calcd for $C_{20}H_{32}O_2$ 304.2400, found 304.2400.

11a from **11** as colorless needles (90%): mp 117 °C (benzene); IR (CCl_4) 3632, 3584, 2936, 1642, 1210 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.43 (1 H, b t, J = 8.3 Hz), 4.8 (3 H, m), 4.72 (1 H, d, J = 2.4 Hz), 3.82 (1 H, d, J = 9.5 Hz), 3.45 (1 H, dd, J = 9.5, 3.0 Hz), 1.77 (3 H, s), 1.63 (6 H, s), 1.55 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 144.8 (s), 133.9 (s), 133.3 (s), 131.8 (s), 128.7 (d), 127.2 (d), 122.0 (d), 115.6 (t), 80.1 (d), 75.5 (d), 45.2 (d), 39.0 (t), 36.5 (t), 28.7 (t), 26.9 (t), 24.8 (t), 21.6 (q), 15.7 (q), 15.5 (q), 11.4 (q); MS m/z 304 (M^+, 4), 286, 234, 203, 109, 95, 81 (100). Anal. Calcd for $C_{20}H_{32}O_2$: C, 78.90; H, 10.59. Found: C, 78.72; H, 10.53.

12a from **12** as colorless needles (58%): mp 89 °C (benzene-/hexane); IR (CCl_4) 3624, 2924, 1442, 1386, 1062, 1006, 900 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.52 (1 H, b t, J = 8.0 Hz), 5.0 (2 H, m), 4.85 (1 H, m), 4.70 (1 H, m), 4.04 (1 H, d, J = 3.1 Hz), 3.76 (1 H, dd, J = 7.9, 3.1 Hz), 1.70 (3 H, s), 1.65 (6 H, s), 1.55 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 145.1 (s), 134.0 (s), 133.5 (s), 133.0 (s), 127.8 (d), 127.3 (d), 122.0 (d), 115.5 (t), 80.0 (d), 77.1 (d), 44.0 (d), 39.6 (t), 36.2 (t), 28.5 (t), 26.6 (t), 24.6 (t), 21.6 (q), 15.8 (q), 15.3 (q), 11.8 (q); MS m/z 304 (M^+, 4), 286, 271, 203, 137, 121, 109, 95, 84 (100); HRMS calcd for $C_{20}H_{32}O_2$ 304.2400, found 304.2403.

Supplementary Material Available: ^1H NMR for compounds **2a-e, 5b-e, 6b, 6c, 6e, 7b-e, 8b, 8c, 9c-e, 10a, 10c, 10e, 11, 11a, 12, 12a,** and **13** (29 pages). Ordering information is given on any current masthead page.

Improved Preparation of the Clathrate Host Compound Tri-*o*-thymotide and Related Trisalicylide Derivatives

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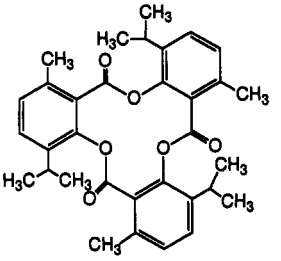
In order to improve the relatively low yield (ca. 35%) previously observed in the synthesis of tri-*o*-thymotide (TOT, **1**) from *o*-thymotic acid (**2**), the cyclodehydration was studied using a variety of conditions. The low yield is due to the formation of di-*o*-thymotide (DOT, **3**), previously reported, and at least three other products (**4-6**), which apparently result from the acid-catalyzed decarboxylation of **2** and subsequent condensation with thymol (**7**). Using pyridine as a solvent, side-product formation is inhibited. Under appropriate conditions, namely, neat $POCl_3$ at 50 °C, the yield of **1** is 93%. Other salicylic acid derivatives also give high yields of the corresponding "trimers" under these conditions, thus providing a general, improved preparation of a family of potential clathrate host substances.

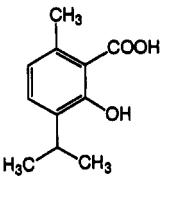
Introduction

The study of clathrate inclusion phenomena continues to command the attention of chemists and technologists because of the intrinsic scientific interest in clathrate formation and properties (bringing two different substances together in a crystalline array and generating new and different properties compared to either of the components) and also because of the many potential applications of such systems.[1-4] The well-known host substance tri-*o*-thymotide (TOT, **1**) has been especially well-studied:[5] cage- and channel-type inclusion complexes and six additional clathrate types have been recognized;[6-11] most TOT (**1**) complexes are chiral[11] (i.e., they have enantiomorphic space groups). Some of the specific applications for which TOT (**1**) clathrates have been used include the following: (a) media for chemical reactions of included guests,[6] as well as asymmetric reactions;[12] (b) agents for optical resolutions and configuration determination of guest species;[13] (c) chromatography supports;[14] (d) host species for studying guest molecular motion;[15] (e) matrix isolation of labile species;[16] (f) separation of terpenes (menthone, carvacrol, etc.) in essential oils;[17] (g) separation of specific hydrocarbons from complex mixtures;[18] (h) a medium for effecting second harmonic generation (nonlinear optical effect).[19]

