

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

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

Since a Hungarian group¹ has reported the conversion of *cis*-2-oxabicyclo[3.3.0]oct-6-en-3-one(1) into *cis*-(7-acetoxy-6-acetoxy-methyl)-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)

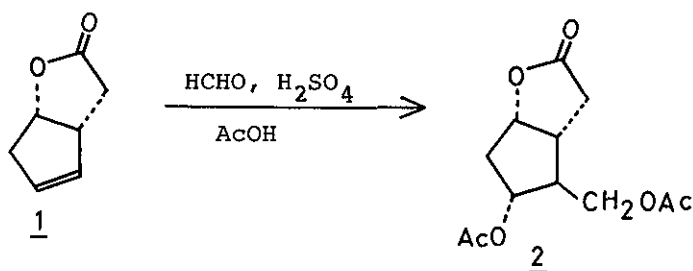
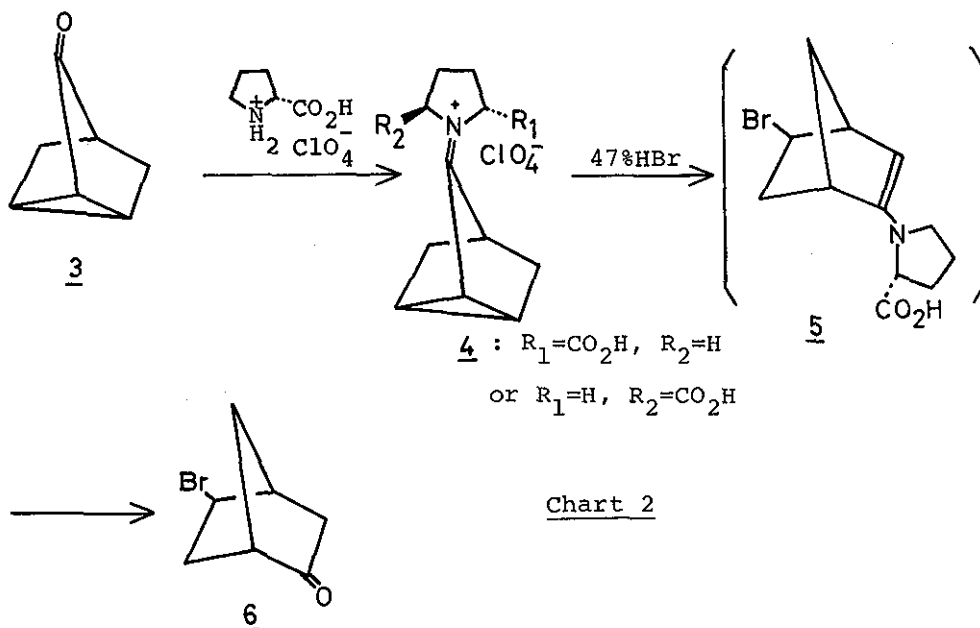


Chart 1

We now report a simple synthesis of the lactone (1) in a racemic form from readily accessible nortricyclanone (3)⁶ via *exo*-5-bromonorcamphor (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 (\pm)-bromo-ketone (6) into the (\pm)-lactone (1) would be promising a chiral synthesis. (Chart 2)



Treatment of nortricyclanone (3) with 47% hydrobromic acid (1 molar equiv) in boiling acetic acid gave *exo*-5-bromonorcamphor⁸ (6), bp 119-122° (17 mm Hg), mp 26.5-27.5° (lit.⁸ mp 31-32°), $\nu_{\text{max}}^{\text{Nujol}} (\text{cm}^{-1})$ 1745, $\delta^{\text{CDCl}_3} (\text{ppm})$ 4.17 (1H, m, $-\overset{|}{\text{C}}\text{HBr}$), in 96% yield. Baeyer-Villiger oxidation of 6 with *m*-chloroperbenzoic acid (1.2 molar equiv) gave the bromo- δ -lactone⁹ (7), mp 74-76°, $\nu_{\text{max}}^{\text{Nujol}} (\text{cm}^{-1})$ 1715, $\delta^{\text{CDCl}_3} (\text{ppm})$ 4.83 (1H, m, $-\overset{|}{\text{C}}\text{H}-\overset{\text{O}}{\text{C}}-$), 4.30 (1H, m, $-\overset{|}{\text{C}}\text{HBr}$) in 92% yield as a single product.

Refluxing the δ -lactone(7) with ethanol in the presence of a catalytic amount of *p*-toluenesulfonic acid¹⁰ formed the unstable ethyl ester(8), oil, $\nu_{\max}^{\text{neat}}(\text{cm}^{-1})$ 1720, quantitatively, which, without further purification, upon treatment with silver perchlorate¹⁰ (1.5 molar equiv) in aqueous dimethoxyethane at room temperature, afforded the γ -lactone alcohol(9), mp 76-77°, $\nu_{\max}^{\text{Nujol}}(\text{cm}^{-1})$ 3445, 1745, $\delta^{\text{CDCl}_3}(\text{ppm})$ 5.13(1H, br.t, $-\overset{|}{\text{C}}\text{HOC}$), 4.50(1H, m, $-\overset{|}{\text{C}}\text{HOH}$), in 91% yield. (Chart 3)

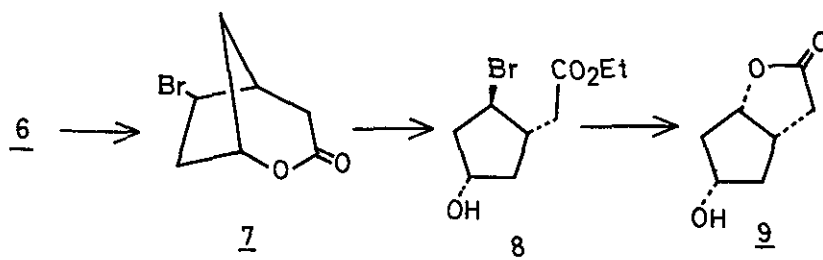


Chart 3

After various attempts were carried out on the derivatives of the alcohol(9), such as the chloride¹¹(10), the xanthate¹²(11), the tosylate¹³(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°, $\nu_{\max}^{\text{Nujol}}(\text{cm}^{-1})$ 1750, $\delta^{\text{CDCl}_3}(\text{ppm})$ 5.03-5.50(2H, m, $-\overset{|}{\text{C}}\text{HOC}$ - and $-\overset{|}{\text{C}}\text{HOSO}_2$ -), 3.05(3H, s, CH_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



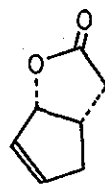
10



11 : R=MeSC(=S)-

12 : R=*p*-MeC₆H₄SO₂

13 : R=MeSO₂



14

Chart 4

Table 1

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

^aa determined by NMR spectra

^bb starting material

^cc heated in sealed tube

References and Notes

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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*-toluene-sulfonyl 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 spectra¹⁵.
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 referees for pointing out the possibility of the thermal conversion of 14 into 1.

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