Chelation-controlled Regioselective Epoxide–Carbonyl Rearrangement: a Ring Enlargement Route to (±)-Modhephene

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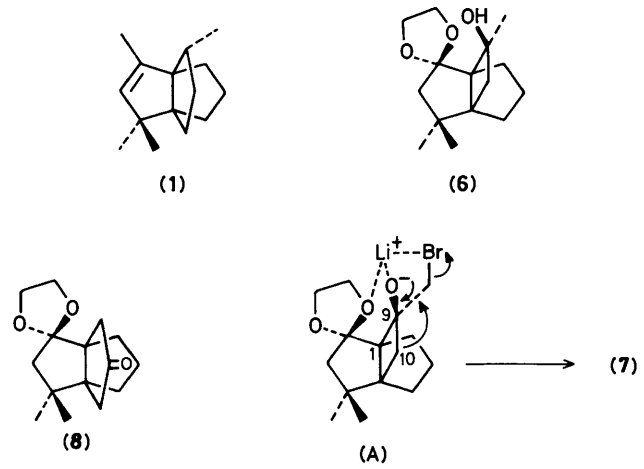
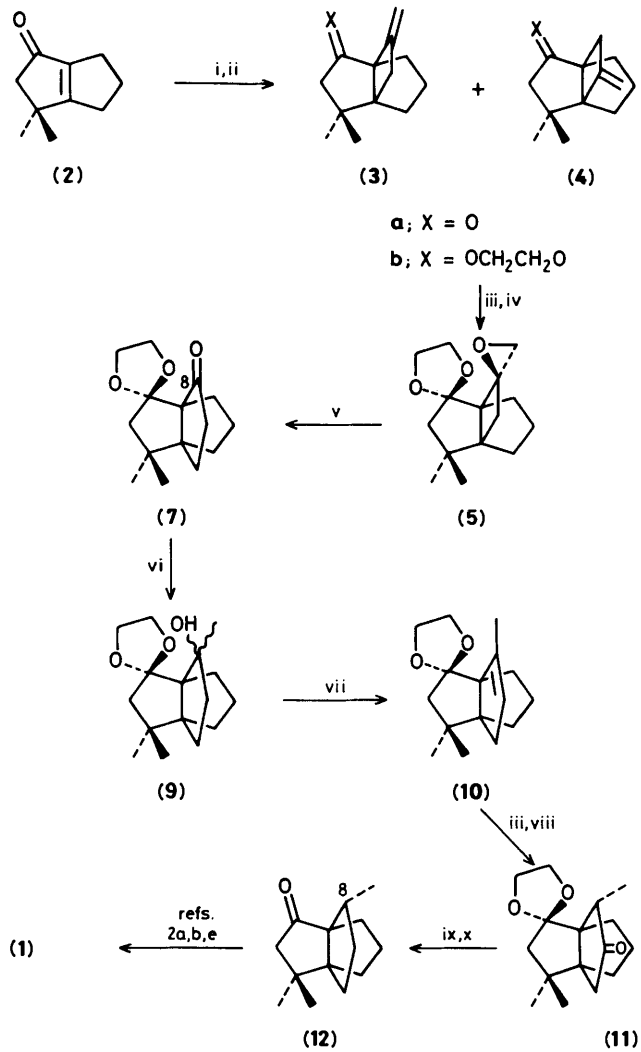
A new formal total synthesis of (±)-modhephene (**1**) employing a chelation-controlled regioselective epoxide–carbonyl rearrangement as the key step is described.

Modhephene (**1**), the first carbocyclic [3.3.3]propellane isolated from natural sources,[1] has attracted considerable synthetic interest because of its unique carbon framework and several efficient routes to (±)-(**1**) have been reported.[2] We report herein a regio- and stereo-controlled formal total synthesis of (±)-(**1**) with regioselective ring enlargement by means of lithium bromide catalysed epoxide–carbonyl rearrangement[3] as the key step. A notable feature of our route is that the migration regioselectivity in the above rearrangement is critically controlled by chelation of the lithium cation with the acetal oxygen atom leading to the desired regiochemistry.

