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THE TOTAL SYNTHESIS OF 10-(R,S)-C_{30} BOTRYOCOCCENE AND BOTRYOCOCCANE AND A NEW SYNTHESIS OF A GENERAL INTERMEDIATE TO THE BOTRYOCOCCENE FAMILY.

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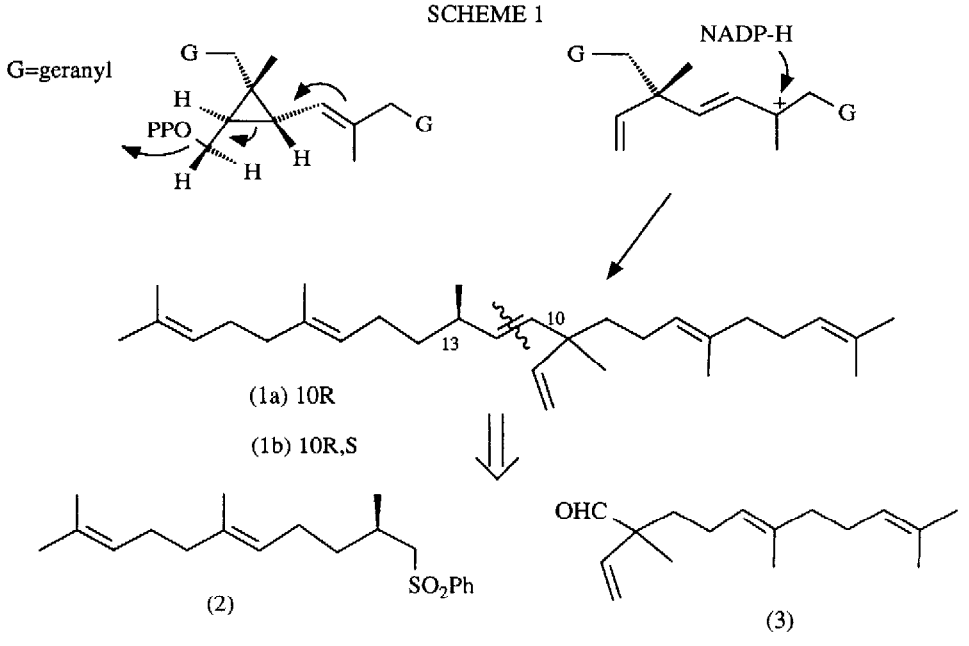
Summary: The first synthesis of a C-30 botryococcene has been achieved by using a modified Julia reaction for the key coupling of fragments (2) and (3). The same strategy has been used in a new synthesis of a known synthetic precursor to the entire botryococcene family.

The C_{30}-C_{37} botryococcenes, for example the parent C_{30} compound (**1a**), comprise an unusual and potentially useful family of hydrocarbon natural products found to date only in the green alga *Botryococcus braunii*[1]. Interest in them stems from their biosynthesis, whereby they are thought to arise from an alternative breakdown of presqualene[2] (SCHEME 1), and from the potential value of the alga as a fuel source since

SCHEME 1



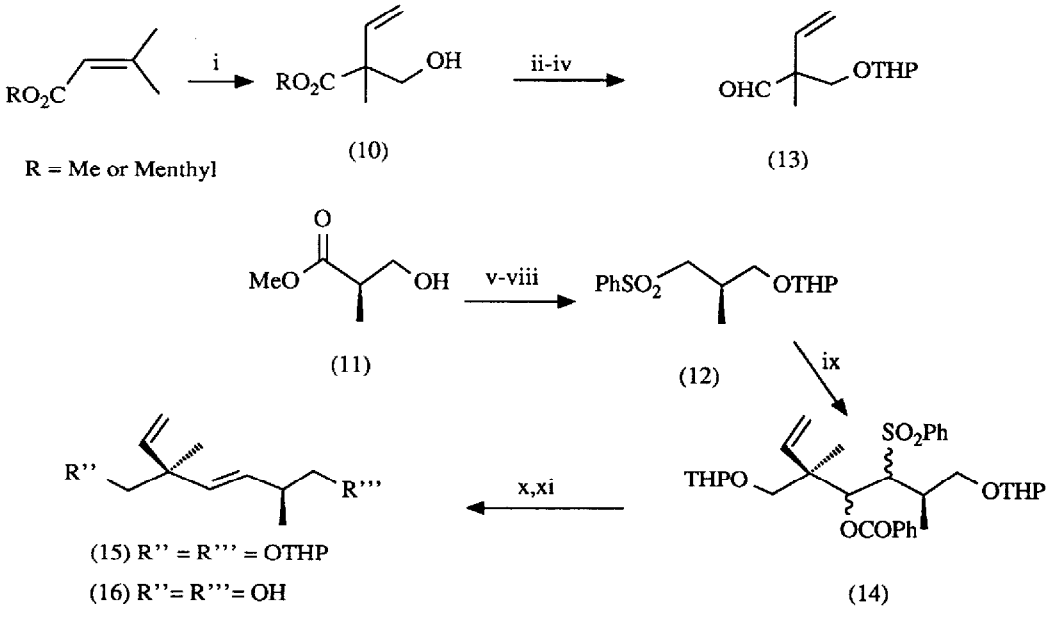
they can occur in remarkably high concentrations[3]. Furthermore, their saturated analogues, botryococcanes, show promise as biological markers in oil exploration studies[4]. Only one synthetic study of them has been reported however[5], which is surprising since their lack of reactive functionality poses an interesting problem for their preparation.

