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SUBSTITUENT MODIFICATION IN TRI-O-THYMOTIDE AND ITS EFFECTS ON HOST GEOMETRY AND GUEST ENCLATHRATION .1. SYNTHESIS[■,1]

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Abstract – A new synthesis is described for the preparation of tri-o-thymotide (1, TOT) and some TOT analogues. The methodology is based on the sequential coupling of appropriately substituted and protected salicylic acid monomers followed by cyclization of the deprotected open-chain trimers. A variety of protecting methodologies and coupling sequences are discussed. The procedure seems generally applicable for the preparation of salicylides and has been used to prepare TOT in 25% overall yield (for the coupling-deprotection-coupling-deprotection-cyclization sequence). In addition, two new modified TOT-analogues 9 (25%), and 10 (14%) were prepared in which the isopropyl group(s) ortho to the phenolic units in TOT is replaced by one (9) or two (10) ethyl groups. A third analogue 66, where the methyl group ortho to the carboxyl group is removed in one of the salicylic acid monomer units of TOT, requires only the last cyclization step for completion of its synthesis. This methodology represents an important breakthrough for the controlled preparation of selected thymotide (salicylide) trimers and allows easy access to a variety of modified thymotides (salicylides) for structural, conformational and host-guest studies.

INTRODUCTION

Clathrate inclusion complexes, where guest molecules are encapsulated in cavities generated by the packing arrangement of crystalline hosts, have been known for many years.[2,3] These complexes have generated significant interest recently because they provide useful systems for studying biochemical phenomena[4,5] and controlled chemistry in the solid state.[6,7,8]

Among the many known hosts[9,10] (which include ureas, perhydrotriphenylene, cyclotriveratrylene, salicylides, thymotides, anthranilides, deoxycholeic acid, cyclodextrins, crown ethers, cryptates and cyclophanes) tri-o-thymotide (TOT, 1) is unique in a number of ways. TOT complexes with a greater number, and larger variety of guests than most hosts. More than one hundred TOT clathrates are known in which the encapsulated guests are linear, globular and planar in shape. The guests vary in size from 5-20 Å or more and contain halogen, ether, ester, ketone, alcohol and olefin functionality on their hydrocarbon framework.[11,12]

TOT also forms a variety of clathrate structural forms which are greater in diversity than any other known host. In addition to the trigonal cage[13,14] and hexagonal channel types,[14] there are triclinic[15] and monoclinic forms[11] which are all different from the orthorhombic form in which uncomplexed TOT crystallizes. Other clathrate types have also been recognized.[16-21] In addition, although TOT does not possess a chiral atom the molecule has a chiral propeller

■Dedicated to Professor Saul G. Cohen

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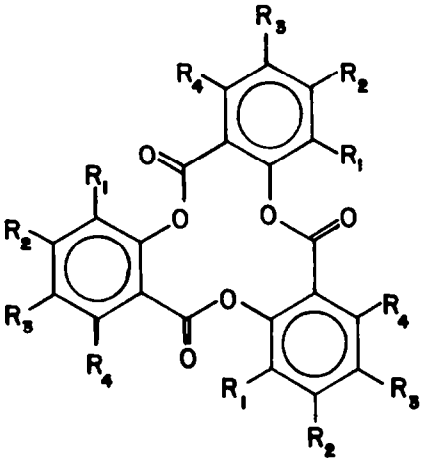
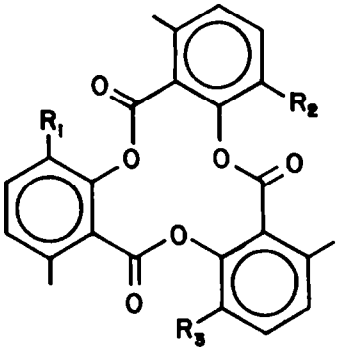
shape in solution[22-24] and in the solid state.[25] This allows for chiral discrimination of host and guest during enclathration. Thus, while uncomplexed TOT crystals are racemic,[21] most of the known TOT clathrates are chiral[24] where, within a given crystal, only one of the two enantiomeric propeller forms of TOT is present. This spontaneous resolution of TOT has been demonstrated using a large variety of non-chiral guests.[11] When TOT is crystallized from chiral guest solutions, one guest enantiomer is included preferentially in a given crystal[21] where again only one of the two enantiomeric propeller forms of TOT is present.



	R_1	R_2	R_3	R_4
1	i-Pr	H	H	Me
2	H	H	H	H
3	Me	H	H	H
4	H	Me	H	H
5	H	H	Me	H
6	Me	H	H	Me
7	H	i-Pr	H	Me
8	Me	H	H	i-Pr



	R_1	R_2	R_3
9	i-Pr	i-Pr	Et
10	i-Pr	Et	Et
11	Et	Et	Et

Though many TOT clathrates are known, little is understood concerning why TOT is such a unique host. Thus, while trimers of salicylic acid[27] and o-, m- and p-cresotic acids[28] are known (compounds 2, 3, 4, and 5), none except tri-p-cresotide (6) seems to be capable of forming a clathrate and in this case it is questionable whether a complex is formed at all.[28] In addition, trimers of 4-isopropyl-6-methyl salicylic acid (7) and 6-isopropyl-3-methyl salicylic acid (carvacrotic acid) (8),[29] where the isopropyl group (relative to that in TOT) is removed from the position ortho to the phenolic unit or where the methyl and isopropyl units are interchanged, do not form any complexes whatsoever. Furthermore, thio-analogues of salicylides and cresotides also do not form clathrates,[30,31] and while some anthranilids do,[32-34] they do not form complexes with the diversity that TOT does. That these relatively minor changes in the gross structural features of TOT should have such a dramatic effect on the clathration properties of TOT begs the search for the basis of the unique clathrating characteristics of this molecule. Though the propellar and helical conformations of these trimers[32] are important structural features, which no doubt play an important role in its clathration properties, conformational characteristics of the host alone cannot account for the unique clathrating properties of TOT.

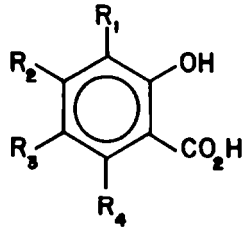
Crystal structure analyses of a number of the TOT cage clathrates have revealed considerable detail of the host-host, as well as host-guest interactions.[16-21] In general, the guest is surrounded by six host molecules,[35] and it has been observed that the TOT-TOT

interactions are all weak, i.e., there are no excessively short intermolecular contacts. Of special interest is the fact that not all of the six methyl units of the three isopropyl groups on each TOT are involved in host-host interactions. A single methyl unit of one isopropyl group is clearly directed into the interior of the cage-cavity. This suggests that removal of this methyl unit, as observed in molecule 9, would provide a new potential host with TOT-type characteristics, but one having a considerably enlarged cavity volume. The removal of two methyl groups, to give the new potential host 10 might also have sufficient similarity to TOT to form clathrates. The potential host 11, though of interest, may possess too few of the host-host interacting units, and may not form clathrates.

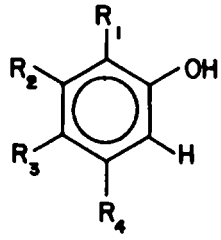
In view of the fact that substituent changes or positional changes on the salicylide ring units in TOT have such a dramatic effect on its clathration properties, and in view of the fact that the isopropyl unit in TOT plays such an important role in crystal packing, we embarked on a study of defining the effects of substituent modification on the clathration properties of TOT. Herein we report on the first phase of our work,i.e., the development of a general synthetic strategy for the preparation of modified TOT trimers. This strategy involves building open-chain dimers and then trimers by coupling appropriately protected and activated monomeric and dimeric salicylide units followed by deprotection and cyclization. Though for the present our focus is on the modification of the isopropyl group(s) in TOT, the methodology should be general and useful for preparing tri-salicylide structures with a variety of functionality anywhere on the aromatic rings and even for the preparation of analogues containing aromatic units based on ring systems other than benzene. The ability to prepare new molecules, based on the structural motif of the unique TOT host, should provide a greater diversity of TOT host structural types which will greatly advance the understanding of the clathration properties of TOT and its analogues along with affording the potential of providing new and perhaps better and more versatile host structures.

RESULTS

In order to be able to define some important parameters associated with enclathration, it is necessary to prepare analogues of TOT in which one, two or three of the isopropyl groups, and/or one, two or three of the methyl groups are modified or replaced by other groups. Tri-salicylide (2) tri-cresotides (3-5) and TOT (1) have previously been prepared by cyclodehydration of the respective salicylic (12), cresotic (13-15) and thymotic (16) acids in the presence of a variety of dehydrating agents like thionyl chloride or phosphorous oxychloride.[27-29]



	R_1	R_2	R_3	R_4
12	H	H	H	H
13	Me	H	H	H
14	H	Me	H	H
15	H	H	Me	H
16	i-Pr	H	H	Me
17	i-Pr	H	H	H
18	Et	H	H	Me

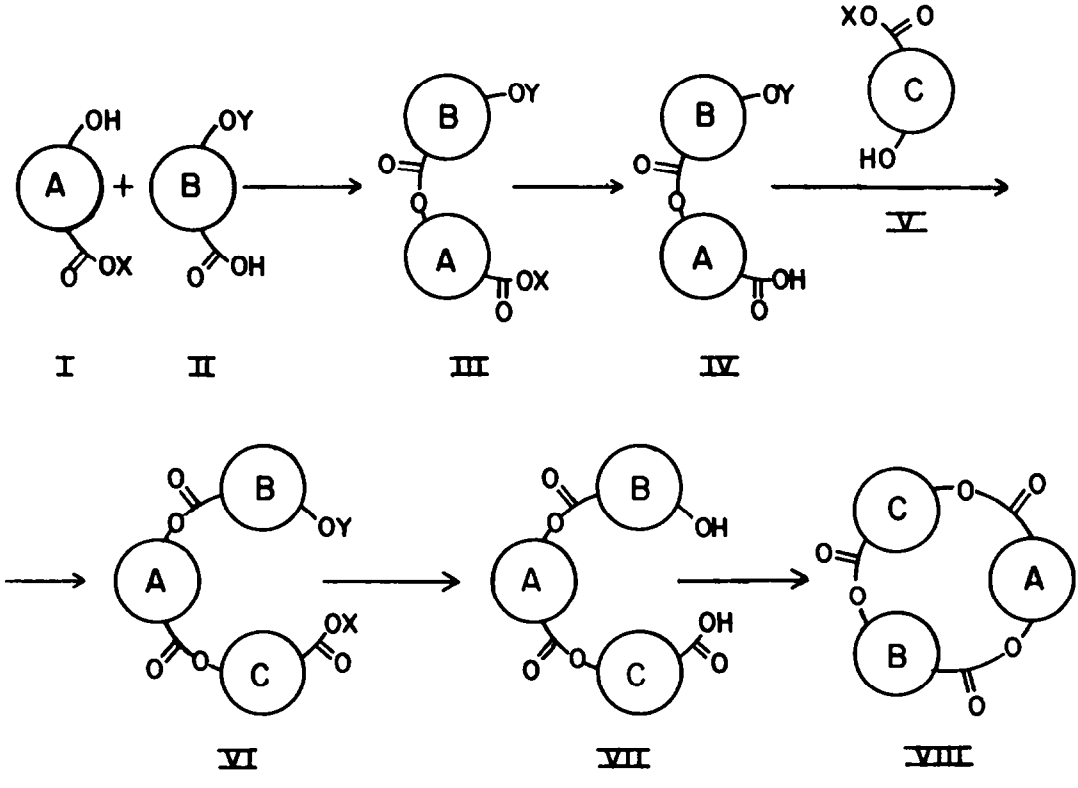


	R_1	R_2	R_3	R_4
19	i-Pr	H	H	Me
20	i-Pr	H	H	H
21	Et	H	H	Me

This method, however, suffers from a number of drawbacks. First, cyclic and acyclic dimers, tetramers, hexamers and higher oligomers, in addition to the cyclic trimers, are produced in the reaction, requiring lengthy and tedious purification steps. Second, under the reaction conditions ($POCl_3$; Δ) cyclic trimers are not completely stable and are easily converted to tetramers and hexamers, and decarboxylated products reducing the yield of trimer.[27] Third, the classical cyclodehydration method is only applicable to the preparation of tri-salicylide analogues having identical salicylide units. Trimerization of a mixture of different substituted salicylic acids would result in a very complex mixture of products, and such a synthesis would be almost useless from a preparative standpoint for specific analogues.

The synthesis of mixed tri-salicylide analogues, where one or more of the salicylic acid units is different (e.g. 13 or 14), therefore requires a multistep approach in which appropriately substituted and protected salicylic acid units are added to a growing chain one at a time. The open-chain trimer thus prepared can give rise to specific cyclic-trimers and when carried out with the proper dilution techniques should give increased yields of the desired trimer because of the intramolecular nature of the ring closure reaction.

