrene) (**70**) has been carried out at room temperature. It is known in the literature that decomposition of sodium hypobromite, with formation of sodium bromide and sodium bromate, begins immediately at 0 ^{o}C and is complete within two days.[114]

Scheme XVIII. Mechanism of Bromination

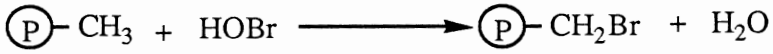
Formation of NaOBr



Formation of HOBr

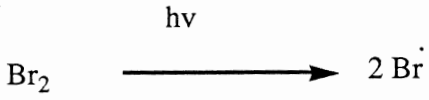


Bromination by HOBr



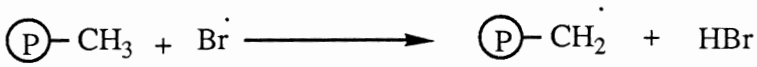
Bromination by $Br^{\cdot}$

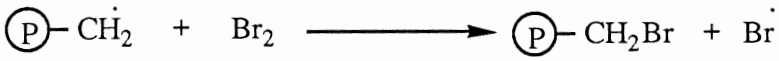
Initiation



Propagation

1)





For comparison, a conventional reagent for free radical bromination, bromine in carbon tetrachloride, was tried also (experiment 4, Table XII). The ^{13}C NMR analysis of the brominated poly(*p*-methylstyrene) (**117**) showed DF = 0.18. The bromomethyl polymers **117** were subjected to elemental analysis. The product from bromination reactions with NaOBr (experiments 1, and 2), showed less bromine by ^{13}C NMR than by elemental analysis. However, in the case of bromination with bromine in carbon tetrachloride (experiment 4), more bromine was detected by elemental analysis than by ^{13}C NMR analysis. This could be due to incorporation of bromine into the polymer at locations not detected by NMR spectral analysis. Because of acid-catalysed electrophilic aromatic substitution, it seems likely that aromatic hydrogens in the polymer **117** have been substituted. The aromatic bromination might be detectable by ^{13}C NMR, because the brominated carbon signals at 123-124 ppm would not be hidden by the protonated aromatic carbon signals at 124-126 ppm, but no such signals were observed. Analysis of brominated poly(*p*-methylstyrene) (**117**) was not possible by IR, because the bromomethyl peak at 1200 cm^{-1} was overlapped by the poly(*p*-methylstyrene) (**70**) peaks. The results reported in the Table XII, clearly show that for selective bromination of the methyl groups of the poly(*p*-methylstyrene) (**70**), sodium hypobromite treatment is the method of choice.

For syntheses of most average size peptides 0.2 to 0.4 mmol/g is a satisfactory amino acid substitution. Short peptides (5-10 amino acids) may be synthesized on resin with a higher degree of amino-acid substitution (0.4 mmol/g). The attachment of the first amino acid has been carried out on two kinds of polymers, one with the desirable range of chloromethyl groups (polymers 7 and 8), and the other with higher chloromethyl content (2.4 mmol Cl/g) (experiment 16, Table XVI). The polymer with high amino-acid substitution cannot be used for solid phase synthesis, because it is generally believed that such a polymer cannot swell enough to accomodate a polypeptide of more than ten residues. However, the polymers **7** and **8** are suitable for the solid phase synthesis and show satisfactory conversions. The chlorinated poly(*p*-methylstyrenes) (**71**) used to

demonstrate the attachment of the first Boc-amino acid clearly show an advantage over the chloromethylated resins presently being used in the SPPS, by involving a cheap and safe, phase transfer catalysed chlorination of poly(*p*-methylstyrene) (**70**). The low substitution required for the solid phase synthesis can easily be achieved selectively (Table XI). The resins currently in use are prepared by the Lewis acid catalyzed chloromethylation, which is usually performed with the carcinogenic chloromethyl methyl ether and its unavoidable contaminant, the far more potent carcinogen bis(chloromethyl) ether.[80]

The residual chloromethyl groups can be converted to the polymer-bound amino acid by using excess cesium salt of the Boc-amino acid, or reactions can be run for longer times and can be repeated in order to effect complete substitution. The residual chloromethyl groups could cause problems in the later coupling reactions, because when an amino group is deprotected for the next coupling step, the free amine could react with the residual chloromethyl groups to cause the termination of the growing peptide and an increase in the cross-linking of the polymer. Also, new peptide chains can start from secondary amine groups, resulting in peptide purification problems.

Conclusions

Chloromethylated polystyrenes **71** are key intermediates in the preparation of anion-exchange resins, supports for solid-phase peptide synthesis, and supports for polymeric reagents and catalysts. Chlorination of poly(*p*-methylstyrene) (**70**) with commercial or laundry bleach provides a much safer alternative to the current method of chloromethylation to prepare functional derivatives of polystyrene. The chlorination and bromination of the methyl groups of poly(*p*-methylstyrene) (**70**) to chlorinated poly(*p*-methylstyrene) (**71**) and brominated poly(*p*-methylstyrene) (**117**) was achieved with sodium hypochlorite (laundry bleach or freshly prepared) and sodium hypobromite (freshly prepared) in the presence as well as in the absence of the phase transfer catalyst benzyltriethylammonium

chloride. Another method involves the copolymerization of vinylbenzyl chloride with styrene.[83] This method is expensive, and the vinylbenzyl chloride commercially available is a 70/30 *meta/para* mixture. Using sodium hypochlorite the *para* isomer has been prepared selectively, and low conversions suitable for solid phase peptide synthesis (SPPS) have been obtained with no detectable dichloromethyl groups (Table XI).

A comparison of bromination with sodium hypobromite and with bromine in carbon tetrachloride showed that to convert selectively methyl groups of poly(*p*-methylstyrene) (**70**) to bromomethyl groups, sodium hypobromite is the reagent of choice. Bromine in carbon tetrachloride introduces bromine at unidentified places in the polymer.

The chloromethyl polymer was converted to a trimethylammonium chloride anion-exchange resin and to amino-acid esters suitable for SPPS. The Boc-amino acid resins can be further used to explore their utility for the preparation of small and long size peptides. They may avoid some of the problems associated with the chlorinated polymers prepared by existing methods.

CHAPTER IV

DIECKMANN CYCLIZATION EXPERIMENTAL

Reagents and Solvents

Tetrahydrofuran (THF) was dried and distilled from sodium / benzophenone. Toluene, xylenes and benzene were dried and distilled from sodium and stored over 4Å molecular sieves under argon. N,N-dimethylformamide (DMF) was treated at room temperature with KOH and after filtering was distilled from 4 Å molecular sieves. Dimethylsulfoxide (DMSO) was distilled from 4Å molecular sieves under reduced pressure. *o*-Dichlorobenzene was distilled under vacuum and was stored under argon. Thionyl chloride was purified by refluxing with quinoline for three hours and then fractionated to remove the acid impurities.[117] The distillate was refractionated as before from boiled linseed oil. The collected thionyl chloride was transparent and colorless, and it was kept under argon. Sodium ethoxide was prepared by dissolving a weighed amount of freshly cut sodium metal in a measured volume of ethanol in an argon atmosphere. Potassium *t*-butoxide (from Aldrich Chemical Co.) was reagent grade. The potassium salt of 3-ethyl-3-pentanol was prepared by dissolving freshly cut potassium metal in 3-ethyl-3-pentanol using toluene as a solvent. The potassium triethylcarbinolate contents were determined from titration with 5 N HCl using bromthymol blue as an indicator. Lithium bis(trimethylsilyl)amide was freshly prepared from hexamethyldisilazane and *n*-BuLi in hexane at room temperature. Similarly lithium diphenylamide was prepared by adding *n*-BuLi in hexane at room temperature to diphenylamine.*n*-Butyl lithium was standardized

using the diphenylacetic acid method.[118] Diethyl ether (Fischer Scientific Co. and E. Merck Co.) and absolute ethanol (USP, US Industrial Chemical Co.) were used as receieved. Styrene (Aldrich Chemical Co.), *p*-methylstyrene (Mobil Chemical Co. PMSA25 monomer) and 55-60 % active divinylbenzene (Polysciences) were distilled under argon at reduced pressure. After working up all the reactions, the organic layer was dried over anhydrous $MgSO_4$ and solvent was evaporated on a rotary evaporator. For flash chromatography the petroleum ether had b.p 37.7 ^{o}C-56.9 ^{o}C (Fischer Chemical Co.). All other chemicals were reagent grade and were used without further purification unless noted otherwise. Reaction temperatures of -10 ^{o}C to -20 ^{o}C were achieved by use of an ice / salt bath, while -78 ^{o}C was achieved using acetone / dry ice mixture. Silica gel was from J.T. Baker Chemical Co. (average particle size 40 μm), from EM Science (Grade 62, -60+200 mesh) or from Aldrich Chemical Co. (Grade 923, -100+200 mesh). For the flash chromatography the reaction mixture was always absorbed on the silica gel and added to a pre-packed silica gel column. For preparative thin layer chromatography (TLC), precoated silica gel (GF) TLC plates, 2000 μm thick (Analtech) were used. For thin layer chromatography (TLC) scored glass plates were used (10 x 20 cm, 250 μm, Analtech).

Sodium Hydride and Potassium Hydride Washing

The NaH (80 wt % in mineral oil) was weighed in a dry glove bag under nitrogen. The KH (35 wt % in mineral oil) was weighed in mineral oil. Both were taken in a three neck flask having a fritted disk at the bottom, equipped with mechanical stirrer at the top, and a constant supply of argon. The KH was washed under argon three times (3 x 20 mL) with petroleum ether and with THF while being stirred mechanically. Sodium hydride was washed with hexane (3 x 20 mL) and with THF.

Analyses and Spectra

Melting points were determined on a Mel-temp apparatus and are uncorrected. Mass spectral analyses were done on a high resolution double focusing mass spectrometer CEC model 21-110B with Data General DS-50S data system at 70 eV. ^{1}H NMR and ^{13}C NMR spectra at 300 and 75.4 MHz were obtained in $DCCl_3$, DMSO-d_6 and D_3COD on a Varian model XL-300 instrument with tetramethylsilane [$(CH_3)_4Si$] as an internal standard. ^{13}C NMR spectra at 25.2 MHz were obtained on a Varian model XL-100 instrument. IR spectra were recorded on a Perkin Elmer model 681 instrument with wafers prepared from 4 mg of polymer and 190 mg of anhydrous potassium bromide. The sample was ground in a Wig-L-Bug (Crescent Dental Mfg. Co.) for 3 min and pressed into translucent wafers. Elemental analyses were carried out by Desert Analytics (Tucson, Arizona), by Galbraith Laboratories (Knoxville, TN), and by Huffman Laboratories Inc. (Wheat Ridge, Colorado).

General Experimental Conditions to All Polymer Samples

All polymer samples were washed and dried in a vacuum oven before use. All reactions and washings of air sensitive polymers were conducted under argon using a three neck, round bottom flask with a fritted disk at the bottom and equipped with overhead stirrer, serum stopper, an argon inlet, and a reflux condenser (whenever needed). Polymer samples were allowed to swell in the solvent without stirring before starting a reaction. The teflon blade of the stirrer was positioned high enough to avoid friction between the beads and walls of the flask, so polymer samples were recovered with little or no breakage of beads. For heating the polymer reaction mixtures an IR lamp was used, while for solution reactions a heating mantle was used. All polymer filtration and washing was performed in medium and coarse porosity fritted funnels from Kimble Glass Co.

General Procedure for the Suspension Polymerization of Styrene Containing DVB as Cross-Linker.[83]

10 % Cross-Linked Polystyrene-25 % Vinylbenzyl Chloride (VBC) (**81**)

The general procedure was followed with 93.7 g styrene, 30.0 g divinylbenzene, 41.3 g vinylbenzyl chloride, and 0.825 g of 2,2'-azobis-(2-methylpropionitrile) (AIBN). The weight of the polymer recovered was 119.2 g (72 %) with the following particle size distribution : 8.7 % on 40, 10.8 % on 60, 14.8 % on 100, 45.1 % on 200 and 20.6 % on 325 mesh sieves. Calcd for Cl, 5.8 %, (DF, 0.19, based on monomer used).

Preparation of 10 % Cross-Linked Polystyrene-10 % VBC (**81**)

The general procedure was followed with 118.6 g styrene, 30.0 g DVB, 16.5 g VBC, and 0.825 g AIBN. The weight of the polymer recovered was 138.1 g (84 %) with the following particle size distribution : 8.9 % on 60, 54.0 % on 100, 20.1 % on 140, 9.8 % on 200, 5.9 % on 325, and 1.3 % on 400 mesh sieves. Calcd for Cl, 2.34 %, (DF, 0.07, based on monomer used).

Preparation of 6 % Cross-Linked Polystyrene-10 % VBC (**81**)

The general procedure was followed with 130.6 g styrene, 18.0 g DVB, 16.5 g VBC, and 0.825 g AIBN. The weight of the polymer recovered was 119.3 g (72 %) with the following particle size distribution : 6.6 % on 40, 16.5 % on 100, 34.3 % on 140, 21.5 % on 200, 16.7 % on 325, and 4.4 % on 400 mesh sieves. Calcd for Cl, 2.34 %, (DF, 0.07, based on monomer used).

Preparation of 1 % Cross-Linked Poly(*p*-Methylstyrene) (**70**)

The general procedure was followed with 162.8 g *p*-methylstyrene, 2.88 g DVB and 0.89 g AIBN. The weight of the polymer recovered was 136.7 g (82 %) with the following particle size distribution: 21.8 % on 60, 48.4 % on 100, 21.7 % on 200, and 8.1 % on 400 mesh sieves. Calcd for $-CH_3$ groups (DF, 0.985, based on monomer used).

Preparation of Methyl 5-(Chloroformyl)-Pentanoate (**85**)

To 25.0 g (156.1 mmol) of adipic acid monomethyl ester (**84**), 37.1 g (312.2 mmol) of $SOCl_2$ was added at room temperature, and the mixture was stirred for 24 h at room temperature. The SO_2 and HCl evolved were trapped in a beaker containing water. The excess of $SOCl_2$ was removed at aspirator pressure at room temperature. Distillation of the methyl 5-(chloroformyl)pentanoate (**85**) at 0.1 mmHg and 61 ^{o}C gave 29.24 g (97 %). IR (neat) 1815 (s, acid chloride C=O stretch), 1750 (s, ester C=O stretch), 1255 [br, CC(=O)-O stretch], 1210 (br), 1183 cm^{-1} (m, O-C-C stretch); ^{1}H NMR ($DCCl_3$) δ 1.72 (m, 4 H), 2.36 (t, 2 H), 2.98 (t, 2 H), 3.68 (s, 3 H); ^{13}C NMR (75.5 MHz, $DCCl_3$) δ 23.2 and 24.1 [$C(O)CH_2\underline{C}H_2$], 32.8 [$COO\underline{C}H_2$], 46.2 [$\underline{C}H_2C(O)Cl$], 51.0 ($O\underline{C}H_3$), 172.6 and 172.7 ($\underline{C}$=O of ester and acid chloride).

Methyl Triethylcarbinyl Adipate (**87**)

To a solution of 25.0 mL (310.0 mmol) of pyridine (dried and stored over 4 Å molecular sieves) in 130 mL of tetrahydrofuron (THF), 43.6 mL (310.0 mmol) of 3-ethyl-3-pentanol (triethylcarbinol) (**86**) was added at room temperature under argon. The mixture was heated to reflux and 55.3 g (310.0 mmol) of methyl 5-(chloroformyl)-pentanoate (**85**) was added. The mixture turned to violet color for a while and then to

orange with the precipitation of pyridine hydrogen chloride. It was refluxed for 1 h while being stirred vigorously under argon. After cooling to room temperature the precipitate was filtered using a fritted funnel and washed with ether. The filtrate was washed with water (3 x 100 mL), and was extracted with a saturated solution of sodium bicarbonate to remove any unreacted acid chloride **85**. The organic layer was extracted with ether from water and treated with 2 N HCl. The ether layer was washed with water until the washings were neutral and extracted with ether from water. The TLC of the ether layer (developed in 10 % EtOAc in petroleum ether) showed two spots, of the desired product **87** and of unreacted acid chloride **85**. After drying over $MgSO_4$ the ether was evaporated on a rotary evaporator to give an orange oil, whose IR spectrum confirmed the presence of unreacted acid chloride **85**. The orange oil was treated with 2 N NaOH and then was acidified with 2 N HCl. The product was extracted with ether from water and the ether layer was washed with water until the washings were neutral. After drying, evapotation (rotary evaporator) of the ether gave 54.0 g (68 %) of slightly yellow oil. TLC showed a minor impurity and IR showed a weak -OH band. To remove the impurity, it was fractionally distilled under vacuum to yield 40.0 g (50 %) of colorless methyl triethylcarbinyl adipate (**87**), whose purity was confirmed by TLC (developed in 10 % EtOAc in petroleum ether). IR (neat) 1750 and 1740 (s, ester C=O), 1265 (br), 1205 (br), 1140 (s) cm^{-1}. There was no 1815 cm^{-1} peak. ^1H NMR ($DCCl_3$) δ 0.82 (t, 9 H), 1.66 (m, 4 H), 1.83 (q, 6 H), 2.28 (t, 2 H), 3.67 (s, 3 H); ^{13}C NMR (75.5 MHz, $DCCl_3$) δ 7.7 [$OC(CH_2\underline{C}H_3)_3$], 24.5 and 24.6 [$C(O)CH_2\underline{C}H_2$], 26.8 [$OC(\underline{C}H_2CH_3)_3$], 33.7 and 35.0 [$C(O)\underline{C}H_2$], 51.4 ($O\underline{C}H_3$), 88.0 [$O\underline{C}(CH_2CH_3)_3$], 172.7 [$\underline{C}$=O of esters].

Selective Hydrolysis of Methyl Triethylcarbinyl Adipate (**87**)

A solution of 4.0 g (15.5 mmol) of mixed diester **87** in 20.0 mL of 2.5 M KOH in methanol (51.0 mmol) was refluxed for 6.5 h. After cooling to 0 ^oC, it was acidified to

pH 3 with 2 N HCl using a pH meter. The adipic acid monotriethylcarbinyl ester (**88**) was extracted with ether from water. The TLC of the ether layer (developed in 10 % EtOAc in petroleum ether) showed one spot. After drying the ether was evaporated to give 3.4 g (90 %) of the monoacid monoester **88** as a light yellow oil. IR (neat) 3300-2500 (br, O-H of the carboxylic acid), 1730 (ester C=O), 1715 (acid C=O), 1250 (br), 1135 (s) cm^{-1}; ^{1}H NMR ($DCCl_3$) δ 0.82 (t, 9 H), 1.68 (t, 4 H), 1.83 (q, 6 H), 2.29 (t, 2 H), 2.37 (t, 2 H); ^{13}C NMR (75.5 MHz, $DCCl_3$) δ 7.3, 24.3, 26.5, 34.7, 88.0, 172.3, 178.0 [COOH].

Benzyl Triethylcarbinyl Adipate (**91**)

To 3.42 g (14.0 mmol) of adipic acid monotriethylcarbinyl ester (**88**), 20.0 mL of DMF and 0.97 g (7.0 mmol) of powdered potassium carbonate were added. The reaction mixture was heated in a 150 °C oil bath, and the temperature inside the flask was 146 °C. The reaction mixture was stirred mechanically at 146 °C for 0.5 h. After cooling to 70 °C, 1.6 mL (14.0 mmol) of benzyl chloride (**90**) (distilled) was added and reaction mixture was heated in a 100 °C oil bath for 1 h. After cooling to room temperature water was added and the product was extracted with ether. After drying the ether was evaporated to give 3.89 g of yellow oil. The IR spectrum was characteristic of the mixed diester **91**, but TLC (developed in 10 % EtOAc in petroleum ether) showed two spots. The crude reaction mixture was absorbed onto 2.0 g of silica gel from diethyl ether. Ether was evaporated and the silica gel was added to the column packed with 40.0 g of silica gel (923, -100+200 mesh from Aldrich Chemical Co.). Sequential elution was effected with 4 %, 5 %, 6 %, 7 % and 8 % ethyl acetate in petroleum ether. The eluents were monitored with thin layer chromatography (TLC) using 10 % ethyl acetate in petroleum ether to develop the plates. Benzyl triethylcarbinyl adipate (**91**) was eluted with 6 % ethyl acetate in petroleum ether to yield 2.7 g (58 %) of colorless liquid. IR (neat) 3440 (C=O overtone), 3080 (w), 3060

(w), 3030 (w), 2960 (s), 2935 (s), 2875 (m), 1730 (s, ester C=O), 1265 (br), 1210 (br), 1175 (br), 745 (br), 695 (s) cm^{-1}; ^1H NMR ($DCCl_3$) δ 0.8 (t, 9 H), 1.64 (m, 4 H), 1.82 (q, 6 H), 2.24 (t, 2 H), 2.36 (t, 2 H), 5.12 (s, 2 H), 7.34 (s, 5 H); ^{13}C NMR (75.5 MHz, $DCCl_3$) δ 7.3, 24.1, 24.3, 26.4, 33.6, 34.6, 65.7 ($O\underline{C}H_2$), 87.6, 127.8, 128.2, 135.8, 171.9 [$\underline{C}OOCH_2$], 172.7. Dibenzyl adipate (**92**) eluted with 8 % ethyl acetate in petroleum ether to yield 0.73 g (16 %) light yellow oil. IR (neat) 3110 (w), 3080 (w), 3050 (m), 2960 (s), 2890 (w), 1750 (s), 1740 (s), 1265 (br), 1210 (br), 1175 (br), 705 (s) cm^{-1}; ^1H NMR ($DCCl_3$) δ 1.58 (m, 4 H), 2.24 (m, 4 H), 5.04 (s, 4 H), 7.3 (m, 10 H); ^{13}C NMR (75.5 MHz, $DCCl_3$) δ 23.7, 33.0, 65.3, 127.5, 127.9, 135.6, 172.1. Adipic acid (**93**) eluted with 20 % ethyl acetate in petroleum ether to yield 0.0433 g (2 %).

Triethylcarbinyl (4-Polystyrylmethyl) Adipate (**94**)

To 0.464 g (3.36 mmol) of powdered potassium carbonate and 1.64 g (6.7 mmol) of adipic acid monotriethylcarbinyl ester (**88**), 60 mL of DMF was added and the mixture was heated in an oil bath to 150 °C for 0.5 h until the potassium carbonate dissolved completely. After cooling to room temperature, partly chloromethylated polystyrene (**81**) (DF, 0.07, 4.0 g, 6.6 mmol of Cl) was added, and mixture was heated in a 150 °C oil bath with mechanical stirring under argon for 1 h. The polymer was filtered, washed with acetone (2 x), water-acetone (1 x), methanol (2 x), and diethyl ether (1 x) and dried under vacuum at 60 °C for 2 h to give 5.0 g (93 %, based on weight gained) of polymer-bound ester **94**. IR (KBr) 1740 (s), 1730 (s), 1200 (br) cm^{-1}. The 1265 cm^{-1} peak for $-CH_2Cl$ was missing. Calcd. for $[(C_{10}H_{12})_{0.07}\cdot(C_{10}H_{10})_{0.09}\cdot(C_8H_8)_{0.77}\cdot(C_9H_9Cl)_{0.02}\cdot(C_{22}H_{32}O_4)_{0.05}]$ (DF, 0.05, determined from weight of adipic acid monotriethylcarbinyl ester (**88**) recovered after hydrolysis).

Selective Hydrolysis of Triethylcarbinyl (4-Polystyrylmethyl) Adipate (**94**)

To 1.0 g of polymer-bound ester **94**, 10.0 mL of THF:H_2O (9:1), and 35.0 mg (0.11 mmol) of tetrabutylammonium bromide were added. To this mixture 3 mL (9.12 mmol) of 3 M KOH in methanol was added, and the mixture was refluxed for 24 h. The polymer was filtered, washed with acetone (2 x), water-acetone (1 x), acetone (2 x), and hexane (1 x), and the filtrate was acidified to pH 2 with 1 N HCl using a pH meter. The filtrate was concentrated on a rotary evaporator, and product was extracted with ether from water. After drying, ether was evaporated to give 160.5 mg of adipic acid monotriethylcarbinyl ester (**88**) (ester 0.42 mmol / g of the polymer) (DF, 0.05). TLC, IR, ^{1}H NMR and ^{13}C NMR data confirmed the structure of **88**. The IR spectrum of the polymer showed complete hydrolysis by absence of ester carbonyl peaks.

Cyclization of the Polymer-Bound Ester **94**

A. With Potassium Triethylcarbinolate in DMF

To polymer-bound ester **94** (DF, 0.05, 2.0 g, 0.84 mmol), 4.0 mL DMF was added in a three neck flask, equipped with overhead mechanical stirrer and condenser under argon. The flask was heated in a 130 ^{o}C oil bath, and 1.0 mL (2.5 mmol) of potassium triethylcarbinolate in toluene was added to the swollen polymer. The reaction mixture turned red at once and then gradually turned yellow with stirring for 15 min. After cooling to 0 ^{o}C in an ice bath, the polymer was filtered and washed with water (3 x), petroleum ether (3 x), diethyl ether (2 x), water (2 x), 1 N HCl (2 x), water (3 x) and diethyl ether (2 x). The filtrate was acidified to pH 7 with 1 N HCl using a pH meter and was extracted with petroleum ether and then by diethyl ether from water. The extracts were combined, dried and evaporated to yield 0.189 g (92 %) of light pink oil. TLC (developed in 10 %

EtOAc in petroleum ether) showed a minor impurity at the origin. IR (KBr) spectrum of the residual polymer showed no ester functionalities. The crude reaction mixture was purified by flash chromatography (40 μm silica gel from J. T. Baker Chemical Co.). Sequential elution was effected with 0 %, 1 %, 2 % and 3 % ethyl acetate in petroleum ether. Triethylcarbinyl 2-cyclopentanonecarboxylate (**96**) was eluted with 3 % EtOAc in petroleum ether to give 0.158 g (77 %) light yellow oil. IR (neat) 3680-3140 (br, O-H due to an enolate), 2970 (s), 2885 (s), 1760 (s, C=O of cyclopentanone), 1725 (s, C=O of ester), 1660 (w, C=C of enolate), 1460 (s), 1255 (s), 1195 (s), 1135 (s) cm^{-1}; ^1H NMR ($DCCl_3$) δ 0.81 (t, 9 H), 1.84 (m, 7 H), 2.12 (m, 1 H), 2.28 (m, 4 H), 3.08 (t, 1 H); ^{13}C NMR (75.5 MHz, $DCCl_3$) δ 7.3 [$OC(CH_2\underline{C}H_3)_3$], 20.7 [$\underline{C}H_2CH_2C(O)CH$], 26.4 [$OC(\underline{C}H_2CH_3)_3$], 27.7 [$C(O)CH\underline{C}H_2$], 38.0 ($\underline{C}H_2C{=}O$), 55.7 ($\underline{C}HC{=}O$), 89.7 [$O\underline{C}(CH_2CH_3)_3$], 168.3 [$\underline{C}OOC$], 212.8 [$CH_2\underline{C}(O)CH$]. Mass spectral data for $C_{13}H_{22}O_3$, no M^+ found, m/e at 55 ($C_3H_3O^+$ base peak), 87 ($C_6H_{15}^+$), 98 ($C_7H_{14}^+$), 110 ($C_6H_5O_2^+$). Anal. Calcd for $C_{13}H_{22}O_3$: C, 68.98; H, 9.80. Found C, 69.49; H, 10.47.

