was removed in vacuo. Purification by flash chromatography (10% ether–hexane) afforded 89 mg (60%) of the aldehyde **28**: ^{1}H NMR ($CDCl_3$) δ 0.35 (s, 9 H), 3.89 (s, 3 H), 7.0 (dd, J = 7.5, 2.5 Hz, 1 H), 7.2 (d, J = 2.5 Hz, 1 H), 7.87 (d, J = 7.5 Hz, 1 H), 10.01 (s, 1 H); IR (neat) 1695 cm^{-1}; mass spectrum (70 eV) m/e (relative intensity) 208 (M^+, 1.3), 195 (16), 194 (56), 193 (100), 178 (20), 134 (34).

Anal. Calcd for $C_{11}H_{16}O_2Si$: C, 63.45; H, 7.68. Found: C, 63.62; H, 7.35.

1-(2-(Trimethylsilyl)-4-methoxyphenyl)-3-(trimethylsilyl)prop-1-ene (29) was prepared from 0.2 g (0.72 mmol) of the aldehyde **28** (see general method for the preparation of allylsilanes). Purification by distillation under reduced pressure (150 °C (0.2 mm)) afforded 0.18 g (85%) of the allylsilane **29**: ^{1}H NMR ($CDCl_3$) δ 0.1 (s, 9 H), 0.3 (s, 9 H), 1.66 (d, J = 7.7 Hz, 2 H), 3.82 (s, 3 H), 5.6–6.1 (m, 1 H), 6.6 (d, J = 16.5 Hz, 1 H), 6.9 (dd, J = 5.6, 2.5 Hz, 1 H), 7.15 (d, J = 2.5 Hz, 1 H), 7.25 (d, J = 8.5 Hz, 1 H); mass spectrum (10 eV), m/e (relative intensity) 292 (M^+, 20), 180 (10), 189 (59), 73 (100); Anal. (high-resolution mass spectrum) calcd for $C_{16}H_{28}OSi_2$, 292.1679; found, 292.1681.

Methyl (4-Methoxyphenyl)acetate (30). To a solution of 4 g (24 mmol) of (4-methoxyphenyl)acetic acid in 100 mL of methanol was added 8.3 mL of a 5 M HCl solution in dioxane (3% HCl). The solution was brought to reflux for 16 h and then extracted into ether (3 × 50 mL). The combined organic extracts were washed with 100 mL saturated sodium carbonate solution and dried ($MgSO_4$), and the solvent was removed in vacuo to yield 4.32 g of the crude product. Flash chromatography over silica gel and elution with 10% ether–hexane afforded 4.2 g (93%) of the methyl ester **30**: ^{1}H NMR (CCl_4) δ 3.55 (s, 2 H), 3.7 (s, 3 H), 3.82 (s, 3 H), 6.95 (AA'BB', J = 8.5 Hz, $\Delta\nu$ = 0.43 ppm, 4 H); bp 113–115 °C (2 mm) (lit.[29] 155–157 °C (23 mm)).

(2*R,3*S**)-Methyl 2,3-Bis(4-methoxyphenyl)pentanoate (32).** To a solution of 0.40 mL (0.29 g, 2 mmol) of diisopropylamine in THF (5 mL) at −30 °C was added an equivalent of n-butyllithium (1 mL of a 2 M solution in hexane, 2 mmol), and the solution was stirred for 0.5 h. The solution was then cooled to −78 °C, and a solution of the methyl ester **30** (0.36 g, 2 mmol) in THF (5 mL) was added dropwise over 10 min. The solution was stirred for 2 h at −78 °C and then quenched with 0.26 mL of chlorotrimethylsilane (0.21 g, 2 mmol). The solution was then allowed to warm slowly to 0 °C and the THF was removed under reduced pressure (1 mm). After all the THF had been removed, the solution was recooled to −78 °C under nitrogen, and the electrophile **7** (0.45 g, 2.5 mmol) in dichloromethane (10 mL) was added dropwise. Titanium tetrachloride (0.45 mL, 4 mmol) in dichloromethane (10 mL) was then added to the reaction mixture dropwise over 10 min. The reaction mixture was stirred at −78 °C for 1 h when GLC analysis showed disappearance of the starting material. The reaction was quenched with methanol (20 mL) and extracted with ethyl acetate (3 × 50 mL). The organic layer was dried ($MgSO_4$) and the solvent removed in vacuo to yield 0.52 g of the crude product. Preparative thin-layer chromatography (10% ethyl acetate–hexane) afforded 0.47 g (71%) of an oil which was shown by NMR to be a mixture of diastereomers. Fractional crystallization (methylene chloride–hexane) afforded 0.25 g (38%) of the product **32a**, mp 124–126 °C (lit.[6d] 124–125 °C).

(29) Carter, P. R.; Hey, D. H. *J. Chem. Soc.* **1948**, 153.

Acknowledgment. This research was supported by a grant from the National Institutes of Health (PHS AM 15556). High-field NMR spectra were obtained on instruments in the NSF Regional Instrumentation Facility supported by a grant from the National Science Foundation (NSF CHE 79-16100) and high-resolution mass spectrometry was performed on instruments supported by a grant from the National Institutes of Health (PHS GM 27029).

Registry No. **6**, 88932-42-7; **7**, 88932-43-8; **8**, 82482-05-1; **10a**, 78387-60-7; **10b**, 88932-44-9; **11**, 17484-36-5; **13a**, 88932-45-0; **13b**, 88932-46-1; **14a**, 88932-47-2; **14b**, 88932-48-3; **15**, 77525-91-8; **16**, 57559-52-1; **17**, 22996-21-0; **18**, 88932-49-4; **19a**, 88932-50-7; **19b**, 88932-51-8; **20a**, 88932-52-9; **20b**, 88932-53-0; **21a**, 88932-54-1; **21b**, 88932-55-2; **22a**, 88932-56-3; **22b**, 88932-57-4; **25**, 53416-46-9; **26**, 88932-58-5; **27**, 88932-59-6; **28**, 88932-60-9; **29**, 88932-61-0; **30**, 23786-14-3; **32a**, 83303-94-0; **32b**, 88932-62-1; $(CH_3)_3SiCH_2CH{=}PPh_3$, 63922-69-0; anethole, 104-46-1; methyltriphenylphosphonium bromide, 1779-49-3; (iodomethyl)trimethylsilane, 4206-67-1; 4-methoxybenzaldehyde, 123-11-5; 1-(4-methoxyphenyl)ethanol, 3319-15-1; *p*-anisic acid, 100-09-4; 2-amino-2-methyl-1-propanol, 124-68-5; (4-methoxyphenyl)acetic acid, 104-01-8.