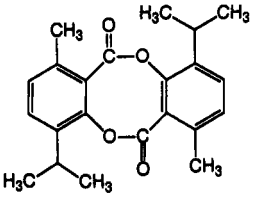
Except for the reported synthesis[20] of **1** in 1952 and a very recent stepwise strategy for preparing nonsymmetrical trimers,[21] no studies on the synthesis of **1** have been described. We herein report a study of the original cyclodehydration reaction and describe the side products pro-



Tri-*o*-Thymotide (TOT, 1)



o-Thymotic acid (2)



Di-*o*-Thymotide (DOT, 3)

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† The Hebrew University.
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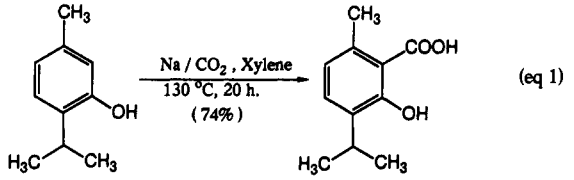
duced. Because of this study we are able to present a simple and high yield method for the preparation of 1.

Results and Discussion

Synthesis of *o*-Thymotic Acid (2). Carboxylation of thymol (7) using the Kolbe–Schmitt reaction proceeded in 35% yield according to Spallino and Provenzal.[22] By increasing the reaction time from 5 to 20 h and by using dry carbon dioxide, dry xylene, and efficient condenser cooling (to prevent the loss of 7 from the refluxing xylene), the yield of *o*-thymotic acid (2) was raised to 74% (eq 1).



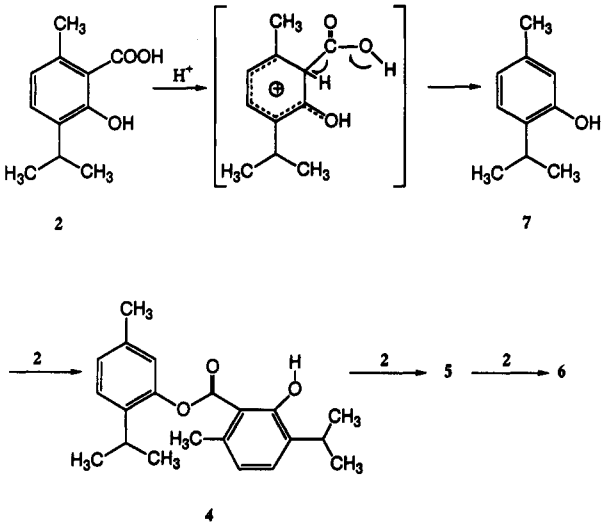
(eq 1)

7 2

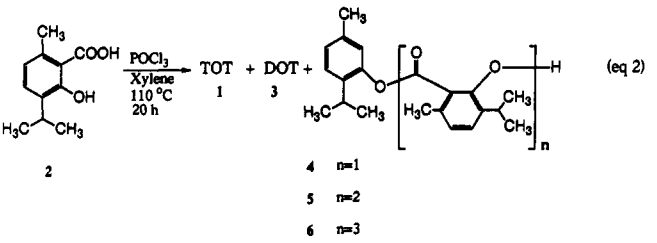
Synthesis of TOT (1). TOT (1) has been synthesized from 2 in several laboratories using a variety of dehydrating agents and conditions.[22-27] All of these methods suffer from a number of drawbacks: (1) low yields of 1 (not more than ca. 35%); (2) cyclic and acyclic dimers along with decarboxylated side products are also generally produced in the reaction, and therefore tedious purification procedures are required in order to obtain pure product; (3) lengthy reaction times (from 14 to 48 h); (4) in some cases dimer, instead of the desired trimer, is obtained.

