Total Synthesis of the Dolastane Diterpenoid (±)-Amijitrienol

Edward Piers* and Richard W. Friesen

Department of Chemistry, University of British Columbia, Vancouver, British Columbia, Canada V6T 1Y6

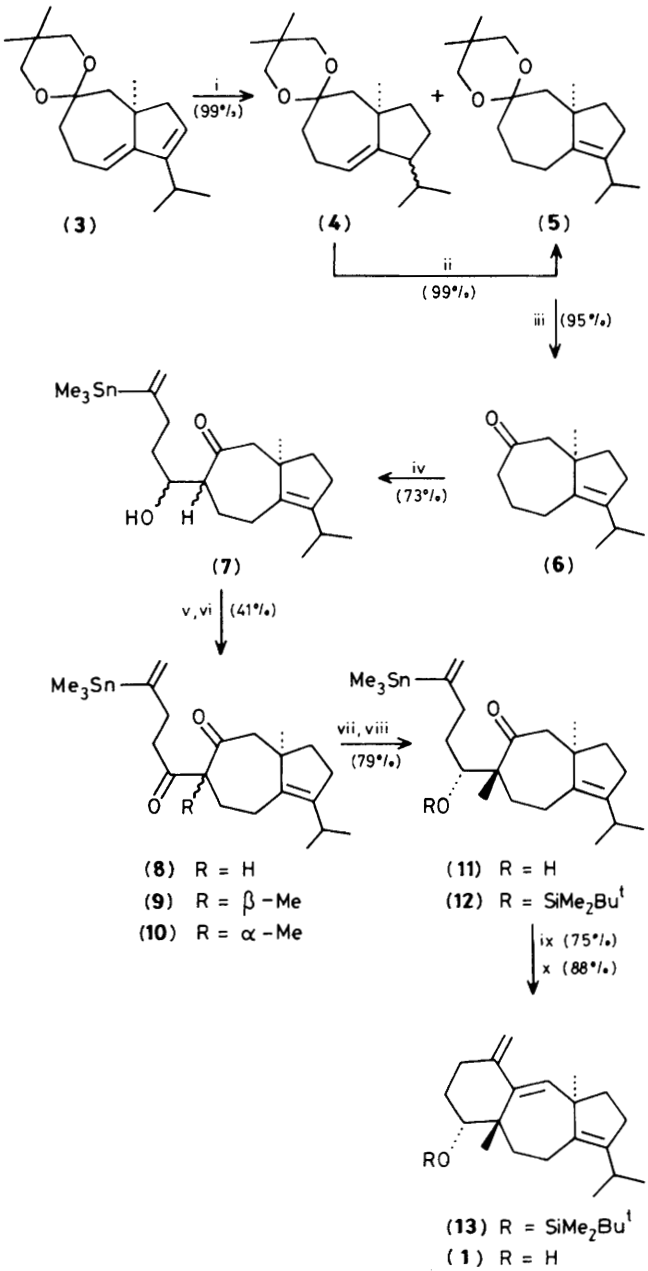
Transformation of the diene acetal (**3**) into the tricyclic diterpenoid (±)-amijitrienol (**1**) was achieved *via* a 10-step sequence of reactions.

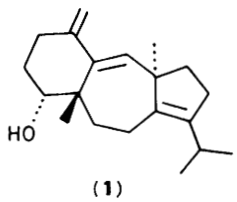
The interesting natural product (+)-amijitrienol, isolated from the brown seaweed *Dictyota linearis*, has been shown to possess structure (**1**) and to exhibit moderate antimicrobial activity against *Staphylococcus aureus* and *Mucor mucedo*.[1] Of the relatively small number of known dolastane-type 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 (±)-(**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 (±)-(14*S*)-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**)].

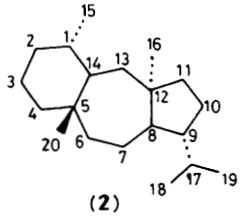
Deprotonation of (**6**) with lithium di-isopropylamide (1.2 equiv.) and treatment of the resultant enolate anion with 4-trimethylstannylpent-4-enal§ provided a mixture of three keto alcohols (**7**). Oxidation of this material gave the dione (**8**), which was quite unstable and, therefore, was methylated 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





(**1**)



(**2**)

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, $LiNPr^i_2$, THF, −78 °C, 30 min; 0 °C, 30 min; 4-trimethylstannylpent-4-enal, THF, −78 °C → room temp.; v, $(COCl)_2$, dimethyl sulphoxide, CH_2Cl_2, −78 °C; Et_3N, −78 °C → room temp.; vi, K_2CO_3, MeI, Me_2CO, reflux, 4 h; vii, Bu^i_2AlH, LiCl (excess), THF, −78 °C, 10 min; viii, $Bu^tMe_2SiOSO_2CF_3$, 4-dimethylaminopyridine (catalyst), Et_3N, CH_2Cl_2, room temp., 1 h; ix, $(Me_3Si)_2NK$, THF, room temp., 30 min; $PhN(SO_2CF_3)_2$, room temp., 30 min; $(Ph_3P)_4Pd$ (5 mol %), Et_3N, MeCN, reflux, 30 min; x, Bu^n_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 $(Me_3Si)_2NK$–$Ph(SO_2CF_3)_2$[4] in THF. Removal of the solvent (reduced pressure) gave a crude enol trifluoromethanesulphonate, which was treated with $(Ph_3P)_4Pd$ in hot MeCN–Et_3N†† to afford the ether triene (**13**). Cleavage of the silyl ether linkage produced (±)-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 (±)-(**1**) rapidly and cleanly isomerised to the C-1–C-2 position when these substances were dissolved in $CDCl_3$ that had not been shaken with Na_2CO_3–$MgSO_4$ and then filtered through basic alumina.

We thank the Natural Sciences and Engineering Research Council of Canada for financial support and for a 1967 Science and Engineering Scholarship (to R. W. F.). We are grateful to Professor M. Ochi for copies of the i.r., ^1H n.m.r., and mass spectra of amijitrienol.

Received, 16th September 1987; Com. 1346

¶ 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 trifluoromethanesulphonates[5] 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.

References

1 M. Ochi, K. Asao, H. Kotsuki, I. Miura, and K. Shibata, *Bull. Chem. Soc. Jpn.*, 1986, **59**, 661.
2 For previous reports related to the synthesis of dolastane-type diterpenoids, see: (a) G. Pattenden and G. M. Robertson, *Tetrahedron Lett.*, 1986, **27**, 399; (b) E. Piers and R. W. Friesen, *J. Org. Chem.*, 1986, **51**, 3405; (c) L. A. Paquette, H.-S. Lin, D. T. Belmont, and J. P. Springer, *J. Org. Chem.*, 1986, **51**, 4807.
3 E. Piers and J. M. Chong, *J. Chem. Soc., Chem. Commun.*, 1983, 934.
4 *Cf.* J. E. McMurry and W. J. Scott, *Tetrahedron Lett.*, 1983, **24**, 979.
5 *Cf.* E. Piers, R. W. Friesen, and B. A. Keay, *J. Chem. Soc., Chem. Commun.*, 1985, 809.