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A study on the chelation control in the regioselective opening of 2,3-bifunctionalized epoxides

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Abstract—The results obtained in the $MgBr_2$-mediated opening of 2,3-bifunctionalized epoxides are reported. The studies showed that the chelation control of $MgBr_2$ between different functionalities can in some cases be selective.

1. Introduction

Regio- and stereoselective opening of chiral epoxides has been long since the object of many studies as a route to a large variety of compounds in optically active form.[1] It is well known that the nucleophilic attack on unsymmetrical substituted oxiranes, especially monosubstituted ones, occurs at the less substituted carbon, but in general the presence of a C-2 functionality is necessary to better control the reaction's regioselectivity.

In principle, there are two reactive sites in C-2 functionalized epoxides related to the nucleophilic opening of the epoxy ring (C-2 and C-3); chelation control has been largely used to direct the opening at the C-3 position through an intermolecular attack of external nucleophile (Fig. 1, A and B),[2] while opening at the C-2 position is presumed due to an intramolecular nucleophilic attack[3] or in 'non chelating conditions' (Fig. 1, C).[4]

During our studies we have investigated extensively the opening of epoxy alcohols, esters[5] and, more recently, aldehydes[6] with metal halides. As reported in Scheme 1 in every case we established that freshly prepared MgI_2, or the commercially available $MgBr_2$, was able to direct the halide to the C-3 position through a previously postulated chelated complex between the metal (Mg^{2+}) and the two oxygens of the epoxide derivative.

We obtained, only for epoxy esters, C-2 regioselectivity in the opening using NaX/Amberlyst 15 in acetone (Scheme 2); in absence of any coordination between the metal and the two oxygens of α,β-epoxy ester (Na is a poor Lewis acid), the C-2 position is preferred by the halide ion because of the electronic effect of the COOR group.[4]

Regarding the observed one-pot transformation of α,β-epoxy aldehydes, the position of the halide reveals an

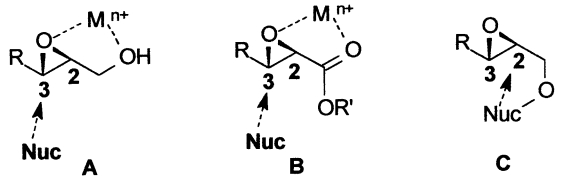
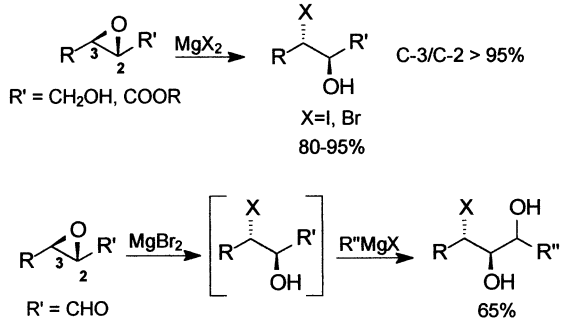
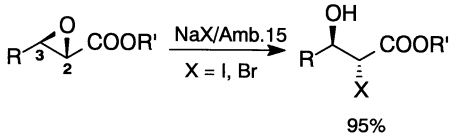


Figure 1. Inter- and intramolecular nucleophilic attack at C-2 functionalized epoxides.



Scheme 1. $MgBr_2$-mediated opening of C-2 functionalized epoxides.



Scheme 2. NaX/Amb.15- mediated opening of α,β-epoxyesters.

Keywords: bifunctionalized epoxides; chelation control; regioselective opening.

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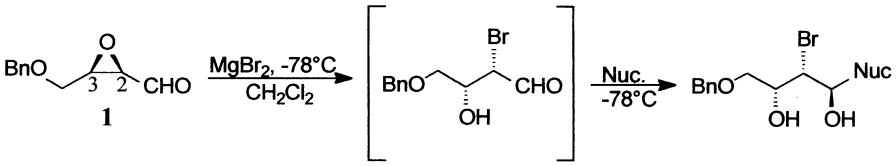


Scheme 3. $MgBr_2$-mediated opening of α,β-epoxyaldehyde **1**.

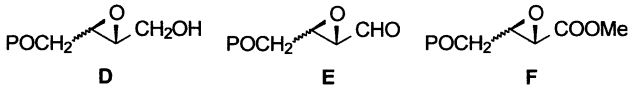


Figure 2. Bifunctionalized epoxides.

Mg-controlled regiochemistry of attack. The same reaction has already been reported for α,β-epoxyaldehyde **1** having an alkoxy group at C-4, and in that case the observed regioselectivity was opposite (Scheme 3).[7]

The possibility that the chelation control of $MgBr_2$ between different functionalities could be selective, has prompted us to further studies on several bifunctionalized epoxides (Fig. 2).

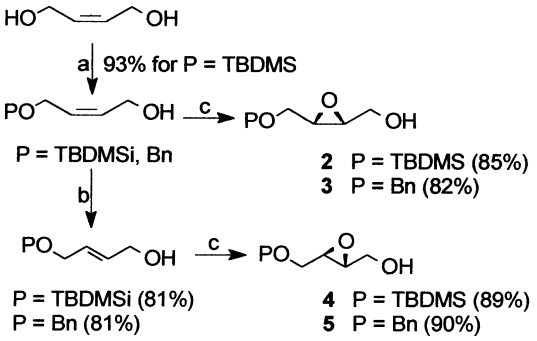
The selected functional groups are those already investigated in our previous studies, where the use of $MgBr_2$ afforded an excellent regioselectivity toward the C-3 position.

