

A Simple Synthesis of *cis*- and *trans*-Fused 14,15-Dinoreudesmanolides

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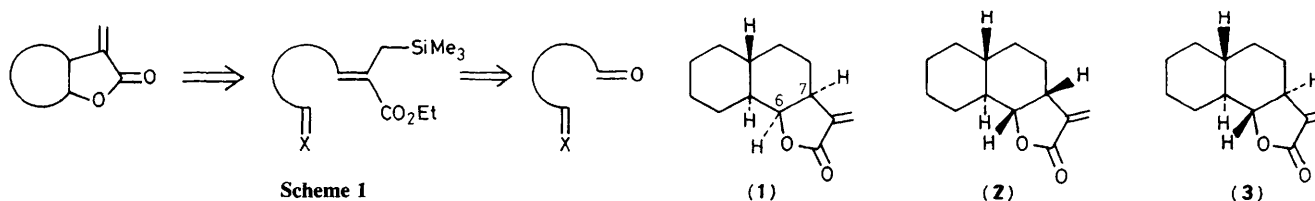
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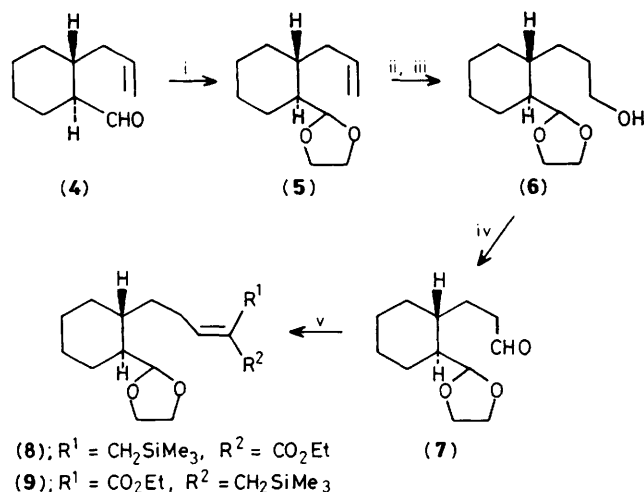
Three possible stereoisomers of 14,15-dinoreudesmanolide, the structure of which consists of an α -methylene- γ -lactone ring fused to a *trans*-decalin ring, have been synthesized from a dialdehyde monoacetal *via* α -trimethylsilylmethyl- α,β -unsaturated esters.

The α -methylene- γ -lactone ring is an important structural unit of many sesquiterpene lactones,¹ some of which show significant biological activity.² Although there have been a number of synthetic studies on this moiety,³ most include lactonization and α -methylenation of a preformed carbon framework. For a one-step synthesis of the *cis*-fused lactone ring, zinc or nickel promoted cyclization was carried out by Semmelhack *et al.*,⁴ and this method was applied to the total synthesis of confertin^{4b} and frullanolide.^{4c} According to Hosomi *et al.*, the α -methylene- γ -lactone ring was formed by the reaction of an aldehyde and an α -trimethylsilylmethyl- α,β -unsaturated ester,⁵ but the stereochemistry of the cyclization reaction was not investigated. We have studied a simple synthesis of α -methylene- γ -lactones, fused to a carbocyclic ring system, *via* an intramolecular application of this reaction using an ω -formyl- α -trimethylsilylmethyl- α,β -unsaturated ester, derived from a simple dialdehyde derivative⁶ by a one-step reaction,⁷ as shown in Scheme 1. We now report an efficient stereoselective synthesis of three possible stereoisomers of 14,15-dinoreudesmanolide, (1), (2), and (3), from a readily available dialdehyde derivative (7) *via* the α -trimethylsilylmethyl- α,β -unsaturated esters (8) and (9).

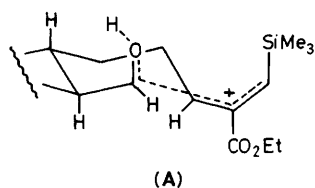
The synthesis of (*Z*)- and (*E*)- α -trimethylsilylmethyl- α,β -unsaturated esters (8) and (9) is shown in Scheme 2. *trans*-2-Allylcyclohexanecarbaldehyde (4),⁸ obtained from 2-allylcyclohexanone by the Wittig reaction [$\text{Ph}_2\text{POCH}_2\text{OMe}$, lithium di-isopropylamide (LDA)], hydrolysis [5% HCl-tetrahydrofuran (THF)], and epimerization [5% KOH-MeOH (aq.)], was converted into the acetal (5) in 93% yield. Hydroboration of (5) with disiamylborane (siamyl, Sia, = $\text{CHMe}_2\text{CHMe-}$) followed by H_2O_2 -NaOH oxidation gave the alcohol (6) (94% yield), which was further oxidized by pyridinium dichromate (PDC) to afford the aldehyde (7) (95% yield). The Wittig reaction of (7) with $(\text{EtO})_2\text{POCH}(\text{CH}_2\text{SiMe}_3)\text{CO}_2\text{Et-NaH}$ in dimethoxyethane (DME)^{7a} gave two α -trimethylsilylmethyl- α,β -unsaturated esters, which were separated by silica gel column chromatography to give (8) and (9) in 30 and 11% yield, respectively [(8): i.r. (neat) 1715 cm^{-1} ; ^1H n.m.r. (CCl_4) δ 1.73 (2H, s, $-\text{CH}_2\text{SiMe}_3$), 6.44 (1H, t, J 7 Hz, $-\text{CH}=\text{C} <$); (9): i.r. (neat) 1715 cm^{-1} ; ^1H n.m.r. (CCl_4) δ 1.65 (2H, s, $-\text{CH}_2\text{SiMe}_3$), 5.55 (1H, t, J 7 Hz, $-\text{CH}=\text{C} <$)].

