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A NOVEL SYNTHETIC ROUTE TO 6-OXABICYCLO[3.1.1]HEPTANE SKELETON

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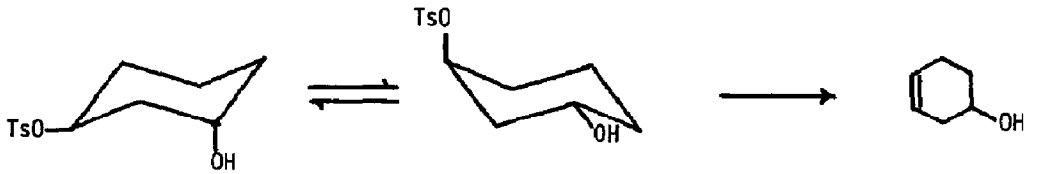
Summary: *6-Oxabicyclo[3.1.1]heptane skeleton is synthesized starting from bicyclo[2.2.1]-heptane skeleton, in which as a key reaction, Baeyer-Villiger oxidation of the tricyclic oxetane (19) is involved.*

In connection with synthetic studies of chemically stable thromboxane A_2 analogs, great attention has recently been paid to an 6-oxabicyclo[3.1.1]heptane skeleton. At the beginning of this work the skeletal synthesis of 6-oxabicyclo[3.1.1]heptane system has been unsuccessful.[1]

As an attempt of a possible route to 6-oxabicyclo[3.1.1]heptane skeleton, Clayton et al. carried out the reaction of *trans*-1,3-cyclohexanediol mono-*p*-toluenesulfonate (1) with sodium methoxide in methanol. However, the elimination product, 3-cyclohexenol (2), was only isolated in 80% yield. One reason for the formation of the unsaturated alcohol is explained by the ready diaxial elimination of *p*-toluenesulfonic acid from the less favorable conformation (1B) of the monotosylate.