Irradiation of the enone (**2**)[2c,e] with an excess of allene in dichloromethane at −78 °C gave the head to head adduct (**3a**)† as the major product [94%; (**3a**) : (**4a**) = 4.5 : 1]. Without separation, the mixture of (**3a**) and (**4a**) was acetalized using the procedure of Noyori[4] to yield the acetals (**3b**) and (**4b**) in 92% yield [(**3b**) : (**4b**) = 4.5 : 1]. The acetals were oxidized with *m*-chloroperbenzoic acid (*m*-CPBA) (Na_2HPO_4, CH_2Cl_2, 0 °C) to give three epoxy acetals from which the major isomer (**5**), m.p. 73—74 °C, was isolated in 61% yield by flash chromatography. The *syn*-head to head stereochemistry of (**5**) was determined by lithium aluminium hydride reduction to the alcohol (**6**), m.p. 45—46 °C, which showed a sharp hydroxy stretching band at 3500 cm^{-1} due to intramolecular hydrogen bonding with the acetal oxygen atom. The epoxide–carbonyl rearrangement of (**5**) [lithium bromide, hexamethylphosphoramide (HMPA),[5] benzene, 80 °C] proceeded in a regioselective manner to afford the desired ketone (**7**), 86%, m.p. 52—53 °C, together with a small amount of the regioisomer (**8**), 9%, m.p. 27—28 °C. It should be noted that, in marked contrast with the regioselectivity in related ring





Scheme 1. i, *hν*, allene, CH_2Cl_2, −78 °C; ii, $Me_3SiOCH_2CH_2OSiMe_3$, $Me_3SiOSO_2CF_3$, CH_2Cl_2, 0 °C; iii, *m*-CPBA, Na_2HPO_4, CH_2Cl_2, 0 °C; iv, separation; v, LiBr, HMPA, C_6H_6, 80 °C; vi, MeMgI, Et_2O; vii, $SOCl_2$, pyridine, 0 °C; viii, BF_3·OEt_2, CH_2Cl_2, 0 °C; ix, N_2H_4·H_2O, K_2CO_3, diethylene glycol; x, H_2SO_4, aq. acetone.

† Satisfactory spectral and analytical data were obtained for all new compounds. Representative spectral data for selected compounds are as follows: (**5**), ^{1}H n.m.r. (CCl_4) δ 1.05 (6H, s), 1.1—1.4 (2H, m), 1.5—2.2 (6H, m), 2.38 (2H, ABq, *J* 5, 8 Hz), 2.52 (1H, d, *J* 14 Hz), 2.67 (1H, d, *J* 14 Hz), 3.4—3.9 (m, 4H). (**6**), i.r. (KBr) 3500 cm^{-1}; ^{1}H n.m.r. (CCl_4) δ 1.00 (3H, s), 1.02 (3H, s), 1.15 (3H, s), 1.3—2.1 (8H, m), 2.33 (1H, d, *J* 14 Hz), 2.92 (1H, d, *J* 14 Hz), 3.54 (D_2O exchangeable, 1H, s), 3.6—4.0 (4H, m). (**7**), i.r. (KBr) 1725 cm^{-1}; ^{1}H n.m.r. (CCl_4) δ 1.02 (3H, s), 1.18 (3H, s), 1.1—2.7 (12H, m), 3.5—3.9 (4H, m). (**8**), i.r. (KBr) 1730 cm^{-1}; ^{1}H n.m.r. (CCl_4) δ 0.98 (6H, s), 1.3—2.3 (10H, m), 2.51 (1H, dd, *J* 2, 19 Hz), 2.90 (1H, dd, *J* 2, 19 Hz), 3.5—4.0 (4H, m). (**9**), i.r. (neat) 3460 cm^{-1}; ^{1}H n.m.r. (CCl_4) δ 0.88 (D_2O exchangeable, 1H, s), 0.98 (3H, s), 1.07 (3H, s), 1.32 (3H, s), 1.2—2.1 (12H, m), 3.6—4.0 (4H, m). (**10**), ^{1}H n.m.r. (CCl_4) δ 0.90 (3H, s), 0.99 (3H, s), 1.1—2.0 (12H, m), 2.45 (1H, dq, *J* 18, 2 Hz), 3.6—4.0 (4H, m), 5.0—5.2 (1H, m). (**11**), i.r. (neat) 1730 cm^{-1}; ^{1}H n.m.r. (CCl_4) δ 0.91 (3H, d, *J* 7 Hz), 1.02 (3H, s), 1.07 (3H, s), 1.2—1.9 (8H, m), 2.00 (1H, d, *J* 13 Hz), 2.66 (1H, dd, *J* 2, 18 Hz), 2.90 (1H, dq, *J* 2, 7 Hz), 3.5—3.9 (4H, m).

enlargements,[3,6] the migration of the less-substituted carbon [C(10)] of (**5**) predominated over that of the more-substituted one [C(1)]. The present regioselectivity may be envisaged as resulting from chelation of the lithium cation with the acetal oxygen atom locking the conformation as that of intermediate (A)[5] in which the C(9)–C(10) bond has an antiperiplanar alignment with the C(11)–Br bond as illustrated.

