## Novel and Enantioselective Total Synthesis of Drimane Type Sesquiterpenes

Kozo Shishido,\* Tomoki Omodani and Masayuki Shibuya Faculty of Pharmaceutical Sciences, University of Tokushima, Sho-machi 1, Tokushima 770, Japan

Two drimane type sesquiterpenoids, (+)-drimane-8,11-diol 1 and (+)-drim-9(11)-en-8-ol 2, have been synthesized in an optically pure form starting from geraniol.

During work directed towards the synthesis of biologically important terpenoids such as drim-9(11)-en-8-ol  $2^1$  and ambrein,<sup>2</sup> we required a versatile and optically pure common intermediate containing suitable functions. The sesquiterpenoid (+)-drimane-8,11-diol 1,<sup>3</sup> isolated from Greek tobacco, with four contiguous stereogenic centres met our purposes. Here we report an enantioselective total synthesis of 1 from geraniol and its conversion into (+)-2, which features the use of a highly diastereoselective intramolecular Diels-Alder reaction.

Sharpless asymmetric epoxidation of geraniol using D-(-)diethyl tartrate provided the epoxide  $3^4$  (94% ee)† in 97% yield. Treatment of 3 with isopropenylmagnesium bromide in the presence of cuprous iodide<sup>5</sup> resulted in the exclusive formation of the 1,3-diol 4<sup>‡</sup> which was converted into the acetonide 5 in 83% overall yield. Selective ozonolysis of the trisubstituted olefin in 5 at -78 °C cleanly provided the

 $<sup>^{\</sup>dagger}$  The ee was determined by the  $^{19}F$  and  $^{1}H$  NMR spectra of the corresponding MTPA ester.

<sup>‡</sup> All new compounds gave spectral data (IR, NMR, MS) in accord with the assigned structure, and satisfactory combustion analysis or accurate mass measurement.

aldehyde **6** in 91% yield based on the consumed starting material. Introduction of a 1,3-diene moiety into **6** was achieved as follows. Treatment of **6** with ethoxycarbonylethylidene-(triphenyl)phosphorane in benzene at 70 °C for 4 h provided the unsaturated ester which was reduced with diisobutylaluminium hydride to give the allylic alcohol as a single product in 99% yield. Oxidation of the alcohol with PDC followed by Wittig methylenation provided the triene **7**\* in 86% yield after purification by silica gel column chromatography (Scheme 1).

A solution of the triene 7 when heated in toluene at 210 °C for 48 h in the presence of a catalytic amount of Methylene Blue<sup>6</sup>



Scheme 1 Reagents: i, 2-Bromopropene, Mg, CuI; ii, 2-methoxypropene, PPTS; iii,  $O_3$ , -78 °C,  $CH_2Cl_2$  then  $Me_2S$ ; iv,  $Ph_3P=C(Me)-CO_2Et$ ; v, DIBAL-H; vi, PDC; vii,  $Ph_3P=CH_2$ 

in a sealed tube gave the cycloadduct as an inseparable diastereoisomeric mixture in a ratio of 15:1 (from the <sup>1</sup>H NMR) in 70% yield (Scheme 2). Although the structure of the major diastereoisomer could not be determined from the spectral properties at this stage, it was suggested that the A<sup>1,3</sup> interaction<sup>7</sup> in transition state 9 leading to the *cis* isomer 11 makes it less favourable than the alternative transition state 8 which favours the desired *trans* ring junction 10. The exact structure including stereochemistry of the major cycloadduct was confirmed by the eventual conversion into 1.

Allylic oxidation<sup>8</sup> of the mixture with chromium trioxide and 3,5-dimethylpyrazole provided the enone 129<sup>†</sup> in 65% yield after silica gel column chromatography. Attempted conjugate addition of either lithium dimethylcuprate or higher order cuprate<sup>9</sup> to 12 met with little or no success. The problem was solved by exposure of 12 to the conditions developed by Yamamoto<sup>10</sup> to provide the keto diol 13 in 60% yield (Scheme 3). Finally, the Wolff-Kishner reduction of 13 provided (+)drimane-8,11-diol 1 (53%), m.p. 118 °C (lit., 3 m.p. 119-120 °C);  $[\alpha]_{D} + 1.8 \ (c \ 0.57, \ CHCl_{3}), \{ lit., ^{3} [\alpha]_{D} + 1.6 \ (c \ 0.63, \ CHCl_{3}) \}.$ The IR and <sup>1</sup>H NMR spectra of synthetic material were indistinguishable from those reported for the natural product. Furthermore, treatment of the monotosylate, derived from 1, with sodium iodide and zinc powder<sup>11</sup> in refluxing dimethoxyethane afforded (+)-drim-9(11)-en-8-ol 2, m.p. 50-53 °C (lit., <sup>1b</sup>; oil),  $[\alpha]_{D}$  + 28.6 (c 0.28, CHCl<sub>3</sub>) {lit., <sup>1b</sup>,  $[\alpha]_{D}$  + 22.5



Scheme 3 Reagents: i, CrO<sub>3</sub>, 3,5-dimethylpyrazole; ii, MeLi, CuI, BF<sub>3</sub>-Et<sub>2</sub>O; iii, (NH<sub>2</sub>)<sub>2</sub>-H<sub>2</sub>O, KOH; iv, TsCl, pyridine, 4-DMAP; v, NaI, Zn

(c 0.60, CHCl<sub>3</sub>)}, the enantiomer of the natural product <sup>1a</sup> with sporogenic activity isolated from a culture filtrate of *Aspergillus* oryzae, in 59% yield, whose spectral properties were also identical with those reported.

