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TETRAHEDRON: *ASYMMETRY*

Protecting group controlled stereoselective alkylation of asymmetrized bis(hydroxymethyl)propanoates (BHYMP*)

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Abstract

The diastereoselective methylation of the enolates derived from some asymmetrized bis(hydroxymethyl)propanoates (BHYMP*) has been studied. Good results were achieved when one of the two hydroxymethyl groups was unprotected. The induction was interpreted on the basis of an acyclic stereocontrol governed by stereoelectronic effects.

1. Introduction

We have recently reported[2] the efficient chemoenzymatic preparation of some new chiral building blocks corresponding to the general formula **1**, i.e. asymmetrized bis(hydroxymethyl)propanoates (BHYMP*) (Scheme 1). In view of the possible application of these compounds in the field of natural product synthesis (for example, of lignan derivatives),[3] we became interested in the diastereoselective derivatization at the α position of the ester, through reaction of an enolate with suitable electrophiles to give adducts **2**. Since the stereogenic centre in **1** bears two synthetically equivalent protected (or unprotected) hydroxymethyl groups, the stereocontrol depends exclusively on the nature of R^1 and R^2, and we can thus speak of a 'protecting group controlled' asymmetric synthesis.[4]

This was anticipated to be a difficult task, since R^1 and R^2 groups are quite far from the stereogenic centre making a purely steric approach unpromising. In the past,[4] we have solved related problems by taking advantage of the different capabilities of some protecting groups in depressing or enhancing the Lewis basicity of oxygen. In this way, only one of the two protected hydroxymethyl groups would be involved in a possible cyclic chelated transition state. For the present case however, the success of this trick would imply the formation of an unprecedented seven-membered chelated enolate **3**.[5–7]

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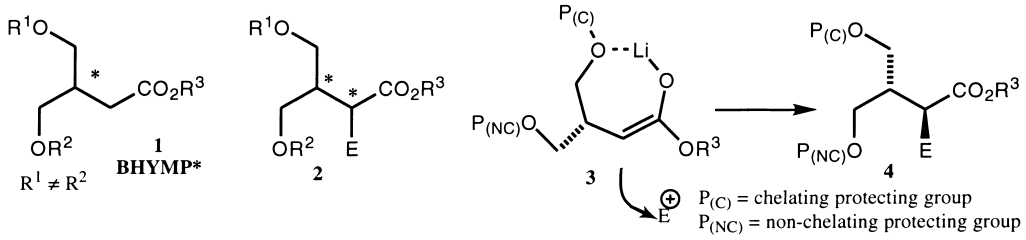
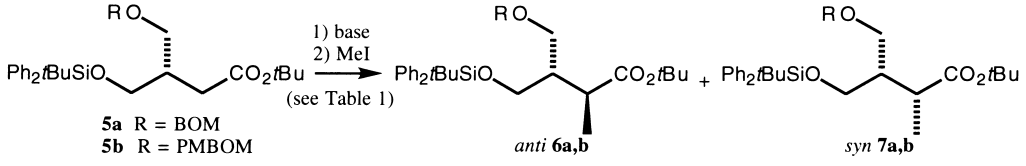


Scheme 1.

2. Results and discussion

We examined first the methylation of lithium enolate derived from *t*-butyl esters **5a** and **5b**, obtained in high e.e. as previously described (Scheme 2).[2] In these esters the two hydroxymethyl groups are, respectively, protected with a 'chelating' (BOM or PMBOM) protecting group and with a 'non-chelating' (Ph_2t-BuSi) one. The results, shown in Table 1, were somewhat disappointing from the point of view of asymmetric induction. Moreover, the main diastereoisomer was not the one predicted on the basis of a chelated enolate such as **3** (see Scheme 1). Since the (*Z*) enolate cannot undergo chelation, we reasoned that a possible cause for the low stereoselection was the kinetic preference for (*Z*) enolization. We thus tried to improve the stereoselectivity by changing the base or the solvent, employing conditions reported to favour kinetic formation of the (*E*) enolate.[8] However, the diastereomeric ratios remained unsatisfactory (entries 2–4, 6).



Scheme 2.