2. Results and discussions

2.1. Preparation of substrates of type D, E and F

Every bifunctionalized epoxide has been synthesized as *E* and *Z* isomer to verify if the chelation control is dependent on molecular geometry. At the moment we have synthesized only racemic epoxides since enantioenriched compounds were not necessary for our studies.

As reported in Scheme 4, (*Z*) and (*E*)-4-*tert*-butyldimethylsilyloxy-2,3-epoxybutan-1-ol (**2** and **4**) and (*Z*) and (*E*)-4-benzyloxy-2,3-epoxybutan-1-ol (**3** and **5**) have been synthesized from the commercially available (*Z*)-2-buten-1,4-diol and (*Z*)-4-benzyloxy-2-buten-1-ol, respectively, through usual and high yielding reactions.[8–10]

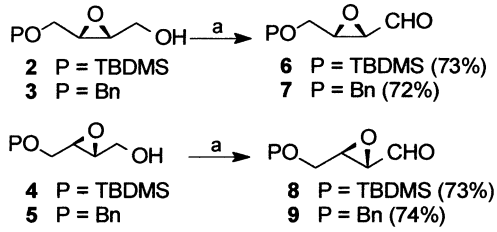


Scheme 4. Preparation of type **D** epoxides a:[8] NaH (1 equiv.), TBDMSiCl (1 equiv.), THF, 0°C; b:[9] (1)PDC, CH_2Cl_2, 0°C (2) $NaBH_4$, MeOH, 0°C; c:[10] Oxone (5 mmol), $NaHCO_3$ (7.75 mmol) $H_2O/(CH_3)_2CO$, rt.

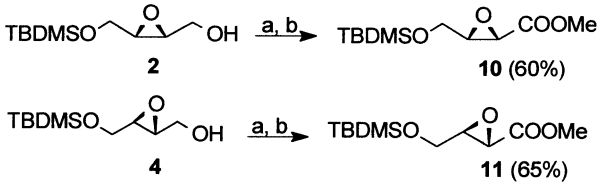
(*E*)-4-*tert*-butyldimethylsilyloxy-2,3-epoxybutanal **8** and (*E*)-4-benzyloxy-2,3-epoxybutanal **9** have been synthesized from the corresponding epoxy alcohols using the Swern oxidation. Since Mg^{2+} did not show any selectivity between the free hydroxy and the protected one (see below), we chose to use the more stable protected derivatives (Scheme 5).[11]

(*Z*)- and (*E*)-Methyl-4-*tert*-butyldimethylsilyloxy-2,3-epoxybutanoate (**10** and **11**) have been prepared by oxidation of the corresponding epoxy alcohols with $RuCl_3$ to the acid[12] and subsequent esterification (Scheme 6).

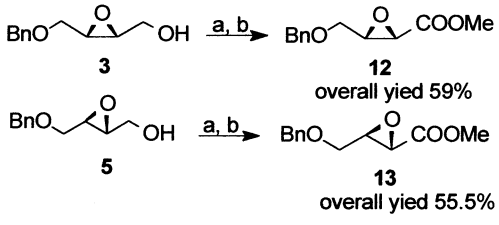
Since it was not possible to synthesize the benzyloxy derivative using the same reaction conditions because of a competitive $RuCl_3$ oxidation of the benzylic position, an alternative synthetic sequence has been used to obtain (*Z*)- and (*E*)-methyl-4-benzyloxy-2,3-epoxybutanoate (**12** and **13**), as reported in Scheme 7.[13,14]



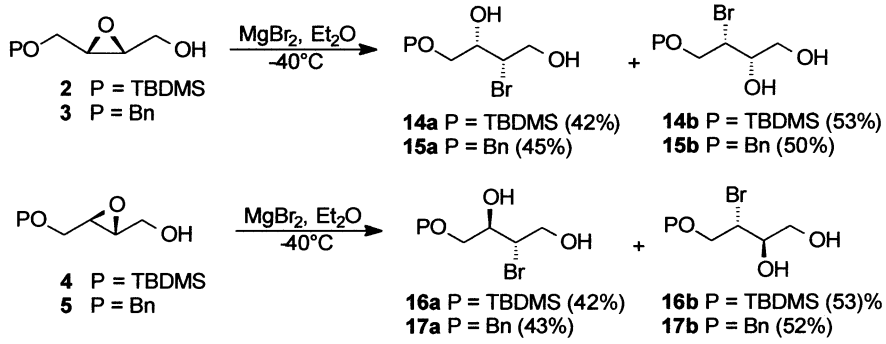
Scheme 5. Preparation of type **E** epoxides a:[11] DMSO, $(COCl)_2$, Et_3N, 60°C.



Scheme 6. Preparation of type **F** epoxides with P=TBDMS a:[12] $NaIO_4$, $RuCl_3$, $H_2O/CCl_4/CH_3CN$, rt; b: CH_2N_2, Et_2O.



Scheme 7. Preparation of type **F** epoxides with P=Bn a:[13]DMSO, $(COCl)_2$, CH_2Cl_2, 60°C; b:[14]PDC, MeOH, DMF.



Scheme 8. Ring opening of type **D** epoxides.

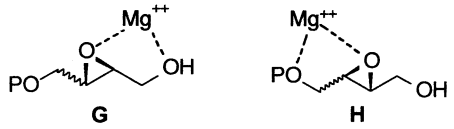


Figure 3. Possible cyclic chelates.

2.1.1. Ring opening of epoxides. The four type **D** substrates were treated with 3 equiv. of $MgBr_2$ at −40°C and in every case we obtained both regioisomers without any selectivity (Scheme 8). To improve the regioisomeric ratio, we also used a lower temperature, but with these conditions the reaction became too slow.

