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Stereoselectivity in the formation and radical reduction of cyclic bromoacetals, key intermediates for the synthesis of δ-hydroxy- and ε-hydroxy-α-methylcarboxylic acid esters

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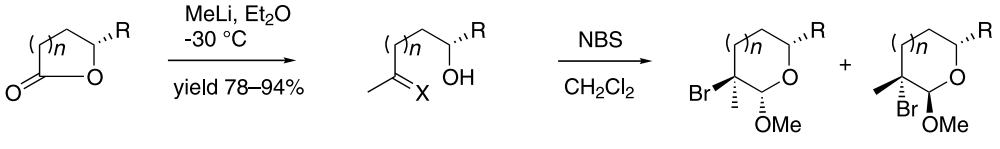
Abstract—We report the stereoselectivity in the formation and radical reduction of six- and seven-membered cyclic bromoacetals. The oxidative ring cleavage of the resulting acetals gave the corresponding acyclic δ-hydroxy- and ε-hydroxy-α-methylcarboxylic acid esters.

During the past decade the stereochemical control of acyclic radical reactions has received considerable attention and significant levels of diastereoselectivity in the reactions involving stereogenic centers adjacent to the radical center (1,2-asymmetric induction) or chiral auxiliaries have been achieved when they adopt preferred conformations.[1] The use of Lewis acids offers the possibility to regulate conformations and improves the stereoselectivity in acyclic radical reactions.[2] We have recently reported the chelation-controlled 1,3-asymmetric induction in the radical-mediated additions to α-methylene-γ-oxycarboxylic acid esters.[3] To extend the stereocontrol in acyclic radical reactions, we have attempted the 1,4-asymmetric induction in the radical reactions of α-methylene-δ-oxycarboxylic acid esters in the presence of Lewis acid, but the reactions showed no diastereoselectivity. The poor chemical shift increment values $\Delta\delta = [\delta_H(\text{substrate}+MgBr_2\cdot OEt_2) - \delta_H(\text{substrate})]$ in the complexation experiments with $MgBr_2\cdot OEt_2$ in $CDCl_3$[3d] indicated that the substrates did not form an eight-membered chelate ring.[4] To overcome the limitation of the chelation-mediated stereocontrol in acyclic radical reactions, we examined the indirect asymmetric induction through a series of reactions involving (a) bromoacetalization of acyclic olefinic alcohols **3** (Scheme 1), (b) radical reduction of the resulting cyclic bromoacetals **4** and **5** (Scheme 2), and (c) subsequent ring cleavage yielding acyclic hydroxy esters **10** and **11** (Scheme 3). Kiyooka and co-workers have recently reported the highly diastereoselective radical reduction



Scheme 1. Preparation of olefinic alcohols **3** and their bromoacetalization to **4** and **5**.

Keywords: radical reaction; cyclic bromoacetal; remote asymmetric induction; δ-hydroxy-α-methylcarboxylic acid ester; ε-hydroxy-α-methylcarboxylic acid ester.
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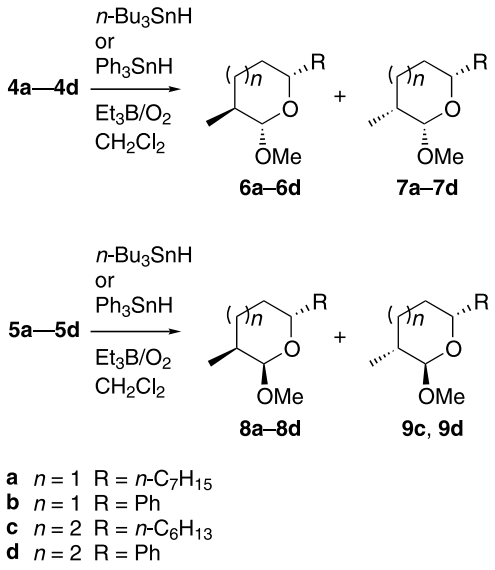
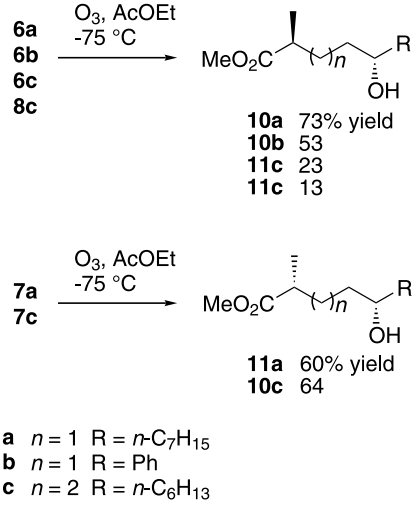


Scheme 2. Radical reduction of bromoacetals **4** and **5**.