B. With Potassium *t*-Butoxide in DMF

To polymer-bound ester **94** (DF, 0.05, 2.0 g, 0.84 mmol), 4.0 mL DMF was added, and mixture was heated in 150 °C oil bath for 5 min under argon, while being stirred mechanically. To this swollen polymer 0.22 g (2.0 mmol) of potassium *t*-butoxide (Aldrich) was added after cooling to room temperature. The reaction mixture was heated in 150 °C oil bath for 15 min under argon, while being stirred mechanically. It was cooled to 0 °C in an ice bath. The polymer was filtered and washed with water (3 x), diethyl ether (3 x), 1 N HCl (2 x), water (3 x) and dithyl ether (2 x) and acetone (1 x). The filtrate was acidified to pH 7 with 1 N HCl using a pH meter and was concentrated on a rotary evaporator, and the product was extracted with petroleum ether from water to yield 0.167 g

(80 %) of triethylcarbinyl 2-cyclopentanonecarboxylate (**96**). TLC (developed in 10 % EtOAc in petroleum ether) showed one spot. IR, ^{1}H NMR and ^{13}C NMR data confirmed the structure of **96**.

C. With Lithium Bis(trimethylsilyl)amide in THF

To polymer-bound ester **94** (DF, 0.09, 2.0 g, 1.44 mmol), 6.7 mL of THF was added. To this swollen polymer 2.9 mL (2.9 mmol) of lithium bis(trimethylsilyl)amide (1.0 M solution in THF) was added at room temperature. Analysis of an aliquot taken after stirring for 2 h at room temperature showed no product by TLC and only starting polymer by IR. The reaction mixture was heated in a 75 ^{o}C oil bath for 4 h and a second aliquot was taken. TLC showed presence of the cyclized product **96**. The reaction mixture was stirred for another 12 h at 75 ^{o}C. After cooling to room temperature, the polymer was filtered and washed with acetone (2 x), water (2 x), acetone (2 x), methanol (2 x) and hexane (1 x). The filtrate was acidified to pH 6 with 2 N HCl using a pH meter, and concentrated on rotary evaporator. The product was extracted with hexane from water. After drying the hexane was evaporated to give 0.014 g (13 %) of triethylcarbinyl 2-cyclopentanonecarboxylate (**96**), confirmed by its TLC (developed in 10 % ethyl acetate in petroleum ether) and IR spectrum.

Dieckmann Cyclization of Methyl Triethylcarbinyl Adipate (**87**)
with Potassium Triethylcarbinolate in Toluene

To 1.0 g (3.88 mmol) of methyl triethylcarbinyl adipate (**87**), 1.41 mL (7.75 mmol) of potassium triethylcarbinolate in toluene was added at room temperature, and the reaction mixture was stirred for 16 h. The reaction mixture was neutralized with 1 N HCl to pH 3 using a pH meter at 0 ^{o}C, and the product was extracted with ether from water. After

drying the ether was evaporated to give 3.02 g of yellow oil, whose TLC (developed in 10 % EtOAc in petroleum ether) showed the presence of impurities along with the desired cyclized product **96**. The crude reaction mixture absorbed on 2.0 g of silica gel was added to a column packed with 40.0 g of silica gel (40 μm from J. T. Baker Chemical Co.). Sequential elution was effected with 0 % and 1 % ethyl acetate in petroleum ether. The eluents were monitored with thin layer chromatography (TLC) using 5 % EtOAc in petroleum ether to develop the plates. Triethylcarbinyl 2-cyclopentanonecarboxylate (**96**) was eluted with 1 % ethyl acetate in petroleum ether to yield 0.422 g (48 %). IR, ^{1}H NMR and ^{13}C NMR data confirmed the structure of **96**.

Dieckmann Cyclization of Benzyl Triethylcarbinyl Adipate (**91**) with

A. Potassium Triethylcarbinolate in DMF

To 0.51 g (1.5 mmol) of mixed diester **91** were added 9.0 mL of DMF and 1.2 mL (3.0 mmol) of potassium triethylcarbinolate in toluene, and the reaction mixture was stirred at room temperature for 6 h. Water was added, and the reaction mixture was acidified to pH 3 with 2 N HCl using a pH meter. The product was extracted with ether from water and was concentrated on a rotary evaporator. The concentrate was extracted again with petroluem ether from water. After drying petroleum ether was evaporated. Concentration in vacuo gave 0.26 g (75 %) of triethylcarbinyl 2-cyclopentanonecarboxylate (**96**). TLC (developed in 10 % ethyl acetate in petroleum ether) showed one spot. IR, ^{1}H NMR and ^{13}C NMR data confirmed the structure of **96**.

B. Potassium *t*-Butoxide in DMF

To 0.25 g (0.77 mmol) of the mixed diester **91** were added 6.5 mL of DMF and 0.17 g (1.55 mmol) of potassium *t*-butoxide at room temperature under argon. After 15 min the reaction mixture was poured into a beaker containg ice and was acidified to pH 7 with 2 N HCl using a pH meter. The product was extracted with petroleum ether from water. After drying petroleum ether was evaporated to give 0.129 g of yellow oil. TLC (developed in 10 % EtOAc in petroleum ether) showed three spots at R_f 0.8, 0.54 and 0.2. The yellow oil absorbed on 2.0 g of silica gel was purified by flash chromatography. Dibenzyl ether (**98**) 0.033 g (19 %) eluted with 3 % ethyl acetate in petroleum ether. IR (neat) 3100 (w), 3075 (w) and 3040 (w, aromatic C-H stretch), 2930 (br) and 2865 (br, CH_2 C-H stretch), 1500 (m) and 1460 (s, C=C ring stretch), 1255 (br, asymmetric C-O-C stretch), 1030 (m, symmetric C-O-C stretch), 740 (br, out of plane C-H bending), 695 (s, out of plane ring C-H bending) cm^{-1}; ^1H NMR ($DCCl_3$) δ 4.56 (s, 4 H), 7.38 (m, 10 H); ^{13}C NMR (75.5 MHz, $DCCl_3$) δ 72.1 (O-$\underline{C}H_2$), 127.6, 127.7, 128.4, 138.2. Triethylcarbinyl 2-cyclopentanonecarboxylate (**96**) 0.1225 g (70 %) eluted with 4 % ethyl acetate in petroleum ether. IR, ^1H NMR and ^{13}C NMR data confirmed the structure of **96**. After eluting Dieckmann product **96**, elution with diethyl ether gave 0.015 g of yellow oil containing adipic acid monotriethylcarbinyl ester **88**, confirmed by its TLC (developed in 10 % EtOAc in petroleum ether) and IR spectrum.

C. Lithium Bis(trimethylsilyl)amide in THF

To 0.31 g (0.94 mmol) of the mixed diester **91** were added 6.3 mL of THF and 1.9 mL (1.9 mmol) of lithium bis(trimethylsilyl)amide (1.0 M solution in THF). The reaction mixture was stirred at room temperature for 1 h under argon. Water was added, and the reaction mixture was acidified to pH 7 with 2 N HCl using a pH meter. The product was

extracted with petroleum ether from water, dried and evaporated to yield 0.154 g of yellow oil. TLC (developed in 10 % EtOAc in petroleum ether) of the yellow oil showed four spots. The yellow oil absorbed on 2.0 g of silica gel was flash chromatographed. Triethylcarbinyl 2-cyclopentanonecarboxylate (**96**) 0.009 g (6 %) eluted with 4 % ethyl acetate in petroleum ether. IR, ^{1}H NMR and ^{13}C NMR data confirmed the structure of (**96**). A second fraction containing benzyl 2-cyclopentanonecarboxylate (**97**) also eluted with 4 % ethyl acetate in petroleum ether to give 0.169 g (81 %) light yellow oil. IR (neat) 3640 (w) and 3460 (w, carbonyl overtones), 3095 (w), 3065 (w), 3035 (w), 2970 (br), 2890 (w), 1765 (s), 1735 (s), 1660 (w, enolate C=C), 1615 (w), 1260 (s), 1185 (s), 1005 (s), 750 (br), 700 (s) cm^{-1}; ^{1}H NMR ($DCCl_3$) δ 1.84 (m, 1 H), 2.10 (m, 1 H), 2.30 (m, 4 H), 3.2 (t, 1 H), 5.2 (s, 2 H), 7.38 (m, 5 H); ^{13}C NMR (75.5 MHz, $DCCl_3$) δ 20.9 [$\underline{C}H_2CH_2C(O)CH$], 27.4 [$C(O)CH\underline{C}H_2$], 38.0 ($\underline{C}H_2C=O$), 54.7 ($\underline{C}HC=O$), 67.0 ($O\underline{C}H_2$), 128.0, 128.2, 128.5, 135.6, 169.2 [$\underline{C}OOC$], 212.8 [$CH_2\underline{C}(O)CH$]. Mass spectral data for $C_{13}H_{14}O_3$: no M^+ found, m/e at 55 ($C_3H_3O^+$ base peak), 65 ($C_2H_5^+$), 77 ($C_6H_5^+$), 79 ($C_6H_7^+$), 91 ($C_7H_7^+$), 107 ($C_7H_7O^+$), 108 ($C_7H_8O^+$). Anal for $C_{13}H_{14}O_3$: C, 71.53; H, 6.47. Found C, 71.5; H, 6.73.

D. Sodium Hydride in DMF

To 0.08 g (3.3 mmol) of NaH (pre-washed) and 10.0 mL of THF, 0.55 g (1.64 mmol) of benzyl triethylcarbinyl adipate (**91**) was added at room temperature while being stirred mechanically. From an aliquot taken after 50 min, TLC showed no Dieckmann product, but along with starting material some low R_f value compound was present. Almost the same result was obtained when a second aliquot was taken after 4 h. The reaction mixture was stirred at room temperature overnight, and was acidified with dilute HCl. The product was extracted with ether from water, dried and evaporated to yield 0.46 g of yellow oil. TLC (developed in 10 % EtOAc in petroleum ether) of the yellow oil

showed two spots. The yellow oil was purified by flash chromatography. Triethylcarbinyl 2-cyclopentanonecarboxylate (**96**) 0.138 g (37 %) eluted with 5 % ethyl acetate in petroleum ether. IR, ^{1}H NMR and ^{13}C NMR data confirmed the structure of **96**.

E. Potassium Triphenylmethide in THF

To 0.76 g (18.9 mmol) of KH (pre-washed), 30.0 mL of THF was added and stirred mechanically to disperse KH homogeneously in THF. To this 5.13 g (21.0 mmol) of triphenylmethane was added at room temperature. The mixture was stirred mechanically at room temperature for 1 h under argon. During this time the mixture turned to peach red color with the complete consumption of KH. To this 2.01 g (6.02 mmol) of benzyl triethylcarbinyl adipate (**91**) dissolved in 12.0 mL of THF was added at room temperature through a syringe. The reaction mixture was stirred at room temperature for 30 min under argon, and was poured into a beaker containing ice. It was acidified to pH 7 with 2 N HCl using a pH meter. The product was extracted with ether from water, dried and evaporated to yield 7.134 g of crude product. TLC (developed in 10 % EtOAc in petroleum ether) of the ether solution showed three spots. The yellow oil absorbed on 2.0 g of silica gel was purified by flash chromatography. Triphenylmethane (5.0 g) eluted with 1 % ethyl acetate in petroluem ether. The second fraction containing dibenzyl ether eluted with 2 % ethyl acetate in petroluem ether to yield 0.20 g (17 %), characterized by TLC, IR, and ^{1}H NMR spectra. Triethylcarbinyl 2-cyclopentanonecarboxylate (**96**) also eluted with 2 % ethyl acetate in petroleum ether to give 0.60 g (44 %). IR, ^{1}H NMR and ^{13}C NMR data confirmed the structure of **96**. The fourth fraction containing benzyl 2-cyclopentanonecarboxylate (**97**) eluted with 4 % ethyl acetate in petroleum ether to yield 0.041 g (3 %), confirmed by TLC, IR and ^{1}H NMR spectra. The fifth fraction eluted with 5 % ethyl acetate in petroleum ether to yield 0.356 g (55 %) of benzyl alcohol (**99**) confirmed by TLC, IR and ^{1}H NMR spectra. The final fraction containing adipic acid

monotriethylcarbinyl ester (**88**) eluted with 6 % ethyl acetate in petroleum ether to yield 0.082 g (6 %), confirmed by TLC, IR and ^{1}H NMR spectra.

Hexadecanedioic Acid (**100**)

To 150.0 mL of ethanol (anhyd. USP grade), 9.5 g (413 mmol) of freshly cut sodium was added. The mixture was stirred under argon until all the sodium dissolved. To the cold solution of sodium ethoxide, 65.0 mL (428.0 mmol) of diethyl malonate was added. A solution of 50.0 g (152.4 mmol) of 1,12-dibromododecane (**104**) in 120.0 mL of anhydrous ethanol was added to the above solution at room temperature. The reaction mixture was refluxed for 24 h while being stirred under argon. It was cooled to room temperature, and product was extracted with ether from water, dried and evaporated to yield 56.0 g (76 %) of diethyl 2,15-dicarboethoxyhexadecanedioate (**106**), a thick yellow oil. IR (neat) 2990 (m), 2935 (s) and 2865 (s, C-H stretch), 1760 (s), 1740 (s), 1470 (m) and 1370 (s, C-H bending), 1250-1155 [br, C-C(=O)-O stretch], 1035 (s, O-C-C stretch), 855 (m, $-CH_2$ rocking) cm^{-1}; ^{1}H NMR ($DCCl_3$) δ 1.30 (t, 32 H), 1.9 (m, 4 H), 3.34 (t, 2 H), 4.23 (q, 8 H); ^{13}C NMR (25.2 MHz, $DCCl_3$) δ 13.8 ($-\underline{C}H_3$), 27.0, 28.5, 29.0, 29.2, 51.7 (-$\underline{C}$H), 60.8 ($-O-\underline{C}H_2$), 169.0 ($\underline{C}$=O). To tetraethyl ester **106** in 500 mL of ethanol was added 56.0 g (1.0 mol) of KOH in 100 mL of water. The mixture was refluxed for 15 min, cooled to room temperature and acidified to pH 2 with 15 % HCl using a pH meter. The tetracarboxylic acid **107** was extracted with ether from water, dried and evaporated. The residue (light yellow shiny solid) was heated in an oil bath of 190 ^{o}C, until gas stopped bubbling out to give 39.71 g (91 %, recrystallized from benzene) of the hexadecanedioic acid (**100**), mp 121-122 ^{o}C (lit[111] 124-124.2 ^{o}C). IR (neat) 3700-2250 (br, O-H of carboxylic acid), 2935 (s), 2860 (s), 1710 (s), 1470 (s), 1435 (s), 1418 [s, C(=O)-O-H], 1305 (s) and 1260 [s, C(=O)-O], 940 (br, O-H out of plane bending), 725 (m) and 690 (m, $-CH_2$ rocking) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.24 (s, 20 H), 1.6

(t, 4 H), 2.3 (t, 4 H); ^{13}C NMR (75.5 MHz, $DCCl_3$+ D_3COD) δ 24.0 ($\underline{C}H_2CH_2COOH$), 28.2, 28.3, 28.5, 28.6,33.0 ($\underline{C}H_2COOH$), 175.8 ($\underline{C}OOH$); GLC Retention time (min) 8.7 (100 % by peak area).

Diethyl Hexadecanedioate (**109**)

To 5.0 g (17.7 mmol) of hexadecanedioic acid (**100**) were added 150.0 mL of ethanol and ten drops of concd H_2SO_4. The reaction mixture was refluxed overnight. Ethanol was removed completely on a rotary evaporator, and the residue was extracted with ether from water. After drying the ether was evaporated to give 5.79 g (95 %) of crude diethyl ester **109**. TLC (developed in 5 % EtOAc in petroleum ether) of the ether solution showed three spots with R_f values 0.88, 0.58 and 0.33. The crude product absorbed on 2.0 g of silica gel was purified by flash chromatography (silica gel, Grade 62, -60+200 mesh, from EM Science). Diethyl hexadecanedioate (**109**) eluted with 3 % ethyl acetate in petroluem ether to give 5.19 g (86 %) white crystalline solid, mp 37-38 °C (lit[111] 39 °C). IR (neat) 3460 (overtone), 2980 (m), 2930 (br), 2860 (s), 1740 (s), 1465 (m), 1370 (m), 1245 (br), 1180 (br), 1035 (br) cm^{-1}; ^1H NMR ($DCCl_3$) δ 0.92 (s, 26 H), 1.2 (m, 4 H), 1.7 (t, 4 H), 3.1 (q, 4 H); ^{13}C NMR (75.5 MHz, $DCCl_3$) δ 14.3 (-$\underline{C}H_3$), 25.0 ($\underline{C}H_2CH_2COO$), 29.1, 29.6, 34.4 ($\underline{C}H_2COO$), 60.1 (-O-$\underline{C}H_2$), 173.9 ($\underline{C}OO$).

Hexadecanedioic Acid Monoethyl Ester (**111**)

A solution of 0.532 g (1.55 mmol) of diethyl hexadecanedioate (**109**) and 5.0 mL (11.1 mmol) of 2.2 M KOH in methanol was refluxed for 10 min under argon. It was cooled to room temperature and was acidified with 1 N HCl. The product was extracted with ether from water. After drying the ether was evaporated to give 0.43 g of crude product. TLC (developed in 10 % EtOAc in petroleum ether) of the ether solution showed

three spots. The crude product was purified by flash chromatography. Hexadecanedioic acid monoethyl ester (**111**) eluted with 10 % ethyl acetate in petroluem ether to give 0.201 g (41 %) of white solid. IR (neat) 3700-2600 (br), 2980 (w), 2920 (br), 2850 (m), 1735 (br), 1710 (br), 1465 (br), 1370 (m), 1250 (br), 1180 (br), 1030 (br) cm^{-1}; ^1H NMR ($DCCl_3$) δ 1.27 (s, 23 H), 1.6 (m, 4 H), 2.05 (t, 2 H), 2.3 (t, 2 H), 4.13 (q, 2 H); ^{13}C NMR (75.5 MHz, $DCCl_3$) δ 14.3, 25.0, 25.8, 28.7, 29.2, 29.3, 29.5, 29.6, 32.8, 34.4, 62.9, 170.0, 173.9.

Dimethyl Hexadecanedioate (**108**)

To a solution of 20.45 g (71.5 mmol) of hexadecanedioic acid (**100**) in 200 mL of methanol, 0.43 g (4.4 mmol) of concd H_2SO_4 was added at room temperature. The mixture was refluxed for 2 h, cooled to room temperature and treated with a saturated solution of sodium carbonate. The product was extracted with ether from water. After drying the ether was evaporated to yield 21.28 g (95 %, recrystallized from methanol) of dimethyl hexadecanedioate (**108**): mp 47-48 °C (lit[111] 50 °C): IR (neat) 3470 (overtone), 2930 (br), 2860 (s), 1740 (br), 1465 (s), 1440 (s), 1250 (br), 1200 (br) and 1170 (br) cm^{-1}. (Methyl esters of long chain fatty acids present a three band pattern for the O-C-C band. The band near 1170 cm^{-1} is the strongest).[119] ^1H NMR ($DCCl_3$) δ 1.27 (s, 20 H), 1.64 (t, 4 H), 2.33 (t, 4 H), 3.70 (s, 6 H); ^{13}C NMR (75.5 MHz, $DCCl_3$) δ 25.0 ($\underline{C}H_2CH_2COO$), 29.2, 29.3, 29.4, 29.6, 34.1 ($\underline{C}H_2COO$), 51.4 (-O-$\underline{C}H_3$), 174.3 ($\underline{C}OO$); GLC Retention time (min), 8.18 (100 % by peak area).

Hexadecanedioic Acid Monomethyl Ester (**110**)

A solution of 20.0 g (63.7 mmol) of dimethyl hexadecanedioate (**108**) in 450.0 mL of methanol and 3.6 g (64.4 mmol) of 10 % KOH in methanol was refluxed for 4 h.

Methanol was removed on a rotary evaporator, 300.0 mL of water was added to the residue, and the mixture was acidified with concd HCl. The product was extracted with ether from water, dried and evaporated. TLC of the concentrate (developed in 20 % EtOAc in petroleum ether) showed three spots with R_f values 0.92, 0.50 and 0.08. The concentrate absorbed on 3.0 g of silica gel was flashed chromatographed. Dimethyl hexadecanedioate (**108**) eluted with 8 % ethyl acetate in petroleum ether to yield 13.14 g (66 %) white crystalline solid, confirmed by TLC. Hexadecanedioic acid monomethyl ester (**110**) eluted with 15 % ethyl acetate in petroleum ether to give 5.63 g (86 %, on the basis of recovered dimethyl ester **108**) of white crystalline solid, mp 66-68 ^{o}C (lit[111] 65-67 ^{o}C). IR (neat) 3400-2480 (br, O-H of carboxylic acid), 2930 (s), 2860 (s), 1745 (s, ester C=O), 1710 (br, acid C=O), 1475 (m), 1440 (m), 1415 (m, C-OH in plane bending), 1305 (br, C-O stretch), 1215 [br, C(=O)-O-C], 940 (br, O-H out of plane bending) cm^{-1}; ^{1}H NMR ($DCCl_3$) δ 1.3 (s, 20 H), 1.5 (m, 4 H), 2.3 (t, 2 H), 3.62 (s, 3 H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 24.4 ($\underline{C}H_2CH_2COO$), 29.0, 33.2 ($\underline{C}H_2COOCH_3$), 33.9 ($\underline{C}H_2COOH$), 51.4 (-O-$\underline{C}H_3$), 173.1 ($\underline{C}OOH$), 174.3 ($\underline{C}OOCH_3$).

Methyl 15-(Chloroformyl)-Pentadecanedioate (**125**)

To 1.0 g (3.3 mmol) of hexadecanedioic acid monomethyl ester (**110**), 5.0 mL (68.1 mmol) of $SOCl_2$ was added, and the mixture stirred at room temperature for 24 h. The SO_2 and HCl evolved were trapped in a beaker containing water. The excess $SOCl_2$ was removed at aspirator pressure at room temperature. Concentration in vacuo gave 0.97 g (91 %) of methyl 15-(chloroformyl) pentadecanedioate (**125**), mp 41-42 ^{o}C. IR (neat) 3590 and 3470 (carbonyl overtones), 2935 (br), 2860 (s), 1810 [br, C(O)Cl], 1750 (br, ester C=O), 1470 (m), 1440 (m), 1250 (br), 1200 (br), 1170 (br), 950 (w) cm^{-1}; ^{1}H NMR ($DCCl_3$) δ 1.26 (s, 20 H), 1.62 (t, 2 H), 1.68 (t, 2 H), 2.28 (t, 2 H), 2.86 (t, 2 H), 3.66 (s, 3 H); ^{13}C NMR (75.5 MHz, $DCCl_3$) δ 25.0 ($\underline{C}H_2CH_2COOC$), 25.1

($\underline{C}H_2CH_2COCl$), 28.4 ($\underline{C}H_2CH_2CH_2COCl$), 29.1, 29.2, 29.3, 29.4, 29.5, 29.6, 29.8, 34.1 ($\underline{C}H_2COOCH_3$), 47.1 ($\underline{C}H_2COCl$), 51.4 (-O-$\underline{C}H_3$), 173.7 ($\underline{C}OCl$), 174.3 ($\underline{C}OOCH_3$).

Methyl Triethylcarbinyl Hexadecanedioate (**112**)

To 0.55 g (1.74 mmol) of methyl 15-(chloroformyl)-pentadecanedioate (**125**) dissolved in 15.0 mL of toluene, 0.46 mL (2.1 mmol) of potassium triethylcarbinolate in toluene was added at room temperature. The reaction mixture was refluxed for 7 h under argon, and progress of the reaction was monitored by TLC (developed in 40 % EtOAc in petroleum ether). It was cooled to room temperature and was acidified to pH 4 with 1 N HCl using a pH meter. The product was extracted with ether from water. After drying the ether was evaporated to yield 0.594 g of yellow oil. TLC of the yellow oil (developed in 40 % EtOAc in petroleum ether) showed two spots. The yellow oil absorbed on 2.0 g of silica gel was flash chromatographed. Methyl triethylcarbinyl hexadecanedioate (**112**) eluted with 5 % ethyl acetate in petroleum ether to yield 0.23 g (33 %) of yellow oil. IR (neat) 3460 (carbonyl overtone), 2980 (s), 2940 (br), 2865 (s), 1750 (s), 1740 (s), 1460 (m), 1440 (m), 1360 (br), 1255 (br), 1200 (br), 1140 (s), 920 (br), 735 (s) cm^{-1}; ^1H NMR ($DCCl_3$) δ 0.8 (t, 9 H), 1.24 (s, 20 H), 1.58 (m, 4 H), 1.82 (q, 6 H), 2.2 (t, 2 H), 2.3 (t, 2 H), 3.66 (s, 3 H); ^{13}C NMR (75.5 MHz, $DCCl_3$) δ 7.7 [$OC(CH_2\underline{C}H_3)_3$], 25.0 and 25.3 ($\underline{C}H_2CH_2COO$), 26.8 [$OC(\underline{C}H_2CH_3)_3$], 29.2, 29.3, 29.4, 29.5, 29.6, 29.8, 34.1 ($\underline{C}H_2COOCH_3$), 35.5 ($\underline{C}H_2COOC$), 51.4 (-O-$\underline{C}H_3$), 87.8 [$O\underline{C}(CH_2CH_3)_3$], 173.0 ($\underline{C}OOC$), 174.3 ($\underline{C}OOCH_3$).

