A Simple Synthesis of a Basic Skeleton of Isoatisirene

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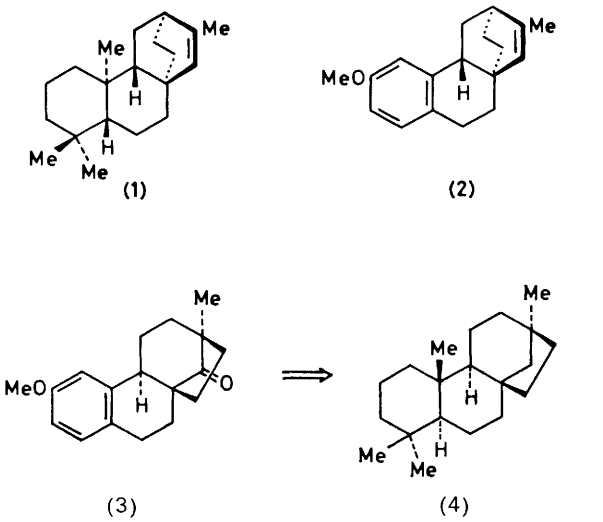
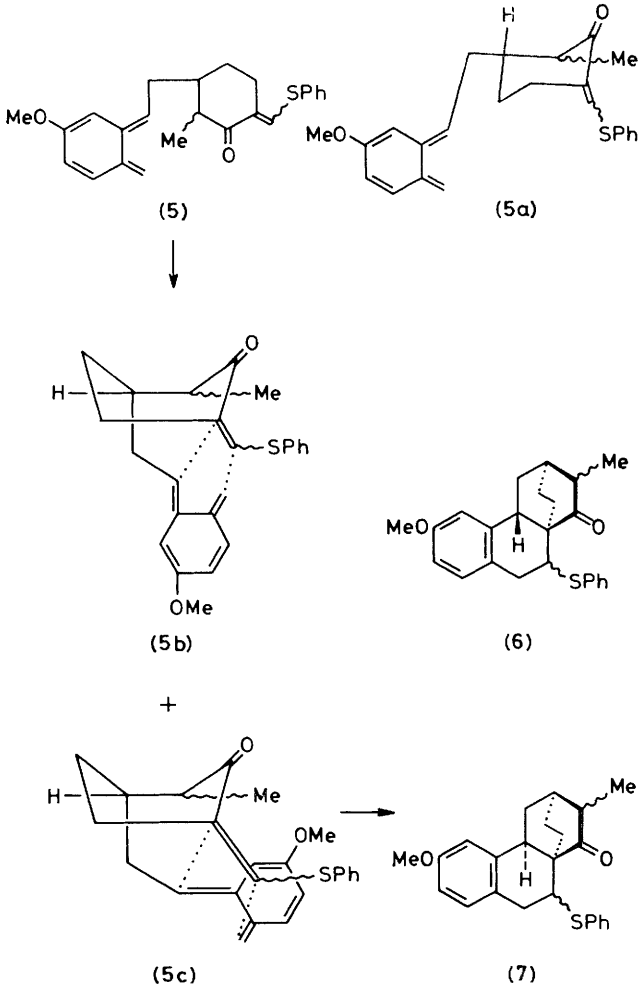
The 3-methoxy-7-methyl-4b,5,6,8a,9,10-hexahydro-6,8a-ethanophenanthrenes (**2**) and (**26**), potential intermediates for the synthesis of isoatisirene (**1**), have been synthesised by using an intramolecular cycloaddition reaction of the *o*-quinodimethan (**5**), which was itself derived thermally from 5-methoxy-1-(2-methyl-3-oxo-4-phenylthiomethylenecyclohexylmethyl)-1,2-dihydrocyclobutabenzene (**17**).

Since the bridged bicyclo[2.2.2]octane constitutes an integral part of the structure of a large class of diterpenoids and diterpene alkaloids,[1,2] many efforts have been made to construct this unique ring system.[3–8] In connection with our interest[9–11] in the development of synthetic cycloaddition reactions of *o*-quinodimethans based on dihydrocyclobutabenzenes, we have investigated a facile route to the potential intermediate (**2**) for the synthesis of isoatisirene (**1**), since we had already found an efficient method for the stereoselective conversion of (**3**) into dihydrohibaene (**4**),[12] which might be applied to the transformation of (**2**) into (**1**) (Scheme 1).

