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A Revised Mechanism for Chemoselective Reduction of Esters with Borane–Dimethyl Sulfide Complex and Catalytic Sodium Tetrahydroborate Directed by Adjacent Hydroxyl Group

Seiki Saito,* Teruhiko Ishikawa, Akiyoshi Kuroda, Kazuya Koga, and Toshio Moriwake*
Department of Applied Chemistry, Faculty of Engineering, Okayama University, Tsushima, Okayama, Japan 700

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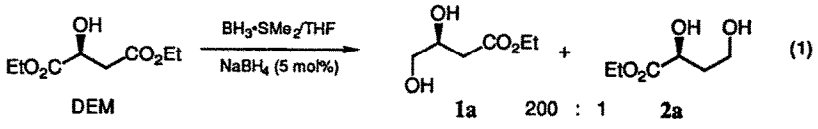
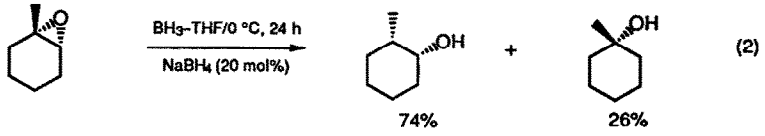
Abstract: The plausible mechanism for the reduction of the ester groups with a strong preference for one located α to the hydroxyl groups of (*S*)-malates and (*R,R*)-tartrate–based derivatives has been proposed together with some results with regard to its applications to the syntheses of chiral synthons.

Introduction

Inexpensive and replenishable sources of chiral carbon compounds such as carbohydrates, α-amino acids, or hydroxy acids have been enjoying large popularity in organic synthesis, in particular, enantiomerically pure natural product synthesis, over the years.[1] Among them, the hydroxy acids should be useful because they hold carboxylic acid groups which are not shared by other chiral carbon sources except for the α-amino acids. Unfortunately because available entries, except for (*S*)-lactic acid, are dicarboxylic acids such as (*S*)-malic acid or (*R,R*)-tartaric acid, these are not readily amenable to site selective reduction, and in general, submission to metal-hydride reduction gives poly-hydroxyl compounds and, consequently, there survives no carbonyl functionality.[1] This is probably because an efficient method for site-selective transformations of the carboxyl groups has been lacking with a few exceptions, for instance, partial hydrolysis of diethyl 2,3-*O*-isopropylidene-L-tartrate[1b,c] or enzymatically differentiated hydrolysis of dimethyl (*S*)-malate.[2]



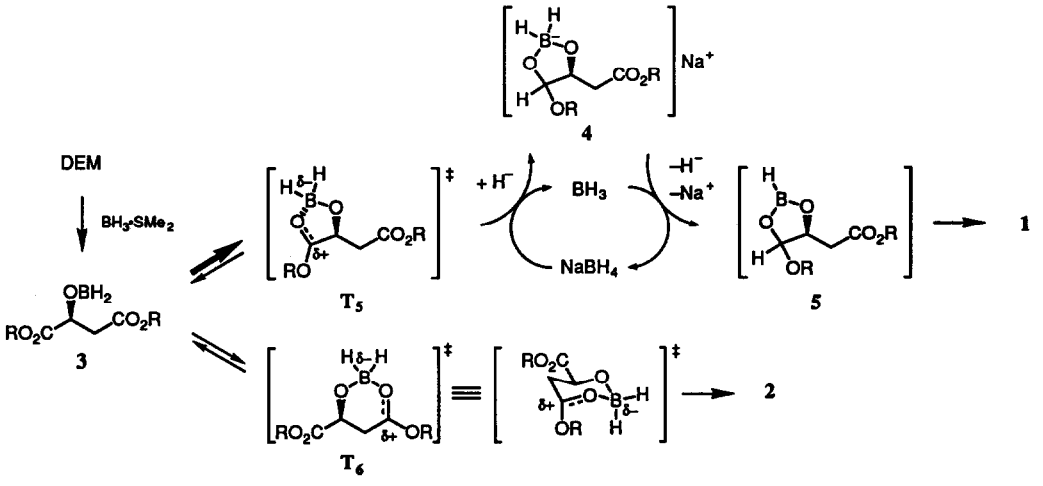


After long-standing endeavor toward this issue, we succeeded in reducing the ester group α to the hydroxyl group in diethyl (*S*)-malate (DEM) in an extremely selective manner with the combination of borane-dimethyl sulfide complex (BMS) and catalytic sodium tetrahydroborate ($NaBH_4$) (Eq 1).[3] This solution bases on knowledge that a given epoxide can be reduced with borane-THF complex much faster in the presence of catalytic

$NaBH_4$ or $LiBH_4$ than without the catalyst as has been observed by Brown and Yoon (Eq 2).[4] They pointed out that borane coordinates to the epoxide, which enhances the polarization of its C—O bond, resulting in facile delivery of hydride from added borate anion to the carbon concerned. Although the synthetic potential of this chemistry had never been exploited in organic synthesis, a mechanistic description had provided us with a valuable clue with respect to how we can achieve the site selective reduction of the ester group α to the hydroxyl group even in the presence of the β-ester group for (*S*)-malates or (*R*,*R*)-tartrate-based diesters.

Although a possible mechanism for such a process had been tentatively presented in a separated paper,[5] which is shown again below (Scheme I), there had been no idea for the fate of the intermediate (**4** or **5**) or what's happening during the course of **5** → **1**. It had been also unclear whether the reaction was kinetically controlled or not. In this article we disclose a revised mechanism in these contexts based on the results obtained from additional significant experiments. We also provide some chiral synthons available through the selective reduction as a key step.

Scheme I.

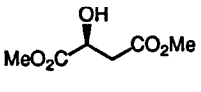


Results and Discussion

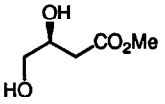
Selective reduction of (S)-malic acid diesters. When DEM was treated with one-mole equivalent BMS in THF at room temperature, evolution of hydrogen gas took place immediately and ceased after 45 minutes, the amount of which was equivalent to a molar quantity of the DEM employed. Diagnosis by TLC at this stage indicated that no reduction had proceeded yet, only one spot corresponding to the starting DEM being visualized. This fact clearly suggests that the initial product should be oxyborane-type intermediate **3** (Scheme I). After $NaBH_4$ (5 mol%) was added to the reaction mixture, immediate TLC monitoring indicated that reduction actually started and required one hour at room temperature for completion followed by EtOH addition for quenching the reduction: it should be noted that only a small amount of hydrogen gas evolved on this operation, which probably means that nearly all hydrogens having existed on the boron atom were consumed for the reduction.[6]

After neutralizing sodium ethoxide stemming from the catalyst with *p*-toluenesulfonic acid and ensuing evaporative workup, the residual mixture was subjected to column chromatography (SiO_2), giving rise to ethyl (3*S*)-3,4-dihydroxybutanoate **1a** in 88–97% yield. Attempted distillation of this chromatographically pure diol

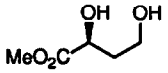
ester resulted in significant decomposition of the product. Treatment of crude **1a** with 2,2-dimethoxypropane in acetone in the presence of *p*-toluenesulfonic acid gave the corresponding 3,4-*O*-isopropylidene derivative **6a**. Careful capillary GLC analysis of this acetonide indicated that it consisted of **6a** and a very small amount of **7a**,[7] corresponding to β-ester-reduction product **2a**, in a ratio 200 : 1. It turned out that there exist enough differences between these acetonides in terms of GLC retention times[8] and TLC R_f values.[9] Separation of a mixture of **6a** and **7a** by fractionation or column chromatography to give optically and chemically pure **6a** which, on spectroscopic diagnosis (IR, ^{1}H-NMR, ^{13}C- NMR, and mass), was totally consistent with the expected structure.



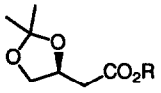
DMM



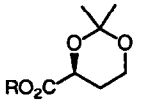
1b



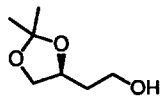
2b



6a: R=Et
6b: R=Me



7a: R=Et
7b: R=Me



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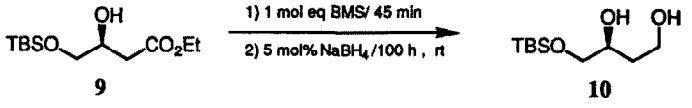
Dimethyl (*S*)-malate (DMM) was also reduced in the same way as that for DEM and subsequently transformed to the corresponding acetonide **6b** and **7b**[10] in a ratio 99:1. The optical rotation value of **6b** was identical with that derived from DMM via enzymatically-promoted hydrolysis and ensuing *"BMS"* reduction of the resulting carboxylic acid functionality.[2] Reduction of **6b** with LAH afforded (2*S*)-1,2-*O*-isopropylidene-1,2,4-butanetriol **8**, which indicated physical and spectral properties as well as optical rotation value identical with those reported by Meyers.[11]

Revised Mechanism. The initial formation of the oxyborane intermediate **3** seems highly probable in this process as mentioned above. Accordingly, actual reduction must ensue from **3**. This means, in turn, that the observed site selectivity in this reduction should reflect an activation energy difference between two possible transition states where the boron atom intramolecularly coordinates on either of the carbonyl oxygens to form the five or six-membered structures, $\mathbf{T_5}$ or $\mathbf{T_6}$ (Scheme I). It is well known that the probability of neighboring-group participation is dependent on the ring size formed in a transition state. In most cases, neighboring-group participation is most favored for five-membered cyclic array as a result of the balance between strain energy and entropy factors under kinetically controlled conditions.[12] In addition, rather severe 1,3-diaxial interaction between the ester alkoxy-group and the hydrogen on the boron atom should be involved in the transition state $\mathbf{T_6}$ because of short boron-oxygen bond length. The following experimental result falls in line with this interpretation.