Scheme 3. Ring cleavage of **6**–**8** yielding acyclic hydroxy esters **10** and **11**.

of α-bromo-α-methyl-δ-lactones yielding 2,4-*syn* dialkyl γ-lactone, which would be converted to a variety of acyclic derivatives.[5] In our case the diastereoselectivity of the radical reduction would be controlled by the methoxy group attached to the newly created stereogenic center in the cyclic bromoacetals.[6,7]

The bromoacetals **4** and **5** were prepared from lactones **1** (Scheme 1 and Table 1). δ-Phenyl-δ-lactone **1d**[8] was prepared from diethyl glutarate in 19% overall yield [(i) PhLi, Et_2O, −70°C to rt; (ii) $NaBH_4$, EtOH, 0°C; *p*-TsOH, PhH, rt]. Bulky substituents *n*-C_7H_{15}, Ph or *n*-C_6H_{13} were chosen to decrease volatility.

The bromoacetalization of **3a** (*E*:*Z*=4:1) with *N*-bromosuccinimide (NBS) in CH_2Cl_2 at 0°C gave a mixture of two diastereomers **4a** and **5a** in high yield with a diastereomer ratio of 5.1:1 (Table 1, entry 1).[9,10] Among the four possible diastereomers, **4a** and **5a** were obtained preferentially. The diastereoselectivity increased as the temperature was lowered (entry 2). The bromoacetalization of **3b** (*E*:*Z*=7:1) at 0°C also gave a mixture of **4b** and **5b** in a diastereomer ratio of 10.1:1 (entry 3). The reaction performed at −70°C showed a higher selectivity (13.0:1) (entry 4). Treatment of the homologous substrates **3c** and **3d** with NBS in CH_2Cl_2 under reflux gave the seven-membered cyclic bromoacetals **4c**/**5c** and **4d**/**5d**, respectively, but the yields were lower because of the difficulty of ring closure (entries 5 and 6).[11] The yields decreased as the temperature was lowered. Moreover, the diastereoselectivity was not ameliorated even at low temperature. The reaction was furthermore attempted under high dilution condition using a syringe pump, but the yield was not improved.[12] The bromoacetals **4** and **5** were, fortunately, separated by silica gel column chromatography (hexane–benzene 10:1).

The relative configurations between C-2 and C-6 of bromoacetals **4a**,**b**, **5a** and **5b** were established based on their NOE experiments. The *trans* relationship between the substituents Br and OMe was assigned based on the chemical shift values of 3-Me (δ_C=22.0 for the axial Me of more polar **4a**,**b**; δ_C=30.3 and 30.4 for the equatorial Me of less polar **5a**,**b**, respectively).[13] The configurations at C-2 and C-7 of bromoacetals **4c**,**d** and **5c**,**d** were also established based on their NOE experiments, but the stereochemistry at C-3 was tentatively assigned from the polarity of the bromoacetals; the more polar products were assigned to **4** and the less polar products were assigned to **5**.

