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Study on the stereochemical control of dihydroxylation of vinyl epoxides and their derivatives

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ABSTRACT

The results obtained from a study on the stereochemical control in the dihydroxylation of the double bond of vinyl epoxides and their derivatives (bromo derivatives, azido derivatives and vinyl aziridines) are presented herein. A significant diastereoselectivity was observed for the bromo derivatives, azido derivatives and *N*-protected vinyl aziridines, whereas vinyl epoxides and unprotected vinyl aziridines showed no diastereoselectivity. The results obtained are generally consistent with the Kishi model.

1. Introduction

Optically active aminopolyalcoholic fragments[1] can be found in a wide range of natural or synthetic biologically active compounds such as azasugars,[2] sphingoid structures[3] and sialic acids.[4] Our research group has been focused for many years on this field and the elaboration of optically active aziridines and epoxides has been targeted as a convenient approach to the synthesis of these fragments.[5] Recently we have developed suitable methodologies[6,7] for the regio- and stereoselective nucleophilic opening of vinyl epoxides and vinyl aziridines. As shown in Fig. 1 it is possible to regioselectively introduce a nucleophile, such as halides or azides, in the allylic position exploiting its inherent reactivity.

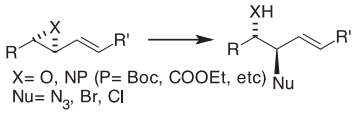

Fig. 1. Regioselective and stereospecific nucleophilic opening reactions of vinyl epoxides and aziridines.

A subsequent dihydroxylation reaction of the alkene could lead to four adjacent stereogenic centres in a controlled fashion, thus providing useful precursors of aminopolyalcoholic structures. The dihydroxylation reaction is characterized by a *syn* stereospecificity. Moreover a preexisting stereocenter adjacent to the double bond can direct the osmium tetroxide approach preferentially on one of the two faces of the olefin leading to different extents of diastereoselectivity.[8] A large number of studies have appeared in the literature on this matter but only a few of them[9] pertain to vinyl epoxides, vinyl aziridines and their derivatives, substrates of choice for this work.

2. Results and discussion

With the purpose of identifying the substrate leading to the best stereochemical control of the dihydroxylation and therefore the most suitable for synthetic applications, the reaction was carried out on: unsaturated azidoalcohols (type A), bromohydrins (type B), epoxides (type C) and differently protected aziridines (type D) (Fig. 2). Moreover the R group and the protective group (P) on the aziridine ring were varied in order to investigate the possible influence of steric hindrance on the diastereoselectivity of the reaction.

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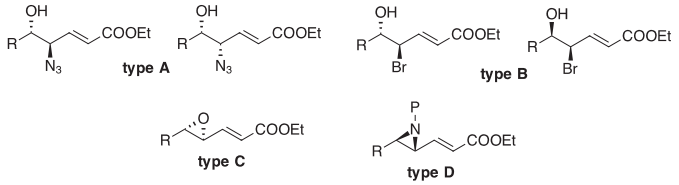
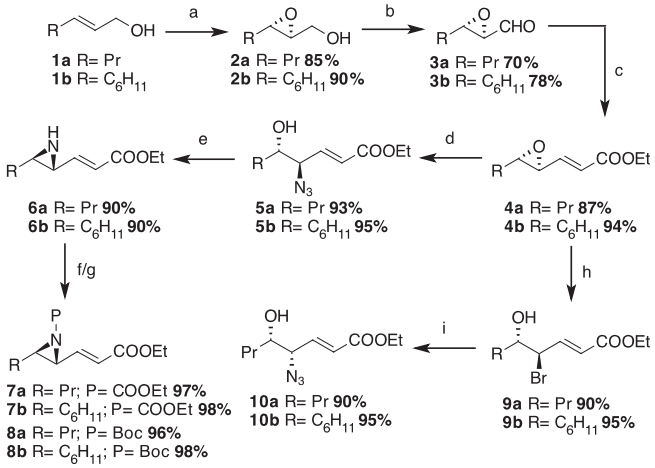


Fig. 2. Substrates of choice.

2.1. Synthesis of the substrates

All the substrates were synthesized starting from the corresponding allylic alcohol[10] following the same synthetic path (Scheme 1).