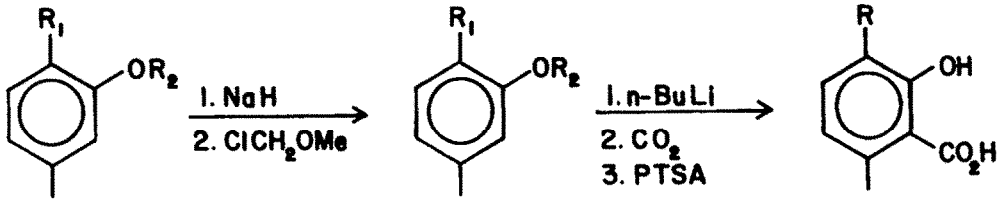
The general strategy is given broadly in Scheme 1 where X and Y represent appropriate phenolic and carboxylic protecting groups. Thus, coupling appropriately protected salicylic acid units I and II should give rise to a diprotected open-chain dimer III. After selective deprotection of III, (which can theoretically be done in two ways), dimer IV can be coupled with an appropriately protected salicylic acid unit V giving rise to the diprotected open-chain trimer VI. Deprotection of VI and cyclodehydration of VII should generate cyclic trimer VIII. A similar stepwise sequence has been reported by Ollis et al.[23,36-38] for the preparation of a variety of tri-anthranilides, but the sequence was used to prepare tri-amides only, where all three anthranilic acid units were identical.



SCHEME 1

Preparation of Substituted Salicylic Acids

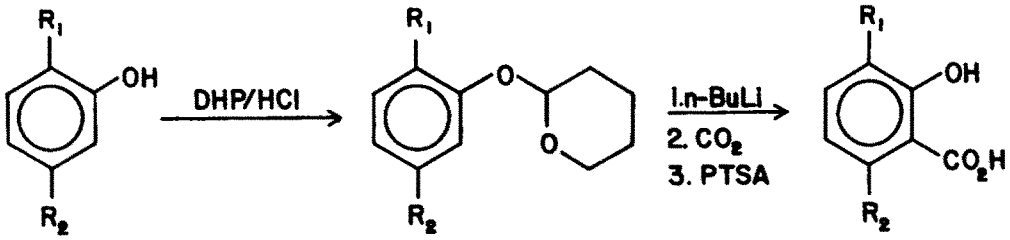
Carboxylation of thymol (19) and 2-ethyl-5-methylphenol (21) by the Kolbe method gave poor yields (< 30%) of the corresponding acids (16 and 18, respectively). Since modified salicylic acids would be used as the basic building unit for the trimers, a good and efficient source of the former was necessary. We therefore attempted to improve the carboxylation of the phenols by using modern methodologies involving directed metallation[39] (protection of the phenol, metallation ortho to the protected phenol, carboxylation and deprotection). Initially the methoxymethyl group ($MeOCH_2$-) was used. Thymol (19) and 2-ethyl-5-methylphenol (21) were converted to the corresponding methoxymethyl phenyl ethers 19a and 21a (> 80%) as shown in Scheme 2. Lithiation with n-butyl lithium followed by quenching afforded the lithium carboxylates. These were hydrolyzed with acid giving thymotic acid (16; 57%) and 3-ethyl-6-methyl salicylic acid (18; 38%). Though the yields of the acids in these sequences varied widely, they were superior to those observed in the Kolbe reaction. Because of the above and since chloromethyl methyl ether is carcinogenic and expensive, we also tested the tetrahydropyranyl (THP) group for protecting and directing abilities.



	R_1	R_2		R_1	R_2		R
19	i-Pr	H	19a	i-Pr	CH_2OMe	16	i-Pr
21	Et	H	21a	Et	CH_2OMe	18	Et

SCHEME 2

The THP ether of thymol (22) was readily prepared by treating thymol with dihydropyran (DHP) in acidified ethyl acetate as described in Scheme 3.



	R_1	R_2		R_1	R_2		R_1	R_2
19	i-Pr	Me	22	i-Pr	Me	16	i-Pr	Me
20	i-Pr	H	23	i-Pr	H	17	i-Pr	H

SCHEME 3

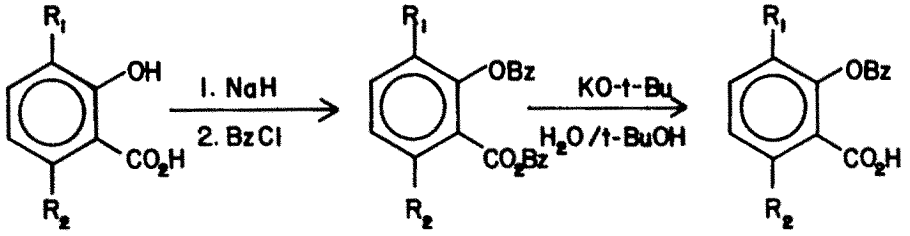
Though purification of the THP ether required careful fractional distillation, yields ranging from 72-91% were consistently obtained. Metallation gave yields of the anion in greater than 90% when 21 was treated with 10% excess n-butyl lithium for five hours in hexane (with TMEDA). Pouring the anion over fresh, finely crushed dry ice, followed by acid hydrolysis, afforded thymotic acid (16) in yields as high as 85%. Though the yields of the acid were somewhat

variable in this sequence as well,[40] they were consistently higher than 50%, and in general, better than those obtained using the methoxymethyl group.

3-Isopropylsalicylic acid (17) was prepared in a similar fashion although in lower yields. Thus, treatment of 2-isopropylphenol with DHP afforded the THP ether (23) in 61-78% yield after fractional distillation. Metallation, carboxylation and hydrolysis afforded 17 in 59% yield.

Preparation of Phenolic Protected Salicylic Acids

The protective unit chosen for the phenolic end of the chain was the benzyl group.[41,42] It was envisioned that this group would provide a relatively inert protecting unit. It would remain intact during all of the coupling reactions (formation of the ester linkages) and the deprotection reactions occurring at the carboxyl end of the chain, and it could be removed from the open-chain trimer at the end of the sequence by hydrogenolysis. Phenolic protection was best accomplished[43] as depicted in Scheme 4 by bis-benzylation followed by selective hydrolysis. Thus, when thymotic acid (16) was treated with slightly more than two equivalents of NaH and benzyl chloride in DMF bis-benzylated thymotic acid (24) was obtained quantitatively and in high purity. Direct hydrolysis of 24 in ether with eight molar equivalents of KO-t-Bu in the presence of two molar equivalents of water,[44] for from six to ten days, gave 64-70% isolated yields of O-benzylthymotic acid (27). Similarly, O-benzyl-3-isopropylsalicylic acid (28) and O-benzyl-3-ethyl-6-methylsalicylic acid (29) were prepared in yields of 49% and 50%, respectively.



	R_1	R_2		R_1	R_2		R_1	R_2
16	i-Pr	Me	24	i-Pr	Me	27	i-Pr	Me
17	i-Pr	H	25	i-Pr	H	28	i-Pr	H
18	Et	Me	26	Et	Me	29	Et	Me

SCHEME 4

Preparation of Carboxyl Protected Salicylic Acids

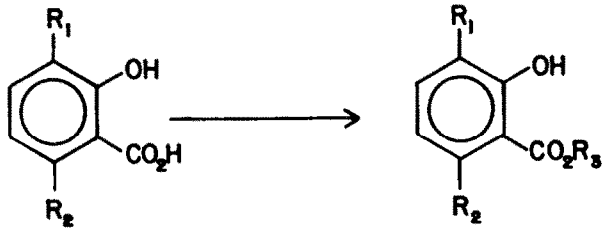
Since the preparation of different modified TOT's would require coupling of different monomeric and dimeric salicylic acid units with potentially different reactivities for coupling and deprotection (see Scheme 1), we chose to have a number of carboxyl protecting groups available in our arsenal. The three that were chosen were the benzyl (Bz), phenacyl (Pac) and phthalimidomethyl (Pim) groups.[41,42]

The Bz group was potentially the most useful and versatile. This was because hydrogenolysis could be used to deprotect both the phenolic and carboxylic ends of the open chain-trimer simultaneously (see VI in Scheme 1, when X = Z = Bz). Selective hydrogenolysis could also be used to deprotect the carboxyl end of the open-chain dimer (see III in Scheme 1, where X = Y = Bz). However, since this latter selectivity was based on a very slight potential difference in reactivity towards hydrogenolysis of the benzyl ether vs. the benzyl ester units, the phenacyl and phthalimidomethyl groups were also considered.

These latter two groups had advantages beside the potential of providing highly crystalline monomeric and dimer units. First, they both could be easily removed in high yield by Zn/HCl reduction in the presence of the benzyl ether protection. Second, each group could provide its own unique advantages. The phenacyl group, like the benzyl group, is removable by catalytic hydrogenation. Thus, if the third unit of the chain is protected as the phenacyl ester (see VI

in Scheme 1, X = Bz; Z = Pac), both the benzyl and phenacyl groups can be removed simultaneously. The phthalimidomethyl group, on the other hand, is inert to catalytic reduction, which offers the possibility of selectively removing the benzyl ether group at the dimer stage (see III in Scheme 1, X = Bz, Y = Pim) and constructing the chain in the reverse direction through the phenolic oxygen.[45]

In the event, benzyl esters 30-32 were prepared in 82%, 78% and 76% yield respectively, when the corresponding acids 16-18 were treated with sodium hydride in DMF followed by alkylation with benzyl chloride as depicted in Scheme 5. All these esters (new) were liquids and were characterized spectrally. Similarly, phenacyl esters 33-35 and phthalimidomethyl esters 36-38 were prepared in yields ranging from 62%-88% by treating acids 16-18 with phenacyl bromide or phthalimidomethyl bromide in the presence of KF and DMF.[46] All of these compounds were highly crystalline, easily purifiable solids which were characterized by spectral and combustion analysis.



	R_1	R_2			R_1	R_2	R_3
16	i-Pr	Me	a →	30	i-Pr	Me	Bz
			b →	33	i-Pr	Me	Pac
			c →	36	i-Pr	Me	Pim
17	i-Pr	H	a →	31	i-Pr	H	Bz
			b →	34	i-Pr	H	Pac
			c →	37	i-Pr	H	Pim
18	Et	Me	a →	32	Et	Me	Bz
			b →	35	Et	Me	Pac
			c →	38	Et	Me	Pim

a) NaH/DMF/BzCl; b) KF/DMF/PacBr; c) KF/DMF/PimBr

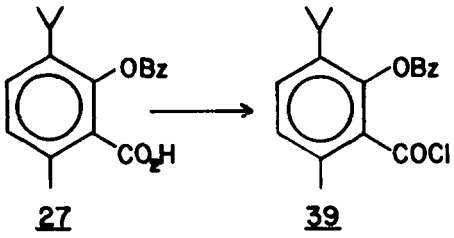
SCHEME 5

Coupling of Protected Salicylic Acid Monomers and Selective Deprotection of Open-Chain Dimers

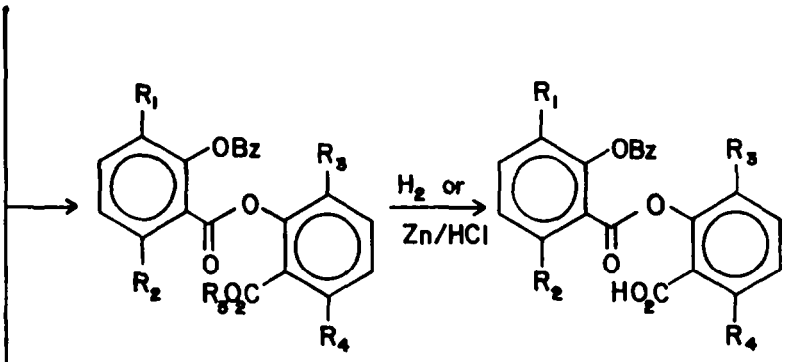
Activation of the free carboxylic end, as an acid chloride, and the free phenolic end, as the sodium phenoxide salt, was carried out in order to couple monomers I and II (see Scheme 1). This was required since these ester couplings involve sterically hindered sites and early coupling attempts involving the free carboxyl and phenolic ends, either alone or in the presence of dehydrating agents, were unsuccessful. After attempting the preparation of the acid chloride of 27 with a variety of reagents,[47] the use of $SOCl_2$ and 1-chloro-N,N,2-trimethylpropenylamine[50] proved most useful with the latter reagent ultimately being used exclusively.

