

Total Synthesis of the Dolastane Diterpenoid (\pm)-Amijitrienol

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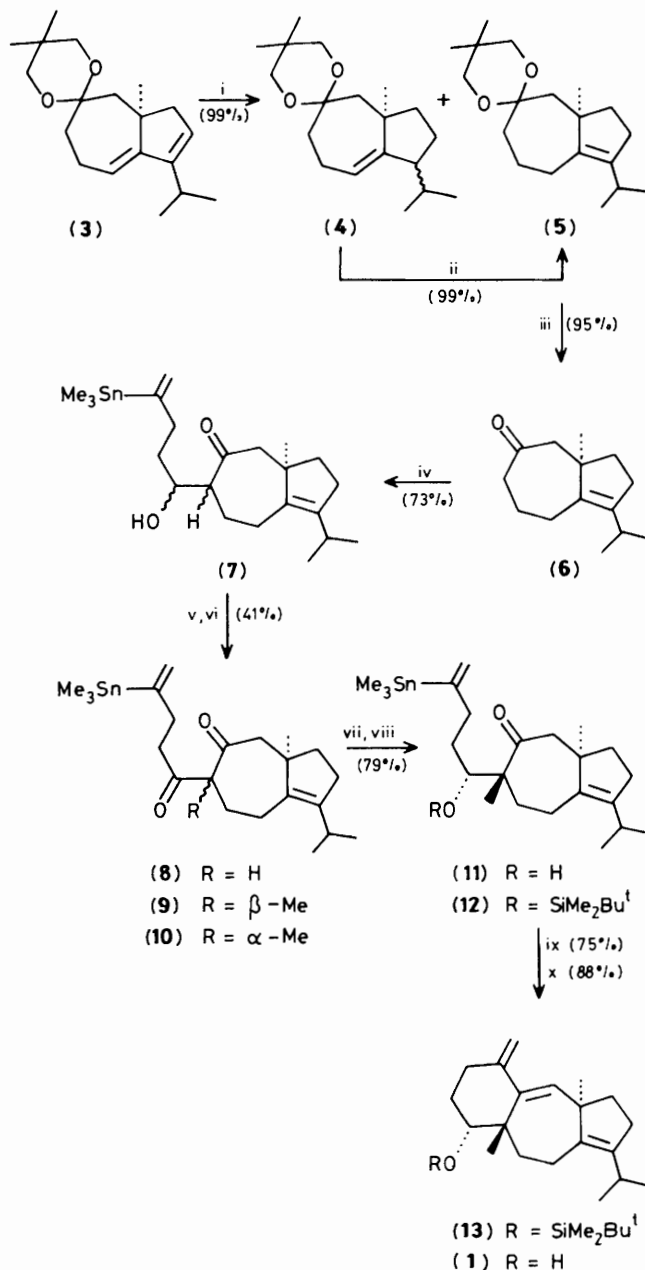
Transformation of the diene acetal (**3**) into the tricyclic diterpenoid (\pm)-amijitrienol (**1**) was achieved via a 10-step sequence of reactions.

The interesting natural product (+)-amijitrienol, isolated from the brown seaweed *Dictyota linearis*, has been shown to possess structure (**1**) and to exhibit moderate antimicrobial activity against *Staphylococcus aureus* and *Mucor mucedo*.¹ Of the relatively small number of known dolastane-type diterpenoids [carbon skeleton and numbering system shown in structure (**2**)], amijitrienol is the only one that includes, as part of the linearly fused 6-7-5 ring system, a conjugated diene function connecting carbons 13, 14, 1, and 15. We report here the first total synthesis of (\pm)-(**1**)² via the route outlined in Scheme 1.

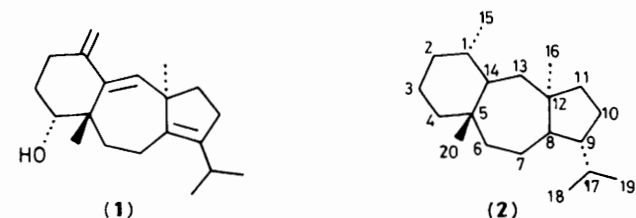
Lithium-ammonia reduction of the diene acetal (**3**), which had served previously as a key intermediate in a total synthesis of (\pm)-(14S)-dolasta-1(15),7,9-trien-14-ol,^{2b} gave a 15:85 mixture of the isomeric alkenes (**4**) and (**5**). The latter proved very difficult to separate, but, fortunately, treatment of the mixture with a small amount of iodine in refluxing hexane caused quantitative isomerisation of (**4**) into (**5**). Mild acid hydrolysis of (**5**) provided the ketone (**6**)^{†‡} [93% from (**3**)].