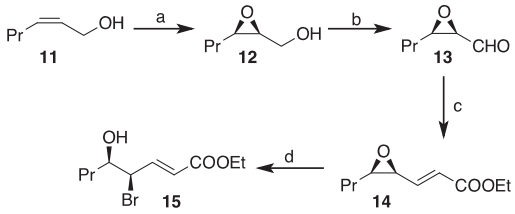


Scheme 1. Reagents and conditions: (a) *m*-CPBA, CH_2Cl_2, 0 °C; (b) TEMPO, IBDA, CH_2Cl_2, rt; (c) LiOH, TEPA, THF, 70 °C; d) $BF_3{\cdot}Et_2O$, $TMSN_3$, CH_2Cl_2, 0 °C to rt; (e) PPh_3, acetonitrile, rt to 70 °C; (f) Et_3N, ClCOOEt, dry Et_2O, 0 °C to rt; (g) Boc_2O, DMAP, dry CH_2Cl_2, rt; (h) LiBr, Amberlyst15, acetone, rt; (i) NaN_3, dry DMF, rt.

Epoxy alcohols **2a** and **2b** were obtained via a non-asymmetric epoxidation[11] reaction and then converted into the corresponding epoxy aldehydes **3a** and **3b** using the well known TEMPO/IBDA method, which is mild enough to preserve the epoxide function. A subsequent Horner–Emmons reaction afforded α,β-unsaturated epoxy esters **4a** and **4b**, which are the first substrates of study.

The oxirane ring of compounds **4a** and **4b** was then regio-selectively and stereo-specifically opened using a method[12] recently developed by our group. Using $BF_3{\cdot}OEt_2$ as the Lewis acid and $TMSN_3$ as the azide source it is possible to exploit the reactivity of the allylic position and regio-selectively introduce the azide group in this position, obtaining *anti*-azidoalcohols **5a** and **5b**. These compounds were then converted into the corresponding aziridines **6a** and **6b** via a well-known procedure.[13] The aziridines were finally protected as ethyl and *tert*-butyl carbamate (compounds **7a**, **7b**, **8a**, **8b**). α,β-Unsaturated esters **4a** and **4b** were also used to prepare four more substrates. A first regio- and stereoselective LiBr/Amberlyst15 mediated ring opening reaction[14] led to the corresponding *anti*-bromohydrins **9a** and **9b**. Then a substitution reaction using NaN_3 in DMF afforded *syn*-azidoalcohols **10a** and **10b**.

syn-Bromohydrin **15** was obtained starting from *cis*-2-hexen-1-ol following the same synthetic pathway described before for compounds **10a** and **10b** (Scheme 2).

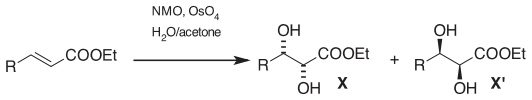


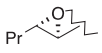
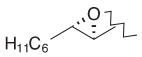
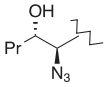
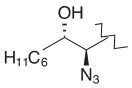
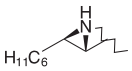
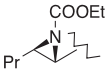
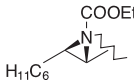
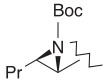
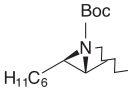
Scheme 2. Reagents and conditions: (a) *m*-CPBA, CH_2Cl_2, 0 °C (83%); (b) TEMPO, IBDA, CH_2Cl_2, rt (72%); (c) LiOH, TEPA, THF, 70 °C (88%); (d) LiBr, Amberlyst15, acetone, rt (90%).

2.2. Dihydroxylation reactions

All the compounds synthesized were then submitted to the dihydroxylation reaction. The results are summarized in Table 1. The ratio of the two diastereomers was determined from the integrals of the ^1H NMR spectra of the mixture. The attribution of each signal to the appropriate diastereomer was made in different ways depending on the class of the substrate.

