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

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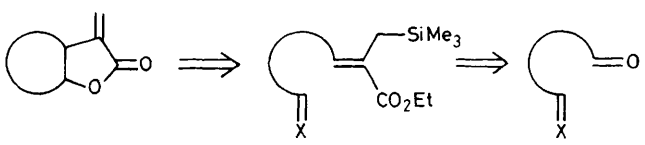
Three possible stereoisomers of 14,15-dinoreudesmanolide, the structure of which consists of an α-methylene-γ-lactone ring fused to a *trans*-decalin ring, have been synthesized from a dialdehyde monoacetal *via* α-trimethylsilylmethyl-α,β-unsaturated esters.

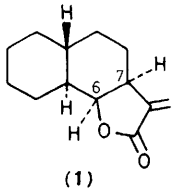
The α-methylene-γ-lactone ring is an important structural unit of many sesquiterpene lactones,[1] some of which show significant biological activity.[2] Although there have been a number of synthetic studies on this moiety,[3] most include lactonization and α-methylenation of a preformed carbon framework. 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 derivative[6] 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 [Ph_2POCH_2OMe, 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, = $CHMe_2CHMe$–) 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 $(EtO)_2POCH(CH_2SiMe_3)CO_2Et$–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, $-CH_2SiMe_3$), 6.44 (1H, t, *J* 7 Hz, –CH=C <); (**9**): i.r. (neat) 1715 cm^{-1}; ^1H n.m.r. (CCl_4) δ 1.65 (2H, s, $-CH_2SiMe_3$), 5.55 (1H, t, *J* 7 Hz, –CH=C <)].

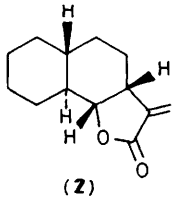
The cyclization was then examined. When (**8**) was treated with a catalytic amount of toluene-*p*-sulphonic acid in acetone



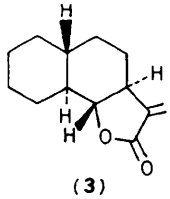
Scheme 1



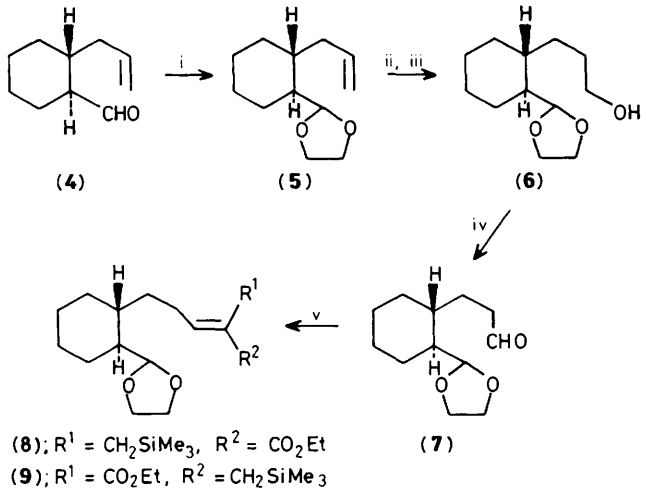
(1)



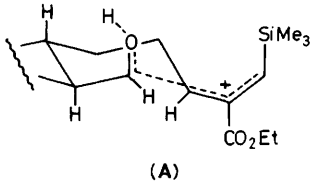
(2)



(3)

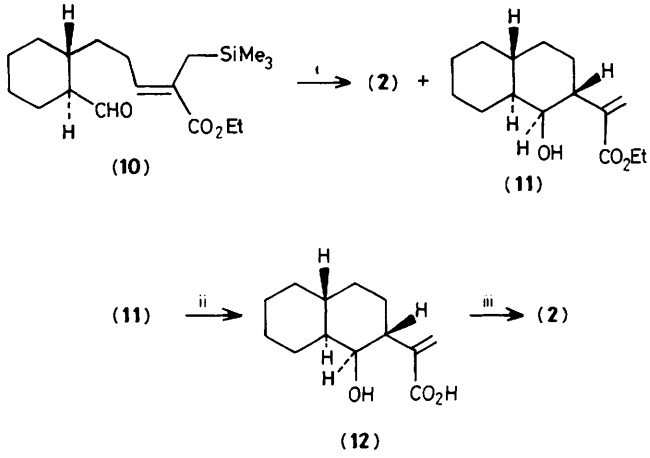


Scheme 2. *Reagents and conditions:* i, $HO(CH_2)_2OH$, pyridinium toluene-*p*-sulphonate (PPTS), PhH; ii, Sia_2BH, diglyme, room temp.; iii, H_2O_2, NaOH; iv, PDC, CH_2Cl_2, room temp.; v, $(EtO)_2POCH(CH_2SiMe_3)CO_2Et$, NaH, DME, 0 °C, then room temp.



(reflux, 3 h), the acetal was hydrolysed to afford (**10**) [99% yield; i.r. (neat) 1725, 1710 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, $w_{\frac{1}{2}}$ 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 cm^{-1}; ^1H n.m.r. ($CDCl_3$) δ 3.76 (1H, m, $w_{\frac{1}{2}}$ 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^n_4NF, THF, −5 °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 toluene[10] (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 1 H, > $C=CH_2$)]. 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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