With access to the key intermediate (**7**) secure, we focused on the stereoselective introduction of the *anti* C(8) methyl group in order to obtain the precursor (**12**)[2a,b,e] of (±)-(**1**). Thus, reaction of (**7**) with an excess of methylmagnesium iodide (Et_2O, 25 °C) gave the single alcohol (**9**) in 70% yield (stereochemistry undetermined). Since attempts at direct deoxygenation of (**9**) resulted in dehydration or led to the formation of an epimeric mixture, the conversion of (**9**) into (**12**) with the C(8) methyl group *anti* was achieved as follows. Dehydration of (**9**) (thionyl chloride, pyridine, 0 °C) afforded the olefin (**10**) in 78% yield. Buffered epoxidation of (**10**) (*m*-CPBA, Na_2HPO_4, CH_2Cl_2, 0 °C)‡ followed by treatment with boron trifluoride–diethyl ether (CH_2Cl_2, 0 °C) gave the ketone (**11**) in 52% yield. Wolff–Kishner reduction of (**11**) (N_2H_4, K_2CO_3, diethylene glycol) and subsequent deprotection (H_2SO_4, aqueous acetone) furnished (**12**) in 67% yield. The spectral data of (**12**) (i.r., mass, and 360 MHz ^1H n.m.r.) were identical with those of an authentic sample. Since (**12**) could be efficiently converted into (±)-modhephene (**1**) in two steps,[2a,b,e] the formal total synthesis of (±)-(**1**) was thus completed.

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‡ The stereochemistry of the epoxide is assumed to be *anti* in view of the stereoselectivity in a related epoxidation (ref. 2c).

References

1 L. H. Zalkow, R. N. Harris, III, and D. Van Derveer, *J. Chem. Soc., Chem. Commun.*, 1978, 420.
2 (a) A. B. Smith, III, and P. J. Jerris, *J. Am. Chem. Soc.*, 1981, **103**, 194; (b) M. Karpf and A. S. Dreiding, *Tetrahedron Lett.*, 1980, **21**, 4569; (c) H. Schostarez and L. A. Paquette, *J. Am. Chem. Soc.*, 1981, **103**, 722; (d) W. Oppolzer and F. Marazza, *Helv. Chim. Acta*, 1981, **64**, 1575; (e) W. Oppolzer and K. Bättig, *ibid.*, p. 2489; (f) P. A. Wender and G. B. Dreyer, *J. Am. Chem. Soc.*, 1982, **104**, 5805; (g) J. Wrobel, K. Takahashi, V. Honkan, G. Lannoye, J. M. Cook, and S. H. Bertz, *J. Org. Chem.*, 1983, **48**, 139.
3 M-L. Leriverend and P. Leriverend, *Chem. Ber.*, 1976, **109**, 3492; B. M. Trost and L. H. Lantimer, *J. Org. Chem.*, 1978, **43**, 1031; D. R. Morton, Jr., and F. C. Brokaw, *ibid.*, 1979, **44**, 2880; E. Wenkert and T. S. Arrhenius, *J. Am. Chem. Soc.*, 1983, **105**, 2030.
4 T. Tsunoda, M. Suzuki, and R. Noyori, *Tetrahedron Lett.*, 1980, **21**, 1357.
5 B. Rickborn and R. M. Gerkin, *J. Am. Chem. Soc.*, 1971, **93**, 1693.
6 C. D. Gutsche and D. Redmore, 'Carbocyclic Ring Expansion Reactions,' Academic Press, New York, 1968; S. Knapp, A. F. Trope, M. S. Theodore, N. Hirata, and J. J. Barchi, *J. Org. Chem.*, 1984, **49**, 608, and references cited therein.