Syntheses of Hydroxy Ketones from Lactones

Silvia Cavicchioli, Diego Savoia,* Claudio Trombini, and Achille Umani-Ronchi*

Istituto Chimico "G. Ciamician", Università di Bologna, 40126 Bologna, Italy

Received May 17, 1983

γ-Hydroxy ketones (**4**, n = 2) are cleanly obtained by the addition of 1.1 equiv of n-butyllithium to γ-lactones dissolved in ether at −90 °C, since in these conditions the formation of diols by double organometallic attack is avoided, especially in the case of substituted lactones. The corresponding reactions performed in tetrahydrofuran are less satisfactory. The method cannot be applied to δ-valerolactone and to ε-caprolactone, as well as to β-lactones, from which extremely complex mixtures are obtained in low yields. Furthermore the reactions of Grignard reagents with lactones in ether or in tetrahydrofuran are quite poor. From those lactones which behave unsatifactorily toward n-butyllithium in ether, the corresponding β-, δ-, and ε-hydroxy ketones (**4**, n = 1, 3, 4) are prepared in two steps. The reactions with α,α-dilithioalkyl phenyl sulfones in tetrahydrofuran at low temperatures afford the ω-hydroxy-β-keto sulfones (**12**), which are successively cleaved with aluminum amalgam to afford **4** in satisfactory overall yields.

Introduction

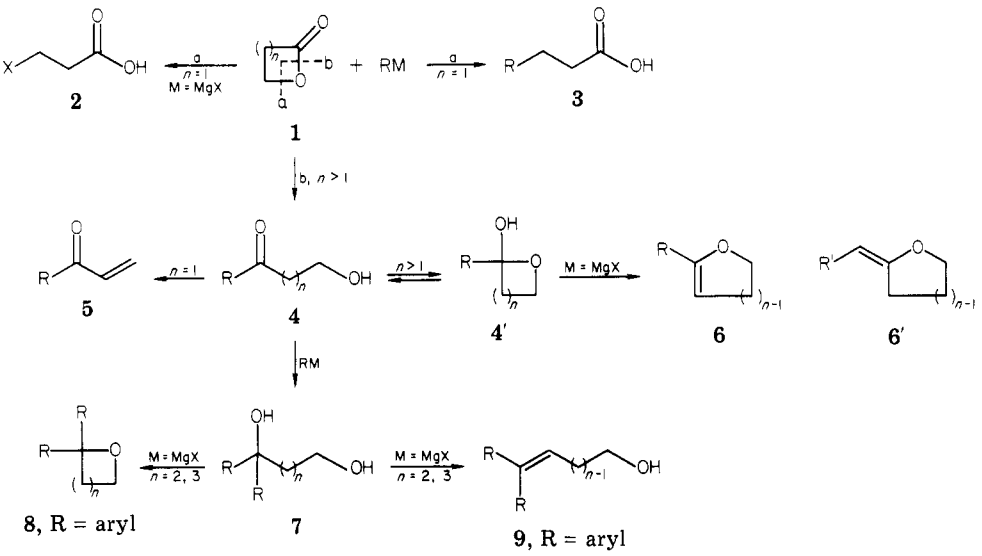
The reaction of lactones with organometallic reagents is a useful tool for the homologation of a carbon chain. The ring opening can follow different pathways (a and b, Scheme I), depending principally on the ring size and the nature of the organometallic reagent.

The sterically constrained β-lactones (**1**, n = 1) react with organolithium, -magnesium, and -cadmium compounds to give mixtures of β-halopropionic acids (**2**, from Grignard reactions), carboxylic acids (**3**), β-hydroxy ketones (**4**, n = 1), vinyl ketones (**5**), and diols (**7**, n = 1).[1] The use of organocuprates of Grignard reagents under the catalytic

(1) Gresham, T. L.; Jansen, J. E.; Shaver, F. W.; Bankert, R. A. *J. Am. Chem. Soc.* **1949**, *71*, 2807. Bankert, R. A. U.S. Patent 2 510 364 (1950) (C.A. *1950*, *44*, 8373; Stuckwisch, C. G.; Bailey, J. V. *J. Org. Chem.* **1963**, *28*, 2362. Fujisawa, T.; Sato, T.; Takeuchi, M. *Chem. Lett.* **1982**, 71.

0022-3263/84/1949-1246$01.50/0

Scheme I



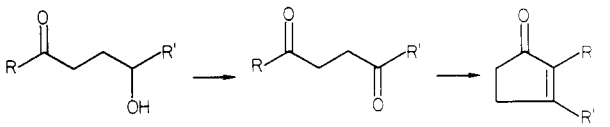
action of copper salts affords a convenient route to **3**.[2,3]

Homologous saturated lactones (**1**, $n > 1$) commonly undergo double organometallic attack to give diols (**7**)[4,5] through the intermediate hydroxy ketones (**4**); however, cyclic enol ethers (**6** or **6'**), α,α-disubstituted cyclic ethers (**8**), and unsaturated alcohols (**9**) have been obtained in some Grignard reactions.[6]

The preparation of hydroxy ketones (**4**, $n = 2, 3, 4$) is possible, depending on several factors: the size and the substitution pattern of the lactone, the nature of the organometallic reagent, the temperature, and the solvent, apart from steric reasons due to hindered organometallics or lactones.[7]

The effect of the ring size was evinced from comparative reactions of homologous lactones with vinylmagnesium bromide[8] and lithium acetylides;[9a] the yields of the corresponding unsaturated products decreased in the order

Scheme II



$n = 3 > 2 > 4$, reflecting the ease for the reaction intermediate (metal salt) to internally protect the carbonyl group by forming the cyclic hemiketal (**4'**).

The reaction of lithium acetylides with unsubstituted lactones[9a-d] were best performed in tetrahydrofuran (THF) as solvent at −78 °C, whereas more complex lactones worked at room temperature in ether,[9d-i] even with an excess of reagent.[9g] Magnesium acetylides proved to be less suitable.[9i,j]

The addition of 1 equiv of lithium alkyls to γ- and δ-lactones carrying at least one substituent in the α- or ω-position gave clean conversion to **4** ($n = 2, 3$),[10] working at −78 °C, generally in THF.