When DEM was treated with BMS *in toluene in place of THF* at room temperature, *the evolution of hydrogen gas was observed likewise,* indicating the formation of **3**. Unlike THF, *the reduction has never proceeded to an any extent in this solvent even after overnight standing of the solution.* The addition of catalytic $NaBH_4$ to the solution at this stage immediately initiated the reduction. The reaction completed within 2 hours, giving rise to the diol esters in almost the same yield as in the case of THF solvent. The site selectivity, however, turned out to be 92:8 (**6a**:**7a**) as verified by GLC analysis. In addition, prolonged standing of **3** in toluene (3 days) and subsequent reduction by a addition of catalytic $NaBH_4$ did not change the ratio. These results provide strong support that the standard conditions (45 minutes with BMS and 1 hour exposure to $NaBH_4$) allow the reduction to proceed under

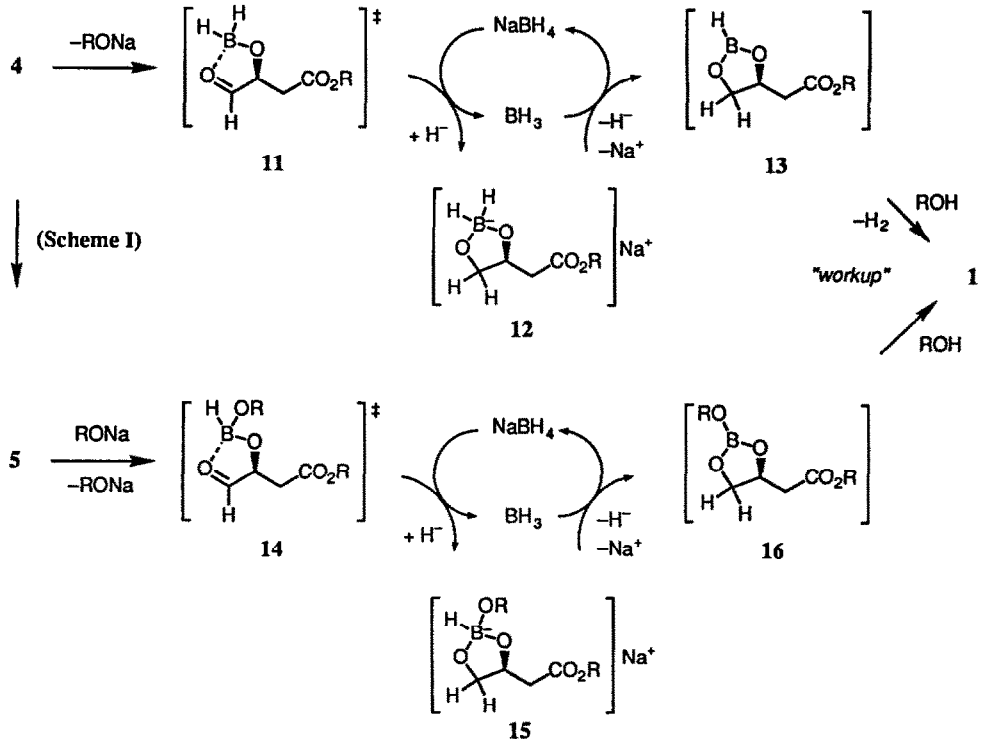
kinetically controlled conditions and that the reduction proceeded almost exclusively through T_5, leading to **1**. Much better selectivity observed for DEM (200 : 1) as compared with DMM (99 : 1) can be explained on this basis: the ethoxy group involved in T_6 must suffer from somewhat larger non-bonded repulsion than the methoxy group. We also examined the reduction of ethyl (3*S*)-4-(*tert*-butyldimethylsilyloxy)-3-hydroxybutanoate **9**, derived from **1a** through selective silylation, to **10** under the standard conditions as mentioned above. As expected, it was observed that completion of the reduction required extremely longer time, clearly indicating that T_6 transition state is fairly unfavorable.

Scheme II.



9 **10**

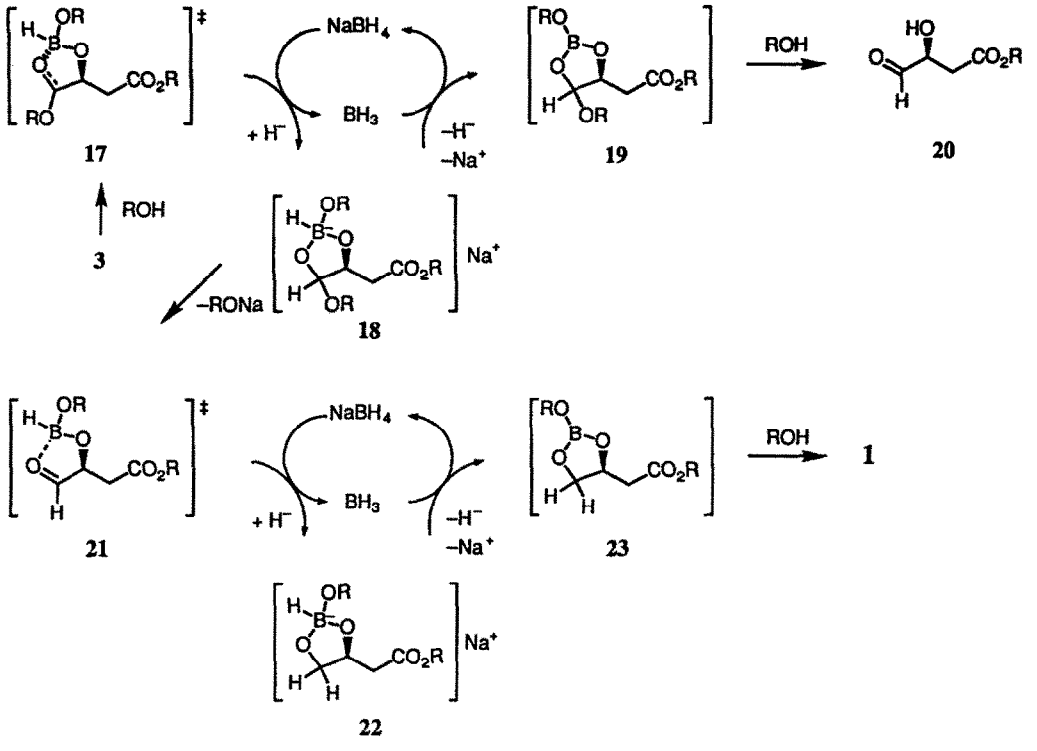
Scheme III.



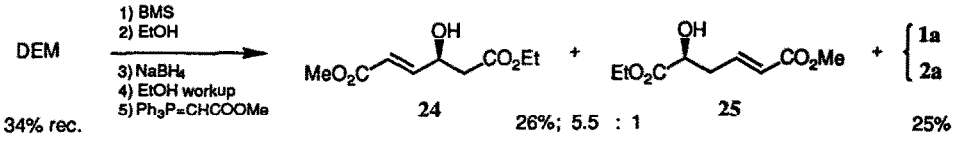
11 **13** **12** **14** **16** **15**

We described in the previous mechanism (Scheme I) that only **5** leads to **1**. However, in the revised proposal, we should consider another possible pathway that **4** can release sodium alkoxide to give an aldehyde which is immediately followed by activation of itself through boron-coordination (**11**) (Scheme III). Thus, the reduction of **11** proceeds likewise as the process **4** to **5**, giving rise to **13** via **12**. On the other hand, sodium alkoxide-induced

Scheme IV.



Scheme V.



rearrangement of the ethoxy group to the boron atom in **5** results in the formation of **14**. The aldehyde group of **14** coordinating with the boron atom is quickly reduced in the same manner as **11** to **13** to furnish one of the final products **16**. Otherwise **5** would be led to an aldehyde by an alcohol workup. Indeed, when the reduction of DEM was conducted in the presence of Wadsworth–Emmons reagent (Na salt) or the reaction mixture before or after workup was treated with the same reagent, no enoate was detected at all. This indicates that an aldehyde was not one of final products or, even if exists as an intermediate in this process, it is very quickly reduced.

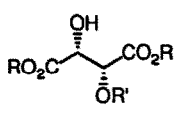
As has already mentioned, the addition of alcohol to the reaction (workup) was accompanied by an only small amount of hydrogen evolution.[6] This probably means that boron–hydrogen bond remained only in limited species at the final stage of the reduction. The revised mechanism suggests that the species having boron-hydrogen bond should be **13**, the amount of which may correspond to that of $NaBH_4$ added. In line with this assumption, an

amount of hydrogen gas evolved turned out to be roughly paralleled to such expectation.[6]

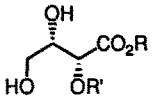
If the revised mechanism is to be the case, the mechanism outlined in Scheme IV can be proposed when **3** is treated with equimolar amount of an alcohol prior to the addition of $NaBH_4$. In this case, two reaction pathways commencing from **17** produced from **3** are to afford not only **1** but also α-hydroxyaldehyde (**20**) via the final products **19** and **23**, respectively. In the event, to a solution of DEM in THF was added BMS to effect the formation of **3** followed by the addition of EtOH (molar equivalent) and the mixture was stirred until evolution of hydrogen completed. Then, a catalytic amount of $NaBH_4$ was added to the reaction mixture and the reaction was continued for 1 h. Indeed, after usual workup (ethanol addition), the reaction mixture was treated with methoxycarbonylmethylenetriphenylphosphorane to give a mixture of γ- and δ-hydroxy-α,β-unsaturated ester (**24** and **25**) in 26% yield together with unchanged DEM (34%) and a mixture of **1a** and **2a**. It should be mentioned that the reduction through **17** resulted in significant damage on the site-selectivity as 5.5 : 1. This probably stems from an increase in Lewis acidity of the boron atom as a consequence of the additional appendage of an electronegative group to it (dioxyborane intermediate **17**) as compared with **3**, which provided an increasing opportunity for the boron to coordinate with the β-carbonyl group.

Thus, it is a well-founded conjecture that the reduction of malic acid diesters involves the formation of **3** as the initial intermediate which allows quick hydride delivery from $NaBH_4$ to itself. Thus-generated second intermediate **4** is destined to be partitioned into two reaction pathways leading to **11** and **14**. The catalytic action assembled among **11**, **14**, and $NaBH_4$ must be invoked in order to explain unusually large rate enhancement exhibited by added $NaBH_4$. In any event, BMS can offer one hydride for the formation of the oxyborane intermediate **3** which plays a crucial role in activating neighboring carbonyl functionality site-selectively. Two hydrides involved in BMS can be efficiently supplied to the carbonyl carbon by way of **3**, no hydrides of BMS being consumed wastefully.

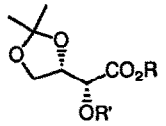
Reduction of tartaric acid derivatives. We recorded only three examples for the application of the site-selective reduction of α-hydroxy ester as mentioned above to tartaric acid family in the previous reports.[3,5,13] In order to gain more insight into the mechanism, in particular, with regard to transition state model, systematic studies on the site-selective reduction of this class of compounds have been conducted.



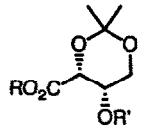
26a–d



27a–d

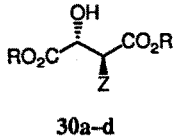


28a–d

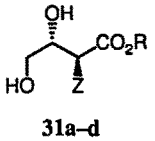


29a–d

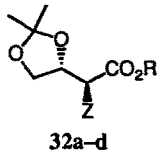
(**a**: R = Et, R'= THP; **b**: R = Et, R'= *t*Bu; **c**: R = Me, R'= Pival; **d**: R = Me, R'= Bn)



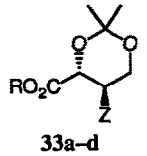
30a–d



31a–d



32a–d



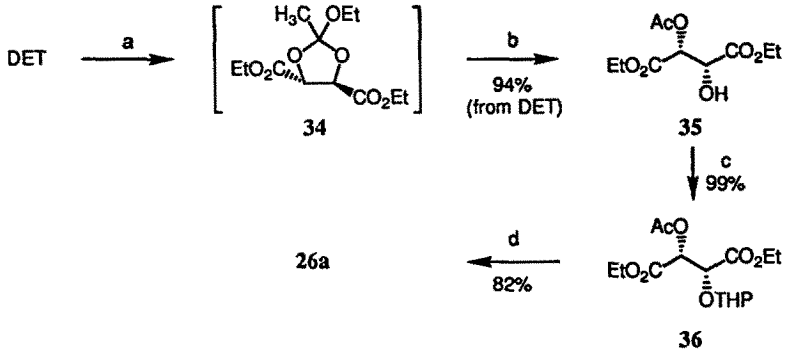
33a–d

(**a**: R = Me, Z = Br; **b**: R = Me, Z = Cl, **c**: R = Et, Z = Me; **d**: R = Et, Z = N$_3$)

Thus, to explore a trend in the site selectivity for the tartrate series, **26a-d** were prepared from dimethyl or diethyl (*R*,*R*)-tartrate (DMT or DET) by (1) a conventional method for alcohol protection[14] followed by isolation

of mono-*O*-protected product by column chromatography over SiO_2 from a statistical product mixture, (2) *O*-stannylene acetal strategy,[15] or (3) a newly developed method for the selective protection of tartrates featuring mono-*O*-acetyl tartrate followed by ready deprotection of the acetyl group. The third method makes it easy to introduce a desired protective group onto a remaining hydroxyl group (Scheme VI).[16] The anti-series **30a-d** were obtained according to the published methods.[17]

Scheme VI.



