A New Route to (±)-*cis*-2-Oxabicyclo[3.3.0]oct-6-en-3-one, A Prostaglandin Synthon

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A new route to (±)-*cis*-2-oxabicyclo[3.3.0]oct-6-en-3-one(1), an important prostaglandin synthon, has been developed using a symmetrical starting material(3).

Since a Hungarian group[1] has reported the conversion of *cis*-2-oxabicyclo[3.3.0]oct-6-en-3-one(1) into *cis*-(7-acetoxy-6-acetoxymethyl)-2-oxabicyclo[3.3.0]octan-3-one(2), a key prostaglandin intermediate[2], *via* a regio- and stereospecific addition of formaldehyde by the Prins reaction, synthetic importance of hitherto less valuable lactone(1), especially in a chiral form, was greatly increased. There have been some interesting reports on the chiral synthesis of the lactone(1)[3,4,5], however, they still have rooms for improvement from the practical point of view. (Chart 1)

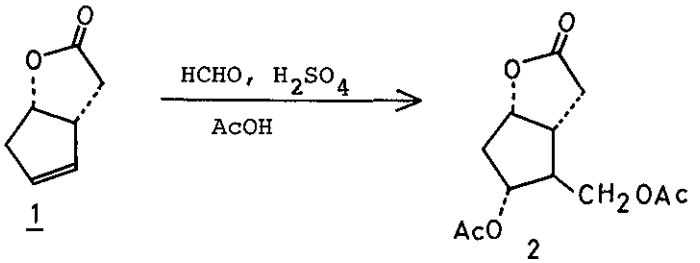

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Chart 1

We now report a simple synthesis of the lactone(1) in a racemic form from readily accessible nortricyclanone(3)[6] *via* exo-5-bromo-norcamphor(6) intending a chiral synthesis. Since a chiral bromo-ketone(6) has been obtained by treating the iminium salt(4)[7] with *hydrobromic acid*, a *conversion* of (±)-bromo-ketone(6) into the (±)-lactone(1) would be promissing a chiral synthesis. (Chart 2)