Hexadecanedioyl Chloride (**101**)

To 20.0 g (70.0 mmol) of hexadecanedioic acid (**100**), 55.0 mL (754.0 mmol) of $SOCl_2$ was added, and the reaction mixture was refluxed overnight. The SO_2 and HCl evolved were trapped in a beaker containing water. The excess of $SOCl_2$ was removed at aspirator pressure at room temperature. Concentration in vacuo gave 22.0 g (97 %) of hexadecanedioyl chloride (**101**) yellow oil. IR (neat) 3590 (carbonyl overtone), 2935 (br), 2860 (s), 1810 (s), 1470 (br), 1405 (m), 1120 (br), 955 (br), 725 (br), 680 (s) cm^{-1}; ^1H NMR ($DCCl_3$) δ 1.24 (s, 20 H), 1.7 (t, 4 H), 2.9 (t, 4 H); ^{13}C NMR (75.5 MHz, $DCCl_3$) δ 25.1 ($\underline{C}H_2CH_2COCl$), 28.4, 28.5, 28.9, 29.1, 29.2, 29.3, 29.5, 29.6, 47.1 ($\underline{C}H_2COCl$), 173.7 [$\underline{C}(O)Cl$].

Hexadecanedioic Acid Monotriethylcarbinyl Ester (**102b**)

To a solution of 22.0 g (68.1 mmol) of hexadecanedioyl chloride (**101**) in 280.0 mL of toluene was added 13.9 g (90.0 mmol) of potassium triethylcarbinolate in toluene, and the reaction mixture was refluxed for 17 h under argon. About 250.0 mL of toluene was distilled off, and the residue was boiled with 50.0 mL of saturated solution of sodium carbonate for 15 min. After cooling to room temperature it was acidified to pH 3 with 4 N HCl using a pH meter. The product was extracted with ether from water. After drying the ether was evaporated to yield 25.9 g of the crude product. TLC of the crude product (developed in 40 % EtOAc in petroleum ether) showed three spots. The crude product absorbed on 2.0 g of silica gel was flash chromatographed. Di(triethylcarbinyl)-hexadecanedioate (**103**) eluted with 3 % ethyl acetate in petroluem ether to yield 5.12 g (16 %) of light yellow oil. IR (neat) 3420 (carbonyl overtone), 2970 (s), 2930 (s), 2885 (s), 1730 (s), 1460 (br), 1250 (br), 1185 (br), 1135 (br), 920 (br), 870 (br) cm^{-1}; ^1H NMR ($DCCl_3$) δ 0.8 (t, 18 H), 1.26 (s, 20 H), 1.58 (t, 4 H), 1.82 (q, 12 H), 2.24

(t, 4 H); ^{13}C NMR (75.5 MHz, $DCCl_3$) δ 7.7 [OC($CH_2\underline{C}H_3$)$_3$], 25.3 ($\underline{C}H_2CH_2COO$), 26.8 [OC($\underline{C}H_2CH_3$)$_3$], 29.3, 29.4, 29.5, 29.6, 35.5 ($\underline{C}H_2COOC$), 87.8 [O$\underline{C}$(CH_2CH_3)$_3$], 173.0 ($\underline{C}OOC$). Hexadecanedioic acid monotriethylcarbinyl ester (**102b**) eluted with 12 % ethyl acetate in petroluem ether to yield 8.26 g [38 % on the basis of recovered hexadecanedioic acid (**100**)]. IR (neat) 3500-2440 (br, O-H of carboxylic acid), 2970 (s), 2930 (br), 2855 (s), 1730 (s, ester C=O), 1715 (s, acid C=O), 1465 (br), 1240 (br), 1190 (br), 1135 (br), 925 (br), 870 (br), 720 (br) cm^{-1}; ^{1}H NMR ($DCCl_3$) δ 0.82 (t, 9 H), 1.27 (s, 20 H), 1.6 (m, 4 H), 1.82 (q, 6 H), 2.24 (t, 2 H), 2.36 (t, 2 H); ^{13}C NMR (75.5 MHz, $DCCl_3$) δ 7.7 [OC($CH_2\underline{C}H_3$)$_3$], 24.7 ($\underline{C}H_2CH_2COOC$), 25.3 ($\underline{C}H_2CH_2COOH$), 26.8 [OC($\underline{C}H_2CH_3$)$_3$], 29.1,29.3, 29.4, 29.5, 29.6, 34.1 ($\underline{C}H_2COOH$), 35.5 ($\underline{C}H_2COOC$), 87.9 [O$\underline{C}$(CH_2CH_3)$_3$], 173.1 ($\underline{C}OOH$), 180.0 ($\underline{C}OOC$).

Benzyl Triethylcarbinyl Hexadecanedioate (**114**)

To 0.83 g (2.2 mmol) of hexadecanedioic acid monotriethylcarbinyl ester (**102b**), 15.0 mL of DMF and 0.15 g (1.1 mmol) of powdered potassium carbonate were added. The reaction mixture was heated in a 150 ^{o}C oil bath, while being stirred mechanically with an overhead stirrer for 15 min. To this was added 0.27 g (2.2 mmol) of benzyl chloride (**90**) (distilled), and the reaction mixture was heated in a 150 ^{o}C oil bath for 20 min. Water was added after cooling to room temperature and the product was extracted with petroleum ether from water. After drying the petroleum ether was evaporated on a rotary evaporator. Concentration in vacuo gave 0.97 g (94 %) of benzyl triethylcarbinyl hexadecanedioate (**114**) as a light yellow oil. TLC (developed in 10 % EtOAc in petroleum ether) showed one spot. IR (neat) 3560 and 3420 (carbonyl overtones), 3090 (w), 3070 (w) and 3035 (w, aromatic C-H stretch), 2970 (m), 2930 (br), 2860 (s), 1745 (s), 1735 (s), 1500 (w), 1460 (br), 1255 (br), 1170 (br), 1135 (br), 745 (br), 695 (m) cm^{-1}; ^{1}H NMR ($DCCl_3$) δ 0.82 (t, 9 H), 1.24 (s, 20 H), 1.6 (m, 4 H), 1.82 (q, 6 H), 2.23

(t, 2 H), 2.32 (t, 2 H), 5.13 (s, 2 H), 7.37 (s, 5 H); ^{13}C NMR (75.5 MHz, $DCCl_3$) δ 7.7, 25.0, 25.3, 26.8, 29.1, 29.3, 29.4, 29.5, 29.6, 29.8, 34.3, 35.5, 66.0 ($O\underline{C}H_2$), 87.7, 128.1, 128.5, 136.2, 172.9, 173.6.

Triethylcarbinyl (4-Polystyrylmethyl) Hexadecanedioate (**115**)

To 0.86 g (6.25 mmol) of powdered potassium carbonate and 4.8 g (12.5 mmol) of hexadecanedioic acid monotriethylcarbinyl ester (**102b**), 22.0 mL of DMF was added, and the mixture was stirred mechanically under argon. It was heated in a 150 °C oil bath for 15 min, until potassium carbonate dissolved completely. Chloromethyl polystyrene (**81**) (DF, 0.07, 25.0 g, 16.5 mmol of Cl) was added, and the mixture was heated in a 160 °C oil bath, while being stirred mechanically under argon for 17 h. The polymer was filtered, washed with petroleum ether (2 x), acetone (2 x), water (2 x), acetone (2 x), dichloromethane (1 x), acetone (2 x), and diethyl ether (1 x) and dried under vacuum at 65 °C for 12 h to give 28.1 g (48 % conversion of -CH_2Cl to polymer-bound ester from hydrolysis of the polymer-bound ester **115**). IR (KBr) 3110 (w), 3090 (w), 3065 (m), 3035 (s), 2970 (w), 2930 (br), 2860 (s), 1735 (s), 1602 (s), 1270 (w, residual -CH_2Cl group), 1185 (w), 1155 (w), 1030 (br) cm^{-1}; ^{13}C NMR (75.5 MHz, $DCCl_3$) δ 7.3 [$OC(CH_2\underline{C}H_3)_3$], 24.4 and 24.8 ($\underline{C}H_2CH_2COOC$), 26.4 [$OC(\underline{C}H_2CH_3)_3$], 28.8, 29.0, 29.3, 29.7, 35.6 ($\underline{C}H_2COO$), 40.4, 65.8 ($O\underline{C}H_2$), 87.8 [$O\underline{C}(CH_2CH_3)_3$], 173.2 ($\underline{C}OO$).

Selective Hydrolysis of Triethylcarbinyl (4-Polystyryl-methyl) Hexadecanedioate (**115**)

To 1.0 g of polymer-bound ester **115**, 10.0 mL of THF:H_2O (9:1), and 50.0 mg (0.15 mmol) of tetra-*n*-butylammonium bromide were added. To this mixture 1.5 mL (5.25 mmol) of 3.5 M KOH in methanol was added, and the mixture was refluxed for 24

h. The polymer was filtered, washed with acetone (2 x), water (2 x), acetone (2 x), dichloromethane (1 x), acetone (2 x), diethyl ether (1 x) and dried under vacuum at 64 ^{o}C for 8 h to give 0.885 g. The filtrate was acidified to pH 2 with 1 N HCl using a pH meter. The filtrate was concentrated on a rotary evaporator and product was extracted with ether from water. After drying the ether was evaporated to give 0.139 g of crude product. TLC (developed in 40 % ethyl acetate in petroleum ether) showed three spots. The crude product was refluxed with methanol and concd. HCl for 2 h. The product was extracted with ether from water. After drying the ether was evaporated to give 0.098 g of dimethyl hexadecanedioate (**108**). TLC (developed in 40 % ethyl acetate in petroleum ether), IR and ^{1}H NMR data confirmed the structure of **108**. Calcd for $[(C_{10}H_{12})_{0.07}\cdot(C_{10}H_{10})_{0.09}\cdot(C_{8}H_{8})_{0.77}\cdot(C_{9}H_{9}Cl)_{0.04}\cdot(C_{32}H_{52}O_{4})_{0.03}]$: ester functionality 0.31 mmol / g of the polymer (DF, 0.03). IR (KBr): the 1735 cm^{-1} peak due to ester carbonyl was absent.

Dieckmann Cyclization Reactions in Solution

Dieckmann Cyclization of Diethyl Hexadecanedioate (**109**) Using Potassium *t*-Butoxide as a Base

The procedure was a modification of that described by Leonard and Schimelpfenig.[34] To 40.0 mL of xylene (dried and distilled over sodium), 20.0 mL of *t*-butyl alcohol and 3.43 g (30.6 mmol) of potassium *t*-butoxide were added. The mixture was heated to reflux and stirred mechanically under argon. To this refluxing solution, 2.0 g (6.4 mmol) of diethyl hexadecanedioate (**109**) dissolved in 5.0 mL of xylene was added using a syringe pump over a period of 30 h. During this period of addition an argon atmosphere was maintained and stirring and refluxing were continued. The reaction mixture was refluxed for an additional 1 h, cooled to room temperature and acidified with excess glacial acetic

acid. The product was extracted with diethyl ether from water. All the extracts were combined and washed with water (3 x 100 mL). After drying the solution was concentrated to a small volume by distillation at reduced pressure. To the residue was added 5.0 mL of ethanol and 10.0 mL of 3 N HCl; hydrolysis and decarboxylation were effected by refluxing overnight. The mixture was cooled to room temperature and extracted with ether from water. After drying the ether was evaporated to give 1.7 g (a yellow residue). TLC (developed in 30 % ethyl acetate in petroleum ether) showed five spots with Rf 0.85, 0.76, 0.54, 0.27 and 0.14. The yellow residue absorbed on 2.0 g of silica gel was flash chromatographed. A fraction eluted with 5 % ethyl acetate in petroleum ether (R_f 0.89 on TLC, developed in 20 % ethyl acetate in petroleum ether) to yield 0.907 g of a yellow oil, which solidified upon sitting.

GLC Conditions

Gas chromatographic analyses were performed on a Hewlett-Packard model 5840A instrument equipped with a thermal conductivity detector and a 6 ft x 0.125 in. o.d. nickel column of 5 % SE-30 on 80/100 mesh Chromosorb Q. Instrumental conditions were attenuation 2^6, injector temperature 300 ^oC, TCD temperature 350 ^oC, and He flow rate 40 mL min^{-1}. The program was 100 ^oC for 1 min, increase of 25 ^oC min^{-1} to 250 ^oC, and 250 ^oC for 20 min. Quantitative GLC analyses were carried out in duplicate. The relative response factor of cyclopentadecanone (Aldrich Chemical Co.) was determined relative to cycloheptanone as an internal standard ($C_7H_{12}O$, 1.00; $C_{15}H_{28}O$, 0.74). Yield was calculated from the relative response factors and peak areas. Quantitative GLC analysis of yellow oil using cycloheptanone as an internal standard revealed cycloheptanone 82.66 % (peak area %), 4.23 % (peak area % of an unknown), and 13.10 % (peak area %) cyclopentadecanone (**116**). Retention times (min) were cycloheptanone 2.36, unknown 4.66 and cyclopentadecanone 7.13 min.

Dieckmann Cyclization of Benzyl Triethylcarbinyl Hexadecanedioate (**114**) with Potassium Triethylcarbinolate in Toluene

To a solution of 0.77 g (1.6 mmol) of benzyl triethylcarbinyl hexadecanedioate (**114**) in 160.0 mL of toluene was added 0.65 g (4.2 mmol) of potassium triethylcarbinolate (6 M in toluene) dropwise over a period of 20 min at room temperature. After 4 h of stirring under argon, the reaction mixture was concentrated in vacuo. TLC (developed in 10 % ethyl acetate in petroleum ether) of the concentrate showed three spots. The concentrate absorbed on 2.0 g of silica gel was added to the column packed with 40.0 g of silica gel (Grade 62, -60+200 mesh, from EM Science). Sequential elution was effected with 0 %, 1 %, 2 %, 4 %, 6 % and 10 % ethyl acetate in petroleum ether. Di(triethylcarbinyl)-hexadecanedioate (**103**) eluted with 1 % ethyl acetate in petroluem ether to yield 0.312 g (46 %, on the basis of the starting material **114** recovered). IR, ^{1}H NMR and ^{13}C NMR data confirmed the structure of **103**. A second fraction containing the starting material **114** eluted with 2 % ethyl acetate in petroluem ether to yield 0.109 g (14 %). IR, ^{1}H NMR and data confirmed the structure of **114**. Benzyl alcohol (**99**) eluted with 6 % ethyl acetate in petroluem ether to yield 0.083 g (55 %, on the basis of the starting material **114** recovered). IR and ^{1}H NMR data confirmed the structure of **99**.

CHAPTER V

HALOGENATION EXPERIMENTAL

Reagents and Solvents

The polymer 1 % cross-linked poly(*p*-methylstyrene) (**70**) was prepared from *p*-methylstyrene (Mobil Chemical Co. PMSA25 monomer) and 55-60 % active divinylbenzene (Polysciences) by suspension polymerization.[83] The percent cross-linking reported is weight percent of active divinylbenzene. The sodium hypochlorite solutions used were laundry bleach (Clorox) and sodium hypochlorite freshly prepared from sodium hydroxide and chlorine.[116] The sodium hypobromite was prepared fresh from sodium hydroxide and bromine.[116] Reagents, catalysts and reagent grade solvents were used as received from Aldrich Chemical Co. (1, 2-dichloropropane), Mallinckrodt (carbon tetrachloride), Fisher Scientific (chloroform), Eastman [benzyltriethylammonium chloride (PTC)], Peninsula Laboratories Inc. (Boc-L-Valine and Boc-L-Phenylalanine), Matheson Co. (trimethylamine), J. T. Baker Chemical Co. (sodium carbonate, sodium thiosulphate), K & K Laboratories Inc. (cesium carbonate).

Analyses and Spectra

Elemental analyses were performed by Desert Analytics (Tucson, AZ). ^{13}C NMR spectra of polymer gels swollen in $DCCl_3$ were run at 75.43 MHz on a Varian XL-300 spectrometer at 24 ^{o}C using 5 mm o.d. tubes, 4 K data points, a 18.0 μs 90^{o} pulse width,

a 5-6 sec delay between acquisitions, 1000 acquisitions per spectrum, 20,000 Hz sweep width, and an exponential line broadening factor of 4 Hz unless noted otherwise. Peak areas were measured by triangulation with correction of the base line of the chloromethyl peak for the underlying backbone methylene carbon resonances. Analyses were performed with full ^{1}H decoupling, and peak areas were corrected for nuclear Overhauser enhancement factors (Table XI and Table XII). The NOE's were independently determined to be 1.674 and 1.816 (peak area with full ^{1}H decoupling / peak area with ^{1}H decoupling only during data acquisition) for the methyl and chloromethyl carbon peaks in a 1 % cross-linked gel polymer.[84] Similarly NOE's were independently measured to be 1.656 and 1.870 (peak area with full ^{1}H decoupling / peak area with ^{1}H decoupling only during data acquisition) for the methyl and bromomethyl carbon peaks in a 1 % cross-linked gel polymer. Swelling ratios were determined by volume as swollen volume in $DCCl_3$ / dry volume. Infrared spectra were recorded with KBr disks on a Perkin-Elmer Model 681 spectrophotometer. Samples of polymers (4 mg) were mixed with 190 mg of anhydrous potassium bromide in a Wig-L-Bug (Crescent Dental Mfg. Co.) for 3 min and pressed into translucent wafers. For quantitative analyses IR spectra were recorded in absorbance mode and were analysed for $-CH_2Cl$ groups (1265 cm^{-1} peak). The peak at 1110 cm^{-1} was used as standard. The quantitative analyses were done by cutting and weighing the peaks as well as measuring the peak heights of 1265 cm^{-1} and 1110 cm^{-1} peaks (Table XI). The results were calibrated with the samples already analysed by ^{13}C NMR spectroscopy.

Concentrations of aqueous sodium hypochlorite and sodium hypobromite were determined by iodometric titration.[121] Water used in all titrations was deionised and glass-distilled.

Chlorination of 1% Cross-Linked Poly(*p*-methyl-styrene) (**70**) with 5.23 % NaOCl

In a 2-L round-bottom flask fitted with a mechanical stirrer having a Teflon blade 1 cm above the bottom of the flask, poly(*p*-methylstyrene) (**70**) with DF = 0.984 $[(C_{10}H_{10})_{0.008}\cdot(C_{10}H_{10})_{0.009}\cdot(C_9H_{10})_{0.984}]$ (50 g, 416.5 mmol of -CH_3 groups) was swollen in 413 mL of chloroform. A solution of 1200 mL of Clorox (904.0 mmol, 5.23 % by weight NaOCl solution, neutralized to pH 8.4 with concentrated HCl) was added to the flask. After addition of 9.66 g (42.4 mmol) of benzyltriethylammonium chloride (PTC), the reaction mixture was stirred at 457 rpm at room temperature for 2 h. The polymer was filtered and washed with water (2x), acetone (2x), water (2x), acetone (2x), CH_2Cl_2 (1x), acetone (1x), and methanol (2x), and was dried under vacuum at 60 ^oC for 26 h to give 60.1 g of chlorinated poly(*p*-methylstyrene) (**71**). IR (KBr) 1265 cm^{-1} (-CH_2Cl); ^{13}C NMR 46.2 ppm (-$\underline{C}H_2Cl$), 72.0 (-$\underline{C}HCl_2$). Anal. Calcd for **71** (from ^{13}C NMR analysis): Cl, 20.9 % (5.7 meq / g of the polymer, from IR analysis). Found: Cl, 18.0 % (5.1 meq / g of the polymer, from elemental analysis) (DF = 0.61).

Chlorination of 1% Cross-Linked Poly(*p*-methylstyrene) (**70**) with 5.23 % NaOCl and No PTC

To the poly(*p*-methylstyrene) (**70**) (DF = 0.984, 1.0 g, 8.3 mmol of -CH_3 groups) swollen in 10.0 mL of chloroform, 10.0 mL of clorox bleach (7.5 mmol, 5.23 % by weight NaOCl solution, neutralized to pH 8.4 with concentrated HCl) was added. The mixture was stirred at room temperature for 30 min. The solid was filtered, washed with water:methanol (1:1) (2x), methanol (2x), water (3x), methanol (3x), and dried under vacuum at 60 ^oC for 3 h to give 1.15 g of yellow polymer (**71**). IR (KBr) 1265 cm^{-1} (strong peak due to -CH_2Cl group) (DF = 0.26, Table XI).

(Polystyrylmethyl)trimethylammonium Chloride (**118**)

(**A**) With dry trimethylamine: To the chlorinated poly(*p*-methylstyrene) (**71**) (DF = 0.61, 3.0 g, 13.5 mmol of Cl) swollen in 15.0 mL of 1, 2-dichloropropane in a round bottom flask equipped with dry ice condenser and mechanical stirrer, was added trimethylamine 41.0 mL (26.1 g, 441.0 mmol). The mixture was stirred at room temperature for 5.5 h. IR (KBr) 1485 and 1475 cm^{-1} (-CH_3 attached to N^+). The band at 1265 cm^{-1} due to -CH_2Cl was missing. ^{13}C NMR ($DCCl_3$+$DOCD_3$) δ 21.0 (polymer-$\underline{C}H_3$), 40.3, 52.3 [$^+N(\underline{C}H_3)_3$], 68.5 (-$\underline{C}H_2$ N^+). To determine the anion-exchange capacity (AEC) (Table XIII), dried polymer was weighed out accurately in an Erlenmeyer flask and was swollen in 20 mL of methanol. To this 25 mL of 10 % aqueous $NaNO_3$ was added and stirred at room temperature for 30 minutes. Polymer was filtered and washed with water and methanol. The filtrate was taken in a 250 mL volumetric flask and was diluted to the mark with water. Fifty mL of the solution was pipetted into an Erlenmeyer flask and was titrated with standard $AgNO_3$ solution after addition of three drops of 5 % K_2CrO_4 as an indicator. The samples were also submitted for combustion analysis (Table XIII). Calcd for $[(C_{10}H_{10})_{0.008}\cdot(C_{10}H_{10})_{0.009}\cdot(C_9H_{10})_{0.31}\cdot(C_9H_9Cl)_{0.54}\cdot(C_9H_8Cl_2)_{0.07}\cdot(C_{12}H_{18}NCl)_{0.06}]$: N, 3.3 % (from anion exchange capacity determination):, Found N, 3.3 %, Cl 13.2 %.

(**B**) With aqueous trimethylamine solution: The chlorinated poly(*p*-methylstyrene) (**71**) (DF = 0.61, 3.0 g, 13.5 mmol of Cl) swollen in 15.0 mL of 1,2-dichloropropane was also treated with aqueous trimethylamine (41.0 mL, 25 wt %, 173.4 mmol). The mixture was stirred at room temperature for 8.75 h. Polymer was filtered and washed with water (4x), acetone (3x), methanol (1x), chloform (1x), acetone (3x), and petroleum ether (4x), and was dried under vacuum at 60 ^oC for 3 h to give 3.32 g of light yellow polymer **118**.

IR (KBr) 1260 cm-1 (residual -CH_2Cl). Anal. Found N, 1.6 % (0.44 mmol / g) (Table XIII).

Preparation of Sodium Hypobromite (NaOBr . 5 H_2O)

A 40 % sodium hydroxide solution (219.0 g, 5.5 mol, 153 mL) was stirred and cooled to -3 ^oC in a three-neck 1-L flask fitted with mechanical stirrer, thermometer and a pressure equalizing additional funnel. Bromine (157 g) was added slowly. The temperature of the reaction mixture was held between -3 and -8 ^oC. Cooling below -8 ^oC should be avoided to prevent freezing. During the addition of bromine, NaBr. 2 H_2O separated out. After completion of the addition of bromine, the mixture was allowed to stand for 1 h at -8 ^oC. It was then filtered through a glass frit filter. The thick yellow filtrate was collected in a suction flask cooled to -78 ^oC with dry ice acetone mixture. The filtrate (2.99 g, NaOBr and NaBr mixture) was taken in a 100 mL volumetric flask and was diluted to the mark. Sodium hypobromite solution (5 mL) was pipetted into a 500 mL volumetric flask and diluted to the mark. Sodium hypobromite content determined by the iodometric titration[3] method was 15.55 percent by weight.

Bromination of 1% Cross-Linked Poly(*p*-methyl-styrene) (**70**) with 3.11 % NaOBr

In a 100.0 mL three neck flask, fitted with a mechanical stirrer and condenser, the poly(*p*-methylstyrene) (**70**) (DF = 0.984, 1.0 g, 8.3 mmol of -CH_3 groups) was swollen in 10.0 mL of chloform, and 25.0 mL of sodium hypobromite (3.11 % by weight neutralized to pH 8.5 with 48 % HBr solution) was added to the flask. The mixture was stirred at room temperature for 2 h. Yellow polymer was filtered (filtrate pH was 4.1), washed with water (6x), and methanol (3x), and dried under vacuum at 60 ^oC for 3 h to

give 1.45 g of **117**. IR (KBr) 1225 and 610 cm^{-1} (very strong peaks due to -CH_2Br). ^{13}C NMR δ 34.4 (-$\underline{C}H_2$Br), 21.6 (residual -$\underline{C}H_3$). Calcd for $[(C_{10}H_{10})_{0.008}\cdot(C_{10}H_{10})_{0.009}\cdot(C_9H_{10})_{0.61}\cdot(C_9H_9Br)_{0.37}]$: Br, 9.0 % (2.5 meq/g of the polymer, from ^{13}C NMR analysis), (DF = 0.37):, Found Br, 19.7 % (2.5 meq/g of the polymer) (Table XII).

