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Stereoselective Reduction of Bicyclic Ketals. An Efficient Synthesis of (-)-(R,R)-(cis-6-Methyltetrahydropyran-2-yl)-acetic Acid, an Enantiomer of Civet Cat Constituent

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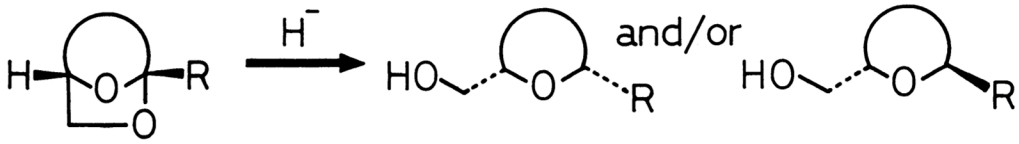
(-)-(R,R)-(cis-6-Methyltetrahydropyran-2-yl)acetic acid, an enantiomer of civet cat constituent, was prepared in high yield by using a stereoselective reduction of bicyclic ketals as a key step.

The reductive cleavage of acetals and ketals is a very useful procedure in protection chemistry and asymmetric synthesis. Recently, we reported an efficiently mild reduction of such functionalities with $Zn(BH_4)_2/Me_3SiCl$.[1] In the course of our studies in this field, we have been interested in the stereoselectivity of bicyclic ketals as illustrated in Scheme 1. Survey of the literature has revealed

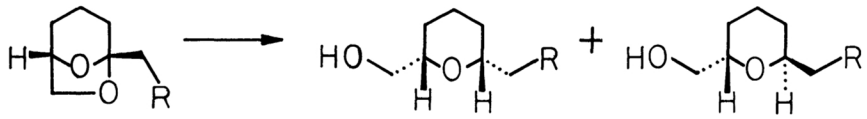


Scheme 1.

a few precedents of the application of this type of reaction to natural product synthesis.[2] And in addition, there is a lack of the systematic study on its stereoselectivity. Very recently, Ishihara et al. has reported a stereoselective reduction of bicyclic acetals.[3] This result prompts us to report our independent investigation of the stereoselective reduction of bicyclic ketals and its application to the total synthesis of one of the constituents of civet cat.[4]

To clarify the stereoselectivity of the reduction of bicyclic ketals we have studied the reduction of 1, which is readily available in either a racemic or an optically active form, by using several reducing agents with or without Lewis acid. The results were summarized in Table 1. It is apparent that the Mundy's conditions showed low selectivity (run 4) and our reagent was fruitless in this case (run 13). Fortunately, we found the use of Et_3SiH-$TiCl_4$ gave a cis-product in an almost complete selectivity (runs 3, 10, 15).[5] On the contrary, DIBAL showed a high trans-selectivity (runs 9, 12). Interestingly, when the reaction was conducted in the presence of Lewis acid, in every case the cis-product was mainly obtained except for run 4. The fact that the reaction of 1a was faster than those of 1b and 1c seems to be ascribed to the favored coordination of Lewis acid as shown in A. Thus