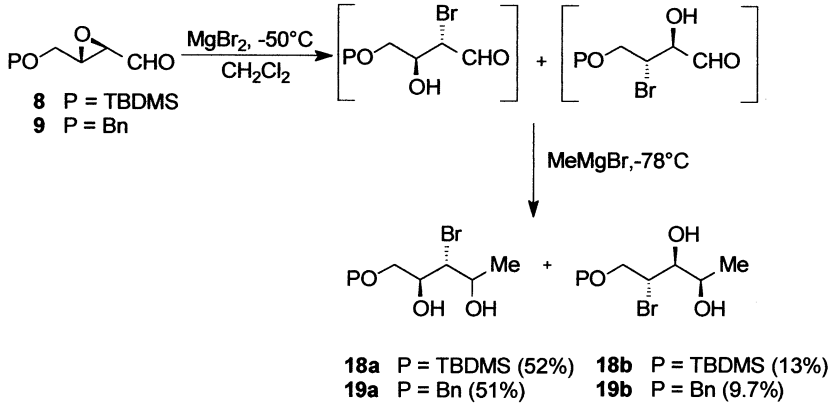
This result can be explained assuming that the chelate between Mg^{2+}, epoxide oxygen and free hydroxyl group (**G**) has the same stability of that between Mg^{2+}, epoxide oxygen and protected hydroxyl group (**H**) (Fig. 3). Consequently in this type of substrate the use of $MgBr_2$ does not allow discrimination of the attack position.

The $MgBr_2$-mediated opening of (*Z*)-isomers of type **E** epoxides, followed by an in situ alkylation, have already been studied by Procter, furnishing the 2-bromo derivatives as the major product (see Scheme 3).[7] Our results on the (*E*) isomers of type **E** substrates were in accordance with this observation, in fact the same reaction conditions provided an 8:2 mixture of C-2/C-3 regioisomers (Scheme 9).

In this case the results suggest that the chelate between Mg^{2+}, epoxide oxygen and aldehydic carbonyl (**I**) is less stable than that formed between Mg^{2+}, epoxide oxygen and protected hydroxyl group (**C**), especially in the (*Z*)-isomers. The lower regioselectivity observed in the (*E*)-isomers leads to presume that in this case the chelate is formed with more difficulty with respect to (*Z*)-isomers.

The obtained results explain the inversion of the regioselectivity of the $MgBr_2$-attack when an alkyl group is present in the C-4 position (C-3 attack)[6] instead of an alkoxy group (C-2 attack).[7] Fig. 4.

Compounds **10**–**13** (type **F** epoxides) were subjected to $MgBr_2$-mediated ring opening under the same reaction conditions previously reported for α,β-epoxy esters (4 equiv. of $MgBr_2$ in Et_2O at −40°C).[5c]



Scheme 9. Ring opening of type **E** epoxides.

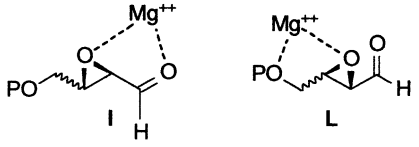
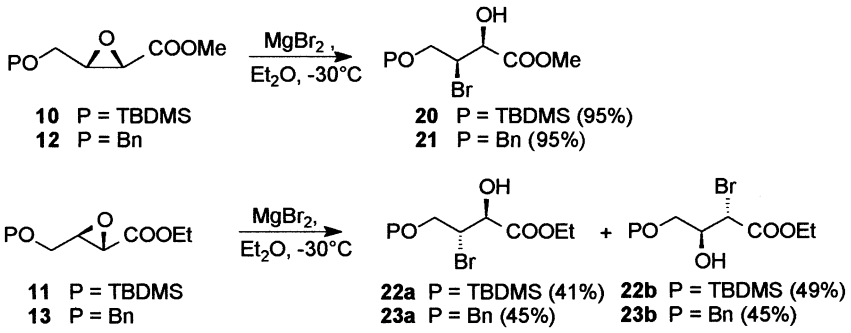


Figure 4. Possible cyclic chelates.

We observed an excellent C-3 regioselectivity only on the (*Z*)-isomers, while the (*E*)-isomers gave a mixture of the two regioisomeric bromo derivatives in a 1:1 ratio (Scheme 10).

Also in this case, at least for the (*Z*)-isomer, we supposed that the regiochemistry of the halide attack is governed by the formation, in the TS* of the reaction, of a chelate



Scheme 10. Ring opening of type **F** epoxides.

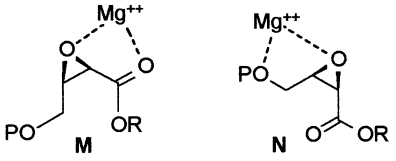
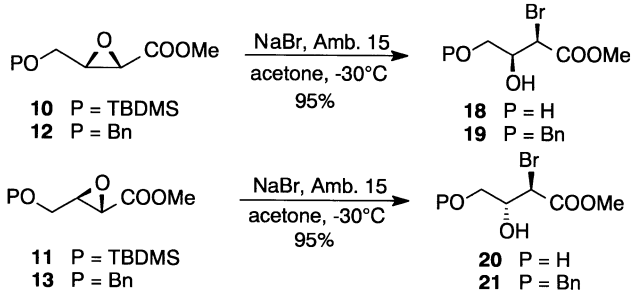


Figure 5. Possible cyclic chelates.

between Mg^{2+}, epoxide oxygen and carboxylic oxygen (**M**) which is more likely than that between Mg^{2+}, epoxide oxygen and protected hydroxyl group (**N**) (Fig. 5).