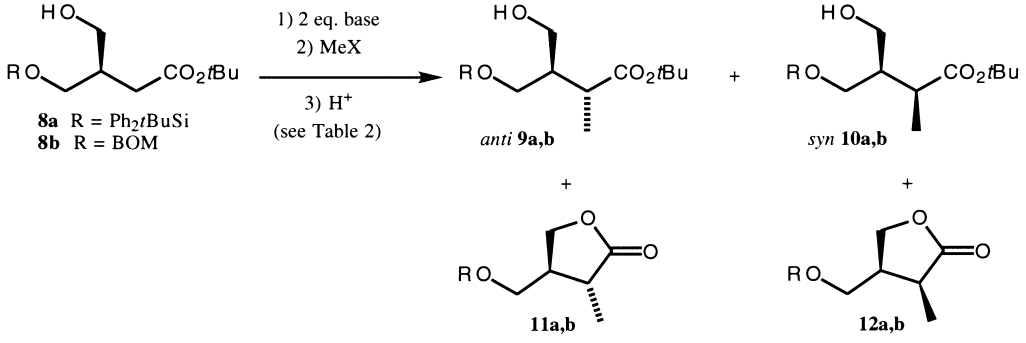
In order to increase further the Lewis basicity of the oxygen participating in chelation, we switched to monoprotected diols **8a**,**b** (Scheme 3 and Table 2). In this case, an alkoxide, a group particularly predisposed to chelation, would be formed under the reaction conditions. The methylation of the enolates was complicated by the formation of the corresponding lactones via intramolecular transesterification. Interestingly, this lactonization seems to occur only after methylation.[9] In the case of the monoprotected diol **8a** where the greater bulkiness makes methylation slower, it was not possible to obtain reasonable

Table 1
Results of methylation with MeI of enolates of diprotected esters **5a**,**b**

Entry	Substrate	Base[a]	Solvent[b]	Temperature	Conversion[c]	Yield[d]	*anti* : *syn*[e]
1	**5a**	LDA	THF	-78°C→ -5°C	92%	79%	43 : 57
2	**5a**	LDA	THF-DMPU	-78°C→ 0°C	98%	86%	36 : 64
3	**5a**	LDA	THF-HMPA	-78°C→ 0°C	99%	78%	52 : 48
4	**5a**	LHDMS	THF-DMPU	-78°C→ 0°C	38%	35%	53 : 47
5	**5b**	LDA	THF	-78°C→ 0°C	93%	86%	43 : 57
6	**5b**	LHDMS	THF-HMPA	-78°C→ 0°C	20%	n.d.	51 : 49

[a] LHDMS = lithium hexamethyldisilazide. [b] The cosolvent was added prior to enolization. DMPU = 1,3-dimethyl-2-oxohexahydropyrimidine. HMPA = hexamethylphosphoric triamide. [c] Determined by HPLC. [d] Isolated yield after chromatography. [d] Determined by HPLC.

yields of the open chain esters **9a**–**10a**.[10] On the other hand, starting from **8b**, methylation was faster, cleaner and by carefully controlling the temperature and reaction time, it was possible to nearly suppress lactone formation, at least with MeI. Employing the less reactive Me_2SO_4, however, lactonization of the methylated esters again became important. The best results are those of entry 3, where a good stereoselectivity is accompanied by high conversion and good yield. Allowing the reaction to proceed for a longer time or at higher temperature led to an increase of diastereomeric ratio (entry 1), but this fact was due to the insurgence of lactonization, and to the fact that *anti* adduct **9b**, which gives the *trans* lactone **11a**, reacted faster.



Scheme 3.

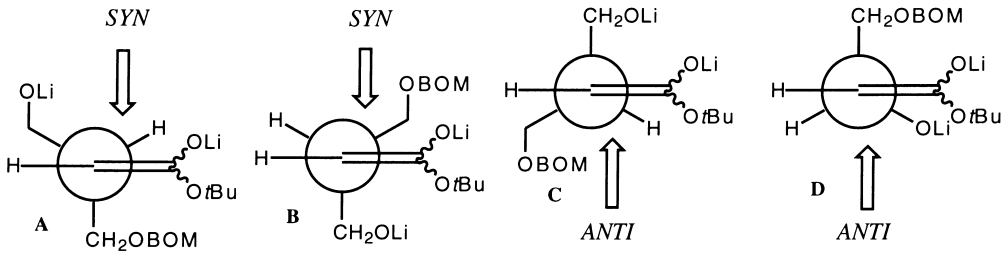
Surprisingly, also in this case, the main diastereoisomer was not the one predicted by the intermediacy of a chelated enolate. Thus it seems that the good stereoselectivity obtained in this case is due to an acyclic stereocontrol.