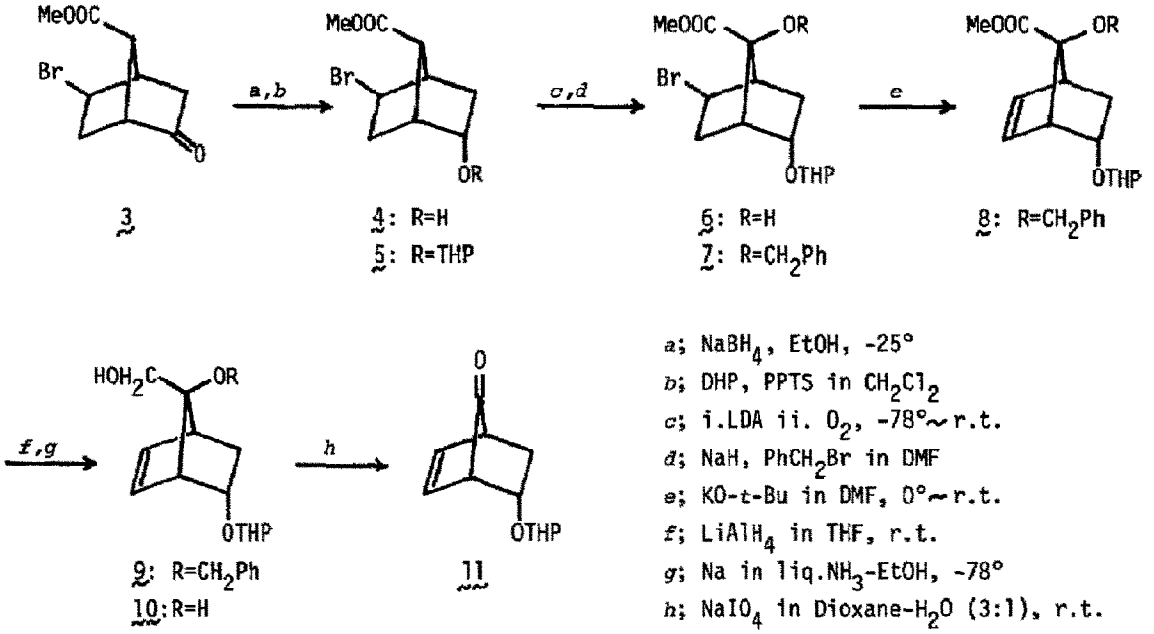
1A 1B 2

Developement of the strategy which produces 6-oxabicyclo[3.1.1]heptane skeleton was initiated in order to investigate its chemical stability and also its effect on platelet aggregation activity. The very recent publication by Maxey and Bundy[2] concerning an elegant construction of the 6-oxabicyclo[3.1.1]heptane skeleton prompted us to report our different strategy which utilizes the bicyclo[2.2.1]heptane skeleton in fixing the conformation of a cyclohexane ring.

The key intermediate for the preparation of the 6-oxabicyclo[3.1.1]heptane skeleton is the bicyclic ketone (11) which was readily available in *ca.* 25% yield from methyl 5-oxo-*exo*-2-bromobicyclo[2.2.1]heptane-7-carboxylate (3)[3] as outlined in Scheme I. The bicyclic ketone (11) (ν_{max}^{neat} 1778 cm-1) was reduced with sodium borohydride in ethanol at -78° to give a

mixture of epimeric secondary alcohols (ratio, 2:1). Based on the NMR spectra[4] the major alcohol was assigned to the *anti*-alcohol (12) and the minor alcohol to the *syn*-alcohol (13). The latter alcohol with undesired configuration[5] could be recycled to the ketone (11) by oxidation with Collins reagent (40-50% yield). Protection of the alcohol (12) with a benzyl group, followed by deprotection of THP ether, afforded the *endo*-alcohol (14). Direct epoxidation with *m*-chloroperbenzoic acid in the stereospecific manner[6] resulted in the formation of the *exo*-epoxide (15) in 57% overall yield from the *anti*-alcohol (12).

Scheme I.