The loss of regioselectivity observed for the (*E*)-isomer could be explained in the same manner seen before for the compounds **8** and **9**.

To confirm this hypothesis we thought that under 'non-chelated' conditions the behaviour of both the (*Z*) and (*E*)-olefins had to be the same. To this end we have performed the opening of the oxirane ring by NaBr/Amberlyst 15 in acetone of the compounds **10**–**13** with the already reported procedure[4a] obtaining only the C-2 attack for both (*Z*) and (*E*)-isomers (Scheme 11).



Scheme 11. Ring opening of type **F** epoxides under non-chelating conditions.

The reaction proceeds with excellent yield and stereoselectivity; moreover, the TBDMS protective group is removed by the exchange resin. Probably, as already mentioned, in absence of any coordination between the metal and the oxygens (Na is a poor Lewis acid), the C-2 position proves more reactive.

3. Conclusions

The studies carried out show that the opening of bifunctionalized epoxides in $MgBr_2$-chelating conditions leads to different results depending on the type of substrates; summarizing we can say:

1. With type **D** epoxides there is no regioselectivity in the halide attack.
2. With type **E** epoxides halide attack α to the carbonyl group is preferred, especially with (*Z*)-isomers.
3. With type **F** epoxides, at least in the (*Z*)-isomers, halide attack β to the carboxyl group is preferred. In these particular substrates the NaBr/Amb.15-mediated opening of both isomers reverses the regioselectivity of the halide attack.

These results make the type **F** compounds an attractive starting material for the synthesis of natural products. In fact, by changing only the metal halide, we are able to control the regioselectivity in the opening of the oxirane ring; the subsequent transformation of halide in amino group will allow to obtain suitable precursors for the synthesis of sphingosine, phytosphingosine, aminosugars.[15] Studies regarding these synthetic applications and the employment of molecular modelling to better understand the bifunctionalized epoxides behaviour are currently underway.

4. Experimental

4.1. General

^1H and ^{13}C NMR spectra were recorded at 200 and 50.3 Hz, respectively. Reactions were monitored by TLC using Merck silica gel 60 F-254 plates with UV indicator or/and visualized with phosphomolybdic acid (10% solution in EtOH). Flash column chromatography on silica gel was normally used for purification of the reaction mixtures. All solvents were purified before use with standard drying procedures, unless otherwise specified. Elemental analyses for C, H were performed by the Servizio Microanalisi of the Dipartimento Chimica of the Università of Roma 'La Sapienza'.

4.1.1. (*Z*)-4-*tert*-Butyldimethylsilyloxy-2-buten-1-ol,[16] **(*E*)-4-*tert*-butyldimethylsilyloxy-2-buten-1-ol,**[17] **and (*E*)-4-benzyloxy-2-buten-1-ol.**[18] They are known compounds.

4.2. General preparation procedure for the preparation of (*E*)- and (*Z*)-epoxy alcohol

To a solution of 4-protected-2-buten-1-ol (1 mmol) in acetone (7.5 mL) and water (5 mL) at 0°C, was added a mixture of oxone (3.07 g, 5 mmol) and $NaHCO_3$ (0.650 g, 7.75 mmol) in four equal portions at intervals of 15 min; after 1 h (TLC monitoring), the reaction mixture was filtered, concentrated and extracted with AcOEt. The organic layer was dried on Na_2SO_4 and the solvent was evaporated in vacuo, affording the title compound.

4.2.1. (2*R,3*S**)-4-*tert*-Butyldimethylsilyloxy-2,3-epoxybutan-1-ol 2,**[19] **(2*R**,3*S**)-4-benzyloxy-2,3-epoxybutan-1-ol 3,**[20] **(2*S**,3*S**)-4-*tert*-butyldimethylsilyloxy-2,3-epoxybutan-1-ol 4,**[21] **(2*S**,3*S**)-4-benzyloxy-2,3-epoxybutan-1-ol 5.**[22] They are known compounds.

4.3. General preparation of 4-protected-2,3-epoxybutanal

4.3.1. Representative procedure for the preparation of (2*R,3*R**)-4-*tert*-butyldimethylsilyloxy-2,3-epoxybutanal 6.** To a stirred solution of $(COCl)_2$ (0.1 mL, 1.1 mmol) in dry CH_2Cl_2 (2.5 mL) at −60°C, DMSO (0.12 mL, 2.2 mmol) dissolved in CH_2Cl_2 (0.5 mL) was added dropwise. Stirring was continued at −60°C for 10 min followed by addition of **2** (218 mg, 1 mmol) dissolved in CH_2Cl_2 (1 mL). After 15 min was added Et_3N (0.7 mL, 5 mmol) and then the mixture was allowed to warm to room temperature. After TLC monitoring, the reaction mixture was quenched with water (5 mL) and the organic layer separated. The aqueous phase was re-extracted many times with CH_2Cl_2. The combined organic layer was dried on Na_2SO_4 and concentrated in vacuo. The crude product was purified by column chromatography (silica gel, hexane/ether 9:1) affording **6** (160 mg, 73%) as a pale yellow oil. ν_{max} (liquid film): 2950, 1720, 1250, 990 cm^{-1}.^{1}H NMR: δ 9.45 (1H, d, J=4.4 Hz, C*H*O), 3.98 (1H, dd, J=11.2, 2.6 Hz, SiOCH_aH$_b$), 3.88 (1H, dd, J=11.2, 3.8 Hz, SiOCH$_a$$H_b$), 3.42–3.3 (2H, m, C*H*OC*H*), 0.84 (9H, s, SiC(CH_3)$_3$), 0.03 (6H, s, Si(CH_3)$_2$).^{13}C NMR: δ^{13}C NMR: δ 197.9, 60.2, 59.7, 57.6, 25.7, 18.3, −5.6. $C_{10}H_{20}O_3Si$ (216.35): C 55.52, H 9.32; found C 55.7, H 9.5.