In the past, several attempts have been made to predict the direction of diastereoselectivity in electrophilic attack onto double bonds with an α stereogenic centre.[11] The proposed models are either based on the bulkiness of substituents at the stereocentre,[11a] or on their electronic properties.[11b–d] In the case of **8b**, due to the remoteness of the steric difference between CH_2O^- and CH_2OBOM, we believe that an interpretation based on stereoelectronic arguments would be more useful in rationalizing the results. All the previously discussed models place a substituent perpendicular to the double bond. We have thus considered the four conformations **A**–**D** shown in Scheme 4, not taking into account the two having the H perpendicular, since they are anticipated to be disfavoured for both steric and electronic reasons.[11]

Table 2
Results of methylation of dianion derived from ester **8b**[a]

Entry	Solvent	MeX	Temperature / Time Time	Convers.[b]	**9-10/ 11-12**[b]	Yield[c]	**9** : **10**[b]	**11** : **12**[b]
1	THF	MeI	-78°C→-20°C / 2h	79%	54 : 46	35%	10 : 90	28 : 72
2	THF	MeI	-78°C (3h)/ -78°C→-50°C (0.5h)	85%	98 : 2	78%	19 : 81	-
3	THF	MeI	-78°C / 6 h	83%	98 : 2	77%	17 : 83	-
4	THF-HMPA[d]	MeI	-78°C / 3.75 h	86%	98 : 2	70%	36 : 64	-
5	THF	Me_2SO_4	-78°C→-50°C (2h)/ -50°C (1h)	79%	33 : 67	21%	6 : 94	40 : 60
6	THF	Me_2SO_4	-78°C / 5h	36%	88 : 12	24%	9 : 91	60 : 40

[a] Dianion formation was always performed with LDA. [b] Determined by GC. [c] Isolated yield of **9b+ 10b**. [d] HMPA (hexamethylphosphoric triamide) was added after enolization.



Scheme 4.

Hehre[11c] has suggested, through theoretical work, that in electron-rich alkenes the preferred conformation is the one placing the substituent with the higher −I effect in a position perpendicular to the double bond. On the other hand, both Hehre[11c] and McGarvey[11b] have proposed that the most reactive conformation is the one placing in perpendicular the most electrodonating group, since in this case, a π–σ interaction increases the HOMO energy. However, the latter statement is quite general, being made specifically for considering simple alkenes. Enolates are undoubtely a limiting case of an electron-rich alkene. From the first point of view (that is looking at the most stable conformation), one would expect **A** and **D** to be favoured. From the second (that is looking at the most reactive conformation), **B** and **C** would be better. Between these two pairs, the conformations placing the CH_2O-group 'inside' (**B** and **D**) are expected to be disfavoured for steric reasons and (in the case of **D**) also for the presence of an electrostatic repulsion between the two negatively charged oxygens. The outcome of the present reaction indicates that **A** is the conformation giving the correct prediction, and this fact is in line with the data recently collected by Mohrig et al.[11d] on the protonation of enolates of various esters β-substituted with heteroatoms. Thus it seems that the stability of ground state conformation plays the key role in this type of stereocontrol. This is not however surprising, since the enolate double bond is much more reactive towards electrophiles than a simple alkene, and the transition state is expected to be reagent-like. In other words, the increase of HOMO energy is not, in this case, so necessary to promote reaction of the electrophile with the LUMO. Obviously in the case of electrophilic additions to simple alkenes, the situation could be completely different, and the π–σ interaction with the perpendicular bond may be, in that case, decisive.

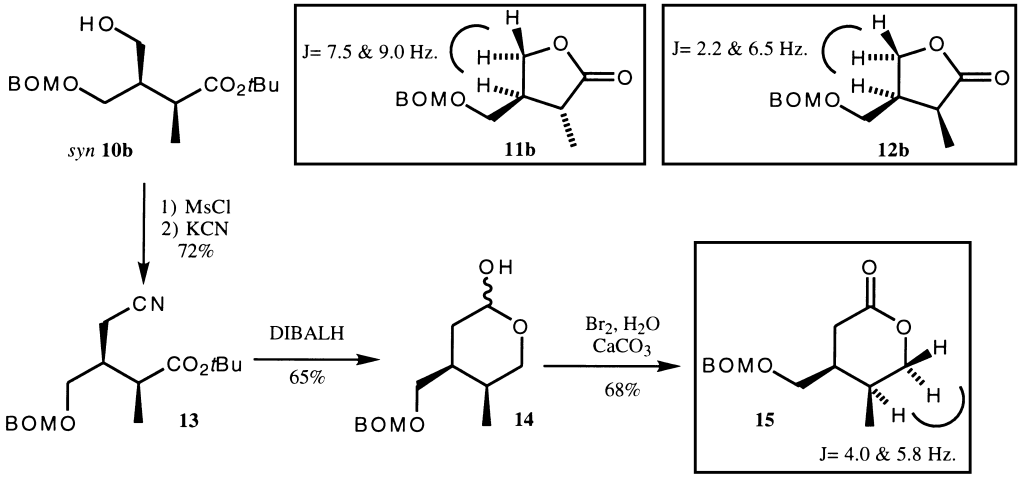
Finally, it should be pointed out that the preference of **A** towards **C** may be also explained by electrostatic interactions. In **A**, the negatively charged oxygens are indeed nearly at 180°.