Grignard reagents in THF at −78 °C have been employed in the case of α-oxygen-substituted γ-lactones.[11a,b] The addition of 4-pentenylmagnesium bromide to δ-caprolactone in ether at −15 °C afforded the corresponding δ-hydroxy ketone in 50% yield;[11c] however, this method gave low yields of **4** from δ-valerolactone and could not be

(2) Normant, J. F.; Alexakis, A.; Cahiez, G. *Tetrahedron Lett.* **1980**, *21*, 935. Fujisawa, T.; Sato, T; Kawara, T.; Kawashima, M; Shimizu, H; Ito, Y. *Ibid.* **1980**, *21*, 2181. Sato, T; Kawara, M.; Fujisawa, T. *Chem. Lett.* **1980**, 571. Fujisawa, T.; Sato, T.; Kawara, T.; Nishizawa, A.; Obinata, T. *Tetrahedron Lett.* **1980**, *21*, 2533. Sato, T.; Kawara, T.; Nishizawa, A.; Fujisawa, T. *Ibid.* **1980**, *21*, 3377. Fujisawa, T.; Sato, T.; Kawara, T.; Ohashi, K. *Ibid.* **1981**, *22*, 4823. Sato, T.; Kawara, T.; Sakata, K.; Fujisawa, T. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 505. Sato, T.; Kawara, T.; Kawashima, M.; Fujisawa, T. *Chem. Lett.* **1982**, 569. Fujisawa, T.; Sato, T.; Kawara, T.; Noda, A. *Tetrahedron Lett.* **1982**, *23*, 3193. Fujisawa, T.; Sato, T.; Kawara, T.; Tago, H. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 345.

(3) β-Vinyl-β-propiolactone (a), β-ethynyl-β-propiolactone (b), and γ-vinyl-γ-butyrolactone and δ-vinyl-δ-valerolactone (c) undergo S_N2' type reactions with organocopper reagents: (a) Sato, T.; Takeuchi, M.; Itoh, T.; Kawashima, M.; Fujisawa, T. *Tetrahedron Lett.* **1981**, *22*, 1817. Fujisawa, T.; Sato, T.; Itoh, T. *Chem. Lett.* **1982**, 219. Fujiisawa, T.; Sato, T.; Itoh, T. *Ibid.* **1982**, 71. (b) Sato, T.; Kawashima, M.; Fujisawa, T. *Tetrahedron Lett.* **1981**, *22*, 2375. (c) Fujisawa, T.; Sato, T.; Kawashima, M.; Naruse, K.; Tamai, K. *Ibid.* **1982**, *23*, 3583.

(4) (a) Nützel, K. In "Methoden der Organischen Chemie"; Müller, E., Ed.; G.Thieme Verlag: Stuttgart, 1973; Vol 13/2a, p 281. (b) Belov, V. N.; Tarnopol'skii, Yu. I. *Zh. Organ. Khim.* **1965**, *1*, 634; *Chem. Abstr.* **1965**, *63*, 5579g.

(5) The reaction of α,ω-diyldimagnesium dihalides follows this pathway also with β-propiolactone: Canonne, P.; Foscolos, G. B.; Belanger, D. *J. Org. Chem.* **1980**, *45*, 1828.

(6) Kohn, M. *Monatsh. Chem.* **1913**, *34*, 1729. Weiss, R.; Fastmann, P. *Ibid.* **1926**, *47*, 727. Vozza. J. F. *J. Org. Chem.* **1959**, *24*, 720. Blicke, F. F.; Brown, B. A. *Ibid.* **1961**, *26*, 3685. Dehal, S. S.; Marples, B. A.; Stretton, R. J. *Tetrahedron Lett.* **1978**, 2183. Fuentes, L. M.; Larson, G. L. *Ibid.* **1982**, *23*, 271.

(7) Baddeley, G. V.; Carpio, H.; Edwards, J. A. *J. Org. Chem.* **1966**, *31*, 1026. Lenz, G. R.; Dorn, C. R. *Ibid.* **1983**, *48*, 2696 and references cited therein.

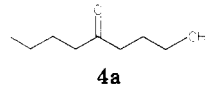
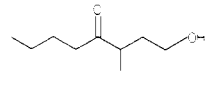
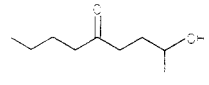
(8) Cohen, N.; Banner, B. L.; Blount, J. F.; Tasai, M.; Saucy, G. *J. Org. Chem.* **1973**, *38*, 3229 and previous papers in the series.

(9) (a) Chabala, J. C.; Vincent, J. E. *Tetrahedron Lett.* **1978**, 937. (b) Audin, P.; Doutheau, A.; Gore, J. *Ibid.* **1982**, *23*, 4337. (c) Larock, R. C.; Liu, C. L. *J. Org. Chem.* **1983**, *48*, 2151. (d) Phillips, C.; Jacobson, R.; Abrahams, B.; Williams, H. J.; Smith, L. R. *Ibid.* **1980**, *45*, 1920. (e) Jacobson, R.; Taylor, R. J.; Williams, H. J.; Smith, L. R. *Ibid.* **1982**, *47*, 3140. (f) Colvin, E. V.; Malchenko, S.; Raphael, R. A.; Roberts, J. S. *J. Chem. Soc., Perkin Trans 1* **1978**, 658. (g) Lin, C. H.; Alexander, D. L. *J. Org. Chem.* **1982**, *47*, 615. (h) Baker, R.; Boyes, R. H. O.; Broom, D. M. P.; Devlin, J. A.; Swain, C. J. *J. Chem. Soc., Chem. Commun.* **1983**, 829. (i) Ogura, H.; Takahashi, H.; Itoh, T. *J. Org. Chem.* **1972**, *37*, 72. (j) Luthy, C.; Konstantin, P.; Untch, K. C. *J. Am. Chem. Soc.* **1978**, *100*, 6211.

(10) (a) Arzeno, H. B.; Sanchez, E. L. *Rev. Latinoam. Quim.* **1979**, *10*, 65; *Chem. Abstr.* **1979**, *91*, 210942p. (b) Fukuyama, Y.; Wang, C-L. J.; Kishi, Y. *J. Am. Chem. Soc.* **1979**, *101*, 260. (c) Collum, B. D.; McDonald, J. H. III; Still, W. C. *Ibid.* **1980**, *102*, 2117. (d) Collum, B. D.; McDonald, J. H. III; Still, W. C. *Ibid.* **1980**, *102*, 2120. (e) Strunz, G. M.; Lal, G. S. *Can. J. Chem.* **1982**, *60*, 2528. (f) Williams, D. R.; Barner, B. A. *Tetrahedron Lett.* **1983**, *24*, 427. See also ref 9d.

(11) (a) Collum, B. D.; McDonald, J. H. III; Still, W. C. *J. Am. Chem. Soc.* **1980**, *102*, 2118. (b) McGuirk, P. R.; Collum, B. D. *Ibid.* **1982**, *104*, 4496. (c) Taub, D; Girotra, N. N.; Hoffsommer, R. D.; Kuo, C. H.; Slates, H. L.; Weber, S.; Wendler, N. L. *Tetrahedron* **1968**, *24*, 2443. (d) Ley, S. V.; Lygo, B. *Tetrahedron Lett.* **1982**, *23*, 4625 (we greatly acknowledge Prof. Ley for kindly communicating his results to us).