4.3.2. (2*R,3*R**)-4-Benzyloxy-2,3-epoxybutanal 7,**[21] **(2*R**,3*S**)-4-*tert*-butyldimethylsilyloxy-2,3-epoxybutanal 8**[17] **and (2*R**,3*S**)-4-benzyloxy-2,3-epoxybutanal 9.**[23] They are known compounds.

4.4. General procedure for the preparation of methyl-4-*tert*-butyldimethylsilyloxy-2,3-epoxybutanoate

4.4.1. Representative preparation of (2*S,3*S**)-methyl-4-*tert*-butyldimethylsilyloxy-2,3-epoxybutanoate 10.** To a vigorously stirred mixture of compound **2** (218 mg, 1 mmol), in CCl_4 (2 mL), CH_3CN (2 mL), H_2O (3 mL), $NaIO_4$ (877 mg, 4.1 mmol), $NaHCO_3$ (420 mg, 5 mmol) and $RuCl_3{\cdot}H_2O$ (5 mg, 0.022 mmol) were added. The mixture was stirred at 20°C for 2 h (TLC monitoring) and then was filtered on Celite path and extracted with CH_2Cl_2. The organic layer was concentrated and to the residue, diluted in ether, CH_2N_2 was added until the reaction was complete (TLC monitoring). The reaction mixture was then concentrated, diluted with EtOAc and washed with NaCl s.s. The organic layer was dried over Na_2SO_4 and concentrated in vacuo, affording a crude mixture which was then cromatographed on silica gel (petroleum ether/EtOAc 8:2) to give **10** (148 mg, 60%). Colourless oil. ν_{max} (liquid film): 2950, 1735, 1250, 940 cm^{-1}.^{1}H NMR: δ 3.90 (1H, dd, J=11.8, 5.5 Hz, SiOCH_aH$_b$), 3.78 (1H, dd, J=12, 5.5 Hz, SiOCH$_a$$H_b$), 3.69 (3H, s, OMe), 3.56 (1H, d, J=4.5 Hz, OC*H*COOMe), 3.36 (1H, dd, J=5.5, 4.5 Hz, OC*H*CH$_2$), 0.89 (9H, s, SiC(CH_3)$_3$), 0.09 (6H, s, Si(CH_3)$_2$).^{13}C NMR: δ 168.3, 60.4, 57.4, 52.3, 51.7, 25.7, 18.2, −5.5. $C_{11}H_{22}O_4Si$ (246): C 53.63, H 9.00; found C 53.7, H 8.2.

4.4.2. (2*R,3*S**)-Methyl-4-*tert*-butyldimethylsilyloxy-2,3-epoxybutanoate 11.**[24] This is a known compound.

4.5. General procedure for the preparation of methyl-4-benzyloxy-2,3-epoxybutanoate

To a solution of 4-benzyloxy-2,3-epoxybutanal (**7** or **9**) (1 mmol) and MeOH (0.24 mL, 6 mmol) in dry DMF (0.39 mL, 5 mmol) PDC (2.25 g, 6 mmol) was added at room temperature and under N_2. The reaction was stirred for 20 h and then poured in 150 mL of a hexane/50 mL H_2O solution and filtered on Celite pad. The aqueous phase was extracted with EtOAc (3×50 mL) and the organic layer washed with NH_4Cl s.s., dried over Na_2SO_4 and concentrated in vacuo, affording a crude mixture which was then cromatographed on silica gel (petroleum ether/EtOAc 95:5) to give the title compound.

4.5.1. (2*S,3*S**)-Methyl-4-benzyloxy-2,3-epoxybutanoate 12 and (2*R**,3*S**)-methyl-4-benzyloxy-2,3-epoxybutanoate 13.**[25] They are known compounds.

4.6. General procedure for the reaction of type D and F epoxides with $MgBr_2$[26]

To a solution of epoxide (1 mmol) in dry Et_2O (10 mL) was added $MgBr_2{\cdot}Et_2O$ (516.5 mg, 2 mmol). The solution was stirred at −30°C for 2 h (TLC monitoring), then was filtered on Celite pad and the solvent evaporated in vacuo. The residue was then cromatographed on silica gel (petroleum ether/EtOAc).

Compounds **2**, **3**, **4**, **5**, **11** and **13**, submitted to $MgBr_2$-mediated opening, gave mixture of regioisomers (≈50:50). The same reaction on compound **6** and **7** was already studied by Procter, giving prevalently the C-2 attack (C-2/C-3=95/5).[7]

4.6.1. Compounds 14a and 14b. (1.2:1 Mixture of regioisomers): ^{1}H NMR: δ 4.21–3.85 (4H, m), 3.85–3.72 (2H,m), 2.5 (0.4H, bs, O*H*), 2.1 (0.6H, bs, O*H*), 1.9 (0.4 H, bs, O*H*), 1.7 (0.6 H, bs, O*H*), 0.88 (9H, s, SiC(CH_3)$_3$), 0.09 (6H, s, Si(CH_3)$_2$). The regioisomeric ratio was determined after the acetylation of mixture, employing the integral values corresponding to C*H*OAc signals (δ 5.2 and 5.6).