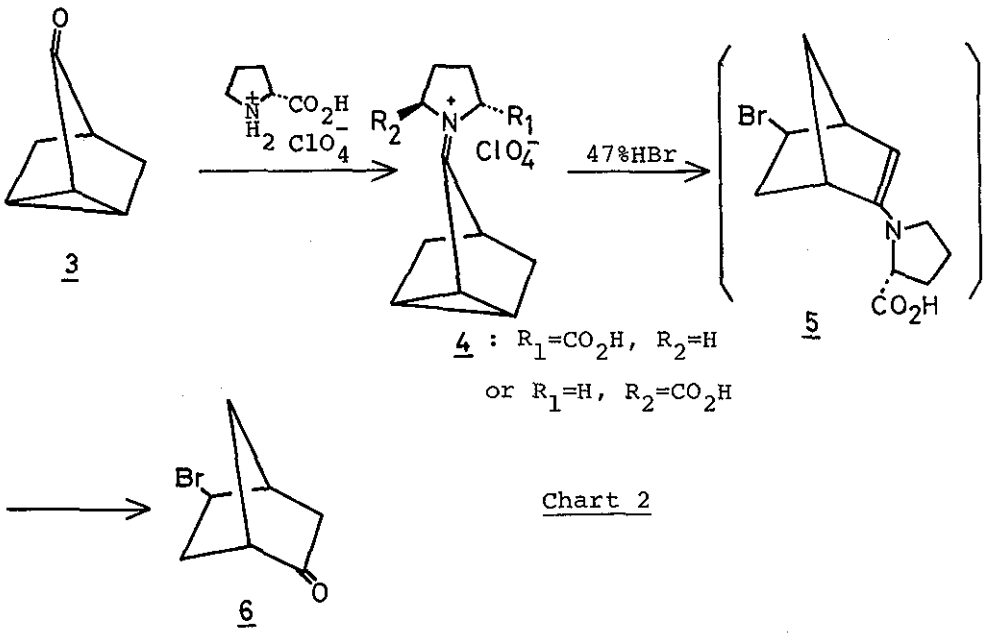

Chart 2

Treatment of nortricyclanone(3) with 47% hydrobromic acid(1 molar equiv) in boiling acetic acid gave exo-5-*bromonorcamphor*[8](6), bp 119-122°(17 mm Hg), mp 26.5-27.5°(lit.[8] mp 31-32°), ν_{max}^{Nujol}(cm^{-1}) 1745, δ^{CDCl_3}(ppm) 4.17(1H, m, -C<u>H</u>Br), in 96% yield. Baeyer-Villiger oxidation of <u>6</u> with *m*-chloroperbenzoic acid(1.2 molar equiv) gave the bromo-δ-lactone[9](7), mp 74-76°, ν_{max}^{Nujol}(cm^{-1}) 1715, δ^{CDCl_3}(ppm) 4.83(1H, m, -C<u>H</u>-OC(=O)-), 4.30(1H, m, -C<u>H</u>Br) in 92% yield as a single product.

Refluxing the δ-lactone(7) with ethanol in the presence of a catalytic amount of *p*-toluenesulfonic acid[10] formed the unstable ethyl ester(8), oil, ν_{max}^{neat}(cm^{-1}) 1720, quantitatively, which, without further purification, upon treatment with silver perchlorate[10](1.5 molar equiv) in aqueous dimethoxyethane at room temperature, afforded the γ-lactone alcohol(9), mp 76-77°, ν_{max}^{Nujol}(cm^{-1}) 3445, 1745, δ^{CDCl_3}(ppm) 5.13(1H, br.t, -C<u>H</u>OC(=O)-), 4.50(1H, m, -C<u>H</u>OH), in 91% yield. (Chart 3)

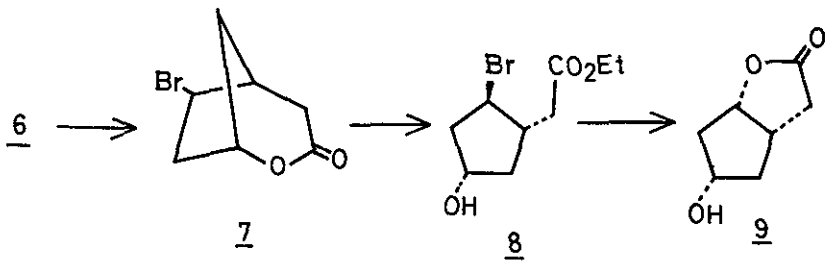

Chart 3

After various attempts were carried out on the derivatives of the alcohol(9), such as the chloride[11](10), the xanthate[12](11), the tosylate[13](12), and mesylate(13), the desired lactone(1) was obtained at best in 71% yield as a single product from the mesylate(3)(see Table 1, Entry 14). (Chart 4)

Thus, treatment of 9 with methanesulfonyl chloride in methylene chloride containing triethylamine gave the mesylate(13), mp 80-80,5°, ν_{max}^{Nujol}(cm^{-1}) 1750, δ^{CDCl_3}(ppm) 5.03-5.50(2H, m, -C<u>H</u>-OC(=O)- and -C<u>H</u>-OSO_2-), 3.05(3H, s, $C\underline{H}_3SO_2$-) in 98% yield. Heating 13 with two molar equivalents of pyridine in benzene solution in a sealed tube at 240-250° led to a regioselective olefin formation to

give (±)-*cis*-2-oxabicyclo[3.3.0]oct-6-en-3-one(1) in 71% yield. In the final stage, application of high temperature was most important since a concurrent formation of unseparable isomer, (±)-*cis*-2-oxabicyclo[3.3.0]oct-7-en-3-one[14,15](14), was predominant at lower temperature(see Table 1).[16]