Table 1. Stereoselective Reduction of Bicyclic Ketals

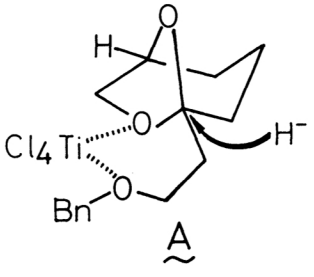


1a : R=CH_2OBn
b : R=C_6H_5
c : R=COOEt

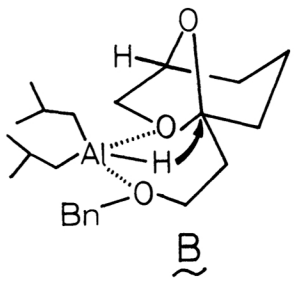
cis trans

Run	1	Reagent[a]/Lewis acid[b]	Solv	Temp/°C, Time/h	Yield/%[c]	cis:trans[d]
1	a	$Zn(BH_4)_2/ZnBr_2$	THF	0, 24	no reaction	
2	a	$Zn(BH_4)_2/TiCl_4$	CH_2Cl_2	-78, 0.25	100	98.9:1.1
3	a	$Et_3SiH/TiCl_4$	CH_2Cl_2	-78, 0.05	100	99.93:0.07
4	a	$LiAlH_4/AlCl_3$[e]	ether	40, 17	69(17)	15.5:84.5
5	a	$LiAlH_4/AlBr_3$[f]	ether	-78, 3.5	17(60)	84.4:15.6
6	a	$LiAlH_4/AlBr_3$[f]	ether	0, 0.25	83	85.6:14.4
7	a	$DIBAL/TiCl_4$	CH_2Cl_2	-78–25, 3	73(27)	83.4:16.6
8	a	$DIBAL/ZnBr_2$	THF	20, 20	40(60)	88.8:11.2
9	a	DIBAL/——	CH_2Cl_2	0, 0.25	100	4:96
10	b	$Et_3SiH/TiCl_4$	CH_2Cl_2	-78, 0.5	92	99:1
11	b	$Zn(BH_4)_2/TiCl_4$[g]	CH_2Cl_2	-78, 0.25	91	96:4
12	b	DIBAL/——	CH_2Cl_2	0, 0.25	83	2:98
13	c	$Zn(BH_4)_2/Me_3SiCl$	ether	0, 6	no reaction	
14	c	$Zn(BH_4)_2/TiCl_4$[g]	CH_2Cl_2	-25, 0.25	59	97:3
15	c	$Et_3SiH/TiCl_4$	CH_2Cl_2	-78–25, 1.5	59	99:1

a) 4 equiv. was used except for $Zn(BH_4)_2$(1.2 equiv.) and $LiAlH_4$(1.5 equiv.). b) 1.2 equiv. was used unless otherwise noted. c) Isolated yield, values in parentheses are recovery. d) Determined by capillary GLC. e) Mundy's conditions were used. See Ref. 2a. f) 4.5 equiv. was used. g) 3 equiv. was used.