The most challenging feature of this study is the cyclo-

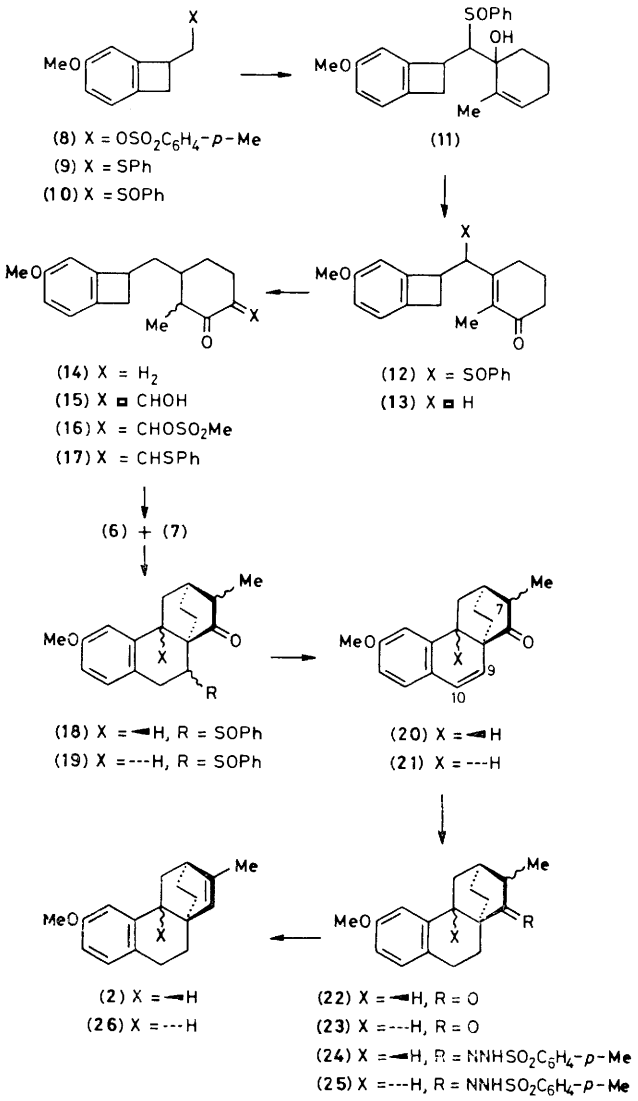


Scheme 1



Scheme 2

addition to the *o*-quinodimethan (**5**) through a conformationally unfavoured intermediate in either the *exo*- (**5b**) or *endo*- (**5c**) form, having a boat-like conformation of the cyclohexane ring, leading to (**6**) and (**7**) respectively; rather than the conformationally favoured intermediate (**5a**) which has a chair-like conformation and in which the diene and dienophile are too far apart to interact with each other (Scheme 2).



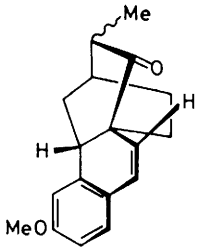
Scheme 3

The synthesis of the cyclobutabenzene (**17**), a source for generating the *o*-quinodimethan (**5**), was straightforward and as follows (Scheme 3). The sulphoxide (**10**), prepared in 86% overall yield from the *p*-toluenesulphonate (**8**)[12] *via* the sulphide (**9**) by successive treatment with sodium thiophenolate in dimethylformamide followed by *m*-chloroperbenzoic acid in CH_2Cl_2, was condensed with 2-methylcyclohex-2-enone[13] in tetrahydrofuran (THF) in the presence of lithium di-isopropylamide to give the compound (**11**) [*m/z* 382 (M^+)] in 38% yield. The enone (**13**) [ν_{max} ($CHCl_3$) 1650 cm^{-1}, *m/z* 256 (M^+)], obtained in 81% overall yield by treating (**11**) with pyridinium chlorochromate in CH_2Cl_2 and the resulting product (**12**) with zinc in AcOH, was hydrogenated in MeOH in the presence of palladium–carbon under an atmosphere of hydrogen to afford the cyclohexanone (**14**) [ν_{max} ($CHCl_3$) 1700 cm^{-1}, *m/z* 258 (M^+)] in 70% yield. Introduction of the dienophile moiety into the cyclohexanone (**14**) was carried out effectively in 60% overall yield *via* the hydroxymethylene derivative (**15**) and the methanesulphonate (**16**) by successive treatment of (**14**) with ethyl formate in benzene in the presence of sodium hydride and then the product (**15**) with mesyl chloride, followed by thiophenol in pyridine furnishing the thiomethylene derivative (**17**) [ν_{max} ($CHCl_3$) 1660 cm^{-1},

