Methylenecyclopentane Annulation: A Synthesis of the Sesquiterpenoid (±)-Pentalenene

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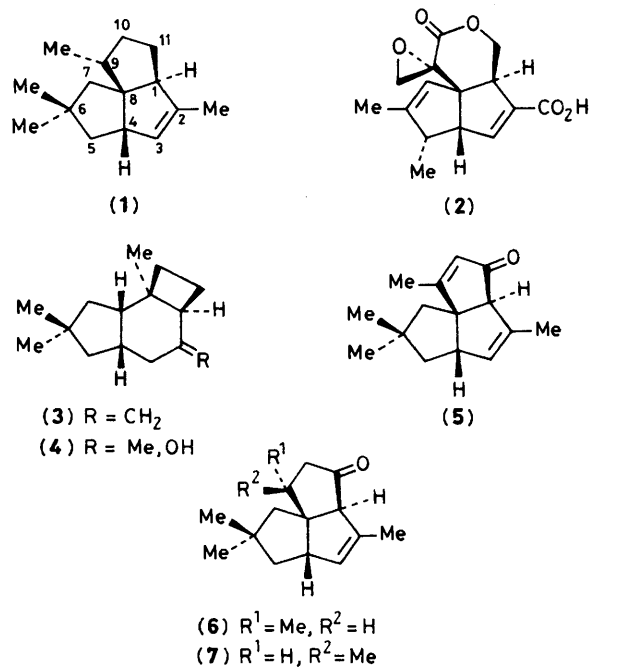
Transformation of the readily available keto acetal (**10**) into the novel sesquiterpenoid (±)-pentalenene (**1**) is accomplished *via* a 12-step synthetic sequence, the key conversion [(**13**) into (**15**)] of which involves a new, recently developed methylenecyclopentane annulation process.

The structurally interesting natural product (+)-pentalenene (**1**), isolated from *Streptomyces griseochromogenes*,[1] represents the parent hydrocarbon of the pentalenolactone family of sesquiterpenoid antibiotics. Indeed, (**1**) has been shown[2] to be a biosynthetic precursor of pentalenolactone (**2**) and, since the absolute configuration of the latter substance has been established,[3] (+)-pentalenene is (1*S*,4*S*,8*R*,9*R*)-2,6,6,9-tetramethyltricyclo[6.3.0.0^{4,8}]undec-2-ene (**1**).

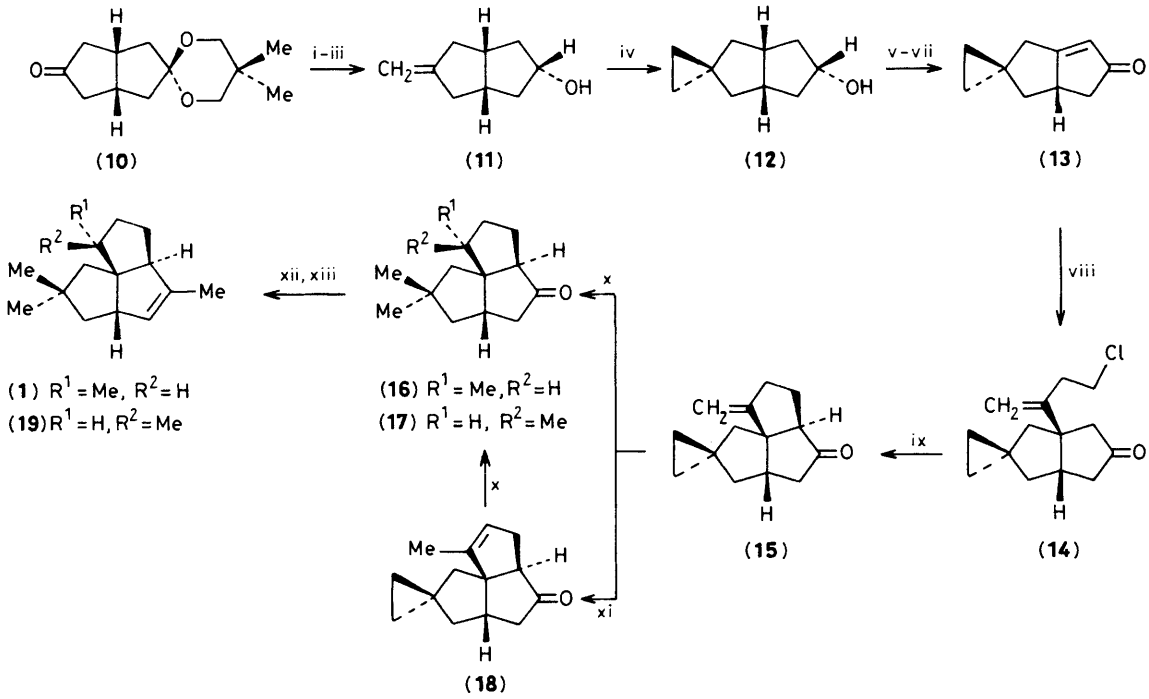
Two previous syntheses of (±)-(**1**) have been reported.[4,5] In the first of these,[4] (±)-(**1**) was obtained as a minor product from the acid-catalysed rearrangement of the synthetic alkene (**3**) or the corresponding tertiary alcohols (**4**). From a stereochemical point of view, the important step of the more recent synthesis[5] involved reduction of the enone (**5**) with $(Ph_3P)_3RhCl$–Et_3SiH. This process provided the two epimers (**6**) and (**7**) in a ratio of 1 : 2.24 and thus, after Wolff–Kishner reduction of this mixture, (±)-pentalenene (**1**) was obtained as a minor product.

