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The use of monoterpenes to synthesize complex cyclic structures

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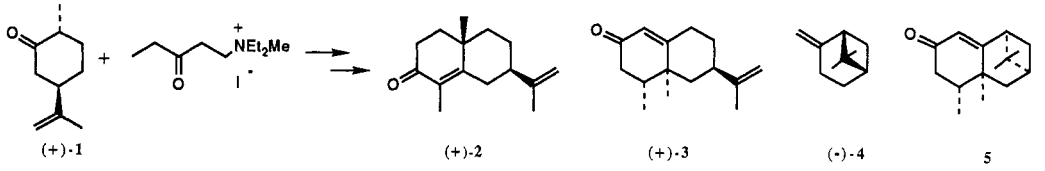
Abstract - The constraints to formation of an additional six-membered ring fused to the pinane or carane skeleton using the Robinson cyclization are discussed. Examples of the construction of five-membered rings to pinane are also given. The epoxidation of 10,10-dimethyl-*cis*-tricyclo[7.1.1.$0^{2,7}$]-undec-2-en-3-one led to a novel dimerization, possibly caused by steric constraints of the pinane skeleton. In the course of a Wagner-Meerwein rearrangement of another tricyclo[7.1.1.$0^{2,7}$]undecenone, the tetracyclo-[6.2.1.$0^{1,6}$.$0^{6,10}$] ring system was prepared.

An industrial problem using monoterpene hydrocarbons is how to upgrade them. The most common of these hydrocarbons are probably the pinenes, 3-carene, and (+)-limonene. Our work on these compounds involved the use of the Robinson annulation (ref. 1) to form an additional ring, and I mention a reaction leading to a tetracyclic structure.

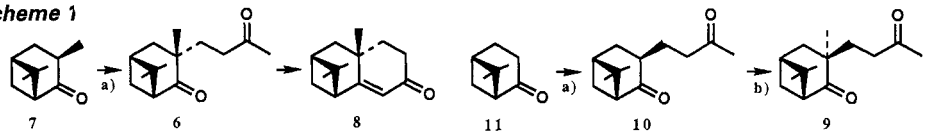
The earliest use of this annulation was to dihydrocarvone **(1)** by Robinson himself, when he obtained α-cyperone **(2)** (ref. 2). It was later clearly shown that (+)-**(1)** gave (+)-**(2)** (ref. 3). Recently, Elguero and Shimizu have developed various syntheses from annulations to menthone (ref. 4) and pulegone (ref. 5).



(+)-1 (+)-2 (+)-3 (-)-4 5

Twenty years ago we considered a synthesis of (+)-nootkatone **(3)** from the common (-)-β-pinene **(4)**. This route was also being examined by van der Gen (ref. 6), and Bessière (ref. 7). Van der Gen decided that the intermediate **(5)** could not be formed for steric reasons (although this stereochemistry does not correspond to that of natural nootkatone **(3)**). The French workers applied the Robinson reaction to the diketone **(6)** derived from *cis*-methylnopinone and cyclized this ketone satisfactorily to the tricyclic ketone **(8)**, but could not cyclize the epimeric diketone **(9)** (Scheme 1). This was the opposite of what was expected, and of what was predicted by van der Gen.

Scheme 1

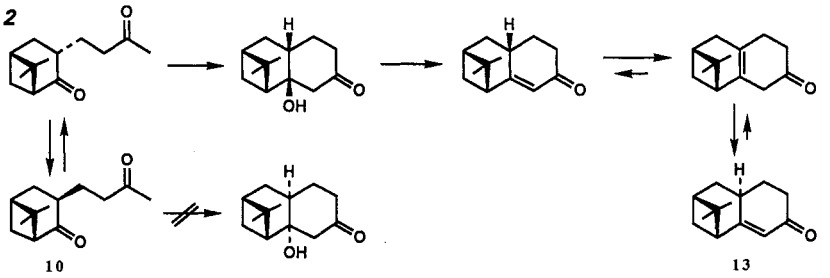


7 6 8 11 10 9

a) *via* enamine; b) Base/CH_3I;

Together with the French group, we repeated the preparation of the unsubstituted diketone **(10)** (made by the reaction of methyl vinyl ketone on the enamine of nopinone **(11)**). Using cyclizing conditions (base) for a limited time, we recovered some unchanged diketone, but

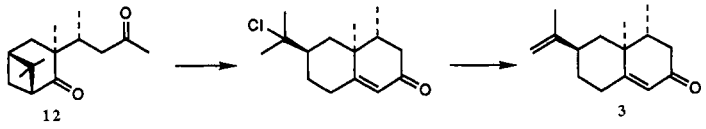
Scheme 2



10 13

while initially the diketone contained the *cis*- and *trans*-isomers, the recovered material was only *cis*. This corresponds to the result with the methyl-substituted compounds, but requires a further rearrangement because the final product has the thermodynamically more stable *cis*-ring junction. The whole system is in Scheme 2 (ref. 8).