Diprotected open-chain dimers 44-47 were prepared as described in Scheme 6 by coupling the acid chloride of 27 with the appropriate phenoxide salt of 30, 33, 36, and 35. Dimer 44 was prepared by adding a hexane solution of O-benzylthymoyl chloride (39) (prepared by treating 27 with $SOCl_2$ for 2 hours followed by evaporation of excess $SOCl_2$) to a suspension of an excess of previously formed phenoxide salt 40 in hexane and allowing the mixture to stir at ambient

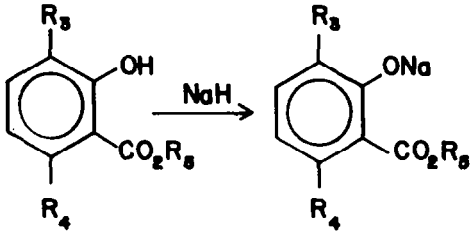
temperature for 5-6 hours. After workup and chromatography, 44 was obtained as an oil in 92.5% yield. Dimer 45 was prepared somewhat differently. After preparing acid chloride 39 as above, it was added to an anhydrous etheral solution of an equivalent of 33 and NaH. Stirring overnight at ambient temperature, followed by extraction and crystallization of the residue from i-PrOH, gave 45 in 68% yield as pale yellow crystals.



27 39



	R_1	R_2	R_3	R_4	R_5		R_1	R_2	R_3	R_4
44	i-Pr	Me	i-Pr	Me	Bz	48	i-Pr	Me	i-Pr	Me
45	i-Pr	Me	i-Pr	Me	Pac					
46	i-Pr	Me	i-Pr	Me	Pim					
47	i-Pr	Me	Et	Me	Pac	49	i-Pr	Me	Et	Me



	R_3	R_4	R_5		R_3	R_4	R_5
30	i-Pr	Me	Bz	40	i-Pr	Me	Bz
33	i-Pr	Me	Pac	41	i-Pr	Me	Pac
36	i-Pr	Me	Pim	42	i-Pr	Me	Pim
35	Et	Me	Pac	43	Et	Me	Pac

SCHEME 6

In the preparation of dimers 46 and 47, O-benzylthymoyl chloride (39) was prepared using 1-chloro-N,N,2-trimethyl propenylamine. This was done by reacting the enamine reagent with 27 for 30-45 minutes. Infrared analysis was used to determine the degree of formation of acid chloride. (A second treatment of enamine reagent was necessary when complete formation of the acid chloride was not observed spectrally.) After complete formation of 39 and removal of excess reagent, ester 36 was added in anhydrous ether along with an equivalent amount of NaH. Overnight stirring at ambient temperature, followed by workup and crystallization from i-PrOH, afforded 46 as colorless crystals in 67% yield. Dimer 47 was prepared similarly and obtained as a pale yellow oil (85%) which did not crystallize.

Selective removal of the carboxyl protecting group in 44-47 gave crystalline O-benzyl dimeric acids 48 and 49 in moderate to good yield. Hydrogenolysis of pure 44 in ethanol at STP over 10% Pd/C using one equivalent of H_2 afforded a viscous liquid. Crystallization from hexane afforded crystalline 48 in 73% yield. Though this selective hydrogenolysis was successfully carried out once on chromatographically pure 44, subsequent attempts at selective reduction of the crude coupling mixture were not successful. In these trials, despite the immediate removal of H_2 after the uptake of just one equivalent, only recovered starting material and fully deprotected dimer 50 was obtained. These subsequent reductions were carried out on impure dimer 44, however, which was obtained in coupling reactions involving 39 prepared using $SOCl_2$. The potential of sulfur poisoning during these reductions was great and could have had the effect of changing the selectivity of the reduction. Because the Pac and Pim derivatives of the dimer (45 and 46) could be obtained in crystalline form after coupling, which did not involve tedious chromatographic purification, preparing dimer by selective hydrogenolysis of the benzyl ester group was discontinued. However, further work may be warranted since the overall yield in the two steps (coupling 39 and 40, followed by selective hydrogenolysis) was good (67.5%).

Zinc/HCl reduction of the phenacyl ester group in 45 consistently gave 48 in high yield and high purity. After treatment of 45 in THF with Zn/HCl for one hour, workup and crystallization from hexane afforded analytically pure 48 in yields ranging from 83-90%. The deprotection of the identical group in 47 afforded 49 in an overall yield (for coupling and phenacyl deprotection) of 49%.

The phthalimidomethyl group in 46 was removed by reduction with Zn/HCl and gave a disappointingly low isolated yield of 48 (37%). At this time it is not clear whether the problem lies in the reduction itself or in the isolation and purification of the dimer. The by product of the reduction is methylphthalimide. This material is insoluble in hexane and complicates an already difficult recrystallization.[51] Despite this apparent drawback, the phthalimidomethyl group offers the advantage of not containing acidic hydrogens, and this may prove useful in certain specific situations involving the preparation of salicylides.

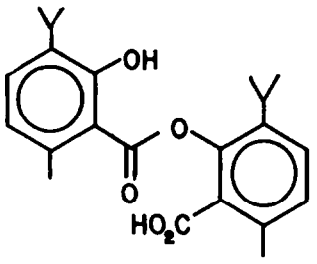
Presently, the coupling and deprotection method which is most reliable and which gives the most consistent results for the preparation of monoprotected open-chain dimers involves the use of the enamine reagent for acid chloride formation and the use of the phenacyl protecting group for easy, selective reductive cleavage. The other protecting groups and deprotecting reactions will be further developed as their use may be required in other sequences.

Preparation of Open-Chain Trimers

As depicted in Scheme 1, the general sequence for preparing open-chain trimer involves similar reactions to that used to prepare dimer except a monomeric unit must be coupled with a dimeric unit. The protecting groups and deprotecting reactions were envisioned to be the same, and activation of the participating free carboxyl and phenolic groups, as the acid chloride and phenolate anion, was also deemed necessary to ensure ester formation.

$SOCl_2$ proved to be a poor reagent for the preparation of the acid chloride of 48, but allowed for efficient generation of cyclic dimer 51. When $SOCl_2$ was purified and distilled before use, the major product (50%) was di-o-thymotide 51.[53] This product was obtained even before NaH and 57 was added to the reaction mixture (see Scheme 7). Benzyl chloride was also identified (by ^1H NMR spectral analysis) in the reaction mixture and its presence suggested that the benzyl ether group in 48 was being cleaved with cyclization of the open-chain dimer. Though

$SOCl_2$ could therefore not be used to prepare the required acid chlorides (52 or 53) for the planned coupling, it is of interest that this reagent could be used to form the cyclic dimer from O-benzyl protected open-chain dimer 48. This method could be useful in preparing a wide variety of cyclic dimers where the two salicylide units differ. These mixed dimers would be of great interest for studying the effects of substituent changes on the conformational properties of modified dimers.[23,54]



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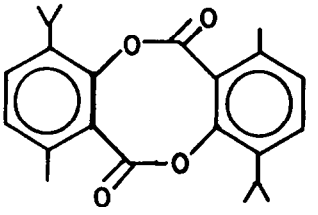
48 $\xrightarrow{SOCl_2}$



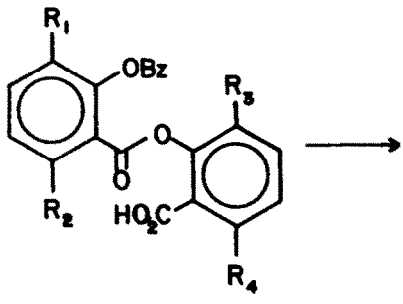
51

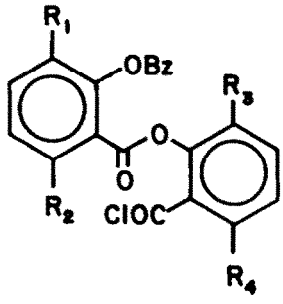
SCHEME 7

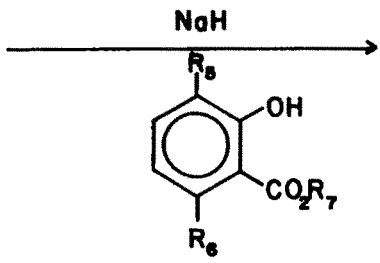
Returning to our initial discussion, acid chlorides 52 and 53 of O-benzyl open-chain dimeric acids 48 and 49, respectively, were successfully prepared using 1-chloro-N,N,2-trimethylpropenylamine. In a typical procedure, one equivalent of the enamine reagent was allowed to react with the dimeric open-chain acid in CH_2Cl_2 for 30 to 45 minutes. The solvent was removed under reduced pressure and the resulting oil was analyzed by infrared spectroscopy to determine the degree of acid chloride formation. If there was any evidence of unreacted carboxylic acid, the oil was redissolved in solvent and further treated with the enamine reagent. After an additional 30 to 45 minutes, the solvent was removed and the acid chloride was used, as generated, for the coupling reaction. In this way, acids 48 and 49 were converted very cleanly and in high yield to acid chlorides 52 and 53 with absolutely no indication of cyclic dimer formation as was obtained using $SOCl_2$.

Coupling 48 with 54 and 55 in ether, in the presence of sodium hydride, using a procedure otherwise identical to that used to form the dimers, gave quantitative crude yields of the bis-benzyl-protected open-chain trimers 57 and 58, respectively, (see Scheme 8). They were isolated as oils and were reduced directly with hydrogen over 10% Pd/C at STP, to remove both benzyl groups, giving open-chain trimeric acid 61 and 62, respectively. These compounds were isolated as oils in quantitative yields after reduction and in overall isolated yields of 59% and 61% (from dimeric acid 48) after crystallization from hexane. Both open-chain acids were white crystalline solids with spectral and microanalytical data consistent with their structures.

Using procedures identical to that described above, bis-protected open-chain trimer 59 was prepared by reacting acid chloride 53 with 55 in ether in the presence of NaH. The oil, thus obtained, was hydrogenolyzed directly over 10% Pd/C giving open-chain trimer acid 63. The acid was crystallized from ethanol and the overall isolated yield from 49 was 43%. Similarly, open-chain trimer acid 64 was prepared in 53% yield.



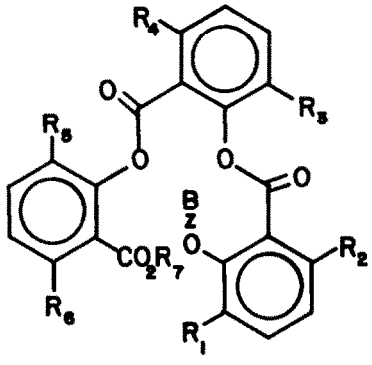


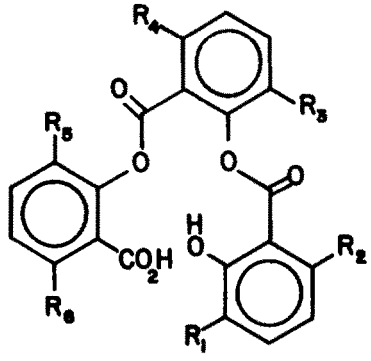


	R_1	R_2	R_3	R_4
48	i-Pr	Me	i-Pr	Me
49	i-Pr	Me	Et	Me

	R_1	R_2	R_3	R_4
52	i-Pr	Me	i-Pr	Me
53	i-Pr	Me	Et	Me

	R_5	R_6	R_7
54	i-Pr	Me	Bz
55	Et	Me	Bz
56	i-Pr	H	Bz





	R_1	R_2	R_3	R_4	R_5	R_6	R_7
57	i-Pr	Me	i-Pr	Me	i-Pr	Me	Bz
58	i-Pr	Me	i-Pr	Me	Et	Me	Bz
59	i-Pr	Me	Et	Me	Et	Me	Bz
60	i-Pr	Me	i-Pr	Me	i-Pr	H	Bz

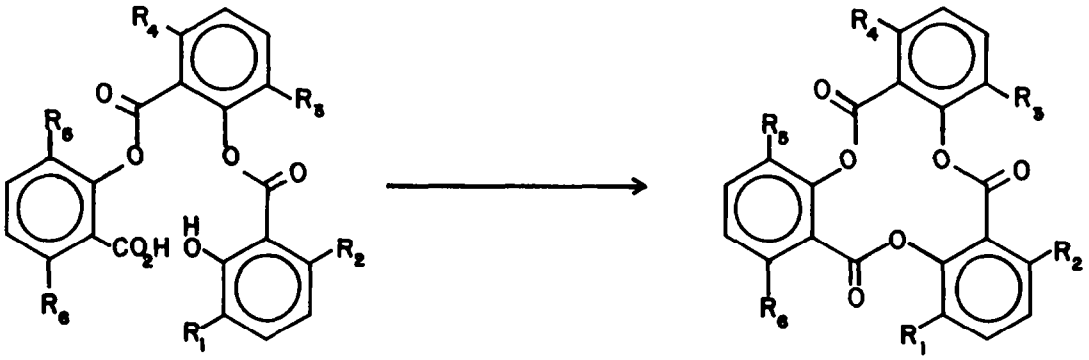
	R_1	R_2	R_3	R_4	R_5	R_6
61	i-Pr	Me	i-Pr	Me	i-Pr	Me
62	i-Pr	Me	i-Pr	Me	Et	Me
63	i-Pr	Me	Et	Me	Et	Me
64	i-Pr	Me	i-Pr	Me	i-Pr	H

SCHEME 8

Cyclization of Open-chain Trimers. TOT and TOT Analogues.