(a) 5eq $MeC(OEt)_3$/TsOH/THF/rt/2.5h; (b) EtOH/TsOH/rt/1.5h, cc purification; (c) 1.2 eq DHP/CSA/CH_2Cl_2/rt/0.5h, cc purification; (d) 1.0 eq NaOEt/EtOH/0°C/1h, cc purification.

The reductions were carried out under the standard conditions established for the tartrate series (2 hours with BMS and two-hour exposure to $NaBH_4$ in THF at room temperature) and the site selectivity was analyzed with GLC for the corresponding acetonides **28**, **29**, **32** and **33**. These results are shown in Table 1.

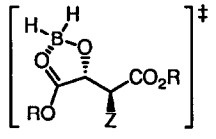
Contrary to our expectation, the site selectivity of the tartrate series changed from substrate to substrate with poor to excellent selectivity. Site selectivity of the reduction in this series should be also controlled by relative population of boron-coordinated species **Ta5** and **Ta6**, or **Ts5** and **Ts6**, corresponding to **T5** and **T6**, respectively. For instance, **30a** (Z = Br) can take the cyclic structure involving six atoms where the bromine holds equatorial (**Ta6**: Z = Br) and anti-periplanar relationship to the ester carbonyl group coordinating with the boron atom. The C—Br bond dipole may enhance the polarization of the adjacent C=O bond, which may result in significant electrophilic coordination by the boron atom. Accordingly, increasing population of **Ta6** can result as compared with DEM. This can consistently explain the observed site selectivity ratio 4 : 1 (entry 5 in Table1). Much better selectivity for **30b** (Z = Cl), 19 : 1 (entry 8 in Table 1), can be also explained on the basis of a less polar nature of a C—Cl bond. In line with this discussion, non-polar groups such as methyl or azido upgraded the selectivity to 99 : 1 (entries 9 and 10 in Table 1).

A method capable of improving the site selectivity of the reduction for **30a** may be an introduction of more bulky alkyl groups into the ester moiety because they would exert more non-bonded repulsion as recognized from the structure of **Ta6**. This idea gave a primary answer to the problem. As indicated in Table 1, diethyl or diisopropyl esters **30a'** (R = Et) or **30a"** (R = *i*-Pr) gave **31a'** (R = Et) or **31a"** (R = *i*-Pr) in improved ratios such as 9 : 1 (entry 6) or 99 : 1 (entry 7), respectively, though the reduction required much longer time and the chemical yields decreased to 64% and 50%, respectively.

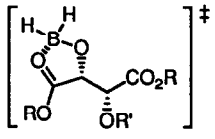
Table 1. Selective Reduction of Tartrate Derivatives.[a]

	Substrate			*Acetonide*	
					Ratio[b]
Entry		R' or Z	R	Yield/%[c]	5-mem. : 6-mem.
1	**26a**	THP[d]	Et	80[e]	40 (28a)[e] 1 (29a)[e]
2	**26b**	*t*-Bu	Et	80	8 (28b) 1 (29b)[f]
3	**26c**	pival[g]	Me	76	9 (28c) 1 (29c)[f]
4	**26d**	Bn	Me	55	2 (28d) 1 (29d)
5	**30a**	Br	Me	74	4 (32a) 1 (33a)
6	**30a'**[h]	Br	Et	64[i]	9 (32a')[j] 1 (33a')[j]
7	**30a"**[k]	Br	*i*-Pr	50[i]	99 (32a")[l] 1 (33a")[l]
8	**30b**	Cl	Me	82	19 (32b)[m] 1 (33b)[m]
9	**30c**	CH_3	Et	65	99 (32c) 1 (33c)
10	**30d**	N_3	Et	75	99 (32d) 1 (33d)

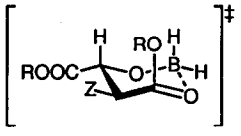
(a) 1. BMS (1.02 mol eq)/THF/rt/2 h; 2. $NaBH_4$ (5 mol%)/rt/2 h; 3. 2,2-dimethoxypropane/acetone/TsOH(cat)/rt/completion of the reaction by TLC; (b) Determined by capillary GLC: the 6–membered actonides were always eluted more slowly; (c) For chromatographically pure product: before converting these products to the corresponding acetonides, the structure of each regioisomer given by the reduction was determined by an NMR spectroscopy for the corresponding primary-*O*-TBDMS-protected derivatives, in some cases, because they were able to be easily separated by LC; (d) Diastereomeric mixtures at stereogenic center of THP moiety; (e) Acetonide, not synthesized: this ratio was obtained after converting the reduction mixture to ethyl 4-(*tert*-butyldimethylsiloxy)-3(or 2)-mesyloxy-2(or 3)-hydroxybutanoate (see ref. 5); (f) The formation of the 6–membered acetonide required a large excess of 2,2-dimethoxypropane and prolonged reaction time: otherwise the 5–membered acetonide was exclusively formed (see text); (g) 2,2-Dimethylpropanoate; (h) Diethyl ester; (i) Required much longer reaction time; (j) The *O*–alkyl group of **32a'** should be a ethyl group; (k) Diisopropyl ester; (l) The *O*–alkyl group of **32a"** should be a isopropyl group. (m) Acetonide, not synthesized: this ratio was obtained after converting the reduction mixture to methyl 4-(*tert*-butyldimethylsiloxy)-2(or 3)-chloro-3(or 2)-hydroxybutanoate



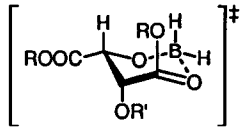
Ta5



Ts5



Ta6



Ts6

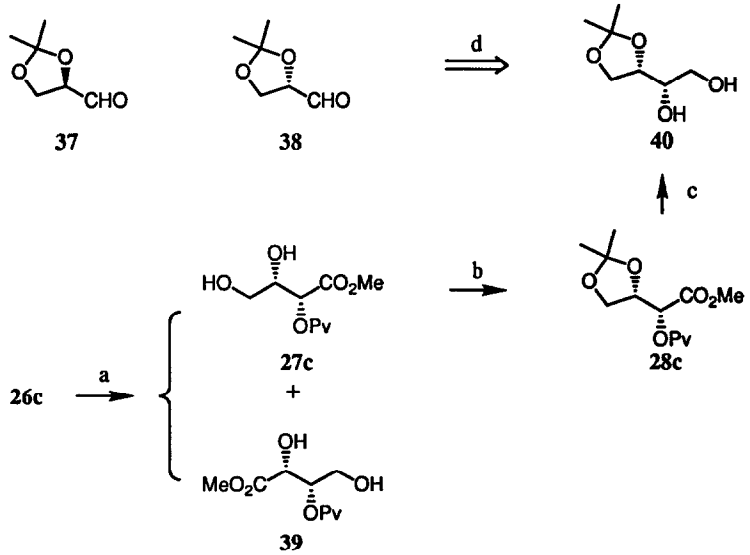
On the other hand, regiochemical outcomes for (*R*,*R*)-type substrates such as **26a-d** seem to depend on a delicate balance between steric and electronic factors. We had hoped that the corresponding six-membered boron-

coordinated species **Ts6** would interfere the hydride anion to approach the carbonyl group because of axial arrangement of the protected hydroxyl groups, which would increase α-reduction selectivity. However, this is not the case except for **26a** (THP-protection: Entry 1 in Table 1). Reasonable explanation for the relative population between **Ts5** and **Ts6** in this series must await future investigations.

Synthetic applications: An easy access to diol esters **1** from malates and α-substituted diol esters **27** or **31** from tartrate-based diesters has made approach to potent chiral synthetic intermediates possible. We have already reported on the synthetic works concerning with otherwise risky access to such compounds.[3,5,12,18] In addition, several other laboratories have announced interesting syntheses[19] employing **1a** or **1b** prepared after our method.[3] Here, we present additional efforts to synthesize valuable chiral synthons.

(A) Synthesis of (S)-2,3-O-isopropylideneglyceraldehyde. (*R*)- and (*S*)-2,3-*O*-Isopropylideneglyceraldehyde **37** and **38**, respectively, are well-accepted as highly versatile chiral synthons in organic synthesis.[20] Whereas the (*R*)-isomer has been within our facile reach over fifty years,[21] the (*S*)-antipode has been rather hard to access until recently.[22] Because it can fulfill various synthetic requirements, a practical route to the (*S*)-isomer has been investigated and two representative protocols beginning with L-ascorbic acid[23] and L-tartaric acid[24] have been published so far. The site selective reduction of **26c** opens the third entry to this area (Scheme VII). In the event, under the standard conditions for the tartrate series, the reduction of **26c** resulted in the formation of **27c** and **39** in the ratio 9 : 1. The mixture of **27c** and **39** was directly treated with 2,2-dimethoxypropane and acetone in CH_2Cl_2 to effect the formation of only five-membered crystalline acetonide **28c** in 73% yield after distillation: to our delight, no sign of a six-membered isomer was detected by a capillary GLC or ^{13}C-NMR diagnosis. Higher-purity grade **28c** was available, if necessary, by recrystallization. Usual LAH reduction of **28c** and non-aqueous workup (see experimental) led to L-threitol-1,2-acetonide **40** in 94% yield after distillation, the immediate precursor for **38**.[24b] Indeed **40** was led to **38** through oxidative C—C bond cleavage ($NaIO_4$) as reported.[24b] Both **28c** and **40** exhibited so high stability that they could be stored in a refrigerator for years without any detectable deterioration.

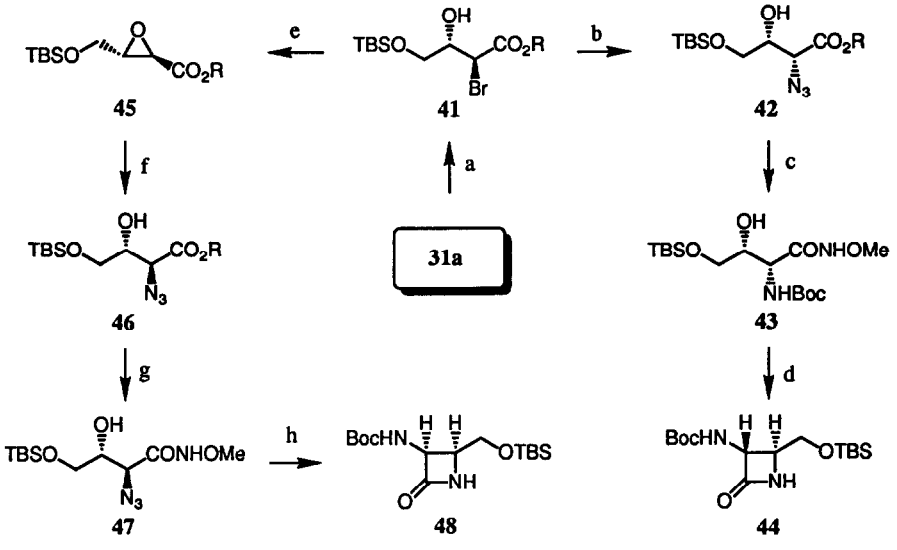
Scheme VII.



a) BMS /THF/rt/2 h and, then, $NaBH_4$/THF/rt /2 h; b) 2,2-dimethoxypropane/acetone/ TsOH/CH_2Cl_2/rt/3 h:; c) LAH /THF/0 °C ~ rt/2 h; d) $NaIO_4$.