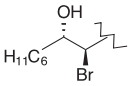
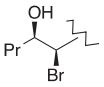
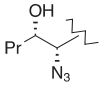
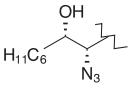
Table 1
Diasteroselective dihydroxylation reaction on differently functionalized vinyl compounds: results



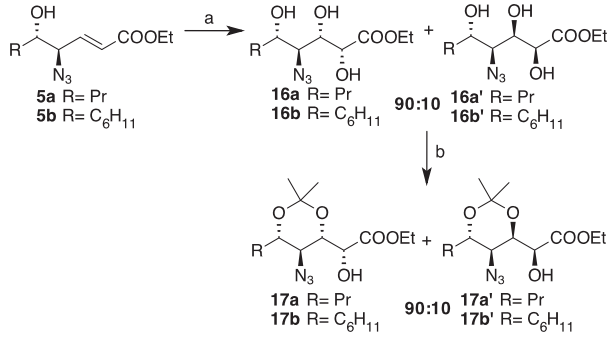
Entry	Olefin	R	Diols	Ratio
1	**4a**		**24a**/**24a′**	60:40
2	**4b**		**24b**/**24b′**	55:45
3	**5a**		**16a**/**16a′**	90:10
4	**5b**		**16b**/**16b′**	90:10
5	**6a**		**27a**/**27a′**	50:50
6	**6b**		**27b**/**27b′**	50:50
7	**7a**		**28a**/**28a′**	90:10
8	**7b**		**28b**/**28b′**	90:10
9	**8a**		**29a**/**29a′**	85:15
10	**8b**		**29b**/**29b′**	87:13
11	**9a**		**20a**/**20a′**	75:25

(*continued on next page*)

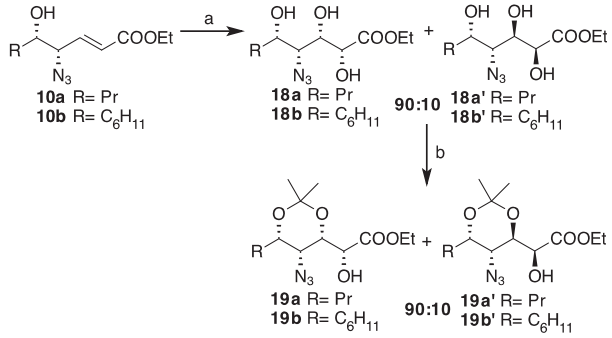
Table 1 (*continued*)

Entry	Olefin	R	Diols	Ratio
12	**9b**		**20b**/**20b′**	70:30
13	**15**		**22a**/**22a′**	75:25
14	**10a**		**18b**/**18b′**	90:10
15	**10b**		**18a**/**18a′**	90:10

2.2.1. Azido derivatives. As shown in Schemes 3 and 4 the dihydroxylation reaction on both *anti* (**5a**, **5b**) and *syn* (**10a**, **10b**) azido derivatives led to a mixture of diols in a 90:10 diastereomeric ratio. In both cases the recognition of the stereochemistry of the major product was made by converting the mixture into the corresponding 1,3-acetonides. It is known[15] that these compounds have characteristic signals in the ^{13}C NMR spectrum depending on their stereochemistry: an *anti*-acetonide (e.g., compound **17a′**) shows a signal at ~100 ppm for the ketalic carbon and two very close signals at ~25 ppm for the $C(CH_3)_2$, whereas in a *syn*-acetonide (e.g., compound **17a**) the ketalic carbon shows a signal at ~98 ppm and the $C(CH_3)_2$ two different signals at ~19 and ~30 ppm. In both cases the major product proved to be a *syn*-acetonide indicating that the major diols were compounds **16a**, **16b**, **18a** and **18b**.



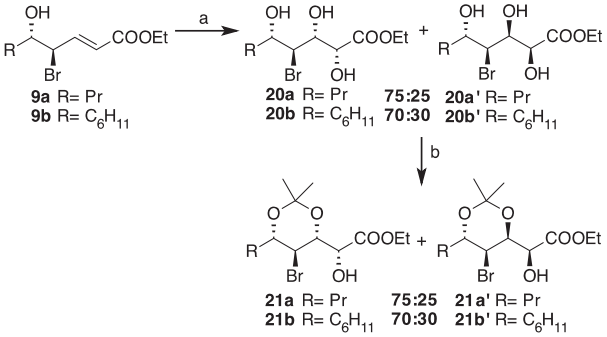
Scheme 3. Reagents and conditions: (a) OsO_4, NMO, H_2O/acetone, rt (84–87%); (b) 2,2-dimethoxypropane, *p*-toluensulfonic acid, acetone, rt (90–95%).