The cyclization of the open-chain trimers 61-63 required the use of a strong dehydrating agent and high dilution conditions to keep oligomer formation to a minimum. Initially, dehydrating agents like those used in classical TOT and trisalicylide preparations ($POCl_3$, $SOCl_2$, etc.) were used. These cyclizations, however, were too sterically encumbered at the reactive sites and the conditions sufficiently harsh that the trimers were isolated in poor yield (see Scheme 9). In one such cyclization attempt, open-chain trimer 62 was heated at 110 °C in dry xylene containing 100 fold molar excess of $POCl_3$. After workup a brown oil was obtained. Crystallization from ethanol gave TOT analogue 9 (33%) as impure brown crystals. Chromatography of the mother liquor afforded greater than 65% of the original weight of the starting material isolated as a fast moving fraction on thin layer chromatography plates.

Infrared and ^1H NMR spectral analysis indicated that a substantial amount of ester cleavage in 62 and subsequent decarboxylation of the fragmented trimer had occurred.



	R_1	R_2	R_3	R_4	R_5	R_6			R_1	R_2	R_3	R_4	R_5	R_6
61	i-Pr	Me	i-Pr	Me	i-Pr	Me	a or c →		1	i-Pr	Me	i-Pr	Me	i-Pr	Me
62	i-Pr	Me	i-Pr	Me	Et	Me	a or b →		9	i-Pr	Me	i-Pr	Me	Et	Me
63	i-Pr	Me	Et	Me	Et	Me	a →		10	i-Pr	Me	Et	Me	Et	Me
64	i-Pr	Me	i-Pr	Me	i-Pr	H			66	i-Pr	Me	i-Pr	Me	i-Pr	H

a) $POCl_3$; b) $SOCl_2$; c) TFAA

SCHEME 9

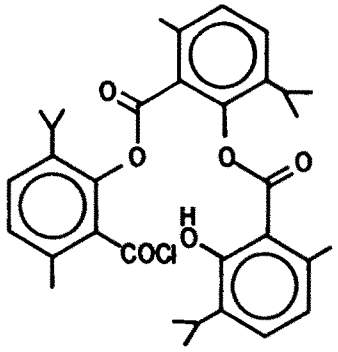
Improved cyclization yields could be obtained when a solution of 62 and $POCl_3$ was added over a period of 3-6 hours to refluxing $POCl_3$. Continued refluxing for 1 hour and workup afforded material, which in some instances could be crystallized and in others had to be chromatographed. When the crude residue was crystallized directly from hexane/CH_2Cl_2, TOT analogue 9 (41%) could be obtained. Under otherwise similar conditions, when the residue was chromatographed, 9 was obtained in 60% yield as an amorphous solid.

Despite the fact that 9 could be obtained using $POCl_3$, the results indicated that the open-chain and/or cyclic trimer was undergoing competitive decomposition under the reaction conditions. Indeed, it had previously been observed that when TOT was heated in toluene for from 6-15 hours at 100 °C, decomposition occurred along with formation of tetra-and hexa-thymotides. In addition, we have found that when open-chain trimer 61 is heated in DMSO at 200 °C for 2 hours, thymol (19) is obtained almost exclusively. We therefore searched for a reagent and conditions which would allow us to carry out the cyclization at lower temperature and under milder conditions.

The use of $SOCl_2$ was tested on open-chain trimer 61. Using high dilution conditions, 61 in benzene was dripped into benzene at 60 °C containing 100 molar excess of $SOCl_2$. After 24 hours at 60 °C, thin layer chromatography indicated essentially a single compound which was not TOT. An infrared spectrum of the residue after evaporation of the volatiles indicated ester and acid chloride absorptions suggesting at least that acid chloride 65 had been formed. This material was then dissolved in ether, treated with NaH and stirred for two days. After aqueous workup, an oily solid was obtained whose ^1H NMR and IR spectra indicated the presence of TOT (1) along with starting acid 61. Crystalline TOT, identical in all respects with that reported in the literature, was obtained from this residue in 21% yield after crystallization from hexane[53].

Since 1-chloro-N,N,2-trimethylpropenylamine had been used successfully to prepare the monomeric and dimeric acid halides for coupling, we considered the possibility of using this reagent in the cyclization of the open-chain trimers. When 61 was treated with excess enamine reagent and the resulting acid chloride 65 heated at reflux in benzene overnight, no TOT was formed (by TLC). However, when this cooled solution was treated with excess NaH, thin layer

chromatography indicated the formation (though not complete) of TOT (1) after one hour at ambient temperature. Continued stirring overnight and heating at reflux did not seem to change the initial amount of TOT (1) formed. After workup, chromatography and crystallization from ethanol, TOT (1) was isolated as its ethanol complex in 22% yield. A substantial amount of starting acid 61 was indicated by ^{1}H NMR spectroscopic analysis of the residue.



65

Other attempts at improving the yield of cyclization using 1-chloro-N,N,2-trimethylpropenyl amine in ether along with NaH, or using a variety of other reagents like pyridine or DCC[55,56], were unsuccessful. In all instances, though TOT was formed, it was generated in poor yield. The major material obtained was recovered starting acid 61.

The formation of cyclic trimers 1, 9, and 10 were most simply and directly prepared in high crystalline purity and in good yield by using trifluoroacetic anhydride (TFAA) as the dehydrating reagent.[57,58] Thus, when open chain trimer 61 was treated in dry benzene with 15 molar equivalents of TFAA at 10 °C for 24 hours, an oily residue was obtained which, when treated with ethanol, afforded white crystalline TOT in 57% isolated yield. The procedure is simple and mild, and also afforded TOT analogues 9 and 10 in greater than 65% isolated yield from 62 and 63, respectively.

CONCLUSIONS

The above description defines a new sequential method of preparing TOT and TOT analogues. Overall isolated yields of 1, 9 and 10 from the protected monomeric units are 25%, 25% and 14%, respectively. The method seems general and has the potential of being used to prepare cyclic di- or trisalicylides (and perhaps higher order oligomers) where: (a) the substitution pattern in the salicylic acids units may be varied, (b) the salicylic acid units making up the salicylides may be different from one another and, (c) the aromatic rings may be changed. The ability to prepare such a wide variety of cyclic trimeric salicylide structures easily and in high purity will now allow the study of the clathrating properties of these molecules to proceed in order to better understand what substituent factors govern clathration in TOT-type host-guest clathrates. The sequential synthetic scheme might also lend itself to the preparation of other cyclic systems where the bridging ester linkage is replaced by methylenoxy ($-CH_2O-$) or methylenoxo ($-CH_2CO-$) units. Such systems might also prove important in understanding conformational properties in these cyclic trimers and can also potentially be clathrating hosts.

In addition, with this quick, reliable and relatively high yield method of preparing these analogues, in abundance and high crystalline purity, there will be a better opportunity to study the chemical reactivity and interconvertability of these unique TOT host systems. Presently we are continuing our synthetic studies and are preparing other analogues of TOT which will incorporate the unique acetyl, (CH_3CO-), and isopropenyl ($-CCH_3=CH_2$) groups, as well as, chiral groups like haloethyl (CH_3CHX-) and sec-butyl ($-CHCH_3Et$). We will also now begin to study the conformational properties and crystal structures of these modified TOT compounds and attempt to form clathrates with typical guests that are enclathrated in TOT itself. Comparison structural

studies between TOT and its clathrates and the TOT analogues and their clathrates (?) will help shed light on the effect of the substituents on clathration in TOT. With a better understanding of the factors which control clathration, specific clathrates can hopefully be engineered which will ultimately allow for chemistry to be performed within the complex and between TOT host and guest.

EXPERIMENTAL

General

Melting points were determined with a Thomas-Hoover Capillary Melting Point Apparatus and are uncorrected. Boiling points were measured at the pressure indicated and are uncorrected. Elemental analyses were determined by Galbraith Laboratories Inc. Knoxville, Tennessee. Infrared spectra were recorded on a Perkin Elmer 683 Infrared Spectrophotometer. ^{1}H NMR spectra were recorded on a Varian EM390 Spectrometer and are reported in parts per million (δ) from TMS. Samples were dissolved in $CDCl_3$ containing 5% TMS as an internal standard and lock reference.

Anhydrous diethyl ether was further dried by storage over sodium and distillation immediately before use. Anhydrous DMF was dried initially over CaH, distilled at reduced pressure and sequentially dried over three fresh portions of 4 Å or 5 Å molecular sieves. TMEDA was initially dried over KOH pellets, distilled from Na, and stored over 4 Å molecular sieves. Xylenes were purified by distillation. t-BuOH was purified by distillation from Na and stored over 3 Å molecular sieves. Phosphorous oxychloride and thionyl chloride were purified by distillation immediately before use. Ultrapure thionyl chloride was prepared by a three step procedure previously described.[59]

All other solvents, reagents and chemicals were used as obtained from commercial sources (generally Aldrich Chemical Co. and Fisher Scientific) except NaH (which was purchased as a 60% dispersion in mineral oil). The weight of NaH recorded in the experimental section is the weight of NaH plus the weight of oil and NOT the weight of the NaH alone. The mineral oil was removed by washing the NaH with two portions of hexane just prior to use. All reactions involving the use of air sensitive reagents were run under a N_2 atmosphere. Following extraction, organic solutions were dried over $MgSO_4$, unless otherwise noted, and the solvent evaporated on a rotary evaporator, unless otherwise noted. TLC was performed on silica-gel coated glass plates.

(2-Isopropyl-5-methylphenyl) Methoxymethyl Ether (19a)

To a stirred suspension of sodium hydride (21 g, 0.525 mol, 60% NaH dispersion) in anhydrous DMF (100 mL) at room temperature was added a solution of thymol (19) (60 g, 0.4 mol) in DMF (100 mL). Stirring was continued until the evolution of hydrogen ceased and the solution was cooled to 0 °C. A solution of chloromethyl methyl ether in hexane was then added and stirring was continued until completion of the reaction (TLC). Hexane and DMF were then removed under reduced pressure. Water was added to the resulting mixture and the methoxymethyl ether was extracted with hexane. The hexane extract was dried over anhydrous Na_2SO_4. Hexane was removed and the residue distilled under reduced pressure. Ether 19a (61 g, 78.7%) was collected as a clear liquid (bp 119-128 °C, aspirator pressure). ^{1}H NMR (CCl_4) δ 1.07 (d, J = 7 Hz, 6 H), 2.13 (s, 3 H), 3.22 (septet, 1 H), 3.23 (s, 3 H) 4.93 (s, 2 H), 6.62 (s, 1 H), 6.75 (ABq, J = 7.5 Hz, 2 H).

o-Thymotic Acid (16) from Ether 19a[61]

n-Butyl lithium (300 ml of 1.6 N, 0.48 mol) in hexane was added to TMEDA (72 mL, 0.48 mol) with stirring at 20 °C. The resulting solution was stirred at 20 °C for another 15 minutes and then cooled to 0 °C. To the cooled solution was added a solution of the methoxymethyl ether 19a (61 g, 0.316 mol) in hexane, maintaining the temperature between 0°-4 °C. After completion of the addition, the reaction mixture was stirred for another hour. The solution was then added slowly, with a cannula, to a flask containing crushed dry ice. After transfer, the reaction was stirred for an additional hour and filtered. The solid, thus obtained, was the lithium carboxylate salt of 16.

The salt was dissolved in MeOH, acidified with dilute HCl and p-toluene sulfonic acid and allowed to stand at ambient temperature until deprotection was complete (TLC). Removal of methanol and crystallization of the residue from hexane afforded thymotic acid (35 g, 57.4%; mp 127 °C).[60] ^{1}H NMR (CCl_4) δ 1.24 (d, J = 7 Hz, 6 H), 2.60 (s, 3 H), 3.33 (septet, 1 H), 6.97 (ABq, 2 H), 10.0-11.5 (bs, 2 H).

