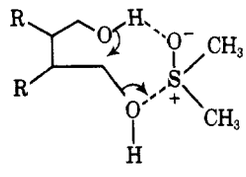
Table I. Dehydration of Benzyl Alcohols to Ethers in Dimethyl Sulfoxide[a]

Starting alcohol	Reaction time, h	Yield[b] of ether, %
α-Methylbenzyl alcohol	5[c]	99[d]
α-Methylbenzyl alcohol (+ fourfold excess of cyclohexanol)	3	65 (unsymmetrical ethers)
p-Methylbenzyl alcohol	3	89
p-Methoxybenzyl alcohol	0.5	85
p-Fluorobenzyl alcohol	8	99
p-Nitrobenzyl alcohol	22	

[a] Reactions were run using a 16:1 molar ratio of benzyl alcohol to Me_2SO. The reaction temperature was 175 °C. [b] Yields are for isolated, pure products. [c] Reaction was actually complete after 15–30 min. [d] Product consisted of a mixture of meso and *dl* ethers.



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If the intermolecular reaction of benzyl alcohols were proceeding through a cyclic transition state analogous to **1**, the dehydration of optically active α-methylbenzyl alcohol should give only meso product. However, when *l*-α-methylbenzyl alcohol (91% optically pure), resolved via its brucine salt,[9] was reacted with Me_2SO for 5 min at 175 °C, the NMR spectrum of the product indicated that it consisted of a nearly 50:50 mixture of the meso and *dl* ethers. Recovered starting material was found to be 77% racemized. These results together with the observed substituent effects on the reaction rate rule out a transition state such as **1**. Instead, an unimolecular pathway is indicated, although alkoxysulfonium salts may be involved. Further mechanistic studies are necessary to clarify the exact nature of the intermediate.

Experimental Section

Reagents and Materials. Dimethyl sulfoxide was obtained from the Fisher Scientific Co. and was dried over Linde type 3A molecular sieves before use. The starting alcohols were all available commercially and were used without further purification. Silica gel 60F-254 TLC plates were purchased from Merck and used to monitor all reactions. Silica gel 60 (70–230 mesh) obtained from Merck was heated overnight to 160 °C before use in the chromatographic separation of alcohols and ethers.

Sample Procedure for the Dehydration of Benzyl Alcohols. Two grams (0.0164 mol) of p-methylbenzyl alcohol and 0.08 g (0.001 mol) of dimethyl sulfoxide (molar ratio of 16:1) were heated to 175 °C for 3 h. The disappearance of starting material and appearance of product were monitored conveniently by thin layer chromatography (50% ether/hexane). The reaction mixture was chromatographed directly on a silica gel column giving 1.65 g (0.0073 mol, 89%) of bis(p-methylbenzyl) ether after removing solvent and drying in vacuo. The ethers obtained were pure by TLC and NMR.

Properties of the Substituted Dibenzyl Ethers. Bis(p-methylbenzyl) ether, mp 62–63 °C, reported[10] 63–63.5 °C; bis(p-methoxybenzyl) ether, mp 38–38.7 °C, reported[11] 39–39.5 °C; Bis(α-methylbenzyl) ether, bp (10 Torr) 144–150 °C, n^{23}_D 1.540, reported[2] bp (10 Torr) 145 °C, n^{20}_D 1.539.

Bis(p-fluorobenzyl) ether was previously unreported. Combustion analysis of our product gave satisfactory results (±0.2%) for carbon, hydrogen, and fluorine.

Cyclohexyl (α-methylbenzyl) ether was previously unreported. The NMR spectrum of our product was consistent with the ether structure.

Acknowledgments. We are grateful to the National Science Foundation (GM-05811) and to the Mobil Foundation for their financial support.

Registry No.—Me_2SO, 67-68-5; *l*-α-methylbenzyl alcohol, 1445-91-6; cyclohexanol, 108-93-0; p-methylbenzyl alcohol, 589-18-4; p-methoxybenzyl alcohol, 105-13-5; p-fluorobenzyl alcohol, 459-56-3; p-nitrobenzyl alcohol, 619-73-8; bis-(p-methylbenzyl) ether, 38460-98-9; bis-(p-methoxybenzyl) ether, 5405-95-8; *dl*-bis-(α-methylbenzyl) ether, 53776-69-5; *meso*-bis-(α-methylbenzyl) ether, 53776-68-4; bis-(p-fluorobenzyl) ether, 61812-54-2; cyclohexyl (α-methylbenzyl) ether, 61812-55-3.

