Tetrahedron Letters,Vol.28,No.47,pp 5945-5948,1987 0040-4039/87 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

AN ENANTIOSELECTIVE APPROACH TO DOLASTANE DITERPENES. TOTAL SYNTHESIS OF MARINE NATURAL PRODUCTS (+)-ISOAMIJIOL AND (+)-DOLASTA-1(15),7,9-TRIEN-14-OL

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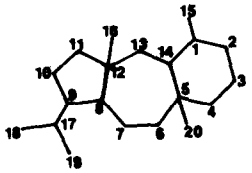
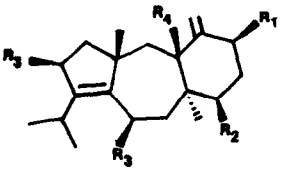
Summary: A general approach to dolastane diterpenes from (R)-(+)-limonene resulting in the total synthesis of the title compounds is described.

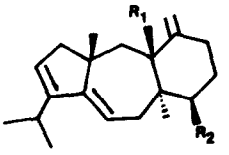
The dolastane-type diterpenes, embodying a unique 5-7-6 fused carbocyclic system **1**, were first discovered in Nature from a poisonous Indian Ocean sea-hare in 1976.[1a] Since then, they have frequently surfaced among sea weeds and presently over 16 natural products based on skeleton **1** with varying degrees of unsaturation and oxygen functionalisation are known.[1] Typical examples are the doubly unsaturated alcohols (-)-amijiol **2**,[1b] (-)-isoamijiol **3**,[1b] (-)-amijidictyol **4**[1c] and the triply unsaturated compounds **5**[1e] and (-)-**6**.[1f] Many of the dolastanes have been shown to exhibit promising biological activity and their absolute configuration has been established.[1f,2] The tricyclic dolastanes have aroused considerable synthetic interest,[3,4] and while the present work was in progress, total syntheses of **3** and **5** in racemic form have been reported by the groups of Pattenden[3a] and Piers[3b], respectively. Herein, we describe the first enantioselective approach to dolastanes, providing an access to the ent-series and culminating in the total synthesis of (+)-isoamijiol and (+)-dolasta-1(15),7, 9-trien-14-ol.



1



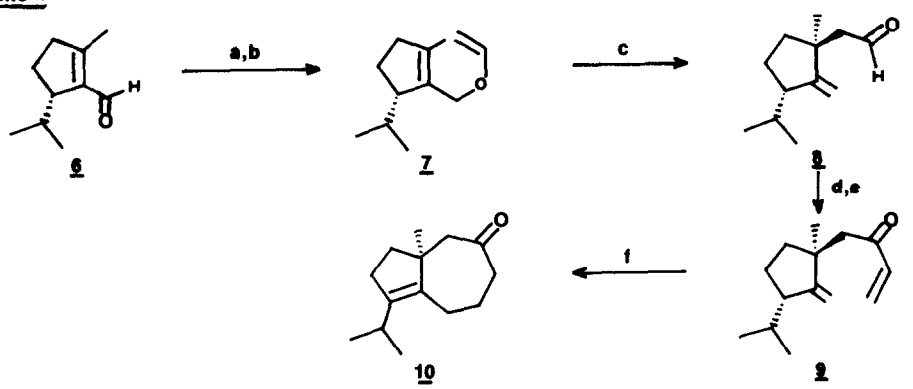
2. $R_1 = R_3 = H, R_2 = R_4 = OH$
3. $R_1 = R_4 = OH, R_2 = R_3 = H$
4. $R_1 = H, R_2 = R_4 = OH, R_3 = OAc$



5. $R_1 = OH, R_2 = H$
6. $R_1 = OH, R_2 = OAc$

Our approach to dolastanes envisaged enantioselective construction of the pivotal hydroazulenone **10** and stereoselective appendage of the remaining six-membered ring. Towards this end, α, β-unsaturated aldehyde[5] **6**, readily available from (R)-(+)-limonene was chosen as the chiron