(2-Ethyl-5-methylphenyl) Methoxymethyl Ether (21a)

Under a nitrogen atmosphere, DMF (50 mL) was added. To a stirred suspension of sodium hydroxide (5.3 g) in DMF (50 mL, 60% NaH dispersion) was slowly added a solution of 2-ethyl-5-methylphenol (21) (15 g, 0.11 mol) in DMF (30 mL) while maintaining the temperature at about 30 °C. The reaction mixture was stirred until the evolution of hydrogen ceased (ca. 2-3 hrs). If the reaction mixture formed a cake, an additional amount of DMF was added. A solution of chloromethyl methyl ether (10 mL, freshly distilled) in hexane was then added slowly while maintaining the reaction temperature between 10-20 °C. After the completion of addition, the reaction mixture was stirred for 2 hours at ambient temperature. Excess sodium hydride was destroyed with methanol, followed by the addition of toluene (150 mL) and water (75 mL). The organic phase was separated from the aqueous phase, washed with NaOH solution and water and dried over anhydrous Na_2SO_4. Toluene was removed under reduced pressure. Product ether 21a was distilled under reduced pressure (aspirator, bp 110 °C) and was obtained as a clear colorless liquid (17.2 g, 87%). ^{1}H NMR ($CDCl_3$) δ 1.16 (t, J = 8 Hz, 3 H), 2.25 (s, 3 H), 2.56 (q, J = 8 Hz, 2 H), 3.40 (s, 3 H), 5.06 (s, 2 H), 6.70 (s, 1 H), 6.72 (ABq, J = 8 Hz, 2 H). IR (neat) 2960-2800 broad (m), 1510 (m), 1255 (m), 1155 (s), 1130 (s), 1080 (s), 1015 (s), 925 (m), 812 (m) cm^{-1}.

3-Ethyl-6-methylsalicylic Acid (18)[61]

n-BuLi (138 mL, 1.6 M in hexane, 0.22 mol) was added with stirring and under nitrogen to cooled (20 °C) TMEDA (27 mL). The resulting solution was stirred at that temperature for 1/2 hr and then cooled to 10 °C. To the cooled solution was added a solution of methoxymethyl ether

(21a) (28.9 g, 16 mol) in hexane maintaining the temperature between 0 and 4 °C. After addition, the dark purple reaction mixture was stirred for 1 hr. The solution was then slowly added, through a cannula, onto crushed dry ice. The dry ice reaction mixture was stirred for one hour and then filtered. The lithium carboxylate could thus be obtained in about 75% yield. ^{1}H NMR (D_2O) δ 1.5 (t, J = 8 Hz, 3 H), 2.57 (s, 3 H), 2.97 (q, J = 8 Hz, 2 H), 3.93 (s, 3 H), 5.39 (s, 2 H), 7.42 (ABq, J = 8 Hz, 2 H).

The lithium salt was dissolved in MeOH/H_2O (1 : 1) and with cooling conc. HCl (23 mL, diluted in MeOH/H_2O, 1 : 1) was added. After addition of the HCl, the mixture was stirred for 1/2 hr at ambient temperature, p-toluene sulfonic acid (1 g) was added and the mixture heated to reflux for 3 hrs. Methanol was then removed and the aqueous layer extracted three times with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and the CH_2Cl_2 was removed leaving behind a viscous orange-brown liquid which solidified on standing. Crystallization and recrystallization from CCl_4 afforded acid 18 (11.1 g, 38%; mp 140.5° -142 °C).[62] ^{1}H NMR ($CDCl_3$) δ 1.22 (t, J = 8 Hz, 3 H), 2.61 (s, 3 H), 2.78 (q, J = 8 Hz, 2 H), 6.96 (ABq, J = 8 Hz, 2 H), 10.92 (bs, 2 H). IR (KBr) 3300-2100 broad (s), 1635 (s), 1605 (s) cm^{-1}. Anal. Calcd for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.31; H, 6.59.

Thymol 2-Tetrahydropyranyl Ether (22)

A solution of thymol (150.2 g, 1 mol) and dihydropyran (500 mL, 5.5 mol) in EtOAc (1.5 L) was treated with EtOAc saturated with anhydrous HCl (100 mL). The solution was allowed to stand at ambient temperature overnight and then washed successively with two portions of 3 N NaOH, (2 x 500 mL), H_2O (500 mL) and saturated NaCl (500 mL). The organic layer was dried and concentrated to give 220.5 g of a colorless liquid. Fractional distillation gave 22 (214 g, 91.6%) as a colorless liquid, bp 93-106 °C (0.3 Torr). ^{1}H NMR ($CDCl_3$) δ 1.20 (d, J = 7 Hz, 6 H), 1.40-1.98 (m, 6 H), 2.30 (s, 3 H), 3.04-4.05 (m, 3 H), 5.31-5.48 (m, 1 H), 6.64-7.14 (m, 3 H). IR (neat) 3050 (w), 3030 (w), 2950 (s), 2870 (s), 1600 (m), 1500 (s), 1250 (s), 1200 (s), 970 (s), 905 (s), 805 (s). Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.69; H, 9.18.

o-Thymotic Acid (16) from Ether 22

A mechanically stirred solution of THP ether 22 (93.72 g, 0.4 mol) and TMEDA (66.4 mL, 0.44 mol) in hexane (500 mL) was cooled to 10 °C and to it was added n-BuLi (284 mL, 1.55 M in hexane, 0.44 mol). The solution immediately turned bright yellow and then orange. After addition, the cooling bath was removed and stirring was continued at ambient temperature. A heavy precipitate began to form within 1 hr. The mixture was stirred for 5 hrs and poured, with vigorous stirring, onto fresh, finely crushed, dry ice. After the dry ice had completely sublimed, the mixture was diluted with water (1 L), transferred to a separatory funnel and shaken until the solid dissolved. The layers were separated and the hexane layer was extracted with water (200 mL) containing enough 1 N NaOH to make the extract strongly basic. The combined aqueous extracts were washed with hexane (300 mL). The hexane washing was combined with the original hexane layer, dried and concentrated to give 14.06 g of recovered ether 22.

The combined aqueous extracts were acidified to pH 1 with 3 N HCl and the gummy mass which formed was extracted with ether (3 x 500 mL). The combined ether extracts were dried and concentrated to give a yellow oil. This oil was dissolved in MeOH (1 L), treated with p-TsOH and allowed to stand at ambient temperature for 5 hrs. The solution was diluted with water (400 mL) and slowly concentrated with slight warming and addition of seed crystals to allow the oil which initially formed to crystalize. When a volume of 200 mL was reached, the mixture was cooled in an ice bath and the solid was collected by filtration to give 66.53 g of the crude acid as a pale yellow solid. The solid was dissolved with warming in hexane (2 L) and allowed to stand at ambient temperature for 5 hrs. The solid impurities, (which included a diacid),[40] were removed by filtration and the filtrate was concentrated to dryness. The residue was recrystallized from hexane to give 55.8 g of 16 as pale yellow crystals, mp 120-126 °C [lit.[60] mp 127 °C]. The mother liquor gave an additional 2.64 g of slightly less pure, but usable product, as colorless crystals, mp 117-124 °C. The two crops represent a combined yield of 85.5%.

(2-Isopropylphenyl)-2-Tetrahydropyranyl Ether (23)

2-Isopropylphenol (20) (134.6 g, 1 mol) and dihydropyran (500 mL, 5.5 mol) were added to EtOAc (1.5 L), treated with EtOAc saturated with HCl (500 mL) and allowed to stand overnight at ambient temperature. The solution was washed successively with two portions of 1 N NaOH (2 x 500 mL) water (500 mL), and saturated NaCl (500 mL), then dried and concentrated to give a dark oil. Fractional distillation gave 54.4 g of impure product, (bp 86-91 °C, 0.1 Torr) and pure 23 (133.7 g, 60.7%; bp 91-94 °C, 0.1 Torr); ^{1}H NMR ($CDCl_3$) δ 1.24 (d, J = 7 Hz, 6 H), 1.40-2.15 (m, 6 H), 3.18-4.08 (m, 3 H), 5.30-5.49 (m, 1 H), 6.79-7.20 (m, 4 H). IR (neat) 3080 (w), 3030 (w), 2950 (s), 2870 (s), 1600 (m), 1590 (s), 1230 (s), 1200 (s), 965 (s), 920 (s), 750 (s) cm^{-1}. Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.32; H, 9.15. Found: C, 76.06; H, 9.04.

3-Isopropylsalicylic Acid (17)

With mechanical stirring and under a N_2 atmosphere, n-BuLi (137.5 mL, 1.6 N, 0.22 mol) was added to a cooled (10 °C) solution of 23 (44.1 g, 0.2 mol) and TMEDA (33.2 mL, 0.22 mol) in hexane (200 mL). The solution immediately turned bright orange. After the addition was complete, the cooling bath was removed and stirring was continued at ambient temperature. A thick precipitate formed within 1 hr. Stirring was continued for 5 hrs and the mixture was poured onto fresh, finely crushed, dry ice. The mixture was stirred until the dry ice had sublimed, and then diluted with water (500 mL), transferred to a separatory funnel and shaken until the solid dissolved. The hexane layer was extracted with water (100 mL) containing sufficient 1 N NaOH to make the extract strongly basic. The combined aqueous extracts were washed with hexane (200 mL) and the combined hexane layers were dried and concentrated to give recovered ether 23 (11.81 g). The combined aqueous extracts were acidified to pH 1 (3 N HCl) and the oil which formed was extracted with ether (3 x 400 mL). The combined ether extracts were dried and concentrated to give a yellow oil. This oil was dissolved in MeOH (500 mL), treated with p-TsOH and allowed to stand at ambient temperature for 3 hrs. The solution was diluted with water (250 mL) and slowly concentrated with warming to allow the oil which initially formed to crystallize. The mixture was concentrated to a volume of 100 mL, cooled in

an ice bath and the solid was removed by filtration. Drying overnight under reduced pressure gave 33.6 g of crude acid as a yellow solid. Recrystallization from hexane (60 mL) gave 17 (12.8 g) as colorless crystals, mp 69-71 °C, (lit.[63] mp 71-72 °C). The mother liquor was adjusted to a volume of 100 mL and slowly cooled to -50 °C to give an additional 8.56 g of 17 as pale yellow crystals, mp 68-70 °C. The two crops represent a combined yield of 59.2%. ^{1}H NMR ($CDCl_3$) δ 1.28 (d, J = 7 Hz, 6 H), 3.42 (septet, J = 7 Hz, 1 H), 6.93 (t, J = 8 Hz, 1 H), 7.52 (dd, J = 8 Hz and 1.5 Hz, 1 H), 7.90 (dd, J = 8 Hz and 1.5 Hz, 1 H), 10.78 (s, 1 H), 12.22 (s, 1 H). IR (KBr) 3500-2300 broad (m), 1655 (s), 1608 (m) cm^{-1}.

O-Benzylthymotic Acid (27)

o-Thymotic acid (16) (38.84 g, 0.2 mol) was added to a suspension of NaH (17.6 g, 0.44 mol) in DMF (350 mL). The mixture was stirred at ambient temperature for 1 hr, treated with benzyl chloride (50.6 mL, 0.44 mol) and heated to reflux for 2 hrs. The DMF was removed by evaporation and the residue was dissolved in hexane (1.3 L). The hexane solution was washed with water (2 x 400 mL) to which had been added a small amount of NaOH to insure that the washings were basic, dried and concentrated to give benzyl-O-benzyl thymoate (24, 75.28 g) as a yellow oil. ^{1}H NMR ($CDCl_3$) δ 1.20 (d, J = 7 Hz, 6 H), 2.27 (s, 3 H), 3.32 (septet, J = 7 Hz, 1 H), 4.88 (s, 2 H), 5.26 (s, 2 H) 6.91 (d [of ABq], J = 8 Hz, 1 H), 7.15 - 7.50 (m, 11 H).

The above oil was dissolved in anhydrous ether (3.5 L) treated with KO-t-Bu (179.5 g, 1.6 mol) and water (7.2 mL, 0.4 mol) and stirred mechanically for 10 days. The mixture was extracted twice with water (first with 1200 mL, then with 600 mL). The combined aqueous extracts were washed with ether (300 mL) and acidified to pH 1 with 3 N HCl. The oil which formed was extracted with CH_2Cl_2 (3 x 300 mL). The combined organic extracts were dried and concentrated to give crude 27 as an oily solid (58.9 g). Recrystallization from hexane gave 27 as colorless crystals (40.0 g, 70.4%; mp 99-102 °C). A second recrystallization from hexane gave an analytical sample of 27, mp 101-102 °C. ^{1}H NMR ($CDCl_3$) δ 1.2 (d, J = 7 Hz, 6 H), 2.38 (s, 3 H), 3.29 (septet, J = 7 Hz, 1 H), 4.90 (s, 2 H), 6.67-7.64 (m, 7 H), 11.05 (bs, 1 H). IR (KBr) 3400-2200 broad (m), 1695 (s) cm^{-1}. Anal. Calcd for $C_{18}H_{20}O_3$: C, 76.03; H, 7.09. Found: C, 75.89; H, 6.95.

