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A NEW METHOD OF SYNTHESIS OF STEREOSPECIFICALLY 7,7-DIFUNCTIONALIZED BICYCLO [2.2.1] HEPTENE DERIVATIVES

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Abstract.- The cyclopropyl carbinol group of the adducts 7a and 7b undergoes anchimerically-assisted solvolytic ring opening, leading to a stabilized 7-norbornenyl cation which collapses, stereospecifically, to 7,7-difunctionalized bicyclic/2.2.1/heptene derivatives 8 and 9.

The current general methodology for the synthesis of 7-alkyl,7-hydroxy disubstituted bicyclo[2.2.1]heptene derivatives 1 involves the alkylation of a 7-norbornenone 2 by an organometallic reagent[1,2] (scheme I). Unfortunately, a direct synthesis of 2 by a Diels Alder reaction with cyclopentadienone 3 is not possible[3] and the synthesis of compounds of type 1 needs to be resolved by a circuitous method using a synthetic equivalent of 3 such as 4 or 5. However, the Diels Alder reaction of the dienone ketals 4 is limited to the use of the highly reactive dienophiles[4] and, although the chlorinated diene[5] 5 reacts with a wide range of them,[6] the attractiveness of this synthon is offset by the necessity to reductively dechlorinate the resulting adducts, despite recent efforts to improve the yields of these reactions.[7]

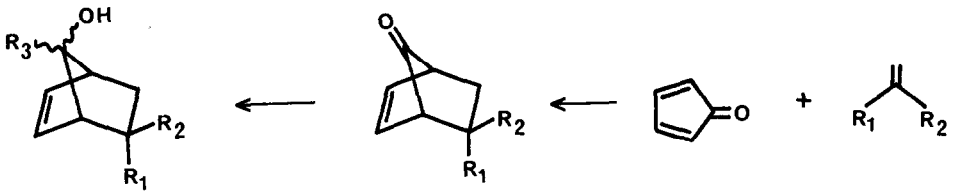
We were intrigued by the simplest approach to the bicyclic framework 1 as shown in the retrosynthetic analysis in scheme II. Since the difficulties associated with the synthesis of 5,5-disubstituted cyclopentadienes such as 6 are well-known[8], attention was devoted to devising an alternative way equivalent to that shown in scheme II. The present investigation originated from the assumption that the solvolytic opening of the cyclopropane ring of compound 7 (scheme III) should be selectively directed by the driving force constituted by the generation of an anchimerically stabilized 7-norbornenyl cation.[9] Nucleophilic capture of the intermediate should provide 7-disubstituted derivatives 8 and/or 9 stereospecifically.

To test the validity of the hypothesis, in view of the importance of compounds of type 1 in mechanistic and synthetic studies,[10] particularly in the stereocontrolled construction of cyclopentane rings of biological interest by oxygen ring insertion[11] reactions in stereospecifically disubstituted norbornenones, we set out to prepare compounds of type 7.

The syntheses of compounds 7a and 7b were straightforward using a Diels Alder reaction, with quantitative yield, of the readily accessible[12] spirodiene 10 with methyl acrylate and methyl vinyl ketone respectively[13] followed by mesylation.[14] When the mesylates 7a and 7b were stirred on silica gel (Cl_2CH_2, 25°C) a fast reaction took place producing gratifying rearrangement products 8a, 9a and 8b, 9b in ratio 70:30 (85% yield from 10) and 72:28 (80% yield from 10) respectively. A dramatic increase in selectivity (99:1) was obtained when the rearrangement of 7a was performed with activated silica gel.

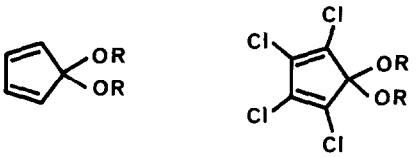
The stereochemistries of 8 and 9 were assigned on the basis of spectroscopical, mechanistic and chemical evidence. The single, crystalline compound 8b (mp 58-59°C) was converted to a mixture of endo and exo isomers[15] from which the new epimer was chromatographically separated as