Similar arguments can be used to explain the moderate preference for *syn* adducts in the case of **5a**,**b**. In this case, the electronic difference between the two groups is, however, small, and thus the higher stability of conformations placing the CH_2OSiPh_2t-Bu perpendicular is probably mainly due to steric reasons.

The relative configurations of adducts **6a**, **7a**, **9b** and **10b** were determined in the following way. First they were all converted stereospecifically[12] into lactones **11b** and **12b**. In the case of **6a** and **7a** this was done by reaction with *n*-$Bu_4NF\cdot 3H_2O$ in THF. Under these conditions, the expected alcohols **9b** and **10b** could not be isolated, but underwent spontaneous lactonization to afford **11b** (from **7a**) and **12b** (from **6a**). On the other hand, **9b** and **10b** were converted into **11b** and **12b**, respectively, by treating them with CF_3CO_2H in CH_2Cl_2.

The ^1H NMR spectra of these lactones allowed only the coupling constants shown in Scheme 5 to be determined precisely. The conformational equilibrium was examined by force field calculations.[13] In the *trans* lactone, a single conformation was found (the others all had definitely higher energy), and the dihedral angles fitted well with the experimental J values. On the other hand, minimization of the *cis* lactone gave two comparable conformations. In both, the predicted value for J_{cis} is about 6 Hz, while

J_{trans} is ~8 and 0 Hz, respectively. The observed value of 2.2 Hz is compatible with an equilibrium mixture with the conformation having a nearly null J prevailing. What is clear is that the experimental J values found for **12b** are not compatible with the predicted conformation of the *trans* lactone.



Scheme 5.

In order to gain further evidence for the relative configuration attribution, we also converted the *syn* alcohol **10b** into δ-lactone **15**, by the sequence shown in Scheme 5. This straightforward transformation also represents a significant example of the synthetic versatility of these building blocks. It should be noted that in the transformation of **13** into **14**, the oxidation state of the two carboxylic derivatives is diversified by the different behaviour toward DIBALH. From the ^{1}H NMR of **15** we could measure only the two J values shown in Scheme 5. Also in this case, force field calculations were carried out on lactone **15** and on its *trans* diastereoisomer. In the latter, one of the two main conformations (with both substituents equatorial) is distinctly more stable. The dihedral angles of 56° and 173° for the shown hydrogens are incompatible with the two J values observed. In the case of **15** the two main conformations were found to have comparable energy, and the observed J values (4.0 and 5.8 Hz) are in agreement with nearly a 1:1 equilibrium.

In conclusion, a new type of 'protecting group controlled' asymmetric synthesis, not based on a cyclic chelated transition state, has been developed. It takes advantage of the different electronic properties of CH_2O^- and CH_2OR groups, and affords good levels of diastereoselection even if the first point of difference in the two synthetically equivalent side arms is two atoms away from the stereogenic centre. Extension to other electrophiles and application in the field of natural product synthesis are in progress.

3. Experimental

NMR spectra were taken in $CDCl_3$, at 200 MHz (^{1}H), and 50 MHz or 20 MHz (^{13}C). Chemical shifts are reported in ppm (δ scale), coupling constants are reported in hertz. Peak assignment in ^{1}H NMR spectra, was also made with the aid of double resonance experiments. In ABX systems, the proton A is considered downfield and B upfield. Peak assignment in ^{13}C spectra was made with the aid of DEPT or off-resonance experiments. GC–MS was carried out on an HP-5971A instrument, using an HP-1 column (12 m long, 0.2 mm wide), electron impact at 70 eV, a mass temperature of about 167°C, and starting the mass range from m/z=33. Unless otherwise indicated, analyses were performed

with a constant He flow of 0.9 ml/min, starting at 100°C for 2 min and then raising the temperature by 20°C/min. t_R are measured in minutes from injection. GC analyses were performed on a capillary RSL-150 column (25 m×0.25 mm i.d.) using FID as detector. HPLC analyses were carried out on an ERBASIL column (250 mm×4.6 mm, packed with 10 μm silica gel) with a UV detector (254 nm). IR spectra were measured with a Perkin–Elmer 881 instrument as $CHCl_3$ solutions. TLC analyses were carried out on silica gel plates, which were developed by UV or by dipping into a solution of $(NH_4)_4MoO_4 \cdot 4H_2O$ (21 g) and $Ce(SO_4)_2 \cdot 4H_2O$ (1 g) in H_2SO_4 (31 ml) and H_2O (469 cc) and warming. R_f were measured after an elution of 7–9 cm. Chromatography was carried out on 220–400 mesh silica gel using 'flash' methodology. Petroleum ether (40–60°C) is abbreviated as PE. In extractive work-up, aqueous solutions were always reextracted three times with the appropriate organic solvent. Organic extracts were dried over Na_2SO_4 and filtered, before evaporation of the solvent under reduced pressure. All reactions employing dry solvents were carried out under a nitrogen atmosphere. The purity of all compounds was established by TLC, ^{1}H NMR, GC–MS or HPLC.