(B) ***Synthesis of optically active β-lactams.*** The synthetic potential of **41** as a *trans*-3-amino-β-lactam framework is noteworthy. This bromo ester is available through recourse to the site-selective reduction of **30a** followed by its primary hydroxy protection in a high yield. For instance, an S_N2 displacement of the C-2 bromine of **41** with HN_3–amine reagent (*i*-Pr_2EtNHN_3: 2.2 eq) in DMF proceeded to afford 2-azidobutanoate (**42**) in 75% yield, in which no epimerization at the stereogenic centers was detected.[25] The reaction of **42** with methoxyamine hydrochloride mediated by trimethylaluminum[26] afforded an *N*-methoxyamide in 55% yield. Subsequent execution of a single-pot procedure for N_3 to NHBoc conversion[27] effected the formation of the corresponding *N*-boc-amino-*N'*-methoxyamide (**43**) in 86% yield. This was led to the *trans*-β-lactam (**44**: $J_{3,4}$ = 1.5 Hz) in 70% yield under the Mitsunobu conditions[28] followed by reductive demethoxylation. In addition, *cis*-β-lactam (**48**) was available from *trans*-epoxyester (**45**) accessible again from **31a** via **41**.[5] Through highly regioselective cleavage of the epoxy group at C-2 with the same azide reagent as above, **46** bearing anti–azidohydrin arrangement was provided.[29] Essentially the same sequence of transformations from **46** as for **42** except for a reversed execution of the Mitsunobu reaction and N_3 to NHBoc conversion[27] provided the *cis*-β-lactam (**48**: $J_{3,4}$ = 5.1 Hz) in 38% overall yield (4 steps). TBS-deprotected **48** was identified with the corresponding reported compound[30] in all respects. Thus, four possible stereoisomers become available in a formal sense with very high enantiomeric and diastereomeric purity from tartaric acid–based chiral synthons such as 2-bromo-3-hydroxy- and 2,3-epoxybutanoate derivatives because the availability of their antipodes is now self-evident when starting from D-tartaric acid.

Scheme VIII.



(a) TBS-Cl/imidazole/THF/rt, 20 min; (b) R=Me (*i*-Pr)$_2$EtNHN$_3$/DMF/40°C, 10 h; (c) 1. H_2/Pd–C/Boc_2O/AcOEt/rt, 3–3.5h, 2. NH_2OMe/$AlMe_3$/PhH/50°C, 3–4 h; (d) 1. DEAD/Ph_3P/THF/rt, 2. Na/NH_3/*t*-BuOH /THF/–60°C, 10 min; (e) R=Me NaOMe/MeOH/0°C (1 h)— rt (45 min); (f) (*i*-Pr)$_2$EtNHN$_3$/ DMF/rt, 24 h; (g) NH_2OMe/$AlMe_3$/PhH/50°C, 3-4 h; (h) 1. DEAD/Ph_3P/THF/rt, 2. H_2/Pd–C/Boc_2O/AcOEt/rt, 3–3.5h, 3. Na/NH_3/*t*-BuOH /THF/–60°C, 10 min.

Concluding remark. The mechanism which seems plausible has been proposed from the observations that workup resulted in a small amount of hydrogen evolution corresponding to catalytic $NaBH_4$ and the replacement

of one of two hydrides existing on the boron atom with an alkoxide group at the stage of **3** led to the formation of a significant amount of formyl derivatives. However, its unambiguous description, in particular, the catalytic cycle illustrated in Scheme I, is open to future studies including isotope scrambling experiments.

The method for the selective reduction of vicinal hydroxy-ester functionality to 1,2-diol framework requires only BMS and catalytic $NaBH_4$. This procedure can be carried out on as large as a 35-g scale with operational simplicity at ambient temperature. The site selectivity observed for a number of cases turned out to be, in general, high and, more importantly, one of the ester groups was left behind unchanged. The survived ester group was able to be incorporated into molecules to serve as an important functional group for further elaboration.

Experimental Section

General Methods. Melting points were determined on a Yamato capillary melting point apparatus and are uncorrected. IR spectra were obtained with a Hitachi 215 grating infrared spectrometer, only the major absorptions being cited. The ^{1}H-NMR spectra, 60, 100, 200, 300, and 500 MHz, were recorded on JEOL PMX-60-SI, JEOL FX-100, Varian VXR-200, Varian VXR-300, and Varian VXR-500 instruments, respectively. The ^{13}C-NMR experiments operated at 25, 50, 75, and 126 MHz were carried out on the JEOL FX-100, Varian VXR-200, Varian VXR-300, and Varian VXR-500, machines, respectively. Deuteriochloroform containing tetramethylsilane (TMS: 1%) or without TMS was used for the JEOL instruments or the Varian machines, respectively, where the chemical shifts are given in δ units relative to internal TMS for the former or relative to internal $CHCl_3$ for the latter. Multiplicities are reported with the following abbreviations: s = singlet (NMR) or shoulder (IR), d = doublet, t = triplet, q = quartet, m = multiplet, b = broad. Optical rotation were taken on a JASCO DIP-4 digital polarimeter using a 3.5 mmϕ x 0.5 dm pyrex cell. Mass spectra were obtained on a JEOL JMS-DX303 instrument operated in the chemical ionization (CI) mode. Elemental analyses were made with a Perkin–Elmer 2400 CHN Elemental Analyzer. GLC analyses were carried out on a Shimazu GC-8A gas chromatograph employing a glass-capillary column (Thermon–1000: 30 m x 0.25 mmϕ). Analytical TLC was executed on pre-coated Merck silica gel 60 F_{254} (0.25 mm thickness).

THF and ether were distilled from sodium benzophenone ketyl just before use. Toluene was distilled from sodium. Acetonitrile, benzene, dichloromethane, pyridine, and triethylamine were distilled from CaH_2. Acetone was distilled after drying over molecular sieves (4Å). Ethanol and methanol were distilled from magnesium. Borane–dimethyl sulfide complex (BMS) is purchased from Aldrich. Sodium tetrahydroborate ($NaBH_4$) was obtained from Kishida Chem. Co. in 98% purity (specific grade tablets for arsenic analysis) and ground to powder under nitrogen atmosphere when it is put to use. Organic sulfonic acids were used as its hydrate. Diesters of (*S*)-malic acid or (*R*,*R*)-tartaric acid were prepared following the published method.[31]

Column chromatography was carried out with Merck product (silica gel 60-7743) and abbreviated as "CC (weight of SiO_2 used)". A procedure expressed as "concentration" (or "be concentrated") means rotatory evaporation of solvent or combined extracts under suction at 30–40 °C. Description such as "a workup" corresponds to a series of experimental procedures involving washing with brine, drying ($MgSO_4$ for ether extract and Na_2SO_4 for other solvents), filtration, and concentration. All reactions were carried out under an atmosphere of dry nitrogen or argon, employing flame-dried glasswares.

Ethyl (3*S*)-3,4-Dihydroxybutanoate (1a) and Ethyl (3*S*)-3,4-*O*-Isopropylidene-3,4-dihydroxybutanoate (6a). *Caution! Dimethyl sulfide complexed with borane is released during the course of the reaction, in particular, rapidly after the addition of $NaBH_4$. This experiment should be carried out in a well-ventilated hood.*

In a 1-L, two-necked, round-bottomed flask mounted with a short reflux condenser was placed a solution of

DEM (33.5 g, 0.176 mol) in THF (380 mL). To this was added BMS (10 M, 1.03 eq) dropwise at 20 °C under stirring during 30 min. The solution was stirred at that temperature until evolution of hydrogen ceased (30 min). Then, the flask was cooled with a water-ice bath (10 °C) and stirring was continued for 10 min. To the solution was added $NaBH_4$ powder (333 mg, 5 mol%) in one portion (exothermic) under vigorous stirring at that temperature. When the exothermic reaction subsided, the water bath was removed and the reaction was continued at room temperature until the disappearance of DEM (30 min–1 h) on TLC diagnosis [R_f-values with hexane–AcOEt (1:19): 0.5 (DEM) and 0.2 (**1a**)] . To the reaction were added EtOH (60 mL) and *p*-TsOH (1.67 g, 5 mol%) and resulting slightly cloudy solution was stirred for 30 min at room temperature, followed by concentration to give a colorless gum. This was dissolved in benzene-EtOH (1:1; 380 mL) and the resulting solution was concentrated again: this operation was repeated. To the residue was added benzene (300 mL) and the solution was concentrated, which was repeated to eliminate EtOH and $B(OEt)_3$ as thoroughly as possible to give a clear, colorless gum. CC (120 g) of this crude diol using EtOAc afforded **1a** (32.1 g) in 97% yield after overnight treatment of the residual diol under high vacuum (0.05 mmHg): $[\alpha]^{25}_D$ +6.22° (c 1.22, $CHCl_3$): the continuing elution with AcOEt–MeOH (85 : 15) gave 1,2,4-triol (0.13 g, 0.8%). Attempted distillation of the chromatographically pure **1a** under reduced pressure resulted in a significant decomposition.

A part of the diol (1.82 g, 12.3 mmol) in acetone (6.5 mL) with 2,2-dimethoxypropane (1.7 mL) and *p*-TsOH (0.12 g) was stirred at room temperature for 20 min, neutralized with Et_3N, diluted with Et_2O (20 mL), and filtered through a silica gel pad (15 x 30 mm), the pad being rinsed with Et_2O (60 mL). The combined Et_2O solutions were concentrated by distillation (Vigreux column) to give a colorless oil: GLC analysis (140 °C, carrier gas N_2; 5 mL/min) indicated that the oil consisted of **6a** (t_R=11.1 min) and **7a** (t_R=16.1 min) in the ratio 200:1. R_f values for **6a** and **7a** with hexane–AcOEt (4:1) were 0.26 and 0.45, respectively. An authentic sample of **7a** was prepared as reported by Mori[7] and used as a standard in the GLC and TLC analyses. The ^{13}C–chemical shifts of the acetal carbons are typical for **6a** (109.9 ppm) and **7a** (99.0 ppm) and highly diagnostic. CC (15 g) of this oil with 150 mL of hexane–Et_2O (5:1) afforded **6a** (2.0 g, 86%) free from **7a** after distillation: bp 110 °C/23 mmHg; $[\alpha]^{24}_D$ +27.0° (c 1.17, $CHCl_3$), $[\alpha]^{24}_D$ +15.4° (c 1.34, EtOH); ^1H-NMR (100 MHz) δ 1.27 (t, 3H, CH_3), 1.36 (s, 3H, CH_3), 1.41 (s, 3H, CH_3), 2.49 (dd, 1H, J_{gem} = 15.8 Hz, J_{vic}= 7.1Hz, C*H*H), 2.74 (dd, 1H, J_{gem} = 15.8 Hz, J_{vic}= 6.1 Hz, CH*H*), 3.65 (dd, 1H, J_{vic} = 6.3 Hz, J_{gem} = 8.2 Hz, ring-C*H*H), 4.16 (q, 2H, CO_2CH_2), 4.16 (dd, 1H, J_{vic} = 5.8 Hz, J_{gem} = 8.2 Hz, ring-CH*H*), 4.51 (m, 1H, ring-CH); ^{13}C-NMR (25 MHz) δ 14.2(q), 25.5 (q), 26.9 (q), 39.0 (t), 60.5 (t), 69.2 (t), 72.2 (d), 109.9 (s), 170.4 (s); exact mass, m/z 188.1042 (calcd for $C_9H_{16}O_4$, m/z 188.1049). Anal. Calcd for $C_9H_{16}O_4$, C, 57.43; H, 8.57. Found: C, 57.31; H, 8.47.

