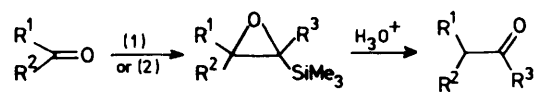
A Short Synthesis of (*R*)-(+)-Frontalin and *Latia* Luciferin Using New Organosilicon Reagents

By PHILIP MAGNUS* and GLENN ROY

(*Evans Laboratory, The Ohio State University, 140 West 18th Avenue, Columbus, Ohio* 43210)

Summary 3*R*-(−)-Linalool and β-dihydroionone have been converted into 3*R*-(+)-frontalin (**3**) and *Latia* luciferin (**4**), respectively, using α,β-epoxysilanes as the key intermediates.

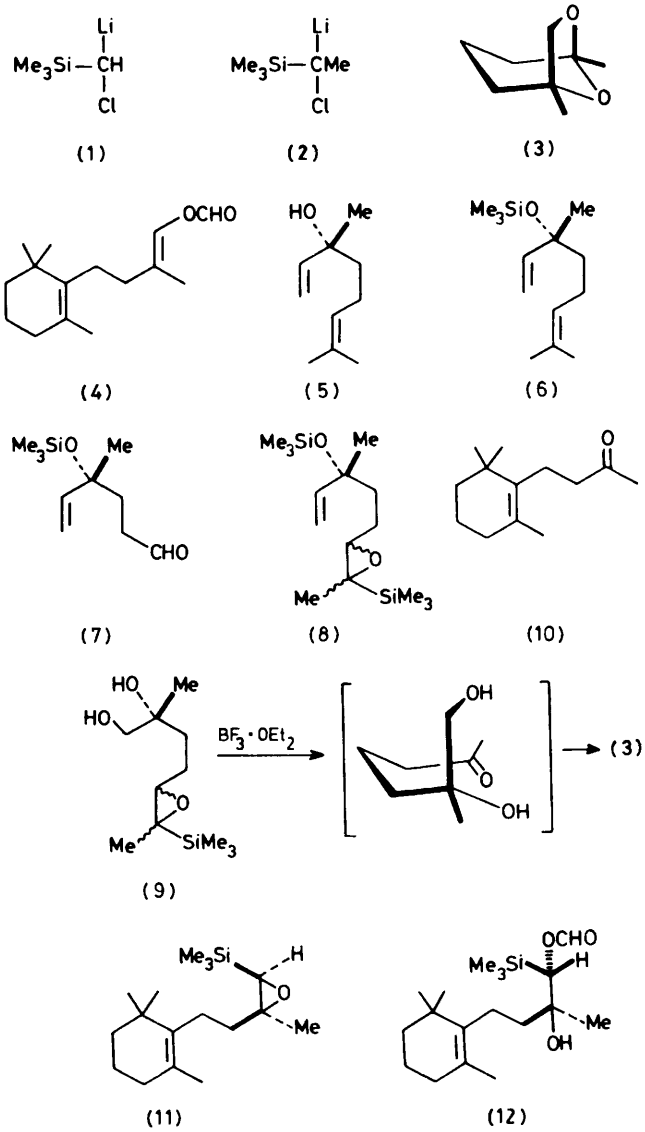
RECENTLY we described two new reagents, α-chlorotrimethylsilyl (**1**)[1] and α-methyl-α-chlorotrimethylsilyl (**2**)[2] carbanions, which convert ketones and aldehydes into the homologous aldehydes and methylketones, respectively (Scheme). Here we report an illustration of the use of these reagents for the synthesis of (*R*)-(+)-frontalin (**3**) and *Latia* luciferin (**4**).



SCHEME. R^3 = Me or H.

Frontalin (**3**), the aggregation pheromone of the southern pine beetle *Dendroctonus frontalis*[3] can be considered (at least from the point of view of synthesis) as a bis-nor-monoterpene (C_8), and as such might be synthesized from a chiral monoterpene. A suitable starting material having the crucial asymmetric centre at C-3 is (3*R*)-(−)-linalool (**5**). Conversion of (**5**) into its trimethylsilyl ether (**6**) was achieved using conventional procedures[4] (hexamethyldisilazane–pyridine–trimethylchlorosilane), 98%, b.p. 45 °C at 0·17 mmHg. Selective ozonolysis of (**6**) (−78 °C,