Scheme 4. Reagents and conditions: (a) OsO_4, NMO, H_2O/acetone, rt (85–89%); (b) 2,2-dimethoxypropane, *p*-toluensulfonic acid, acetone, rt (90–95%).

These results seem to indicate that the stereochemistry of the reaction is not affected by the azide group in the allylic position and may be driven instead by the OH group in the homoallylic position. These data also indicate that the steric hindrance of the R group on the epoxide ring does not influence the stereochemistry of the reaction.

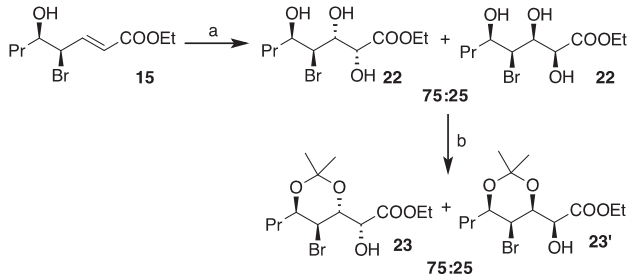
2.2.2. Bromo derivatives. Similar considerations can be made for the *anti*-bromohydrins **9a** and **9b** (Scheme 5). We can assert again that the steric hindrance of the R group has little influence on the reaction.



Scheme 5. Reagents and conditions: (a) OsO_4, NMO, H_2O/acetone, rt (70–80%); (b) 2,2-dimethoxypropane, *p*-toluensulfonic acid, acetone, rt (90–95%).

The bromotriols mixtures obtained were chromatographically inseparable. Therefore, to fully characterize the major products, the mixtures were converted into the corresponding 1,3-acetonides: the prevalent compounds turned out to be *syn*-acetonides **21a** and **21b** thus indicating an *anti* correlation between the Br and the diol in compounds **20a** and **20b** (major products of the dihydroxylation reaction).

An *anti* correlation between the bromine and the diol moiety was also observed in the dihydroxylation of *syn*-bromohydrin **15** (Scheme 6).

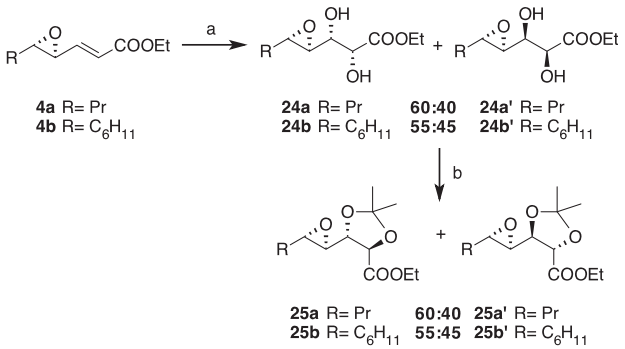


Scheme 6. Reagents and conditions: (a) OsO_4, NMO, H_2O/acetone, rt (75%); (b) 2,2-dimethoxypropane, *p*-toluensulfonic acid, acetone, rt (93%).

Unlike that observed with the azidoalcohols, these results seem to indicate that the configuration of the bromine is actually able to influence the OsO_4 attack, leading in all cases to a product with an *anti* correlation between the Br and the diol moiety. This could be justified by the different steric hindrance exerted by bromine compared to the azide.

2.2.3. Epoxides. In the case of vinyl epoxides, the oxirane ring did not affect the diastereoselectivity of the dihydroxylation reaction:

4a and **4b** gave an inseparable mixture with a *syn* correlation between the ring and the diol moiety in the main product (Scheme 7).



Scheme 7. Reagents and conditions: (a) OsO_4, NMO, H_2O/acetone, rt (70%); (b) 2,2-dimethoxypropane, *p*-toluensulfonic acid, acetone, 0 °C (80%).

At first the stereochemical assignment of the epoxy-diols was based on their spectroscopic characteristics. As reported in the literature,[16] the general trend for epoxy alcohols is that the ^{1}H NMR signal for the C*H*OH of the *syn*-diastereomer is more shielded than the one for the *anti*-diastereomer (Fig. 3). Our experimental data were in line with the literature: the signal of the C*H*OH adjacent to the oxirane ring falls at ~3.8 ppm for compounds **24a** and **24b** and is shifted 0.1 ppm upfield in compounds **24a′** and **24b′** (~4.0 ppm).