Table I. Reactions of γ-Lactones with *n*-Butyllithium at −90 °C

lactone	product[a,b]	yield in Et_2O, %	yield in THF, %
 1b	 4a	58[c]	34[d]
 1b	 4b	85[e]	51[f]
 1c	 4c	60[e]	45[g]

[a] For identification and quantitative evaluation of diols present in the crude reaction mixtures, authentic specimens were prepared by reaction of lactones with 2 equiv of *n*-BuLi. [b] Satisfactory elemental analyses were obtained for all compounds (C,H ± 0.3%). [c] Isolated yield after column chromatography; GLC analysis of the crude reaction mixture revealed the presence of approximately 6 mol% of diol and other minor impurities. [d] Isolated yield after column chromatography; the reaction afforded a complex mixture of products, including a consistent amount of diol, as evaluated by GLC analysis. [e] Yield of crude product, pure by GLC and spectroscopic analyses. [f] Isolated yield after column chromatography; the diol was successively eluted in 15% yield. [g] Isolated yield after column chromatography; GLC analyses of the crude reaction mixture showed the presence of about 3 mol% of diol.

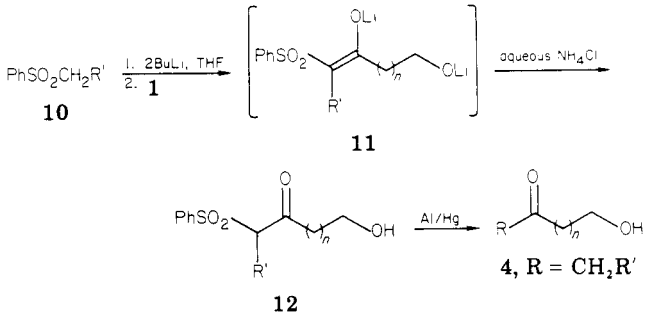
applied to γ-butyrolactone.[11d,4b]

Results and Discussion

Since we have been concerned with the preparation of γ-hydroxy ketones (**4**, $n = 2$), key intermediates in the construction of alkyl-substituted cyclopentenones through γ-dicarbonyl compounds (Scheme II),[12a,b] we have observed that the literature lacked comparative studies aimed at defining the role that the different organometallic species, as well as solvents, can have. We have undertaken a study in order to determine the optimum experimental conditions for the preparation of homologous ω-hydroxy ketones. The results obtained by using *n*-butyllithium and Grignard reagents, both in ether and in THF, in a series of reactions on unsubstituted or methyl-substituted β- to ε-lactones are discussed. In every case 1.1 equiv of organometallic reagent were slowly added to a solution of the lactone stirred at −90 °C under argon, and the reaction mixture was quenched with aqueous ammonium chloride after 2 h at the same temperature.

In the case of γ-lactones the best results were provided by the use of *n*-butyllithium in ether, especially for the substituted rings (**1b,c**), from which pure γ-hydroxy ketones (**4b,c**) were obtained (Table I). Compound **4a**, instead, derived from γ-butyrolactone (**1a**), was accompanied by a definite amount (6 mol%) of the diol coming from double addition of the reagent, thus indicating that the presence of the ring substituent has a slight influence

Scheme III



on the course of the reaction, probably favoring the cyclization of the intermediate salt (**4** to **4'**).[13] The reactions performed on the same lactones with *n*-butyllithium in tetrahydrofuran were less satisfactory, since the compounds **4a–c**, especially **4a**, were recovered in lower yields after chromatographic separations from the diols and other impurities.

Our results are in agreement with the previously reported syntheses of 2-hydroxyundecan-5-one and (*Z*)-2-hydroxyundec-8-en-5-one by the reactions of *n*-hexyllithium and (*Z*)-3-hexenyllithium, respectively, with γ-valerolactone (**1c**) at −78 °C in ether.[10a]

We obtained unsatisfactory results in the reaction of δ-valerolactone (**1g**) and ε-caprolactone (**1h**) with *n*-butyllithium, despite several attempts to determine suitable experimental conditions.

The reactions of β-propiolactone (**1d**) and β-butyrolactone (**1f**) with *n*-butyllithium in ether and in THF at −90 °C gave in low yields complex mixtures, containing a plethora or byproducts; they were given up without any effort of product indentification. The steric constraint of the ring, which makes easy the attack at the β-position, and the analogous instability of the hemiketalic form (**4'**) accounts for the negative results obtained even at low temperature.

Shifting from *n*-butyllithium to Grignard reagents, we found that the reactions of γ-lactones (**1a,c**) with *n*-butyl- and *n*-hexylmagnesium bromide in ether or in THF at −90 °C gave low yield mixtures in which the diols predominated.

α,α-Dilithio Sulfones. The aforementioned problems can be circumvented by the use of α,α-dilithio derivatives of alkyl phenyl sulfones (**10**) as organometallic reagents;[12,14] since they are gem-dimetallic compounds, the attack of the lactone affords an intermediate enolate (**11**).[15] The reaction product (**12**), obtained by quenching with aqueous ammonium chloride, is then submitted to reductive cleavage by aluminum amalgam,[16] to afford the required compound **4** (Scheme III).

(12) (a) Mussatto, M. C.; Savoia, D.; Trombini, C.; Umani-Ronchi, A. *J. Org. Chem.* **1980**, *45*, 4002. (b) Savoia, D.; Trombini, C.; Umani-Ronchi, A. *Ibid.* **1982**, *47*, 564. For analogous examples see: Bartlett, P. A.; Green, F. R. III; Rose, E. H. *J. Am. Chem. Soc.* **1978**, *100*, 4852. Ghera, E.; Een-David, Y. *Tetrahedron Lett.* **1983**, *24*, 3533.

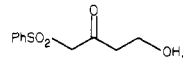
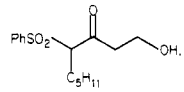
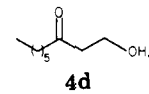
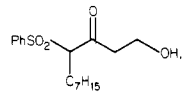
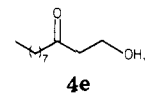
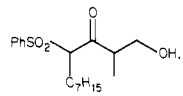
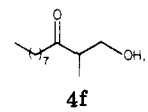
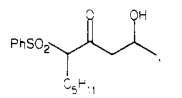
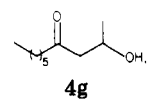
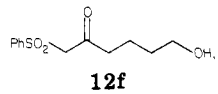
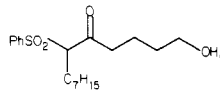
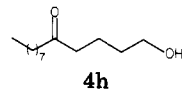
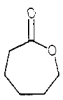
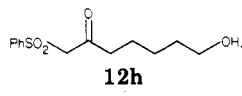
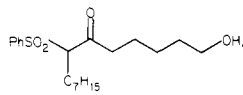
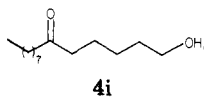
(13) It is known that the rate of cyclization reactions is enhanced by the presence of substituents: Ingold, C. K. *J. Chem. Soc.* **1921**, *119*, 305, 951. Allinger, N. L.; Zalkov, V. *J. Org. Chem.* **1960**, *25*, 701. For ring-chain tautomerism of linear hydroxy ketones see: Joris, L.; Schleyer, P. von R. *J. Am. Chem. Soc.* **1968**, *90*, 4599 (footnote 56). Cottier, L.; Descotes, G. *Bull. Soc. Chim. Fr.* **1971**, 4557.