In summary, we have described a novel and efficient synthesis of drimane-8,11-diol, which would serve as a valuable intermediate in the synthesis of chiral terpenoids, and its conversion into (+)-drim-9(11)-en-8-ol from an acyclic precursor in an enantiocontrolled fashion.

## Experimental ‡

Selective Ozonolysis of the Diene 5.—Ozone was passed into a solution of the diene 5 (8.0 g, 32 mmol) in dry dichloromethane (190 ml) at -78 °C and the progress of the reaction was monitored by TLC. After 20 min, dimethyl sulphide (9.9 g, 160 mmol) was added at -78 °C and the mixture was stirred at the same temperature for 10 min and then at room temperature for 20 min. Evaporation of the solvent gave a residue which was dissolved in dichloromethane and the solution was washed with brine, dried (MgSO<sub>4</sub>) and finally evaporated. The residue was column-chromatographed on silica gel using hexane–ethyl acetate (95:5, v/v) as eluent to give the starting diene 5 (3.5 g) as an oil. From the later fractions, the aldehyde 6 (3.6 g, 91% based on the consumed starting material) was obtained as a labile oil;  $v_{max}$ (CHCl<sub>3</sub>)/cm<sup>-1</sup> 2714, 1719 and 1655;  $\delta_{H}$ (200 MHz; CDCl<sub>3</sub>) 1.31, 1.33, 1.44 (3 H each, s), 1.78 (3 H, br s), 1.90 (2 H, t, J 7.3),

<sup>\*</sup> The homogeneity was confirmed by the <sup>1</sup>H and <sup>13</sup>C NMR spectra. † Selected spectral data. For 12: $[\alpha]_D$  +60.6 (c 0.39, CHCl<sub>3</sub>);  $\nu_{max}$ (CHCl<sub>3</sub>)/cm<sup>-1</sup> 1660 and 1610;  $\delta_H$ (200 MHz, CDCl<sub>3</sub>) 0.86, 1.41, 1.43, 1.48 and 1.93 (each 3 H, s), 3.83 (1 H, dd, J 11.0 and 6.8), 3.93 (1 H, t, J 11) and 5.88 (1 H, br s);  $\delta_C$ (50 MHz, CDCl<sub>3</sub>) 13.69, 21.58, 21.93, 24.82, 28.76, 28.99, 39.80, 41.35, 49.76, 51.95, 52.15, 57.81, 73.26, 99.01, 126.52, 162.00 and 197.98; *m/z* 278.1900 (calc. for C<sub>1.7</sub>H<sub>26</sub>O<sub>3</sub>: *M*, 278.1882).

 $<sup>\</sup>ddagger J$  Values in Hz and  $[\alpha]_D$  values in  $10^{-1} \text{ deg cm}^2 \text{ g}^{-1}$ .

2.52 (3 H, m), 3.70 (1 H, dd, J 11.8 and 4.5), 4.00 (1 H, dd, J 11.8 and 11.1), 4.75 (1 H, m), 4.93 (1 H, m) and 9.75 (1 H, t, J 2.1).

## **Acknowledgements**

We thank Dr. N. Shoji, Tokushima Bunri University, for the use of a polarimeter.

## References

- (a) K. Wada, S. Tanaka and S. Marumo, Agric. Biol. Chem., 1983, 47, 1075; (b) M. A. F. Leite, M. H. Sarragiotto, P. M. Imamura and A. J. Marsaioli, J. Org. Chem., 1986, 51, 5409.
- 2 L. Ruzicka and F. Lardon, Helv. Chim. Acta, 1946, 29, 912.
- J. R. Hlubucek, A. J. Aasen, S.-O. Almqvist and C. R. Enzell, Acta Chem. Scand., Ser. B, 1974, 28, 289.

- 4 T. Katsuki and K. B. Sharpless, J. Am. Chem. Soc., 1980, 102, 5974.
- 5 (a) M. A. Tius and A. H. Fauq, J. Org. Chem., 1983, 48, 4131; (b) J. A. Marshall and D. G. Cleary, J. Org. Chem., 1986, 51, 858.
- 6 (a) D. F. Taber and S. A. Saleh, J. Am. Chem. Soc., 1980, 102, 5085; (b)
  D. F. Taber and S. A. Saleh, Tetrahedron Lett., 1982, 23, 2361; (c) M.
  Ihara, I. Sudow, K. Fukumoto and T. Kametani, J. Chem. Soc., Perkin Trans. 1, 1986, 117.
- 7 F. Johnson, Chem. Rev., 1968, 68, 375.
- 8 W. G. Salmond, M. A. Barta and J. L. Havens, J. Org. Chem., 1978, 43, 2057.
- 9 C. P. Jasperse and D. P. Curran, J. Am. Chem. Soc., 1990, 112, 5601.
- 10 Y. Yamamoto and K. Maruyama, J. Am. Chem. Soc., 1978, 100, 3240.
- 11 Cf. Y. Fujimoto and T. Tatsuno, Tetrahedron Lett., 1976, 3325.

Paper 1/02649F Received 3rd June 1991 Accepted 8th July 1991