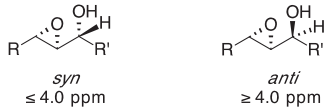
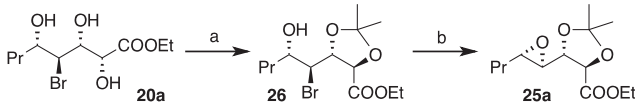


Fig. 3. Chemical shifts for a general C*H*OH adjacent to an oxirane ring as reported in the literature.

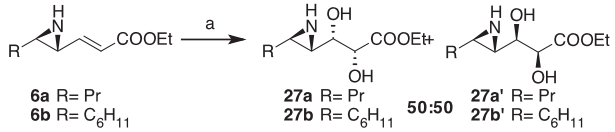
To confirm the stereochemical assignment, the previously determined stereochemistry of the bromotriols was exploited. Compound **20a** was converted into a 1,2-acetonide (**26**), subsequently submitted to a ring closing reaction that gave an epoxy acetonide, which proved to be spectroscopically identical to **25a** (Scheme 8), the major epoxy acetonide obtained from the protection of the **24a**/**24a′** mixture.



Scheme 8. Reagents and conditions: (a) 2,2-dimethoxypropane, *p*-toluensulfonic acid, acetone, 0 °C (80%); (b) KOH, MeOH, reflux.

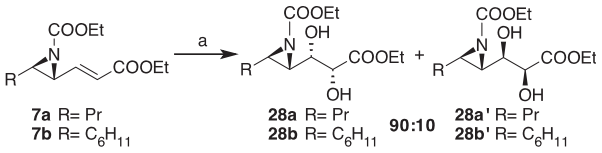
2.2.4. Aziridines. The unprotected aziridine ring did not affect the diastereoselectivity of the reaction leading for both compounds **6a** and **6b** to a chromatographically inseparable mixture with a diastereomeric ratio of 50:50 (Scheme 9).

As shown in Table 1 completely different results were obtained when the nitrogen was protected as carbamate. The



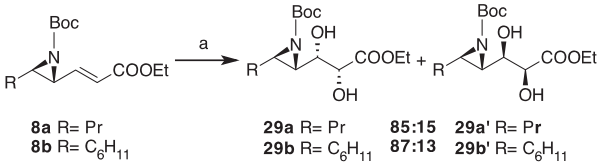
Scheme 9. Reagents and conditions: (a) OsO_4, NMO, H_2O/acetone, rt (70%).

dihydroxylation reaction on both the COOEt protected compounds **7a** and **7b** led to a mixture with a 90:10 diastereomeric ratio (Scheme 10).



Scheme 10. Reagents and conditions: OsO_4, NMO, H_2O/acetone, rt (70–73%).

Similarly, the diol mixtures obtained from Boc protected compounds **8a** and **8b** showed a diastereomeric ratio of 85:15 and 87:13 (Scheme 11).



Scheme 11. Reagents and conditions: OsO_4, NMO, H_2O/acetone, rt (70–75%).

This extremely different reactivity between protected and unprotected aziridines can be explained by the high steric hindrance exerted by the protective group on the double bond.

The stereochemical assignment of the major diastereomers was made, as well as for the epoxy-diols, by comparison with literature data,[17] which pointed, in all our cases, towards the compounds with an *anti* correlation between the ring and the diol moiety as the major ones. We want to point out that the comparison was made with aziridino-alcohols, assuming that their chemical shift trend is similar to the aziridino diols one as it has been noted for epoxides. Therefore this assignment is still speculative.

3. Conclusions

In conclusion, the results obtained from this study show that the presence of a bromo alcohol, an azido alcohol or an *N*-protected aziridine moiety on the double bond is able to induce a significative stereochemical control in the dihydroxylation reaction. In contrast, when the olefin is substituted with an epoxide or an unprotected aziridine almost no stereoselectivity is observed. These results are consistent with Kishi's model,[18] where the osmium attack occurs leading to a product characterized by an *anti* correlation between the diol and the group adjacent to the double bond. The azido derivatives and the epoxides are exceptions: in the former case the osmium attack seems to be led by the OH group in the homoallylic position; the latter case seems to represent an exception to the Kishi's rule as no selectivity is observed.