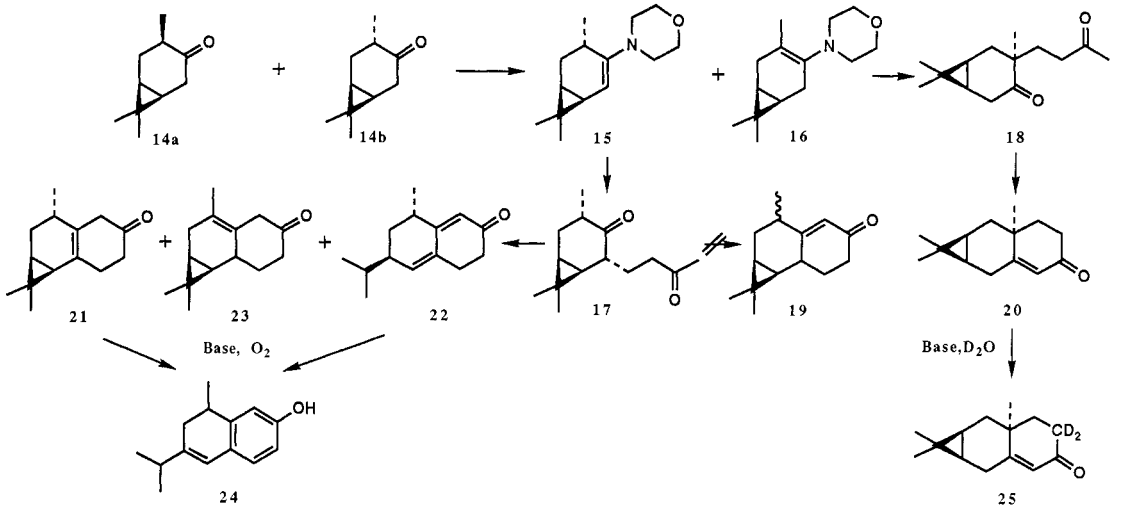
The nootkatone-from-pinene problem was solved (1980) by Yoshikoshi, who cyclized the diketone **(12)** with concomitant ring-opening by hydrogen chloride, thus avoiding the base-catalyzed cyclization (ref. 9). By now, we had been found that **(13)** was useful for perfumery, and it was named "Tricyclone". We therefore examined related compounds, to see whether they too might be of value.



12 3

Apart from adding methyl groups to **(13)** and doing simple chemistry on it, we considered another readily accessible starting material, caranone **(14)**. At first a mixture of *cis*- and *trans*-isomers was available commercially, but we later had to make our own caranone. By hydroboration-oxidation of 3-carene, we made the *cis*-isomer **(14a)**. There was no difference, because a single stereoisomer of the enamine **(15)** is formed, accompanied by some of the alternative enamine **(16)**. Conventional wisdom has it that the latter will not undergo Michael addition with methyl vinyl ketone because such additions cannot occur at the quaternary centre, and under the conditions of the addition, the two enamines could interconvert, so only the addition product **(17)** from **(15)** should be formed. Conventional wisdom is, however, wrong, and both diketones **(17** and **18)** are formed, which, on base-catalyzed cyclization should give two tricyclic compounds **(19** and **20)**. The carane system does not behave like the pinanes, and the major product was the unconjugated ketone **(21)**, accompanied by the conjugated ketone **(20)**, a compound already prepared by base-catalyzed addition of methyl vinyl ketone to caranone **(14)** (Scheme 3, ref. 10).

