# Improved General Method of Ortho Alkylation of Phenols Using Alkyl Isopropyl Sulfide, Sulfuryl Chloride, and Triethylamine. An Expedient Synthesis of Representative Oxygen Heterocycles and (2*R*,4'*R*,8'*R*)-$\alpha$-Tocopherol

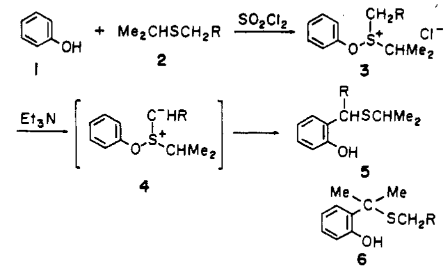
*Summary:* Functionalized alkyl groups have been introduced regioselectively into the ortho position of phenols via [2,3] sigmatropic rearrangement of isopropylphenoxysulfonium alkylide, providing a quite efficient synthesis of precursors for chromans, chromens, coumarins, and *d*-$\alpha$-tocopherol.

*Sir:* Regioselective ortho alkylation of phenols is one of the most important reactions in organic synthesis. An effective method of such transformation is [2,3] sigmatropic rearrangement of phenoxysulfonium ylides,[1,2] which was exploited by Gassman and co-workers.[1] The success of this [2,3] sigmatropic rearrangement methodology depends on the effective generation of extremely labile phenoxysulfonium salt **3**. When a sulfide is used as a starting material, coupled with such a conventional activator as *N*-chlorosuccinimide, the initially formed azasulfonium salt[3] is sparingly soluble in the reaction solvent; hence the formation of **3** is slow. Moreover, the process cannot afford **3** in a quantitative yield owing to the reaction equilibrium.[4] We recently reported an alternative procedure of the [2,3] sigmatropic rearrangement utilizing dialkyl sulfoxides and thionyl chloride for the generation of activated sulfonium salts.[5] Here we report an improved method of ortho alkylation of phenols, which should permit introduction of variously functionalized alkyl groups under very mild reaction conditions.

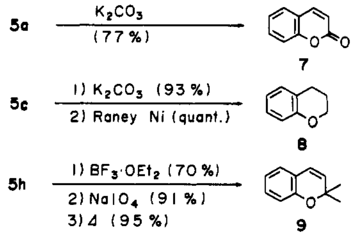
In a typical procedure, a slightly excess amount of freshly distilled sulfuryl chloride (0.65 mL, 8 mmol) was added via syringe to a stirred solution of methyl 3-(isopropylthio)propionate (**2a**) (1.15 g, 7 mmol) and phenol (**1a**) (1.98 g, 21 mmol) in 25 mL of dichloromethane at −40 °C (Scheme I). The reaction mixture was stirred for 15 min and a solution of triethylamine (3.5 g, 35 mmol) in 3 mL of dichloromethane was added dropwise over a period of 7 min while the temperature was kept below −35 °C. The reaction mixture was allowed to warm up to room temperature and worked up by standard procedures to give methyl 3-(2-hydroxyphenyl)-3-(isopropylthio)propionate (**5a**) (1.37 g, 77% yield on the basis of sulfide, 81% yield on the basis of phenol consumed). The individual results are listed in Table I. The structure of **5** was established on the basis of spectroscopic properties of the product itself and of the desulfurized derivative.

The site specificity of the ylide formation between isopropyl and the other alkyl groups of sulfide **2** is remarkable in the present rearrangement reaction, the formation of the isomeric product **6** being almost negligible (less than 1%) irrespective of bulkiness of the amine used to generate an ylide. This fact is very interesting considering the observation that diisopropyl sulfide is reactive in the present reaction and gives 2-(1-(isopropylthio)-1-methylethyl)phenol in 51% yield (99% based on the phenol consumed) and both thioanisole and methyl 3-(*tert*-butylthio)propionate are completely inactive under similar reaction conditions.