The reduction of the major bromoacetal **4a** with *n*-Bu_3SnH (2 equiv.) and Et_3B (1 equiv.) in CH_2Cl_2 at 0°C gave acetals **6a** and **7a** in a ratio of 2.1:1 (Scheme 2., Table 2, entry 1). Bulky reducing reagent Ph_3SnH gave

Table 1. Bromoacetalization of **3a**–**d** with *N*-bromosuccinimide in CH_2Cl_2

Entry	Substrate (*E*:*Z*)	Temp. (°C)	Product	Yield (%)	Diastereomer ratio (**4**:**5**)
1	**3a** (4:1)	0	**4a**, **5a**	93	5.1:1
2		−70		98	6.8:1
3	**3b** (7:1)	0	**4b**, **5b**	88	10.1:1
4		−70		95	13.0:1
5	**3c** (6:1)	Reflux	**4c**, **5c**	50	1.2:1
6	**3d** (7:1)	Reflux	**4d**, **5d**	32	1.3:1

Table 2. Radical reduction of bromoacetals **4** and **5** with tin hydride and Et_3B

Entry	Bromoacetal	Tin reagent	Temp. (°C)	Product	Yield (%)	d.r. (**6**/**7** or **8**/**9**)
1	**4a**	*n*-Bu_3SnH	0	**6a**,**7a**	91	2.1:1
2		Ph_3SnH	0		97	4.3:1
3	**4b**	Ph_3SnH	0	**6b**,**7b**	92	6.0:1
4	**4c**	*n*-Bu_3SnH	0	**6c**,**7c**	98	1:4.2
5		*n*-Bu_3SnH	−70		90	1:11
6		Ph_3SnH	−70		90	1:2.5
7	**4d**	*n*-Bu_3SnH	0	**6d**,**7d**	90	1:2.5
8		*n*-Bu_3SnH	−70		90	1:6.3
9		Ph_3SnH	−70		90	1:1.8
10	**5a**	*n*-Bu_3SnH	0	**8a**	90	
11	**5b**	*n*-Bu_3SnH	0	**8b**	77[a]	
12	**5c**	*n*-Bu_3SnH	−70	**8c**,**9c**	90	16:1
13		Ph_3SnH	−70		80	5.7:1
14	**5d**	*n*-Bu_3SnH	−70	**8d**,**9d**	89	12:1
15		Ph_3SnH	−70		89	3.2:1

[a] Substrate **5b** was recovered in 20% yield.

a higher diastereoselectivity 4.3:1 (entry 2). The reaction temperature did not affect the diastereoselectivity. Bromoacetal **4b** was reduced with Ph_3SnH to give **6b** and **7b** in 92% yield and with a diastereomer ratio of 6.0:1 (entry 4). The diastereomeric mixtures of the reduction products were separated by silica gel column chromatography (hexane–benzene 10:1). The reduction of the minor bromoacetals **5a** and **5b** with *n*-Bu_3SnH gave exclusively **8a** and **8b**, respectively. The iodoacetalization of **3a** and **3b** with *N*-iodosuccinimide and the subsequent reduction of the resulting iodoacetals proceeded in similar yields and diastereomer ratios. However, the separation of the diastereomeric products was not attained because of the too small differences of polarity among them.

The configurations at C-2 of the acetals **6**, **7** and **8** were assigned based on the NOE difference spectra. The equatorial methoxy group attached to the carbon atom neighboring to radical center increase the amount of axial attack of the tin reagent to give preferentially **6a** and **6b**.[5] The axial methoxy group in the bromoacetals **5a** and **5b** shield the lower face of the radical center to give exclusively **8a** and **8b**, respectively.[5,14]

In contrast to the reduction of the bromoacetals **4a** and **4b**, the diastereoselectivity in the reduction of the homologous bromoacetals **4c** and **4d** with *n*-Bu_3SnH remarkably depended on the reaction temperature (entries 4, 5, 7 and 8). Higher diastereoselectivities were attained at lower temperature. In the reaction of **4c**, **4d**, **5c** and **5d**, Ph_3SnH was inferior to *n*-Bu_3SnH in diastereoselectivity (entries 5 versus 6; 8 versus 9; 12 versus 13; 14 versus 15). The diastereomeric mixtures **8** and **9** were separated by silica gel column chromatography (hexane–benzene 10:1).

The configurations of methyl group at C-2 of the acetals **6c**, **7c**, **8c** and **9c** were assigned based on the NOE difference spectra and the conformational analysis of the flexible seven-membered rings performed with CONFLEX program using the MM2 force field for energy minimization.[10] The configurations of the phenyl substituted acetals **6**–**9** were assigned by comparing their ^1H NMR spectral data with those of **6c**, **7c**, **8c** and **9c**.

