A Total Synthesis of (±)-Isobicyclogermacrenal

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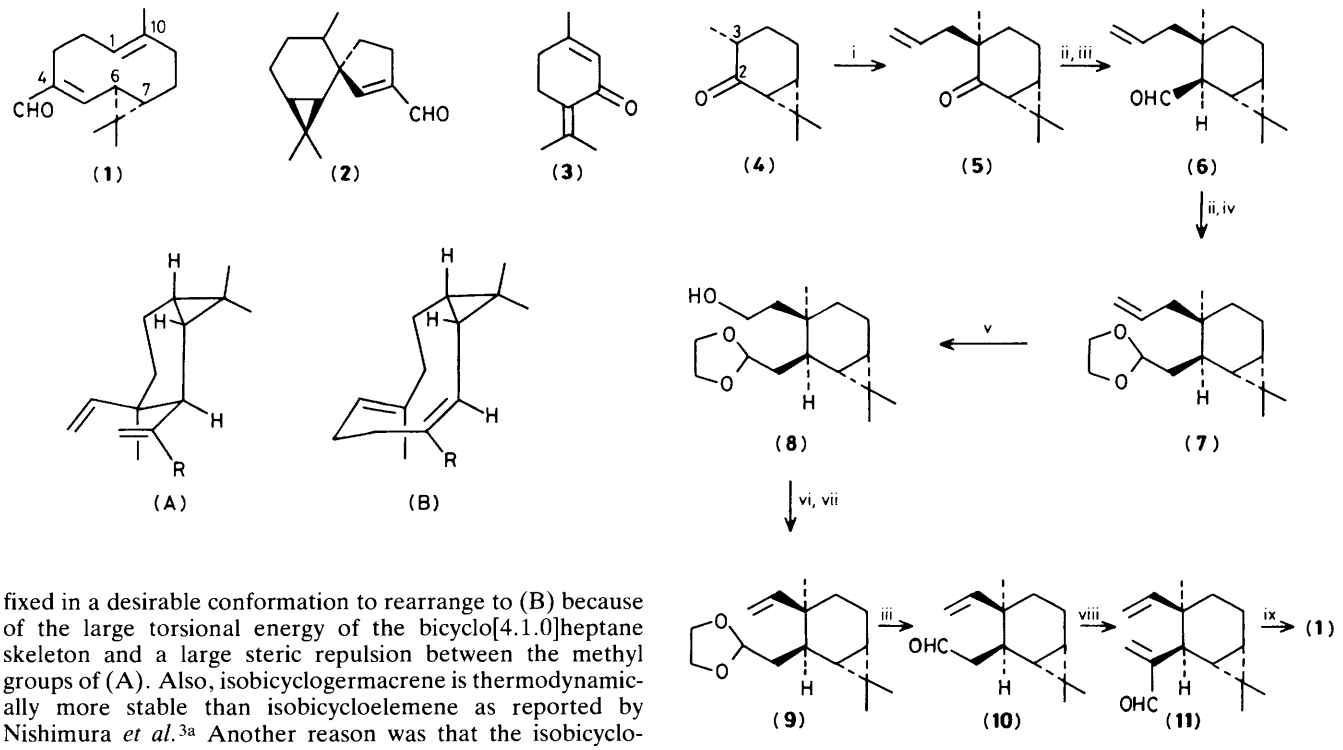
(±)-Isobicyclogermacrenal (**1**), a bicyclo[8.1.0]undecane sesquiterpene aldehyde, has been synthesized from piperitenone (**3**) in a stereoselective manner *via* 14 steps in an overall yield of 36%.

(−)-Isobicyclogermacrenal (**1**), which has been isolated from the liverwort *Lepidozia vitrea* Steph., is a sesquiterpene aldehyde possessing a unique bicyclo[8.1.0]undecane skeleton and plant growth inhibitory activity. The structure of (−)-(**1**) including its absolute configuration has been determined by chemical transformation and single crystal *X*-ray analysis.[1]

We have previously reported the total synthesis of (±)-vitrenal (**2**), which is also a plant growth inhibitory substance isolated from the same liverwort together with (**1**), from the monoterpene piperitenone (**3**).[2] In this communication, we report the total synthesis of (±)-isobicyclogermacrenal (**1**) from the same starting material (**3**).