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Fluoroisoprenyl Synthesis Using Ethyl 2-Fluoroacetoacetate[1]

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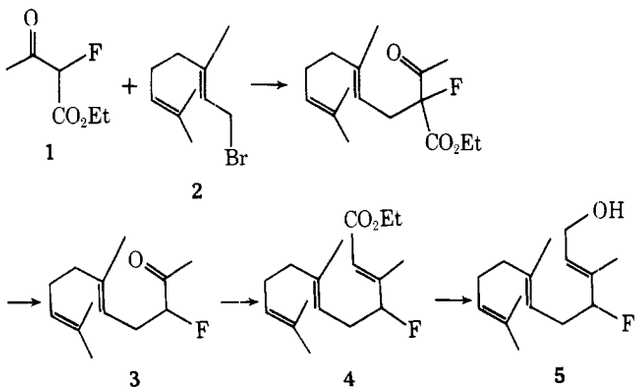
Fluorine substituted isoprenyl derivatives have aroused interest as potential insect juvenile hormone substitutes,[2] hyperlipidaemic drugs,[3] and, most recently, cancer chemotherapeutic agents.[4] The study of fluorinated isoprenoids in these and other contexts, however, has been hindered by a lack of convenient methods for their synthesis. Although 3-trifluoromethyl-2-butenol[5] and the 3-trifluoromethyl analogue of methyl farnesoate[2] have recently been prepared from trifluoroacetone and ethyl 1,1,1-trifluoroacetoacetate, respectively, most fluorinated isoprenyl compounds have been synthesized via schemes involving perchloryl fluoride fluorination.[3,6,12] The detonation hazards associated with this reagent,[7] however, discourage its use outside of specially equipped laboratories. We have developed a route to monofluorinated isoprenols involving base-catalyzed condensations of ethyl 2-fluoroacetoacetate (**1**), illustrated here by the preparation of 4-fluorofarnesol (**5**), whose general applicability is suggested by the widespread utility of ethyl acetoacetate itself in the assembly of carbon skeletons. Analogous condensations with ethyl 2-fluoroacetoacetate have not, to our knowledge, been previously reported.[8]

Ethyl 2-fluoroacetoacetate is readily prepared from inexpensive precursors, albeit in moderate yield, by base-promoted condensation of ethyl fluoroacetate and acetyl chloride.[8] Ethyl fluoroacetate is toxic but not otherwise hazardous,[9] and therefore can be handled with care by conventional techniques. Addition of geranyl bromide[10] to a solution of **1** in sodium methoxide–methanol gave in 63% isolated yield, after in situ base hydrolysis, 3-fluorogeranylacetone (**3**). Wadsworth–Emmons[11] condensation of **3** with diethyl 1-carboethoxyethylphosphonate gave ethyl 4-fluorofarnesoate (**4**)



as a 9:1 mixture of 2-*E* and 2-*Z* isomers. The assignment of stereochemistry to the two isomers was based on the relative position of the C-2 proton in their NMR spectra, that of the major (2-*E*) isomer appearing at 5.85 ppm, while that of the minor (2-*Z*) isomer appeared at 5.68 ppm. This downfield shift of the vinyl proton when cis to a fluorinated carbon has been demonstrated in closely related systems.[2,5] The assignment of 2-*E* stereochemistry to the major isomer is consistent with its longer GLC retention time.[13] Ethyl 4-fluorofarnesoate (**4**) was cleanly reduced by lithium aluminum hydride to the previously described 4-fluorofarnesol (**5**).[12]

Experimental Section

All reactions were carried out under strictly anhydrous conditions under a nitrogen atmosphere. Infrared spectra were run as thin films on a Perkin-Elmer 337 spectrophotometer. ^{1}H NMR spectra were taken on a Varian A-60A in $CDCl_3$. Chemical shifts are reported in parts per million downfield from an internal tetramethylsilane standard. Analytical GLC was performed on a Varian 2100 Model equipped with flame ionization detectors and 6 ft × 2 mm i.d. glass columns packed with 3% OV-225 on 100–200 mesh Varaport 30 (18 mL/min N_2 carrier gas). Mass spectra were obtained on an AEI MS-9 adapted to a chemical ionization mode (isobutane gas). Microanalyses were done by the Berkeley Microanalytical Laboratory.

6,10-Dimethyl-3-fluoro-5(*E*),9-undecadien-2-one (3).[6] Ethyl 2-fluoroacetoacetate[8] (1.092 g, 7.37 mmol) was added to 0.40 g (7.40 mmol) of sodium methoxide in 15 mL of anhydrous methanol at 0 °C. After 10 min, 1.54 g (7.1 mmol) of geranyl bromide[10] was added and the mixture stirred for 1 h at ambient temperature, at which time no starting bromide remained (TLC). A solution of 0.40 g of NaOH in 15 mL of H_2O was added and the mixture was refluxed for 3 h at 60 °C. After addition of 50 mL more of water, the mixture was exhaustively extracted with CH_2Cl_2, the extracts dried over $MgSO_4$, and the solvent removed. The crude orange oil thus obtained was bulb-to-bulb distilled (75 °C, 0.20 mm), yielding 0.9532 g (63%) of colorless oil (better than 96% pure by GLC): IR 1730 cm^{-1}; NMR 1.62 and 1.68 (singlets, 9 H, vinyl methyls), 2.00–2.17 (m, 4 H, allyl CH_2), 2.20 (d, J = 4.5 Hz, 3 H, $COCH_3$ coupled to fluorine), 2.53 (doublet of triplets, J = 26 and 6 Hz, 2 H, CH_2CF), 4.67 (doublet of triplets, J = 50 and 6 Hz, 1 H, CHF), and 5.00–5.30 ppm (m, 2 H, vinyl H); CIMS *m/e* 213 (MH^+), 193 ($MH^+ - HF$). Anal. Calcd for $C_{13}H_{21}FO$: C, 73.54; H, 9.97. Found: C, 73.53; H, 9.93.