Methyl (3*S*)-3,4-*O*-Isopropylidene-3,4-dihydroxybutanoate (6b): bp 79–80 °C/6 mm; $[\alpha]^{22}_D$ +18.2° (c 5.03, $CHCl_3$), $[\alpha]^{22}_D$ +8.62° (c 5.01, EtOH), (lit.[2] $[\alpha]_D$ +17.0° (c 2.00, $CHCl_3$); ^1H-NMR (100 MHz) δ 1.36 (s, 3H, CH_3), 2.52 (s, 3H, CH_3), 2.52 (dd, 1H, J_{gem} = 15.7 Hz, J_{vic} = 6.8 Hz, C*H*H), 2.71 (dd, 1H, J_{gem} = 15.7 Hz, J_{vic} = 6.4 Hz, CH*H*), 3.65 (dd, 1H, J_{gem} = 8.3 Hz, J_{vic}=6.3 Hz, ring-C*H*H), 3.70 (s, 3H, OCH_3), 4.16 (dd, 1H, J_{gem} = 8.3 Hz, J_{vic} = 5.9 Hz, ring-CH*H*), 4.45 (m, 1H, ring-CH); ^{13}C-NMR (50 MHz) δ 25.4 (q), 26.8 (q), 38.7 (t), 51.6 (q), 69.0 (t), 71.9 (d), 109.1 (s), 170.9 (S); IR (film) 1745, 1421, 1385, 1375, 1215, 1070 cm^{-1}; mass m/z (EI, 70 eV) 159 (M – CH_3).

(2*S*)-1,2-*O*-Isopropylidene-1,2,4-butantriol (8). To a cooled solution of **6b** (2.58 g, 14.8 mmol) in THF (25 mL) was added a solution of $LiAlH_4$ in THF (1.32 M, 0.55 mol eq) at –40 °C. The clear solution was stirred at –40 – –30 °C for 3 h and, then, CH_2Cl_2 (25 mL) was introduced to it. The reaction was quenched by careful, dropwise addition of THF-H_2O (1:1), which operation was stopped when the formation of colorless and unsticky precipitates was effected. The solids were removed by filtration through celite pad and the filter cake was rinsed

with CH_2Cl_2. The combined organic solutions were dried (Na_2SO_4), concentrated, and distilled to give **8** (1.95 g, 90%): bp 49–50 °C/0.35 mmHg; $[\alpha]^{21}_D$ –1.49° (c 9.83, MeOH) (lit.[11] bp 55–61 °C/0.05 mmHg; $[\alpha]_D$ –2.23° (c 9.8, MeOH)).

Ethyl (3*S*)-4-(*tert*-Butyldimethylsilyoxy)-3-hydroxybutanoate (9). To a stirred solution of **1a** (4.78 g, 32.3 mmol) in THF (33 mL) were added imidazole (2.77g, 1.3 eq) and TBDMSi-Cl (5.21 g, 1.05 eq) at 0 °C. The mixture became immediately milky and was stirred for 2 h at 0 °C, being diluted with ether (300 mL), followed by the addition of H_2O (100 mL). A workup gave a pale yellow oil, which, on CC afforded **9** (8.05 g, 95%): $[\alpha]^{27}_D$ –5.95° (c 1.32, $CHCl_3$); IR (film) 3480, 1745, 1475, 1265, 1125, 840, 785 cm^{-1}; ^{1}H-NMR δ 0.10 (s, 6H, $Si(CH_3)_2$), 0.95 (s, 9H, $SiC(CH_3)_3$), 1.30 (t, 3H, CH_3), 2.53 (d, 2H, J = 6.0 Hz, CH_2), 3.63 (m, 2H, OCH_2), 3.82–4.30 (m, 1H, OCH), 4.71 (q, 2H, OCH_2); Anal. Calcd for $C_{12}H_{26}O_4Si$, C, 54.92; H, 9.99. Found: C, 54.72; H, 9.81.

Diethyl (*R*,*R*)-*O*-(2'-Tetrahydropyranyl)tartrate (26a). *Method A*; A mixture of diethyl (*R*,*R*)-tartrate (DET: 48.2 g, 0.234 mol), dihydropyrane (22.0 mL, 1.5 eq), and D-camphorsulfonic acid (1.1 g, 0.02 eq) in CH_2Cl_2 (250 mL) was stirred at rt for 3.5 h. The mixture was diluted with CH_2Cl_2 (250 mL), washed with saturated $NaHCO_3$ and H_2O to remove almost all of unchanged DET. A workup and CC (50 g) with hexane–EtOAc (1:1) gave a clear colorless oil (67.4 g) consisted of **26a**, bis-THP derivative, and DET in a mole ratio 17:11:1 as determined by HPLC analysis. The second CC (2.6 kg) with hexane–EtOAc (2:1) and (1:1) effected separation of **26a** (33.3 g) and the bis-THP derivative (27.2 g): the bis-THP derivative was partially deprotected with *p*-TsOH in EtOH to be converted into the three-component mixture which was submitted to CC to save **26a**. **26a**: ^{1}H-NMR (60 MHz) δ 1.30 and 1.33 (t, 6H, diastereomeric CH_3), 1.20–1.80 (m, 4H, ring-CH_2), 3.10–3.75 (m, 4H, ring-CH_2O), 4.28 (q, 4H, OCH_2), 4.30–4.75 (m, 1H, OCH), 4.86 (bs, 1H, anomeric CH).

Method B; A mixture of DET (2.66 g, 13.0 mmol), triethyl orthoacetate (11.8 mL, 64.5 mmol), and *p*-TsOH (37 mg, 0.15 eq) in THF (70 mL) was stirred at rt for 2.5 h. Neutralization with Et_3N (0.027 mL, 0.15 eq) and concentration gave an oil, which was dissolved in EtOH (30 mL) followed by the addition of *p*-TsOH (37 mg, 0.15 eq) and water (5 mL). The solution was stirred at rt for 1.5 h. Neutralization with Et_3N (0.027 mL, 0.15 eq), concentration, and CC with hexane–EtOAc (1:3) gave a colorless oil (3.03 g = mono-*O*-acetyl-DET **35**; 94%). A mixture of the oil, DHP (1.34 mL, 1.2 eq), and D-camphorsulfonic acid (60 mg, 0.02 eq) in CH_2Cl_2 (20 mL) was stirred at rt for 0.5 h. Neutralization with Et_3N (0.035 mL, 0.02 eq), concentration, and CC with hexane–EtOAc (1:3) gave *O*-acetyl-*O'*-THP-DET (**36**) as a colorless oil (4.13 g, 99%). Deacetylation from this was performed successfully with an equimolar amount of NaOEt in EtOH at 0 °C for 1 h. The desired **26a** was obtained in 82% yield after aqueous citric acid (10%) treatment, extraction with Et_2O, a workup, and CC.

Diethyl (*R*,*R*)-*O*-(*tert*-Butyl)tartrate (26b). Into a measuring pressure bottle cooled in a dry ice-acetone bath, was condensed 2-methylpropene (16.5 mL, 1.2 eq). The outlet of the pressure bottle was connected by a double ended needle with a flask charged with a solution of diethyl (*R*,*R*)-tartrate (DET: 30 g, 0.145 mol) in CH_2Cl_2 (250 mL) containing H_2SO_4 (98%: 2 mL), which was cooled to –20 °C. Then, the dryice-acetone bath was removed and, as a result, the olefin was transferred into the tartrate solution. The mixture was stirred at –20 °C—rt for 5.5 h, and a workup gave a colorless oil which was submitted to CC (60 g). The column was eluted successively with hexane and hexane–EtOAc (10:1). The hexane–EtOAc fractions afforded **26b** (19.3 g, 50%). **26b**: $[\alpha]^{22}_D$ +16.8° (c 4.92, $CHCl_3$); ^{1}H-NMR (60 MHz) δ 1.16 (s, 9H, $C(CH_3)_3$), 1.32 (t, 6H, CH_3), 4.01–4.65 (m, 6H, OCH, OCH_2); IR (film) 3500, 1768, 1755 (s), 1735 (s), 1372, 1260, 1192, 1132, 1100, 1035 cm^{-1}; exact mass, m/z 262.1408 (calcd for $C_{12}H_{22}O_6$, m/z 262.1417). Anal. Calcd for $C_{12}H_{22}O_6$, C, 54.95; H, 8.45. Found: C, 54.70; H, 8.37.

Dimethyl (*R*,*R*)-*O*-(1,1-Dimethylpropanoyl)tartrate (26c). To a solution of DMT (16.5 g, 0.0926 mol) in

pyridine (165 mL), cooled to –20 °C, was added pivaloyl chloride (11.2 g, 0.0926 mol) dropwise during 10 min. The reaction was continued at –20 °C for 3 h. The pyridine was removed under reduced pressure (10 mmHg, finally <1 mmHg) for several hours to give a viscous oil which, on TLC (hexane-EtOAc (1:1)), showed three spots with *Rf*-values 0.14 (DMT), 0.56 (**26c**), and 0.92 (bis-pivaloyl derivative). This oil was subjected to CC (160 g) and the column was eluted successively with hexane-EtOAc (8:1), (4:1), and (2:1), affording the bis-pivaloyl derivative (5.60 g, 17.5%), **26c** (15.0 g, 61.8%), and DMT (3.3 g, 20.5%), respectively. **26c**: bp 100–101 °C/0.06 mmHg; $[\alpha]^{28}_D$ –13.4° (c 6.65, $CHCl_3$) (lit.[15] $[\alpha]^{23}_D$ –12.1° (c 1.76, $CHCl_3$); IR (film) 3480, 1775 (s), 1745, 1270, 1145, 1075 cm^{-1}; ^{1}H-NMR (100 MHz) δ 1.23 (s, 9H, $C(CH_3)_3$), 3.80 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 4.77 (d, 1H, J = 2.4 Hz, CH(OH)), 5.42 (d, 1H, J = 2.4 Hz, CH(OPv)); exact mass, m/z 262.1049 (calcd for $C_{11}H_{18}O_7$, m/z 262.1052). Anal. Calcd for $C_{11}H_{18}O_7$, C, 50.38; H, 6.92. Found: C, 50.29; H, 6.66. Bis-pivaloyl derivative: $[\alpha]^{22}_D$ –14.2° (c 3.10, $CHCl_3$); ^{1}H-NMR (200 MHz) δ 1.19 (s, 18H), 3.70 (s, 6H), 5.59 (s, 2H); ^{13}C NMR (50 MHz) δ 26.7, 38.7, 52.6, 70.5, 166.3, 176.8.