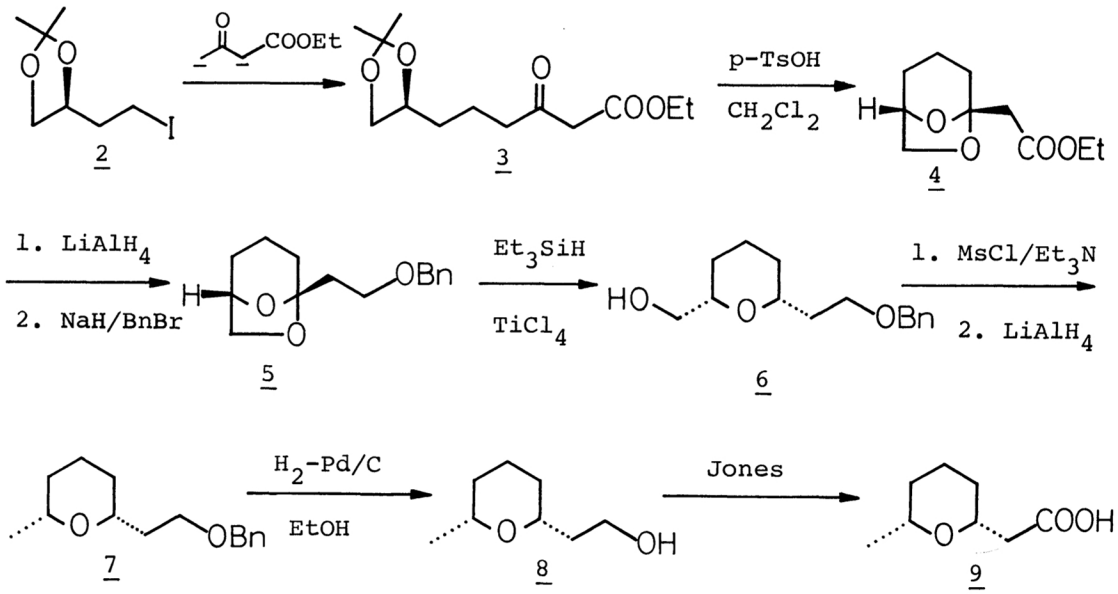
A



B

the transition state A, in which hydride attacks from the rear side of the coordinated ketal oxygen, seems to explain the high cis-selectivity. In the case of DIBAL reduction the intramolecular reduction must proceed through an intermediate like B to result in the preferential formation of trans-products.[6]

In order to demonstrate the utility of the above reaction, a synthesis of the target molecule was undertaken (Scheme 2).[7] The starting iodide 2 was easily pre-



Scheme 2.

pared from L-malic acid in a large amount. Alkylation of 2 with the dianion of ethyl acetoacetate (2 equiv. of LDA) gave 3, which was smoothly converted into 4 by treatment with a catalytic amount of p-TsOH in 96% yield. Reduction and thence protection of the side chain gave 5 in 91% yield. Sequential treatment of 5 with $Et_3SiH/TiCl_4$,[8] $MsCl/Et_3N$, and $LiAlH_4$ gave 7 almost quantitatively. Finally, deprotection of benzyl ether followed by Jones oxidation yielded the desired product 9, $[\alpha]_D^{20}$ -40.8°(c 1.0, C_6H_6), -24.8°(c 1.0, $CHCl_3$)(lit.[4d] $[\alpha]_D^{22}$ +43.8°(c 2.52, C_6H_6), +18.6°(c 2.77, $CHCl_3$)), in 91% yield as an enantiomer of natural product. The route involves 9 steps from 2 and the overall yield was 79.6%. Since (R)-malic acid is now accessible,[9] the procedure provides a convergent approach to the synthesis of this natural product.

We are now currently studying the further application of this reaction to the other compounds containing a medium- and large-sized ether ring.

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References

1) H. Kotsuki, Y. Ushio, N. Yoshimura, and M. Ochi, J. Org. Chem., 52, 2594(1987).
2) a) Y. Kim and B. P. Mundy, J. Org. Chem., 47, 3556(1982), and references cited therein; b) Y. Masaki, Y. Serizawa, K. Nagata, and K. Kaji, Chem. Lett., 1983, 1601.

3) K. Ishihara, A. Mori, and H. Yamamoto, Tetrahedron Lett., 28, 6613(1987).

4) For previous synthesis of (cis-6-methyltetrahydropyran-2-yl)acetic acid, see the following papers. In natural form: a) D. Seebach and M. Pohmakotr, Helv. Chim. Acta, 62, 843(1979); b) D. Seebach, M. Pohmakotr, C. Schregenberger, B. Weidman, R. S. Mali, and S. Pohmakotr, ibid., 65, 419(1982); c) F. W. Lichtenthaler, F. D. Klingler, and P. Jarglis, Carbohydr. Res., 132, C1(1984); d) E. Keinan, K. K. Seth, and R. Lamed, J. Am. Chem. Soc., 108, 3474(1986); e) J. B. Jones and R. S. Hinks, Can. J. Chem., 65, 704(1987); f) Ref. 2b. In racemic form: g) S. V. Ley, B. Lygo, H. Molines, and J. A. Morton, J. Chem. Soc., Chem. Commun., 1982, 1251; h) H. A. Bates and P. N. Deng, J. Org. Chem., 48, 4479(1983); i) M. F. Semmelhack and C. J. Bodurow, J. Am. Chem. Soc., 106, 1496(1984); j) S. V. Ley, B. Lygo, and H. Molines, J. Chem. Soc., Perkin Trans. 1, 1984, 2403; k) T. Gallagher, J. Chem. Soc., Chem. Commun., 1984, 1554; l) C. Nussbaumer and G. Fráter, Helv. Chim. Acta, 70, 396(1987); m) Ref. 2a; n) Ref. 3.