Ethyl 4-Fluorofarnesoate (4). Reaction of **3** with diethyl 1-carboethoxyethylphosphonate by the procedure of Machleidt[6] gave crude **4** as a 9:1 (by GLC) 2-*E* to 2-*Z* isomeric mixture (retention times at 150 °C: 20.25 and 12.75 min, respectively). Fractional distillation provided pure **4** in 69% isolated yield, the 2-*E*:2-*Z* isomer ratio increasing from about 1:1 in the first fraction to better than 99:1 in the final ones: 2-*E* isomer (bp 108–110 °C, 0.05 mm) IR 1725, 1660 cm^{-1}; NMR 1.27 (t, J = 7 Hz, 3 H, ethyl CH_3), 1.60 and 1.68 (singlets, 9 H, vinyl methyls), 1.97–2.20 (m, 4 H, allyl CH_2), 2.12 (d, J = 2 Hz, 3 H, 3-Me), 2.47 (doublet of triplets, J = 23 and 6 Hz, 2 H, CH_2CF), 4.15 (q, J = 7 Hz, 2 H, CH_2O), 4.82 (doublet of triplets, $J \simeq 50$ and 6 Hz, 1 H, CHF), 4.90–5.33 (m, 2 H, vinyl H), and 5.85 ppm (m, 1 H, vinyl H); CIMS *m/e* 283 (MH^+), 263 ($MH^+ - HF$). Anal. Calcd for $C_{17}H_{27}FO_2$: C, 72.30; H, 9.64. Found: C, 72.07; H, 9.50. The 2-*Z* isomer had similar spectral properties, except for appearance of the C-2 vinyl proton in the NMR at 5.68 rather than 5.85 ppm.

4-Fluorofarnesol (5). Ester **4** was reduced with $LiAlH_4$ in 98% yield as previously described[12] to give **5**: IR 3325 cm^{-1} (OH); NMR 1.60 and 1.67 (singlets, 12 H, vinyl methyls), 1.98–2.17 (m, 4 H, allyl CH_2), 2.37 (doublet of triplets, J = 26 and 6 Hz, 2 H, CH_2CF), 2.93 (m, 1 H, OH), 4.02–4.33 (m, 2 H, CH_2O), 4.73 (doublet of triplets, $J \simeq 48$ and 6 Hz, 1 H, CHF), 4.92–5.30 (m, 2 H, vinyl H), and 5.45–5.82 ppm (m, 1 H, vinyl H); CIMS *m/e* 241 (MH^+), 223 ($MH^+ - H_2O$), and 221 ($MH^+ - HF$). Anal. Calcd for $C_{15}H_{25}FO$: C, 74.95; H, 10.48. Found: C, 74.74; H, 10.43.

Registry No.—**1**, 1522-41-4; **2**, 6138-90-5; **3**, 61812-56-4; **4** (2*Z* isomer), 61812-57-5; **4** (2*E* isomer), 2599-71-5; **5**, 5979-63-5; diethyl 1-carboethoxyethylphosphonate, 3699-66-9.

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Aporphines. 23. Normorphothebaine Derivatives: Synthesis of an Aporphine Nitrogen Mustard

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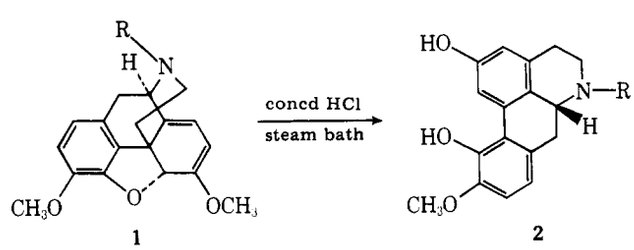
The known CNS activity[1-5] of a number of aporphine alkaloids led to the choice of this tetracyclic ring system for the synthesis of potential CNS penetrating antitumor agents bearing an alkylating function. The selection of normorphothebaine (**2b**) as the carrier base was governed chiefly by its ease of synthesis, its adaptability to large-scale preparations, and the availability of the natural alkaloid, thebaine. In the present communication we wish to report the synthesis of normorphothebaine (**2b**) and its derivatives, **3–5** and **7–10**.

The rearrangement of morphine alkaloids to apomorphine derivatives has been hampered by the requirement of excessively strong acids (80–85% H_3PO_4 or CH_3SO_3H)[5,6] at high



1 **2**

a, R = CH_3
b, R = H