Cesium Salt of Boc-L-Valine **122**[109]

Boc-L-Valine (**120**) (2.0 g, 9.2 mmol) was dissolved in 15.0 mL of ethanol and diluted with 3.0 mL of water. The pH was adjusted to 7.0 using a pH meter by adding 2 M aquous cesium carbonate. The water was rotary evaporated, 5.0 mL of benzene was added, and evaporation was repeated. Drying in vacuo with vacuum pump overnight gave 3.2 g (100 %) cesium salt of Boc-L-valine **122** as white powder (hygroscopic, kept in a vacuum desiccator).

Attachment of Boc-L-Valine Cesium Salt **122** to Chlorinated Poly(*p*-methylstyrene) (**71**)[109]

To partly chlorinated poly(*p*-methylstyrene) (**71**) (DF, 0.08, 0.50 g, 0.30 mmol of Cl) swollen in 5.0 mL of DMF was added 0.105 g of the cesium salt of Boc-L-Valine (**122**). The mixture was stirred for 39.0 h in a 55 °C oil bath. The polymer was filtered, washed with water (2x), acetone (2x), dichloromethane (1x), acetone (1x), and methanol (2x) and dried under vacuum at 60 °C for 4 h to give 0.55 g of Boc-L-valine resin **124** (66 %, 0.63 mmol / g, based on residual chloride analysis by the modified Volhard titration method[6]). IR (KBr) 3430 (br, N-H stretch), 2965 (br, methyl C-H stretch), 2920 (C-H stretch of CH_2), 1735 (br, ester C=O), 1720 (urethane C=O), 1385 and 1375 (m, doublet of isopropyl group), 1160 cm^{-1} [br, C(=O)-O stretch]; ^{13}C NMR (75.5 MHz, $DCCl_3$) δ

17.5 and 19.0 [-CH($\underline{C}H_3)_2$], 21.0 (polymer-$\underline{C}H_3$), 28.3 [-C($\underline{C}H_3)_3$], 31.3 [-$\underline{C}H(CH_3)_2$], 39.9 (polymer backbone methine carbons), 58.5 [C(=O)$\underline{C}$HNH], 66.8 (polymer-$\underline{C}H_2$-O), 79.7 [-$\underline{C}(CH_3)_3$], 127.0, 128.5 and 136.0 (*o*-, *m*-, and *p*-carbons of the aromatic ring respectively), 171.3 and 172.3 ($\underline{C}$=O).

Attachment of Boc-L-Phenylalanine Cesium Salt **121**
to Chlorinated Poly(*p*-methylstyrene) (**71**)[109]

To partly chlorinated poly(*p*-methylstyrene) (**71**) (DF, 0.06, 1.0 g, 0.46 mmol of Cl) swollen in 5.0 mL of DMF was added 0.20 g of the cesium salt of Boc-L-phenylalanine **121**. The mixture was stirred for 21.5 h in a 55 ^{o}C oil bath. The polymer was filtered, washed with water (3x), acetone (2x), dichloromethane (1x), acetone (2x), and methanol (2x) and dried under vacuum at 40 ^{o}C for 4 h to give 1.06 g of Boc-L-phenylalanine resin **123** (75 %, 0.43 mmol of amino acid / g of the polymer, based on chloride analysis by the modified Volhard method[115]). IR (KBr) 3430 (br, N-H stretch), 2965 (br, methyl C-H stretch), 2920 (C-H stretch of CH_2), 1735 (br, ester C=O), 1720 (urethane C=O), 1505 (br, C=C ring stretch), 1240 (br), 1160 [br, C(=O)-O stretch], 730 (br, aromatic C-H out of plane bending) cm^{-1}; ^{13}C NMR (75.5 MHz, $DCCl_3$) δ 21.0 (polymer-$\underline{C}H_3$), 28.3 [-C($\underline{C}H_3)_3$], 38.2 [-$\underline{C}H_2C_6H_5$], 39.9 (polymer backbone methine carbons), 54.4 [C(=O)$\underline{C}$HNH], 67.0 (polymer-$\underline{C}H_2$-O), 79.6 [-$\underline{C}(CH_3)_3$], 127.0, 128.5 and 136.0 (*o*-, *m*-, and *p*-carbons of the aromatic ring respectively), 171.3 and 172.0 ($\underline{C}$=O).

General Procedure for the Determination of the Degree of Chlorination[115]
of Boc-Amino Acid Resin Esters (**123** and **124**)

To 0.20 g of the polymer bound amino acid in a round bottom flask 3.0 mL pyridine was added, and the mixture was heated for 2 h at 100 ^{o}C. The mixture was transfered

quantitatively to a 125 mL Erlenmeyer flask with 30.0 mL of 50 % acetic acid, and 5.0 mL of concd HNO_3 was added. The liberated chloride was analyzed by the modified Volhard method.[115] The polymer was filtered and washed with water. The filtrate was taken in a 250 mL volumetric flask and was diluted to the mark with water. Three 50 mL aliquots of the solution were transfered into 250 mL Erlenmeyer flasks and to each 20.0 mL of standard 0.07 M $AgNO_3$ and four drops of ferric alum indicator were added. The mixtures were kept for 5 min protected from the light. Toluene (20.0 mL) was added so that a 1/4 inch layer was made on the water surface. The mixture was stirred magnetically and titrated with standard 0.1 N NH_4SCN solution. The first permanent tinge of red-brown indicates the end point.

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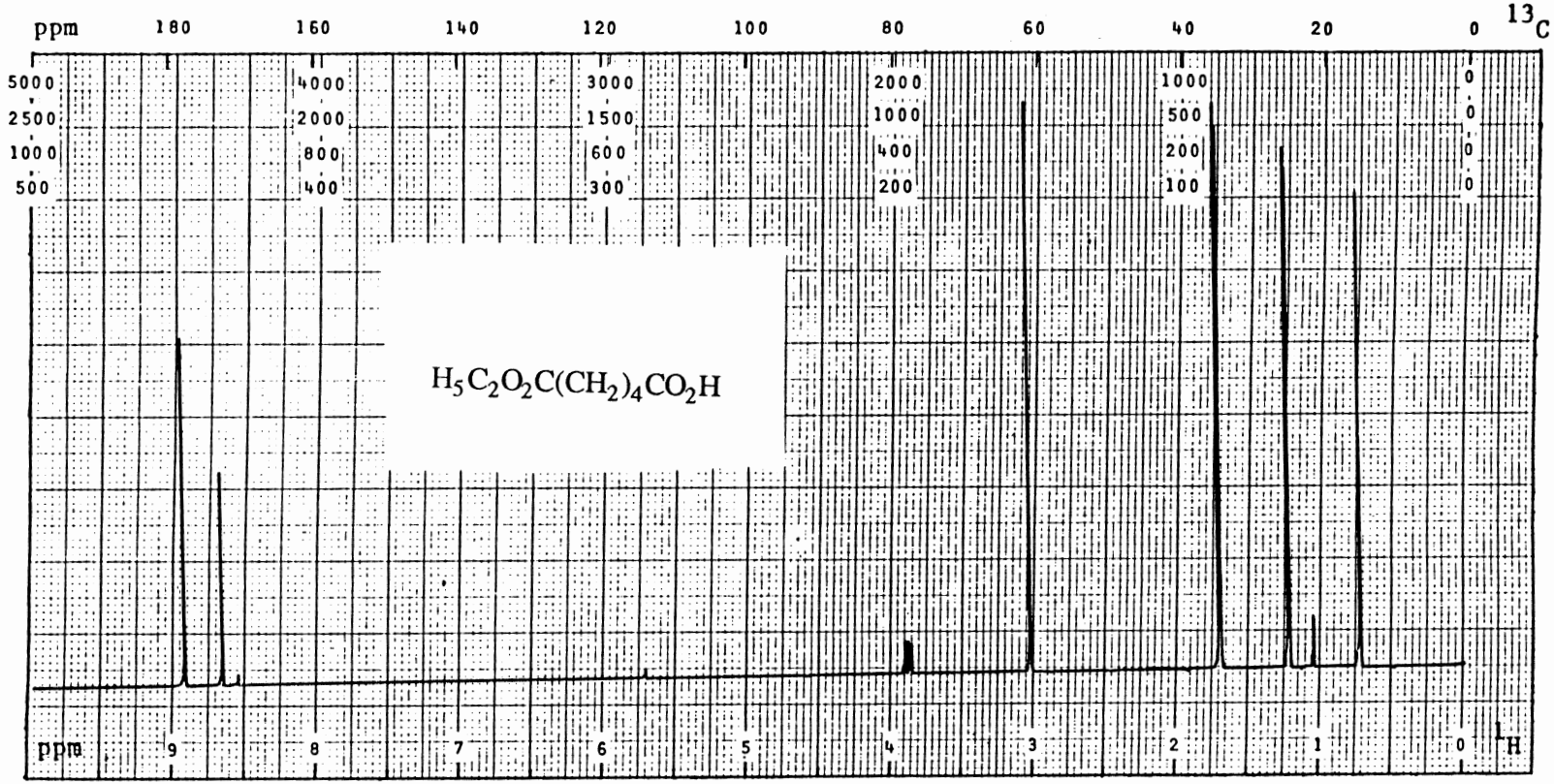
APPENDIX

SELECTED NMR SPECTRA

Spectrum No. I



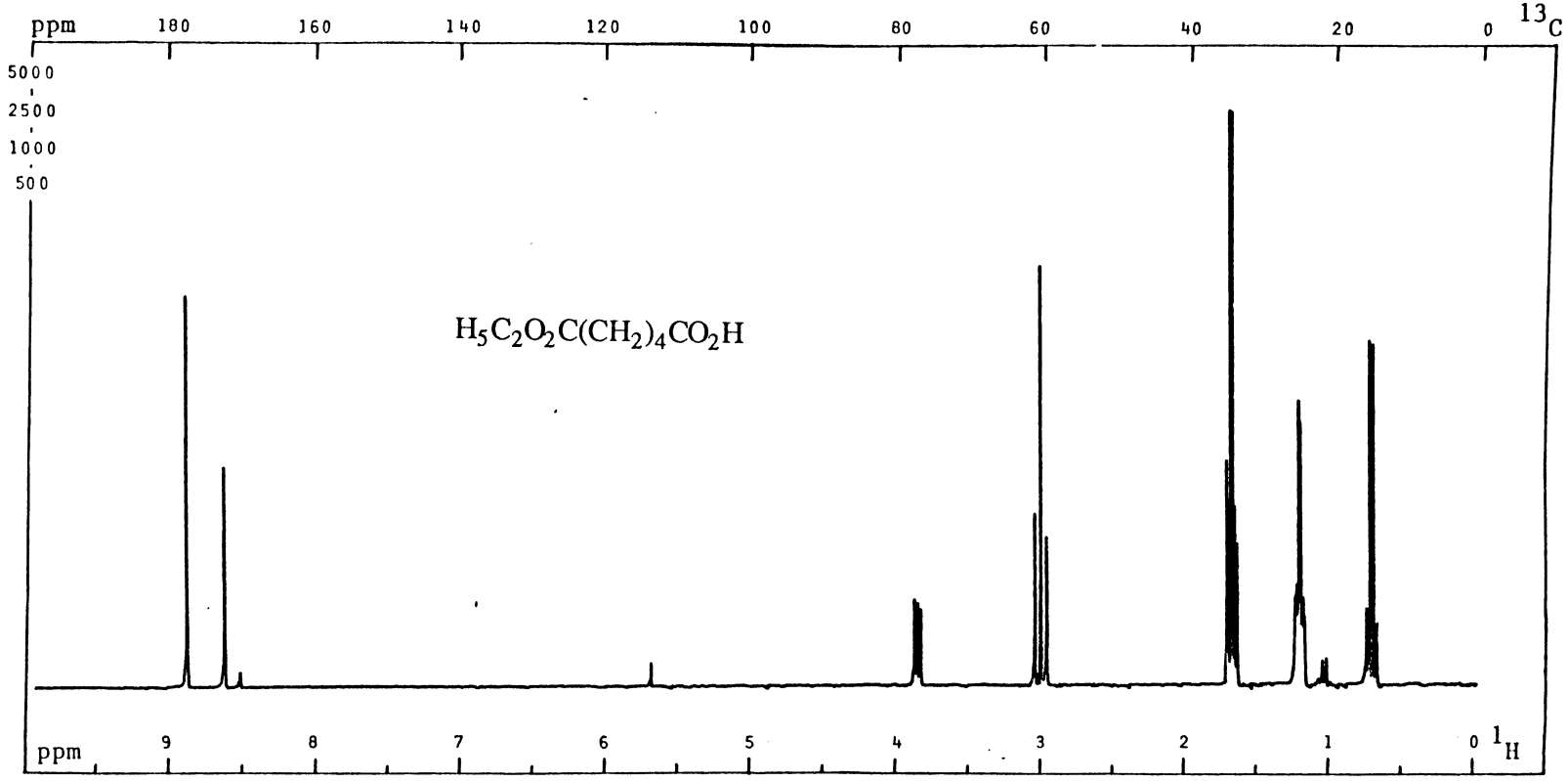
^{13}C NMR Spectrum of Adipic Acid Monoethyl Ester (111)

PFT X CW _ ; Solvent: $DCCl_3$; SF: 75.429 MHz; WC: I5085.9Hz; T: RT °C; NT: 40

Size: I6 K; PW/RF: I8.0 μs/dB; TO: 0 Hz; FB: NA Hz; Lock: D ; D1,D5 : 4.0 s.

DC: Y, N ; Gated Off: A or D ; DO: 0 Hz; RF(Power): I0 W/dB; NBW: 200 Hz; LB: I.5 Hz.

Spectrum No.II

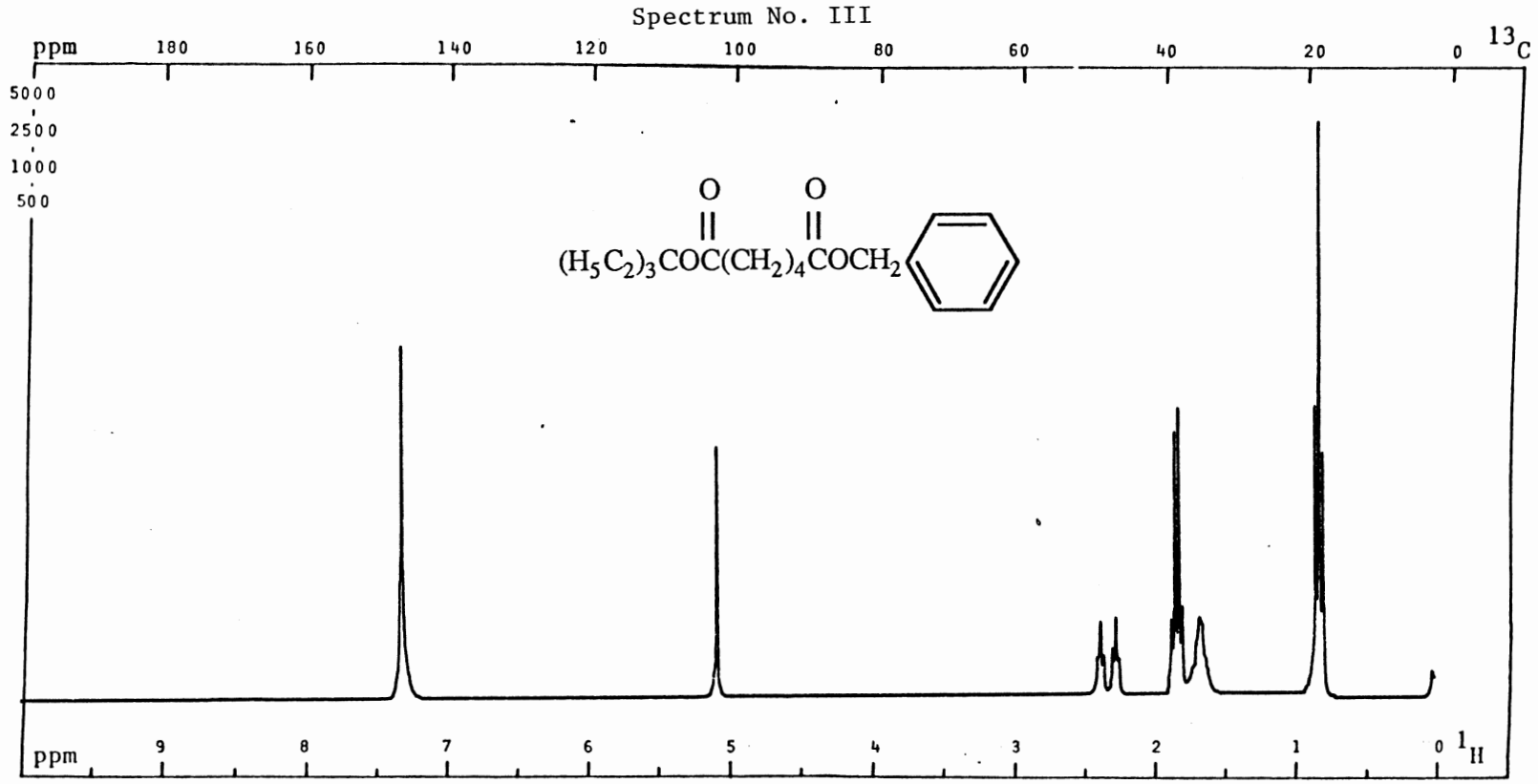


Off-resonance Decoupled ^{13}C NMR Spectrum of Adipic Acid Monoethyl Ester (111)

PFT X CW _ ; Solvent: $DCCl_3$; SF: 75.429 MHz; WC: 15085.9 Hz; T: RT °C; NT: 60 .

Size: 16 K; PW/RF: 18.0 μs/dB; TO: 1000 Hz; FB: NA Hz; Lock: D ; D1,D5: 4.0 s.

DC: Y, N ; Gated Off: A or D ; DO: -2500 Hz; RF(Power): 0 W/dB; NBW: 200 Hz; LB: 2.0 Hz.

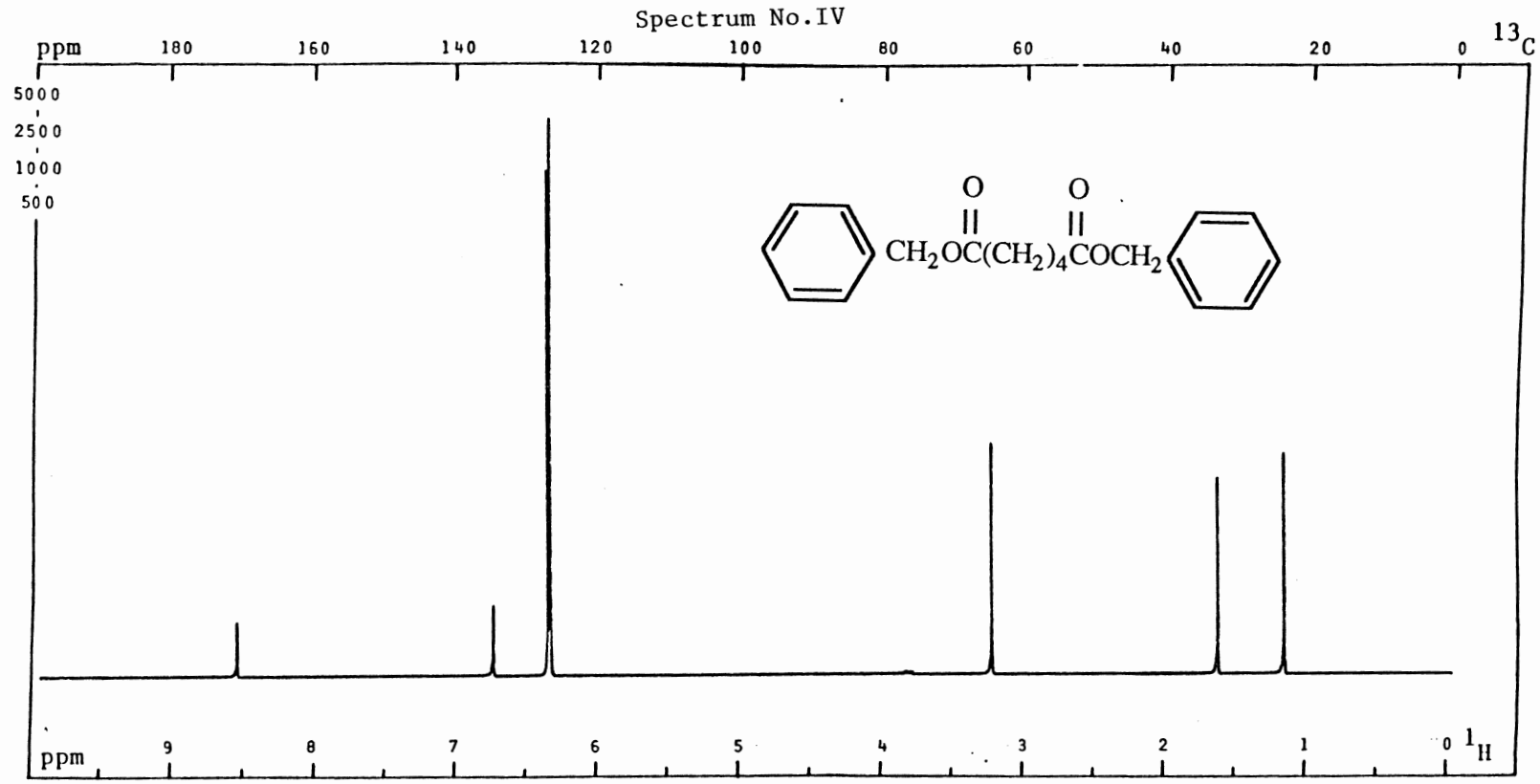


^{1}H NMR Spectrum of Benzyl triethylcarbinyl adipate (91)

PFT X CW _ ; Solvent: $DCCl_3$; SF: 299.944 MHz; WC: 2999.4 Hz; T: RT °C; NT: 16 .

Size: 12 K; PW/RF: 5.0 μs/dB; TO: 0 Hz; FB: NA Hz; Lock: D ;D1,D5: 0.5 s.

DC: Y, N ; Gated Off:A or D ; DO: 750 Hz; RF(Power): 0 W/dB; NBW: 200 Hz; LB: 0 Hz.



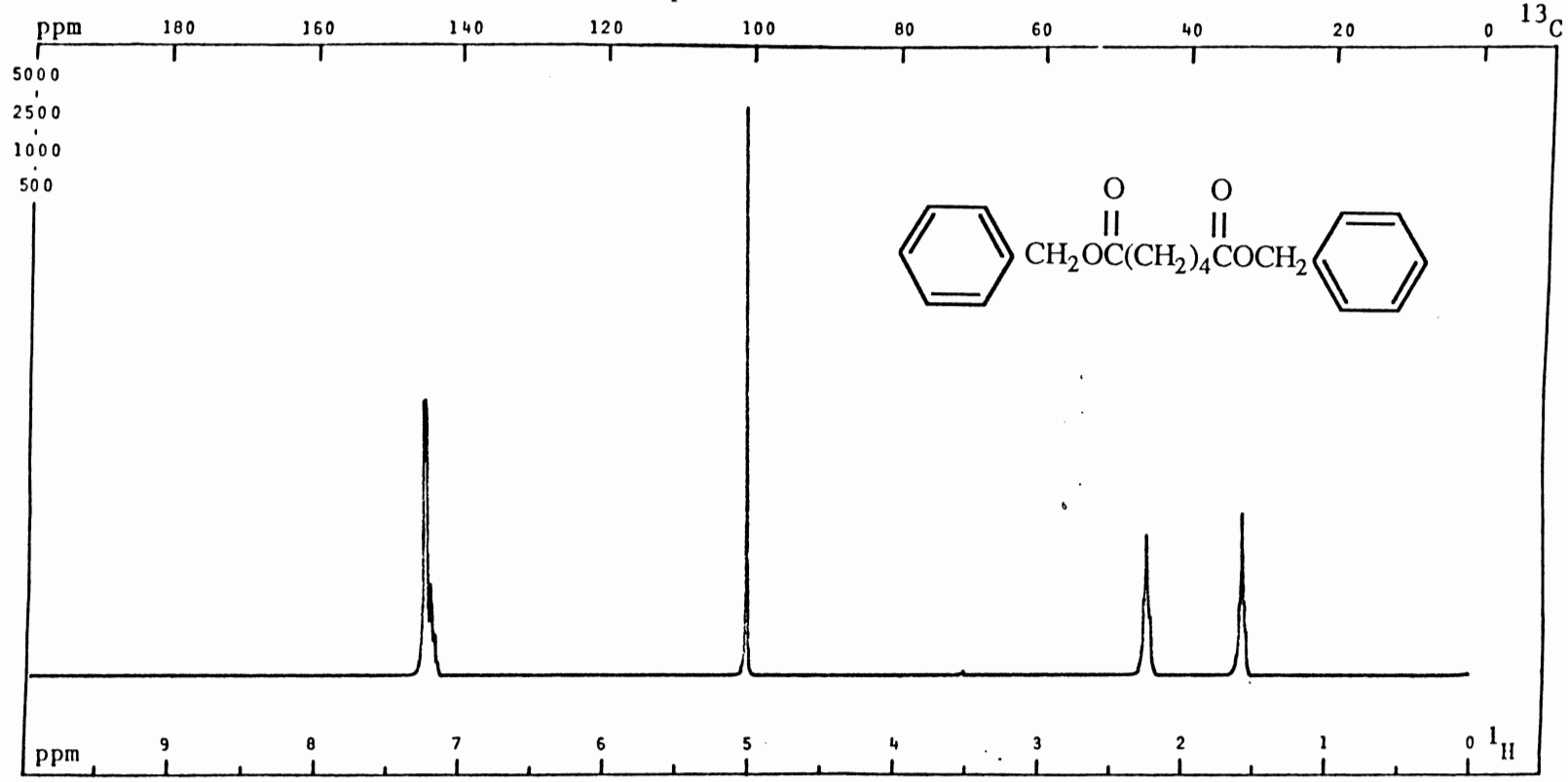
^{13}C NMR Spectrum of Dibenzyl adipate (92)

PFT X CW _ ; Solvent: $DCCl_3$; SF: 75.429 MHz; WC: 15085.9 Hz; T: RT °C; NT: 32

Size: 16 K; PW/RF: 12.0 μs/dB; TO: 1000 Hz; FB: NA Hz; Lock: D ; D1,D5: 4.0 s.