Scheme 3



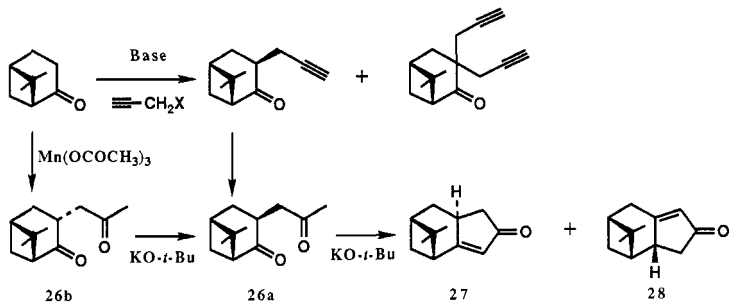
We identified the two other main products of the cyclization as the ring-opened **22**, and the unconjugated isomer **(23)** of **21**. The latter could never be obtained pure because of its tendency to isomerize to **21** and **22**, but after achieving about 75% purity, spectra of the pure substance were obtained by subtracting the spectra of the contaminating **21**. The methyl group is pseudo-axial, and one might think that mild basic treatment of these ketones would equilibrate this. Unfortunately when we heated **21** or **22** with 10% sodium hydroxide in methanol, we did not exclude air, and the only compound isolated was the phenol **(24)**. This implies that enolization occurs preferentially at the methylene group of **22** adjacent to the carbonyl group, so that the *cis*-orientation of the substituents in **22** would be unlikely. Base-catalyzed deuterium exchange of **20** shows that in this case, enolization is exclusively towards the methylene group adjacent to the carbonyl group, because only a dideuteriated compound **(25)** was isolated.

Preparation of a ring-contracted Tricyclone was carried out as shown in Scheme 4. We were unable to cyclize the diketones **(26a, 26b)** with sodium hydroxide in toluene (our preferred reagent for Tricyclone), but had to use the "academic" reagent potassium *tert*-butoxide. A mixture of two isomers **(27, 28)** was obtained, the desired product **(27)** predominating.

The aldol condensation product which must be an intermediate in the formation of Tricyclone

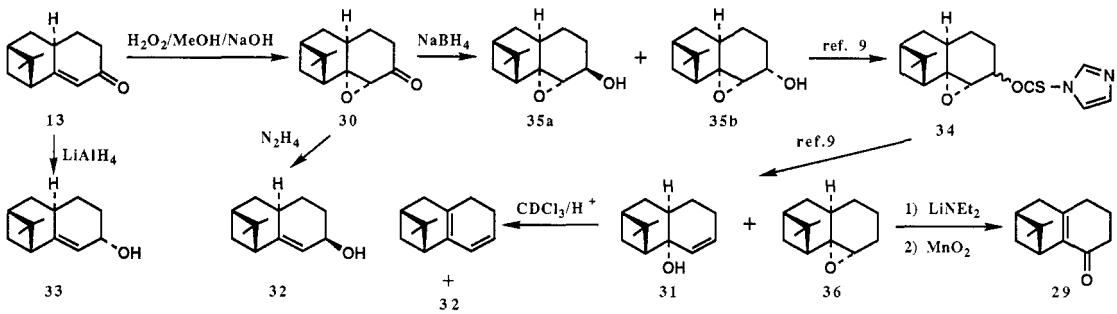
has a hydroxyl group at the bridgehead (Scheme 2), and we felt that one of the isomers could not be formed (ref. 8). We thought it might be instructive to prepare a compound with this hydroxyl group, and used the first step of a synthesis designed to make a Tricyclone isomer (**29**) to attempt this preparation. Base-catalyzed epoxidation of Tricyclone gave the epoxide (**30**). The stereochemistry is in no doubt, and is supported by ample NMR data. Treatment

Scheme 4



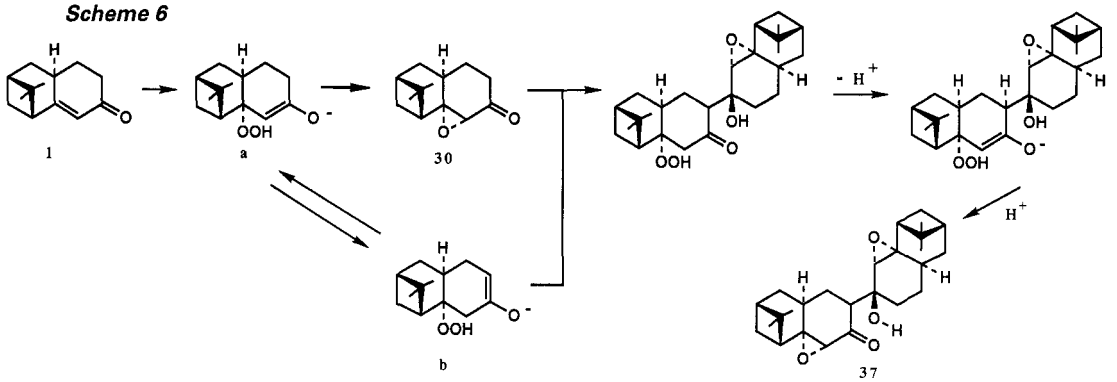
of epoxyketones with hydrazine [Wharton reaction (ref. 11)] should lead to the unsaturated alcohol (**31**), but instead, we isolated its allyl rearrangement product (**32**), the stereochemistry of which was certain, since the epimeric alcohol (**33**) is obtained by metal hydride reduction of Tricyclone. Barton and Motherwell's alternative to the Wharton reaction (treatment of an epoxyalcohol with thiocarbonyldiimidazole) gave two products (**34**, both epoxyalcohols (**35**) behaving in the same way) and these products were then subjected to a radical fragmentation initiated by tributylstannane in presence of azobisisobutyronitrile (ref. 12). We thus obtained (mainly) the epoxide (**36**), with some allyl alcohol (**31**). Handling **31** was tricky, because of its tendency to dehydrate and to rearrange allylically (to **32**), even in the chloroform of the NMR measurement. Conversion of the epoxide **36** to the isomer (**29**) of Tricyclone was straightforward (Scheme 5, ref. 13).

