Annelation of Phenols with Epoxides Derived from 2-Cycloalken-1-ones

Summary: The annelation of phenol to give tricyclic benzofuran **6** involves the intramolecular acylation–rearrangement of lactone **4**.

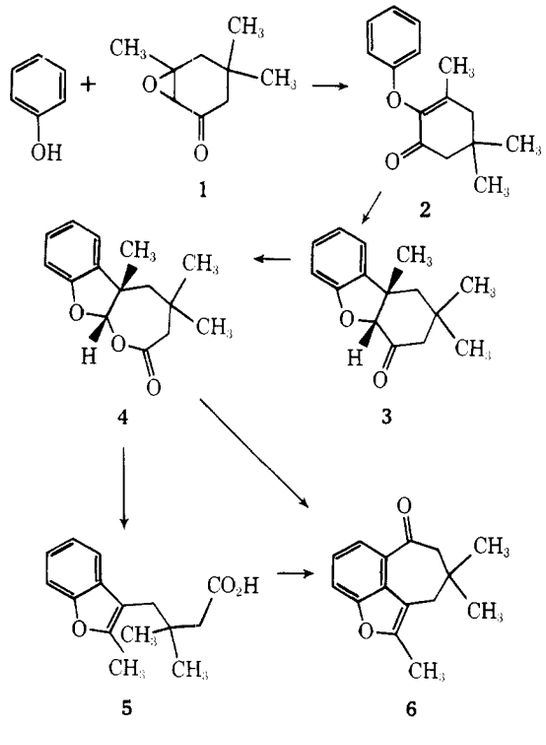
Sir: The annelation of an aromatic nucleus to form a multicyclic ring system is an important tactic in organic synthesis. Many annelation methods have been developed, but with most of these, electrophilic aromatic substitution (Friedel–Crafts acylation) is used in the formation of the initial bond in the annelation sequence; consequently, problems with regioselectivity are often encountered. In this communication, we report methodology for accomplishing aromatic ring annelation with high regiochemical control. The annelation reagents are epoxides derived from 2-cycloalken-1-ones containing n ring atoms, from which $n - 1$ atoms are incorporated into the new ring; only C(2) is excluded. The method is demonstrated here by annelation of phenol with isophorone epoxide ($n = 6$).

We have shown that potassium hydride initiated reaction of phenol with isophorone epoxide (**1**) gives 2-phenoxy-3,5,5-trimethyl-2-cyclohexen-1-one (**2**) in 91% yield; photochemical cyclization of **2** (heteroatom directed photoarylation) produces dihydrofuran **3** in 95% yield (Scheme I).[1] Thus, the initial carbon–carbon bond to the aromatic ring is formed in a completely regioselective manner.

Baeyer–Villiger oxidation of **3** with *m*-chloroperbenzoic acid in methylene chloride solution at 25 °C gives lactone **4** in 97% isolated yield (mp 111 °C).[2,3] Generation of the lactone carbonyl in **4** provides a means for completion of the annelation via intramolecular acylation of the aromatic ring.

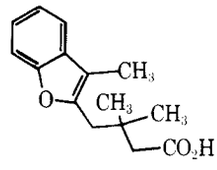
The acylation, accompanied by rearrangement to a benzofuran, is accomplished by refluxing a methylene chloride

Scheme I



solution of lactone **4** with excess titanium tetrachloride. Partitioning the reaction components between ether and 1 N sodium hydroxide solution gives pure ketone **6** (mp 88–89 °C, 94% isolated yield) in the organic layer. Acidification of the sodium hydroxide layer gives, after ether extraction, carboxylic acid **7** in 1.4% yield.

We have studied the Lewis acid induced rearrangement of ϵ-lactones (e.g., **4** and **9**) in some detail. Treatment of **4** with 1.5 equiv of $TiCl_4$ in CH_2Cl_2 at −78 °C for 2 h gives carboxylic acids **5** (98%) and **7** (trace). Although $SnCl_4$ may be used in the



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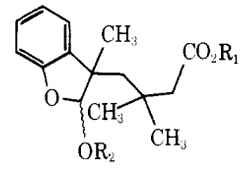
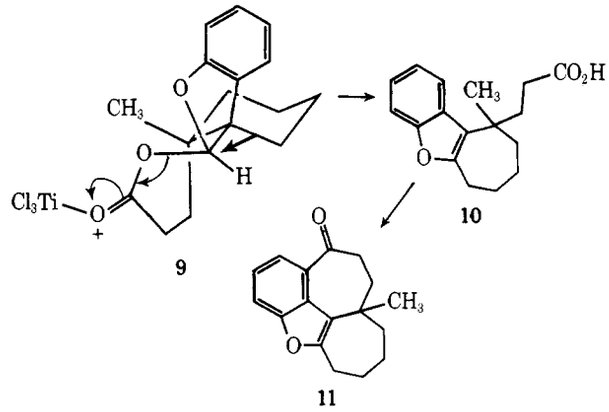