The origin of the high diastereoselectivity for the reactions of acetals **4c**,**d**, **5c** and **5d** can be rationalized on the basis of the structural analysis of the low energy conformers of the radical intermediates. The exhaustive searches of low-energy conformers of the flexible seven-membered radical intermediates **A** and **B** were performed with CONFLEX program,[10] followed by semi-empirical molecular orbital calculations (PM3) of the resulting low energy conformers.[3d,e] The low energy conformers including the global energy minimum conformer **A-1** show that the hydrogen atom transfer proceeds preferentially from the less hindered upper face to give **7d**, whereas the hydrogen atom transfer to the global energy minimum conformer **B-1** proceeds preferentially from the lower face to give **8d** (Fig. 1).

Finally, the acetal rings of **6a**–**6c**, **7a**, **7c**, and **8c** were cleaved by treating with ozone in ethyl acetate at −75°C

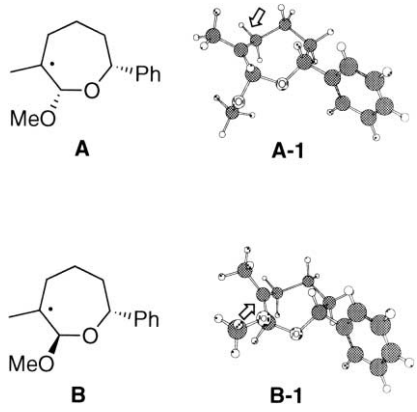


Figure 1. Global energy minimum conformers of the radical intermediates **A** and **B** generated from bromoacetals **4d** and **5d**, respectively.

to give **10a**–**10c**, **11a** and **11c**, respectively, following the procedures reported by Delongchamps and co-workers[15] (Scheme 3). The reaction of acetal **8a** having an axial methoxy group did not proceed as predicted from the literature.

In summary, we reported the stereoselectivity in the formation and radical reduction of cyclic bromoacetals **4** and **5**. The oxidative ring cleavage of the resulting acetals **6**–**8** gave the acyclic δ- and ε-hydroxy-α-methyl-carboxylic acid esters **10** and **11**. The overall yields of **10a**–**10c** from **3a**–**3c** were 48, 37 and 14%, respectively.

