Alternative Synthetic Route to the Cembrene Skeleton

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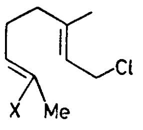
Summary The cembrene derivative (VI; Z = SO_2Ph) has been prepared by coupling of the geranyl units (I) and (II) to give the seco-cembrene derivatives (IIIa) or (IIIb), followed by reduction (IIIa) or hydrolysis (IIIb), conversion into the bromide, (V; Y = Br), and ring closure with lithium di-isopropylamide.

SYNTHESIS of the unique carbon skeleton of cembrenoids, a novel family of diterpenes, has attracted much attention.[1] We have recently developed a route for the construction of the cembrene skeleton starting from geranylgeranic acid chloride and demonstrated the synthetic scope of our methods.[2] In view of the recent discovery of various types of highly oxygenated naturally occurring cembrenoids,[3] we sought an alternative route which enables functional groups to be introduced at specific positions in the cembrene skeleton, and we now describe our results.

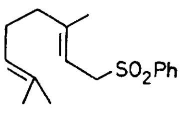
Our new method consists of the coupling of two geranyl units and subsequent ring formation of the resulting seco-cembrene bearing appropriate functional groups. The regiospecific coupling of the two geranyl units was achieved by the reaction of (Ia)† with 1·1 mol equiv. of geranyl phenyl sulphone (II) under Friedel–Crafts conditions [$SnCl_4$ (1 mol equiv.) in CH_2Cl_2; −94 °C; 3 h]. The resultant mixture was purified with column chromatography‡ on silica, to give (IIIa) in 44% yield. Similarly, (IIIb) was obtained in 28% yield from the corresponding acetate (Ib)§ at −76 °C by similar treatment; ^1H n.m.r. δ ($CDCl_3$): (IIIa) 1·53 (s, 2 × CClMe), 3·64 (s, CO_2Me), 3·66 (2H, d, J 7·0 Hz, 1-CH_2), 5·10 br (2H, t, J 7·0 Hz, 2- and 8-H), 6·60 (1H, m, 12-H) and 7·3—7·9 (SO_2Ph); (IIIb), 1·54 (2 × CClMe), 1·98 (OAc), and 4·35 (CH_2OAc).



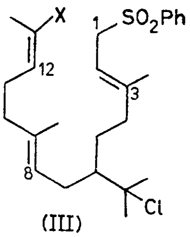
(I)

a; X = CO_2Me

b; X = CH_2OAc



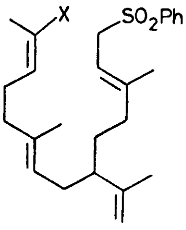
(II)



(III)

a; X = CO_2Me

b; X = CH_2OAc

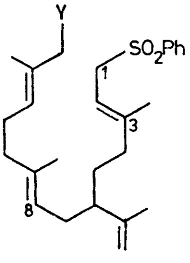


(IV)

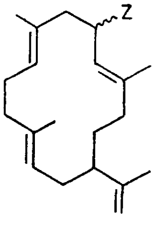
a; X = CO_2Me

b; X = CH_2OAc

c; X = CH_2OH



(V)



(VI)

To investigate appropriate conditions for ring-forming reactions of (IIIa) or (IIIb) leading to the cembrene skeleton, (±)-neocembrene (VI, Z=H), a termite trail pheromone,[4] was selected as a model target molecule. Dehydrochlorination of (IIIa) or (IIIb) with LiBr–Li_2CO_3 in dimethylformamide at 100 °C for 36 h gave a 1 : 1 mixture of (IVa) or (IVb), respectively, and the isomeric isopropylidene derivative in 80% yield. However, (IVa) and (IVb) were the exclusive products (*ca.* 80% yield after chromatography on SiO_2) when (IIIa) and (IIIb), respectively, in ether were sprayed on a Kieselgel plate and kept at room temperature for 4 days. Compound (IVa) was reduced with $LiAlH_4$ at −20 °C to give the allyl alcohol (IVc), which was also obtained quantitatively from (IVb) by mild hydrolysis with methanolic KOH at 0 °C; ^1H n.m.r. δ ($CDCl_3$): (IVa), 4·63 and 4·70 ($C{=}CH_2$); (IVb), 1·97 (OAc), 4·35 (CH_2OAc), and 4·63 and 4·70 ($C{=}CH_2$). The alcohol (IVc) was converted into the corresponding allyl bromide (V, Y = Br) by reaction with Ph_3P–CBr_4 (1·3 mol. equiv.) in MeCN at room temperature for 30 min. The cembrene derivative (VI, Z = SO_2Ph) was obtained in 56% yield when the freshly prepared allyl bromide (V, Y = Br) was treated with 1 mol. equiv. lithium di-isopropylamide[5] in anhydrous tetrahydrofuran at −78 °C. It is noteworthy that the corresponding allyl chloride (V, Y = Cl) remains unchanged under the same conditions. Although t.l.c. of the resulting product (VI, Z = SO_2Ph) shows only one spot under several conditions, it was shown to be a 1 : 1 mixture with respect to the phenylsulphonyl and isopropenyl groups by its ^1H n.m.r. spectrum, which showed the 3-Me signals at δ 1·10 (d, J 1·5 Hz) and 1·17 (d, J 1·5 Hz), in a ratio of *ca.* 1 : 1. The phenylsulphonyl group was reductively removed with Li in $EtNH_2$ (−78 °C; 5 h), giving a hydrocarbon in 69% yield which was identical with (±)-neocembrene.

