

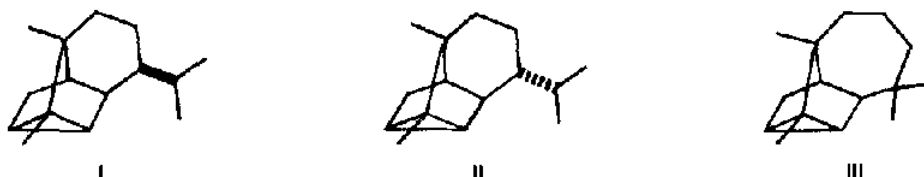
A NEW SYNTHETIC APPROACH TO CYCLOSATIVENE AND SIMILAR TETRACYCLIC SESQUITERPENES AND SYNTHESIS OF A TETRACYCLIC MONOTERPENE

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The tetracyclic sesquiterpenes cyclosativene I, its epimer cyclocopacamphene II and longicyclene III have been the subject of important synthetic work of several groups (1)



It is noteworthy that these three compounds have a common structural feature, namely the tricyclo(2,2,1,0²⁻⁶) heptane part, which is also present in α -santalene and its derivatives (2).

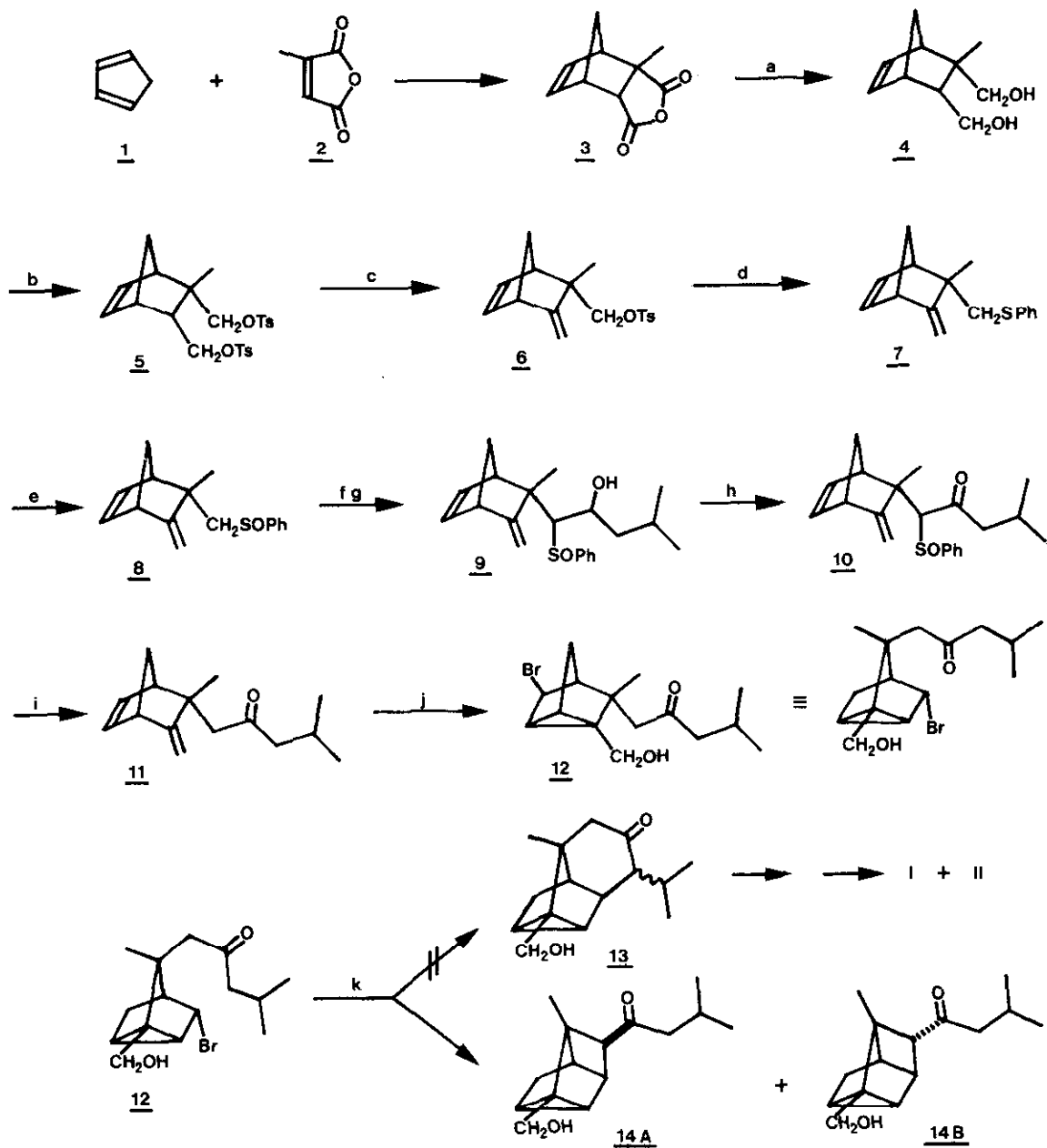
Previous work on allylic halogenation of enol acetates or aldehydes, done in our laboratory (3), has led to an elegant construction of this tricyclic structure which, in fact, arises from an electrophilic addition to a multiple bond with participation of a homoallylic one :



Thus, our work has been directed towards the preparation, by this synthetic route, of a synthon of type VIIIa or VIIIb that should permit, on principle, the edification of the fourth cycle.