References

1. For reviews and books, see: (a) Smadja, W. *Synlett* **1994**, 1–26; (b) Porter, N. A.; Giese B.; Curran, D. P. *Acc. Chem. Res.* **1991**, *24*, 296–304; (c) RajanBabu, T. V. *Acc. Chem. Res.* **1991**, *24*, 139–145; (d) Renaud, P.; Sibi, M. P. *Radicals in Organic Synthesis*; VCH: Weinheim, 2001; Vols. 1–2; (e) Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions*; VCH: Weinheim, 1996.
2. For reviews see: (a) Sibi, M. P.; Porter, N. A. *Acc. Chem. Res.* **1999**, *32*, 163–171; (b) Renaud, P.; Gerster M. *Angew. Chem., Int. Ed.* **1998**, *37*, 2562–2579; (c) Guindon, Y.; Guérin, B.; Rancourt, J.; Chabot, C.; Makintosh, N.; Ogilvie, W. W. *Pure Appl. Chem.* **1996**, *68*, 89–96. For recent examples, see: (d) Iserloh, U.; Curran, D. P.; Kanemasa, S. *Tetrahedron: Asymmetry* **1999**, *10*, 2417–2428; (e) Watanabe, Y.; Mase, N.; Furue, R.; Toru, T. *Tetrahedron Lett.* **2001**, *42*, 2981–2984; (f) Halland, N.; Jorgensen, K. A. *J. Chem. Soc., Perkin Trans. 1*, **2001**, 1290–1295.
3. (a) Nagano, H.; Toi, S.; Yajima, T. *Synlett* **1999**, 53–54; (b) Nagano, H.; Hirasawa, T.; Yajima, T. *Synlett* **2000**, 1073–1075; (c) Nagano, H.; Matsuda, M.; Yajima, T. *J. Chem. Soc., Perkin Trans. 1* **2001**, 174–182; (d) Nagano, H.; Toi, S.; Matsuda, M.; Hirasawa, T.; Hirasawa, S.; Yajima, T. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2525–2538; (e) Nagano, H.; Ohkouchi, H.; Yajima, T. *Tetrahedron* **2003**, *59*, 3649–3663.
4. Unpublished data.
5. Kiyooka, S.-i; Li, Y.-N.; Shahid, K. A.; Okazaki, M.; Shuto, Y. *Tetrahedron Lett.* **2001**, *42*, 7299–7301.
6. For diastereofacial selectivity in reactions of substituted cyclohexyl radicals, see: Damm, W.; Giese, B.; Hartung, J.; Hasskerl, T.; Houk, K. N.; Hüter, O.; Zipse, H. *J. Am. Chem. Soc.* **1992**, *114*, 4067–4079.
7. Recently radical haloacetal cyclizations (Ueno–Stork reaction) controlled by the acetal center have been reported: (a) Villar, F.; Kolly-Kovac, T.; Equey, O. Renaud, P. *Chem. Eur. J.* **2003**, *9*, 1566–1577; (b) Corminboeuf, O.; Renaud, P.; Schiesser, C. H. *Chem. Eur. J.* **2003**, *9*, 1578–1584.
8. (a) Downham, R.; Edwards, P. J.; Entwistle, D. A.; Hughes, A. B.; Kim, K. S.; Ley, S. V. *Tetrahedron: Asymmetry* **1995**, *6*, 2403–2440; (b) Bosci, A.; Chiappe, C.; De Rubertis, A.; Ruasse, M. F. *J. Org. Chem.* **2000**, *65*, 8470–8477.
9. The analysis of low energy conformers of the intermediate bromonium ions in the bromoacetalization of enol ether (*E*)-**3b** calculated by the use of CONFLEX (Ref. 10) and subsequent PM3 programs shows that the lowest energy conformer yielding the minor bromoacetal **5b** is 2.5 kcal mol^{-1} higher in energy than the global minimum energy conformer of the bromonium ion yielding the major bromoacetal **4b**. The calculations for the minor (*Z*)-**3b** suggest the preferential formation of **4b**.
10. (a) Goto, H.; Osawa, E. *J. Am. Chem. Soc.* **1989**, *111*, 8950–8951; (b) Goto, H.; Osawa, E. *J. Chem. Soc., Perkin Trans. 2* **1993**, 187–198.
11. (a) Illuminati, G.; Mandolini, L. *Acc. Chem. Res.* **1981**, *14*, 95–102; (b) Casadei, M. A.; Galli, C.; Mandolini, L. *J. Am. Chem. Soc.* **1984**, *106*, 1051–1056.
12. Macrocyclic iodoacetals have been prepared in good yields under high dilution conditions: Nagano, H.; Tada, A.; Isobe, Y.; Yajima, T. *Synlett* **2000**, *1*, 1193–1195.
13. The chemical shift values of 3-Me for **4a**,**b** and **5a**,**b** are estimated from the δ values of 1-bromo-4-*tert*-butyl-1-methylcyclohexane (Ref. 5) and the substituents effects of OH (instead of OMe) and ring oxygen atom: (a) Schneider, H.-J.; Hoppen, V. *J. Org. Chem.* **1978**, *43*, 3866–3873; (b) Lambert, J. B.; Vagenas, A. R. *Org. Magn. Reson.* **1981**, *17*, 265–269; (c) Booth, H.; Dixon, J. M.; Khedhair, K. A.; Readshaw, S. A. *Tetrahedron* **1990**, *46*, 1625–1652.
14. The shielding of radical center by the neighboring methoxy group has been reported: Nagano, H.; Azuma, Y. *Chem. Lett.* **1996**, 845–846.
15. (a) Deslongchamps, P.; Moreau, C. *Can. J. Chem.* **1971**, *49*, 2465–2467; (b) Taillefer, R. J.; Thomas, S. E.; Nadeau, Y.; Fliszár, S.; Henry, H. *Can. J. Chem.* **1980**, *58*, 1138–1143; (c) Li, S.; Deslongchamps, P. *Tetrahedron Lett.* **1993**, *34*, 7759–7762.