*3.1. (2*S*,3*S*)- and (2*R*,3*S*)*-tert-*Butyl 3-(((benzyloxy)methoxy)methyl)-4-((*tert-*butyldiphenylsilyl)oxy)-2-methylbutanoates **6a** and **7a***

3.1.1. Representative procedure

A solution of **5a** (prepared as described by Banfi et al.[2]) (200 mg, 364 μmol) in dry THF (10 ml) was cooled to −78°C, and treated first with DMPU (5 ml), and then with a 0.45 M solution of LDA in THF/hexanes (prepared at −15°C from 1.56 ml of diisopropylamine and 6.25 ml of 1.6 M *n*-BuLi in hexanes in 14.4 ml of THF) (2.43 ml, 1.09 mmol). After 10 minutes, the solution was treated with methyl iodide (120 μl, 1.93 μmol). The temperature was allowed to rise slowly to 0°C over 3.5 h. The reaction was quenched with saturated aqueous NH_4Cl and extracted with Et_2O to give, after usual work-up and chromatography (PE:AcOEt 95:5), the inseparable mixture of **6a** and **7a** (176 mg, 86%) (R_f 0.38, PE:AcOEt 95:5, det. A,B) as an oil. The diastereomeric ratio (36:64) was determined by HPLC (*n*-hexane:Et_2O 96:4). GC–MS: not feasible. ^{1}H NMR: δ 1.05 [9H, *s*, $(CH_3)_3CSi$]; 1.08 [**7a**] and 1.09 [**6a**] [3H, d, CH_3–CH, J 7.2]; 1.35 [**7a**] and 1.40 [**6a**] [9H, s, $(CH_3)_3CSi$]; 2.07–2.39 [1H, m, $CH(CH_2O)_2$]; 2.60 [**6a**] and 2.63 [**7a**] [1H, quintuplet, CH–CH_3, J 7.1]; 3.59–3.85 [4H, m, CH_2O]; 4.55 [2H, s, $PhCH_2O$]; 4.68 [2H, s, O–CH_2O]; 7.30–7.50 [11H, m, aromatics]; 7.60–7.72 [4H, m, aromatics].

*3.2. (2*S*,3*S*)- and (2*R*,3*S*)*-tert-*Butyl 3-((((4-methoxy)benzyloxy)methoxy)methyl)-4-((*tert-*butyldiphenylsilyl)oxy)-2-methylbutanoates **6b** and **7b***

Compounds **6b** and **7b** were prepared by the same procedure employed for **6a**,**b**, except for the addition of DMPU. Starting from 115.1 mg of **5b** (see Banfi et al.[2]) (199 μmol), we obtained, after chromatography (PE:AcOEt 95:5 → 80:20), 100.4 mg of the inseparable mixture of **6b** and **7b** as an oil (85%) (R_f 0.56, PE:Et_2O 8:2). The diastereomeric ratio (43:57) was determined by HPLC (*n*-hexane:Et_2O 93:7). GC–MS: not feasible. ^{1}H NMR: δ 1.05 [9H, *s*, $(CH_3)_3CSi$]; 1.08 [3H, d, CH_3–CH, J 7.2]; 1.35 [**7b**] and 1.40 [**6b**] [9H, s, $(CH_3)_3CSi$]; 2.07–2.39 [1H, m, $CH(CH_2O)_2$]; 2.60 [**6b**] and 2.63 [**7b**] [1H, quintuplet, CH–CH_3, J 7.1]; 3.59–3.85 [4H, m, CH_2O]; 3.80 [3H, s, OCH_3]; 4.48 [2H, s, $ArCH_2O$]; 4.65 [2H, s, O–CH_2O]; 6.86 [2H, d, aromatics, J 8.0]; 7.24 [2H, d, aromatics, J 8.0]; 7.30–7.50 [6H, m, aromatics]; 7.60–7.72 [4H, m, aromatics].