We now wish to report the results of our synthetic approach to cyclosativene I, and possibly to its epimer II (12). The condensation of cyclopentadiene 1 with citraconic anhydride 2 led nearly quantitatively to the expected Diels-Alder adduct 3, whose reduction with



a) LiAlH₄, ether (yield 85%) ; b) TsCl, pyridine (81%) ; c) t-BuOK, DMSO (85%) ;
 d) PhSK, DMF (98%) ; e) MCPBA, CH₂Cl₂ (90%) ; f) n-BuLi, THF, -78°C ; g) (CH₃)₂CHCH₂CHO
 (93%) ; h) Collins reagent (85%) ; i) zinc dust, AcOH/EtOH, 2/3, (68%) ; j) NBS, DMSO,
 H₂O (87%) ; k) t-BuOK, t-BuOH (88%).

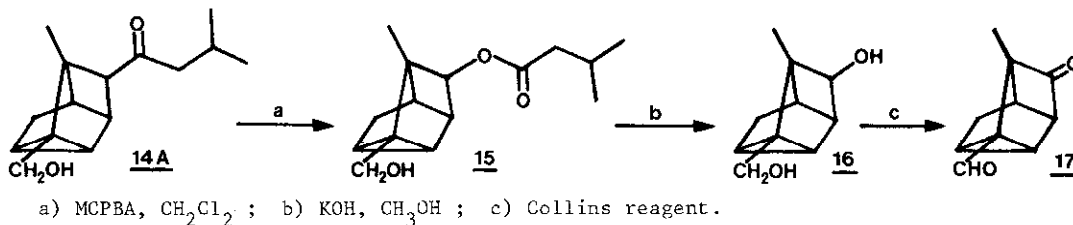
LiAlH_4 afforded diol 4 in 85% yield. Reaction of the subsequently derived ditosylate 5, obtained in 81% yield, with potassium t-butoxide in DMSO at room temperature gave the dienic tosylate 6 (85% yield).

It should be pointed out that this neopentyl-type tosylate 6 is almost inert towards nucleophiles, even without steric hindrance and weakly solvated by polar aprotic solvents with large dielectric constants (e.g. $\text{CN}^\ominus/\text{DMSO}$). In fact, only nucleophiles with a sulfur atom as attacking group are soft enough to induce substitution.

Thus, reaction of 6 with potassium thiophenate in DMF at 110°C led quantitatively to thioether 7, which was afterwards oxidized to sulfoxide 8 with m-chloroperbenzoic acid (MCPBA) in 90% yield (4). Treatment of sulfoxide 8 with n-butyllithium in THF at -78°C , followed by addition of isovaleraldehyde, afforded the β -hydroxy sulfoxide 9 in 93% yield. The latter was oxidized to β -keto sulfoxide 10 either with COLLINS reagent (5) or with pyridinium chlorochromate (6) (85% yield for both methods). Reductive cleavage of 10 to ketone 11 was achieved by reaction with zinc dust, in 68% yield (7). Use of aluminium amalgam (8) proved to be much less satisfactory.

The edification of the tricyclic skeleton was then obtained successfully by treatment of ketone 11 with NBS in aqueous DMSO, which afforded the bromoketone 12 in 87% yield.

At this point, we expected that the tetracyclic target skeleton could be built up by cyclisation of compound 12. However, treatment of 12 with potassium t-butoxide in t-butyl alcohol afforded, in 88% yield, a 7:3 mixture of epimeric tetracyclic keto-alcohols (9) to which structures 14A and 14B could be assigned on the basis of spectral data (250 MHz PMR, IR, MS) (10) and following chemical evidence :



The Baeyer-Villiger oxidation of epimer 14A followed by saponification of the resulting ester 15 and Collins oxidation of the obtained diol 16 yielded the keto-aldehyde 17 (IR : ν^{CCl_4} 1780, 1695 cm^{-1} ; PMR (60 MHz) : δ^{CCl_4} 3:1.39 (3H, s, $-\text{CH}_3$), 2.99 (1H, t, $J=2.5\text{Hz}$ $>\text{CH}-\text{CO}-$), 9.37 (1H, s, $-\text{CHO}$).

An examination of a molecular model, in fact, accounts for the cyclisation of 12 to a cyclobutane : geometric factors seem to favour the formation of a transition state leading to such a cycle rather than to a cyclohexane. Recently, G. STORK *et al* (11) noticed an analogous case during the study of cyclisation of epoxynitriles.

To our knowledge, the tetracyclic (2,2,1,1³⁻⁷, 0²⁻⁶) octane skeleton is a new one, and keto aldehyde 17 is the first example of a tetracyclic monoterpene.

The introduction of a suitable side-chain on synthon 8 followed by cyclisation to the six-membered fourth ring of the cyclooctatetraene skeleton is under investigation.

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- 9) Separable by chromatography on silica gel column using hexane/ethylacetate/pyridine (70/28.5/1.5) as eluent.
- 10) In particular, one notices, in the IR spectrum of 14A, the absence of an absorption corresponding to a free OH group, when it is present in that of 14B. This can be explained by the existence of a hydrogen bond between OH group and carbonyl group only geometricaly possible in the case of epimer 14A ; it is supported by 250 MHz PMR spectra : hydrogen bond, by blocking the CH₂OH group, strongly marks the non-equivalence of methylene protons whose chemical shift difference is 0.16 ppm for 14A and 0.07 ppm only for 14B.
- 11) G. STORK, J.F. COHEN - J. Amer. Chem. Soc. (1974), 96, 5270
- 12) Satisfactory analytical and spectral (60 MHz PMR, 250 MHz PMR for compounds 11, 12, 14A, and 14B, IR, MS) data were obtained for all new compounds.