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STEREOCHEMISTRY OF THE NUCLEOPHILIC RING-OPENING OF ACTIVATED BICYCLO-[3.1.0]HEXANES.

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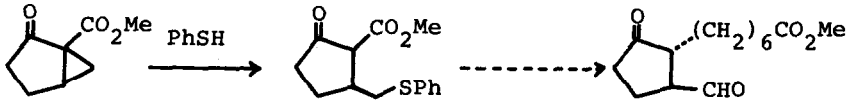
The nucleophilic ring-opening reaction of 2-oxobicyclo[3.1.0]hexane-1-carboxylate (1) to afford an intermediate for the synthesis of prostanoid has recently been reported.[1] If the same type of ring cleavage may occur with a 6-substituted bicyclo[3.1.0]hexane derivative, the reaction will provide a shorter route to prostanoid. In order to materialize this idea, it became necessary to know the stereochemistry of the intramolecular carbenoid addition and the ring-opening reaction of the resulting bicyclohexane.



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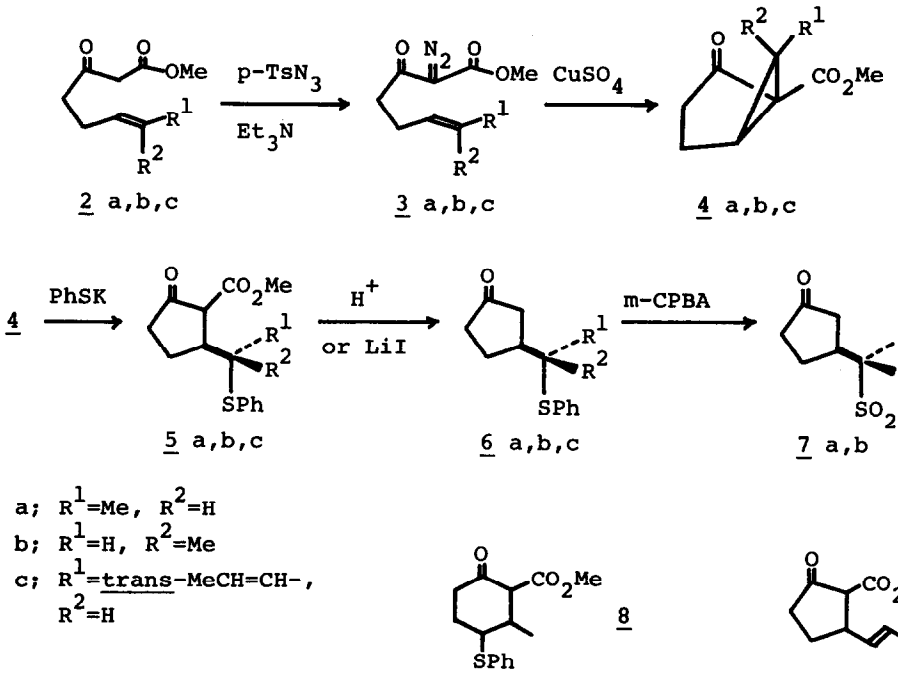
Methyl 3-oxo-trans-6-octenoate (2a)[2] (bp 110-112°/16 mmHg, ν_{max}970 cm^{-1}) was prepared by condensation of trans-crotyl chloride[3] with the dianion derived from methyl acetoacetate.[4] Methyl 3-oxo-cis-6-octenoate (2b)[2] (bp 134-136°/24 mmHg) was similarly prepared from 1-bromo-2-butyne and by partial reduction of the resulting product using Lindlar catalyst. Similar condensation of the dianion with sorbyl bromide[5] afforded the decadienoate (2c) (bp 93-96°/0.2 mmHg). Diazotizations of 2a, 2b, and 2c by treatment with TsN_3[6] and thermolyses of the resulting diazo compounds, 3a, 3b, and 3c, by heating in PhH in the presence of anhydrous $CuSO_4$ gave methyl exo-6-methyl-2-oxobicyclo[3.1.0]hexane-1-carboxylate (4a) [ν_{max}1755, 1730 cm^{-1}; nmr(CCl_4) δ1.19(d, J=6Hz, 3H), 1.46-1.76(m, 1H), 1.76-2.58(m, 5H), 3.65(s, 3H)], the corresponding endo-isomer (4b) [ν_{max}1755, 1732 cm^{-1}; nmr(CCl_4) δ1.14(d, J=6Hz, 3H), 1.65-2.58(m, 6H), 3.66