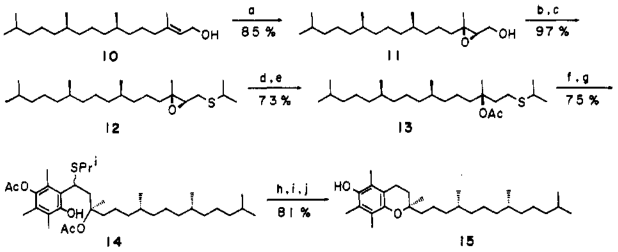
Scheme I



Scheme II



Scheme III[a]



[a] Key: (a) $Me_3COOH$, $Ti(OCHMe_2)_4$, D-(−)-DMT, $CH_2Cl_2$, −20 °C; (b) TsCl, pyridine, 0 °C; (c) $Me_2CHSNa$, MeOH, 50 °C; (d) $LiAlH_4$, THF, reflux; (e) $Ac_2O$, TsOH, room temperature; (f) trimethylhydroquinone 4-acetate, $SO_2Cl_2$, $CH_2Cl_2$, −40 °C; (g) $NEt_3$, $CH_2Cl_2$, −40 °C to room temperature; (h) Raney Ni, EtOH, reflux; (i) $LiAlH_4$, $Et_2O$, room temperature; (j) TsOH, $C_6H_6$, reflux.

The present method is characterized by several significant features. First, the present method utilizes sulfides as starting alkylating agents which are more easy to handle than extremely hygroscopic sulfoxides which are in turn prepared from the corresponding sulfides and were used in our previous method.[5] Second, the use of liquid sulfuryl chloride[6] is more advantageous than gaseous chlorine as an activating reagent for sulfides, which is strongly recommended to be used in an equimolar to only slightly excess amount of sulfide. Third, the use of sulfuryl chloride enables us to measure out a sulfide and a phenol into a reaction vessel prior to the addition of sulfuryl chloride to activate the sulfide; thus the reaction procedure has been substantially simplified.

*o*-Alkylphenols thus obtained were converted into various oxygen heterocycles by the simple cyclization (**5a**) or cyclization followed by reductive (**5c**) or oxidative desulfurization (**5h**) as shown in Scheme II.[7]

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(1) Gassman, P. G.; Amick, D. R. *J. Am. Chem. Soc.* **1978**, *100*, 7611.

(2) For recent application of [2,3] sigmatropic rearrangement of sulfur ylides, see: (a) Gassman, P. G.; Roos, J. J.; Lee, S. L. *J. Org. Chem.* **1984**, *49*, 717. (b) Gassman, P. G.; Lee, S. L. *Ibid.* **1986**, *51*, 267. (c) Vedejs, E. *Acc. Chem. Res.* **1984**, *17*, 358. (d) Cerè, V.; Paolucci, C.; Pollicino, S.; Sandri, E.; Fava, A. *J. Org. Chem.* **1981**, *46*, 3315. (e) Nickon, A.; Rodriguez, A. D.; Ganguly, R.; Shirhatti, V. *J. Org. Chem.* **1985**, *50*, 2767. (f) Cohen, T.; Kosarych, Z.; Suzuki, K.; Yu, L.-C. *Ibid.* **1985**, *50*, 2965.

(3) Vilsmaier, E.; Sprügel, W. *Tetrahedron Lett.* **1972**, 625.

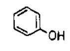
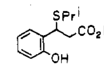
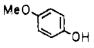
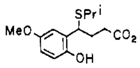
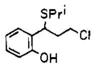
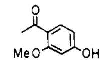
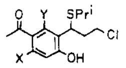
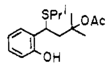
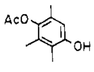
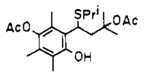
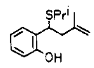
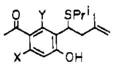
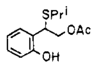
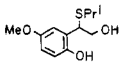
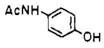
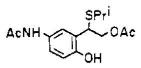
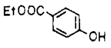
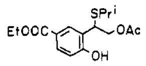
(4) Claus, P.; Rieder, W. *Tetrahedron Lett.* **1972**, 3879.

(5) (a) Sato, K.; Inoue, S.; Ozawa, K.; Tazaki, M. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2715. (b) Sato, K.; Inoue, S.; Ozawa, K.; Kobayashi, T.; Ota, T.; Tazaki, M. *Ibid.* **1987**, 1753.

(6) For a review, see: Tabushi, I.; Kitaguchi, H. In *Synthetic Reagents*; Pizey, J. S., Ed.; Ellis Horwood Limited: Chichester, England, 1981; Vol. 4, pp 336–396. For other example of the use of sulfide–sulfuryl chloride combination, see: Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651.