8a, $R_1 = CH(CH_3)_2$; $R_2 = H$
b, $R_1 = CH_3$; $R_2 = H$
c, $R_1 = CH_3$; $R_2 = CH_3$

rearrangement of **4** to **5**, substitution of titanium tetraisopropoxide results in lactone ring opening to give the isopropyl ester **8a**; similarly, sodium methoxide in methanol gives the methyl ester **8b**. Finally, methanolic hydrogen chloride gives the methyl ester acetal **8c**, but lactone **4** is recovered unchanged from its solution in refluxing methylene chloride saturated with hydrogen chloride.

We note that the $TiCl_4$ induced rearrangement **4** → **5** is highly stereoselective; the carbon chain (here, the C(3) methyl group) in an anti orientation to the leaving carboxylate function undergoes preferential migration to C(2). In order to examine the generality of this rearrangement, lactone **9**[4] (mp 127–128 °C) was treated with 1.5 equiv of $TiCl_4$ in CH_2Cl_2 at 25 °C for 30 min, after which tricycle **10** was isolated as the major reaction product (94%). Polyphosphoric acid cyclodehydration of **10** at 110 °C for 1.5 h gave tetracyclic ketone **11** (mp 101–102 °C).[5]



The methyl-substituted furan carbon–carbon double bond in **6** represents a latent ketone carbonyl group, from which diketone **12** (Scheme II) can be liberated in 84% isolated yield (70% overall from phenol to diketone **12**). Furthermore, simple reactions coupled to the oxidative cleavage of **6** allow for preparation of monoketones **13** and **14** as well (Scheme II).[6]

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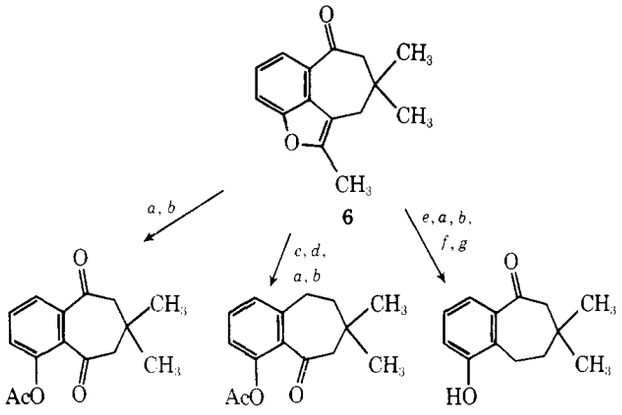
Scheme II



[a] O_3/CH_2Cl_2 (−78 °C). [b] CH_3SCH_3 (25 °C). [c] $TsNHNH_2$/EtOH. [d] $NaCNBH_4$.[7] [e] $LiAlH_4$/THF. [f] H_2NNH_2, KOH/H_2O. [g] H_2CrO_4/CH_3COCH_3.

Cathy Stein for preparation of lactone **9** and early studies of the behavior of **9** with Lewis acids.

References and Notes

(1) A. G. Schultz and R. D. Lucci, *J. Org. Chem.*, **40**, 1371 (1975).
(2) For a related conversion of an α-alkoxycyclohexanone to a seven-membered lactone, see Y. Kishi, M. Aratani, T. Fukuyama, F. Nakatsubo, T. Goto, S. Inoue, H. Tanino, S. Sugiura, and H. Kakoi, *J. Am. Chem. Soc.*, **94**, 9217 (1972).
(3) The Baeyer–Villiger reaction has been demonstrated to occur with retention of configuration; see J. A. Berson and S. Suzuki, *J. Am. Chem. Soc.*, **81**, 4088 (1959), and H. O. House and T. M. Bare, *J. Org. Chem.*, **33**, 943 (1968).
(4) A. G. Schultz and W. Y. Fu, *J. Org. Chem.*, **41**, 1483 (1976).
(5) Construction of the ring system in **11** represents an interesting potential approach to the alkaloid colchicine.
(6) Compounds **2–4, 6, 11, 12–14** give correct elemental analyses.
(7) R. O. Hutchins, C. A. Milewski, and B. E. Maryanoff, *J. Am. Chem. Soc.*, **95**, 3662 (1973).
(8) Undergraduate research participant, Cornell University, 1975–1976.