At the final synthetic stage, we planned to apply a Cope rearrangement of bicycloelemene derivative (A) to construct the isobicyclogermacrene (B) skeleton.[3] There were several reasons: One was that the cyclohexane ring of (A) would be



Reagents and conditions: i, LDA, allyl bromide, tetrahydrofuran (THF); ii, $Ph_2P(O)CH_2OMe$, LDA, THF; iii, dil. HCl, acetone; iv, $(CH_2OH)_2$, *p*-$MeC_6H_4SO_2OH$, PhH; v, O_3–$CHCl_3$; $NaBH_4$–aq. EtOH; vi, *o*-$NO_2C_6H_4SeCN$, Bu_3P, THF; vii, 30% H_2O_2, THF; viii, KH, HCHO, THF; ix, SiO_2, room temp.

fixed in a desirable conformation to rearrange to (B) because of the large torsional energy of the bicyclo[4.1.0]heptane skeleton and a large steric repulsion between the methyl groups of (A). Also, isobicyclogermacrene is thermodynamically more stable than isobicycloelemene as reported by Nishimura *et al.*[3a] Another reason was that the isobicycloelemene derivative could be prepared stereospecifically from isocaran-2-one (**4**) *via* the stereoselective introduction of the substituents into the C-2 and C-3 positions on the opposite side of cyclopropane ring.

Isocaran-2-one (**4**), which was derived from piperitenone (**3**),[2] was treated with lithium di-isopropylamide (LDA) followed by allyl bromide to give the 3β-allylated compound (**5**) stereospecifically in 84% yield.† Treatment of (**5**) with a lithium derivative of diphenyl(methoxymethyl)phosphine oxide[2,4] followed by hydrolysis afforded an aldehyde (**6**) as the sole stereoisomer in 83% yield. The stereochemistry of (**6**) was deduced from the assumption that (**6**) would be the thermodynamically controlled product.‡ The aldehyde (**6**) was again treated with the same Wittig–Horner reagent followed by ethylene glycol and an acid catalyst to afford an acetal (**7**) in 90% yield. The stereochemistry of this compound (**7**) was confirmed by the analysis of the ^{1}H n.m.r. spectra including the use of COSY and NOESY routines; that is, all of the important proton signals could be assigned including their stereochemical configuration. The allyl group of (**7**) was degraded into a vinyl group in three steps. Ozonolysis of (**7**) followed by reductive work-up gave an alcohol (**8**) (90% yield). The alcohol (**8**) was converted into an *o*-nitrophenylselenide (93% yield),[5] which was then converted by an oxidative elimination reaction into the vinyl derivative (**9**) quantitatively. Aldehyde (**10**), which was obtained from (**9**) by deprotection of the acetal group in 97% yield, was treated with KH[6] followed by gaseous HCHO in tetrahydrofuran (THF) to afford α-methylene aldehyde (**11**) in 87% yield. Compound (**11**) was introduced onto a silica gel column and left at room temperature overnight. Cope rearrangement was found to have taken place smoothly to afford (±)-isobicyclogermacrenal (**1**), in 93% yield.§

† All compounds prepared are racemic; an enantiomer is depicted to denote relative stereochemistry. The structures of all new compounds were confirmed spectroscopically.

Selected spectroscopic data: (**5**): I.r. (neat) 1690, 1645 cm^{-1}; ^{1}H n.m.r. (CCl_4) δ 0.95 (3H, br. s), 1.01 (3H, s), 1.16 (3H, s), 4.7—5.1 (2H, m), and 5.3—6.0 (1H, m); ^{13}C n.m.r. ($CDCl_3$) δ 16.31 (q), 18.53 (q), 18.83 (t), 24.35 (q), 27.63 (s), 32.69 (t), 33.64 (d), 35.81 (t), 37.76 (s), 43.93 (d), 115.90 (t), 136.65 (d), and 213.93 (s); mass *m/z* 192.1484 (M^+; $C_{13}H_{20}O$).