DC: Y, N ; Gated Off: A or D ; DO: 0 Hz; RF(Power): 10 W/dB; NBW: 200 Hz; LB: 1.5 Hz.

Spectrum No. V



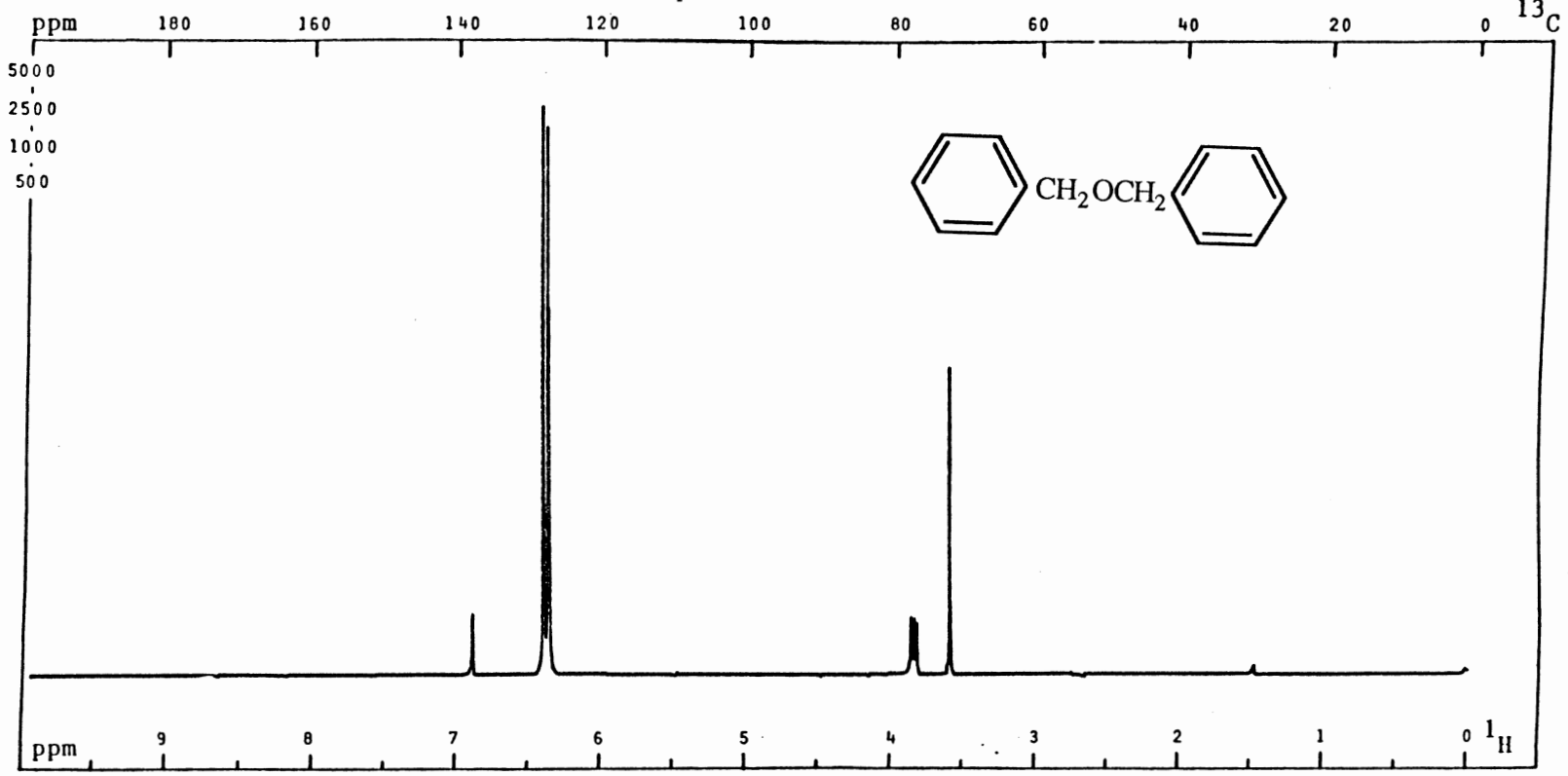
^{1}H NMR Spectrum of Dibenzyl adipate (92)

PFT X CW _ ; Solvent: $DCCl_3$; SF: 299.944 MHz; WC: 2999.4 Hz; T: RT °C; NT: 16

Size: 12 K; PW/RF: 5.0 μs/dB; TO: 0 Hz; FB: NA Hz; Lock: D ; D1,D5: 0 s.

DC: Y, N ; Gated Off:A or D ; DO: 0 Hz; RF(Power): 0 W/dB; NBW: NA Hz; LB: 0 Hz.

Spectrum No.VI

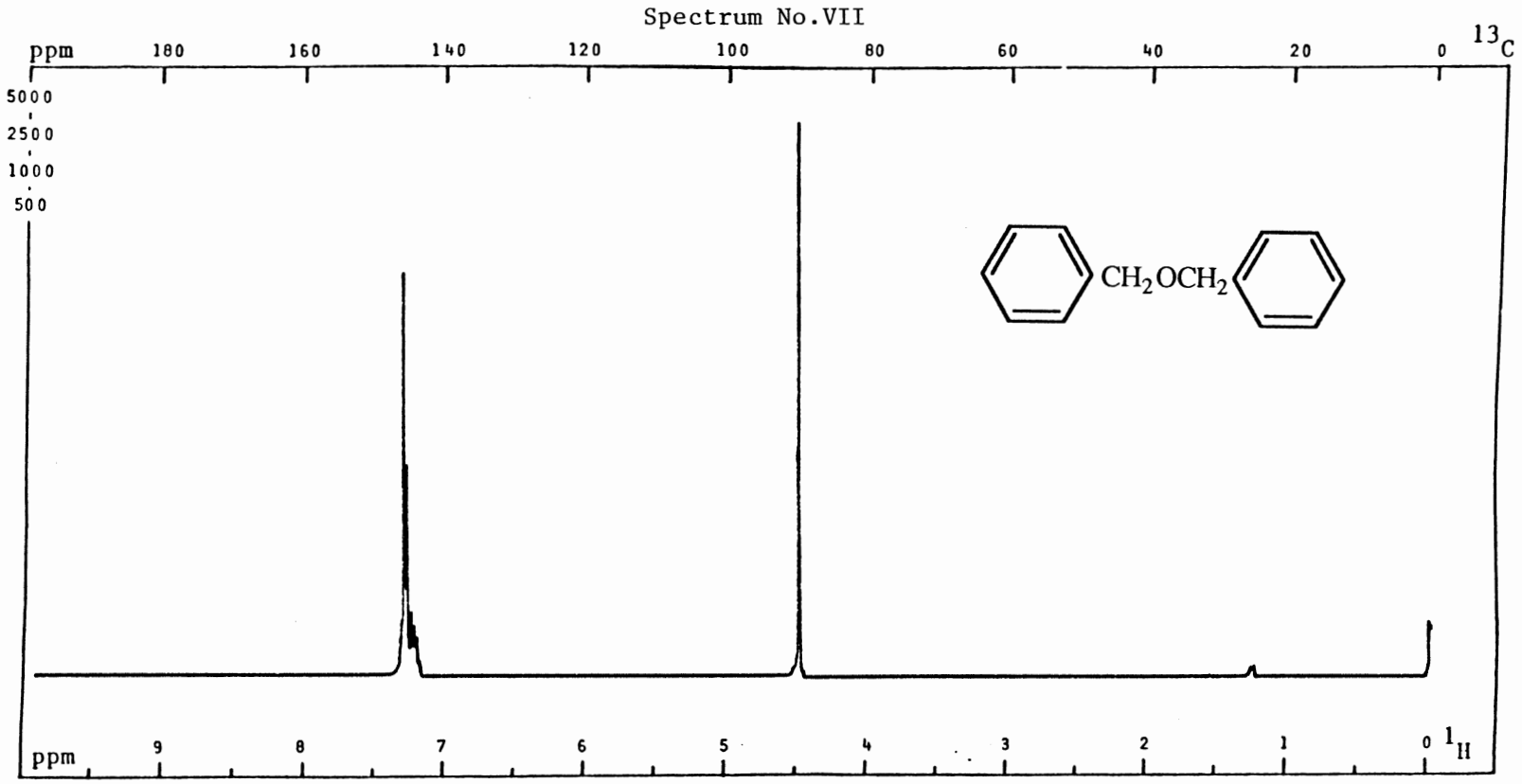


^{13}C NMR Spectrum of Dibenzyl ether (98)

PFT _X CW _ ; Solvent: $DCCl_3$; SF: 75.429 MHz; WC: 2999.4 Hz; T: RT °C; NT: 4 .

Size: 12 K; PW/RF: 12.5 μs/dB; TO: 0 Hz; FB: NA Hz; Lock: D ; D1,D5: 0 s.

DC: Y, N ; Gated Off:A or D ; DO: 0 Hz; RF(Power): 0 W/dB; NBW: NA Hz; LB: 0 Hz.



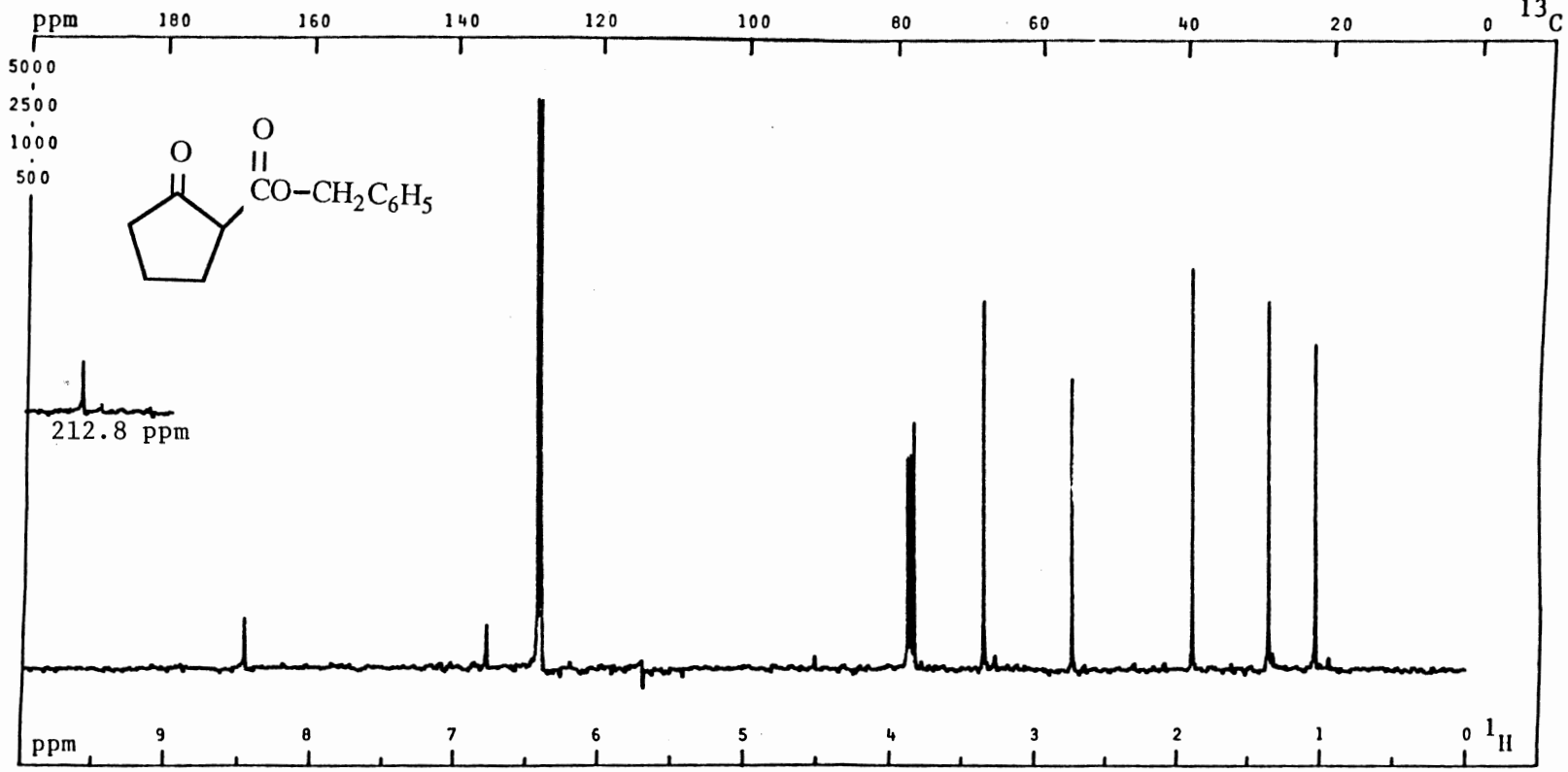
^{1}H NMR Spectrum of Dibenzyl ether (98)

PFT X CW _ ; Solvent: $DCCl_3$; SF: 299.94 MHz; WC: 15085.9 Hz; T: RT °C; NT: 40 .

Size: 16 K; PW/RF: 12.0 μs/dB; TO: 700 Hz; FB: NA Hz; Lock: D ; D1,D5: 6.0 s.

DC: Y, N ; Gated Off: A or D ; DO: 0 Hz; RF(Power): 0 W/dB; NBW: 200 Hz; LB: 5.0 Hz.

Spectrum No. VIII

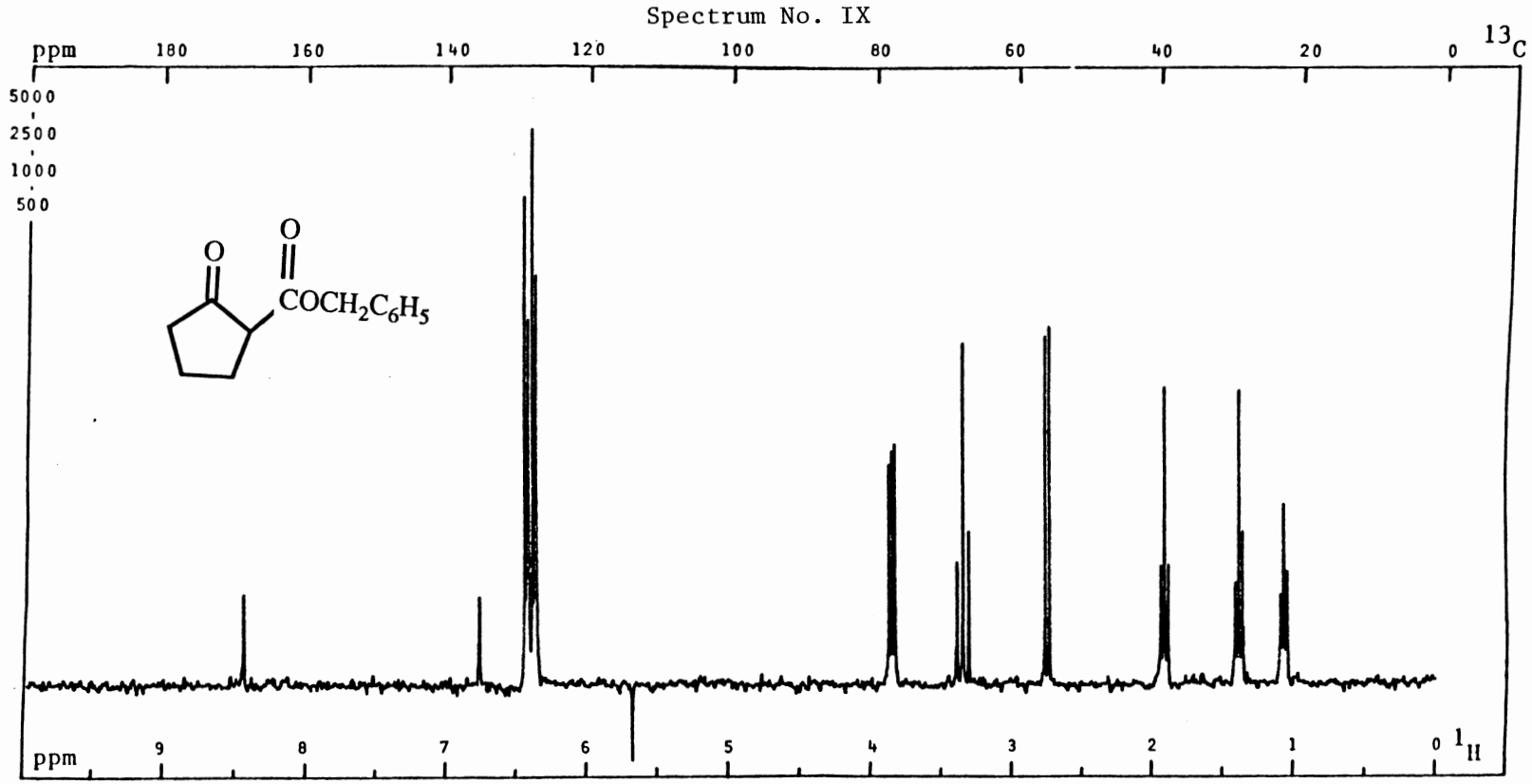


^{13}C NMR Spectrum of Benzyl 2-cyclopentanonecarboxylate (97)

PFT X CW _ ; Solvent: $DCCl_3$; SF: 75.429 MHz; WC:15085.9 Hz; T: RT °C; NT: 80 .

Size: 16 K; PW/RF: 12.0 µs/dB; TO: 1000 Hz; FB: NA Hz; Lock: D ;D1,D5: 4.0 s.

DC: Y, N ; Gated Off:A or D ; DO: 0 Hz; RF(Power): 0 W/dB; NBW: 200 Hz; LB: 2.0 Hz.



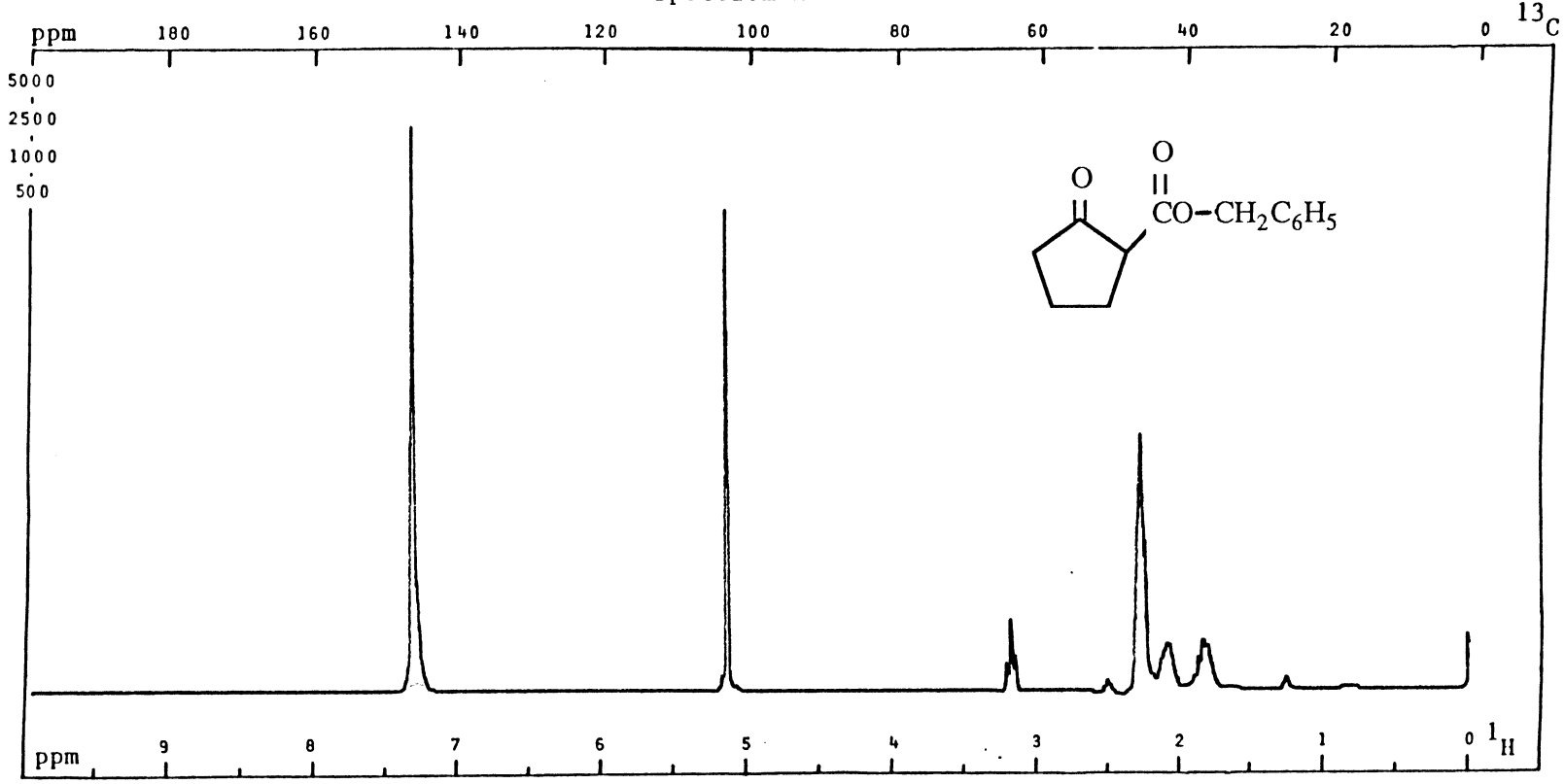
Off-resonance Decoupled ^{13}C NMR Spectrum of Benzyl 2-Cyclopentanonecarboxylate (97)

PFT X CW _ ; Solvent: $DCCl_3$; SF: 75.429 MHz; WC: 15085.9Hz; T: RT °C; NT: 80 .

Size: 16 K; PW/RF: 12.0 μs/dB; TO: 1000 Hz; FB: NA Hz; Lock: D ;D1,D5: 4.0 s.

DC: Y, N ; Gated Off:A or D ; DO: -2500 Hz; RF(Power): 0 W/dB; NBW: 200 Hz; LB: 2.0 Hz.

Spectrum No. X



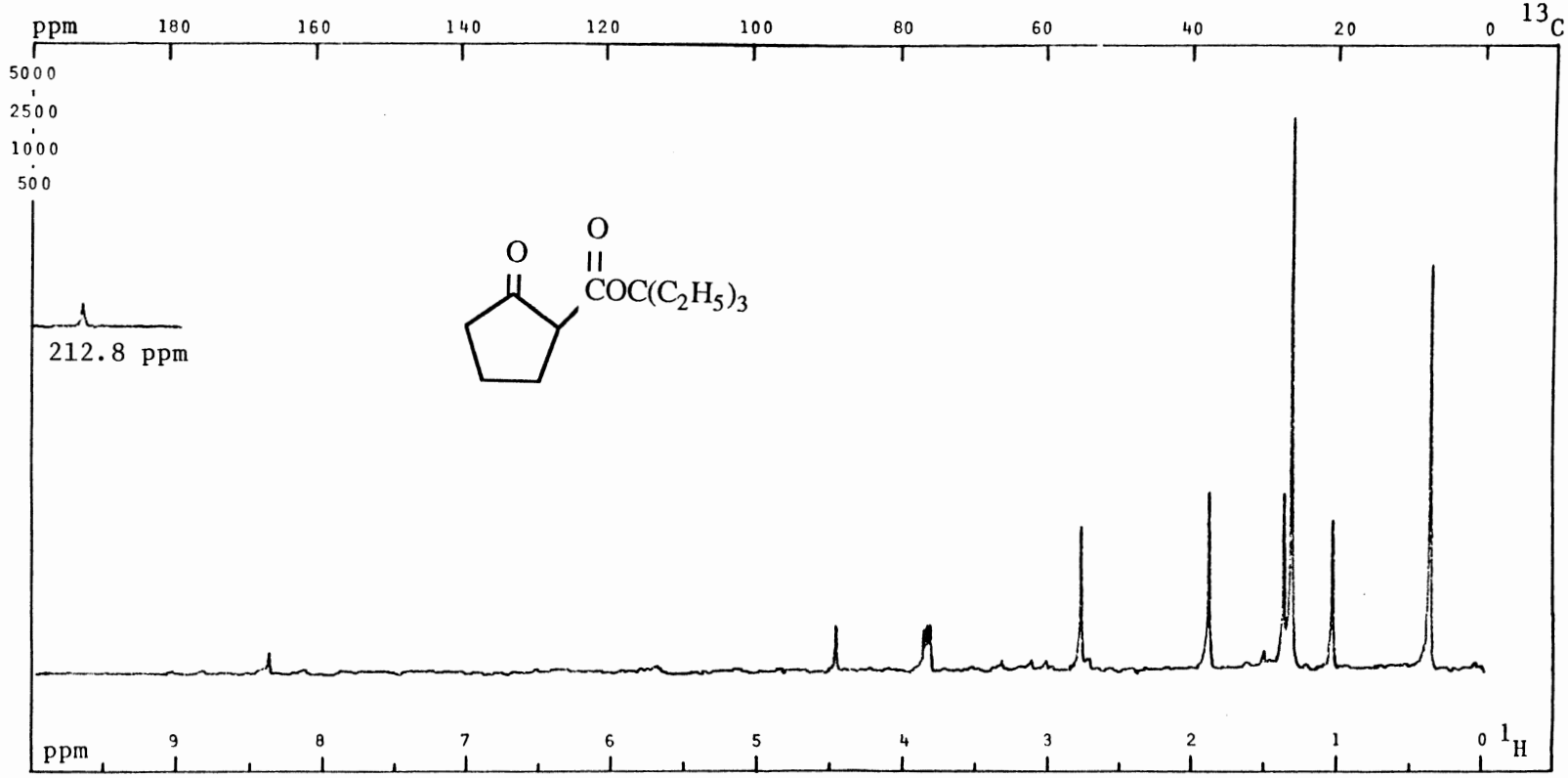
^{1}H NMR Spectrum of Benzyl 2-cyclopentanonecarboxylate (97)

PFT X CW _ ; Solvent: $DCCl_3$; SF: 299.944 MHz; WC: 2999.4 Hz; T: RT °C; NT: 16 .