The cyclization was then examined. When (8) was treated with a catalytic amount of toluene-*p*-sulphonic acid in acetone



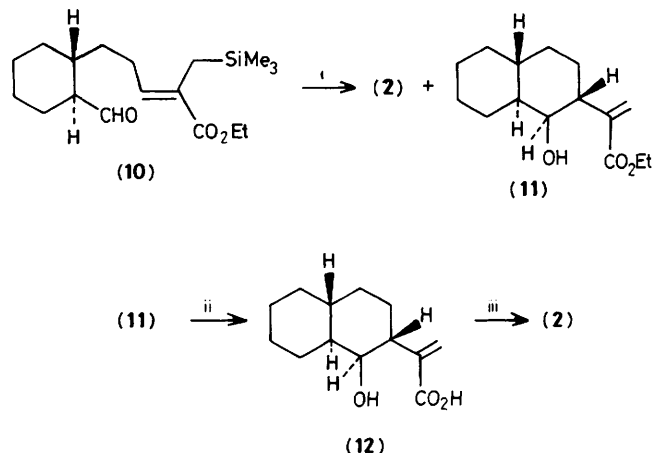


Scheme 2. Reagents and conditions: i, $HO(CH_2)_2OH$, pyridinium toluene-*p*-sulphonate (PPTS), PhH; ii, Sia_2BH , diglyme, room temp.; iii, H_2O_2 , NaOH; iv, PDC, CH_2Cl_2 , room temp.; v, $(EtO)_2POCH(CH_2SiMe_3)CO_2Et$, NaH, DME, $0^\circ C$, then room temp.



(reflux, 3 h), the acetal was hydrolysed to afford (10) [99% yield; i.r. (neat) $1725, 1710\text{ cm}^{-1}$; 1H n.m.r. (CCl_4) δ 1.68 (2H, s, $-CH_2SiMe_3$), 6.38 (1H, t, J 7 Hz, $-CH=C<$), 9.44 (1H, d, J 3 Hz, $-CHO$)]. However, if (8) was treated with an excess of toluene-*p*-sulphonic acid in acetone (reflux, 7 h), cyclization occurred and the desired lactone (1) was obtained as the sole product in 78% yield [(1): u.v. (EtOH) 210 nm (ϵ 8000); i.r. (KBr) 1760 cm^{-1} ; 1H n.m.r. ($CDCl_3$) δ 2.88 (1H, ddd, J 5, 7, 10 Hz, 7-H), 4.23 (1H, dd, J 5, 1.5 Hz, 6-H), 5.49 and 6.04 (each 1H, $>C=CH_2$)]. The J value observed for 6-H and 7-H indicates that (1) has a *cis*-lactone structure with 6α -H and 7α -H, which was confirmed by a decoupling experiment. The same lactone (1) was also obtained by treatment of (10) under the same conditions. Thus, we assume the lactone (1) was formed from (8) via the aldehyde (10). The *cis*-stereoselectivity in the cyclization step can be explained by the conformation of the transition state (A).⁹

On the other hand, cyclization of (10) with tetrabutylammonium fluoride in dry THF provided lactone (2) and hydroxy ester (11) in 62 and 5% yield, respectively [(2): u.v. (EtOH) 209 nm (ϵ 13 000); i.r. (neat) 1760 cm^{-1} ; 1H n.m.r. ($CDCl_3$) δ 3.15 (1H, m, w_1 11 Hz, 7-H), 4.18 (1H, t, J 8 Hz, 6-H), 5.46 and 6.25 (each 1H, $>C=CH_2$); (11): i.r. (neat) $3520, 1715\text{ cm}^{-1}$; 1H n.m.r. ($CDCl_3$) δ 3.76 (1H, m, w_1 4 Hz, 6-H), 5.67 and 6.25 (each 1H, $>C=CH_2$)]. The coupling pattern observed for 7-H of lactone (2) shows that (2) has a 7β -H configuration (equatorial). This, together with the J value observed for 6-H, leads to an alternative *cis*-lactone structure for (2). This was confirmed by conversion of the hydroxy ester (11) into the same lactone. Thus, treatment of (11) with sodium hydride gave the hydroxy acid (12) (96% yield), and



Scheme 3. Reagents and conditions: i, Bu_4NF , THF, $-5^\circ C$; ii, NaH, THF, room temp.; iii, $Me_2NCH(OCH_2CMe_3)_2$, toluene, reflux.

no lactonization was observed in this reaction. This fact and the coupling pattern observed for 6-H show that (11) has a 6β -hydroxy group (axial) and a 7α -side chain (axial). Lactone (2) was obtained in 89% yield with inversion at C-6 by treatment of (12) with *N,N*-dimethylformamide dineopentyl acetal in toluene¹⁰ (Scheme 3).

The third possible stereoisomer, lactone (3), was produced as the sole product from (*E*)-ester (9) by similar treatment with acid (excess of toluene-*p*-sulphonic acid in acetone, reflux, 6 h) [(3): 78% yield; u.v. (EtOH) 209 nm (ϵ 9000); i.r. (film) 1765 cm^{-1} ; 1H n.m.r. ($CDCl_3$) δ 3.42 (1H, t, J 10 Hz, 6-H), 5.33 and 6.04 (each 1H, $>C=CH_2$)]. Lactone (3) must have a *trans*-lactone structure, which is compatible with the large J value observed for 6-H.

Since all three possible lactone isomers (1), (2), and (3) were synthesized selectively, this method should be useful for the simple synthesis of various stereoisomeric eudesmanolides.

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