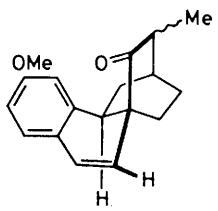
δ(CCl_4) 1.20 (3H, d, *J* 8 Hz, Me), 3.66 (3H, s, OMe), 6.36—6.90 (3H, m, ArH), and 7.30 (6H, br. s, >C=CH–S–ArH), *m/z* 378 (M^+)].

Heating (**17**) in *o*-dichlorobenzene at 200 °C for 10 h in a current of nitrogen afforded the tetracyclic compounds (**6**) and (**7**) as an inseparable stereoisomeric mixture [ν_{max} ($CHCl_3$) 1705 cm^{-1}, *m/z* 378 (M^+)] in 95% yield. The stereochemistry at the ring junction of (**6**) and (**7**) was easily deduced by converting (**6**) and (**7**) into the styrenes (**20**) and (**21**) and then into (**2**) and (**26**), respectively. Thus, oxidation of (**6**) and (**7**) with *m*-chloroperbenzoic acid and then elimination of the phenylsulphinyl group from the resulting sulphoxides (**18**) and (**19**) gave the styrenes (**20**) [ν_{max} ($CHCl_3$) 1705 cm^{-1}, *m/z* 268 (M^+)] and (**21**) [ν_{max} ($CHCl_3$) 1705 cm^{-1}, *m/z* 268 (M^+)] in 14% and 37% overall yields, respectively, after purification by chromatography on silica gel [n-hexane–benzene (4:1)]. The n.m.r. spectra of (**20**) and (**21**) could be diagnostic for the stereochemical assignment; namely, an olefinic proton at C-9 of (**20**), suffering from the deshielding effect of the carbonyl group, was observed at δ 6.08 as a doublet having *J* 10 Hz. For (**21**), the corresponding olefinic proton would not be expected to be deshielded by the carbonyl group and the resonances were observed at normal positions, δ 5.35 and 5.38, as doublets having *J* 10 Hz.†

Finally, the olefinic ketones (**20**) and (**21**) were hydrogenated in methanol in the presence of palladium–carbon under an atmosphere of hydrogen to give the ketones (**22**) and (**23**) in 45% and 59% yields, respectively, the tosylhydrazides (**24**) and (**25**) of which were subjected to the Shapiro reaction using n-butyl-lithium in THF furnishing the initial target compounds (**2**) [δ ($CDCl_3$) 1.78 (3H, d, *J* 1.0 Hz, Me), 3.65 (3H, s, OMe), 5.6 (1H, br. s, olefinic H), and 6.5—7.0 (3H, m, ArH), *m/z* 254 (M^+)] and (**26**) [δ ($CDCl_3$) 1.70 (3H, d, *J* 1.0 Hz, Me), 3.76 (3H, s, OMe), 5.60 (1H, br. s, olefinic H), and 6.42—7.0 (3H, m, ArH), *m/z* 254 (M^+)].



(**20**)



(**21**)

† Since the methyl group at C-7 of (**20**) was observed at δ 1.15 and 1.26 as doublets having *J* 6 Hz and that of (**21**) at δ 0.98 and 1.10 having *J* 8 Hz, respectively, the compounds (**20**) and (**21**) were found to be stereoisomeric mixtures at C-7. This was confirmed by converting (**20**) and (**21**) into stereoisomerically pure (**2**) and (**26**) respectively.

Thus we report a simple and novel route for the synthesis of the potential intermediate (**2**) for preparing isoatisirene (**1**), and show that the stereochemical course of the cycloaddition reaction of the *o*-quinodimethan (**5**) is *via* (**5b**) and (**5c**) by overcoming the conformational disadvantage.

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