For the small scale experiment, *O*-stannylene acetal strategy[15] was employed.

Dimethyl (*R,R*)-*O*-(Benzyl)tartrate (26d). The known mono-benzyl ether was prepared after Ohno:[15] $[\alpha]^{25}_D$ +87.6° (c 2.12, $CHCl_3$) (lit.[15] $[\alpha]^{22}_D$ +87.5° (c 1.17, $CHCl_3$).

Dimethyl (2*S*,3*R*)-2-Bromo-3-hydroxysuccinate (30a). This was prepared according to Mori's procedure[17a] with small modifications. To DMT (25.3 g, 0.142 mol) placed in a 0.5-L flask, cooled in an ice bath was slowly added a solution of 30%-HBr in acetic acid (120 mL) under stirring. The cooling bath was removed and the mixture was stirred at rt for 10 h. The mixture was poured onto ice-water (470 g), extracted with ether (200 mL x 4), and a workup gave a colorless oil. To the oil were added MeOH (150 mL) and acetyl chloride (3.0 mL), resulting mixture being heated under reflux for 6 h. The solution was concentrated and distilled to give a colorless oil which, on CC (200 g) eluted with CH_2Cl_2, furnished **30a** (24.6 g, 72%) after recrystallization from ether-hexane: mp 41–41.5 °C; $[\alpha]^{26}_D$ –46.6° (c 1.57, CH_2Cl_2); IR (4.5% in $CHCl_3$) 3530, 3025, 1760 (s), 1750, 1735 (s), 1435, 1270 cm^{-1}; ^{1}H-NMR (60 MHz) δ 3.40-3.75 (m, 1H, exchangeable with D_2O), 3.84 (s, 4H, OCH_3), 4.67 (dd, 1H, CH(OH)), 4.74 (s, 1H, CH(Br)); exact mass, m/z 239.9625 (calcd for $C_6H_9O_5Br$, m/z 239.9633). Anal. Calcd for $C_6H_9O_5Br$, C, 29.90; H, 3.76. Found: C, 29.88; H, 3.70.

Diethyl (2*S*,3*R*)-2-Bromo-3-hydroxysuccinate (30a': R = C_2H_5): prepared after Mori's procedure;[17a] bp 102–103 °C/0.5 mmHg; $[\alpha]^{10}_D$ –29.9° (c 4.51, $CHCl_3$) (lit.[17a] $[\alpha]^{21}_D$ –28.9° (neat)); ^{1}H-NMR (60 MHz) δ 1.32 (t, 6H, CH_3), 3.38–3.66 (m, 1H, exchangeable with D_2O and changed into singlet with a trace of CF_3CO_2H), 4.22 (q, 4H, CH_2O), 4.44–4.70 (m, 2H, CHBr and CHOH)); ^{13}C-NMR (25 MHz) δ 13.9 (q), 14.1 (q), 47.6 (d), 65.5 (t), 62.8 (t), 72.6 (d), 166.7 (s), 170.3 (s).

Diisopropyl (2*S*,3*R*)-2-Bromo-3-hydroxysuccinate (30a'': R = *i*-C_3H_7): prepared similarly as R = CH_3; bp 110–111 °C/0.8 mmHg; $[\alpha]^{9}_D$ –19.9° (c 6.42, $CHCl_3$); ^{1}H-NMR (60 MHz) δ 1.27 (d, 12H, $C(CH_3)_2$), 3.53 (m, 1H, exchangeable with D_2O), 4.47–4.77 (m, 2H, CH-Br, CHOH), 5.13 (m, 1H, OCH), 5.18 (m, 1H, OCH).

Dimethyl (2*S*,3*R*)-2-Chloro-3-hydroxysuccinate (30b).[17b] To a mixture of dimethyl (*R,R*)-*O*-acetyl-tartrate (4.70 g, 19.0 mmol) prepared after Freudenberg and Brauns,[32] pyridine (0.72 mL), and $CHCl_3$ (5 mL) was added $SOCl_2$ (1.92 mL) at –10 °C. After several minutes, the mixture was allowed to be warmed up to rt and solidified soon. Then, the mixture was heated at 110 °C for 15 min, concentrated in vacuo, and distributed between ether and H_2O. A workup and distillation (bp 138–140 °C/9 mmHg) gave an oil (4.55 g, 82%). This chlorohydrin acetate was dissolved in 30% HBr in acetic acid (34 mL) and MeOH (1.2 mL), the mixture being heated under reflux for 4 h and concentrated in vacuo to give an oil, which, on CC, afforded **30b** (3.35 g, 84%). **30b**: $[\alpha]^{21}_D$ –34.1° (c 1.35, CH_2Cl_2); ^{1}H NMR (60 MHz) δ 3.59 (bd, 1H, exchangeable with D_2O), 3.80 (s, 3H, OCH_3), 4.60-

4.90 (m, 2H, CHCl, CHOH).

Diethyl (2*S*,3*R*)-3-Hydroxy-2-methylsuccinate (30c): prepared after Mori's procedure;[17a] $[\alpha]^{25}_D$ +9.80° (c 2.15, Et_2O) (lit.[17a] $[\alpha]^{20}_D$ +9.75° (c 1.90, Et_2O)) ; ^{1}H-NMR (60 MHz) δ 1.24 (t, 3H, CH_3), 1.27 (d, 3H, CH_3), 1.30 (t, 3H, CH_3), 3.01 (dq, 1H, CH(Me)), 3.21 (d, 1H, exchangeable with D_2O), 4.13 (q, 3H, CH_2O), 4.25 (q, 3H, CH_2O), 4.0-4.4 (m, 1H, CH-O).

Diethyl (2*S*,3*R*)-2-Azido-3-hydroxysuccinate (30d). To a solution of diethyl (2*R*,3*R*)-2,3-epoxysuccinate[17a] (1.27 g, 6.73 mmol) in DMF (3.7 mL) was added a solution of HN_3 in DMF, prepared by mixing trimethylsilyl azide (1.79 mL, 13.5 mmol) and MeOH (0.54 mL, 13.5 mmol) at 0 °C, followed by the addition of DMF (3 mL), and the mixture was stirred at 60 °C for 12 h. Then, a solution of 5% HCl in MeOH (1 mL) was added to the mixture, the solution being stirred at rt for 1 h and concentrated under reduced pressure to give an oil, which, on CC eluted with hexane-EtOAc (1:1), led to **30d** (1.51 g, 97%): $[\alpha]^{17}_D$ +16.5° (c 1.47, CH_2Cl_2); IR (film) 3500, 2160, 1750 cm^{-1}; ^{1}H-NMR (60 MHz) δ 1.30 (t, 6H, CH_3), 3.44 (d, 1H, J = 5.5 Hz, OH), 4.23 (q, 4H, OCH_2), 4.30 (d, 1H, J = 4.0 Hz, CHN_3), 4.61 (dd, 1H, J = 5.5 Hz, 4.0 Hz, CHOH); exact mass, m/z 231.0856 (calcd for $C_8H_{13}N_3O_5$, m/z 231.0856). Anal. Calcd for $C_8H_{13}N_3O_5$, C, 41.56; H, 5.57. Found: C, 41.44; H, 5.46.

Structure Determination for Products in the Selective Reduction of Tartrate Series. The following description with regard to structure determination for products obtained from the selective reduction of **26d** is representative. Corresponding acetonides or, in some cases, 4-*O*-*tert*-butyldimethylsilyl derivative from **27** or **31** were carefully analyzed by an NMR except for **27a**. Attempted acetonidation (2,2-dimethoxypropane/acetone/ $TsOH/CH_2Cl_2$) of the reduction product (**27a** + β-reduction product) obtained from **26a** resulted in the formation of a complex mixture. Accordingly, its structure was determined after converting the mixture to ethyl 4-(*tert*-butyldimethylsiloxy)-2(or 3)-hydroxy-3(or 2)-mesyloxybutanoate via a series of routine reactions (for detail, see ref. 5).

Typical experiment: To a solution of **26d** (3.07 g, 11.5 mmol) in THF (23 mL) was added BMS (1.20 mL, 1.05 eq) at rt and the mixture was stirred for 2 h. $NaBH_4$ (22 mg, 5 mol%) was added to the mixture, the reaction being continued for 2 h at rt. After workup as described for the reduction of DEM, the crude product was dissolved in THF (12 mL), the solution being cooled to 0°C. To this THF solution was added TBDMSi–Cl (1.73 g, 1eq) followed by an addition of imidazole (1.73g, 1 eq), the reaction being continued at 0°C for 1 h. The reaction mixture was diluted with ether (250 mL) and a workup gave a colorless oil consisted of two products as shown by TLC. Purification of the oil by CC (90 g) furnished less polar product (***A***: 0.75 g, 18.3%) and more polar product (***B***: 1.50 g, 36.7%). ***A***: $[\alpha]^{26}_D$ +18.5° (c 2.64, $CHCl_3$); ^{1}H NMR (60 MHz) δ 0.6 (s, 6H), 0.88 (s, 9H), 2.93 (d, 1H, J = 8 Hz, OH), 3.61 (s, 3H), 3.70–3.80 (bs, 3H, TBSOCH_2 and CH(OBn)), 4.32 (bd, 1H, J = 8 Hz, CH(OH)), 4.49 and 4.65 (ABq, 2H, J = 11.5 Hz), 7.40 (s, 5H). ***B***: $[\alpha]^{21}_D$ +57.1° (c 5.83, $CHCl_3$); ^{1}H NMR (60 MHz) δ 0.8 (s, 6H), 0.88 (s, 9H), 2.51 (bd, 1H, J = 6.1Hz, OH), 3.58–4.10 (m, 3H, TBSOCH_2 and CH(OH)), 3.80 (s, 3H), 4.19 (d, 1H, J = 2.2 Hz, CH(OBn)), 4.48 and 4.81 (ABq, 2H, J = 12 Hz), 7.29 (s, 5H). Anal. Calcd for $C_{18}H_{30}O_5Si$, C, 60.98; H, 8.53. Found: C, 60.70; H, 8.61.

A part of the crude reduction product was treated overnight with a large excess of 2,2-dimethoxypropane in acetone containing 5% p-TsOH at rt to give a mixture of acetonides. After evaporation of the volatile, the residual oil was analyzed by a ^{13}C–NMR which indicated that the major product was a 5-membered acetonide and the minor one was a 6-membered acetonide based on the typical chemical shifts of acetal carbon (**28d**: δ 110 and **29d**: 99 ppm). GLC analysis of this acetonide mixture led to the same conclusion as that from the ^{13}C–NMR analysis as just mentioned based on the general trend of the order of elution (*vide supra*). The GLC analysis also provided the ratio of **28d** and **29d** precisely.