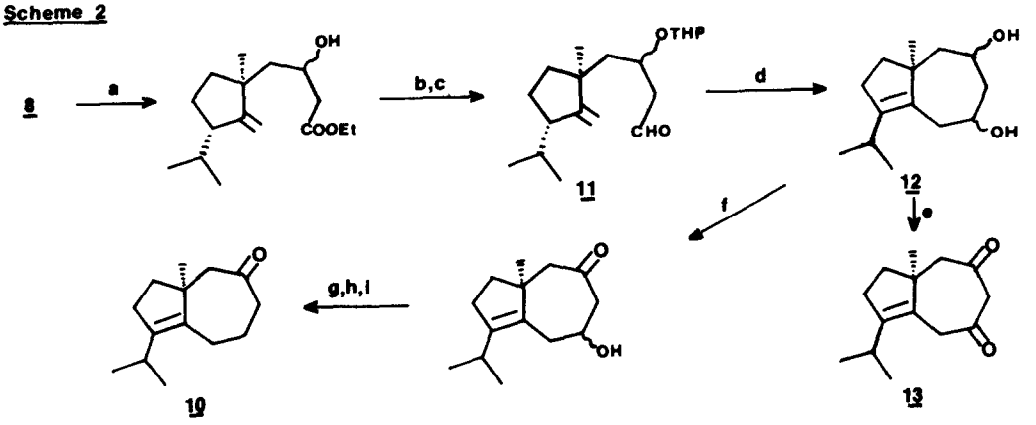
Scheme 1



Reagents & Yields : (a) $NaBH_4$, MeOH, 0°C, 90%. (b) $CH_3CH_2OCH{=}CH_2$, $Hg(OAc)_2$, RT, 80%. (c) Δ 200°C, 90%. (d) $CH_2{=}CHMgBr$, THF, RT, 75%. (e) PDC, DCM, RT, 60%. (f) 70% $HClO_4$, EtOAc, RT, 65%.

and transformed into **10** in a short sequence, as indicated in Scheme 1. The key steps involved were the stereospecific claisen rearrangement (**7** → **8**)[6] and the facile acid catalysed olefin-enone cyclisation (**9** → **10**).[6] In an overall sense, our sequence involves chirality transfer from (+)-limonene to the quaternary carbon centre of **10**. The hydroazulenone **10** was also approached from **8** by an alternate route shown in Scheme 2. The efficiency of the key intramolecular ene reaction (**11** → **12**) could not be improved further despite the use of several Lewis acids and variation in reaction conditions. However, an advantage of Scheme 2 lay in having access to the dione **13**[6] which is potentially serviceable for the more highly oxygenated dolastanes.

Scheme 2

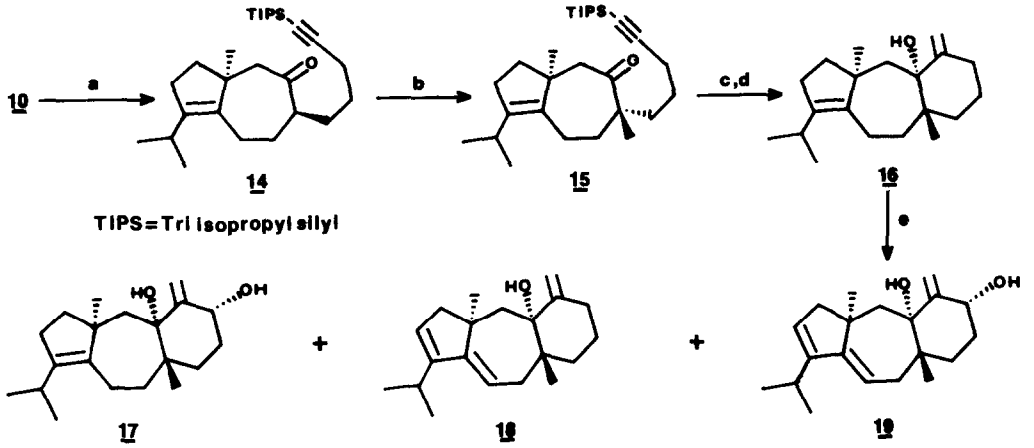


Reagents & Yields : (a) Zn, $BrCH_2COOEt$, Dioxane, 72%. (b) Dihydropyran, PPTS, DCM, RT, 85%. (c) DIBAL-H, DCM, -78°C, 65%. (d) $SnCl_4$, DCM, 0°C, 20%. (e) PCC, DCM, RT, 60%. (f) PCC, DCM, 0°C, 50%. (g) CH_3SO_2Cl, Py, 0°C, 74%. (h) LAH, Ether, RT, 65%. (i) PCC, DCM, RT, 68%.