In order to improve the yield of 1, the reactions of 2 with a variety of condensation agents, e.g., trifluoroacetic anhydride (TFAA), dicyclohexylcarbodiimide (DCC), and phosphorus oxychloride ($POCl_3$), were carried out. Since TFAA[28] had been used successfully[21] to prepare 1 from the corresponding open chain trimer (9), we considered the possibility of using this reagent directly in the cyclodehydration of 2. However, when 2 was treated with 30 molar equiv of TFAA, 1 was not formed. IR and ^1H NMR spectral analysis showed a complex mixture of open-chain ester products. Cyclodehydration of 2 with DCC gave, after workup, an oil which solidified on cooling. Crystallization from ethanol gave the cyclic dimer (DOT, 3). Chromatography of the residue afforded 1 in 5% yield as a white solid. Baker and co-workers studied[20] the action of P_2O_5 or $POCl_3$ in 2 in boiling xylene. In each case they obtained 3 and 1, which were separated by fractional crystallization and hand sorting. Higher anhydro derivatives (tetramer, pentamer, or hexamer) were not formed, and no additional products were reported. Until now 1 has most conveniently been prepared from 2 by reaction with $POCl_3$ in xylene at 100 °C for 12 h, in 35% yield.[20]

Scheme I



A careful reinvestigation of the synthesis described above indicated that besides the dimer (3), three other side products (4–6) were formed[29] (method A). The five products 1 and 3–6 (eq 2) were isolated and purified by column chromatography and identified by mp, microanalysis, and mass, ultraviolet, and proton NMR spectral analyses. The esters 4–6 were also hydrolyzed in aqueous base and afforded a 2:7 ratio of 1:1, 2:1, and 3:1, respectively, as expected from their constitution.



(eq 2)

The Mechanism of Decarboxylation. Side products 4–6 arise from acid-catalyzed decarboxylation of 2. Thymol (7) that is formed can then condense with one or more molecules of 2 to yield the observed products (Scheme I). The intermediate structure (a protonated β-keto acid) shown, involving ipso addition of a proton to 2, may be analogous to addition of Br^+ to salicylic acids which leads to their decarboxylation.[30] The formation of acid certainly occurs immediately upon reaction of $POCl_3$ with 2. Consistent with this mechanism is the finding that the reaction in the presence of pyridine (3 equiv relative to $POCl_3$) under otherwise identical conditions revealed no detectable amounts of the decarboxylated side products 4–6; only 3 and 1 were formed. Acid-catalyzed decarboxylation of 2

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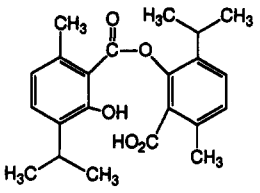
also occurred when a xylene solution was heated with dry HCl. Without acid, decarboxylation does not occur even under drastic conditions. The pure acid **2** could be sublimed unchanged at 127 °C; thus, thermal decarboxylation does not play a role in the formation of **4–6**. The distributions of products **1** and **3–6** were identical when the esterification was performed at 50 or 100 °C.

The facile reaction of **2** with **7** in the presence of $POCl_3$ under the reaction conditions was demonstrated independently using equimolar quantities; the product **4** was isolated in 78% yield. Thus, the bimolecular reaction of **2** with **7** is preferred over reaction between two molecules of **2**.

One might have though that in competition with **3** and **1**, the open-chain dimer **8** or trimer **9** would decarboxylate before ring closure[29] to give **4** and **5**, respectively. However, independently synthesized samples[21] of **8** or **9**, when heated under the reaction conditions (100 °C, 15 h), led in conversion (5–10%) to cyclic products **3** and **1**; **4** and **5** were not detected. Heating the open-chain acids **8** or **9** in xylene alone under the same conditions led to no detectable change. Free acids **8** and **9** probably cannot even exist as such under the reaction conditions but are most probably present as mixed anhydrides of phosphoric acid.[31]



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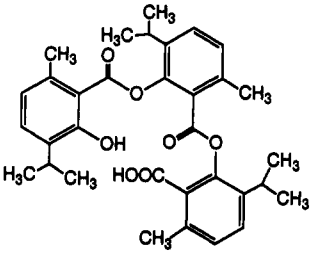
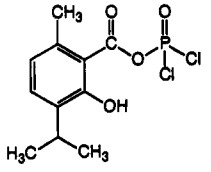


9

The mechanism of the dehydration of **2** by $POCl_3$ has not been investigated and the presence of intermediates such as **10–12** has not been established. Some very preliminary ^{31}P NMR studies showed that several different species are present.