O-Benzyl-3-isopropylsalicylic Acid (28)

In a fashion identical to that used to prepare 27, acid 28 was prepared in 49% yield (mp 80.5-82 °C). ^{1}H NMR ($CDCl_3$) δ 1.25 (d, J = 7 Hz, 6 H), 3.41 (septet, J = 7 Hz, 1 H), 4.97 (s, 2 H), 7.1-7.59 (m, 7 H), 7.89 (dd, J = 1.5 and 8 Hz, 1 H), 11.2 (bs, 1 H). IR (KBr) 3300-2200 broad (m), 1695 (s) cm^{-1}. Anal. Calcd for $C_{17}H_{18}O_3$: C, 75.52; H, 6.72. Found: C, 75.68; H, 6.75.

O-Benzyl-3-ethyl-6-methylsalicylic Acid (29)

In a fashion identical to that used to prepare 27, acid 29 was prepared in 50% yield (mp 66-67.5 °C). ^{1}H NMR ($CDCl_3$) δ 1.20 (t, J = 7 Hz, 3 H), 2.35 (s, 3 H), 2.65 (q, J = 7 Hz, 2 H) 4.93 (s, 2 H), 6.90 (d of ABq, J = 8 Hz, 2 H) 7.15 - 7.50 (m, 5 H), 9.25 (bs, 1 H). IR (KBr) 3300-2200 broad (m), 1695 (s) cm^{-1}. Anal. Calcd for $C_{17}H_{18}O_3$: C, 75.52; H, 6.72. Found: C, 75.51; H, 6.79.

Benzyl-3-ethyl-6-methyl Salicylate (32)

3-Ethyl-6-methylsalicylic acid (18) (5.9 g, 0.033 mol) in anhydrous DMF (10 mL) was added to a suspension of NaH (1.73 g, 0.04 mol) in anhydrous DMF (30 mL). The mixture was stirred for 1 hour at ambient temperature and treated with benzyl chloride (3.77 mL; 0.033 mol). The resulting mixture was heated at reflux for 2 hrs. The DMF was removed by evaporation and the residue was dissolved in hexane (125 mL). The hexane solution was washed with water (2 x 50 mL), dried, and concentrated to give 7.53 g of a brown oil. Purification by fractional distillation gave 32 (6.7 g, 75%) as a yellow liquid (bp 144 °C, 0.15 Torr). ^{1}H NMR ($CDCl_3$) δ 1.15 (t, J = 8 Hz, 3 H), 2.40 (s, 3 H), 2.60 (q, J = 8 Hz, 2 H), 5.22 (s, 2 H), 6.73 (ABq, J = 8 Hz, 2 H), 7.10-7.39 (m, 5 H), 11.55 (bs, 1 H). IR (neat) 3095 (w), 3060 (w), 3035 (w), 2970 (m), 2930 (m) 2875(m), 1655(s), 1615(m) cm^{-1}.

Benzyl Thymoate (30)

In a manner identical to that used for the preparation of 32, ester 30 was prepared in 81.5% yield, bp 163-164 °C (0.1 Torr). ^{1}H NMR (CCl_4) δ 1.20 (d, J = 7 Hz, 6 H), 2.45 (s, 3 H), 3.31 (septet, J = 7 Hz, 1 H), 5.30 (s, 2 H), 6.80 (ABq, J = 8 Hz, 2 H), 7.30 (m, 5 H), 11.5 (bs, 1 H).

Benzyl-3-isopropyl Salicylate (31)

Using the procedure for the preparation of 32, ester 31 was prepared in 78% yield bp 135-153 °C, (0.32 Torr). ^{1}H NMR ($CDCl_3$) δ 1.22 (d, J = 7 Hz, 6 H), 3.37 (septet, J = 7 Hz, 1 H), 5.30 (s, 2 H) 6.77 (t, J = 7 Hz, 1 H) 7.37 (m, 6 H), 7.70 (dd, J = 7 Hz and 1.5 Hz, 1 H), 11.13 (bs, 1 H). IR (neat) 3300-3000 broad (m), 2960 (m), 2860 (m), 1640 (s), 1615 (m) cm^{-1}.

Phenacyl Thymoate (33)

A mixture of KF (12.80 g, 0.22 mol) and α-bromoacetophenone (19.90 g, 0.1 mol) in anhydrous DMF (100 mL) was stirred for one minute. To the mixture was added thymotic acid (16) (19.4 g, 0.1 mol). After stirring at ambient temperature overnight, the mixture was diluted with ether (750 mL) and washed with three portions of water (250 mL each). The ether layer was dried and concentrated to give a solid residue which was recrystallized from i-PrOH to give 33 (27.49 g, 88.1%) as colorless crystals, mp 101.5-104 °C. ^{1}H NMR ($CDCl_3$) δ 1.23 (d, J = 7 Hz, 6 H), 2.60 (s, 3 H), 3.35 (septet, J = 7 Hz, 1 H), 5.61 (s, 2 H), 6.96 (ABq, J = 8 Hz, 2 H), 7.36-7.67 (m, 3 H), 7.89-8.05 (m, 2 H), 10.98 (s, 1 H). IR (KBr) 3060 (w), 3040 (w), 2980 (m), 2960 (m), 2940 (m), 2920 (m), 2860 (m), 1712 (s), 1660 (s), 1605 (s) cm^{-1}. Anal. Calcd for $C_{19}H_{20}O_4$: C, 73.06; H, 6.45. Found: C, 73.20; H, 6.58.

Using the procedure for the preparation of 33, the following phenacyl and phthalimidomethyl esters were prepared:

Phenacyl-3-isopropyl Salicylate (34): 61.8%; mp 59-61 °C (i-PrOH); ^{1}H NMR ($CDCl_3$) δ 1.23 (d, J = 7 Hz, 6 H), 3.38 (septet, J = 7 Hz, 1 H), 5.55 (s, 2 H), 6.85 (t, J = 8 Hz, 1 H), 7.30-8.05 (m, 7 H), 10.47 (s, 1 H). IR (KBr) 3130 broad (m), 3050 (m), 2980 (m), 2960 (m), 2940 (m), 2915 (m), 2860 (m), 1695 (s), 1660 (s)· 1610 (s), 1595 (s) cm^{-1}. Anal. Calcd for $C_{18}H_{18}O_4$: C, 72.47; H, 6.08. Found: C, 72.44; H, 6.16.

Phenacyl-3-ethyl-6-methyl Salicylate (35): 78%; mp 97-98.5 °C (i-PrOH); ^{1}H NMR ($CDCl_3$) δ 1.20 (t, J = 8 Hz, 3 H), 2.60 (s, 3 H), 2.67 (q, J = 8 Hz, 2 H), 5.60 (s, 2 H), 6.87 (ABq, J = 8 Hz, 2 H), 7.33-8.03 (m, 5 H), 10.88 (s, 1 H). IR (KBr) 3400 b(w), 3150 b(w), 2960 (m), 2910 (m), 2850 (m), 1695 (s), 1665 (m), 1150 (s) cm^{-1}. Anal. Calcd for $C_{18}H_{18}O_4$: C, 72.47; H, 6.08. Found: C, 72.66; H, 6.23.

Phthalimidomethyl Thymoate (36): 81.7%; mp 131.5-134 °C (i-PrOH); ^{1}H NMR ($CDCl_3$) δ 1.20 (d, J = 7 Hz, 6 H), 2.38 (s, 3 H), 3.29 (septet, J = 7 Hz, 1 H), 5.90 (s, 2 H), 6.80 (ABq, J = 8 Hz, 2 H), 7.63-8.00 (symmetric m, 4 H), 11.25 (s, 1 H). IR (KBr) 3100 broad (m), 3080 (m), 3060 (m), 3030 (m), 2960 (m), 2915 (m), 2860 (m), 1780 (m), 1725 (s), 1650 (s), 1610 (m). Anal. Calcd for $C_{20}H_{19}NO_5$: C, 67.98; H, 5.42; N, 3.96. Found: C, 67.96; H, 5.36; N, 3.97.

Phthalimidomethyl-3-isopropyl Salicylate (37): 70%; mp 105.5-107.5 °C (i-PrOH); ^{1}H NMR ($CDCl_3$) δ 1.23 (d, J = 7 Hz, 6 H), 3.36 (septet, J = 7 Hz, 1 H), 5.98 (s, 2 H), 6.75 (t, J = 8 Hz, 1 H), 7.37 (dd, J = 8 Hz and 1.5 Hz, 1 H), 7.60 (dd, J = 8 Hz and 1.5 Hz, 1 H), 7.85 (symmetric m, 4 H), 9.8 (s, 1 H). IR (KBr) 3450 broad (w), 3065 (w), 2965 (m), 2875 (w), 1790 (m), 1745 (s), 1670 (m), 1615 (m) cm^{-1}. Anal. Calcd for $C_{19}H_{17}NO_5$: C, 67.25; H, 5.05; N, 4.13. Found: C, 67.11; H, 5.23; N, 3.94.

Phthalimidomethyl-3-ethyl-6-methyl Salicylate (38): 80.7%; mp 111-111.5 °C (i-PrOH); ^{1}H NMR ($CDCl_3$) δ 1.17 (t, J = 7 Hz, 3 H), 2.40 (s, 3 H), 2.61 (q, J = 7 Hz, 2 H), 5.98 (s, 2 H), 6.83 (ABq, J = 8 Hz, 2 H), 7.83 (symmetric m, 4 H), 10.82 (s, 1 H). IR (KBr) 3200 b(w), 3050 b(w), 2960 (w), 2940 (w), 2870 (w), 1780 (m), 1730 (s), 1660 (s), 1605 (m). Anal. Calcd for $C_{19}H_{17}NO_5$: C, 67.25; H, 5.05; N, 4.13. Found: C, 66.99; H, 5.35; N, 3.92.

Dibenzyl Open-Chain Dimer(44):

The coupling of acid 27 with phenol 30 to give 44 was carried out in three consecutive steps as follows:

Sodium Salt 40: To a stirred suspension of sodium hydride (0.55 g, 13.75 mmol) in hexane (150 mL) was slowly added a solution of the benzyl thymoate (30) (3.6 g, 12.68 mmol) in hexane. The resulting suspension was stirred for 2-3 hrs in order to allow for complete salt formation (40). The hexane suspension of the sodium salt was neither isolated nor characterized and was used as such in further reactions.

Acid Chloride 39: To freshly distilled thionyl chloride (10 mL), O-benzylthymotic acid (27) (2 g, 7.04 mmol) was added. The resulting solution was refluxed for two hrs. Most of the excess thionyl chloride was removed by ordinary distillation and the last traces were removed under reduced pressure to constant weight of the residual acid chloride. ^{1}H NMR ($CDCl_3$) δ 1.18 (d, 6 H), 2.33 (s, 3 H), 3.32 (septet, 1 H), 4.92 (s, 2 H), 7.67 (m, 7 H). IR (neat) 1785 cm^{-1}. The viscous acid chloride was dissolved in hexane (30 mL) and used in the next reaction.

Coupling of Sodium Salt 40 with Acid Chloride 39: To a stirred suspension of the sodium salt of benzyl thymoate (40) (3.93 g, 12.68 mmol) in hexane (150 mL) at ambient temperature was added a solution of O-benzylthymoyl chloride (39) (2.1 g, 7 mmol) in hexane (30 mL). The resulting suspension was stirred at ambient temperature for 5-6 hrs. The completion of the reaction was followed by TLC. The suspension was filtered and the filtrate concentrated to give a viscous liquid. The filtered solid was dissolved in water and extracted with hexane. The hexane extract was dried and concentrated to give a liquid. This liquid was combined with the viscous initial liquid and purified by column chromatography (silica gel; hexane/methylene chloride). The first fraction to be eluted was benzyl thymoate (30) (1.6 g). The second fraction, eluted as an oil, was diprotected open-chain dimer 44 (3.7 g, 92.5%). ^{1}H NMR ($CDCl_3$) δ 0.88 (d, J = 7.5 Hz, 6 H), 1.21 (d, J = 7.5 Hz, 6 H), 2.19 (s, 3 H), 2.41 (s, 3 H), 3.14 (m, 2 H), 4.86 (s, 2 H), 5.15 (s, 2 H), 7.15 (m, 14 H).