Deprotonation of (**6**) with lithium di-isopropylamide (1.2 equiv.) and treatment of the resultant enolate anion with 4-trimethylstannylpent-4-enal§ provided a mixture of three keto alcohols (**7**). Oxidation of this material gave the dione (**8**), which was quite unstable and, therefore, was methylated immediately. On the basis of molecular models and literature precedents,^{2a,b} one might expect that alkylation of the dione (**8**) at C-5 (dolastane numbering) would take place preferentially from the side opposite the C-12 angular methyl group. In the event, methylation of (**8**) afforded a 2:1 mixture of the epimeric products (**9**) and (**10**), which were readily separated by chromatography on silica gel. The isolated yield of (**9**) from the ketol (**7**) was 41%.

A number of methods aimed at differentiating chemically between the two carbonyl groups of (**9**) were investigated. Eventually, it was found that treatment of a tetrahydrofuran (THF) solution of (**9**) with excess LiCl (*ca.* 10 equiv.), followed by cooling of the mixture to -78°C and addition of



Scheme 1. Reagents and conditions: i, Li, NH_3 , THF, -48°C , 1.75 h; NH_4Cl , H_2O ; ii, I_2 , hexane, reflux, 3 h; iii, HCl, H_2O , Me_2CO , room temp., 1 h; iv, LiNPr_2 , THF, -78°C , 30 min; 0°C , 30 min; 4-trimethylstannylpent-4-enal, THF, -78°C \rightarrow room temp.; v, $(\text{COCl})_2$, dimethyl sulphoxide, CH_2Cl_2 , -78°C ; Et_3N , -78°C \rightarrow room temp.; vi, K_2CO_3 , MeI, Me_2CO , reflux, 4 h; vii, $\text{Bu}_4\text{Me}_2\text{SiOSO}_2\text{CF}_3$, 4-dimethylaminopyridine (catalyst), Et_3N , CH_2Cl_2 , room temp., 1 h; ix, $(\text{Me}_3\text{Si})_2\text{NK}$, THF, room temp., 30 min; $\text{PhN}(\text{SO}_2\text{CF}_3)_2$, room temp., 30 min; $(\text{Ph}_3\text{P})_4\text{Pd}$ (5 mol %), Et_3N , MeCN, reflux, 30 min; x, Bu_4NF , THF, reflux, 3.5 h.



[†] All stable, purified compounds reported herein exhibited spectra in full accord with assigned structures and gave satisfactory results in molecular mass determinations (high resolution mass spectrometry).

[‡] This substance was spectrally identical with material prepared previously by Pattenden and Robertson.^{2a} We are grateful to Professor Pattenden for a copy of the ^1H n.m.r. spectrum of (**6**).

[§] This material was prepared (65–80% yield) by Swern oxidation of 4-trimethylstannylpent-4-en-1-ol (see step v, Scheme 1).³

Bu^i_2AlH (ca. 4–5 equiv.), provided, chemo- and stereoselectively, a *single* alcohol (**11**),[¶] which was readily converted into the silyl ether (**12**) [79% yield from (**9**)].

The ketone (**12**) was treated with $(\text{Me}_3\text{Si})_2\text{NK}-\text{Ph}(\text{SO}_2\text{CF}_3)_2$ ⁴ in THF. Removal of the solvent (reduced pressure) gave a crude enol trifluoromethanesulphonate, which was treated with $(\text{Ph}_3\text{P})_4\text{Pd}$ in hot $\text{MeCN}-\text{Et}_3\text{N}^{\dagger\dagger}$ to afford the ether triene (**13**). Cleavage of the silyl ether linkage produced (\pm)-amijitrienol (**1**), m.p. 119–119.5°C (from hexane), which exhibited spectra identical with those of (+)-(**1**). It should be noted that the exocyclic double bonds of (**13**) and (\pm)-(**1**) rapidly and cleanly isomerised to the C-1–C-2 position when these substances were dissolved in

[¶] Interestingly, reduction of (**9**) with 1 equiv. of Bu^i_2AlH in various solvents (THF, Et_2O , PhMe) at -78°C , in the *absence* of LiCl, yielded complex mixtures containing (**9**), ketols, and diols. The nature of the role played by LiCl in the conversion of (**9**) into (**11**) remains obscure, but co-ordination of the lithium cation with the 1,3-dione system of (**9**) may be important.

^{††} We have found that Pd(0)-catalysed cyclisation of vinylstannane-enol trifluoromethanesulphonates⁵ are faster in MeCN than in THF. In the present reaction Et_3N was added because the diene system in (**13**) was prone to acid-catalysed rearrangement.

CDCl_3 that had not been shaken with $\text{Na}_2\text{CO}_3-\text{MgSO}_4$ and then filtered through basic alumina.

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