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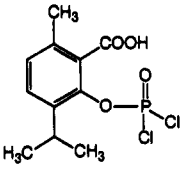

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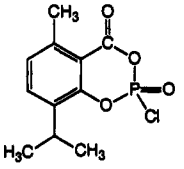

12

Stability of *o*-Thymotides. We have found that *o*-thymotides **1** and **3** are much more stable than the corresponding salicylides and cresotides.[20] They are unaffected chemically under the following conditions: (a) boiling 95% acetic acid in water for 24 h; (b) $POCl_3$, xylene, 100 °C, 15 h; (c) $POCl_3$, xylene, water, 100 °C, 45 h; (d) toluene, 100 °C, 15 h; and (e) xylene, 140 °C, 24 h. They are only very slowly hydrolyzed (after ~3–7 days, yield ~90%) in dilute aqueous NaOH (<30%) heated to reflux. All of these conditions[24,25] cause rapid hydrolysis of disalicylides and dicresotides. Alkaline hydrolysis of both thymotides **1** and **3** was effected, however, under more vigorous conditions. Dimer **3** was hydrolyzed with aqueous NaOH (50%, 100 °C, 3 days), and **1** was hydrolyzed using 10% ethanolic KOH (reflux, 9 h). Both compounds give exclusively acid **2** on hydrolysis. Reaction of **3** with excess benzylamine gave *N*-benzyl-*o*-thymotamide;[20] reaction with 0.5 equiv of benzylamine gave *N*-benzyl-*O*-*o*-thymotoyl-*o*-thymotamide.[20] The latter reactions are of interest because of the potential utility of the open chain protected dimers and trimers in the preparation of tetramers, pentamers, and hexamers as well as other higher order cyclic oligomers. Steric factors probably account for this marked stability of **3** and **1** toward hydrolysis.[20]

Absence of Higher Anhydro Products. In the cresotides and salicylides, larger cycles containing 4- and 6-monomeric members are also formed.[24,25] It is interesting to note that in the *o*-thymotide series, these are not formed in detectable quantities. The presence of **6** suggests that the precursor of the tetra-*o*-thymotide might be formed. One may speculate whether the substituents that are controlling the distribution of products formed from the various monomers change the relative stability of the different cycles or only the rates of their formation. We have not examined this question, but one experiment we have performed implies that **1** *is* more stable than **3**, assuming that the reactions are carried out under equilibrating conditions. In this experiment **3** and **1** (2×10^{-4} mol) were separately heated in xylene (1 mL) containing $POCl_3$ (0.2 mL) for 15 h at 100 °C. No change was observed for either case. However, when water (0.5 mL) was subsequently added to each reaction and the heating was continued for an additional 45 h, **1** was left unchanged while **3** was partially converted to **1** to another unidentified substance; on the basis of mass spectral analysis, this material was not the tetramer or hexamer. Interestingly, similar experiments reported in the literature[24,25] with different cresotides and salicylides show some conversion of smaller to larger rings, the size of the ring being dependent upon the substituents.

Improved Synthesis of 1. On the basis of our results and those of others using various reagents to effect the dehydration step, it appeared that $POCl_3$ was the best reagent for conversion to **1**. We therefore attempted to define the optimal conditions using this reagent, varying the amount and type of solvent, reaction time, and temperature. The most critical factor was found to be the concentration of the reagents. There was a direct correlation between the concentration of the reagents and the selectivity of the reaction for the production of **1**. The higher the concentration of **2**, the more selective the reaction. The optimal conditions were found to be neat $POCl_3$ with a 1:1.1 molar ratio of **2**:$POCl_3$ and a temperature of 100 °C for 2 h (method B). The simple workup is modified as compared with earlier procedures and involves slowly transferring the reaction mixture to ice water and extracting with ethyl acetate, drying, evaporating, and crystallizing from ethanol. This procedure gives an 84% yield of the crystalline ethanol complex. The yield is further improved (93%) by carrying out the reaction at 50 °C, but then the reaction time required is 48 h (method C). It was also possible to filter the product **1** directly after quenching the reaction mixture with water. This crude product is adequate for some purposes but still contains small quantities of **2**. The absence of the side products at high concentration of **2** is believed to be due to the

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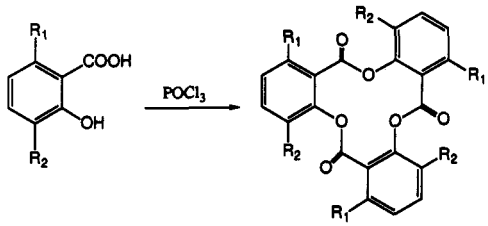
Scheme II



Salicylic acid	R_1	R_2	Trimer	Yield (%) (methods) A	B	C
2	Me	i-Pr	1	31	84	93
13	Me	Et	17	27	64	-
14	H	i-Pr	18	31	76	-
15	H	n-Pr	19	22	84	-
16	i-Pr	Me	20	29	65	-

competition between the pathways of protonation and dehydration with the latter bimolecular reaction being favored at higher concentration of 2.