(14) Alternatively, 2 equiv of α-sulfonyl carbanions should be employed: House, H. O.; Larson, J. K. *J. Org. Chem.* **1968**, *33*, 61. Shono, T.; Matsumura, Y.; Kashimura, S. *Chem. Lett.* **1978**, 69. House, H. O.; Haack, J. L.; McDaniel, W. C.; Van Derveer, D. *J. Org. Chem.* **1983**, *48*, 1643. Batmanderlich, S.; Davidson, A. H.; Procter, G. *Tetrahedron Lett.* **1983**, *24*, 2889.

(15) The preparation of ketones by acylation of (a) diboryl carbanions and (b) sulfur-stabilized boryl carbanions with carboxylic acid derivatives, including γ-butyrolactone, is based on a similar strategy: (a) Matteson, D. S.; Moody, R. J. *J. Am. Chem. Soc.* **1977**, *99*, 3196. Matteson, D. S.; Moody, R. J. *Organometallics* **1982**, *1*, 20. (b) Matteson, D. S.; Arne, K. H. *Ibid.* **1982**, *1*, 280.

(16) Corey, E. J.; Chaykowsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1345.

Table II. Reactions of Lactones with Dilithio Sulfones. Preparation of ω-Hydroxy-β-keto Sulfones (12) and ω-Hydroxy Ketones (4)

lactone[a] (1)	sulfone (10)	12, %[b,c]		4, %[c,d]	
 1d	$PhSO_2CH_3$ 10a	 12a	65		
1d	$PhSO_2C_6H_{13}$ 10b	 12b	55	 4d	92[b]
1d	$PhSO_2C_8H_{17}$ 10c	 12c	61	 4e	99[e]
 1e	10c	 12d	69	 4f	70[b]
 1f	10b	 12e	56	 4g	72[b]
 1g	10a	 12f	78		
1g	10c	 12g	72	 4h	85,[b] 97[e]
 1h	10a	 12h	79		
1h	10c	 12i	66	 4i	73[f]

[a] The reactions were performed in THF at 0 °C in the case of β-lactones, and at −60 °C with δ- and ε-lactones. [b] Isolated yields after column chromatography. [c] Satisfactory elemental analyses (C,H ± 0.3%) were obtained for all compounds. [d] Obtained from 12 by reaction with Al/Hg in refluxing THF/H_2O. [e] Yield of crude product, pure by GLC and spectroscopic analyses. [f] Isolated yield after crystallization from ether–pentane.

The practicality of this route was tested in our previous syntheses of *cis*-jasmone and dihydrojasmone, raw materials in the perfume industry, from γ-valerolactone (**1c**),[12a] and of 2-(6-carboxyhexyl)cyclopent-2-en-1-one, an intermediate in prostaglandin synthesis, from γ-butyrolactone (**1a**).[12b] We now report the completion of that study, concerned with the condensation of dilithioalkyl phenyl sulfones with β-, δ-, and ε-lactones (**1d–h**), thus demonstrating the generality of the method. We would emphasize that all the lactones selected for this study gave poor results in the attempted preparation of the corresponding hydroxy ketones by direct organometallic attack.

The condensation reactions have been carried out and quenched at −60 °C, except for β-lactones, which can be likely put in reaction at 0 °C. The ω-hydroxy-β-keto sulfones (**12**) prepared and the relative yields, determined from the products isolated after column chromatography, are collected in Table II. Discrete amounts (7–17%) of the starting sulfones were also recovered. Hexamethylphosphorictriamide, previously employed as cosolvent,[12a,b] has a slight influence only in reactions involving methyl phenyl sulfone (**10a**) and was not used in this work.

The reductive desulfonation of **12** to ω-hydroxy ketones (**4**) was smoothly accomplished in good yield by means of aluminum amalgam in refluxing $THF–H_2O$[16] (Table II). In certain cases the crude products were obtained in a pure state, otherwise they were purified by column chromatography or crystallization.

Since the steps involved in the sequence (Scheme III) appear to be independent of both the value of "*n*" and the substitution pattern of the starting lactone ring, the method allows the preparation of homologous compounds (**12** and **4**) and, consequently, others from them in which two functionalities along a carbon chain are separated by a number of carbon atoms dependent ultimately from the size of the starting lactone ring. Furthermore, the preparation of β-hydroxy ketones from β-lactones is most attractive and promising from the synthetic view point, since it discloses a methodology alternative to the classic aldol condensation. particularly, one can prepare products, such as **4d–g**, which are ideally derived by the selective condensation of unsymmetrical ketones with formaldehyde

(hydroxymethylation), a process quite difficult to control and resulting in complex mixtures containing polycondensation products as well as Cannizzaro type products.[17]

The full scope of the method is currently under investigation.

Experimental Section

General Procedures. ^1H NMR spectra were determined on a Perkin-Elmer R12B instrument (60 MHz) using tetramethylsilane as the internal standard and $CDCl_3$ as the solvent. Chemical shifts are reported as values. IR spectra were recorded on a Perkin-Elmer 710B spectrophotometer and the absorption are given in reciprocal centimeters. Mass spectra (MS) were obtained on a double focusing Varian MAT 112S instrument at an ionizing voltage of 70 eV.

GLC analyses were performed on a Carlo Erba Fractovap 4160 apparatus using a 15-m glass capillary column coated with OV1 (film thickness 0.1–0.15 mm). TLC assays were made with hexane–ether or hexane–ethyl acetate on plastic sheets of silica gel 60 F_{254} (layer thickness 0.2 mm). Chromatographic separations were accomplished by flash chromatography on silica gel columns (Merck, 230–400 mesh) using hexane–ethyl acetate mixtures.

Diethyl ether and tetrahydrofuran (THF) were distilled from sodium benzophenone ketyl under argon immediately before use.

Melting points (mp) are uncorrected.

Materials. Butyllithium (1.6 M in hexane) was purchased from Fluka and was titrated by standard methods prior to use.

The alkyl phenyl sulfones (**10a–c**) were prepared as previously described[18] from the corresponding halides and polymer-supported benzenesulfinate anion in refluxing benzene.