O-Benzyl Open-Chain Dimer (48) By Hydrogenolysis of 44

To a solution of dibenzyl protected open-chain dimer 44 (1.8 g, 3.27 mmol) in ethanol (40 mL) was added 10% Pd/C (100 mg). The resulting suspension was hydrogenated at atmospheric pressure and ambient temperature. After completion of the hydrogenolysis of the benzyl ester with one equivalent of hydrogen, the hydrogenation was stopped and the solution filtered through celite. Ethanol was removed under reduced pressure giving a viscous liquid which was crystallized from hexane. White crystalline O-benzyl open-chain dimer 48 was obtained, mp 150-153 °C (1.1 g, 73.1%). ^{1}H NMR ($CDCl_3$) δ 0.89 (d, J = 7.5 Hz, 6 H), 1.21 (d, J = 7.5 Hz, 6 H), 2.42 (s, 6 H), 3.21 (m, 2 H), 4.98 (s, 2 H), 7.17 (m, 9 H), 11.05 (bs, 1 H). IR (KBr) 3300-2300 broad (m), 1760 (s), 1695 (s) cm^{-1}.

Phenacyl-O-benzyl Open-Chain Dimer (45)

A solution of 27 (2.98 g, 10.5 mmol) in $SOCl_2$ (20 mL) was heated at reflux for 2 hrs and concentrated to give acid chloride 39 as a viscous yellow oil. Traces of $SOCl_2$ were removed by dissolving the oil in hexane and concentrating. This was repeated a second time and 39 was then dissolved in anhydrous ether (20 mL). This ethereal solution was added to a mixture of phenacyl thymoate (33) (3.27 g, 10.5 mmol) and NaH (420 mg, 10.5 mmol) in anhydrous ether (100 mL) and the resulting mixture stirred overnight at ambient temperature. The mixture was diluted with NaOH (50 mL, 0.2 N) and EtOAc (75 mL), transferred to a separatory funnel and shaken until the solid dissolved. The layers were separated and the organic phase was washed with water (50 mL), dried and concentrated to give 6.28 g of a yellow oily solid. Recrystallization from i-PrOH gave 4.13 g (68%) of 45 as pale yellow crystals (mp 140-141.5 °C). ^{1}H NMR ($CDCl_3$) δ 1.06 (d, J = 7 Hz, 6 H), 1.24 (d, J = 7 Hz, 6 H), 2.54 (s, 6 H), 3.02-3.50 (m, 2 H), 5.01 (s, 2 H), 5.33 (s, 2 H), 6.95-7.90 (m, 14 H). IR (KBr) 3200-2400 broad(m), 1758 (s), 1695 (s) cm^{-1}. Anal. Calcd for $C_{37}H_{38}O_6$: C, 76.79; H, 6.62. Found: C, 76.42; H, 6.60.

O-Benzyl Open-Chain Dimer (48) by Zn/HCl Reduction of 45

A solution of dimer 45 (5.36 g, 9.3 mmol) in THF (200 mL) containing HCl (100 mL, 1N) was treated with Zn dust (6.08 g, 93 mmol) in several small portions over a 15 min period. The mixture was stirred 1 hr and the solution was decanted from the Zn dust and concentrated until all the THF was removed. The viscous oil which formed was extracted into CH_2Cl_2 (2 x 100 mL). The combined organic extracts were dried and concentrated to give 5.63 g of a viscous oil which

slowly crystallized on standing. Recrystallization from hexane was effected by dissolving the solid in a solution of hexane (325 mL) and $CHCl_3$ (20 mL), boiling the solution down to a volume of 150 mL, adding hot hexane (175 mL) and concentrating the solution until crystals began to form. Cooling and collecting the crystals in the normal manner gave 3.75 g (87.6%) of dimer 48 as colorless crystals (mp 149-151 °C). Recrystallization gave an analytical sample (mp 150-151 °C).[64] Anal. Calcd for $C_{28}H_{32}O_5$: C, 75.63; H, 7.00. Found: C, 75.38; H, 6.92.

Phthalimidomethyl-O-benzyl Open-Chain Dimer (46)

A solution of 1-chloro-N,N,2-trimethyl propenylamine (1.34 g, 10 mmol) in CH_2Cl_2 (50 mL) was treated with O-benzylthymotic acid (27) (2.84 g, 10 mmol) and the resulting solution was stirred at ambient temperature for 45 min. Concentration of the solution gave 39 as a colorless oil which was shown by infrared analysis to contain some unreacted 27. The oil was redissolved in CH_2Cl_2, treated with 20 drops of the enamine reagent and stirred at ambient temperature for an additional 45 min. The solution was concentrated, the remaining oil was treated with 36 (3.53 g, 10 mmol) and the mixture was dissolved in anhydrous ether (125 mL) and treated with NaH (400 mg, 10 mmol). The mixture was stirred overnight at ambient temperature, washed successively with NaOH (50 mL of 0.1 N) and water (50 mL), and dried and concentrated to give 5.89 g of colorless solid. Recrystallization from i-PrOH (150 mL) gave 46 (4.16 g, 67.2%) as colorless crystals mp 150-151.5 °C. ^1H NMR ($CDCl_3$) δ 0.9 (d, J = 7 Hz, 6 H), 1.23 (d, J = 7 Hz, 6 H), 2.30 (s, 3 H), 2.50 (s, 3 H), 2.90-3.40 (m, 2 H), 4.90 (s, 2 H), 5.80 (s, 2 H), 6.83-7.44 (m, 9 H), 7.53-7.90 (m, 4 H). IR (KBr) 3060 (w), 3040 (w), 3030 (w), 2970 (m), 2920 (m), 2870 (m), 2850 (m), 1770 (m), 1755 (s), 1730 (s), 1675 (w), 1600 (w), 1220 (m), 1090 (m), 725 (m) cm^{-1}. Anal. Calcd for $C_{38}H_{37}NO_7$: C, 73.65; H, 6.02; N, 2.26. Found C, 73.62; H, 5.97; N, 2.34.

O-Benzyl Open-Chain Dimer (48) By Zn/HCl Reduction of 46

A solution of 46 (3.1 g, 5 mmol) in THF (150 mL) containing HCl (75 mL, 1N) was treated with Zn dust (4.4 g, 67 mmol) in several small portions over a 15 min period. The mixture was stirred 1 hr and the solution was decanted from the Zn dust and concentrated until the THF was removed. The viscous oil which formed was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic extracts were dried and concentrated to give 3.29 g of a colorless oil which failed to crystallize and which could not be dissolved in hot hexane. The oil was taken up in ether (100 mL) and extracted with small portions of NaOH (7 x 25 mL). The combined aqueous extracts were acidified to pH 1 with 3 N HCl and extracted with portions of CH_2Cl_2 (3 x 50 mL). The combined organic extracts were dried and concentrated to give a colorless oil which was crystallized from hexane to give 48 (0.85 g, 37%) as colorless crystals mp 144-149 °C. The spectral data of 48, thus synthesized, was identical to that of 48 prepared by hydrogenolysis of 44 and Zn reduction of 45.

Phenacyl-O-benzyl Open-Chain Dimer (47)

A solution of 1-chloro-N,N,2-trimethylpropenylamine (0.67 g, 5 mmol) in CH_2Cl_2 (50 mL) was treated with 27 (1.42 g, 5 mmol) and the resulting solution was stirred at ambient temperature for 30 min. Solvent was removed to give O-benzylthymoyl chloride (39) as a colorless oil. IR analysis indicated clean and complete formation of 39. (IR, neat, 1785 cm^{-1}). This oil was dissolved in anhydrous ether (50 mL) along with 32 (1.49 g, 5 mmol) and treated with NaH (200 mg, 5 mmol). The resulting mixture was stirred overnight at ambient temperature. The mixture was washed successively with 0.1 N NaOH (25 mL) and water (25 mL), dried and concentrated to give 2.39 g of 47 as a viscous pale yellow oil. The oil could not be crystallized and was used directly in the next reaction. ^1H NMR ($CDCl_3$) δ 0.88-1.34 (m, 9 H), 2.49 (q, J = 8 Hz, 2 H), 2.48 (s, 3 H), 2.50 (s, 3 H), 3.26 (septet, J = 7 Hz, 1 H), 4.98 (s, 2 H), 5.30 (s, 2 H), 6.72-7.87 (m, 14 H).

O-Benzyl Open-Chain Dimer (49) By Zn/HCl Reduction of 47

A solution of 47 (2.39 g, 4.2 mmol) in THF (100 mL) containing HCl (53 mL, 1 N) was treated with Zn dust (2.75 g, 42 mmol) in several small portions over a 10 min period. The mixture was stirred for 1 hr and the solution was decanted from the Zn dust and concentrated until the THF was removed. The viscous oil which formed was extracted with CH_2Cl_2 (2 x 50 mL). The combined organic extracts were dried and concentrated to give 2.0 g of a yellow solid. Recrystallization from hexane gave 49 (1.1 g, 49% for the coupling and reduction) as colorless crystals (mp 171-173 °C). ^1H NMR ($CDCl_3$) δ 0.92 (t, J = 7 Hz, 3 H), 1.36 (d, J = 7 Hz, 6 H), 2.52 (q, J = 8 Hz, 2 H), 2.40 (s, 3 H), 2.46 (s, 3 H), 3.38 (septet, 1 H), 5.03 (s, 2 H), 6.95-7.60 (m, 9 H), 9.28 (bs, 1 H). IR (KBr) 3300-2300 broad (m), 1758 (s), 1695(s) cm^{-1}. Anal. Calcd for $C_{28}H_{30}O_5$: C, 75.31; H, 6.77. Found: C, 75.42; H, 6.77.

Dibenzyl Open-Chain Trimer (57)

A solution of 1-chloro-N,N,2-trimethylpropenylamine (0.54 g, 4 mmol) in CH_2Cl_2 (15 mL) was treated with 48 (1.84 g, 4 mmol) and the resulting solution was stirred at ambient temperature for 45 min. Solvent was removed giving a colorless oil. IR spectroscopic analysis indicated the presence of a small amount of 48 along with 52. The oil was then redissolved in CH_2Cl_2, treated with 25 drops of the chloroenamine and stirred another 45 min. Removal of the solvent and IR analysis showed complete formation of 52. The oil was dissolved in anhydrous ether (50 mL) and 54 (1.136 g, 4 mmol) along with NaH (160 mg, 4 mmol) was added. The resulting mixture was allowed to stir overnight at ambient temperature, washed successively with 0.1 N NaOH (25 ml) and water (25 mL), dried and concentrated to give 3.10 g (103%) of crude trimer 57 as a viscous pale yellow oil. This oil could not be crystallized and was used directly in the next reaction. ^1H NMR ($CDCl_3$) δ 0.92 (t, J = 7 Hz, 3 H), 1.36 (d, J = 7 Hz, 6 H), 2.52 (q, J = 8 Hz, 2 H), 2.40 (s, 3 H), 2.46 (s, 3 H), 3.38 (septet, 1 H), 5.03 (s, 2 H), 6.95-7.60 (m, 9 H).

Open-Chain Trimer (61)

A solution of crude diprotected trimer 57 (3.1 g, 4 mmol) in EtOAc (50 mL) was hydrogenated over 10% Pd/C (400 mg) at 1 atm pressure and ambient temperature. The reaction was allowed to proceed until uptake of hydrogen ceased (240 mL). The catalyst was removed by filtration through celite and the filtrate was concentrated to give 2.36 g of a viscous colorless oil which was crystallized from hexane. Recrystallization from hexane gave 1.29 g (59.1%) of 61 as color-

less crystals (mp 176-178 °C). ^{1}H NMR ($CDCl_3$) δ 0.92 (dd, J = 7 Hz and 3 Hz, 6 H), 1.0-1.3 (m, J = 7 Hz, 12 H), 2.33 (s, 3 H), 2.55 (s, 3 H), 2.65 (s, 3 H), 2.7-3.5 (m, 3 H), 6.68 (d [of ABq], J = 8 Hz, 1 H), 6.9-7.33 (m, 4 H), 7.42 (d [of ABq], J = 8 Hz, 1 H), 7.7 (bs, 1 H), 11.7 (bs, 1 H). IR (KBr) 3500-2300 broad (s), 3100 (m), 3050 (m), 1745 (s), 1700 (s), 1660 (m), 1610 (m), 1220 (s) cm^{-1}. Anal. Calcd for $C_{33}H_{36}O_7$: C, 72.50; H, 7.01. Found: C, 72.72; H, 7.14.