Generality of Improved Method. The high-yield cyclization method would be of further value if it were generally useful for the preparation of substituted salicylic acids. In order to establish the generality of the reaction in neat $POCl_3$, a number of additional salicylic acid derivatives (13–16, Scheme II) were prepared and cyclodehyrated using both standard conditions (method A) and neat $POCl_3$ (method B). In all cases studied the isolated yields are 2–4 times higher with the newer method (method B). As described for 1, the high yield simplifies and expedites the isolation of pure products, 17–20 (Scheme II).

Conclusions

A simple modification of the literature method[20] has allowed us to improve the yield of 1 and other analogues (17–20) several fold. These potential host compounds may now be obtained in high yield and in a high state of purity without the lengthy purification procedure previously used. This provides ready access to new or previously unstudied macrolites for the study of host–guest enclathration phenomena.

Experimental Section

General. Melting points are uncorrected. ^1H NMR spectra were obtained at 100 or 300 MHz. Xylene was purified by distillation and dried over sodium. $POCl_3$ was purified by distillation before use or was obtained from BDH company. TLC was performed on silica gel 60 F_{254} precoated plates (layer thickness 0.2 mm). Silica gel for column chromatography was obtained from Merck and Co. (silica gel 40 A, surface area 67 m^2/g, pore volume 0.68 cm^2/g, mesh size 35–70). The detection of starting material and determination of reaction products was conveniently performed using TLC; the absence of a spot was significant since even traces of all compounds 1–9 and 13–20 could easily be detected.

3-(2-Propyl)-6-methyl-2-hydroxybenzoic Acid (2). Into a three-necked round-bottomed flask (5 L) fitted with a mechanical stirrer, a gas inlet tube, and a efficient condenser, there was introduced first analytical grade xylene (3.75 L) and then 7 (300.0 g 2.0 mol). The mixture was stirred vigorously while sodium (100 g, 4.35 mmol) was added over 5 h. The mixture was stirred and heated (110–130 °C) as a rapid stream of CO_2 was bubbled through the solution for 24 h. The mixture soon became very dark in color. The mixture was cooled, with stirring, to ambient temperature, and then the CO_2 was disconnected. Excess sodium was destroyed by the addition of 2-propanol (500 mL) followed by water (500 mL). The reaction mixture was acidified with aqueous HCl (ca 1:1), and the organic layer was extracted four times with 250-mL portions of $NaHCO_3$ (5%). The combined aqueous extracts were acidified with concentrated HCl, and the precipitate was collected and dried. Recrystallization from *n*-hexane gave 2 (287 g, 74%) as pale yellow crystals, mp 127 °C [lit.[22] mp 127 °C].

The following four compounds (13–16) were prepared in the same manner as 2. The scale (moles of the phenol), solvent volume, reaction temperature, and time are given in that order.

3-Ethyl-6-methyl-2-hydroxybenzoic acid (13): 0.10 mol, 350 mL, 135 °C for 24 h; yield 30%; mp 140–2 °C (CCl_4) [lit.[21] mp 140.5–142 °C].

3-(2-Propyl)-2-hydroxybenzoic acid (14): 0.10 mol, 250 mL, 140 °C for 20 h; yield 38%; mp 67–70 °C (*n*-hexane) [lit.[21] mp 69–71 °C].

3-(1-Propyl)-2-hydroxybenzoic acid (15): 0.17 mol, 200 mL, 135 °C for 14 h; yield 58%; mp 86–89 °C (*n*-hexane); IR (KBr) 1656 cm^{-1} (C=O); MS 180 (M^+, $C_{10}H_{12}O_3$), 162, 151, 147, 134; ^1H NMR ($CDCl_3$) δ 0.97 (t, J = 7 Hz, 3 H), 1.65 (sextet, J = 7 Hz, 2 H), 2.64 (t, J = 7 Hz, 2 H), 6.87 (t, J = 7 Hz, 1 H), 7.36 (d, J = 8 Hz, 1 H), 7.85 (d, J = 8 Hz, 1 H), 9.58 (b s, 2 H). Anal. Calcd: C, 66.65; H, 6.71. Found: C, 66.51; H, 6.54.