The relevant diastereoselection obtained in some cases allows the preparation of attractive compounds having at least four contiguous stereogenic centres, useful intermediates in the synthesis of a wide range of biologically active compounds such as, for example, aminosugars. Studies in this direction are currently under investigation.

4. Experimental

4.1. General

NMR spectra were recorded on a VARIAN Mercury 3000 instrument (^{1}H, 300 MHz; ^{13}C, 75 MHz). Chemical shifts were

calculated from the residual solvent signals of δ_H 7.24 ppm and δ_C 77.0 ppm in chloroform-*d*. HRMS were performed on a Q-TOF MICRO spectrometer (Micromass, now Waters, Manchester, UK) equipped with an ESI source. All chromatographic purifications were performed on silica gel (100–200 mesh from E. Merck, Germany). Thin layer chromatography (TLC) was performed on precoated silica gel 60 F_{254} aluminium sheets (Merck Italia) and spots were visualized under UV torch. Organic solvents used for the chemical synthesis and for chromatography acquired from Merck Italia were of analytical grade.

4.2. Synthesis of the substrates

The following compounds were prepared following already known procedures and all experimental data were consistent with the ones reported in the literature:
2a,**b**,[19] **3a**,[20] **3b**,[21] **4a**,[22] **4b**,[23] **5a**,[7a] **5b**,[24] **8a**.[24]

4.2.1. General procedure for the aziridine ring formation. To a stirred solution of the appropriate substrate (1 mmol) in anhydrous acetonitrile (1 mL), PPh_3 (1.2 mmol, 314 mg) was added under nitrogen atmosphere and the flask equipped with a monitoring device for the nitrogen release. After 2 h the reaction mixture was brought to the reflux temperature and stirred for 12 h. The solvent was then removed under reduced pressure, the crude dissolved in 4 mL of cold Et_2O, filtered, concentrated and purified by flash chromatography on silica gel (hexane/AcOEt 7:3) to give the desired product.

4.2.1.1. (E)-Ethyl 3-((2R,3R*)-3-propylaziridin-2-yl)acrylate (**6a**).* Pale brown oil (166 mg, 90% yield); IR (neat, cm^{-1}): 2935, 2400, 1720; ^1H NMR (300 MHz, $CDCl_3$) δ: 6.30 (1H, dd, *J* 8.8, 15.4 Hz, C*H*=CHCO), 5.87 (1H, d, *J* 15.4 Hz, C*H*CO), 4.20 (2H, q, *J* 7.2 Hz, COCH_2CH$_3$), 2.13 (1H, dd, *J* 2.2, 8.8 Hz, C*H*–CH=CH), 1.94–1.85 (1H, m, CH_2CH–N), 1.42–1.21 (5H, m, $CH_2\times2$+NH), 1.11 (3H, t, *J* 7.2 Hz, $COCH_2CH_3$), 0.78 (3H, t, *J* 7.3 Hz, $CH_2CH_2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 166.2, 148.6, 121.4, 60.2, 40.5, 37.8, 35.4, 20.4, 14.1, 13.7; HRMS (ES Q-TOF): $[M+H]^+$, found 184.1335. $C_{10}H_{17}NO_2$ requires 184.1338.

4.2.1.2. (E)-Ethyl 3-((2R,3R*)-3-cyclohexylaziridin-2-yl)acrylate (**6b**).* Pale yellow oil (90% yield); IR (neat, cm^{-1}): 2940, 2410, 1725; ^1H NMR (300 MHz, $CDCl_3$) δ: 6.41 (1H, dd, *J* 8.8, 15.4 Hz, C*H*=CHCO), 5.99 (1H, d, *J* 15.4 Hz, C*H*CO), 4.18 (2H, q, *J* 7.2 Hz, COCH_2CH$_3$), 2.31 (1H, dd, *J* 2.8, 8.8 Hz, C*H*CH=CH), 1.82 (1H, dd, *J* 2.8, 7.7 Hz, cyclohexyl–C*H*–NH), 1.77–1.56 (6H, m, cyclohexyl+N*H*), 1.20–0.85 (9H, m, cyclohexyl+$COCH_2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 166.0, 148.9, 121.2, 60.2, 46.0, 41.8, 36.7, 30.9, 30.3, 26.2, 25.7, 25.6, 14.1; HRMS (ES Q-TOF): $[M+H]^+$, found 224.1655. $C_{13}H_{21}NO_2$ requires 224.1651.