5) Cis- and trans-isomers are separable by flash column chromatography and each structure was confirmed by NMR or NOE experiments after conversion to the derivatives such as 7 and 9.

6) A. Mori, J. Fujiwara, K. Maruoka, and H. Yamamoto, J. Organomet. Chem., 285, 83 (1985); A. Mori, K. Ishihara, I. Arai, and H. Yamamoto, Tetrahedron, 43, 755 (1987).

7) Spectral data. 2: $[\alpha]_D^{20}$ -20.8°(c 8.0, $CHCl_3$); IR(neat) 1385, 1370, 1250, 1215, 1065 cm^{-1}; NMR($CDCl_3$) δ 1.35, 1.40(each 3H, s), 1.9-2.2(2H, m), 3.24(2H, t, J=7 Hz), 3.4-3.7(1H, m), 3.9-4.3(2H, m). 3: $[\alpha]_D^{20}$ +6.27°(c 6.06, MeOH); IR(neat) 1740, 1715 cm^{-1}; NMR($CDCl_3$) δ 1.28(3H, t, J=7.3 Hz), 1.34, 1.39(each 3 H, s), 1.4-1.9(4H, m), 2.61(2H, m), 3.42(2H, s), 3.4-3.6(1H, m), 3.8-4.1(2H, m), 4.19 (2H, q, J=7.3 Hz). 4: $[\alpha]_D^{20}$ -36.6°(c 0.95, $CHCl_3$); IR(neat) 1735, 1015, 755 cm^{-1}; NMR($CDCl_3$) δ 1.27(3H, t, J=7 Hz), 1.4-2.0(6H, m), 2.73(2H, s), 3.7-4.1(2H, m), 4.17(2H, q, J=7 Hz), 4.54(1H, br, $W_{1/2}$=9 Hz). 5: $[\alpha]_D^{20}$ -40.1°(c 3.0, $CHCl_3$); IR(neat) 1115, 1100, 1015, 905, 895, 855, 740, 700 cm^{-1}; NMR($CDCl_3$) δ 1.3-2.0 (6H, m), 2.06(2H, t, J=7 Hz), 3.64(2H, t, J=7 Hz), 3.7-4.0(2H, m), 4.50(3H, s), 7.31(5H, s). 6: $[\alpha]_D^{20}$ -20.1°(c 6.0, MeOH); IR(neat) 3450, 1500, 1450, 1090, 1045, 780, 695 cm^{-1}; NMR($CDCl_3$) δ 1.0-1.7(6H, m), 1.78(2H, q, J=6 Hz), 2.00(1H, br), 3.3-3.7(6H, m), 4.50(2H, s), 7.32(5H, s). 7: $[\alpha]_D^{20}$ -24.8°(c 4.8, $CHCl_3$); IR(neat) 1495, 1450, 1445, 1200, 1105, 1085, 730, 690 cm^{-1}; NMR($CDCl_3$) δ 1.14 (3H, d, J=6.4 Hz), 1.2-1.7(6H, m), 1.75(2H, q, J=6.4 Hz), 3.2-3.8(4H, m), 4.49 (2H, s), 7.31(5H, s). 9: IR(neat) 3600-3000, 1705 cm^{-1}; NMR($CDCl_3$) δ 1.18(3H, d, J=6.2 Hz), 1.2-2.0(6H, m), 2.47(1H, dd, J=16.8, 5.6 Hz), 2.58(1H, dd, J=16.8, 6.8 Hz), 3.3-3.9(2H, m), 8.55(1H, br). These products gave a satisfactory HRMS result.

8) In a large scale reaction the yield was decreased to 80% due to the concomitant debenzylation. Cf. K. Kon, K. Ito, and S. Isoe, Tetrahedron Lett., 25, 3739 (1984).

9) M. Alpegiani and S. Hanessian, J. Org. Chem., 52, 278(1987).

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