4.6.2. Compounds 15a and 15b. (1.2:1 Mixture of regioisomers): ^{1}H NMR: δ 7.35 (5H, s, C$_6H_5$), 4.55 (2H, s,

PhCH_2O), 4.3–4.21 (1H, m), 4.1–3.95 (1H, m), 3.91 (2H, d, J=8 Hz, BnOCH_2), 3.75–3.5 (2H, m, CH_2OH), 3.05 (1.6H, bs, OH), 2.7 (0.4H, bs, OH). ^{13}C NMR: δ 137.4, 137.2, 128.5, 128.1, 127.9, 127.8, 73.6, 73.5, 72.2, 71.6, 71.4, 70.1, 64.8, 64.5, 58.0, 54.0. The regioisomeric ratio was determined after the acetylation of mixture, employing the integral values corresponding to CHOAc signals (δ 5.3 and 5.7).

4.6.3. Compounds 16a and 16b. (1.2:1 Mixture of regioisomers): ^{1}H NMR: δ 4.15–3.95 (4H, m), 3.95–3.78 (2H, m), 2.9 (0.4H, bs, OH), 2.7 (0.6H, bs, OH), 1.6 (1H, bs, OH), 0.88 (9H, s, SiC(CH_3)$_3$), 0.09 (6H, s, Si(CH_3)$_2$). ^{13}C NMR: δ 74.6, 73.4, 66.0, 65.2, 64.4, 64.3, 54.9, 51.9, 25.8, 25.7, 18.1, −5.4. The regioisomeric ratio was determined after the acetylation of mixture, employing the integral values corresponding to CHOAc signals (δ 5.15 and 5.4).

4.6.4. Compounds 17a and 17b. (1.1:1 Mixture of regioisomers): ^{1}H NMR: δ 7.35 (5H, s, C$_6H_5$), 4.55 (2H, s, PhCH_2O), 4.2–4.15 (1H, m), 4.1–3.85 (1H, m), 3.85–3.73 (2H, m, BnOCH_2), 3.7–3.52 (2H, m, CH_2OH), 3.3 (2H, bs, OH). ^{13}C NMR: δ 137.5, 137.2, 128.2, 128.1, 127.9, 127.8, 73.8, 73.4, 71.8, 71.2, 70.5, 69.7, 64.3, 63.8, 58.6, 54.5. The regioisomeric ratio was determined after the acetylation of mixture, employing the integral values corresponding to CHOAc signals (δ 5.2 and 5.7).

4.7. General procedure for the reaction of type E epoxides with $MgBr_2$

4.7.1. Representative preparation of (3*R,4*S**)-3-bromo-5-*tert*-butyldimethylsilyloxy-2,4-pentandiol 18a.**[27] To a solution of **8** (216 mg, 1 mmol) in dry Et_2O (10 mL) was added $MgBr_2$·Et_2O (516.5 mg, 2 mmol). The solution was stirred for 4 h (TLC monitoring), then MeMgBr (sol. 2 M in THF, 0.75 mL) was added. After ~4 h (TLC monitoring), the reaction was quenched with NH_4Cl sol. sat., diluted with Et_2O and the organic layers were dried over Na_2SO_4 and then evaporated in vacuo. The crude mixture was purified by flash chromatography (hexanes/EtOAc, 8:2) afforded **18a** (164 mg, 52%). Colourless oil. ν_{max} (liquid film): 3220, 2860, 1260, 945, 560 cm^{-1}. ^{1}H NMR: δ 4.25–4.12 (1H, m, CH$_3$CHOH), 4.05–3.9 (2H, m, CHBrCHOHCH$_2$OSi), 3.89–3.78 (2H, m, CH_2OSi), 2.95 (1H, bs, OH), 2.5 (1H, bd, J=6.6 Hz, OH), 1.33 (3H, d, J=6.4 Hz, CH_3CHOH), 0.9 (9H, s, SiC(CH_3)$_3$), 0.11 (6H, s, Si(CH_3)$_2$). ^{13}C NMR: δ 75.0, 69.0, 67.1, 63.6, 28.3, 23.7, −3.0. $C_{11}H_{25}BrO_3Si$ (313): C 42.17, H 8.04; found C 42.3, H 7.4.

4.7.2. (3*S,4*R**)-4-Bromo-5-*tert*-butyldimethylsilyloxy-2,3-pentandiol 18b.** According to the general procedure, compound **8** (216 mg, 1 mmol) afforded **18b** (41 mg, 13%). Colourless oil. ^{1}H NMR: δ 4.3–4.02 (3H, m), 4.02–3.78 (3H, m), 3.05 (1H, bs, OH), 2.92 (1H, bs, OH), 1.35 (3H, d, J=7.2 Hz, CH_3CHOH), 0.9 (9H, s, SiC(CH_3)$_3$), 0.11 (6H, s, Si(CH_3)$_2$). ^{13}C NMR: δ 73.0, 68.5, 64.5, 61.6, 25.7, 20.0, −5.5. The regioisomeric ratio **18a/18b** was determined on the crude mixture, employing the integral values corresponding to CH_3CHOH signals (δ 1.33 and 1.35).