The key to the preparation of the botryococcenes lies in the construction of the C-13 methyl group, the C-11 to C-12 E-alkene and the C-10 quaternary centre, which are common to all members of the family. This

present paper reports on the use of a new approach to them which has resulted in the first total synthesis of 10(R,S)-C_{30} botryococcene (**1b**). Additionally the new route has been shown to be of use in a novel preparation of a known general intermediate to the botryococcenes which incorporates all of the key structural features

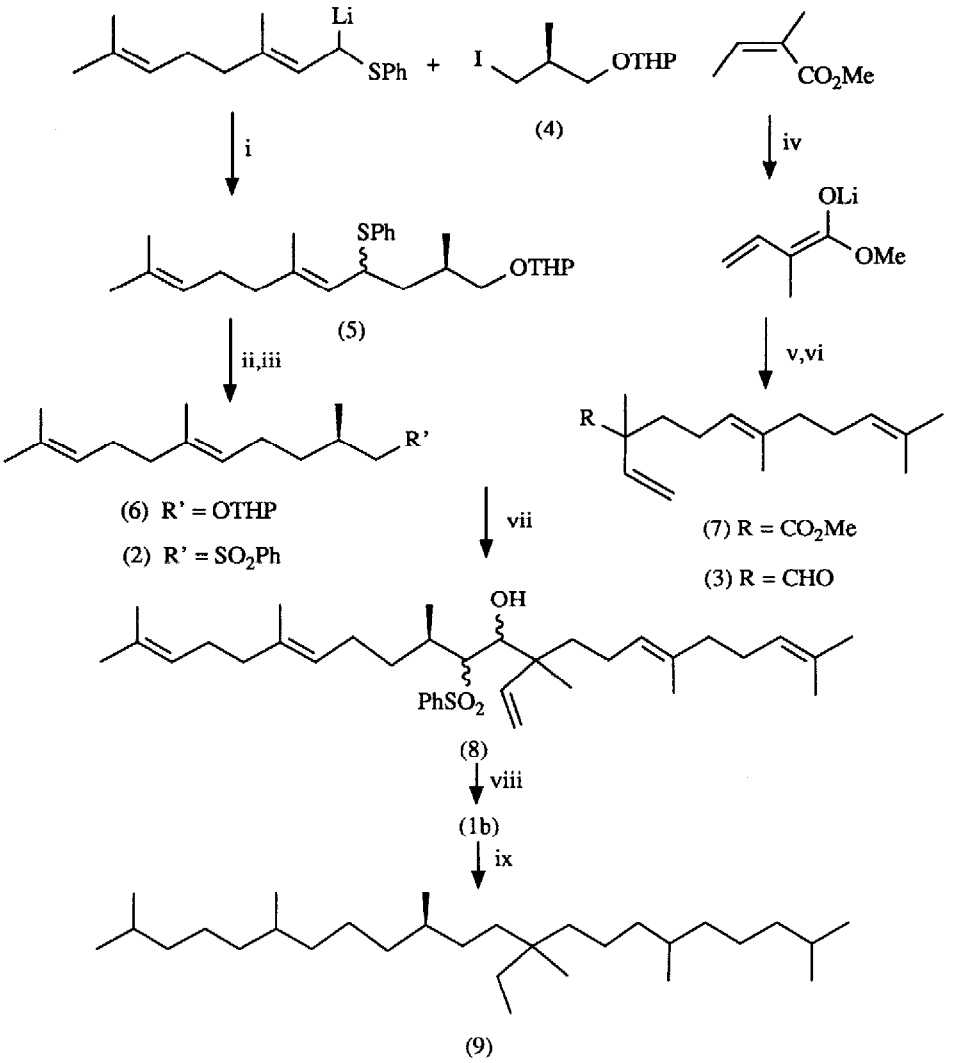
We employed a modified Julia coupling[6] for double bond formation (SCHEME 1), and the alkylation of the dienolate anion of methyl tiglate to form the quaternary centre directly[7](SCHEME 2). The preparation of the sulphone (**2**) involved displacement of the iodide (**4**)[8] with the lithium anion of geranyl thiophenoxide to form the sulphide (**5**). Desulphurisation was best achieved using lithium in ethylamine to give the protected alcohol (**6**)[9] which was converted to the sulphone (**2**) in 24% overall yield from the iodide (**4**). The aldehyde (**3**) was obtained by reaction of the dienolate anion of methyl tiglate with homogeranyl iodide, followed by reduction of the ester and oxidation to aldehyde (**3**) in 54% overall yield. Coupling of the anion of the sulphone (**2**) with the aldehyde (**3**) gave the expected hydroxysulphone (**8**) which after benzoylation and reduction provided the 10 (R,S) C_{30} botryococcene (**1b**) with the required E double bond. One diastereoisomer of this synthetic material co-eluted[10] with C_{30} botryococcene isolated from the alga, confirming it as the correct product. Additionally, exhaustive hydrogenation of (**1b**) gave 10 (R,S) C_{30} botryococcane (**9**) as the only product (confirmed by mass spectrometry), showing that the only by-products produced in the synthesis are double bond isomers[11].