Dibenzyl Open-Chain Trimer (58)

A solution of 1-chloro-N,N,2-trimethyl propenyl amine (0.54 g, 4 mmol) in CH_2Cl_2 (15 mL) was treated with 48 (1.84 g, 4 mmol) and the resulting solution was stirred at ambient temperature for 45 min. Solvent was removed to give 52 as a colorless oil. IR and ^{1}H NMR analysis indicated clean and complete formation of 52. [^{1}H NMR ($CDCl_3$) δ 0.90 (d, J = 7 Hz, 6 H), 1.23 (d, J = 7 Hz, 6 H), 2.40 (s, 3 H), 2.50 (s, 3 H), 3.0-3.5 (m, 2 H), 5.02 (s, 2 H), 7.04 (d, J = 8 Hz, 1 H), 7.10 (d, J = 8 Hz, 1 H), 7.18-7.50 (m, 7 H). IR (neat) 3090 (w), 3060 (w), 3030 (m), 2960 (s), 2930 (s), 2870 (m), 1785 (s), 1750 (s), 1650 (s) cm^{-1}]. This oil was dissolved in anhydrous ether (50 mL) along with 55 (1.08 g, 4 mmol) and treated with NaH (160 mg, 4 mmol). The resulting mixture was stirred overnight at ambient temperature. The mixture was washed successively with 0.1 N NaOH (25 mL) and water (25 mL), dried and concentrated to give 2.85 g of diprotected trimer 58 as a viscous pale yellow oil. A small portion of this oil crystallized on standing and was recrystallized from hexane to give an analytical sample of 58 (mp 99-104 °C). ^{1}H NMR ($CDCl_3$) δ 0.85 (t, J = 8 Hz, 3 H), 0.91 (d, J = 7 Hz, 6 H), 1.18 (d, J = 7 Hz, 6 H), 2.05-2.30 (m, 2 H), 2.18 (s, 3 H), 2.21 (s, 3 H), 2.39 (s, 3 H), 2.9-3.40 (m, 2 H), 5.03 (s, 2 H), 5.19 (s, 2 H), 6.78-7.50 (m, 16 H). Anal. Calcd for $C_{46}H_{48}O_7$: C, 77.50; H, 6.79. Found: C, 77.72; H, 6.68.

Open-Chain Trimer (62)

A solution of 58 (2.85 g, 4 mmol) in EtOAc (50 mL) was hydrogenated over 10% Pd/C (400 mg) at 1 atm pressure and ambient temperature. The reaction was allowed to proceed until the uptake of H_2 ceased (210 mL). The catalyst was removed by filtration through celite and the filtrate was concentrated to give 2.31 g of a colorless viscous oil which slowly crystallized on standing. Recrystallization from hexane gave 1.29 g (60.6%) of 62 as colorless crystals (mp 164-168 °C). A second recrystallization of a small sample gave analytically pure 62 (mp 169-170 °C). ^{1}H NMR ($CDCl_3$) δ 0.85-1.33 (m, 15 H), 2.33 (q, J = 7 Hz, 2 H), 2.33 (s, 3 H), 2.55 (s, 3 H), 2.68 (s, 3 H), 2.82-3.49 (m, 2 H), 6.69 (d [of ABq], J = 8 Hz, 1 H), 6.9-7.3 (m, 4 H), 7.4 (d [of ABq], J = 8 Hz, 1 H), 8.9 (bs, 1 H), 11.19 (bs, 1 H). IR (KBr) 3500-2300 broad (m), 3050 broad (m), 2960 (s), 2920 (s), 2870 (m), 1760 (s), 1700 (s), 1660 (s), 1610 (m), 1220 (s) cm^{-1}. Anal. Calcd for $C_{32}H_{36}O_7$: C, 72.16; H, 6.81. Found: C, 71.85; H, 6.71.

Dibenzyl Open-Chain Trimer (59)

A solution of 1-chloro-N,N,2-trimethylpropenylamine (0.45 g, 3.44 mmol) in CH_2Cl_2 (50 mL) was treated with 49 (1.5 g, 3.4 mmol) and the resulting solution was stirred at ambient temperature for 30 min. Solvent was removed to give acid chloride 53 as a colorless oil. IR spectroscopic analysis indicated clean and complete formation (IR, neat, 1785 cm^{-1}). This oil was dissolved in anhydrous ether (50 mL) along with ester 55 (0.91 g, 3.4 mmol) and treated with NaH (130 mg, 3.4 mmol). The resulting mixture was stirred overnight at ambient temperature. The mixture was then washed successively with 0.1 N NaOH (25 mL) and water (25 mL), dried and concentrated to give diprotected open-chain trimer 59 (2.2 g) as a viscous pale yellow oil. The oil could not be crystallized and was used "as is" in the next reaction. ^{1}H NMR ($CDCl_3$) δ 0.60-1.33 (m, 12 H), 2.00-2.68 (m, 13 H), 3.38 (septet, J = 7 Hz, 1 H), 5.00 (s, 2 H), 5.17 (s, 2 H), 6.70-7.45 (m, 16 H).

Open-Chain Trimer (63)

A solution of 59 (2.2 g, 3.15 mmol) in EtOAc (50 mL) was hydrogenated over 10% Pd/C (35 mg) at 1 atm pressure and ambient temperature. The reaction was allowed to proceed until the uptake of H_2 ceased (173 mL). The catalyst was removed by filtration through celite and the filtrate was concentrated to give 1.35 g of a colorless viscous oil which was crystallized from hexane. This gave open-chain trimer 63 (7 g, 43% for the coupling and reduction) as white crystals. Recrystallization from 95% ethanol gave analytically pure 63 (mp 167-168.5 °C). ^{1}H NMR ($CDCl_3$) δ 0.8-1.35 (m, 12 H), 2.12-2.80 (m, 4 H), 2.34 (s, 3 H), 2.57 (s, 3 H), 2.68 (s, 3 H), 3.26 (septet, J = 7 Hz, 1 H), 6.65 (d [of ABq], J = 8 Hz, 1 H), 6.8-7.48 (m, 4 H), 7.35 (d [of ABq], J = 8 Hz, 1 H), 9.8 (s, 1 H), 11.2 (s, 1 H). IR (KBr) 3500-2300 broad (s), 1755 (s), 1695 (s), 1665 (s), 1610 (m) cm^{-1}. Anal. Calcd for $C_{31}H_{34}O_7$: C, 71.80; H, 6.61. Found: C, 71.76; H, 6.69.

Dibenzyl Open-Chain Trimer (60)

A solution of 0.29 g (2.2 mmol) of 1 chloro-N,N,2-trimethylpropenyl-amine in CH_2Cl_2 (50 mL) was treated with 48 (1.00 g, 2.2 mmol). The resulting solution was stirred at ambient temperature for 30 min. Solvent was removed to give acid chloride 52 as a colorless oil. IR spectroscopic analysis indicated clean and complete formation of 52. This oil was dissolved in anhydrous ether (50 mL) along with 56 (0.59 g, 2.2 mmol) and treated with NaH (89 mg, 2.2 mmol). The resulting mixture was stirred overnight at ambient temperature. The mixture was washed successively with 0.1 N NaOH (25 mL) and water (25 mL), and dried and concentrated to give 1.62 g of 60 as a viscous pale yellow oil. The oil could not be crystallized and was used "as is" in the next reaction. ^{1}H NMR ($CDCl_3$) δ 1.05 (m, 18 H), 2.21 (s, 3 H), 2.51 (s, 3 H), 5.07 (s, 2 H), 5.17 (s, 2 H), 7.30 (m, 17 H).

Open-Chain Trimer (64)

A solution of crude 60 (1.62 g, 2.2 mmol), in EtOAc (100 mL) was hydrogenated over 10% Pd/C (220 mg) at 2 atm pressure. The reaction was allowed to proceed overnight. The catalyst was removed by filtration through celite and the filtrate was concentrated to give 1.17 g of a colorless viscous oil. The oil was crystallized from 95% ethanol and gave 64 (617.9 mg, 53% for the coupling and reduction), mp 194-198 °C. Recrystallization gave an analytical sample mp 202-203.5 °C. ^{1}H NMR ($CDCl_3$) δ 0.88-1.28 (m, 18 H), 2.57 (s, 3 H), 2.6 (s, 3 H), 2.8-3.43 (m, 3 H), 6.67 (d [of ABq], J = 8 Hz, 1 H), 7.0-7.5 (m, 5 H), 7.82 (dd, J = 8 Hz and 1.5 Hz, 1 H), 9.82 (s, 1 H), 11.3 (s, 1 H). IR (KBr) 3500-2200 broad (s), 1740 (s), 1695 (s), 1660 (s), 1610 (m) cm^{-1}. Anal. Calcd for $C_{32}H_{36}O_7$: C, 72.16; H, 6.81. Found: C, 72.35; H, 6.76.

Cyclization of Open-Chain Trimers with Trifluoroacetic Anhydride (TFAA) and Phosphorous Oxychloride ($POCl_3$)

Trifluoroacetic Anhydride (TFAA)

TOT (1)

Open-chain trimer 61 (50 mg, 10.092 mmol) was dissolved in dry benzene (10 mL) and to this solution was added TFAA (0.2 mL, 1.4 mmol). The mixture was placed in the refrigerator (10 °C) overnight. The reaction mixture was then concentrated to give a colorless oil. Crystallization was induced by dissolving the oil in hot absolute ethanol and cooling. Filtration afforded TOT (1) (27.4 mg, 57%) as its ethanol complex (mp 172-200 °C).[53] ^1H NMR ($CDCl_3$) δ 1.13-1.30 (m, 18 H), 2.48 (s, 9 H), 3.02 (septet, J = 7 Hz, 3 H), 7.30 (ABq, J = 8 Hz, 6 H). IR (KBr) 3060 (w), 3030 (w), 2960 (m), 2925 (m), 2870 (m), 1765 (s), 1750 (m), 1215 (s), 1090 (s) cm^{-1}.

Using the procedure for the preparation of TOT (1) the following TOT analogous were synthesized:

9: 60%; mp 210.5-212.5 °C (absolute EtOH); ^1H NMR ($CDCl_3$) δ 1.07-1.44 (m, 15 H), 2.40-2.75 (m, 11 H), 2.88-3.30 (m, 2 H), 7.03-7.50 (m, 6 H). IR (KBr) 3065 (w), 3030 (w), 2970 (m), 2930 (m), 2870 (m), 1765 (s), 1750 (s), 1215 (s), 1090 (s) cm^{-1}. MS (m/e) 514 (M^+), 352, 338, 176, 162, 148. Anal. Calcd for $C_{32}H_{34}O_6$: C, 74.69; H, 6.66. Found: C, 74.80; H, 6.89.

10: 65%; mp 180.5-182 °C (absolute EtOH); ^1H NMR ($CDCl_3$) δ 1.02-1.34 (m, 12 H), 2.38-2.75 (m, 4 H), 2.48 (s, 9 H), 3.04 (septet, J = 7 Hz, 1 H), 7.08-7.52 (m, 6 H). IR (KBr) 3050 (w), 2970 (m), 2930 (m), 2870 (m), 2850 (m), 1760 (s), 1745 (s), 1220 (s), 1105 (s), 825 (m) cm^{-1}. Anal. Calcd for $C_{31}H_{32}O_6$: C, 74.37; H, 6.45. Found: C, 74.50; H, 6.52.

Phosphorous Oxychloride

Cyclic Trimer 9

Method A:

A solution of 62 (532 mg, 1 mmol) in anhydrous xylenes (100 mL) was slowly added over a period of 6-8 hrs to a stirred, hot (110 °C) solution of $POCl_3$ (10 mL) in anhydrous xylenes (500 mL). The solution was stirred overnight at 110 °C and concentrated giving a brown oil. This oil was taken up in CH_2Cl_2 (75 mL), washed successively with water (25 mL) and 1 N NaOH (25 mL), dried and concentrated to give 0.70 g of a brown oil. This oil was dissolved in hot EtOH (20 mL) and allowed to stand at ambient temperature overnight giving cyclic trimer 9 (170 mg, 33.1%) as brown crystals (mp 210-215 °C). The ^1H NMR spectrum was identical with that of the material obtained by cyclization of 62 with TFAA. The mother liquor was concentrated and the residue was chromatographed on a 2 mm thick silica gel plate using C_6H_6 as the eluent. The fastest moving band was removed to give 370 mg of brown oil which was shown by IR spectroscopy to be mostly material resulting from cleavage of the ester groups and subsequent decarboxylation.

Method B:

A solution of the open-chain trimer 62 (100 mg, 0.19 mmol) in freshly distilled $POCl_3$ (30 mL) was added over three hrs to refluxing $POCl_3$ (10 mL). After completion of addition, refluxing was continued for another hr. Most of the $POCl_3$ was removed by ordinary distillation and the last traces were removed under reduced pressure. The residue thus obtained was dissolved in methylene chloride. The solution was then washed with $NaHCO_3$ and dried over Na_2SO_4. Evaporation of the methylene chloride gave a solid (90 mg) which was recrystallized from hexane/CH_2Cl_2 affording cyclic trimer 9 (40 mg, 40.8%) as a white solid (mp 214-217 °C). The ^1H NMR spectrum of this sample of 9 was identical to that obtained from the cyclization of 62 with TFAA.

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