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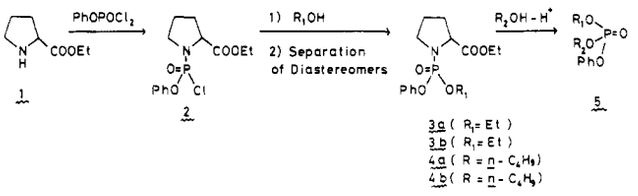
A Practical Method of Preparing Optically Active Dialkyl Phenyl Phosphates

Summary: A practical method for the preparation of optically active dialkyl phenyl phosphates using L-proline ethyl ester and requiring three overall steps is presented.

Scheme I



Sir: For the investigation of mechanistic aspects of chemical and enzymatic solvolysis of phosphotriesters, the use of chiral substrates offers an excellent approach.[1] However, to our knowledge, there have been only two methods for the preparation of optically active phosphotriesters. One[2] utilizes the enzymatic resolution of racemic phosphotriesters, and the other,[3] the first chemical method, employs the stereospecific alcoholysis of optically active tetrahydro-1,3,2-oxazaphosphorine or -oxazaphospholane derivatives. The latter method, however, requires more than five steps[4] to get trialkyl phosphates, and does not seem to be a practical method for obtaining chiral phosphotriesters in general.[5]

Herein we wish to report a new and simple method for the preparation of optically active dialkyl phenyl phosphates using easily available L-proline ethyl ester[6] as a chiral reagent. The reaction sequence of the present method, which is shown in Scheme I, consists of essentially three steps. A separation of diastereoisomeric phosphoramidates and their acid-catalyzed alcoholysis are the key steps.

The phosphoromonochloridate **2**, prepared in situ by the reaction[7] of L-proline ethyl ester (1.3 equiv mol) with phenyl phosphorodichloridate (1 equiv mol) in anhydrous pyridine, was reacted[8] with an excess of ethanol or with 1-butanol to afford a diastereoisomeric mixture of the corresponding alkyl phenyl phosphoramidate (**3** or **4**). The isomers were separated quite easily by column chromatography (silica gel, benzene–ethyl acetate) and isolated by distillation in fair yields: **3a**[9] (40%),[10] bp 173–180 °C (1.5 mm),[11] $[\alpha]^{17}_D$ −67° (*c* 1.7); **3b** (20%), bp 178–179 °C (1.7 mm), $[\alpha]^{16}_D$ −45° (*c* 3.0); **4a** (36%), bp 145 °C (0.015 mm), $[\alpha]^{23}_D$ −60° (*c* 2.6); **4b** (22%), bp 145 °C (0.015 mm), $[\alpha]^{24}_D$ −40° (*c* 3.0).

Acid-catalyzed alcoholysis[13] of each isomer at refluxing temperature gave the corresponding phosphotriester **5**[14] in a state of high optical purity.[15] The yields and physical data are listed in Table I.

Although the result is at present limited to the preparation of optically active dialkyl phenyl phosphates and the yields are not optimized,[16] the present method may well be applicable for the preparation of phosphotriesters in general, and also for other phosphoryl derivatives, such as phosphinates and phosphonates. Research along this line is now in progress in this laboratory and will be reported elsewhere.

Table I. Preparation of Optically Active Dialkyl Phenyl Phosphates by the Acid-Catalyzed Alcoholysis of Diastereomeric Phosphoramidates

Phosphoramidate	Dialkyl phenyl phosphate R_1	R_2	Yield, %	Bp, °C (mm)	$[\alpha]_D$, deg (*c*, °C)
3a	C_2H_5	CH_3	61	80 (0.02)	+3.4 (3.2, 25)
3b	C_2H_5	CH_3	63	76 (0.02)	−3.4 (3.6, 26)
4a	n-C_4H_9	CH_3	51	92 (0.03)	+5.5 (2.7, 21)
4b	n-C_4H_9	CH_3	54	90 (0.02)	−5.1 (2.9, 22)
4a	n-C_4H_9	C_2H_5	28[a]	85 (0.02)	+1.8 (1.5, 19)
4b	n-C_4H_9	C_2H_5	30[b]	85 (0.02)	−2.0 (1.7, 20)
4a	n-C_4H_9	n-C_3H_7	10	100 (0.01)	+0.9 (1.1, 24)
4b	n-C_4H_9	n-C_3H_7	11	100 (0.01)	−0.7 (1.5, 24)

[a] n-Butanolysis of **3b** gave the same compound [$[\alpha]_D$ +2.1° (1.4, 14)] in 19% yield. [b] n-Butanolysis of **3a** gave the same compound [$[\alpha]_D$ −2.0° (1.0, 19)] in 10% yield.