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4: R=H
5: R=THP

6: R=H
7: R=CH_2Ph

8: R=CH_2Ph

9: R=CH_2Ph
10: R=H

11

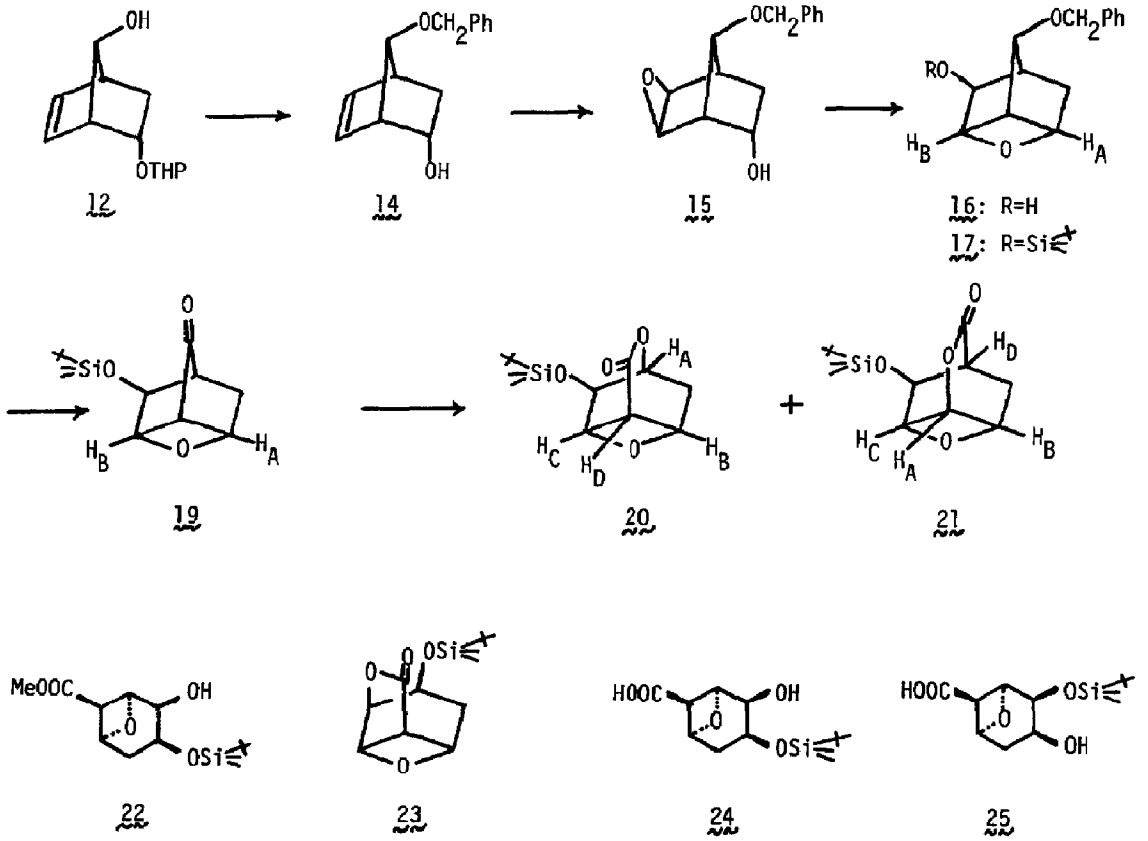
The oxetane formation, one of the most crucial steps in our synthetic route, was best carried out by treatment of 15 with potassium *t*-butoxide in *t*-butanol at room temperature for 13.5 hr to afford the tricyclic oxetane (16) in 85% yield,[7,8] which was protected as *t*-butyldimethylsilyl ether in 89% yield ($\delta_{TMS}^{CDCl_3}$ 4.70 (1H,m,H_A), 4.19 (1H,m,H_B)[9]). The protected tricyclic oxetane (17) was hydrogenolyzed over 5% Pd/C in ethanol to give the alcohol (18) in 88% yield without any decomposition of the oxetane skeleton. Oxidation with Collins reagent to the relatively labile ketone (19) (ν_{max}^{neat} 1778 cm-1, $\delta_{TMS}^{CDCl_3}$ 4.82 (1H,m,H_A), 4.50 (1H,m,H_B)) in nearly quantitative yield and then Baeyer-Villiger oxidation using *m*-chloroperbenzoic acid in the presence of sodium carbonate in methylene chloride at 0-6° gave an unexpected result; that is, the regioisomer (20) of the lactone (ν_{max}^{neat} 1740 cm-1, $\delta_{TMS}^{CDCl_3}$ 5.00 (1H,m,H_A), 4.75 (1H,m,H_B), 4.20 (1H,m,H_C), 4.16 (1H,m,H_D)) was nearly exclusively obtained in 83% yield from the alcohol (18) with a small amount of the other isomer (21) (ν_{max}^{neat} 1760 cm-1, $\delta_{TMS}^{CDCl_3}$ 5.48 (1H,ddd,J=6Hz, 5Hz,2Hz,H_A), 4.80 (1H,m,H_B), 4.50 (1H,m,H_C), 3.32 (1H,m,H_D)) in 9% yield. This nearly exclusive formation of the lactone (20) might be rationalized by the assumption that the migration of the oxetane ring is retarded by the electron-deficient character of the ring.[10]

Hydrolysis of the lactone is the most critical step since it has not been known whether the 6-oxabicyclo[3.1.1]heptane skeleton can be intact under usual ester hydrolysis conditions. Treatment of the lactone (20) with sodium hydroxide (20 equiv.) in methanol at room temperature for 3 hr, followed by acidification to pH 4 and esterification with diazomethane, provided the 6-oxabicyclo[3.1.1]heptane derivative (22) in 46% yield[11] with a small amount of the starting lactone (13% yield) and the 5-membered lactone (23) (ν_{max}^{film} 1775 cm-1) in 2% yield after separation by silica gel column chromatography. Consistent with the result observed by Upjohn chemists,[3] the 6-oxabicyclo[3.1.1]heptane derivative (22) is a reasonably stable compound as indicated by the fact that it can be purified by silica gel column chromatography.

