Total Enantioselective Synthesis of the Marine Sesquiterpene Nanaimoal

Tomoki Omodani and Kozo Shishido*

Institute for Medicinal Resources, University of Tokushima, Sho-machi 1, Tokushima 770, Japan

The first enantioselective total synthesis of (−)-nanaimoal **1** has been achieved from geraniol and the absolute configuration of the only existing quaternary stereogenic centre was found to be (*R*).

Nanaimoal **1**,[1] a fragrant sesquiterpene aldehyde, was isolated from the dorid nudibranch *Acanthodoris nanaimoensis*. The whole structure of nanaimoal was inferred from the spectral properties and the biogenetic isoprene rule and eventually determined by an unambiguous synthesis of its *p*-bromophenylurethane derivative **2**, which was identical to an authentic material derived from natural nanaimoal. The absolute structure of **1** remains unestablished. Owing to its simple but intriguing chemical structure and its pharmacological potential,[2] the sesquiterpene aldehyde **1** has witnessed considerable synthetic interest. Although the syntheses of the racemate[1,3] have been described, no chiral synthesis for this terpenoid has yet been reported. We present here the first enantioselective total synthesis of nanaimoal **1**, thereby establishing its absolute stereochemistry.

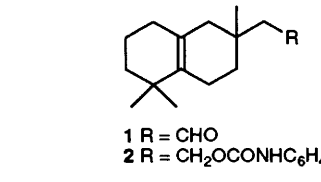
We envisaged that a pivotal construction of the quaternary stereogenic centre in **1** can be realized by employing the organoaluminium-promoted rearrangement[4] of the optically active epoxy silyl ether **3**, generated *via* the Sharpless asymmetric epoxidation, to the configurationally defined aldehyde **4** (Scheme 1).

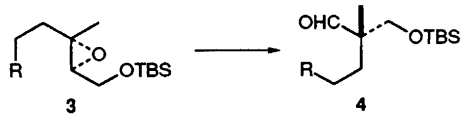
According to Yamamoto,[4] reaction of the epoxy silyl ether **5**, prepared by Sharpless asymmetric epoxidation of geraniol using L-(+)-diethyl tartrate followed by silylation, with 2 equiv. of methylaluminium bis(4-bromo-2,6-di-*tert*-butylphenoxide) **6** proceeded *via* configuration inversion to provide the aldehyde **7** with (*S*)-configuration in 97% yield (95% ee) (Scheme 2). The quaternary stereogenic centre present in **1** was thus constructed. On sequential addition of nitromethane, acetylation and sodium borohydride reduction,[5] **7** was converted into the nitroalkene **8** in 55% overall yield. Treatment of **8**† with *p*-chlorophenylisocyanate and triethylamine gave quantitatively the isoxazoline **10**, an inseparable mixture of two diastereoisomers in a ratio of 2 : 1, *via* the [3 + 2] dipolar cycloaddition[6] of alkenyl nitrile oxide **9**. Subsequent reductive hydrolysis[7] of **10** followed by immediate exposure of the resulting β-hydroxy ketone to a catalytic D-camphor-10-sulfonic acid provided the enone **11**, which was then treated with the conditions of Nozaki–Lombardo methylenation reaction[8] to afford the exocyclic diene **12**‡ in 48% overall yield from **10**.

On heating a solution of **12** and vinylsulfone[9] in benzene at 160 °C in a sealed tube for 48 h, the Diels–Alder adduct **13** was obtained in 43% yield as an inseparable diastereoisomeric 1 : 1 mixture. No regioisomeric products were detected in the crude reaction mixture. Desulfonylation with sodium amalgam followed by desilylation of the resulting **14**‡ provided the alcohol **15**, which was converted into the cyanide **16** by a standard procedure. Finally, reduction of **16** with diisobutylaluminium hydride followed by acidic work up furnished nanaimoal **1** {$[\alpha]_D$ −4.9 (*c* 0.6, $CHCl_3$)},§ which was identical [^{1}H NMR (200 MHz), IR, MS] with authentic nanaimoal, in 70% yield. To confirm the absolute structure and optical purity, synthetic **1** was reduced with sodium borohydride to the corresponding alcohol **17**, nanaimool,[1] whose optical rotation {$[\alpha]_D$ +10.9 (*c* 0.2, MeOH)} was consistent with that reported (lit.[1] $[\alpha]_D$ +10.4 MeOH).

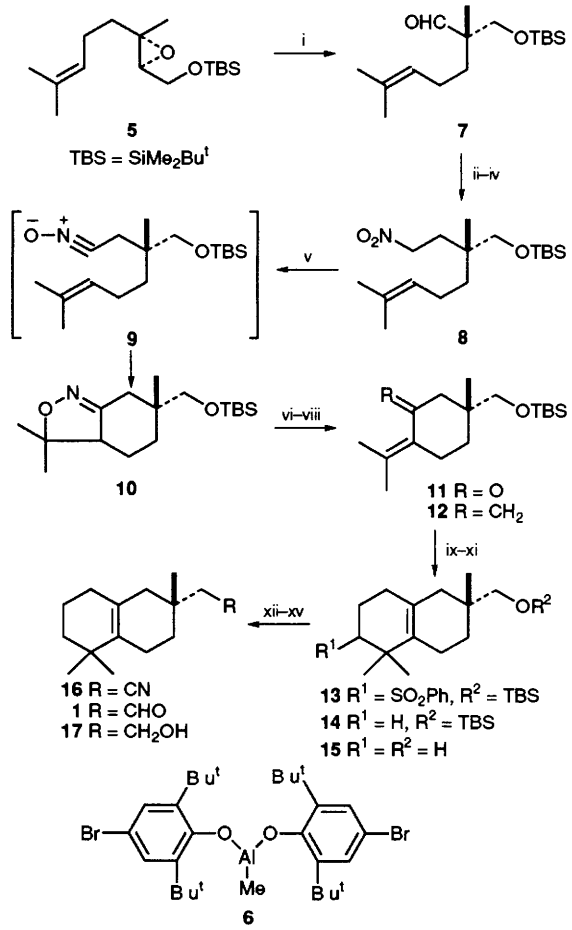
We thank Professor K. Takabe, Shizuoka University, for providing the spectroscopic data of nanaimoal and nanaimool and Professor H. Yamamoto, Nagoya University, for useful advice on organoaluminium-promoted rearrangements.