Scheme 5



During the isolation of epoxide (**30**), less soluble crystals were present, with a m.p. too high for a C_{13} compound. This was a dimer of the epoxide, and contained a hydrogen-bonded hydroxyl group, together with a single ketone function, two epoxide groups, and two pinyl systems. This compound is not formed by simple aldol condensation of the epoxyketone (**30**), and a possible explanation is that the stereochemical constraints of the pinane system allow the initially formed hydroperoxyenolate (**a**) to be partly converted to the (presumably more stable) enolate (**b**) before the dissociation of **a** to **30** is complete. This second enolate can now react with the epoxide (**30**) to give the observed dimer (**37**) (Scheme 6, ref. 13).

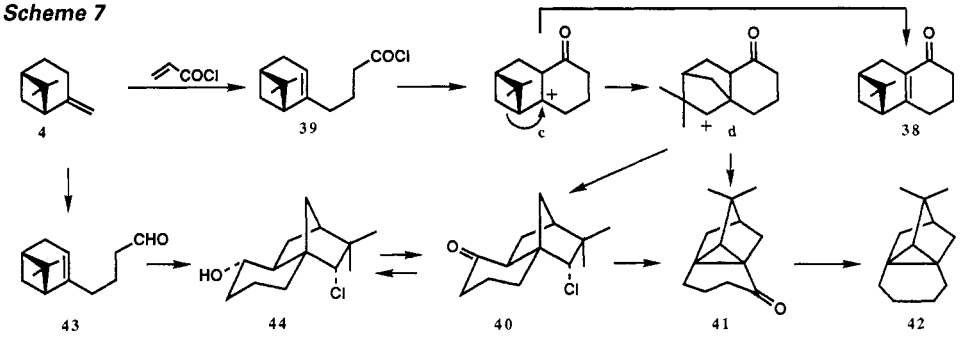
Scheme 6



The known isomer (ref.14) (**38**) of Tricyclone was made from β-pinene and acryloyl chloride

(39) with tributylamine at 150°. A reaction described by Wolinsky (ref. 15) also mentioned formation of a chlorine-containing compound, which we showed to be **40** (ref. 16). A saturated ketone, $C_{13}H_{18}O$, containing four rings was also formed. The two possible structures depended on whether the initially formed carbocation **(c)** rearranged in a bornyl-like way or a fenchyl-like way (to **d**) (Scheme 7). It is the fenchyl rearrangement which occurs (as, indeed, it does to form the chloro-compound, **40**), conforming to the rule about these rearrangements (ref. 17), stating that a substituent adjacent to the carbocation initially formed **(c)** causes the fenchyl rearrangement to be preferred. The ketone we found was indeed **41** (^{13}C-^{13}C coupling), and after Wolff-Kishner reduction, the hydrocarbon **(42)** was achiral.

Scheme 7



Easier access to the new ketone **(41)** is by reaction of β-pinene with acrolein in presence of aluminium chloride. The aldehyde **(43)** has been cyclized in dilute sulphuric acid to give a poor yield of a diol with the same skeleton as the chloride **(40)** (ref.18). If hydrogen chloride in hexane is used for the cyclization, the product **(44)** is the same as that obtained on reduction of the chloride **(40)** with lithium aluminium hydride. This chloro-alcohol is re-oxidized to the ketone **(40)**, so reasonably large amounts of **40** can be prepared. The chloroketone **(40)** is not converted to the tetracyclic ketone **(41)** with tributylamine (*i.e.* **40** is not intermediate in the formation of **41** from ion **d**), but potassium-*tert*-butoxide does effect the conversion. The ring system of this tetracyclic ketone was prepared from isolongifolene by Sukh Dev et al. (ref. 19).

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