All the lactones employed were commercially available from Fluka or Aldrich, with the exception of β-isobutyrolactone (**1e**), which was prepared by a literature procedure:[19] bp 52 °C (10 mm); IR 2980, 1720, 1130, 1115, 1055, 930, 910, 860; NMR δ 4.5 and 4.0 (m, 2 H, CH_2O), 3.75 (m, 1 H, CHC=O), 1.45 (d, 1 H, CH_3).

Reactions of γ-Lactones with *n*-Butyllithium in Ether: Preparation of γ-Hydroxy Ketones (4a–c). General Procedure. *n*-Butyllithium (1.6 M, 7 mL, 11.2 mmol) was added during 30 min to a mechanically stirred solution of lactone (**1a**) (10 mmol) in anhydrous diethyl ether (20 mL) at −90 °C under argon. The reaction mixture was stirred for 2 h, then quenched with saturated aqueous NH_4Cl (20 mL), and allowed to reach room temperature. The organic phase was extracted with ether, washed with 10% aqueous NaOH (10 mL) and then with brine (2 × 10 mL), dried over Na_2SO_4, and evaporated under vacuum to give (**4**) as an oil (Table I). Flash chromatography on a silica gel column, eluting with hexane–ether 70:30, afforded pure **4a**. Crude **4b,c**, similarly prepared from lactones **1b,c**, were pure by spectroscopic and GLC analyses. On an average, a 25% amount of hemiketalic form **4′**, in equilibrium with the open-chain isomer, could be ascertained in the NMR spectra of the γ-hydroxy ketones.[13]

1-Hydroxyoctan-4-one (4a): IR 3420, 1720, 1130, 1065, 1035, 940; NMR 3.7 (t, 2 H, CH_2OH), 3.1 (br s, 1 H, OH), 2.5 (m, 4 H, CH_2C=O), 0.7 (m, 9 H, aliphatic); GC–MS, *m/e* (relative intensity) 55 (100), 44 (88), 41 (82), 84 (82), 97 (74), 57 (74), 58 (66), 43 (57), 126 (15, $(M^+ - H_2O)$).

1-Hydroxy-3-methylundecan-4-one (4b): IR 3410, 1720, 1125, 1060; NMR 4.1 (br s, 1 H, OH), 3.7 (t, 2 H, CH_2OH), 2.4–3.1 (m, 3 H, CH_2COCH), 0.7–2.2 (m, 12 H, aliphatic); GC–MS, *m/e* (relative intensity) 57 (100), 55 (74), 85 (83), 41 (61), 101 (49), 72 (48), 56 (40), 43 (33), 140 $(M^+ - H_2O)$.

2-Hydroxynonan-4-one (4c): IR 3410, 1720, 1130, 1060; NMR 3.8 (m, 1 H, CHOH), 3.5 (br s, 1 H, OH), 2.5 (m, 4 H, CH_2C=O), 0.8–2.1 (m, 12 H, aliphatic); GC–MS, *m/e* (relative intensity) 55 (100), 43 (54), 98 (38), 111 (36), 41 (30), 83 (27), 39 (19), 140 (17, $(M^+ - H_2O)$).

Reactions of Lactones with α,α-Dilithioalkyl Phenyl Sulfones: Preparation of ω-Hydroxy-β-keto Sulfones (12). **General Procedure.** *n*-Butyllithium (42 mmol) was added with stirring under argon to a solution of alkyl phenyl sulfonyl (**10**) (20 mmol) in anhydrous THF (70 mL) at 0 °C. After 30 min a solution of lactone (20 mmol) in anhydrous THF (10 mL) was added over 30 min to the stirred solution of dilithiosulfone, cooled at 0 °C in the case of β-lactones and at −60 °C for δ- and ε-lactones. The reaction was stirred for 3 h, then quenched at the same temperature with saturated aqueous NH_4Cl (50 mL), and allowed to reach room temperature. The organic phase was extracted with ethyl acetate, washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure. Flash chromatography of the residue on a silica gel column using hexane–ethyl acetate mixtures afforded **12** (Table II).

1-(Phenylsulfonyl)-4-hydroxybutan-2-one (12a): IR 3520, 3420, 1720, 1585, 1320, 1310, 1155, 1080, 1050; NMR 7.4–8.1 (m, 5 H, $PhSO_2$), 4.3 (s, 2 H, SO_2CH_2C=O), 3.75 (m, 2 H, CH_2O), 3.4 (br s, 1 H, OH) 2.85 (t, 2 H, CH_2C=O); MS, *m/e* (relative intensity) 43 (100), 51 (90), 77 (60), 42 (34), 45 (33), 39 (30), 49 (26), 55 (15), 73 (14), 211 $(M^+ - H_2O)$, 228 (M^+).

4-(Phenylsulfonyl)-1-hydroxynonan-3-one (12b): IR 3520, 3420, 1720, 1585, 1320, 1310, 1150, 1080, 1050; NMR 7.4–8.0 (m, 5 H, $PhSO_2$), 4.3 (m, 1 H, SO_2CHC=O), 3.8 (m, 2 H, CH_2O), 3.2 (br s, 1 H, OH), 3.0 (m, 2 H, CH_2C=O), 0.7–2.1 (m, 11 H, aliphatic); MS, *m/e* (relative intensity) 55 (100), 143 (69), 77 (60), 43 (57), 78 (54), 73 (50), 41 (46), 91 (45).

4-(Phenylsulfonyl)-1-hydroxyundecan-3-one (12c): IR 3540, 3420, 1720, 1585, 1320, 1150, 1085, 1050; NMR 7.5–8.0 (m, 5 H, $PhSO_2$), 4.2 (t, 1 H, SO_2CHC=O), 3.9 (t, 2 H, CH_2O), 3.0 (m, 3 H, OH and CH_2C=O), 0.7–2.1 (m, 13 H, aliphatic); MS, *m/e* (relative intensity) 55 (100), 43 (51), 77 (42), 143 (41), 41 (35), 73 (30), 142 (22), 57 (18), 91 (16), 45 (16).

4-(Phenylsulfonyl)-2-methyl-1-hydroxyundecan-3-one (12d): IR 3510, 3450, 1720, 1585, 1310, 1150, 1085, 1030; NMR 7.5–8.0 (m, 5 H, $PhSO_2$), 4.6 (m, 1 H, SO_2CHC=O), 3.7 (m, 3 H, CH_2OH), 3.3 (m, 1 H, CHC=O), 0.7–2.1 (m, 16 H, aliphatic); MS, *m/e* (relative intensity) 45 (100), 43 (49), 75 (18), 41 (15), 149 (15), 69 (14), 76 (9), 77 (7).