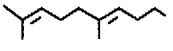
The only other synthesis[5] of a botryococcene (a C_{34}) utilised a central unit, containing the C-10 and C-13 centres common to all botryococcenes. It was of interest to see if our approach could be used in the preparation of the same unit. Thus the use of (-)-menthyl tiglate, instead of methyl tiglate, for the preparation of



i, LDA, THF, -78°, HCHO (g); ii, DHP/H^+; iii, $LiAlH_4$,THF, 76%; iv, PDC, 63%; v, DHP/H^+; vi, $LiAlH_4$; vii, TsCl-Py, NaI, acetone; viii, $PhSO_2Na$, DMF, 20°, 87%; ix, n-BuLi, THF,-78°, 20min-(13), -78°, 30 min; PhCOCl, -78° to 20°, 4h, 77%; x, Na(Hg), THF/MeOH, -15°, 55%; xi, TsOH, MeOH, 74%.

SCHEME 2



i, THF, HMPA, -78°C -RT, 3h (66%); ii, Li/NH_2Et, 0°C, 1h (80%); iii, H^+/TsCl-py/NaI, acetone/$PhSO_2Na$, DMF (45%); iv, LDA, THF, HMPA -78°C; v,  ,THF -78°C, 6h (77%); vi, $LiAlH_4$, THF/ PDC (54%); vii, BuLi, THF,(67%); viii BuLi, hexane -78°C/ PhCOCl/ Na(Hg) MeOH/THF -20°C (61%); ix Pd/C, H_2 (85%).

the quaternary centre gave two diastereoisomers (**10**), in approximately equal amounts, which are separable by chromatography. Conventional transformations then gave the aldehyde (**13**). The tertiary centre containing portion was prepared from (R)-methyl 3-hydroxy-2-methylpropionate (**11**) by protection with dihydropyran and reduction with lithium aluminium hydride to an alcohol which was converted into the sulphone (**12**). Julia type coupling of (**12**) with the aldehyde (**13**) afforded the vicinal benzyloxy-sulphone (**14**). Reduction with sodium gave exclusively (**15**) which was deprotected to give the alcohol (**16**), the key intermediate in the previous synthesis.

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7. All yields are based on isolated and fully characterised material and all new compounds gave satisfactory analytical and/or spectroscopic data.
8. Compound (**4**) was prepared from (S)-methyl 3-hydroxy-2-methylpropionate by standard methods. e.g. K.Mori, *Tetrahedron*, **1983**, 39, 3107.
9. The alcohol (**6**) was contaminated with 5% of double bond isomers which were not separated.
10. GC conditions: OV-1- WCOT capillary column (25 m x 0.30 mm; df-0.17 μm). Temperature programmed at 50^{o}-300^{o}C at 6^{o}C min^{-1}.
11. The final step of the Julia sequence produced minor double bond isomers (ca. 10%) of (**1b**).

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