Received, 13th September 1994; Com. 4/05566G





Scheme 1



Scheme 2 *Reagents and Conditions*: i, **6**, CH_2Cl_2, 97%; ii, $MeNO_2$, KF, 18-crown-6, propan-2-ol; iii, Ac_2O, DMAP, Et_2O; iv, $NaBH_4$, EtOH, 55% from **7**; v, *p*-ClC_6H_4NCO, Et_3N, benzene, 100%; vi, H_2, Raney Ni, $(MeO)_3B$, H_2O–MeOH; vii, D-camphor-10-sulfonic acid, CH_2Cl_2; viii, CH_2Br_2, Zn, $TiCl_4$, THF–CH_2Cl_2, 48% from **10**; ix, $PhSO_2CH{=}CH_2$, benzene, sealed tube, 160 °C, 43%; x, 5% Na–Hg, MeOH; xi, Bu^n_4NF, THF, 49% from **13**; xii, *p*-TsCl, pyridine, xiii, NaCN, DMSO, 86% for 2 steps; xiv, Bu^i_2AlH, hexane–CH_2Cl_2 (1 : 1), then aq. HCl, 70%; xv, $NaBH_4$, EtOH, 73%

Footnotes

† All new compounds gave spectral data (IR, NMR, MS) in accord with the assigned structures, and satisfactory combustion analysis or accurate mass measurements.

‡ *Selected spectroscopic data* for **12**: Colourless oil; $[\alpha]_D$ +5.1 (*c* 0.59, $CHCl_3$); δ_H (200 MHz, $CDCl_3$) 0.01 (6H, s), 0.89 (9H, s), 1.14–1.62 (2H, m), 1.70 (3H, s), 1.78 (3H, s), 1.82–2.45 (4H, m), 3.27 (1H, d, *J* 9.6 Hz), 3.33 (1H, d, *J* 9.6 Hz), 4.62 (1H, br d, *J* 2.8 Hz), 4.88 (1H, br d, *J* 2.8 Hz); MS *m/z* (EI) 294 (M^+). For **14**: Colourless oil; $[\alpha]_D$ +3.6 (*c* 0.56, $CHCl_3$); δ_H (200 MHz, $CDCl_3$) 0.01 (6H, s), 0.83 (3H, s), 0.89 (9H, s), 0.97 (6H, s), 1.28–2.06 (12H, m), 3.22 (1H, d, *J* 9.4 Hz), 3.29 (1H, d, *J* 9.4 Hz); MS *m/z* (EI) 322 (M^+).

§ The optical rotation of **1** has never been reported.

References

1 S. W. Ayer, J. Hellou and R. J. Andersen, *Tetrahedron Lett.*, 1984, **25**, 141.

2 H.-J. Liu, G. Ulibarri and L. A. K. Nelson, *J. Chem. Soc., Chem. Commun.*, 1990, 1419.

3 T. Yamada and K. Takabe, *Chem. Lett.*, 1993, 29.

4 K. Maruoka, T. Ooi and H. Yamamoto, *J. Am. Chem. Soc.*, 1989, **111**, 6431; K. Maruoka, T. Ooi, S. Nagahara and H. Yamamoto, *Tetrahedron*, 1991, **47**, 6983; T. Ooi, K. Maruoka and H. Yamamoto, *Org. Synth.*, 1993, **72**, 95.

5 R. H. Wollenberg and S. J. Miller, *Tetrahedron Lett.*, 1978, 3219.

6 For reviews see: A. P. Kozikowski, *Acc. Chem. Res.*, 1984, **17**, 410; S. Kanemasa and O. Tsuge, *Heterocycles*, 1990, **30**, 719; A. Padwa and A. M. Schoffstall, *Advances in Cycloaddition*, ed. D. P. Curran, JAI Press, Greenwich, 1990, vol. 2, p. 1; W. Carruthers, *Cycloaddition Reactions in Organic Synthesis*, Pergamon, Oxford, 1990, 285.

7 D. P. Curran, *J. Am. Chem. Soc.*, 1982, **104**, 4024.

8 K. Takai, Y. Hotta, K. Oshima and H. Nozaki, *Bull. Chem. Soc. Jpn.*, 1980, **53**, 1698; L. Lombardo, *Org. Synth.*, 1987, **65**, 81.

9 R. V. C. Carr and L. A. Paquette, *J. Am. Chem. Soc.*, 1980, **102**, 853; R. V. C. Carr, R. V. Williams and L. A. Paquette, *J. Org. Chem.*, 1983, **48**, 4976.