5-(Phenylsulfonyl)-2-hydroxydecan-4-one (12e): IR 3520, 3420, 1725, 1585, 1310, 1150, 1080; NMR 7.4–8.0 (m, 5 H, $PhSO_2$), 4.3 (m, 1 H, SO_2CHC=O), 3.3 (br s, 1 H, OH), 2.9 (m, 2 H, CH_2C=O), 0.7–2.0 (m, 12 H, aliphatic); MS, *m/e* relative intensity) 45 (100), 43 (49), 69 (22), 75 (17), 77 (15), 41 (16), 143 (9), 149 (8).

1-(Phenylsulfonyl)-6-hydroxyhexan-2-one (12f): mp 29–30 °C; IR 3480, 1720, 1585, 1320, 1310, 1150, 1080, 1040, 1000; the NMR spectrum was consistent with an approximately 1:1 mixture of the open-chain and cyclic hemiketalic forms: 7.5–8.2 (m, 5 H, $PhSO_2$), 5.0 and 2.1 (s, OH), 4.3 (s, SO_2CH_2C=O), 3.6 (m, SO_2CH_2 and CH_2O), 2.7 (m, CH_2C=O), 1.6 (m, aliphatic); MS, *m/e* (relative intensity) 77 (100), 141 (80), 85 (59), 183 (46), 55 (41), 56 (40), 41 (35), 101 (34), 256 (M^+).

6-(Phenylsulfonyl)-1-hydroxytridecan-5-one (12g): IR 3530, 3420, 1720, 1585, 1320, 1310, 1150, 1085; NMR 7.5–8.0 (m, 5 H, $PhSO_2$), 4.2 (t, 1 H, SO_2CH_2C=O), 3.7 (m, 2 H, CH_2O), 2.8 (m, 2 H, CH_2C=O), 2.5 (br s, 1 H, OH), 0.7–2.2 (m, 19 H, aliphatic); MS, *m/e* (relative intensity) 195 (100), 55 (96), 43 (75), 41 (66), 71 (38), 69 (35), 60 (33), 97 (32), 336 $(M^+ - H_2O)$.

1-(Phenylsulfonyl)-7-hydroxyheptan-2-one (12h): IR 3520, 3400, 1720, 1585, 1320, 1310, 1150, 1080, 1050; NMR 7.5–8.0 (m, 5 H, $PhSO_2$), 4.3 (s, 2 H, SO_2CH_2C=O), 3.7 (m, 2 H, CH_2O), 3.3 (br s, 1 H, OH), 2.7 (m, 2 H, CH_2C=O), 1.3 (m, 6 H, aliphatic); MS, *m/e* (relative intensity) 45 (100), 43 (36), 73 (11), 75 (10), 77 (10), 60 (5), 149 (4), 69 (4).

7-(Phenylsulfonyl)-1-hydroxytetradecan-6-one (12i): IR 3560, 3420, 1720, 1585, 1320, 1310, 1150, 1085, 1055; NMR 7.5–8.0 (m, 5 H, $PhSO_2$), 4.2 (t, 1 H, SO_2CHC=O), 3.7 (m, 2 H, CH_2O), 2.8 (m, 3 H, OH and CH_2C=O), 0.8–2.1 (m, 19 H, aliphatic); MS, *m/e* (relative intensity) 115 (100), 55 (90), 41 (60), 69 (50), 97 (41), 77 (39), 43 (37), 143 (24), 78 (18), 73 (14).

Cleavage of ω-Hydroxy-β-keto Sulfones (12): Preparation of ω-Hydroxy Ketones (4). General Procedure. A solution of sulfone (**12**) (10 mmol) in THF–H_2O (9:1, 180 mL) was added to aluminum amalgam[16] prepared under argon. The mixture was heated at reflux for 3–6 h, following the disappearance of starting material by TLC analysis. Then the solid phase was filtered and washed with THF. Most of the solvent was removed in vacuo,

(17) House, H. O. "Modern Synthetic Reactions", 2nd ed.; Benjamin: New York, 1972; p 654. Mathieu, J.; Weill-Raynal, J. "Formation of C–C Bonds"; G. Thieme Publischer: Stuttgart, 1973; Vol I, p 12.

(18) Manescalchi, F.; Orena, M.; Savoia, D. *Synthesis* **1979**, 445.

(19) Johansson, H. *Chem. Zentr.* **1916**, *87*(II), 557; *Chem. Abstr.* **1917**, *11*, 2576.

ether was added, and the aqueous phase was separated and extracted with ether. The organic phase was dried over Na_2SO_4 and concentrated. The residue was generally chromatographed on silica gel column using hexane–ether as solvent, or crystallized when solid, to afford pure ω-hydroxy ketones (4) (Table II).

1-Hydroxynonan-3-one (4d): IR 3410, 1710, 1130, 1090, 1050; NMR 3.9 (t, 2 H, CH_2O), 3.4 (s, 1 H, OH), 2.3–2.9 (m, 4 H, $CH_2C{=}O$), 0.7–2.0 (m, 11 H, aliphatic); MS, *m/e* (relative intensity) 43 (100), 70 (45), 55 (42), 41 (31), 113 (25), 71 (18), 45 (17), 57 (16).

1-Hydroxyundecan-3-one (4e): IR 3380, 1705, 1130, 1095, 1050; NMR 3.8 (m, 4 H, $CH_2C{=}O$), 0.7–2.0 (m, 15 H, aliphatic); MS, *m/e* (relative intensity) 70 (100), 55 (60), 41 (27), 43 (25), 71 (20), 83 (18), 57 (17), 40 (16), 139 (14).

1-Hydroxy-2-methylundecan-3-one (4f): IR 3460, 1720, 1140, 1040; NMR 3.7 (m, 3 H, CH_2OH), 2.3–2.9 (m, 3 H, CH_2COCH), 0.8–1.9 (m, 18 H, aliphatic); MS, *m/e* (relative intensity) 43 (100), 41 (99), 57 (96), 159 (62), 71 (55), 72 (51), 84 (38), 55 (35), 69 (34), 59 (33), 182 ($M^+ - H_2O$), 200 (M^+).

2-Hydroxydecan-4-one (4g): IR 3460, 1720, 1130, 1060, 1050; NMR 4.2 (m, 1 H, C*H*OH), 3.8 (s, 1 H, OH), 2.3–2.8 (m, 4 H, $CH_2C{=}O$), 0.7–1.9 (m, 4 H, aliphatic); MS, *m/e* (relative intensity) 43 (100), 58 (90), 45 (50), 87 (25), 69 (23), 113 (17), 71 (15), 84 (14), 154 ($M^+ - H_2O$), 172 (M^+).

1-Hydroxytridecan-5-one (4h): IR 3250, 1705, 1150, 1070; NMR 3.7 (m, 2 H CH_2O), 2.9 (br s, 1 H, OH), 2.4 (m, 4 H, $CH_2C{=}O$), 0.8–1.8 (m, 19 H, aliphatic); MS, *m/e* relative intensity) 43 (100), 55 (81), 98 (78), 57 (77), 41 (55), 71 (47), 83 (44), 116 (35), 141 (32), 40 (32), 196 ($M^+ - H_2O$), 214 (M^+).