4.7.3. (3*R,4*S**)-3-Bromo-5-benzyloxy-2,4-pentandiol 19a.** According to the general procedure, compound **9** (192 mg, 1 mmol) afforded **19a** (148 mg, 51%). Colourless oil. ν_{max} (liquid film): 3200, 3010, 2840, 1060, 550 cm^{-1}. ^{1}H NMR: δ 7.32 (5H, s, C$_6H_5$), 4.61 (2H, s, CH_2Ph), 4.3–4.22 (1H, m), 4.05–3.8 (2H, m), 3.78–3.62 (2H, m), 3.1 (1H, bs, OH), 2.6 (1H, bs, OH), 1.34 (3H, d, J=6.4 Hz, CH_3CHOH). ^{13}C NMR: δ 137.1, 128.5, 127.3, 126.8, 74.6, 73.2, 68.3, 67.4, 62.9, 23.5. $C_{12}H_{17}BrO_3$ (289): C 49.84, H 5.93; found C 49.9, H 5.8.

4.7.4. (3*S,4*R**)-4-Bromo-5-benzyloxy-2,3-pentandiol 19b.** According to the general procedure, compound **9** (192 mg, 1 mmol) afforded **19b** (28 mg, 9.7%). Colourless oil. ^{1}H NMR: δ 7.32 (5H, s, C$_6H_5$), 4.61 (2H, s, CH_2Ph), 4.25–3.98 (2H, m), 3.8–3.58 (3H, m), 2.8 (2H, bs, OH), 1.32 (3H, d, J=6.9 Hz, CH_3CHOH). ^{13}C NMR: δ 137.0, 128.5, 128.2, 127.3, 74.5, 71.9, 68.1, 65.1, 60.8, 21.2. The regioisomeric ratio **19a/19b** was determined on the crude mixture, employing the integral values corresponding to CH_3CHOH signals (δ 1.34 and 1.32).

4.7.5. (2*S,3*S**)-Methyl-4-*tert*-butyldimethylsilyloxy-2-hydroxy-3-bromobutanoate 20.** According to the general procedure, compound **10** (246 mg, 1 mmol) afforded **16** (313 mg, 95%). Pale yellow oil. ν_{max} (liquid film): 3250, 2950, 1735, 1250, 1160, 990, 550 cm^{-1}. ^{1}H NMR: δ 4.61 (1H, dd, J=5.7, 0.5 Hz, CHOH), 4.28 (1H, ddd, J=8.0, 6.0, 0.5 Hz, CHBr), 3.94 (1H, dd, J_1=J_2=8.0 Hz, CH_aOSi), 3.85 (1H, dd, J=8.0, 6.0 Hz, CH_bOSi), 3.85 (3H, s, COOCH_3), 2.7 (1H, bd, J=5.7 Hz, OH), 0.88 (9H, s, SiC(CH_3)$_3$), 0.10 (6H, s, Si(CH_3)$_2$). ^{13}C NMR: δ 172.6, 67.0, 63.5, 54.3, 53.1, 25.6, −5.4, −5.5. $C_{11}H_{23}BrO_4Si$ (327): C 40.37, H 7.08; found C 40.4, H 6.9.

4.7.6. (2*S,3*S**)-Methyl 4-benzyloxy-2-hydroxy-3-bromobutanoate 21.** According to the general procedure, compound **12** (222 mg, 1 mmol) afforded **21** (290 mg, 95%). Pale yellow oil. ν_{max} (liquid film): 3200, 3010, 1730, 1260, 1060, 550 cm^{-1}. ^{1}H NMR: δ 7.34 (5H, s, C$_6H_5$), 4.64 (1H, d, J=0.6 Hz, CHOH), 4.60 (2H, s, CH_2Ph), 4.43 (1H, ddd, J=0.6, 6.8, 8.0 Hz, CHBr), 3.94–3.61 (2H, m, CH_2OBn), 3.81 (3H, s, OCH_3), 3.15 (1H, bs, OH). ^{13}C NMR: δ 172.4, 128.5, 127.8, 127.7, 73.4, 70.2, 69.4, 53.1, 52.0. $C_{12}H_{15}BrO_4$ (303): C 47.54, H 4.99; found C 47.9, H 4.1.

4.7.7. Compounds 22a and 22b. (1:1.2 mixture of regioisomers): ^{1}H NMR: δ 4.52 (0.45 H, dd, J=8, 2.6 Hz, CHOHCOOEt), 4.48–4.15 (2.55H, m, CHBrCOOEt+OCH_2CH$_3$), 4.12–3.75 (3H, m, CH_2OSi, SiOCH$_2$CHBr, SiOCH$_2$CHOH), 3.38 (0.45 H, bd, J=5.3 Hz, OH), 3.0 (0.55 H, bd, J=8 Hz, OH), 1.28 (3H, t, J=7.8 Hz, COCH$_2$CH_3), 0.88 (9H, s, SiC(CH_3)$_3$), 0.09 (6H, s, Si(CH_3)$_2$). ^{13}C NMR: δ 171.3, 168.9, 72.2, 71.6, 63.6, 62.04, 52.9, 43.8, 29.6, 25.8, 25.7, 18.2, 14.1, 13.8, −5.5, −5.6. The regioisomeric ratio was determined after the acetylation of mixture, employing the integral values corresponding to CHOAc signals (δ 5.5, d and δ 5.2, ddd).

4.7.8. Compounds 23a and 23b. (1:1 mixture of regioisomers): ^{1}H NMR: δ 7.32 (5H, s, C$_6H_5$), 4.65 (0.5H, d, J=0.5 Hz, CHOHCOOEt), 4.59 (2.5H, s, CHBrCOOEt+CH_2Ph), 4.5–4.35 (0.5H, m, BnOCH$_2$CHBr) 4.2–4.03 (2.5H, m, OCH_2CH$_3$+BnOCH$_2$CHOH), 3.91–3.5 (2H, m,

CH_2OBn), 3.02 (1H, bs, OH), 1.28 (3H, t, J=7.8 Hz, COCH$_2$CH_3).^{13}C NMR: δ 171.2, 169.4, 137.3, 133.4, 129.7, 128.4, 128.3, 127.9, 127.8, 127.7, 73.5, 73.4, 71.7, 71.6, 69.7, 69.6, 63.3, 50.0, 43.7, 14.2, 13.8.