The next stage was the annulation of the 6-membered ring with attendant functionality and this was achieved via a radical cyclisation strategy that has gained currency in recent years for

generating the bridgehead α-hydroxy-exo-methylene moiety.[7,8] The bicyclic ketone **10** was alkylated with the TIPS protected 5-iodo-1-pentyne to give **14** and the second alkylation with methyliododide installed the quaternary C_{20}-methyl group to furnish **15**, Scheme 3. The stereoselective placement

Scheme 3



Reagents & Yields : (a) LiHMDS, THF-HMPA, $I(CH_2)_3C{\equiv}CTIPS$, -10°C, 80%. (b) NaH, MeI, DME, RT, 65%. (c) $nBu_4N^+F^-$,THF, RT, 90%. (d) $C_{10}H_8^-Na^+$, THF, 40%. (e) SeO_2, tBuOOH, DCM, 0°C, 60%.

of the methyl group was a consequence of the topological bias engendered by the pre-existing C_{16}-angular methyl group. The TIPS protective group was now removed and the free acetylene exposed to sodium naphthalenide to yield the cyclised bridgehead hydroxy compound **16** having the dolastane framework with correct stereochemical disposition. Reaction of **16** with catalytic amounts of SeO_2 in the presence of t-BuOOH proved to be sensitive to the reaction conditions but the outcome was quite fortuitous and three products (+)-isoamijiol **17**, (+)-dolasta1-(15),7,9-trien-14-ol **18** $[\alpha]_D^{25}$ +200° (c 0.05, $CHCl_3$) and (+)-dolasta-1(15),7,9-trien-2,14-diol **19** $[\alpha]_D^{25}$ +75° (c 0.05, $CHCl_3$) in a ratio of 2 : 3 : 1 were obtained.[10] While the identity of **17** and **18** was readily established through comparison[11] of their spectral data with those reported in literature, the structure of **19** was independently established.[6]

Acknowledgments:

This research has been supported by UGC through a Special Assistance Programme in Organic Chemistry and COSIST support in Organic Synthesis. NK thanks CSIR for a research fellowship. (R)(+)-limonene used in this work was kindly donated by Dr. T.S. Santhanakrishnan of Bush Boake and Allen (India) Limited.

References & Notes:

1. (a) G.R. Pettit, R.H. Ode, C.L. Herald, R.B. von Dreele, C. Michel, J. Am. Chem. Soc., **98**, 4677, 1976; (b) M. Ochi, M. Watanabe, I. Miura, M. Taniguchi, T. Tokoroyama, Chem. Lett., 1229, 1980; (c) M. Ochi, M. Watanabe, M. Kido, Y. Ichikawa, I. Miura, T. Tokoyorama, Chem.

Lett., 1234, 1980; (d) H.H. Sun, O.J. McConnell, W. Fenical, K. Hirotsu, J. Clardy, Tetrahedron, **37**, 1237, 1981; (e) P. Crews, T.E. Klein, E.R. Hogue, B.L. Myers, J. Org. Chem., **47**, 811, 1982; (f) A.G. Gonzalez, J.D. Martin, M. Norte, P. Rivera, A. Perales, J. Fayos, Tetrahedron, **39**, 3355, 1983. (g) C.B. Rao, K.C. Pullaiah, R.K. Surapaneni, B.W. Sullivan, K. Albizati, D.J. Faulkner, H. Chu-heng, J. Clardy, J. Org. Chem., **51** 2736, 1986.

2. N. Harada, Y. Yokota, J. Iwabuchi, H. Uda, M. Ochi, J. Chem. Soc., Chem. Comm., 1220, 1984.
3. (a) G. Pattenden, G.M. Robertson, Tetrahedron Lett., **27**, 399, 1986; (b) E. Piers, R.W. Friesen, J. Org. Chem., **51**, 3405, 1986.
4. H. Seto, Y. Fujimoto, T. Tatsuno, H. Yoshioka, Syn. Comm., **15**, 1217, 1985; J.H. Rigby, J.Z. Wilson, C. Senanayake, Tetrahedron Lett., 3329, 1986; L.A. Paquette, H-S. Lin, D.T. Belmont, J.P. Springer, J. Org. Chem.,**51**, 4807, 1986.
5. G.L. Lange, E.E. Neidert, W.J. Orrom, D.J. Wallace, Can. J. Chem., **56**, 1628, 1978.
6. All new compounds were fully characterised on the basis of their spectral and analytical data. Selected spectral data for some of the compounds is given below.