2 a,b,c 3 a,b,c 4 a,b,c

5 a,b,c 6 a,b,c 7 a,b

a; R^1=Me, R^2=H
b; R^1=H, R^2=Me
c; R^1=trans-MeCH=CH-, R^2=H

8

9

(s, 3H)], and methyl exo-6-(trans-1-propenyl)-2-oxobicyclo[3.1.0]hexane-1-carboxylate (4c) [ν_{max}1760, 1730, 968 cm^{-1}, nmr(CCl_4) δ1.65(dd, J=1.5 and 6.5 Hz, 3H), 1.82-2.64(m, 6H), 3.66(m, 3H), 5.14(q of dd, J=1.5, 8.5, and 15.5 Hz, 1H), 5.64(dq, J=6.5 and 15.5 Hz, 1H)] in 58, 60, and 64% yields, respectively. The difference between nmr spectra of 4a and 4b and no contamination with each other in their spectra implied that the intramolecular addition of the carbenoid proceeded stereospecifically.[7]

Treatment of 4a with PhSK in t-BuOH at room temp for 3 hrs followed by quenching of the mixture with aq. NH_4Cl afforded a product different from the one obtained from 4b under the same condition. Thus the one (5a) from 4a was crystalline, mp 57-58° (82% yield) and the other (5b) from 4b was an oil (69% yield). Similar treatment of 4c with PhSK also gave (5c) as an oil in 69% yield. In comparison with 1, the bicyclohexane 4 has a substituent on 6-position. This means that, in principle, the steric hindrance for nucleophilic attack would be almost same at 5- and 6-positions. Thus the cyclohexanone 8 would also be a possible product. In the case of 4c, further complexity is foreseeable as the unsaturated bond is present in the side chain. The conju-

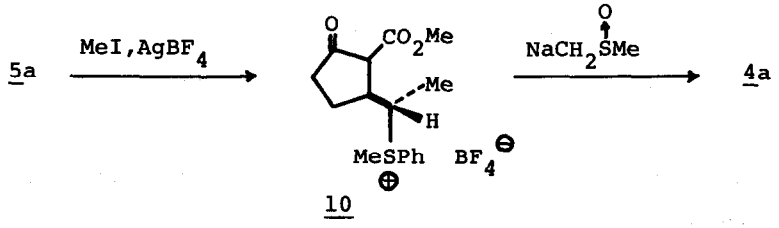
gate addition of thiophenol to the terminal position of the double bond[8] may produce 9. For the assignment of structures, the ir spectra (ν_{max} 1790, 1730, 1660, and 1620 cm^{-1}) of the ring-opened products were not informative because of the presence of keto-enol equilibrium. The nmr spectra were also useless due to the additional complexity accompanied by the presence of cis-trans isomerism, though the spectra of 5a and 5b themselves were completely different from each other.

The cyclopentanone structure was confirmed by the following transformation. Decarboxylations of 5a, 5b (30% H_2SO_4), and 5c (LiI, DMSO) afforded 6a, 6b, and 6c in 88, 98, and 76% yields, respectively. All of 6 exhibited a characteristic absorption of cyclopentanone at 1740-1745 cm^{-1} in ir spectra.[9] The nmr spectra of 6a and 6b were too similar to be differentiated. Accordingly, both samples were further transformed into the sulfone derivatives 7a and 7b in 68 and 48% yields, respectively, by oxidation with m-CPBA in CH_2Cl_2. The methine protones α to the benzenesulfonyl group were observed at 3.19(dq, J=5 and 7Hz) in 7a and at 3.13(dq, J=J=7Hz) in 7b. The exclusive formations of 7a and 7b from 5a and 5b, respectively, mean that the ring-opening reaction is also a stereospecific process.

The attaching position of phenylthio group in the product derived from 5c was determined on the basis of its nmr spectrum using decoupling technique. The methyl and methine (α to phenylthio) protons of the product (6c) were observed at 1.57(d, J=5Hz) and 3.36(m), respectively. Irradiation to the methyl signal induced no change in the shape of the methine absorption and vice versa, though that of absorption assignable to olefinic protons changed considerably. These observations fairly excluded the possibility of structural isomer which would be obtained by the decarboxylation of 9.

The attack of nucleophiles to activated cyclopropanes is known to occur with inversion of configuration.[10] Thus the ring-opened products 5a and 5b should have the configurations as indicated in the scheme. This supposition was finally confirmed by the following sequence of reactions. Treatment of 5a with excess MeI in the presence of $AgBF_4$ afforded the corresponding sulfonium salt 10 (mp 122-124°). Base-promoted cyclization of 10 with dimsyl sodium in

DMSO at room temp regenerated the bicyclohexane 4a as the sole product. Since the intramolecular nucleophilic displacement of sulfonium group is known to proceed with inversion of configuration,[11] the ring-opening step should also be an inversion process.



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In conclusion, both the formation and ring-opening reaction of 6-substituted bicyclo[3.1.0]hexanes 4 proceed stereospecifically and the phenylthio group is introduced regioselectively on the 6-position of the bicyclohexanes with inversion of configuration, even when the substituent is alkenyl being in conjugation with the cyclopropane.

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