Application of the present method to the synthesis of oxygenated cembrenoids is now in progress.[6]

(*Received*, 13*th December* 1977; *Com.* 1261.)

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† (Ia) was prepared from the acetate of 7-formyl-3-methylocta-2,6-dien-1-ol (I, OAc instead of Cl, X = CHO) by oxidation (E. J. Corey, N. W. Gilman, and B. E. Ganem, *J. Amer. Chem. Soc.*, 1968, **90**, 5616) of the formyl group to the methyl ester followed by selective hydrolysis of the acetate (KOH–MeOH; −20 °C; 1 h) followed by conversion of the resulting hydroxy-group into chloride [PPh_3 (1·3 mol. equiv.)–CCl_4; reflux; 1 h].

‡ Unless stated otherwise, SiO_2 column chromatography was carried out with n-hexane–AcOEt in a ratio of 4 : 1 to 6 : 1 as eluant.

§ (Ib) was prepared from tetrahydropyranyl (THP) ether of 7-formyl-3-methylocta-2,6-dien-1-ol (I, OTHP instead of Cl, X = CHO) (K. Mori, M. Ohki, and M. Matsui, *Tetrahedron*, 1974, **30**, 715) by treatment with $NaBH_4$ (MeOH; 0 °C), Ac_2O in pyridine (room temp.; 5 h), *p*-$MeC_6H_4SO_3H$ in MeOH [0 °C; 3 h (selective hydrolysis of the tetrahydropyranyl ether)], and finally with PPh_3–CCl_4 (reflux; 1 h).

[1] (a) W. G. Dauben, G. H. Beasley, M. D. Broadhurst, B. Muller, D. J. Peppard, P. Pesnelle, and C. Suter, *J. Amer. Chem. Soc.*, 1975, **97**, 4973; (b) M. Kodama, Y. Matsuki, and S. Ito, *Tetrahedron Letters*, 1975, 3065; (c) L. Crombie, G. Kneen, and G. Pattenden, *J.C.S. Chem. Comm.*, 1976, 66.

[2] T. Kato, T. Kobayashi, and Y. Kitahara, *Tetrahedron Letters*, **1975**, 3299; (b) Y. Kitahara, T. Kato, T. Kobayashi, and B. P. Moore, *Chemistry Letters*, 1976, 219; T. Kato, C. C. Yen, T. Kobayashi, and Y. Kitahara, *ibid.*, p. 1191; T. Kato, M. Suzuki, M. Takahashi, and Y. Kitahara, *ibid.*, 1977, 465; T. Kato, C. C. Yen, T. Uyehara, and Y. Kitahara, *ibid.*, p. 565; T. Kato, M. Suzuki, Y. Nakazima, K. Shimizu, and Y. Kitahara, *ibid.*, p. 705; T. Kato, C. Kabuto, K. H. Kim, H. Takayanagi, T. Uyehara, and Y. Kitahara, *ibid.*, p. 827.

[3] For an example, see: Y. Kashman, E. Zadock, and I. Neeman, *Tetrahedron*, 1974, **30**, 3615.

[4] A. J. Birch, W. V. Brown, J. E. T. Corrie, and B. P. Moore, *J.C.S. Perkin I*, 1972, 2653.

[5] For the use of allylic sulphoxide or sulphide anions in the construction of the cembrene carbon skeleton, see ref. 1b and also M. Kodama, K. Shimada, and S. Ito, *Tetrahedron Letters*, 1977, 2763.

[6] T. Kato, H. Takayanagi, T. Suzuki, and T. Uyehara, *Tetrahedron Letters*, **1978**, in the press.