3.3. (2R,3R) and (2S,3R) tert-Butyl 3-(((benzyloxy)methoxy)methyl)-4-hydroxy-2-methylbutanoates **9b** and **10b**

3.3.1. Representative procedure

A solution of **8b** (see Banfi et al.[2]) (302 mg, 0.97 mmol) in dry THF (5 ml) was cooled to −78°C, and treated with 0.45 M LDA solution (prepared as described above) (6.5 ml, 2.92 mmol). After stirring at −78°C for 30 minutes, methyl iodide (300 μl, 4.81 mmol) was added. After 6 h at the same temperature, the reaction was quenched with saturated NH_4Cl, extracted with Et_2O, and chromatographed (PE:Et_2O:CH_2Cl_2 1:1:1) to give 210 mg of the inseparable mixture of **9b** and **10b** as an oil (66.5%) (R_f 0.46, PE:Et_2O:CH_2Cl_2 1:1:1) and 41 mg of recovered **8b** (R_f 0.50). Yield from non-recovered starting material=77%. The diastereomeric ratio (17:83) was determined by GC (2 min at 140°C, then 2°C/min). GC–MS: **9b**: t_R 9.03. m/z: 221 (M^+−103, 2.1%); 162 (13.0); 144 (15.0); 143 (14.4); 131 (8.5); 129 (9.6); 120 (15.2); 119 (10.3); 108 (6.2); 107 (8.9); 99 (36.3); 92 (22.0); 91 (100); 71 (6.9); 69 (6.4); 65 (7.5); 59 (20.1); 57 (17.9); 55 (5.8); 45 (5.5); 43 (8.8); 41 (11.7). **10b**: t_R 8.99. m/z: 268 (M^+−56, 0.2%); 221 (M^+−103, 4.8); 162 (18.7); 147 (7.2); 144 (15.7); 143 (23.9); 131 (17.4); 129 (17.6); 120 (19.6); 119 (11.7); 108 (8.2); 107 (8.7); 99 (10.7); 92 (20.8); 91 (100); 71 (13.3); 69 (5.3); 65 (6.2); 59 (12.2); 57 (18.3); 43 (6.2); 41 (8.6). ^{1}H NMR: δ 1.16 [**9b**] and 1.17 [**10b**] [3H, d, C*H*$_3$–CH, J 7.1]; 1.44 [**10b**] and 1.45 [**9b**] [9H, s, (C*H*$_3$)$_3$C]; 2.00–2.20 [1H, m, C*H*(CH$_2$O)$_2$]; 2.27 [**9b**] and 2.43 [**10b**] [1H, t, O*H*, J 5.9]; 2.58 [**9b**] and 2.63 [**10b**] [1H, quintuplet, C*H*–CH$_3$, J 7.2]; 3.57–3.84 [4H, m, C*H*$_2$O]; 4.61 [2H, s, PhC*H*$_2$O]; 4.75 [2H, s, OC*H*$_2$O]; 7.30–7.40 [5H, m, aromatics]. ^{13}C NMR (50 MHz): δ 175.45 [*C*=O]; 137.63, 128.46, 127.86, 127.78 [aromatics]; 94.83 [O*C*H$_2$O]; 80.66 [**9b**] and 80.58 [**10b**] [(CH$_3$)$_3$*C*O]; 69.60 [Ph*C*H$_2$]; 68.86 [**10b**] and 67.75 [**9b**] [*C*H$_2$O]; 63.04 [**9b**] and 62.72 [**10b**] [*C*H$_2$O]; 43.63 [**9b**] and 42.95 [**10b**] [*C*H]; 39.38 [**9b**] and 39.17 [**10b**] [*C*H]; 28.03 [C(*C*H$_3$)$_3$]; 14.85 [**9b**] and 14.37 [**10b**] [*C*H$_3$].

3.4. (2R,3S) and (2S,3S) 3-((Benzyloxy)methoxy)methyl-2-methyl-4-butanolides **11b** and **12b**

(a) From **6a**,**7a**: A solution of a 36:64 diastereomeric mixture of **6a** and **7a** (99.5 mg, 177 μmol) in dry THF (5 ml) was cooled to 0°C, and treated with a 1 M solution of *n*-Bu$_4$NF·3H$_2$O in THF (0.5 ml, 0.5 mmol). After 10 minutes, the temperature was allowed to reach rt. After stirring for 5 h, the reaction was quenched with aqueous saturated NH_4Cl, extracted with Et_2O, and chromatographed (PE:AcOEt 6:4) to give pure **11b** (19.0 mg, 43%) (R_f 0.51, PE:AcOEt 6:4) and **12b** (8.9 mg, 20%) (R_f 0.34).

(b) From **9b**,**10b**: A solution of a 17:83 diastereomeric mixture of **9b** and **10b** (115.9 mg, 357 μmmol) in dry CH_2Cl_2 (2 ml) was treated with trifluoroacetic acid (2 ml). After 20 minutes, the solution was evaporated in the cold. *n*-Heptane was added to the residue and the suspension evaporated again. Chromatography (PE:AcOET 6:4) gave pure **12b** (38.2 mg, 43%) and **11b** (7.5 mg, 8.5%).