In regard to the formation of 22, it seems likely that migration of the t-butyldimethylsilyl group occurred at the hydrolysis step of the lactone,[12] resulting the thermodynamically equilibrated mixture, 24 and 25. Furthermore, it appears that the non-migrated silyl ether (25) was immediately lactonized to the starting lactone after acidification and esterification.

Although our synthetic route to 6-oxabicyclo[3.1.1]heptane skeleton is still relatively long, the present strategy has a various possibility in providing hitherto unknown many 6-oxabicyclo [3.1.1]heptane derivatives. Further studies along this line are currently under investigation.

Scheme II.



REFERENCES AND NOTES

1) For the steroidal oxetanes, see C.C.Addison and N.Hodge, Chem. and Ind., 1315 (1953); R.B.Clayton, H.B.Henbest, and M.Smith, J. Chem. Soc., 1982 (1957).

2) K.M.Maxey and G.L.Bundy, Tetrahedron Lett., 445 (1980).

3) P.A.Grieco, C.S.Pogonowski, S.D.Burke, M.Nishizawa, M.Miyashita, Y.Masaki, C.-L.J.Wang, and G.Majetich, J. Am. Chem. Soc., 99, 4111 (1977).

4) The NMR spectrum of 17 displayed a two protons singlet (δ=4.33) for the benzylic protons, while that of 26 derived from 13 showed a clean two protons quartet (δ=4.68, 4.38, J=12Hz), indicating sterically crowded environment around the benzyl group.

5) Transformation of 13 into the ketone (19) proceeded only in unsatisfactory yield.

6) The stereochemistry of 15 was determined by the fact that the epoxide (15) furnished the oxetane (16) in nearly quantitative yield.

7) H.B.Henbest and B.Nicholls, J. Chem. Soc., 221 (1959).

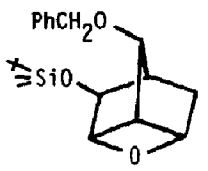
8) Attempts to prepare the tricyclic oxetanes directly from the alcohol (14) by treatment with NBS or PhSeCl resulted in none of the desired products.

9) Assignments of the NMR spectra were determined by the aid of decoupling technique. For the NMR spectrum of this class of compound, see A.K.Saksena, P.Mangiaracina, R.Brambilla, A.T.McPhail, and K.D.Onan, Tetrahedron Lett., 1729 (1978).

10) In Baeyer-Villiger oxidation of the ketone (27), the preferential migration of the cyclobutyl group is observed. See S.A.Monti and S.-S.Yuan, J. Org. Chem., 36, 3350 (1971).

11) ν_{max}^{neat} 3530, 1710 cm-1, $\delta_{TMS}^{CDCl_3}$ 4.70 (2H,ddd,J=7,4,2Hz), 4.44 (1H,ddd,J=7,6,2Hz), 4.17-3.86 (2H,m), 3.69 (3H,s), 3.15 (1H,d,J=10Hz), 2.48 (1H,ddd,15,6,3Hz), 2.24 (1H,dd,15,2Hz), 0.92 (9H,s), 0.14 (6H,s), MS (m/e) 245 [M^+-t-Bu], 271 [M^+-OMe], high resolution mass spectrum, M^+-t-Bu(found): 245.0878, calcd. for $C_{10}H_{17}O_5Si$: 245.0845.

12) For the migration of a t-butyldimethylsilyl group, see Y.Torisawa, M.Shibasaki, and S.Ikegami, Tetrahedron Lett., 1865 (1979); K.K.Ogilvie and N.Y.Theriault, *ibid.*, 2111 (1979); D.P.Reynolds, R.F.Newton, and S.M.Roberts, Chem. Commun., 1150 (1979).



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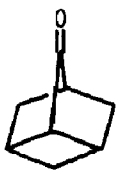

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