0022-3263/87/1952-5495$01.50/0

**Table I. Ortho Alkylation of Phenols with Sulfides via [2,3] Sigmatropic Rearrangement**

| phenol | sulfide | R | amine | product | yield,[a] % |
|---|---|---|---|---|---|
| <br>**1a** | **2a** | $CH_2CO_2Me$ | $Et_3N$ | <br>**5a** | 77 |
| **1a** | **2a** | | $n$-$Bu_3N$ | **5a** | 72 |
| **1a** | **2a** | | $Et_2ChN$[b] | **5a** | 81 |
| <br>**1b** | **2b** | $CH_2CH_2CO_2Me$ | $Et_3N$ | <br>**5b**[d] | 65[d] |
| **1a** | **2c** | $CH_2CH_2Cl$ | $Et_3N$ | <br>**5c** | 73 |
| <br>**1c** | **2c** | | $Et_3N$ | <br>**5d**, X = OMe; Y = H<br>**5e**, X = H; Y = OMe | 46 (1:1)[c] |
| **1a** | **2d** | $CH_2CMe_2OAc$ | $Et_3N$ | <br>**5f** | 87 |
| <br>**1d** | **2d** | | $Et_3N$ | <br>**5g** | 58 |
| **1a** | **2e** | $CH_2CMe{=}CH_2$ | $Et_3N$ | <br>**5h** | 70 |
| **1c** | **2e** | | $Et_3N$ | <br>**5i**, X = OMe; Y = H<br>**5j**, X = H; Y = OMe | 55 (1:1)[c] |
| **1a** | **2f** | $CH_2OAc$ | $Et_3N$ | <br>**5k** | 68 |
| **1b** | **2f** | | $Et_3N$ | <br>**5l**[d] | 71[d] |
| <br>**1e** | **2f** | | $Et_3N$ | <br>**5m** | 62 |
| <br>**1f** | **2f** | | $Et_3N$ | <br>**5n** | 80 |

[a] Yield of isolated pure product(s) on the basis of sulfide. Yield with respect to the consumed phenol is always greater than or equal to the yield described. [b] *N*,*N*-Diethylcyclohexylamine. [c] Ratio of the two isomers. [d] Isolated after hydrolysis with $K_2CO_3/MeOH-H_2O$.

Thus, a simple treatment of **5a** with potassium carbonate in acetone at reflux for 3 h afforded a 77% yield of 2*H*-1-benzopyran-2-one (coumarin, **7**), and successive treatment of **5c** with potassium carbonate in acetone at reflux for 3 h to induce cyclization (93% yield), followed by Raney nickel W4 in ethanol at reflux for 1.5 h (a quantitative yield), yielded 3,4-dihydro-2*H*-1-benzopyran (chroman, **8**) in an excellent overall yield. Another type of cyclization–elimination was realized with **5h**: Lewis acid catalyzed cyclization of **5h** with trifluoroborane–ethyl ether complex in dichloromethane at room temperature for 1.5 h afforded a 70% yield of 3,4-dihydro-2,2-dimethyl-4-(isopropylthio)-2*H*-1-benzopyran, which was treated with sodium periodate in aqueous ethanol at 0 °C for 24 h to give the corresponding sulfoxide in 91% yield, which on heating in toluene at reflux for 2 h furnished 2,2-dimethyl-2*H*-1-benzopyran in 95% yield.

Finally the utility of the overall process leading to oxygen heterocycles is emphasized by the efficient synthesis

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(7) The first example of the synthesis of oxygen heterocycles via the rearrangement methodology is that of benzofurans where phenol is converted via 2-(1-(methylthio)-2-oxopropyl)phenol to 2-methyl-3-(methylthio)benzofuran in 12% yield: Gassman, P. G.; Amick, D. R. *Synth. Commun.* **1975**, *5*, 325.

of natural *d*-α-tocopherol (**15**)[8] (Scheme III). The alkylation of trimethylhydroquinone 4-acetate[9] with sulfide **13** derived from (2*E*,7*R*,11*R*)-phytol (**10**)[10] via (2*R*,3*R*)-2,3-epoxyphytol (**11**)[11,12] afforded tetrasubstituted hydroquinone derivative **14**, $[\alpha]_D^{20}$ −2.22° (*c* 2.21, EtOH), in 75% yield. Reductive desulfurization of **14** with Raney nickel W4 in ethanol, followed by reductive elimination of the two acetyl groups with lithium aluminum hydride, afforded a tocopherol hydroquinone which was directly cyclized with an acid catalyst[8g] to give (2*R*,4′*R*,8′*R*)-α-tocopherol (**15**), $[\alpha]_D^{23}$ −1.1° (*c* 0.85, benzene), in 81% overall yield with an optical purity of 96% ee.[13] In a comparison of its spectral and chromatographic properties, the synthetic material proved identical in all respects with an anthentic sample of natural α-tocopherol.