3-Methyl-6-(2-propyl)-2-hydroxybenzoic acid (16): 0.30 mol, 750 mL, 140 °C for 30 h; yield 45%; mp 143–145 °C (*n*-hexane) [lit.[26] mp 140 °C]; IR (KBr) 1641 cm^{-1} (C=O); MS 194 (M^+, $C_{11}H_{14}O_3$), 176, 161, 148, 136; ^1H NMR ($CDCl_3$) δ 1.26 (d, J = 7 Hz, 6 H), 2.26 (s, 3 H), 3.93 (septet, J = 7 Hz, 1 H), 6.90 (d, J = 8 Hz, 1 H), 7.32 (d, J = 8 Hz, 1 H), 9.33 (b s, 2 H). Anal. Calcd: C, 68.04; H, 7.21. Found: C, 67.70; H, 6.99.

Method A: Tri-*o*-thymotide (1) by the Action of $POCl_3$ on 2 in Xylene. A mixture of 2 (38.8 g, 0.20 mol), analytical grade xylene (0.3 L), and $POCl_3$ (25 mL, 0.27 mol, 41.74 g) was heated in oil bath (110 °C, with stirring) for 20 h. The cooled mixture was poured into water (150 mL). The organic layer was separated, washed with water (300 mL), and dried (Na_2SO_4). The latter was rinsed with ethyl acetate (100 mL). The combined organic layers were evaporated and left a partly crystalline residue (32.69 g), which was dissolved in 50 mL of CH_2Cl_2 and evaporated onto 20 g of added silica gel. The coated silica was placed on a column (100 cm × 7 cm; 800 g of SiO_2) and developed with toluene–ethyl acetate as an eluent. The fractions were monitored by TLC analysis (10% ethyl acetate–hexane), which clearly resolved the five products.

Compound 4: R_f = 0.79; yield 12%; mp 75–77 °C (ethanol); IR (KBr) 1665 cm^{-1} (C=O); MS 326 (M^+, $C_{21}H_{26}O_3$), 176; ^1H NMR ($CDCl_3$) δ 1.24 (m, 12 H), 2.34 (s, 3 H), 2.69 (s, 3 H), 3.01 (septet, 1 H), 3.38 (septet, 1 H), 6.72–7.32 (m, 5 H), 8.44 (b s, 1 H). Anal. Calcd: C, 77.30; H, 7.98. Found: C, 77.05; H, 7.96.

Compound 5: R_f = 0.65; yield 9%; mp 123–4 °C (ethanol); IR (KBr) 1745 cm^{-1} (C=O), 1660 cm^{-1} (C=O); MS 502 (M^+, $C_{32}H_{38}O_5$), 326, 283, 176; ^1H NMR ($CDCl_3$) δ 1.03–1.25 (m, 18 H), 2.12 (s, 3 H), 2.56 (s, 3 H), 2.68 (s, 3 H), 2.94 (septet, 1 H), 3.05 (septet, 1 H), 3.32 (septet, 1 H), 6.51–7.45 (m, 7 H), 8.39 (b s, 1 H). Anal. Calcd: C, 76.49; H, 7.57. Found: C, 76.20; H, 7.50.

Compound 6: R_f = 0.52; yield 4%; IR (neat) 1750 (C=O), 1740 (C=O), 1660 cm^{-1} (C=O); MS 678 (M^+, $C_{43}H_{50}O_7$), 502, 326, 283, 176.

Compound 3: R_f = 0.33; yield 30%; mp 207 °C (methanol) [lit.[20] mp 207 °C]; IR (KBr) 1760 cm^{-1} (C=O); MS 352 (M^+, $C_{22}H_{24}O_4$), 176; ^1H NMR ($CDCl_3$) δ 1.21, 1.29 (2 d, J = 7 Hz, 12 H), 2.31 (s, 6 H), 3.20 (septet, J = 7 Hz, 2 H), 7.00 (d, J = 8 Hz, 2 H), 7.18 (d, J = 8 Hz, 2 H). Anal. Calcd: C, 75.00; H, 6.82. Found: C, 74.99; H, 6.58.