Size: 12 K; PW/RF: 5.0 µs/dB; TO: 0 Hz; FB: NA Hz; Lock: D ;D1,D5: 0 s.

DC: Y, N ; Gated Off:A or D ; DO: 0 Hz; RF(Power): 0 W/dB; NBW: NA Hz; LB: 0 Hz.

Spectrum No. XI



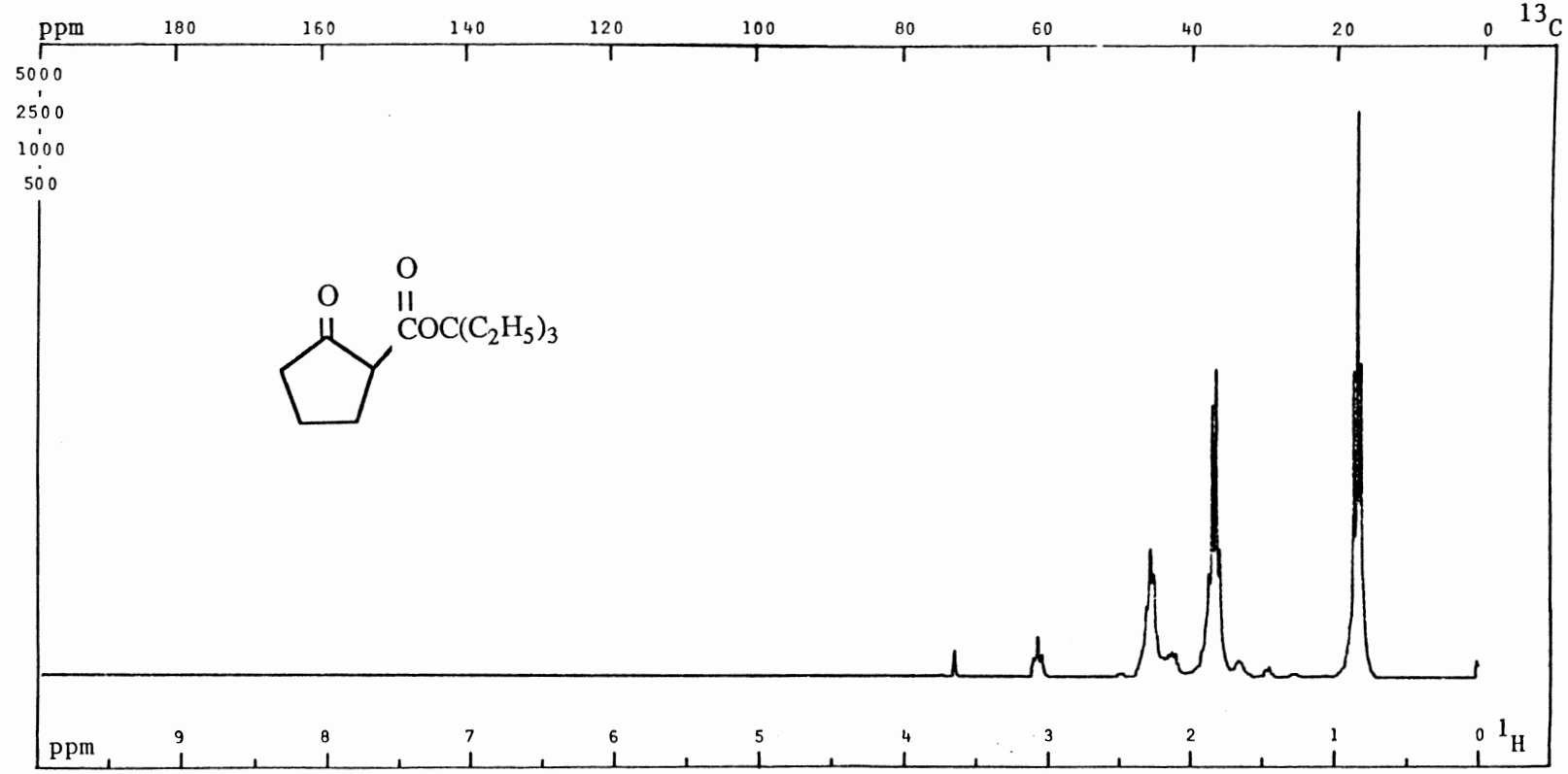
^{13}C NMR Spectrum of Triethylcarbinyl 2-cyclopentanonecarboxylate (96)

PFT X CW _ ; Solvent: $DCCl_3$; SF: 75.429 MHz; WC:15085.9 Hz; T: RT °C; NT: 40 .

Size: 16 K; PW/RF: 12.0 μs/dB; SO: 1000 Hz; FB: NA Hz; Lock: D ; Delay: 3.0 s.

DC: ^{1}H ; Gated Off: NA ; Offset: 0 Hz; RF: 10 W/dB; NBW: 200 Hz; LB: 10.0 .

Spectrum No. XII



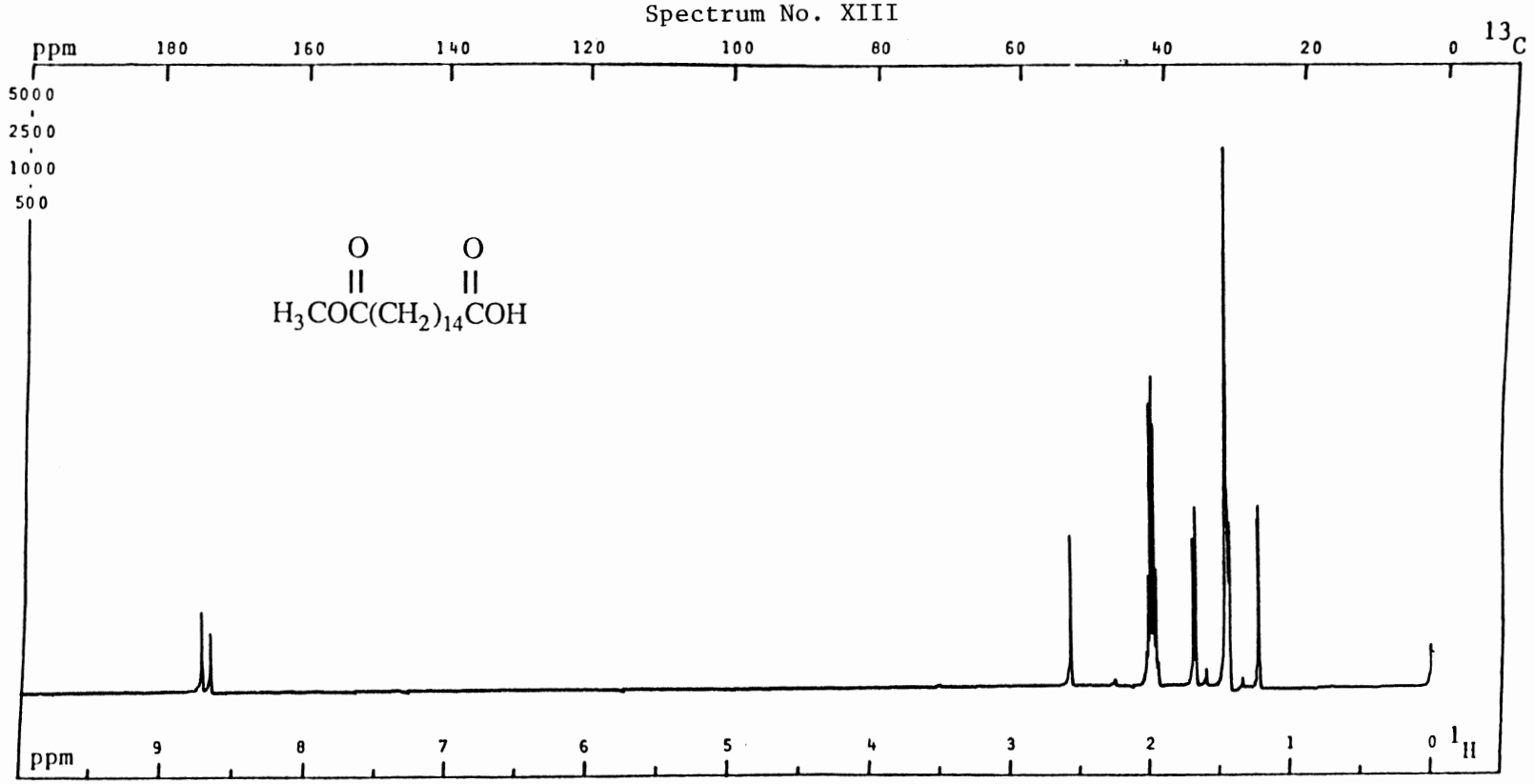
^{1}H NMR Spectrum of Triethylcarbinyl 2-cyclopentanonecarboxylate (96)

PFT X CW _ ; Solvent: $DCCl_3$; SF: 299.944 MHz; WC: 2999.4 Hz; T: RT °C; NT: 40 .

Size: 12 K; PW/RF: 70.0 µs/dB; SO: 0 Hz; FB: NA Hz; Lock: D ; Delay: 0 s.

DC: NA ; Gated Off: NA ; Offset: 0 Hz; RF: 0 W/dB; NBW: NA Hz; LB: 0.5 .

Spectrum No. XIII



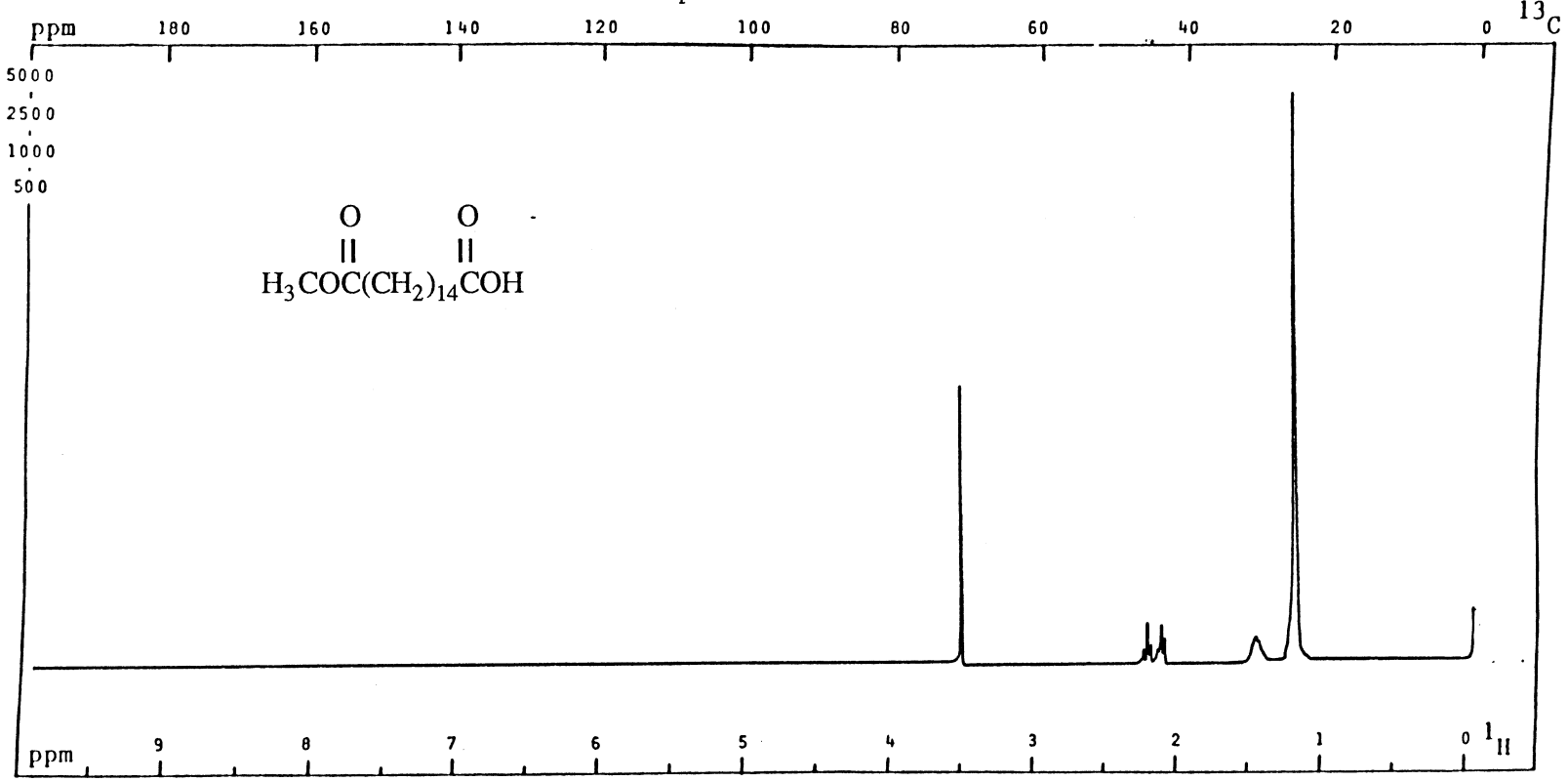
^{13}C NMR Spectrum of Hexadecanedioic acid monomethyl ester (110)

PFT X CW _ ; Solvent: DMSO ; SF: 75.429 MHz; WC: 20000 Hz; T: RT °C; NT: 128 .

Size: 16 K; PW/RF: 12.5 µs/dB; TO: 1000 Hz; FB: NA Hz; Lock: D ;D1,D5: 4.0 s.

DC: Y, N ; Gated Off:A or D ; DO: 0 Hz; RF(Power): 0 W/dB; NBW: 200 Hz; LB: 4.0 Hz.

Spectrum No. XVI



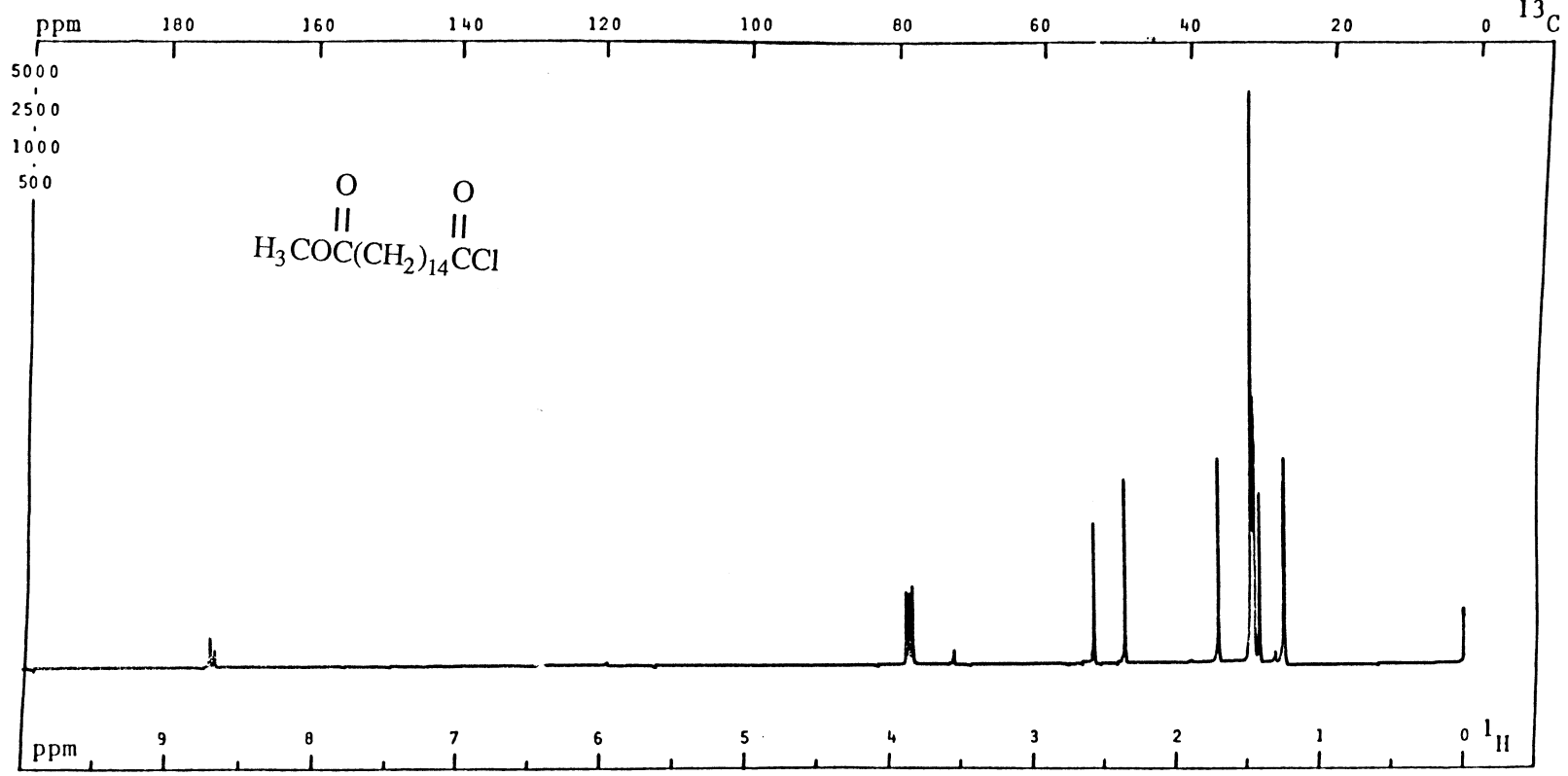
^{1}H NMR Spectrum of Hexadecanedioic acid monomethyl ester (110)

PFT X CW _ ; Solvent: DMSO ; SF: 299.944 MHz; WC: 1540.9 Hz; T: RT °C; NT: 16

Size: 16 K; PW/RF: 5.0 μs/dB; TO: 1500 Hz; FB: NA Hz; Lock: D ; D1,D5: 0 s.

DC: Y, N ; Gated Off: A or D ; DO: 0 Hz; RF(Power): 0 W/dB; NBW: NA Hz; LB: 0 Hz.

Spectrum No. XV



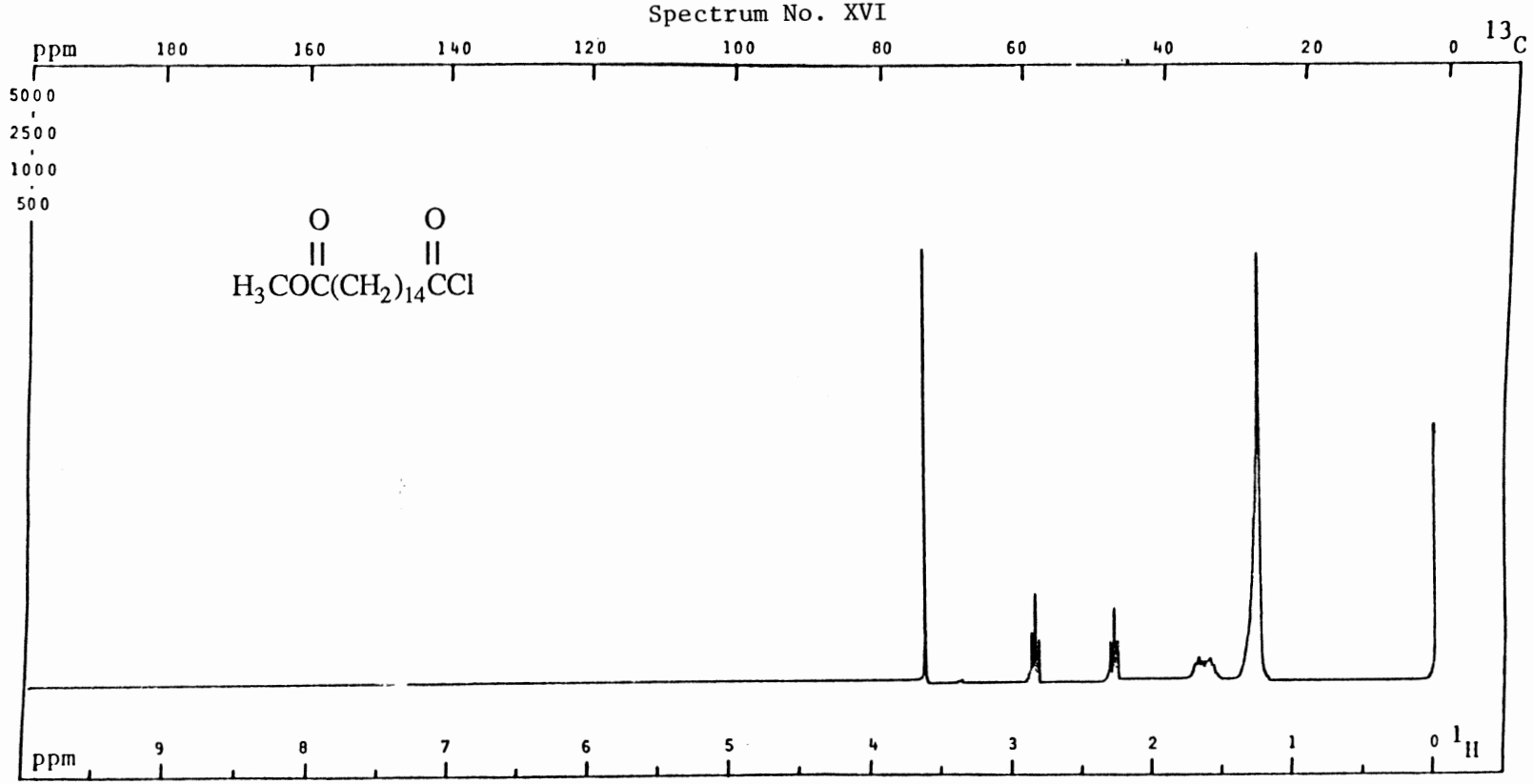
^{13}C NMR Spectrum of Methyl 15-(chloroformyl)-pentadecanoate (125)

PFT X CW _ ; Solvent: $DCCl_3$; SF: 75.429 MHz; WC:15085.9 Hz; T: RT °C; NT: 80

Size: 20 K; PW/RF: 12.5 µs/dB; TO: 1000 Hz; FB: NA Hz; Lock: D ; D1,D5: 4.0 s.

DC: Y, N ; Gated Off:A or D ; DO: 0 Hz; RF(Power): 0 W/dB; NBW: 200 Hz; LB: 2.0 Hz.

Spectrum No. XVI



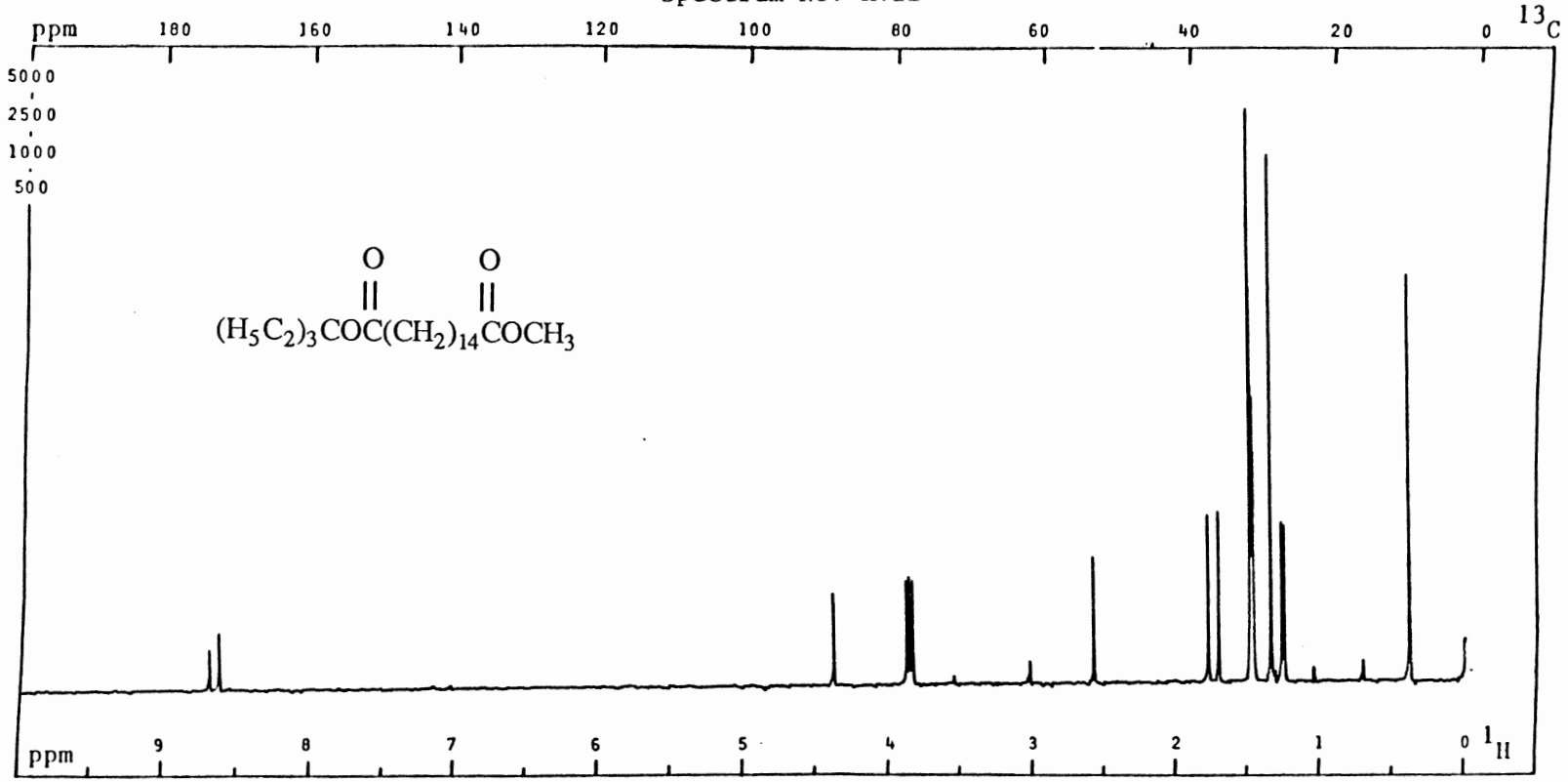
^{1}H NMR Spectrum of Methyl 15-(chloroformyl)-pentadecanoate (125)

PFT X CW _ ; Solvent: $DCCl_3$; SF: 299.944 MHz; WC: 2999.4 Hz; T: RT °C; NT: 16 .