11b: GC–MS: t_R 8.26. m/z: 250 (M^+, 0.08%); 205 (0.6); 144 (9.6); 120 (20.0); 119 (11.8); 107 (11.1); 99 (20.4); 91 (100); 74 (8.3); 71 (32.9); 69 (13.0); 65 (12.0); 55 (8.5); 45 (10.0); 43 (8.8); 41 (12.6); 39 (7.6). ^{1}H NMR: δ 1.27 [3H, d, C*H*$_3$, J 6.9]; 2.30–2.55 [2H, m, C*H*]; 3.61 and 3.69 [2H, AB part of an ABX system, C*H*$_2$OBOM, J_{AB} 9.9, J_{AX} 4.2, J_{BX} 5.9]; 3.99 [1H, t, C*H*HOC=O, J 9.0]; 4.38 [1H, dd, C*H*HOC=O, J 7.5]; 4.60 [2H, s, PhC*H*$_2$O]; 4.77 [2H, s, OC*H*$_2$O]; 7.30–7.40 [5H, m, aromatics].

12b: GC–MS: t_R 8.15. m/z: 250 (M^+, 0.15%); 220 (0.8); 205 (1.0); 189 (4.6); 144 (12.8); 120 (10.8); 119 (9.1); 107 (10.7); 99 (62.7); 91 (100); 79 (5.5); 71 (7.2); 69 (10.5); 65 (12.9); 55 (9.2); 45 (9.8); 43 (10.3); 41 (14.7); 39 (9.1). ^{1}H NMR: δ 1.23 [3H, d, C*H*$_3$, J 7.0]; 2.60–2.90 [2H, m, C*H*]; 3.57 and 3.68 [2H, AB part of an ABX system, C*H*$_2$OBOM, J_{AB} 9.8, J_{AX} 4.0, J_{BX} 6.5]; 4.24 and 4.30 [2H, AB part of an ABX system, C*H*$_2$OC=O, J_{AB} 9.5, J_{AX} 6.5, J_{BX} 2.2]; 4.60 [2H, s, PhC*H*$_2$O]; 4.75 [2H, s,

OCH_2O]; 7.30–7.40 [5H, m, aromatics]. ^{13}C NMR (50 MHz): δ 179.23 [*C*=O]; 137.62, 128.50, 127.83 [aromatics]; 95.06 [O*C*H_2O]; 70.00, 69.26 and 66.07 [*C*H_2O]; 38.84 and 36.12 [*C*H]; 9.84 [*C*H_3].

3.5. (2S,3S) tert-Butyl 3-(((benzyloxy)methoxy)methyl)-4-cyano-2-methylbutanoate **13**

A solution of an 83:17 diastereomeric mixture of **10b** and **9b** (99.4 mg, 306 μmol) in dry CH_2Cl_2 (8 ml) was cooled to −30°C, and treated with triethylamine (130 μl, 933 μmol) and methanesulfonyl chloride (36 μl, 463 μmol). After stirring for 40 minutes at −30°C, the reaction was quenched with saturated aqueous NH_4Cl, and extracted with AcOEt to give, after evaporation a crude product, used as such for the next reaction. It was taken up in dry dimethyl sulfoxide (600 μl), treated with *n*-Bu_4NI (22.9 mg, 62 μmol), and potassium cyanide (66 mg, 1.01 mmol) and warmed at 70°C for 3 h. After cooling, the mixture was diluted with water and extracted with Et_2O. The organic extracts were washed with saturated aqueous NH_4Cl, evaporated, and chromatographed (PE:AcOEt 8:2) to give **13** as an oil, contaminated by ~15% of the diastereoisomer (by ^{1}H NMR) (73.1 mg, 72%). R_f 0.82 (PE:AcOEt 6:4). GC–MS: t_R 9.12. m/z: 277 (M^+−56, 6.1%); 246 (M^+−87, 1.5), 230 (M^+−103, 2.3); 171 (5.1); 170 (12.1); 140 (43.4); 120 (9.9); 119 (5.7); 108 (20.7); 107 (16.9); 92 (17.3); 91 (100); 65 (6.7); 57 (35.4); 41 (9.4). ^{1}H NMR: δ 1.18 [3H, d, C*H*$_3$, J 7.0]; 1.45 [9H, s, (C*H*$_3$)$_3$C]; 2.20–2.40 [1H, m, C*H*]; 2.40–2.70 [3H, m, C*H* and C*H*$_2$CN]; 3.58 and 3.68 [2H, AB part of an ABX system, C*H*$_2$OBOM, J_{AB} 10.4, J_{AX} 5.2, J_{BX} 7.1]; 4.60 [2H, s, C*H*$_2$Ph]; 4.75 [2H, s, OC*H*$_2$O]; 7.30–7.40 [5H, m, aromatics]. ^{13}C NMR (20 MHz): δ 173.66 [*C*=O]; 137.59, 128.41, 127.86, 127.73 [aromatics]; 118.3 [*C*≡N]; 94.86 [O*C*H_2O]; 81.12 [*C*(CH$_3$)$_3$]; 69.77 and 67.51 [*C*H_2O]; 40.71 and 38.45 [*C*H]; 28.08 [C(*C*H$_3$)$_3$]; 17.21 [*C*H_3CH]; 14.53 [*C*H_2CN]. IR: ν_{max} 3016, 2980, 2935, 2887, 2248, 1721, 1453, 1418, 1369, 1244, 1150, 1112, 1041 cm^{-1}.