Recently,[6] we described a new methylenecyclopentane annulation method based on the generalized conversion shown in equation (1). It appeared likely that this process could play a key role in a short synthesis of (±)-pentalenene (**1**). Explicitly, annulation of the bicyclic enone (**8**) would be expected to proceed in the desired stereochemical sense and, if successful, would provide (**9**) [see equation (2)]. Furthermore, it seemed likely that conversion of the latter substance into (±)-(**1**) would be straightforward. We report herein a total synthesis of (±)-(**1**) which is based on this plan.

Conversion (see Scheme 1) of the crystalline (m.p. 48 °C) keto acetal (**10**)† into the olefinic alcohol (**11**) (65% overall) was achieved using standard reactions. Treatment of (**11**) with



† All compounds reported herein exhibited spectra consistent with assigned structures and gave satisfactory molecular mass determinations (high resolution mass spectrometry). Compound (**10**) was prepared from the corresponding diketone (G. Kubiak, J. M. Cook, and U. Weiss, *J. Org. Chem.*, 1984, **49**, 561, and references cited therein). We are very grateful to Professor Cook for providing us with a detailed procedure for preparing the diketone and to Mr. Neil Moss for a generous supply of (**10**).



Scheme 1. *Reagents and conditions:* i, $Ph_3P{=}CH_2$, THF, room temp.; ii, 0.1% sulphuric acid, acetone, room temp.; iii, $LiAlH_4$, Et_2O, −78 °C; iv, CH_2I_2–Et_2Zn, dry air, $PhCH_3$, 50—60 °C; v, $C_5H_5N{\cdot}CrO_3{\cdot}HCl$, NaOAc, CH_2Cl_2; vi, Me_3SiI, Et_3N, CH_2Cl_2, −78 °C; vii, $Pd(OAc)_2$, MeCN, room temp.; viii, see text; ix, KH, THF, room temp.; x, H_2 (3 atm.), Pt, HOAc; xi, toluene-*p*-sulphonic acid, CH_2Cl_2, room temp.; xii, MeLi, Et_2O, −78 °C; xiii, toluene-*p*-sulphonic acid, C_6H_6, reflux.

CH_2I_2–Et_2Zn[7] provided, in 81% yield,‡ the cyclopropyl compound (**12**), which was oxidised to the corresponding ketone. Conversion of this material into the corresponding enol trimethylsilyl ether, followed by oxidation of the latter substance with $Pd(OAc)_2$ in acetonitrile,[8] gave the enone (**13**) [63% from (**12**)].

To a cold (−78 °C) solution of 4-chloro-2-trimethylstannylbut-1-ene[9] in tetrahydrofuran (THF) was added, successively, MeLi (1.1 equiv.), anhydrous $MgBr_2$ (1.2 equiv.), $CuBr{\cdot}Me_2S$ (0.3 equiv.), and the enone (**13**) (0.84 equiv.). After the resultant solution had been stirred at −78 °C for 1.5 h, it was treated with saturated aqueous ammonium chloride. The product (**14**) (83%) was subjected to intramolecular alkylation, providing the tetracylic ketone (**15**) in 80% yield.

Treatment of compound (**15**) with hydrogen in the presence of platinum effected both hydrogenolysis of the cyclopropane ring and hydrogenation of the alkene double bond. The product, formed in 96% yield, consisted of a mixture of the tricyclic ketones (**16**) and (**17**), in a ratio of 42 : 58. Attempts to increase the relative amount of the desired epimer (**16**) by using other hydrogenation conditions proved to be fruitless. Interestingly, hydrogenation of the endocyclic alkene (**18**) [obtained by acid-catalysed isomerisation of (**15**)] produced nearly entirely the β-methyl derivative (**17**) [(**16**) : (**17**) = *ca.* 5 : 95]. Thus, in terms of using this route for the synthesis of (±)-pentalenene (**1**), it is clear that control of the stereochemistry at C-9 was, as in the Paquette synthesis,[5] somewhat problematic.

Treatment of the 42 : 58 mixture of (**16**) and (**17**) with MeLi in diethyl ether, dehydration of the resultant tertiary alcohols, and chromatographic separation (silver nitrate impregnated silica gel) of the mixture of alkenes thus formed provided (±)-pentalenene (**1**) [32%; ^1H n.m.r. ($CDCl_3$, 270 MHz): δ 0.91 (d, 3H, *J* 7 Hz), 0.99 (s, 6H), 1.63 (s, 3H), 2.56 (br. d, 1H, *J* 9 Hz), 2.66 (m, 1H), 5.19 (br. s, 1H)]§ and (±)-9-*epi*-pentalenene (**19**) [33%; ^1H n.m.r. ($CDCl_3$, 270 MHz): δ 0.94 (d, 3H, *J* 7Hz), 0.98 (s, 6H), 1.61 (br. s, 3H), 2.64 (br. d, 1H, *J* 9Hz), 2.90 (m, 1H), 5.21 (s, 1H)]. When the 5 : 95 mixture of (**16**) and (**17**) was subjected to an identical sequence of operations (±)-(**19**) was produced in 68% yield.

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‡ Similar treatment of the olefinic acetal or ketone [derived from steps i and ii, Scheme 1] provided very poor yields of the corresponding cyclopropane derivatives.

§ This material exhibited spectra identical with those of the synthetic (±)-pentalenene prepared by Paquette and Annis (ref. 5). We are very grateful to Professor Paquette for his assistance in making this comparison possible.