Size: 12 K; PW/RF: 5.0 μs/dB; TO: 0 Hz; FB: NA Hz; Lock: D ;D1,D5: 0 s.

DC: Y, N ; Gated Off:A or D ; DO: 0 Hz; RF(Power): 0 W/dB; NBW: 200 Hz; LB: 0 Hz.

Spectrum No. XVII



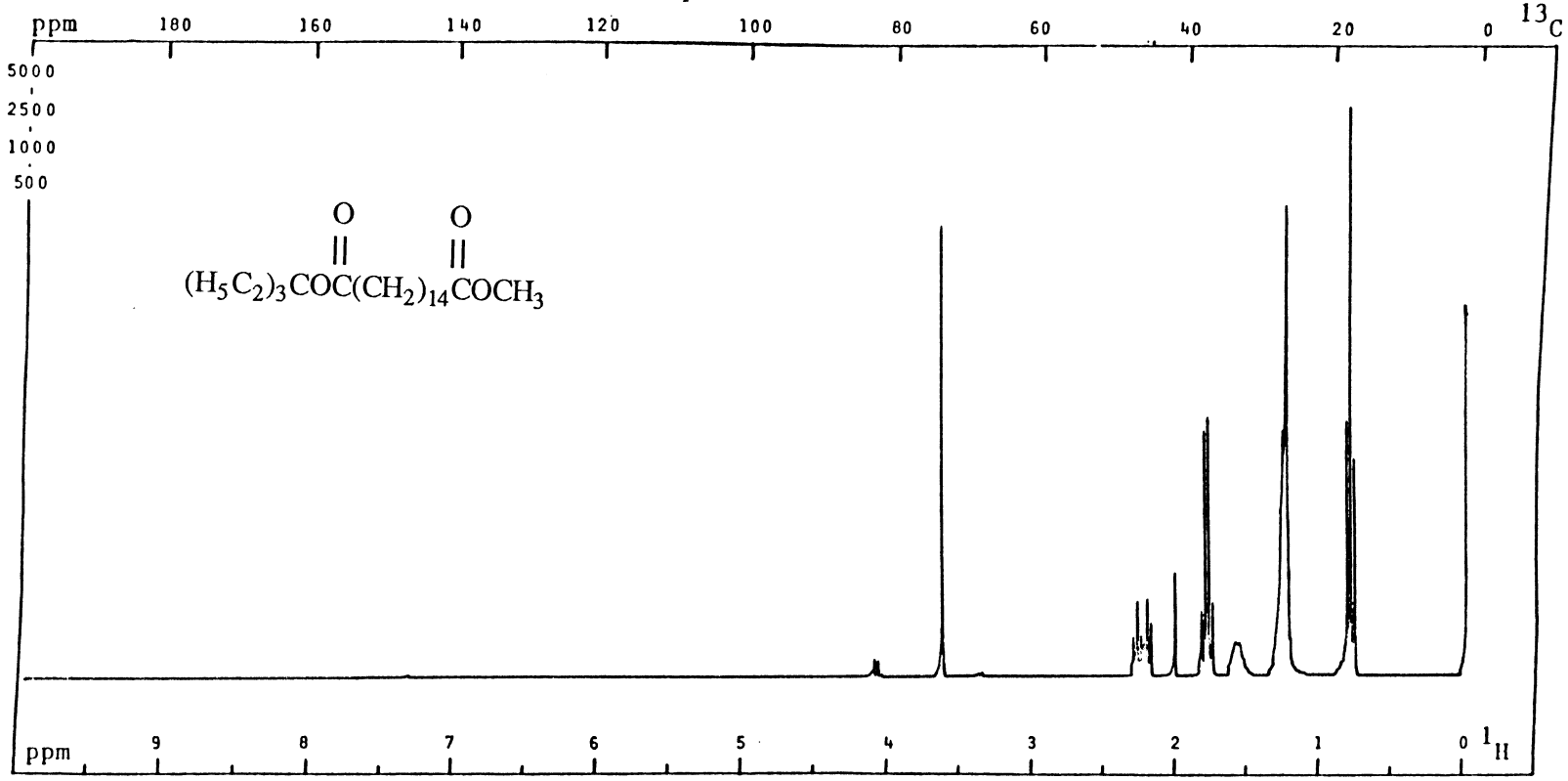
^{13}C NMR Spectrum of Methyl triethylcarbinyl hexadecanedioate (112)

PFT _X_ CW _ ; Solvent: $DCCl_3$; SF: 75.429 MHz; WC: 15085.9 Hz; T: RT °C; NT: 44 .

Size: 20 K; PW/RF: 12.5 µs/dB; TO: 1000 Hz; FB: NA Hz; Lock: D ; D1,D5: 4.0 s.

DC: Y, N ; Gated Off: A or D ; DO: 0 Hz; RF(Power): 0 W/dB; NBW: 200 Hz; LB: 2.0 Hz.

Spectrum No. XVIII



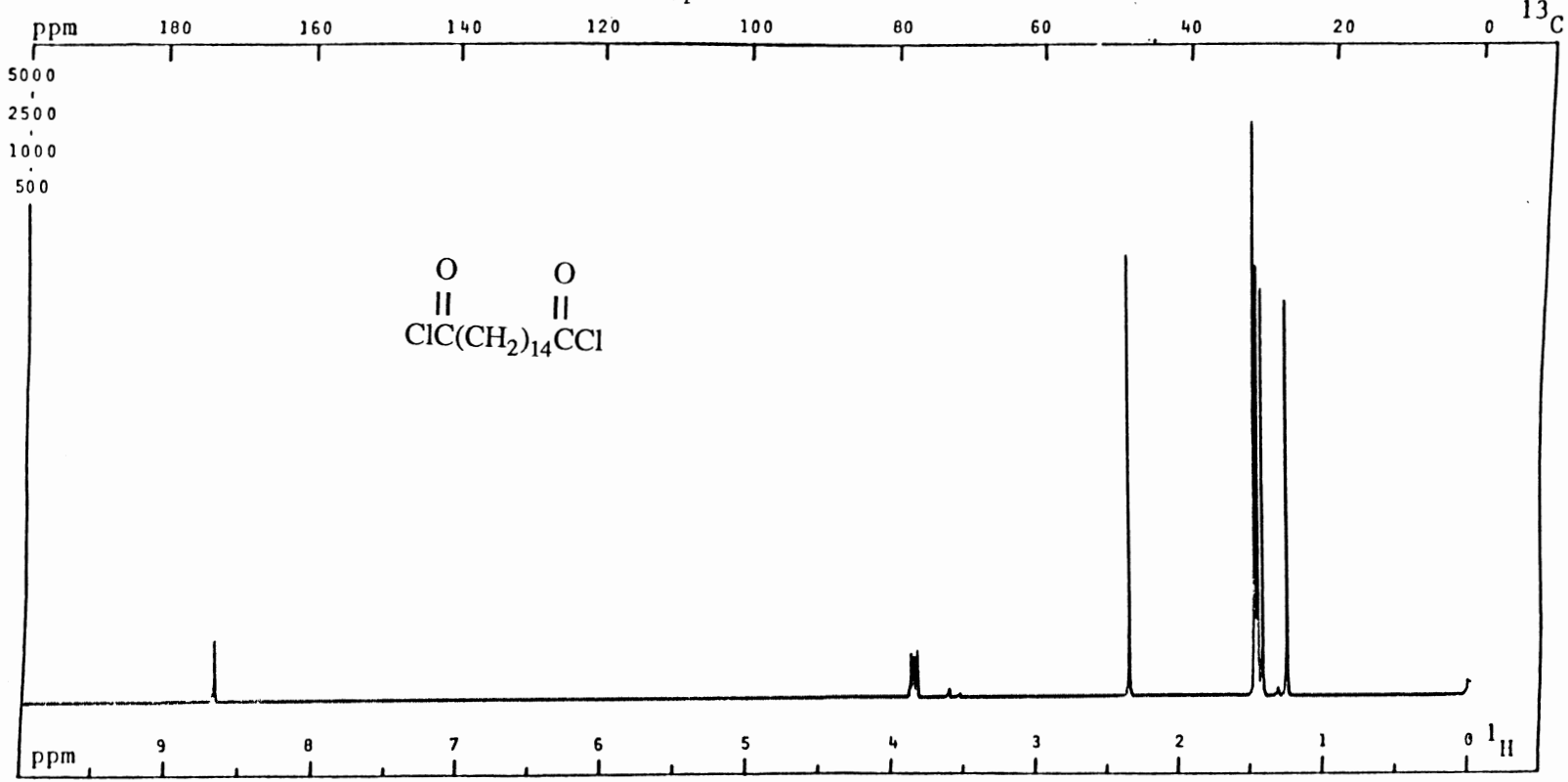
^{1}H NMR Spectrum of Methyl triethylcarbinyl hexadecanedioate (112)

PFT X CW _ ; Solvent: $DCCl_3$; SF: 299.944 MHz; WC: 2999.4 Hz; T: RT °C; NT: 16

Size: 12 K; PW/RF: 5.0 µs/dB; TO: 0 Hz; FB: NA Hz; Lock: D ;D1,D5: 0 s.

DC: Y, N ; Gated Off:A or D ; DO: 0 Hz; RF(Power): 0 W/dB; NBW: 200 Hz; LB: 0 Hz.

Spectrum No. XIX



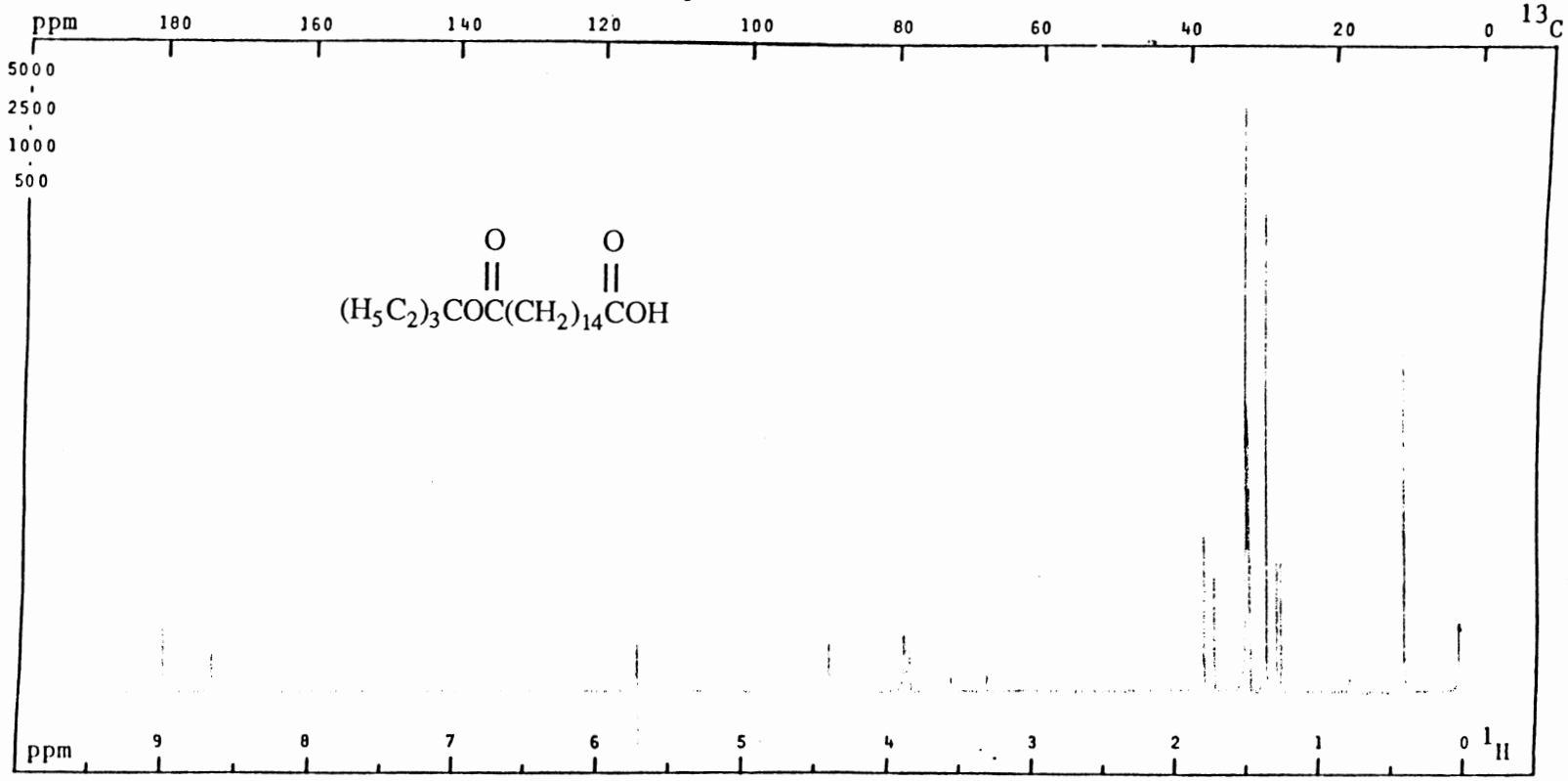
^{13}C NMR Spectrum of Hexadecanedioyl chloride (101)

PFT X CW _ ; Solvent: $DCCl_3$; SF: 75.429 MHz; WC:15085.9 Hz; T: RT °C; NT: 120 .

Size: 20 K; PW/RF: 12.5 µs/dB; TO: 1000 Hz; FB: NA Hz; Lock: D ;D1,D5: 4.0 s.

DC: Y, N ; Gated Off:A or D ; DO: 0 Hz; RF(Power): 0 W/dB; NBW: 200 Hz; LB: 0 Hz.

Spectrum No. XX



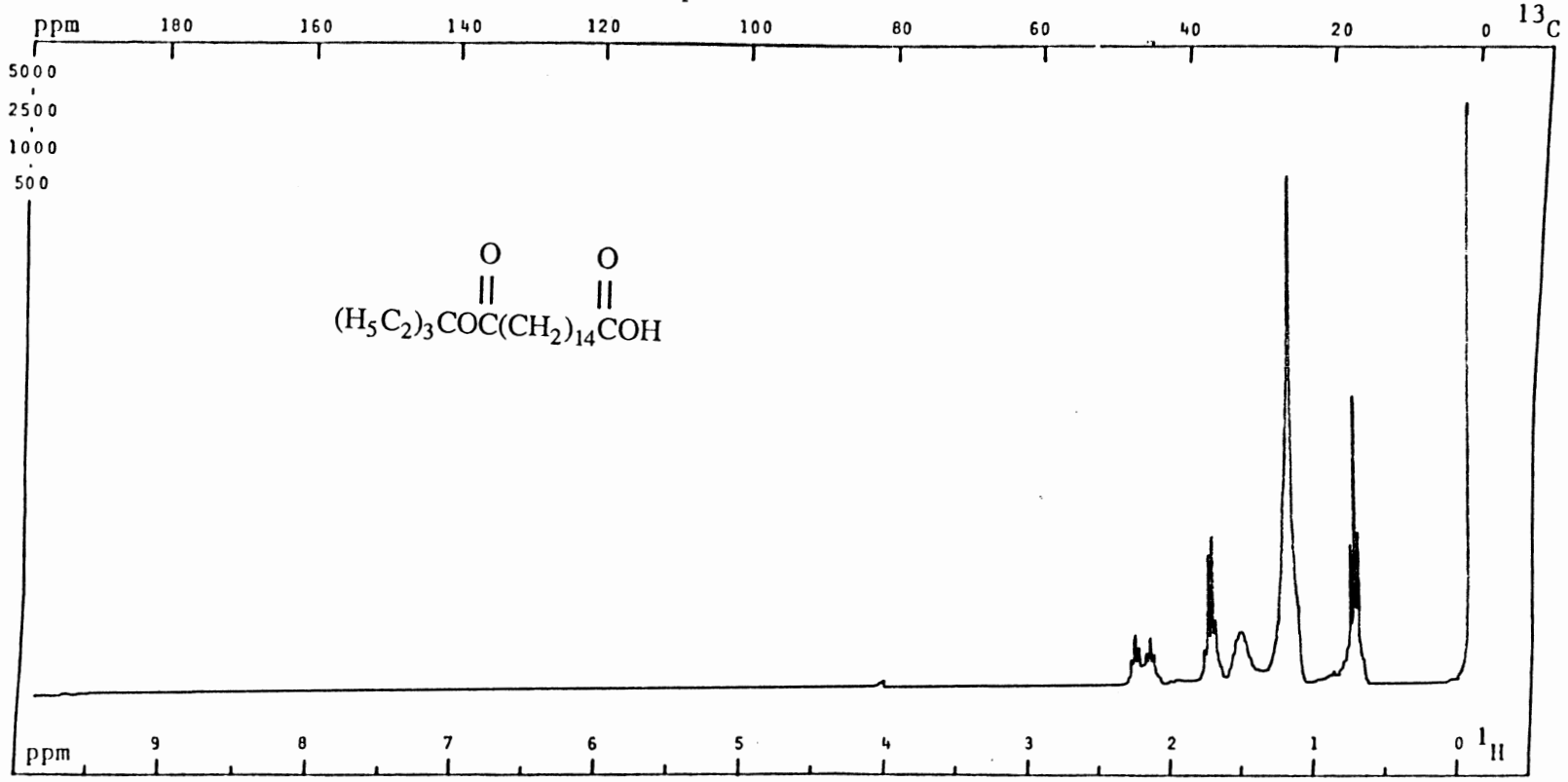
^{13}C NMR Spectrum of Hexadecanoic acid monotriethylcarbinyl ester (102b)

PFT X CW _ ; Solvent: $DCCl_3$; SF: 75.429 MHz; WC: 15085.9 Hz; T: RT °C; NT: 64

Size: 16 K; PW/RF: 14.0 µs/dB; TO: 1000 Hz; FB: NA Hz; Lock: D ; D1,D5: 4.0 s.

DC: Y, N ; Gated Off: A or D ; DO: 0 Hz; RF(Power): 0 W/dB; NBW: 200 Hz; LB: 2.0 Hz.

Spectrum No. XXI



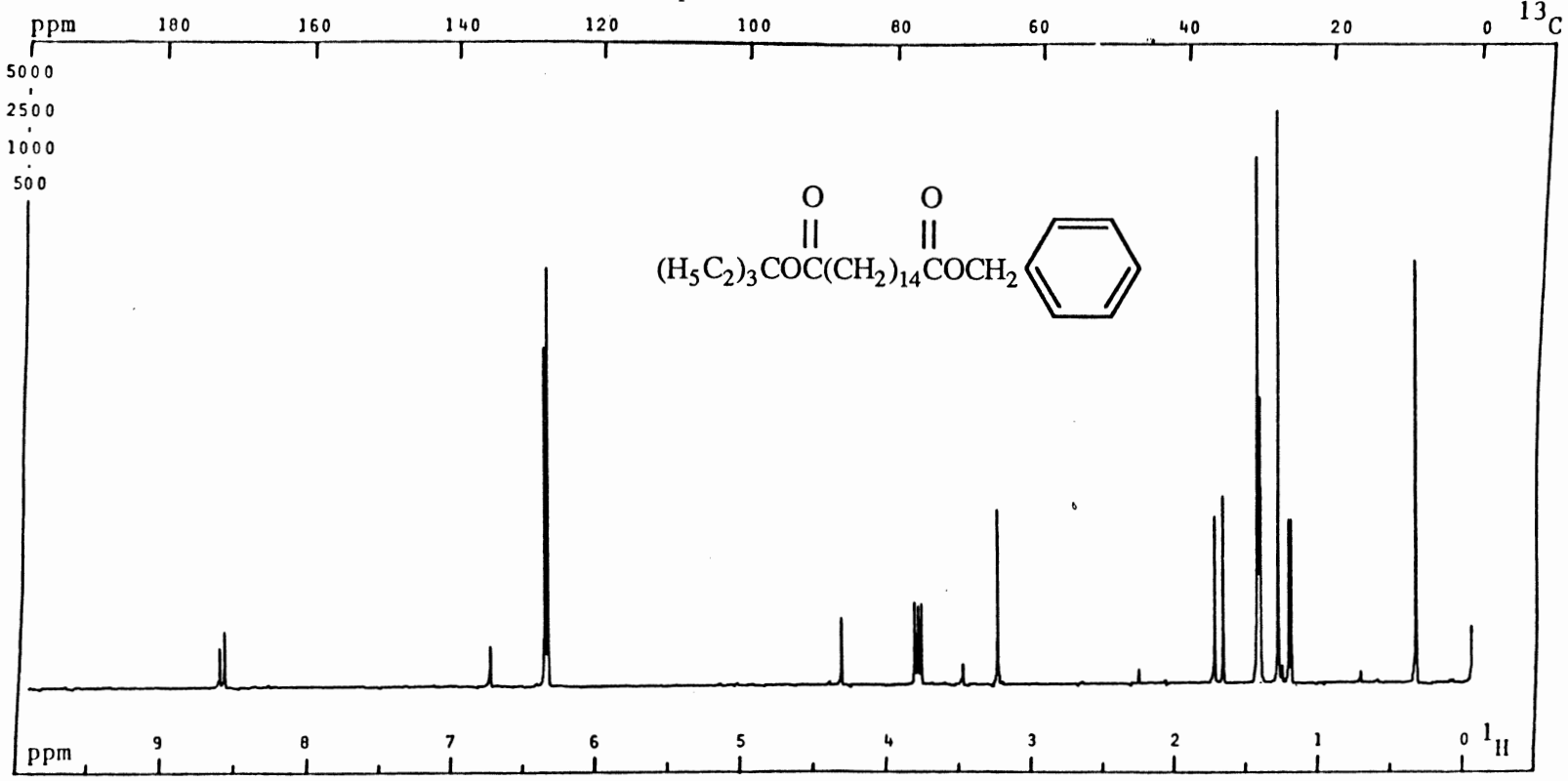
^{1}H NMR Spectrum of Hexadecanedioic acid monotriethylcarbinyl ester (102b)

PFT X CW _ ; Solvent: $DCCl_3$; SF: 299.944 MHz; WC: 2999.4 Hz; T: RT °C; NT: 8 .

Size: 8 K; PW/RF: 5.0 µs/dB; TO: 0 Hz; FB: NA Hz; Lock: D ; D1,D5: 0.5 s.

DC: Y, N ; Gated Off:A or D ; DO: 0 Hz; RF(Power): 0 W/dB; NBW: 200 Hz; LB: 0.5 Hz.

Spectrum No. XXII



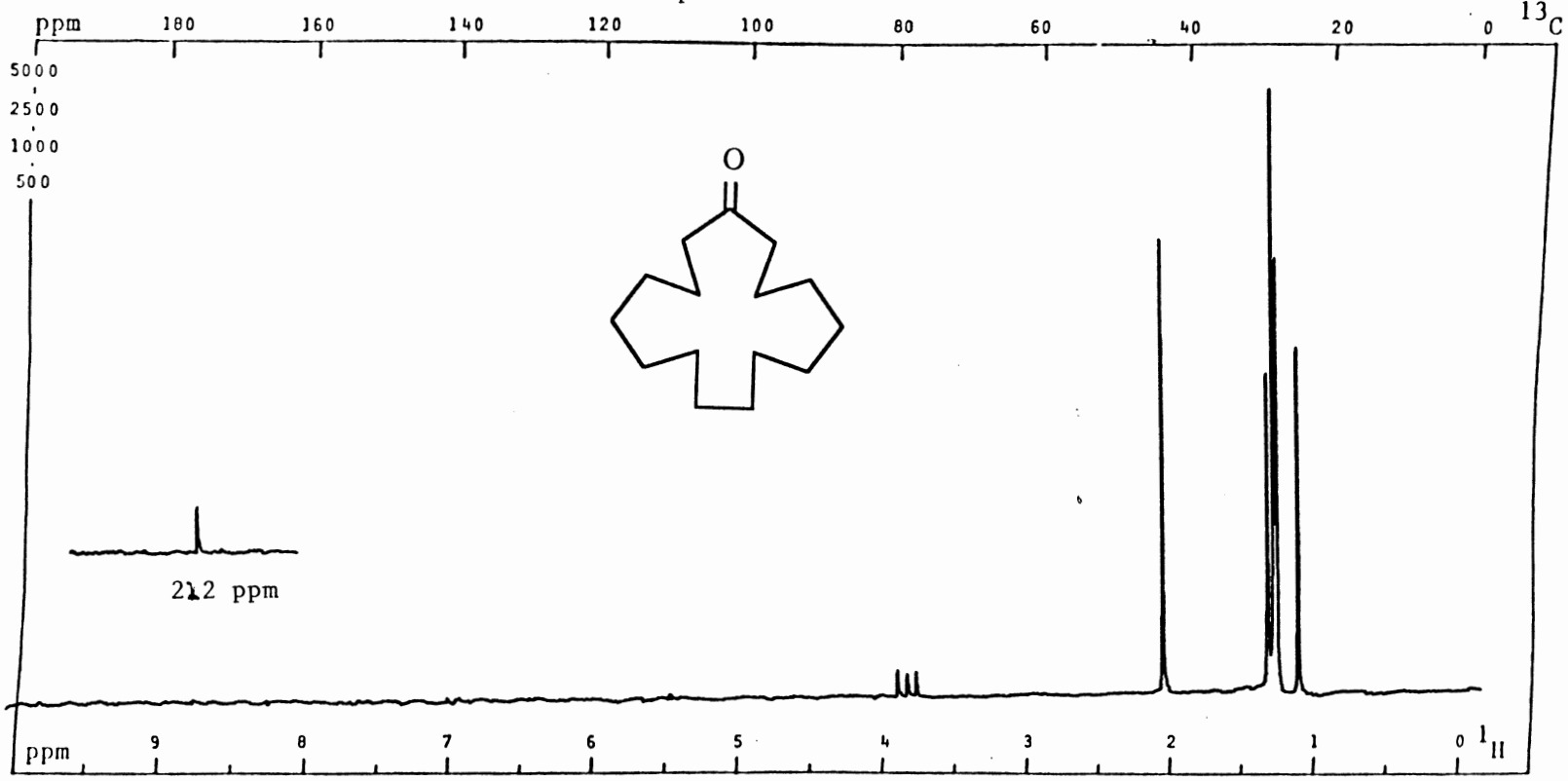
^{13}C NMR Spectrum of Benzyl triethylcarbinyl hexadecanedioate (114)

PFT _X_ CW _ ; Solvent: $DCCl_3$; SF: 75.429 MHz; WC: 15085.9 Hz; T: RT °C; NT: 60

Size: 20 K; PW/RF: 12.5 µs/dB; TO: 1000 Hz; FB: NA Hz; Lock: D ; D1,D5: 4.0 s.