1-Hydroxytetradecan-6-one (4i): IR 3500, 3200, 1700, 1070, 1060; NMR 3.7 (t, 2 H, CH_2O), 2.4 (m, 4 H, $CH_2C{=}O$), 1.9 (s, 1 H, OH), 0.7–1.8 (m, 21 H, aliphatic); MS, *m/e* (relative intensity) 41 (100), 43 (96), 58 (96), 71 (95), 69 (94), 57 (90), 112 (55), 130 (53), 156 (39), 141 (38), 228 (M^+).

Acknowledgment. This work was supported by a grant from M.P.I. (Rome).

Registry No. **1a**, 96-48-0; **1b**, 1679-47-6; **1c**, 108-29-2; **1d**, 57-57-8; **1e**, 1823-54-7; **1f**, 3068-88-0; **1g**, 542-28-9; **1h**, 502-44-3; **4a**, 16378-50-0; **4b**, 88703-44-0; **4c**, 7737-56-6; **4d**, 67801-46-1; **4e**, 82353-69-3; **4f**, 88703-45-1; **4g**, 88729-56-0; **4h**, 88703-46-2; **4i**, 88703-47-3; **10a**, 3112-85-4; **10b**, 16823-63-5; **10c**, 34009-05-7; **12a**, 88703-48-4; **12b**, 88703-49-5; **12c**, 88703-50-8; **12d**, 88703-51-9; **12e**, 88703-52-0; **12f**, 88703-53-1; **12g**, 88703-54-2; **12h**, 88703-55-3; **12i**, 88703-56-4; BuLi, 109-72-8.

Synthesis of ω-Tritiated and ω-Fluorinated Analogues of the Trail Pheromone of Subterranean Termites

Joan F. Carvalho and Glenn D. Prestwich*†

Department of Chemistry, State University of New York, Stony Brook, New York 11794

Received September 15, 1983

A series of unsaturated ω-fluoro alcohols have been prepared stereoselectively. These simple compounds are structural analogues of the trail pheromone of termites in the genus *Reticulitermes*. The toxicity of these ω-fluoro alcohols to *R. flavipes* is maximal for the C_{12} alcohols, and the attractiveness of these C_{12} analogues increases in the order saturated alkanol < (*Z*)-3-alkenol ≪ (*Z,Z*)-3,6-alkadienol. Two [12-^{3}H]-12-fluoro alcohols and a [12-^{3}H]-nonfluorinated analogue were prepared to examine the catabolism of the pheromone analogues.

The latent toxicity of fatty acids possessing an even number of carbons and bearing a single fluorine substituent in the terminal ω position is due to in vivo β-oxidation to fluoroacetate.[1] The potential utility of fluoroacetate-releasing compounds as pesticides is mitigated by their low specificity and their high toxicity for nontarget species.[2] We envisaged the use of the latent toxicity of ω-fluoro fatty acids as delayed-action toxicants in bait-block control schemes for termites[3] and as experimental probes into the nature of intermediates involved in the metabolism of acyl glycerol derivatives in insects. We have reported the toxicity and delay times for a large number of achiral and racemic synthetic ω-fluoroalkyl and ω-fluoroacyl glycerol[4] and cholesterol derivatives[5] as well as three enantiomeric pairs of alkyldiacyl glycerols[6] in feeding tests with the eastern subterranean termite, *Reticulitermes flavipes* (Kollar).

We discovered that the 16-fluoro-(*E*)-9-hexadecen-1-ol was ten-fold more toxic for *Reticulitermes* workers and had a shorter delay time than the corresponding ω-fluoro acid.[4b] We hypothesized that the efficiency of fatty alcohol catabolism in termites was related to the fact that a C_{12} alcohol, (*Z,Z,E*)-3,6,8-dodecatrien-1-ol, acts as a trail pheromone for *Reticulitermes*.[7] Laboratory choice tests using vacuum-impregnated bait blocks suggested that the long-delay time material may not be as effective as chemicals that were attractive, more toxic, and had shorter delay times.[5] We therefore prepared several pheromone analogues and their ω-fluoro derivatives, and we examined both their toxicity and their activity as trail pheromone mimics for subterranean termites (Figure 1).

Furthermore, we wished to establish the metabolic fates of the pheromone analogues in vivo and in vitro. To this end, we used intermediates already in hand to prepare [12-^{3}H]-labeled pheromone analogues in both the terminal fluoromethyl and methyl series. The identification of the metabolites of both the fluorinated and nonfluorinated

†Fellow of the Alfred P. Sloan Foundation (1981–1985) and Camille and Henry Dreyfus Teacher–Scholar (1981–1986).

(1) (a) Pattison, F. L. M. "Toxic Aliphatic Fluorine Compounds"; Elsevier: Amsterdam and London, 1959. (b) Peters, R. A. *Adv. Enzymol* **1957**, *18*, 113. (c) Goldman, P. *Science (Washington, D.C.)* **1969**, *164*, 1123.

(2) Hollingworth, R. M. In "Insecticide Biochemistry and Physiology"; Wilkinson, C. F., Ed.; Plenum Press: New York, 1976; pp 431–506.

(3) (a) Beard, R. L. *Bull.–Conn. Agric. Exp. Stn., New Haven* **1974**, *No.* 748. (b) Esenther, G. R.; Beal, R. H. *J. Econ. Entomal.* **1974**, *67*, 85.

(4) (a) Prestwich, G. D.; Plavcan, K. A.; Melcer, M. E. *J. Agric. Food Chem.* **1981**, *29*, 1018. (b) Prestwich, G. D.; Melcer, M. E.; Plavcan, K. A. *Ibid.* **1981**, *29*, 1023.

(5) Prestwich, G. D.; Mauldin, J. K.; Engstrom, J. B.; Carvalho, J. C.; Cupo, D. Y. *J. Econ. Entomol.* **1983**, *76*, 690.

(6) Carvalho, J. C.; Prestwich, G. D. *Insect Biochem.* **1982**, *12*, 343.

(7) (a) Tai, A.; Matsumura, F.; Coppel, H. C. *J. Org. Chem.* **1969**, *34*, 2180. (b) Howard, R.; Matsumura, F.; Coppel, H. C. *J. Chem. Ecol.* **1976**, *2*, 147. (c) Tai, A.; Matsumura, F.; Coppel, H. C. *J. Insect Physiol.* **1971**, *17*, 181. (d) Prestwich, G. D.; Eng, W.-S.; Deaton, E.; Wichern, D. F. *J. Chem. Ecol.* **1984**, in press.

0022-3263/84/1949-1251$01.50/0