Compound 1: R_f = 0.22; yield 31%; mp 217–8 °C (methanol) [lit.[20] mp 217 °C]; IR (KBr) 1760 cm^{-1} (C=O); MS 528 (M^+, $C_{33}H_{36}O_6$), 352, 176; ^1H NMR ($CDCl_3$) δ 1.19, 1.26 (2 d, J = 7 Hz, 18 H), 2.46 (s, 9 H), 3.08 (septet, J = 7 Hz, 3 H), 7.23 (d, J = 8 Hz, 3 H), 7.42 (d, J = 8 Hz, 3 H); UV: (methylcyclohexane) λ_{max} = 275 nm, $\epsilon \sim 4600$. Anal. Calcd: C, 74.98; H, 6.86. Found: C, 74.82; H, 6.92.

Alkaline Hydrolysis of the Side Products 4–6. Compound 4 (0.250 g) and aqueous NaOH (30%, 10 mL) were heated under reflux for 24 h. Water (100 mL) was added, and the solution was filtered. The aqueous solution was acidified with dilute HCl and extracted with diethyl ether (100 mL). The ethereal layer was extracted twice with 50-mL volumes of $NaHCO_3$ (5%), and the combined aqueous extracts were acidified with concentrated HCl to precipitate 2 (0.140 g, 94%). The ethereal solution was washed

with water (25 mL), dried (Na_2SO_4), and evaporated leaving **7** as a yellow oil (0.110 g, 97%): ^1H NMR ($CDCl_3$) δ 1.17 (d, J = 7 Hz, 6 H), 2.24 (s, 3 H), 3.09 (septet, 1 H), 4.75 (b s, 1 H), 6.61–7.19 (m, 3 H). Compound **5** (0.250 g) underwent hydrolysis to give **2** (0.185 g, 96%) and **7** (0.069 g, 92%). Hydrolysis of compound **6** (0.250 g) gave **2** (0.205 g, 95%) and **7** (0.048 g, 87%).

Method B: Tri-*o*-thymotide (1) by the Action of $POCl_3$ on 2 at 100 °C for 2 h. A mixture of **2** (19.4 g, 0.10 mol) and freshly distilled $POCl_3$ (10.0 mL, 0.1 mol) was heated in oil bath at ~100 °C with stirring for 2 h. The cooled viscous mixture was added slowly, with stirring, to cold water (200 mL) over 30 min. The aqueous mixture was extracted with ethyl acetate (200 mL). The organic layer was separated and washed with $NaHCO_3$ (5%, 100 mL) and water (100 mL), dried (Na_2SO_4), and evaporated to give a yellow solid. Recrystallization from boiling ethanol yielded the ethanol complex of **1** (14.8 g, 84%) as colorless crystals (mp 175–180 °C). The ethanol complex of **1** was recrystallized by extraction with methanol (500 mL) in a Soxhlet apparatus (approximately 10 g is extracted per 10 h). The cooled methanol extracts were filtered to give solvent-free **1**, mp 217–8 °C dec.[20] The yield of solvent-free **1** is 80%.

Method C: Tri-*o*-thymotide (1) by the Action of $POCl_3$ on 2 at 50 °C for 48 h. A higher yield of **1** (93%, ethanol complex) was obtained when the reaction mixture using the above conditions was heated at 50 °C for 48 h. The yield of solvent-free **1** was 89%.

The R_f values of the following compounds, **17–20**, were determined in 10% ethyl acetate–hexane.

Tri-3-ethyl-6-methylsalicylide (17): R_f = 0.19; yield 27% (method A), 64% (method B); mp 228–9 °C (benzene); IR (KBr) 1743 (C=O), 1764 cm^{-1} (C=O): MS 486 (M^+, $C_{30}H_{30}O_6$), 324, 162, 134; ^1H NMR ($CDCl_3$) δ 1.22 (t, J = 7.5 Hz, 9 H), 2.59 (s, 9 H), 2.65 (q, J = 7 Hz, 6 H), 6.70 (d, J = 8 Hz, 3 H), 7.22 (d, J = 8 Hz, 3 H). Anal. Calcd: C, 74.06; H, 6.22. Found: C, 73.95; H, 6.36.

Tri-3-(2-propyl)salicylide (18): R_f = 0.30; yield 31% (method A), 76% (method B); mp 285–6 °C (ethanol); IR (KBr) 1733 cm^{-1} (C=O): MS 486 (M^+, $C_{30}H_{30}O_6$), 324, 162, 134; ^1H NMR ($CDCl_3$) δ 1.16, 1.27 (2 d, J = 8 Hz, 18 H), 3.29 (septet, J = 7 Hz, 3 H), 7.34 (t, J = 7 Hz, 3 H), 7.57 (d, J = 7 Hz, 3 H), 8.28 (d, J = 7 Hz, 3 H). Anal. Calcd: C, 74.06; H, 6.22. Found: C, 74.15; H, 6.20.