   Compound **8**: IR (neat): 2740, 1720, 1640, 890 cm^{-1}; ^{1}H NMR:δ9.7 (1H, t, J = 4 Hz), 4.87 (2H, t, J = 4 Hz), 2.44 (2H, d, J = 4 Hz), 2.1 - 1.2 (6H, m) 1.09 (3H, s), 0.97 (3H, d, J = 7 Hz), 0.79 (3H, d, J = 7 Hz); ^{13}C NMR:δ202.9, 161.0, 104.9, 54.4, 50.7, 44.0, 37.3, 28.8, 27.6, 23.0, 21.7, 16.4.

   Compound **9**: IR (neat): 1680, 1610, 890 cm^{-1}; ^{1}H NMR:δ6.5 - 6.0 (2H, m), 5.8 - 5.6 (1H, m), 4.75 (2H, m), 2.7 - 1.0 (7H, m), 1.08 (3H, s), 0.97 (3H, d, J = 7 Hz), 0.77 (3H, d, J = 7 Hz).

   Compound **10**: $[\alpha]_D^{25}$ -13° (c 1.0, $CHCl_3$), IR (neat): 1690 cm^{-1}; ^{1}H NMR:δ2.8 - 1.4 (11H, m) 2.52 (2H, s), 1.0 (3H, s), 0.98 (3H, d, J = 7 Hz), 0.92 (3H, d, J = 7 Hz), ^{13}C NMR:δ213.0, 141.9, 138.7, 54.8, 47.5, 43.7, 38.0, 27.2, 26.5, 24.7, 24.1, 23.8, 21.3, 20.9.

   Compound **13**: IR (neat): 1700 cm^{-1}; ^{1}H NMR:δ2.43 (2H, dd, J_{gem} = 15 Hz), 2.24 (2H, dd, J_{gem} = 16 Hz), 2.8 - 1.6 (5H, m), 2.58 (2H, s), 1.1 (3H, s), 1.0 (6H, d, J = 7 Hz); ^{13}C NMR:δ203.0, 202.8, 148.8, 141.2, 59.2, 55.3, 49.1, 40.4, 36.7, 27.7, 27.1, 24.4, 21.0, 20.8.

   Compound **16**: mp 92°C, IR (KBr): 3450, 880 cm^{-1}; ^{1}H NMR:δ4.8 (1H, t, J = 2 Hz), 4.72 (1H, br s), 2.8 - 1.4 (17H, m), 1.34 (3H, s), 0.95 (3H, d, J = 7 Hz), 0.92 (3H, d, J = 7 Hz), 0.78 (3H, s).

   Compound **19**: mp 109°C, IR (KBr): 3450, 880 cm^{-1}; ^{1}H NMR:δ5.5 (1H, br s), 5.41 (1H, ABq, $J_1 = J_2$ = 5 Hz) 5.09 (1H, s), 4.95 (1H, s), 4.32 (1H, t, J = 3 Hz), 3.5 (1H, br s), 3.2 - 2.9 (1H, m), 2.6 - 1.4 (10H, m), 1.32 (3H, s), 1.1 (3H, d, J = 7 Hz), 1.06 (3H, d, J = 7 Hz), 0.84 (3H, s).
7. (a) B. Giese, Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds, Pergamon Press, Oxford, 1986; (b) S.K. Pradhan, S.R. Kadam, J.N. Kolhe, T.V. Radha Krishnan, S.V. Sohoni, V.B. Thaker, J. Org. Chem., **46**, 2622, 1981; (c) G. Pattenden, G.M. Robertson, Tetrahedron, **41**, 4001, 1985.
8. The reaction sequence employed by us is similar to that used by Pattenden.[3a]
9. The optical rotation of the natural product has not been reported.[1e]
10. Separation was achieved through repeated column chromatography on $AgNO_3$-SiO_2
11. We thank Professors Pattenden, Piers and Ochi for their help in making available the comparison spectra.

(Received in UK 25 September 1987)