4.8. General procedure for the reaction of type F epoxides with NaBr and amberlyst 15

4.8.1. Representative procedure for the preparation of (2*R,3*S**)-methyl-2-bromo-3,4-dihydroxybutanoate 24.** To a stirred solution of compound **10** (246 mg, 1 mmol) in acetone (10 mL) at −30°C, NaBr (416 mg, 4 mmol) and Amberlyst 15 (218 mg, 1 mmol) were added. The mixture was stirred for 2 h (TLC monitoring), then was filtered on Celite path and the solvent evaporated in vacuo. The residue was diluted in CH_3CN (2 mL) and Amberlyst 15 (218 mg, 1 mmol) was added to cleavage the formed 3,4-*O*-isopropylidene derivative. The mixture was stirred for 2 h (TLC monitoring), then was filtered on Celite path and the solvent evaporated in vacuo to afford **24** (202 mg, 95%). Pale yellow oil.ν_{max} (liquid film): 3250, 2952, 1736, 1260, 1165, 580. ^{1}H NMR: δ 4.24 (1H, d, J=7.6 Hz, CHBr), 4.15–4.03 (1H, m, CHOH), 3.85 (1H, dd, J=6.4, 9.2 Hz, CH_aOH), 3.81 (3H, s, OCH_3), 3.75 (1H, dd, J=5.2, 9.2 Hz, CH_bOH), 2.75 (2H, bs, OH).^{13}C NMR: δ 168.3, 72.3, 63.0, 53.1, 44.0. $C_5H_9BrO_4$ (213): C 28.19, H 4.26; found C 28.5, H 3.8.

4.8.2. (2*S,3*S**)-Methyl-2-bromo-3,4-dihydroxybutanoate 26.** According to the general procedure, compound **11** (246 mg, 1 mmol) afforded **26** (202 mg, 95%). Pale yellow oil. ν_{max} (liquid film): 3250, 2952, 1736, 1260, 1165, 580. ^{1}H NMR: δ 4.25 (1H, d, J=9.2 Hz), 4.05 (1H, ddd, J=2.7, 3.4, 9.2 Hz, CHOH), 3.98 (1H, dd, J=2.7, 11.4 Hz, CH_aOH), 3.83 (1H, dd, J=3.4, 11.4 Hz, CH_bOH), 3.81(3H, s), 2.85 (2H, bs, OH). ^{13}C NMR: δ 168.1, 72.4, 62.8, 53.1, 43.8. $C_5H_9BrO_4$ (213): C 28.19, H 4.26; found C 28.4, H 3.7.

4.8.3. (2*R,3*S**)-Methyl-4-benzyloxy-2-bromo-3-hydroxybutanoate 25.** According to the general procedure, compound **12** (222 mg, 1 mmol) afforded **25** (290 mg, 95%). Pale yellow oil. ν_{max} (liquid film): 3250, 3010, 1730, 1060, 760, 570. ^{1}H NMR: δ 7.32 (5H, s, C$_6H_5$), 4.62 (1H, d, J=4.2 Hz, CHBr), 4.54 (2H, s, CH_2Ph), 4.18–4.08 (1H, m, CHOH), 3.76 (3H, s, OCH_3), 3.60 (2H, dd, J=3.8, 6.2 Hz, CH_2OBn), 3.01 (1H, bs, OH). ^{13}C NMR: δ 169.5, 137.4, 133.4, 129.7, 128.5, 127.9, 73.5, 70.2, 69.7, 53.2, 48.8. $C_{12}H_{15}BrO_4$ (303): C 47.54, H 4.99; found C 48.0, H 4.2.

4.8.4. (2*S,3*S**)-Methyl 4-benzyloxy-2-bromo-3-hydroxybutanoate 27.** According to the general procedure, compound **13** (222 mg, 1 mmol) afforded **27** (290 mg, 95%). Pale yellow oil. ν_{max} (liquid film): 3250, 3010, 1730, 1060, 760, 570. ^{1}H NMR: δ 7.32 (5H, s, C$_6H_5$), 4.58 (2H, d, J=1.8 Hz, CH_2Ph), 4.38 (1H, d, J=8.7 Hz, CHBr), 4.17 (1H, dt, J=8.7, 3.5 Hz, CHOH), 3.79 (3H, s, OCH_3), 3.80 (2H, dd, J=3.5, 10 Hz, CH_2OBn), 2.95 (1H, d, J=7.5 Hz, OH). ^{13}C NMR: δ 169.5, 133.4, 129.8, 128.5, 128.0, 73.6, 71.6, 69.7, 53.1, 43.7. $C_{12}H_{15}BrO_4$ (303): C 47.54, H 4.99; found C 47.9, H 4.2.

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26. The regiochemistry of the bromine opening was established from ^{1}H NMR spectroscopy, by employing a spin-spin decoupling technique on compounds **20**, **21**, **24**–**27** and on their acetyl derivatives for compounds **14**–**19**.
27. Compounds **18a**, **18b**, **19a** and **19b** were obtained as single diastereoisomers. We were not interested in investigating the diastereoselectivity of the Grignard addition, but invoking a cyclic chelate transition state model, always hypothesized when an α-substituent capable of coordination is present, we thought about a *syn* stereoselectivity.