DC: Y, N ; Gated Off: A or D ; DO: 0 Hz; RF(Power): 0 W/dB; NBW: 200 Hz; LB: 1.5 Hz.

Spectrum No. XXIII



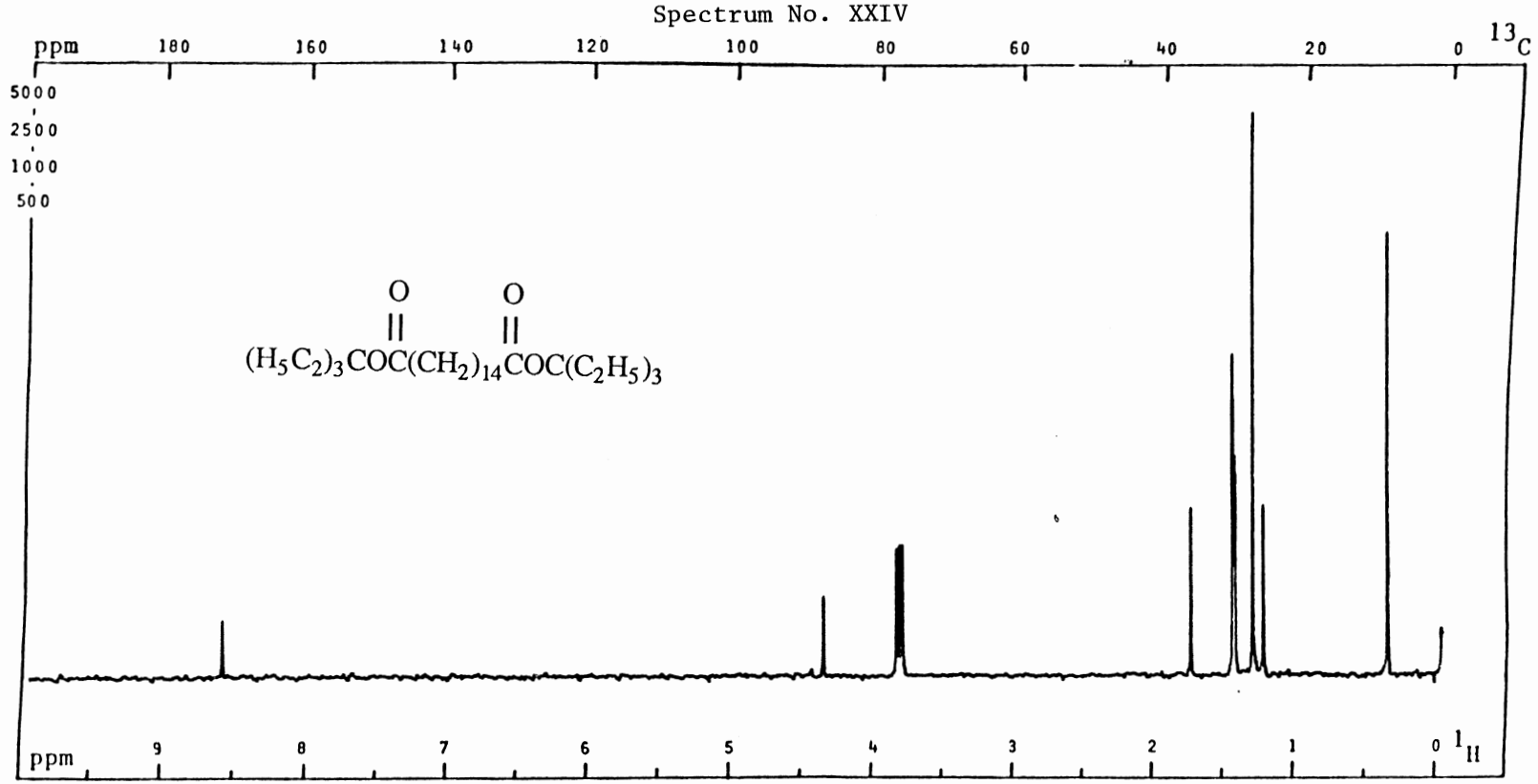
^{13}C NMR Spectrum of Cyclopentadecanone (116)

PFT X CW _ ; Solvent: $DCCl_3$; SF: 25.2 MHz; WC: 3012.4 Hz; T: RT °C; NT: 1000

Size: 8.2K; PW/RF: 20.0 µs/dB; TO: NA Hz; FB: NA Hz; Lock: D ; D1,D5: 4.0 s.

DC: Y, N ; Gated Off: A or D ; DO: NA Hz; RF(Power): NA W/dB; NBW: NA Hz; LB: 0 Hz.

Spectrum No. XXIV



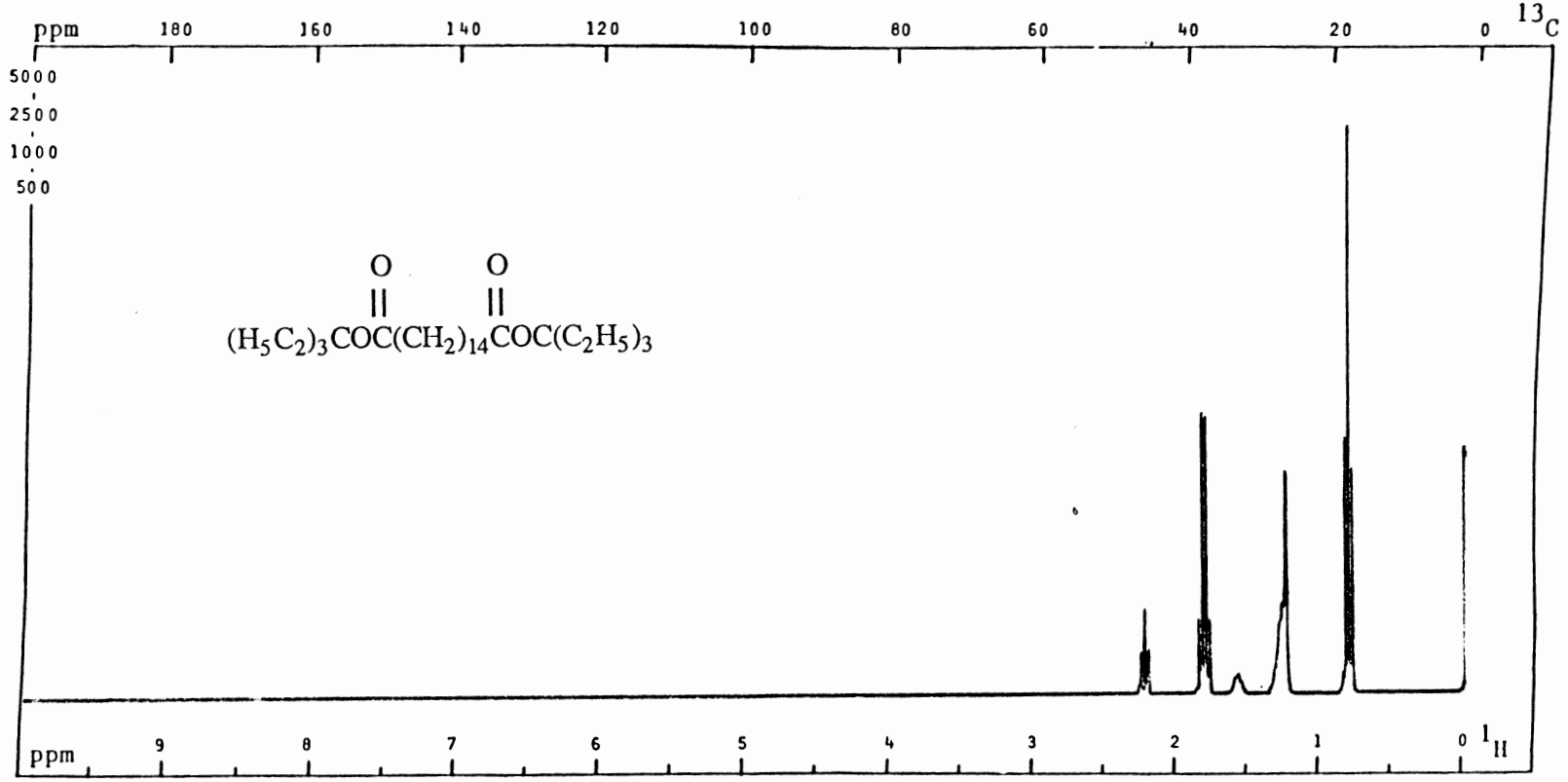
^{13}C NMR Spectrum of Di(triethylcarbinyl)Hexadecanedioate (103)

PFT _X_ CW _ ; Solvent: $DCCl_3$; SF: 75.429 MHz; WC:15085.9 Hz; T: RT °C; NT: 40 .

Size: 20 K; PW/RF: 12.5 µs/dB; TO: 1000 Hz; FB: NA Hz; Lock: D ;D1,D5: 4.0 s.

DC: Y, N ; Gated Off:A or D ; DO: 0 Hz; RF(Power): 0 W/dB; NBW:200 Hz; LB: 3.0 Hz.

Spectrum No. XXV



^{1}H NMR Spectrum of Di(triethylcarbinyl)Hexadecanedioate (103)

PFT X CW _ ; Solvent: $DCCl_3$; SF: 299.944 MHz; WC: 2999.4 Hz; T: RT °C; NT: 16 .

Size: 12 K; PW/RF: 100 µs/dB; TO: 0 Hz; FB: NA Hz; Lock: D ; D1,D5: 0 s.

DC: Y, N ; Gated Off: A or D ; DO: 0 Hz; RF(Power): 0 W/dB; NBW: 200 Hz; LB: 0 Hz.

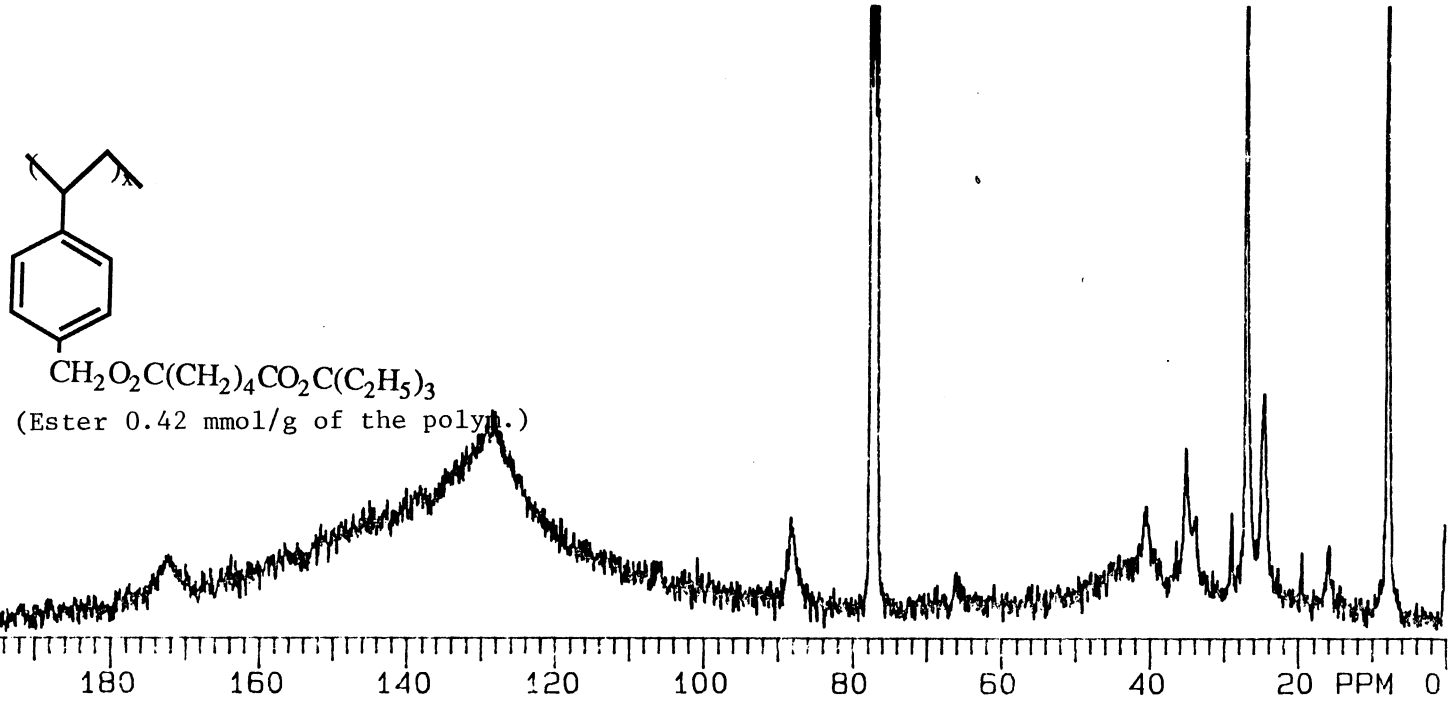
Spectrum No. XXVI

^{13}C NMR Spectrum of Triethylcarbinyl (4-Polystyrylmethyl) Adipate (94)

NT 40000 Size 20 K

D1 5.0 sec AT 0.2 sec

PW 10.0



$CH_2O_2C(CH_2)_4CO_2C(C_2H_5)_3$

(Ester 0.42 mmol/g of the polym.)

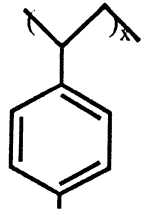
Spectrum No. XXVII

^{13}C NMR Spectrum of Triethylcarbinyl (4-Polystyrylmethyl) Hexadecanedioate (115)

NT 5000 Size 20 K

D1 5.0 sec AT 0.01

PW 17.5



$CH_2O_2C(CH_2)_{14}CO_2C(C_2H_5)_3$

(Ester 0.31 mmol/g of the polym.)

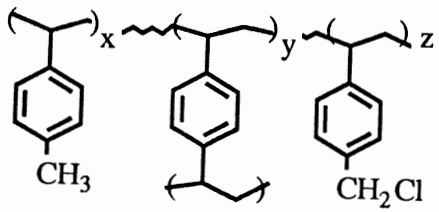
NT 1000 Size 40 K

D1 6.0 sec AT 1.0 sec

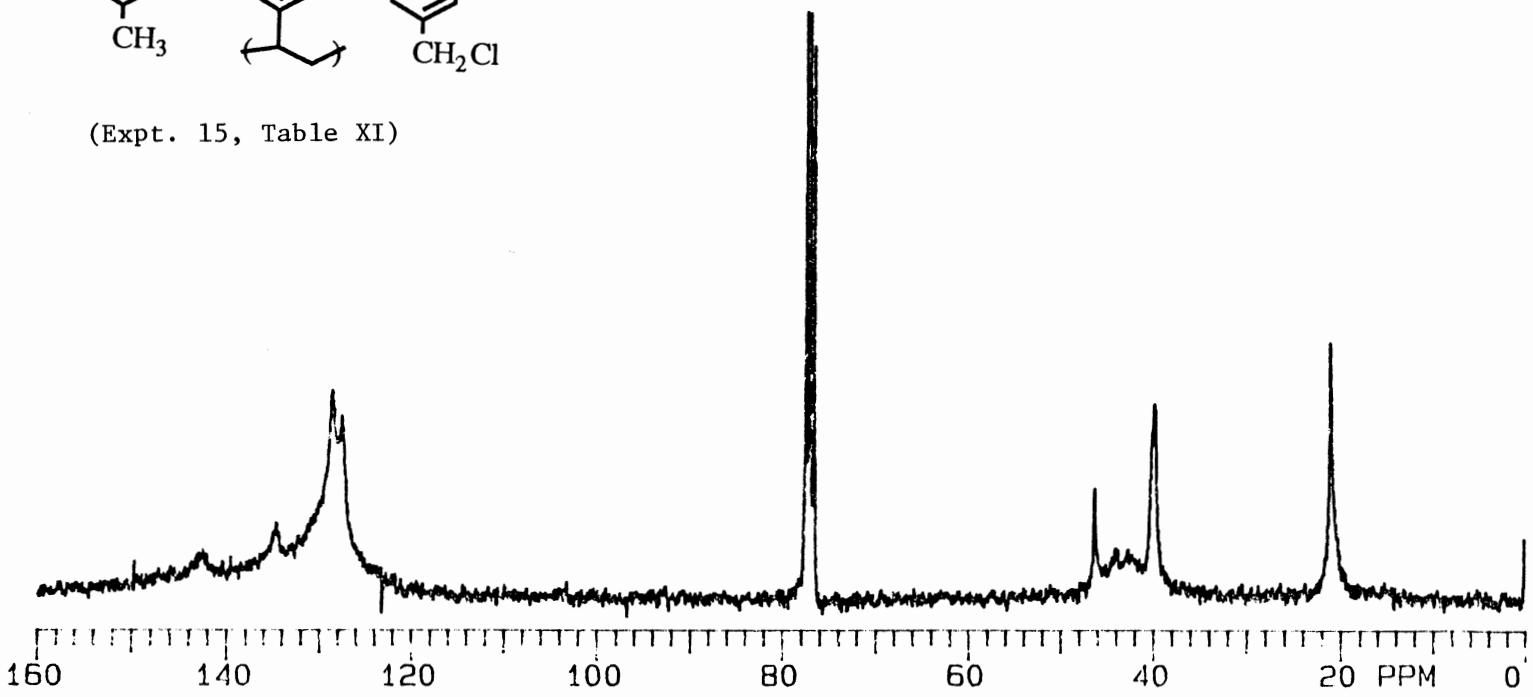
PW 18.0

Spectrum No. XXVIII

^{13}C NMR Spectrum of Chlorinated Poly(p-Methylstyrene) (71)



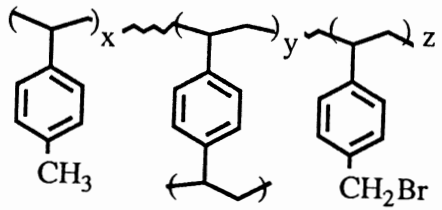
(Expt. 15, Table XI)



Spectrum No. XXIX

NT 1008 size 30 K
D1 3.0 sec AT 0.5 sec
PW 55°(10.0 μsec.)

^{13}C NMR Spectrum of Brominated Poly(p-Methylstyrene) (117)

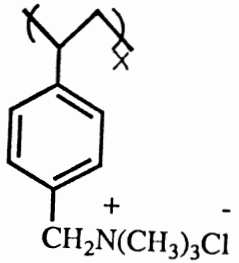


(Expt. 3, Table XII)

NT 2360 size 4K
D1 1.0 sec AT 0.101 sec
PW 67° (12.0 μsec)

Spectrum No. XXX

^{13}C NMR Spectrum of (Polystyrylmethyl)trimethylammonium Chloride (118)

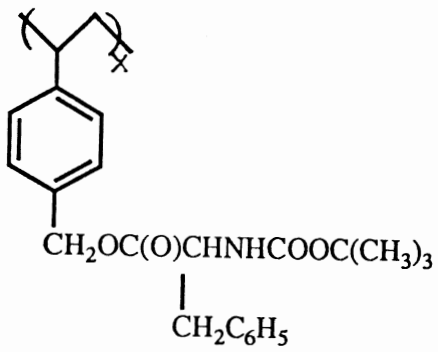


(Expt. 10, Table XIII)

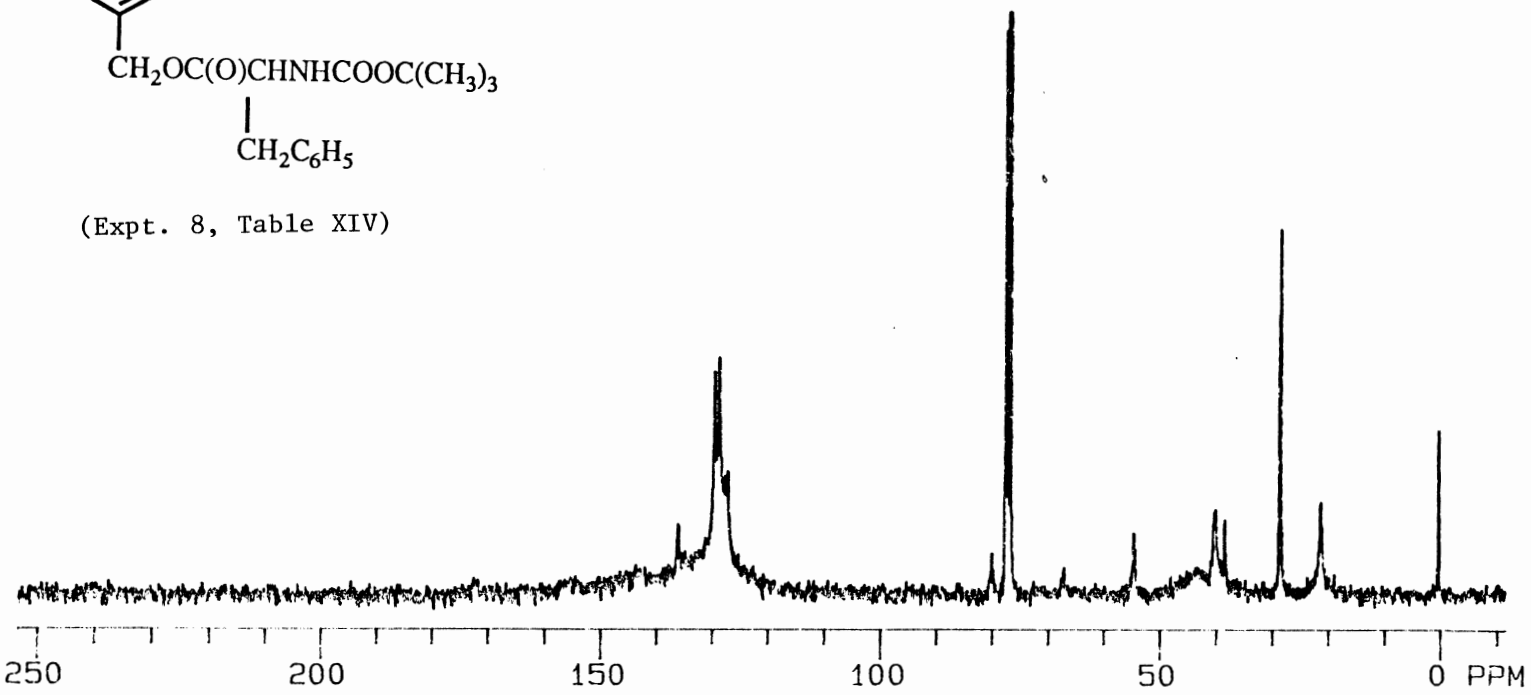
NT 1008 size 40 K
D1 6.0 sec AT 1.0 sec
PW 89°(16.0 μsec.)

Spectrum No. XXXI

^{13}C NMR Spectrum of Boc- L-Phenylalanine Resin (123)



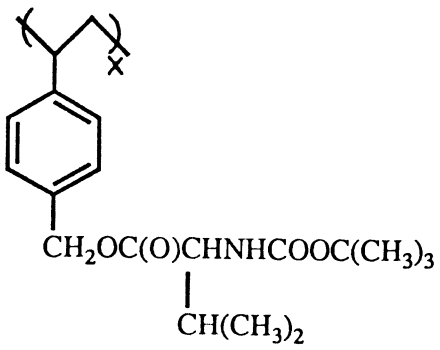
(Expt. 8, Table XIV)



Spectrum No. XXXII

NT 1024 size 4 K
D1 4.0 sec AT 0.101 sec
PW 55°(10.0 μsec)

^{13}C NMR Spectrum of Boc-L-Valine Resin (124)



(Expt. 7, Table XIV)

VITA

Altaf Ellahi Qureshi

Candidate for the Degree of

Doctor of Philosophy

Thesis : DIECKMANN CYCLIZATIONS USING SOLID-SUPPORTS AND HALOGENATION OF POLY(*P*-METHYLSTYRENE)

Major Field : Chemistry

Biographical :

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Professional Experience : Teaching Assistant, Department of Chemistry, Oklahoma State University, August, 1983 to May 1984. Research Assistant, Department of Chemistry, Oklahoma State University, June 1984 to May, 1988.