(**7**): I.r. (neat) 1640 cm^{-1}; ^{1}H n.m.r. ($CDCl_3$) δ 0.27 (1H, dd, *J* 9, 5.5 Hz), 0.59 (1H, br. dd, *J* 9, 8 Hz), 0.74 (1H, ddd, *J* 15, 14, 7 Hz), 0.82 (3H, br. s), 0.94 (3H, s), 1.00 (3H, s), 1.11 (1H, ddd, *J* 12, 5.5, 2.5 Hz), 1.32 (1H, ddd, *J* 14, 8, 1.5 Hz), 1.48 (1H, ddd, *J* 15, 7.5, 1.5 Hz), 1.61 (1H, ddd, *J* 13, 12, 2.5 Hz), 1.7—1.9 (3H, m), 2.30 (1H, dd, *J* 13.5, 7.5 Hz), 3.8—4.0 (4H, m), 4.91 (1H, dd, *J* 7.5, 2.5 Hz), 4.85—5.1 (2H, m), 5.78 (1H, dddd, *J* 17, 10, 7.5, 7.5 Hz); ^{13}C n.m.r. ($CDCl_3$) δ 15.66 (q), 15.95 (t), 17.63 (s), 19.80 (d), 25.79 (q), 26.06 (d), 29.17 (q), 33.78 (s), 34.51 (t), 35.94 (t), 36.81 (t), 38.22 (d), 64.63 (t), 64.82 (t), 104.58 (d), 116.42 (t), and 135.87 (d); mass *m/z* 264.2080 (M^+, $C_{17}H_{28}O_2$).

(**11**): I.r. (neat) 2710, 1700, and 1625 cm^{-1}; ^{1}H n.m.r. ($CDCl_3$) δ 0.25—0.75 (2H, m), 0.79 (3H, s), 1.02 (3H, s), 1.07 (3H, s), 2.48 (1H, d, *J* 6 Hz), 4.7—5.1 (2H, m), 6.03 (1H, s), 6.36 (1H, s), and 6.37 (1H, dd, *J* 17.5, 11.5 Hz); ^{13}C n.m.r. ($CDCl_3$) δ 15.03, 16.31, 18.18, 20.04, 24.16, 26.54, 29.17, 37.81, 38.54, 38.73, 113.66, 135.73, 142.56, 153.91, and 194.46; mass *m/z* 218.1705 (M^+, $C_{15}H_{22}O$).

(**1**): U.v. (EtOH) 261.2 nm (ε 7800); i.r. (neat) 2710, 1680, and 1620 cm^{-1}; ^{1}H n.m.r. ($CDCl_3$) δ 0.7—1.1 (2H, m), 1.21 (3H, s), 1.23 (3H, s), 1.28 (3H, s), 5.07 (1H, br. t, *J* 7.5 Hz), 6.28 (1H, d, *J* 9.5 Hz), and 9.28 (1H, s); ^{13}C n.m.r. ($CDCl_3$) δ 15.76 (q), 17.31 (q), 21.18(s), 23.57 (t), 23.57 (t), 27.85 (t), 28.55 (q), 29.90 (d), 38.22 (d), 39.98 (t), 124.49 (d), 134.43 (s), 143.10 (s), 155.72 (d), and 194.13 (d); mass *m/z* 218.1695 (M^+, $C_{15}H_{22}O$).

‡ This stereochemical assumption could be confirmed from the 2D ^{1}H n.m.r. spectrum of (**7**).

§ Even when (**11**) was heated with benzene in a sealed tube at 200 °C, no 3,3-sigmatropic product could be obtained.

The ^{1}H n.m.r., u.v., and mass spectra of the synthetic (±)-isobicyclogermacrenal were found to be identical with those of natural (−)-(**1**).[1] Reduction of (±)-isobicyclogermacrenal with $LiAlH_4$ gave the corresponding alcohol whose ^{1}H and ^{13}C n.m.r. spectra were also identical with those of (+)-isobicyclogermacrenol derived from natural (−)-(**1**).[1] Thus, (±)-isobicyclogermacrenal (**1**) was synthesized from piperitenone (**3**) in an overall yield of 36% in 14 steps.

We thank Professor Hajime Nagano, Ochanomizu University, for his helpful discussions and obtaining the 270 MHz ^{1}H n.m.r. spectra, and Soda Aromatic Co. Ltd. for the gift of piperitenone (**3**).

Received, 13th April 1987; Com. 486

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