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11 : R=MeSC(=S)-

12 : R=*p*-MeC$_6$H$_4$SO$_2$-

13 : R=MeSO$_2$-

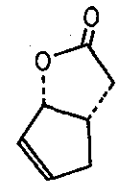

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Chart 4

Table 1

Entry	Starting Material	Condition				Product (ratio*a)			Total yield(%)
		Base (molar equiv)	Solvent	Temperature	Time (h)	1	14		
1	10	DBU(1.1)	DMF	60°	36	1	1.7	*b(0.3)	72
2	11		benzene	200°*c	6	0	0	*b	no reaction
3	11		neat	230-240°	0.5	1.3	1	0	93
4	12	γ-collidine(large excess)		170-180°	2	2	1	0	40.5
5	12	pyridine	benzene	210-220°*c	8	8	1	0	76
6	13	^{t}BuOK(1.2)	DME	0°	3	1	2.25	0	82
7	13	DBU(1.1)	DMF	60°	24	1	1.4	*b(0.7)	99
8	13	pyridine(large excess)		110-120°	20.5	1.4	1	0	37
9	13	2,6-lutidine(large excess)		140-150°	24.5	1.5	1	0	77
10	13	γ-collidime(large excess)		170-180°	2	2	1	0	81
11	13	quinoline(large excess)		230-240°	3	1	0	0	31
12	13	pyridine(2)	benzene	140-150°*c	4	2.1	1	0	47
13	13	pyridine(1)	benzene	210-220°*c	8	6	1	0	81
14	13	pyridine(2)	benzene	240-250°*c	0.5	1	0	0	71

*a determined by NMR spectra

*b starting material

*c heated in sealed tube

References and Notes

1. I. Tömösközi, L. Gruber, G. Kovács, I. Székely, V. Simonidesz, Tetrahedron Lett., 4639 (1976).
2. Cf. K. Sakai and N. Nakamura, J. Synth. Org. Chem. Japan, 36, 93 (1977).
3. J.J. Partridge, N.K. Chadha, and M.R. Uskoković, J. Amer. Chem. Soc., 95, 7171 (1973).
4. S. Takano, K. Tanigawa, and K. Ogasawara, Chem. Commun., 190 (1976).
5. S. Terashima, S. Yamada, and M. Nara, Tetrahedron Lett., 1001 (1977).
6. H.C. Brown and E.N. Peters, J. Amer. Chem. Soc., 97, 1927 (1975) and J. Meinwald, J. Crandall, and W.E. Hymans, Org. Synth. Coll. Vol, 5, 863 and 866 (1973).
7. S. Takano, H. Iwata, and K. Ogasawara, Heterocycles, 9, in press (1978).
8. H. Krieger, Suomen Kemistilehti, 34B, 24 (1961)(Chem. Abstr., 55, 23370f(1961)).
9. Satisfactory analytical data were obtained for all new compounds.
10. Cf. S. Takano, N. Kubodera, and K. Ogasawara, J. Org. Chem., 42, 786 (1977) and S. Takano, N. Kubodera, H. Iwata, and K. Ogasawara, Heterocycles, 8, 325 (1977).
11. Prepared in 73% yield by treating 9 with thionyl chloride in pyridine at 0°.
12. Prepared in 30% yield by treating 9 with carbon disulfide in the presence of sodium hydride followed by with methyl iodide.

13. Prepared in quantitative yield by treating 9 with *p*-toluenesulfonyl chloride in pyridine at room temperature.
14. Compound 14 could not be separated in pure state and its formation and proportion were determined by NMR spectra[15].
15. T.K. Das Gupta, D. Felix, U.M. Kempe, A. Eschenmoser, Helv. Chim. Acta, 55, 2198 (1972).
16. This behavior could be due to a thermal conversion of 14 into 1 which is thermodynamically more stable and the thermal behaviors of the compounds 1 and 14 are now under investigation. We thank one of the refrees for pointing out the possibility of the thermal conversion of 14 into 1.

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