Tri-3-(1-propyl)salicylide (19): R_f = 0.29; yield 22% (method A), 55% (method B); mp 204–6 °C (ethyl acetate): IR (KBr) 1743 (C=O), 1759 cm^{-1} (C=O): MS 486 (M^+, $C_{30}H_{30}O_6$), 324, 162, 134; ^1H NMR ($CDCl_3$) δ 0.93 (t, J = 8 Hz, 9 H), 1.65 (sextet, J = 8 Hz, 6 H), 2.61 (t, J = 8 Hz, 6 H), 7.28 (t, J = 7 Hz, 3 H), 7.49 (d, J = 7 Hz, 3 H), 8.27 (d, J = 8 Hz, 3 H). Anal. Calcd: C, 74.06; H, 6.22. Found: C, 73.81; H, 6.18.

Tri-3-methyl-6-(2-propyl)salicylide (20): R_f = 0.26; yield 29% (method A), 65% (method B); mp 259–260 °C (*n*-hexane) [lit.[26] mp 247 °C]; IR (KBr) 1761 cm^{-1} (C=O); MS 528 (M^+, $C_{33}H_{36}O_6$), 352, 176; ^1H NMR ($CDCl_3$) δ 1.29 (t, J = 8 Hz, 18 H), 2.23 (s, 9 H), 3.18 (septet, J = 7 Hz, 3 H), 7.25 (d, J = 8 Hz, 3 H), 7.39 (d, J = 8 Hz, 3 H). Anal. Calcd: C, 74.98; H, 6.86. Found: C, 74.86; H, 6.69.

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Registry No. 1, 4399-52-4; 1·0.5EtOH, 55217-06-6; 2, 548-51-6; 3, 50397-25-6; 4, 134153-43-8; 5, 134153-44-9; 6, 134153-45-0; 7, 89-83-8; 13, 20717-15-1; 14, 7053-88-5; 15, 22890-52-4; 16, 4389-53-1; 17, 134153-46-1; 18, 134153-47-2; 19, 134153-48-3; 20, 2281-45-0.

Selenium-Mediated Conversion of Alkynes into α-Dicarbonyl Compounds

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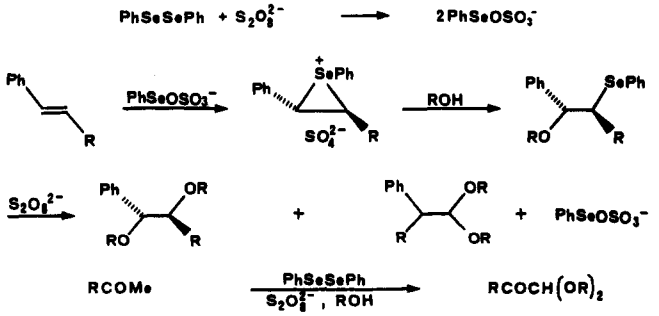
The reaction of terminal and internal alkynes with diphenyl diselenide and ammonium peroxydisulfate in methanol proceeds smoothly to give α-keto acetals and α-keto ketals, respectively. This one-pot procedure is suggested to proceed through the initial formation of phenylselenenyl sulfate, a strong electrophilic reagent which effects the methoxyselenenylation of the alkynes. The addition products thus formed suffer methoxydeselenenylation giving the observed products and regenerating the phenylselenenylating agent. In some cases the reaction can be carried out using only catalytic amounts of diphenyl diselenide. The same reaction carried out in the presence of water or of ethylene glycol gives the unprotected or the diprotected α-dicarbonyl compounds, respectively.

We have recently introduced the use of ammonium peroxydisulfate to convert diphenyl diselenide into a strongly electrophilic phenylselenenylating agent. We suggested that from this very simple reaction phenylselenenyl sulfate is produced (Scheme I). Since the sulfate is a strong electron-withdrawing group, phenylselenenyl sulfate behaves as a phenylselenium cation synthetic equivalent which easily adds to unsaturated compounds. Moreover, the sulfate anion is a very weak nucleophile and therefore it does not interfere with other nucleophiles that can be added to the reaction mixture or that can be present in the molecule of the unsaturated compounds used as substrates. This simple method, which presents several advantages over the other previously described procedures,[1] has been successfully used to effect the methoxy-,[2] hydroxy-,[2] and amidoselenenylation[3] of alkenes. Similarly, several selenium-induced ring-closure reactions have also been carried out. Thus, starting from alkenes containing

Scheme I



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