3.6. (4S,5S) 4-(((Benzyloxy)methoxy)methyl)-5-methyltetrahydropyran-1-one **15**

A solution of **13** (containing ~15% of the diastereoisomer) (61.8 mg, 184 μmol) in dry CH_2Cl_2 (4 ml) was cooled to −40°C and treated with a 1 M solution of diisobutylaluminium hydride in toluene (600 μl, 600 μmol). The temperature was allowed to rise to −20°C and the mixture was stirred for 7 h. Quenching with saturated aqueous NH_4Cl, followed by dilution with saturated Na, K tartrate, extraction with AcOEt, evaporation and chromatography (PE:AcOEt 1:1), gave lactol **14** (R_f 0.41, PE:AcOEt 1:1) (31.9 mg, 65%), which was used as such for the next reaction. It was taken up in methanol (1.2 ml), and treated at rt with $CaCO_3$ (36.0 mg, 360 μmol) and a 0.1 M solution of Br_2 in H_2O (2.4 ml, 240 μmol). After stirring for 4 h, the reaction was quenched with 1 M $NaHSO_3$, diluted with saturated NaCl and adjusted to pH 7 with saturated $NaHCO_3$. Extraction with Et_2O gave, after evaporation and chromatography (Et_2O:*i*-Pr_2O 1:1), diastereomerically pure **15** (21.5 mg, 68%, 80% considering the diastereomeric composition of starting material). R_f 0.37 (Et_2O:*i*-Pr_2O 1:1) (R_f of diastereoisomer=0.40). GC–MS: t_R 9.05 m/z: 204 (M^+−60, 0.2%); 173 (M^+−91, 1.4); 158 (12.9); 120 (5.6); 119 (7.3); 113 (100); 92 (16.0); 91 (83.2); 69 (11.5); 65 (8.8); 55 (8.6); 41 (9.5); 39 (5.0). ^{1}H NMR (signal attribution was made with the aid of a COSY experiment): δ 1.03 [3H, d, C*H*$_3$CH, J 7.0]; 2.15–2.70 [4H, m, C*H* and C*H*$_2$C=O]; 3.56 [2H, d, C*H*$_2$OBOM, J 5.7]; 4.21 and 4.31 [2H, AB part of an ABX system, C*H*$_2$OC=O, J_{AB} 11.1; J_{AX} 4.0; J_{BX} 5.8]; 4.60 [2H, s, C*H*$_2$Ph]; 4.75 [2H, s, OC*H*$_2$O]; 7.30–7.40 [5H, m, aromatics]. ^{13}C NMR (50 MHz): δ 170.40 [*C*=O]; 137.66, 128.51, 127.85 [aromatics]; 94.99 [O*C*H_2O]; 74.47, 69.88, 68.24 [*C*H_2O]; 35.48 [*C*H_2OCO]; 31.36 and 28.84 [*C*H]; 11.35 [*C*H_3].

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9. This assumption descends from the following observations: (a) for both **8a** and **8b** no unmethylated lactone was detected in the reaction mixture; (b) in the case of **8b** (Table 2), the *trans*:*cis* ratio of lactones depended on the relative amount of lactones formed. When the quantity of lactones was higher, the percentage of *cis* lactone increased as well. If methylation occurred after cyclization, this ratio would have been independent from conversion, and the *trans* lactone would have most likely been the major diastereoisomer in any case. The absence of unmethylated lactone is moreover logical, since **8b** is completely converted to the enolate and should have no tendency to undergo intramolecular attack by the alkoxide.
10. After reacting with MeI for 2 h between −78°C and −50°C, conversion was only 48% and the ratio **9**–**10**:**11**–**12** was 39:61. Moreover, a certain amount of desilylated products was detected.
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12. Although the two diastereomeric pairs **6a**,**7a** and **9b**,**10b** could not be separated, starting with compounds with different relative composition, we always observed a relationship between the diastereomeric ratios of the formed lactones with those of the acyclic precursors.
13. Force field calculations were performed with Chem3D Plus by CSC.