Scheme I



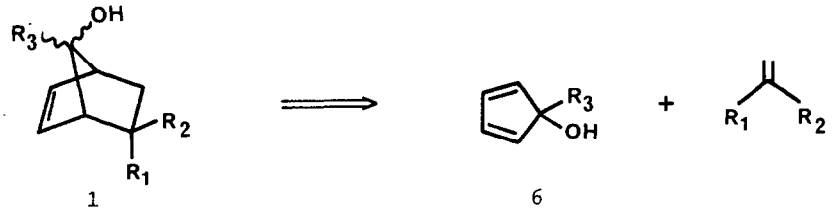
1 2 3

R_1, R_2 = H and/or EWG, R_3 = alkyl



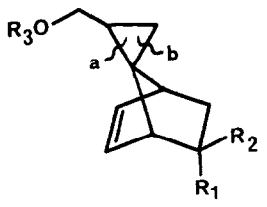
4 5 R = OMe, OEt

Scheme II



1 6

Scheme III



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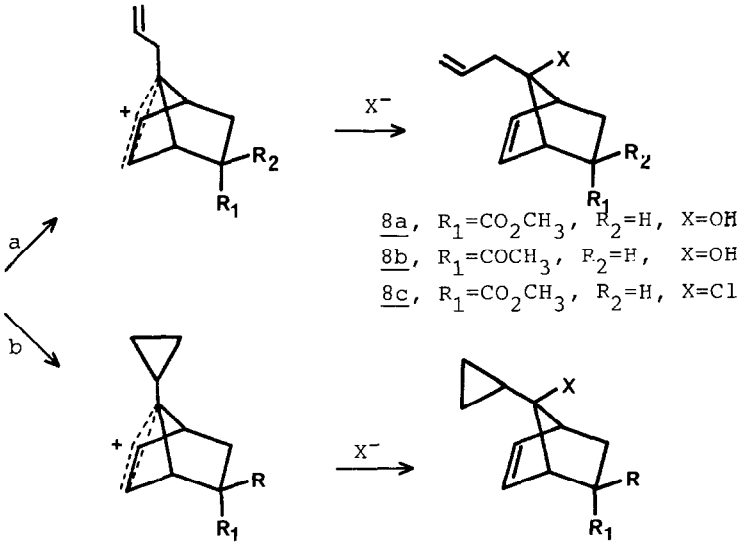
7a, R_1=CO_2CH_3, R_2=H, R_3=Ms

7b, R_1=$COCH_3$, R_2=H, R_3=Ms



8a, R_1=CO_2CH_3, R_2=H, X=OH

8b, R_1=$COCH_3$, R_2=H, X=OH

8c, R_1=CO_2CH_3, R_2=H, X=Cl

9a, R_1=CO_2CH_3, R_2=H, X=OH

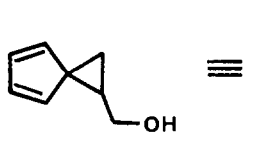
9b, R_1=$COCH_3$, R_2=H, X=OH

R_1, R_2 = H and/or EWG

the less polar compound. Comparison of the ^{1}H-NMR spectra of both led us to assign the exo stereochemistry to the new isomer for the following reasons: 1) the higher field position of the methyl ketone signal in 8b is attributable to shielding by the uplying endocyclic double bond, 2) the ring olefinic protons of the endo isomer appeared as two multiplets and in the exo isomer as a triplet because the acyl group is far enough removed from the olefinic centre to allow the olefinic protons to be equivalent.[16] In the same way, endo stereochemistry was assigned to the acyl group of 8a and to the mixture of adducts 7a and 7b, in which the hydroxymethyl group syn to the double bond was expected[17] due to steric interaction of the diene-dienophile approach in the cycloaddition.

The retention of configuration in the interchange[18] 8a ⇄ 8c agrees with the anchimeric participation of the endocyclic double bond and the exclusively anti attack of the nucleophile was chemically established by the formation of lactone 12 when the dianion of 8a was treated with methyl disulfide.[19] The ^{1}H-NMR spectrum of 8a was essentially identical with that of 8c, establishing the identities of the stereochemistries.

In the overall process described herein we can consider that the stable spirodiene 10 fulfils the function equivalent[20] to that of the difficult to achieve cyclopentadiene derivative 11 and opens an interesting way of access to stereospecifically disubstituted bicyclo[2.2.1]heptenes. Solvolysis of a secondary mesylate derivative and selective trapping of the intermediate by hydride, carbanion or other kinds of nucleophiles, should be an entry to a diversity of mono and dialkyl 7-substituted norbornenes. This in combination with a retro Diels Alder reaction would facilitate the synthesis of 5,5-dialkyl substituted cyclopentadienes, important synthons for which there is no satisfactory methodology[21] at present. Efforts in these directions are under way in these laboratories.



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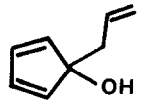

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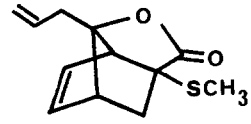

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