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(8) For a synthesis of (2*R*,4′*R*,8′*R*)-α-tocopherol and its precursor, see: (a) Mayer, H.; Schudel, P.; Rüegg, R.; Isler, O. *Helv. Chim. Acta* **1963**, *46*, 650. (b) Scott, J. W.; Bizzarro, F. T.; Parrish, D. R.; Saucy, G. *Ibid.* **1976**, *59*, 290. (c) Cohen, N.; Eichel, W. F.; Lopresti, R. J.; Neukom, C.; Saucy, G. *J. Org. Chem.* **1976**, *41*, 3505. (d) Chan, K.-K.; Specian, A. C., Jr.; Saucy, G. *Ibid.* **1978**, *43*, 3435. (e) Barner, R.; Schmid, M. *Helv. Chim. Acta* **1979**, *62*, 2384. (f) Cohen, N.; Lopresti, R. J.; Saucy, G. *J. Am. Chem. Soc.* **1979**, *101*, 6710. (g) Cohen, N.; Lopresti, R. J.; Neukom, C. *J. Org. Chem.* **1981**, *46*, 2445. (h) Fuganti, C.; Grasselli, P. *J. Chem. Soc., Chem. Commun.* **1982**, 205. (i) Cohen, N.; Banner, B. L.; Neukom, C. *Synth. Commun.* **1982**, *12*, 57. (j) Sakito, Y.; Suzukamo, G. *Tetrahedron Lett.* **1982**, 23, 4953. (k) Solladie, G.; Moine, G. *J. Am. Chem. Soc.* **1984**, *106*, 6097. (l) Takabe, K.; Okisaka, K.; Uchiyama, Y.; Katagiri, T.; Yoda, H. *Chem. Lett.* **1985**, 561.

(9) Weichet, J.; Blaha, L.; Kakac, B. *Collect. Czech. Chem. Commun.* **1966**, *31*, 4598.

(10) For a stereoselective synthesis of (2*E*,7*R*,11*R*)-phytol and the side-chain precursors of (2*R*,4′*R*,8′*R*)-α-tocopherol, see: (a) Karrer, P.; Geiger, A.; Rentschler, H.; Zkinden, E.; Kugler, A. *Helv. Chim. Acta* **1943**, *26*, 1741. (b) Burrell, J. W. K.; Garwood, R. F.; Jackman, L. M.; Oskay, E.; Weedon, B. C. L. *J. Chem. Soc. C* **1966**, 2144. (c) Chan, K.-K.; Cohen, N. De Noble, J. P.; Specian, A. C., Jr.; Saucy, G. *J. Org. Chem.* **1976**, *41*, 3497. (d) Cohen, N.; Eichel, W. F.; Lopresti, R. J.; Neukom, C.; Saucy, G. *Ibid.* **1976**, *41*, 3512. (e) Schudel, M.; Barner, R. *Helv. Chim. Acta* **1979**, *62*, 464. (f) Zell, R. *Ibid.* **1979**, *62*, 474. (g) Fuganti, C.; Grasselli, P. *J. Chem. Soc., Chem. Commun.* **1979**, 995. (h) Fujisawa, T.; Sato, T.; Kawara, T.; Ohashi, K. *Tetrahedron Lett.* **1981**, *22*, 4823. (i) Trost, B. M.; Klun, T. P. *J. Am. Chem. Soc.* **1981**, *103*, 1864. (j) Koreeda, M.; Brown, L. *J. Org. Chem.* **1983**, *48*, 2122. (k) Fujiwara, J.; Fukutani, Y.; Hasegawa, M.; Maruoka, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1984**, *106*, 5004. (l) Bérubé, G.; Deslongchamps, P. *Can. J. Chem.* **1984**, *62*, 1558.

(11) Hamamura, K.; Akasaka, K.; Yamagishi, Y. Eur. Pat. Appl. EP 58945, 1982; *Chem. Abstr.* **1983**, *98*, 72493j.

(12) $[\alpha]_D^{20}$ 4.39° (*c* 2.78, EtOH), lit.[11] $[\alpha]_D^{25}$ 4.3° (*c* 2.8, EtOH). The enantiomeric excess was determined by $^1$H NMR on the corresponding epoxy acetate in the presence of $Eu(hfbc)_3$ to be 95% ee.

(13) The enantiomeric excess was determined by optical rotation of chromatographed $K_3Fe(CN)_6$ oxidation product of synthetic α-tocopherol, $[\alpha]_D^{17}$ +32.4° (*c* 0.17, isooctane), compared with that of natural α-tocopherol, $[\alpha]_D^{19}$ +33.9° (*c* 0.40, isooctane); see ref 8g.