CH_2Cl_2, pyridine) followed by rapid isolation (0·1 equiv. of Me_2S may be added) gave the aldehyde (**7**), 65%, b.p. 34—35 °C at 0·37 mmHg. The aldehyde (**7**) was treated with (**2**)[2]† at −78 °C and the reaction mixture was allowed to warm up to room temperature to give the α,β-epoxysilane (**8**), crude yield 95%. (No attempt was made to purify this product). Crude (**8**) was ozonized in methanol and reduced with sodium borohydride to give the diol (**9**), 65%. (It appears that the trimethylsilyl ether protecting group is removed in this sequence). The crude diol (**9**) was treated with boron trifluoride–diethyl ether in methanol at 0 °C for 2—4 h to give (*R*)-(+)-frontalin (**3**) (74%) in an overall yield from (3*R*)-(−)-linalool of 23—29%. This represents the highest overall yield for a chiral synthesis of (*R*)-(+)-frontalin and provides a useful illustration of the use of the new reagent (**2**) for reductive nucleophilic acylation.



Latia luciferin (**4**),[5] the specific substrate in the bioluminescence enzyme (luciferase) system in the fresh water limpet *Latia* neritoids has been synthesized by two groups.[6] Here we describe a two-step synthesis that takes advantage of the direct conversion of a methyl ketone into an α,β-epoxysilane, and the subsequent transformation of an α,β-epoxysilane into an enol formate. Dihydro-β-ionone (**10**)[7] was treated with (**1**) (2·0 equiv.) at −78 °C to give the α,β-epoxysilane (**11**), 85%, b.p. 90 °C at 0·15 mmHg. The product (**11**) appears to be mainly the *cis*-epoxide which is in agreement with previous results.[1] Treatment of (**11**) with anhydrous formic acid (0·5 h at room temp.) and evaporation of excess of acid (and trimethylsilanol derived residue) gave *Latia* luciferin (**4**), 90% after purification (chromatography over silica gel, eluting with hexane), ν_{max} (film) 1738 and 1160 cm^{-1}. The product is mainly the *trans*-isomer (natural isomer) which results from the *anti*-elimination of trimethylsilanol from the β-hydroxysilane (**12**). A small amount (*ca.* 10%) of the *cis*-isomer was present (n.m.r.).

This synthesis represents an improvement over previous methods[6] and demonstrates the utility of (**1**) and α,β-epoxysilanes in synthesis.

All new compounds gave satisfactory i.r., n.m.r., and mass spectral data. Data for final natural products were compared (i.r., n.m.r., $[\alpha]_D$, and m.s.) with those reported in the literature and, in the case of frontalin, with spectra supplied by Professor Fraser-Reid.

We thank Dr. B. J. Willis, Fritzsche Dodge and Olcott Inc., New York, for a gift of (3*R*)-(−)-linalool, $[\alpha]_D^{20}$ − 17° 40′ (neat).

(*Received, 28th November* 1977; *Com.* 1309.)

† Reagent (**2**) is prepared by treating α-chloroethyltrimethylsilane with s-butyl-lithium in dry tetrahydrofuran at −78 °C. Other bases (*e.g.*, Bu^nLi, Bu^tLi, lithium di-isopropylamide, *etc.*) do not give satisfactory results.

[1] C. S. Burford, F. Cooke, E. Ehlinger, and P. D. Magnus, *J. Amer. Chem. Soc.*, 1977, **99**, 4536.
[2] F. Cooke and P. D. Magnus, *J.C.S. Chem. Comm.*, 1977, 513.
[3] For recent syntheses, see: D. A. Hicks and B. Fraser-Reid, *J.C.S. Chem. Comm.*, 1976, 869; K. Mori, *Tetrahedron*, 1975, **31**, 1381; T. D. J. D'Silva and D. W. Peck, *J. Org. Chem.*, 1972, **37**, 1828; B. P. Mundy, R. D. Otzenberger, and A. R. DeBernardis, *ibid.*, 1971, **36**, 2390.
[4] J. L. Speier, *J. Amer. Chem. Soc.*, 1952, **74**, 1003.
[5] O. Shimomura and F. H. Johnson, *Biochemistry*, 1968, **7**, 1734.
[6] M. G. Fracheboud, O. Shimonura, R. K. Hill, and F. H. Johnson, *Tetrahedron Letters*, 1969, 3951; F. Nakatsubo, Y. Kishi, and T. Goto, *ibid.*, 1970, 381.
[7] A. Caliezi and H. Schinz, *Helv. Chim. Acta*, 1950, **33**, 1129.