All these information confirmed that ***B*** should be assigned as methyl (2*R*,3*S*)-2-(*O*-benzyl)-4-(*O*-*t*-butyldimethylsilyl)-2,3,4-trihydroxybutanoate derived from **27d**, while ***A*** methyl (2*R*,3*S*)-3-(*O*-benzyl)-4-(*O*-*t*-butyldimethylsilyl)-2,3,4-trihydroxybutanoate derived from the β–ester reduction product.

28b: $[\alpha]^{23}_D$ +18.2° (c 6.23, $CHCl_3$); IR (film) 1765, 1750, 1730, 1460, 1375 cm^{-1}; ^1H NMR (60 MHz) δ 1.20 (s, 9H), 1.28 (t, 3H), 1.35 (s, 3H), 1.41 (s, 3H), 3.95–4.50 (m, 6H). Anal. Calcd for $C_{13}H_{24}O_5$, C, 59.98; H, 9.29. Found: C, 59.85; H, 9.22. **28c**: *vide infra*. **32a**: ^{13}C NMR (25 MHz) δ 25.2 (q), 27.0 (q), 44.8 (d), 53.0 (q), 67.4 (t), 76.1 (d), 110.9 (s), 168.5 (s). Anal. Calcd for $C_8H_{13}O_4Br$, C, 37.97; H, 5.18. Found: C, 37.71; H, 5.20. **33a**: ^{13}C NMR (25 MHz) δ 18.8 (q), 28.7 (q), 41.1 (d), 52.6 (q), 64.4 (t), 75.9 (d), 99.9 (s), 168.0 (s). **32c**: ^1H NMR (200 MHz) δ 1.02 (d, 3H), 1.16 (t, 3H), 1.23 (s, 3H), 1.30 (s, 3H), 2.56 (m, 1H), 3.61 (dd, 1H), 3.93 (dd, 1H), 4.06 (q, 2H), 4.19 (m, 1H); ^{13}C NMR (50 MHz) δ 12.5 (q), 14.0 (q), 25.1 (q), 26.4 (q), 42.1 (d), 60.3 (t), 66.5 (t), 76.6 (d), 108.9 (s), 173.9 (s). **32d**: ^1H NMR (100 MHz) δ 1.32 (t, 3H), 1.36 (s, 3H), 1.47 (s, 3H), 3.91–4.09 (m, 3H), 4.28 (q, 2H), 4.45 (m, 1H); ^{13}C NMR (25 MHz) δ 14.1 (q), 25.1 (q), 26.3 (q), 62.1 (t), 63.3 (d), 65.7 (t), 75.3 (d), 110.3 (s), 167.9 (s); IR (CH_2Cl_2) 2120, 1745 cm^{-1}; the underlined signals corresponding to the acetal carbons are highly diagnostic. *Methyl (2S,3S)-4-(tert-Butyldimethylsiloxy)-2-bromo-3-hydroxy-butanoate* (**41**): ^1H NMR (500 MHz) δ 0.09 (s, 3H), 0.10 (s, 3H), 0.91 (s, 9H), 2.94 (d, 1H, *J* = 8.7 Hz, OH), 3.81 (s, 3H), 3.82–3.88 (m, 2H), 4.03–4.09 (m, 1H, C*H*-OH), 4.24 (d, 1H, J = 9.1 Hz, C*H*–Br); ^{13}C NMR (126 MHz) δ –5.53 (q), –5.49 (q), 18.2 (s), 25.8 (q), 43.5 (d), 53.0 (q), 62.7 (t), 72.4 (d), 169.5 (s). *Methyl (2S,3R)-4-(tert-butyldimethylsiloxy)-3-bromo-2-hydroxybutanoate*: ^1H NMR (500 MHz) δ 0.06 (s, 3H), 0.07 (s, 3H), 0.88 (s, 9H), 3.28 (d, 1H, *J* = 5.8 Hz, OH), 3.81 (s, 3H), 3.96–4.00 (m, 2H), 4.34 (ddd, 1H, *J* = 2.7, 5.2, 9.3 Hz, C*H*-Br), 4.57 (dd, 1H, *J* = 2.6, 5.8 Hz, C*H*–OH); ^{13}C NMR (126 MHz) δ –5.58 (q), –5.57 (q), 18.2 (s), 25.7 (q), 52.5 (d), 52.7 (q), 63.4, (t) 71.8 (d), 171.8 (s). *Methyl (2S,3S)-4-(tert-Butyldimethylsiloxy)-2-chloro-3-hydroxybutanoate*: ^1H NMR (500 MHz) δ 0.09 (s, 3H), 0.1 (s, 3H), 0.91 (s, 9H), 2.83 (d, 1H, *J* = 8.7 Hz, OH), 3.78–3.85 (m, 2H), 3.82 (s, 3H), 4.05 (m 1H), 4.26 (d, 1H, J = 8.6 Hz); ^{13}C NMR (126 MHz) δ –5.6 (q), –5.5 (q), 18.3 (s), 25.8 (q), 52.9 (q), 54.9 (d), 62.2 (t), 72.7 (d), 169.1 (s); Anal. Calcd for $C_{11}H_{23}O_4ClSi$, C, 46.71; H, 8.20. Found: C, 46.69; H, 8.11. *Methyl (2S,3R)-4-(tert-Butyldimethylsiloxy)-3-chloro-2-hydroxy-butanoate*: ^1H NMR (500 MHz) δ 0.06 (s, 3H), 0.07 (s, 3H), 0.87 (s, 9H), 3.26 (d, 1H, *J* = 6.1 Hz, OH), 3.90–3.96 (m, 2H), 3.81 (s, 3H), 4.28 (m 1H), 4.54 (d, 1H, J = 8.6 Hz); ^{13}C NMR (126 MHz) δ –5.62 (q), –5.60 (q), 18.3 (s), 25.7 (q), 52.7 (q), 60.8 (d), 63.1 (t), 71.9 (d), 171.8 (s).

Methyl (2*R*,3*S*)-3,4-*O*-Isopropylidene-2-*O*-pivaloyl-2,3,4-(trihydroxy)butanoate (28c). The Selective reduction of **26c** (12.4 g, 47.3 mmol) was carried out in a similar way to that described above for the tartrate series to provide a mixture of **27c** and **39**. The mixture was treated with 2,2-dimethoxypropane (12 mL), acetone (14 mL), and TsOH (0.6 g) in CH_2Cl_2 (50 mL) at rt for 3 h, neutralized by the addition of Et_3N (1 mL), diluted with CH_2Cl_2 (250 mL), and a workup gave a yellow oil. Purification of this oil by CC (120 g) eluted with hexane–EtOAc (8:1) led to the desired **28c** as crystals (9.50 g, 73%) after distillation. **28c**: bp 85–87 °C/0.1 mmHg; mp 43–44 °C; $[\alpha]^{30}_D$ +28.2° (c 9.34, $CHCl_3$); IR ($CHCl_3$) 1770, 1738, 1482, 1440, 1148, 1072 cm^{-1}; ^1H NMR (100 MHz) δ 1.28 (s, 9H, $C(CH_3)_3$), 1.36 (s, 3H, CH_3), 1.46 (s, 3H, CH_3), 3.78 (s, 3H, OCH_3), 3.89 (dd, 1H, J_{gem} = 8.7 Hz, J_{vic} = 5.6 Hz, ring-C*H*H), 4.10 (dd, 1H, J_{gem} = 8.7 Hz, J_{vic} = 6.6 Hz, ring-CH*H*), 4.52-4.68 (m, 1H, ring-CH), 5.09 (d, 1H, *J* = 3.9 Hz, CH-OPv); ^{13}C NMR (25 MHz) δ 25.3 (q), 26.2 (q), 27.0 (q), 38.8 (s), 52.3 (q), 65.4 (t), 71.8 (d) 74.7 (d), 110.2 (s), 168.0 (s), 177.6 (s); GLC (capillary Thermon 1000, 30 m x 0.25 mm, 170 °C) single component with retention time 13.9 min; exact mass, m/z 274.1414 (calcd for $C_{13}H_{22}O_6$, m/z 274.1417). Anal. Calcd for $C_{13}H_{22}O_6$, C, 56.92; H, 8.08. Found: C, 56.88; H, 7.99.

1,2-*O*-Isopropylidene-L-threitol (40). To a solution of **28c** (5.15 g, 18.8 mmol) in THF (100 mL) was added a solution of LAH (1.23 M in THF: 25.9 mL, 1.7 mol eq) slowly at 0 °C under rigorous stirring. The reaction was

stirred at 0 °C – rt during 2 h, cooled in an ice-bath, quenched by an addition of a mixture of THF/H_2O (1:1, 14 mL) to effect formation of colorless, easy-to-filtrate precipitates. The solid was removed by filtration through a celite pad and the filter cake was thoroughly rinsed with CH_2Cl_2. The combined organic solutions were dried (Na_2SO_4) and concentrated to give a colorless oil, which, on distillation, afforded **40** (2.87 g, 94%): bp 101–102 °C/0.1 mmHg; $[\alpha]^{28}_D$ +3.48° (c 6.67, MeOH) (lit.[24a] $[\alpha]_D$ +3.9° (c 1.4, MeOH; lit.[24b] $[\alpha]^{20}_D$ +2.7° (c 2.96, $CHCl_3$); IR (film) 3420, 1380, 1370, 1215, 1060 cm^{-1}; ^1H NMR (100 MHz) δ 1.37 (d, 3H, J = 0.7 Hz, CH_3), 1.45 (d, 3H, J = 0.5 Hz, CH_3), 2.60 (bd, 2H, OH), 3.66 (bs, 3H, CHOH, CH_2OH), 3.77–4.23 (m, 3H, ring-H); ^{13}C NMR (25 MHz) δ 25.2 (q), 26.4 (q), 63.7 (t), 65.7 (t), 72.4 (d), 76.6 (d), 109.3 (s).

(*R*)-1,2-*O*-Isopropylideneglycerol (88% yield) derived from **40** by means of oxidative C—C bond cleavage ($NaIO_4$) and subsequent reduction ($NaBH_4$): $[\alpha]^{25}_D$ –14.6° (c 3.05, MeOH) (lit.[24a] $[\alpha]_D$ –10.6°; lit.[21a] $[\alpha]_D$ –10.76°).

Methyl (2*S*,3*S*)-4-(*tert*-Butyldimethylsiloxy)-2-bromo-3-hydroxybutanoate (41). A mixture of **31a** and methyl (2*S*,3*R*)-2,4-dihydroxy-3-bromobutanoate (4 : 1) (1.73 g, 25.4 mmol) was dissolved in THF (35 mL), and to this solution was added TBDMSi–Cl (3.2 g, 21.2 mmol). The mixture was stirred at rt for 20 min, diluted with ether–hexane (1:1; 260 mL), and washed with H_2O, cold 1%–HCl, and $NaHCO_3$. A workup gave a colorless oil, which was briefly purified by CC (75 g) with hexane–EtOAc (10:1) to afford the protected ester (5.26g, 99%): a mixture of **43** and the silylated methyl 3-bromo-2,4-dihydroxybutanoate.