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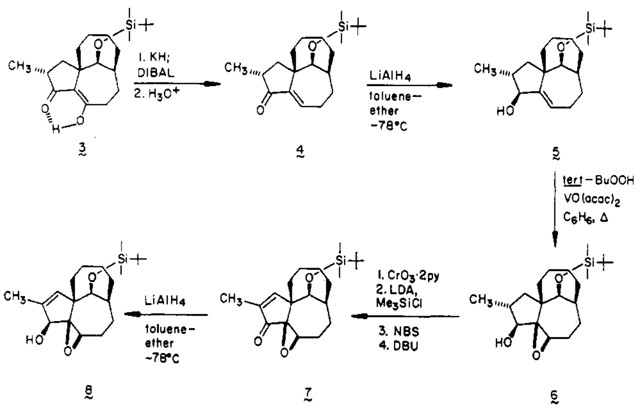
## Ingenane Synthetic Studies. Stereocontrolled Introduction of All Oxygenated and Unsaturated Centers in an Ingenol Prototype

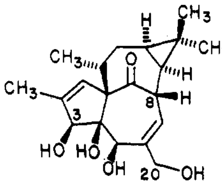
*Summary:* The keto tetrol **2**, a close prototype of ingenol, has been synthesized in highly stereoselective fashion.

*Sir:* In the period 1960–1985, during the course of extensive systematic phytochemical studies of the genus *Euphorbia* (ca. 1600 species), many esters of ingenol (**1**) were isolated and identified as the irritant principles of these plants. Of foremost importance, select 3-acylated derivatives of **1** were shown to possess potent tumor-promoting activity.[2] Kupchan's disclosure that ingenol 3,20-dibenzoate is an antileukemic agent[3] further heightened interest in this class of molecules.

**Scheme I**



X-ray crystallographic analysis of the triacetate of **1**[4,5] revealed its parent tetracyclic diterpenoid nucleus to feature inside–outside stereochemistry about the central bicyclo[4.4.1]undecanone core and to be characterized by an unusually dense all-cis array of contiguous hydroxyl functional groups along the outer periphery of rings A and B. To date, four approaches to construction of the ABC subunit of ingenol have been described.[5-8] Although that devised by Winkler actually leads to the correct intrabridgehead stereochemistry,[8] all products happen to be seriously underfunctionalized.



**1**

Herein, we describe experiments which for the first time properly set in place the second novel structural feature of ingenol, viz. its highly oxidized A/B ring functionality. The protocol, based on the readily available β-diketone **3**,[5] was predetermined to give **2** and ultimately permit bioassay of select fatty acid esters. Noteworthily, no analogues of **1** having inverted stereochemistry at C-8 have previously been available for biological evaluation.

Reductive deoxygenation of **3** was best effected (85%) by Dibal reduction of the potassium enolate at −45 °C with subsequent acidic workup (Scheme I). Enone **4** proved

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(1) National Science Foundation Graduate Fellow, 1982–1985; Amoco Graduate Fellow, 1985–1986.

(2) (a) Hecker, E. *Cancer Res.* **1968**, *28*, 2338. (b) Evans, F. J.; Kinghorn, A. D. *Phytochemistry* **1974**, *13*, 1011. (c) Hecker, E. *Pure Appl. Chem.* **1977**, *49*, 1423. (d) Evans, F. J.; Soper, C. J. *Lloydia* **1978**, *41*, 193. (e) Gotta, H.; Adolf, W.; Opferkuch, H. J.; Hecker, E. *Z. Naturforsch.* **1984**, *39B*, 683.

(3) Kupchan, S. M.; Uchida, I.; Branfman, A. R.; Dailey, R. G., Jr.; Yu Fei, B. *Science (Washington, D.C.)* **1976**, *191*, 571.

(4) Zechmeister, K.; Brandl, F.; Hoppe, W.; Hecker, E.; Opferkuch, H. J.; Adolf, W. *Tetrahedron Lett.* **1970**, 4075.

(5) Paquette, L. A.; Nitz, T. J.; Ross, R. J.; Springer, J. P. *J. Am. Chem. Soc.* **1984**, *106*, 1446.

(6) Rigby, J. H.; Moore, T. L.; Rege, S. *J. Org. Chem.* **1986**, *51*, 2398.

(7) Funk, R. L.; Bolton, G. L. *J. Am. Chem. Soc.* **1986**, *108*, 4655.

(8) Winkler, J. D.; Henegar, K. E.; Williard, P. G. *J. Am. Chem. Soc.* **1987**, *109*, 2850.

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