Methyl (2*R*,3*R*)-2-Azido-3-hydroxy-4-(*t*-butyldimethylsiloxy)butanoate (42). A mixture of **41** and the silylated minor bromodiol stemming from the β-ester-reduction product (ratio 4 : 1) (4.34 g, 13.3 mmol) was dissolved in DMF (15 mL). To this solution were added diisopropylethylamine hydrochloride (4.50 g, 26.5 mmol) and sodium azide (1.80 g, 26.5 mmol) and the mixture was stirred at 40 °C for 10 h. The reaction was diluted with water, extracted with ether, and a workup gave an oil, which was purified by CC (hexane–EtOAc 20:1 – 5:1) to give **42** (2.17 g, 75% based on **31a**). Under the conditions, the β-ester-reduction product or the corresponding azide product therefrom seemed to decompose. **42**: $[\alpha]^{25}_D$ –41.3° (c 2.69, MeOH); IR (film) 3500, 2100, 1740 cm^{-1}; ^1H NMR (MHz) δ 0.08 (s, 3H, 0.90 (s, 9H), 2.49 (d, J = 6.5 Hz, 1H, OH), 3.66 (dd, J = 6.6, 10.1 Hz, 1H), 3.72 (dd, J = 5.9, 10.1 Hz, 1H), 3.84 (s, 3H), 4.05 (d, J = 3.1 Hz, 1H), 4.16 (m, 1H); ^{13}C NMR (126 MHz) δ –5.52, –5.48, 18.2, 25.8, 52.5, 62.8, 63.3, 72.3, 169.7.

(2*S*,3*S*)-2-(*N*-Boc)amino-3-hydroxy-4-(*t*-butyldimethylsiloxy)-*N'*-methoxybutaneamide (43). Azidoester **42** was converted to the corresponding *N*-methoxyamide after Weinreb's procedure[26] in 56% yield. To a suspension of 10% Pd on carbon (30 mg) in EtOAc (7 mL), pre-saturated with hydrogen, was introduced a solution of the amide (0.283 g, 0.93 mmol) and Boc_2O (244 mg, 1.2 eq) in EtOAc (3 mL).[27] The mixture was stirred at rt for 4 h under an atmosphere of hydrogen, filtered through a celite-pad, and concentrated under reduced pressure to give an oil, which, on CC (hexane–EtOAc 1:1), afforded **43** (274 mg, 78% yield) as a colorless crystal. **43**: $[\alpha]^{26}_D$ +15.2° (c 2.68, MeOH); IR (film) 3350, 1670, 1620 cm^{-1}; ^1H NMR (500 MHz) δ 0.053 (s, 6H), 0.88 (s, 9H), 1.43 (s, 9H), 1.89 (bs, 1H, OH), 3.60 (d, 2H, J = 6.5 Hz), 3.76 (s, 3H) , 4.1–4.3 (m, 2H), 5.58 (bd, 1H), 9.5 (bs, 1H); ^{13}C NMR (126 MHz) δ –5.60, –5.55, 14.1, 18.2, 25.8, 28.2, 52.3, 62.8, 64.4, 70.6, 80.7, 156.4, 169.3; Anal. Calcd for $C_{16}H_{34}N_2O_6Si$, C, 50.77; H, 9.05. Found: C, 50.63; H, 9.11.

(3*S*,4*S*)-3-*t*-Butoxycarbonylamino-4-(*t*-butyldimethylsiloxymethyl)-2-azetidinone (44). To a solution of **43** (0.073 g, 0.19 mmol) in THF (3 mL) was added triphenylphosphine (60 mg, 1.2 eq), followed by the addition of diethyl azodicarboxylate (0.035 mL, 1.2 eq). The mixture was stirred at rt for 1 h, concentrated under reduced pressure, and purified by CC (hexane–EtOAc 5:1) to furnish the *N*-methoxyazetidinone in 73% yield as a colorless crystal. A solution of this azetidinone in THF (2 mL)–*t*-BuOH (2 mL) mixed solvent was added to a reducing

agent prepared from liquid ammonia (5 mL) and sodium (50 mg) at –60 °C. After stirring at that temperature for 5 minutes, the reaction was quenched by the addition of saturated aqueous ammonium chloride, extracted with CH_2Cl_2, and a workup gave an oil, which, on CC (hexane–EtOAc 1:1) provided **44** as a colorless oil in 96% yield. **44**: $[\alpha]^{26}_D$ +45.0° (c 2.18, MeOH); IR (film) 3280, 2900, 1760, 1710 cm^{-1}; ^1H NMR (500 MHz) δ 0.054 (s, 3H), 0.059 (s, 3H), 0.88 (s, 9H), 1.43 (s, 9H), 3.60–3.74 (m, 2H), 3.80 (bd, 1H) , 4.44 (bdd, 1H), 5.19 (bd, 1H), 6.10 (bs, 1H); ^{13}C NMR (126 MHz) δ –5.48, –5.40, 18.2, 25.8, 28.3, 58.6, 59.8, 63.5, 80.4, 154.9, 167.2; Anal. Calcd for $C_{15}H_{30}N_2O_4Si$, C, 54.51; H, 9.15. Found: C, 54.44; H, 9.11.

Methyl (2*R*,3*S*)-4-(*tert*-Butyldimethylsiloxy)-*trans*-2,3-epoxybutanoate (45). A mixture of TBSO–ester **41** and the silylated minor bromodiol stemming from the β-ester-reduction product (ratio 4 : 1) (5.22 g, 15.9 mmol) was dissolved in MeOH (50 mL), the solution being cooled in an ice-bath. To the cold solution was slowly introduced a solution of NaOMe in MeOH prepared from NaH (60% suspension in oil: 0.67 g, 16.7 mmol) and MeOH (10 mL) at 0 °C. The reaction was continued at 0 °C for 1 h and 45 min at 0 °C–rt, diluted with ether–hexane (1:1; 300 mL). A workup gave a colorless oil, which was purified by CC (80 g) with hexane–EtOAc (10:1) and subsequent distillation to convergently afford pure **45** (3.05 g, 78%). **45**: bp 90–91 °C/0.7 mm; $[\alpha]^{20}_D$ –24.7° (c 6.96, $CHCl_3$); $[\alpha]^{20}_D$ –39.7° (c 4.39, Et_2O); ^1H-NMR (500 MHz) δ 0.03 (s, 3H, $SiCH_3$), 0.04 (s, 3H, $SiCH_3$), 0.86 (s, 9H, $SiC(CH_3)_3$), 3.28 (m, 1H, ring-H), 3.42 (d, 1H, J = 1.9 Hz, ring-H), 3.74 (dd, 1H, J_{gem} = 12.4 Hz, J_{vic} = 3.6 Hz, CHHO), 3.75 (s, 3H, OCH_3), 3.88 (dd, 1H, J_{gem} = 12.4 Hz, J_{vic} = 2.6 Hz, CHHO); ^{13}C-NMR (50 MHz) δ –5.5 (q), 18.2 (s), 25.7 (q), 50.0 (d), 52.3 (q), 58.1 (d), 61.1 (t), 169.4 (s); Anal. Calcd for $C_{11}H_{22}O_4Si$, C, 53.63; H, 9.00. Found: C, 53.51; H, 8.90.

Methyl (2*S*,3*R*)-2-Azido-3-hydroxy-4-(*t*-butyldimethylsiloxy)butanoate (46). To a solution of **45** (0.865 g, 3.5 mmol) in DMF (3 mL) were added diisopropylethylammonium azide[29] (2.10 g, 11 mmol) and the mixture was stirred at rt for 36 h. The reaction was diluted with water, extracted with ether, and a workup gave an oil, which was purified by CC (hexane–EtOAc 10:1) to give **46** (0.656 g, 65%). **46**: $[\alpha]^{27}_D$ –18.2° (c 1.59, $CHCl_3$); IR (film) 3400, 2900, 2100, 1710 cm^{-1}; ^1H NMR (500 MHz) δ 0.067 (s, 3H), 0.071 (s, 3H), 0.88 (s, 9H), 2.70 (bs, 1H), 3.72 (dd, 1H, J = 3.8, 10.4 Hz), 3.75 (dd, 1H, J = 4.0, 10.4 Hz) , 3.81 (s, 3H), 3.93–3.99 (m, 2H); ^{13}C NMR (126 MHz) δ –5.53, –5.48, 18.3, 25.8, 52.7, 62.7, 62.9, 71.7, 169.4; Anal. Calcd for $C_{11}H_{23}N_3O_4Si$, C, 45.67; H, 8.01. Found: C, 45.60; H, 8.11.

(2*S*,3*R*)-2-Azido-3-hydroxy-4-(*t*-butyldimethylsiloxy)-*N*-methoxybutanamide (47). *N*-Methoxyamidation of **46** was conducted after the procedure by Weinreb[26] to afford **47** in 62% yield. **47**: $[\alpha]^{26}_D$ +6.54° (c 3.12, MeOH); IR (film) 3400, 2100, 1670, 1250 cm^{-1}; ^1H NMR (500 MHz) δ 0.075 (s, 6H), 0.88 (s, 9H), 3.28 (bs, 1H), 3.70–3.75 (bd, 2H) , 3.78 (s, 3H), 3.90–4.10 (m, 2H), 9.17 (bs, 1H); ^{13}C NMR (126 MHz) δ –5.49, –5.40, 18.3, 25.0, 62.2, 63.1, 64.6, 71.9, 166.2; Anal. Calcd for $C_{11}H_{24}N_4O_4Si$, C, 43.40; H, 7.95. Found: C, 43.22; H, 7.80.

(3*S*,4*S*)-3-*t*-Butoxycarbonylamino-4-(*t*-butyldimethylsiloxymethyl)-2-azetidinone (48). A series of reactions involving β-lactam cyclization, single-pot N_3 to NHBoc conversion, and reductive demethoxylation was successfully performed for **47** in the same way as described above for **42** to **44** transformation. **48**: $[\alpha]^{26}_D$ +35.3° (c 1.16, MeOH); IR (film) 3400, 2920, 1760, 1700 cm^{-1}; ^1H NMR (500 MHz) δ 0.061 (s, 3H), 0.076 (s, 3H), 0.88 (s, 9H), 1.41 (s, 9H), 3.75 (dd, 1H, J = 2.0 Hz), 3.82–3.85 (m, 1H) , 3.86 (dd, 1H, J = 2.4 Hz), 5.33 (dd, 1H, J = 4.7 Hz), 5.56 (bd, 1H), 5.80 (bs, 1H); ^{13}C NMR (126 MHz) δ –5.68, –5.48, 18.1, 25.7, 28.2, 54.4, 59.4, 61.0, 80.1, 155.0, 169.1; Anal. Calcd for $C_{15}H_{30}N_2O_4Si$, C, 54.51; H, 9.15. Found: C, 54.33; H, 9.01.

TBS-deprotection of **48** (n-Bu_4NF / THF / rt / 0.4 h) afforded the corresponding 4-hydroxymethylazetidinone in 82% yield with $[\alpha]^{27}_D$ +21° (c 0.21, $CHCl_3$), which is identical as that reported [lit.[30] $[\alpha]^{25}_D$ +21° (c 0.55, $CHCl_3$)].

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(9) Rf values for **6a** and **7a** (hexane : AcOEt = 4 : 1) determined on 0.25 mm thickness TLC plate (Merck pre-coated) were 0.26 and 0.45, respectively.

(10) **7b**: ^{13}C–NMR (25 MHz) δ 19.2 (q), 28.1 (t), 29.5 (q), 52.1 (q), 59.3 (t), 68.6 (d), 99.0 (s), 171.2 (S). The underlined signal is highly diagnostic.

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