4.2.2. General procedure for the COOEt protection. Under nitrogen atmosphere 1 mmol of the appropriate substrate was dissolved in 3 mL of anhydrous diethyl ether. Et_3N of 1.2 mmol (121 mg, 0.2 mL) and 1.2 mmol (130 mg, 0.1 mL) of ethyl chloroformate were then added and the reaction mixture stirred at room temperature for 3 h or until consumption of the substrate (TLC monitoring). The mixture was then filtered through a Celite pad and the solvent evaporated under reduced pressure to give the desired product, which was used without any purification.

4.2.2.1. (E)-Ethyl 3-((2R,3R*)-3-(N-ethoxycarbonyl)propylaziridin-2-yl)acrylate (**7a**).* Pale yellow oil (248 mg, 97% yield); IR (neat, cm^{-1}): 2925, 1720, 1255, 1120; ^1H NMR (300 MHz, $CDCl_3$) δ: 6.40 (1H, dd, *J* 8.8, 15.4 Hz, C*H*=CHCO), 6.09 (1H, d, *J* 15.4 Hz, C*H*CO), 4.22–4.00 (4H, m, COCH_2CH$_3\times2$), 2.81 (1H, dd, *J* 2.8, 8.8 Hz, C*H*–CH=CH), 2.53–2.45 (1H, m, CH_2C*H*), 1.72–1.10 (10H, m, $CH_2\times2$+$CH_3\times2$), 0.78 (3H, t, *J* 7.3 Hz, $CH_2CH_2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 165.1, 160.7, 143.4, 124.0, 62.1, 60.13, 45.4, 43.2, 32.7, 19.8, 14.1, 13.9, 13.2; HRMS (ES Q-TOF): $[M+H]^+$, found 256.1543. $C_{13}H_{21}NO_4$ requires 256.1549.

4.2.2.2. (E)-Ethyl 3-((2R,3R*)-3-(N-ethoxycarbonyl)cyclohexylaziridin-2-yl)acrylate (**7b**).* Pale yellow oil (289 mg, 98% yield); IR (neat, cm^{-1}): 2955, 2860, 1725, 1250; ^1H NMR (300 MHz, $CDCl_3$) δ: 6.29 (1H, dd, *J* 9.4, 15.4 Hz, C*H*=CHCO), 6.08 (1H, d, *J* 15.4 Hz, C*H*CO), 4.22–4.00 (4H, m, COCH_2CH$_3\times2$), 2.89 (1H, dd, *J* 2.8, 9.4 Hz, C*H*–CH=CH), 2.38–2.29 (1H, m, cyclohexyl–C*H*), 1.99–0.96 (17H, m, cyclohexyl+$COCH_2CH_3\times2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 165.2, 161.0, 143.6, 124.2, 62.3, 60.3, 50.3, 42.3, 39.5, 30.2, 29.6, 26.0, 25.5, 25.3, 14.1, 14.0; HRMS (ES Q-TOF): $[M+H]^+$, found 296.1865. $C_{16}H_{25}NO_4$ requires 296.1862.

4.2.3. General procedure for the Boc protection. Under nitrogen atmosphere, 1 mmol of the appropriate substrate was dissolved in 10 mL of anhydrous dichloromethane. Boc_2O of 1.1 mmol (248 mg, 0.2 mL) and a catalytic amount of DMAP were then added and the reaction mixture stirred at room temperature for 12 h or until consumption of the substrate (TLC monitoring). The solvent was then evaporated under reduced pressure to give the desired product, which was used without any purification.

4.2.3.1. (E)-Ethyl 3-((2R,3R*)-3-(N-tert-butoxycarbonyl)cyclohexylaziridin-2-yl)acrylate (**8b**).* Pale yellow oil (317 mg, 98% yield); IR (neat, cm^{-1}): 3020, 2915, 1730, 1245; ^1H NMR (300 MHz, $CDCl_3$) δ: 6.33 (1H, dd, *J* 9.4, 15.4 Hz, C*H*=CHCO), 6.10 (1H, d, *J* 15.4 Hz, C*H*CO), 4.20 (2H, q, *J* 7.2 Hz, COCH_2CH$_3$), 2.87 (1H, dd, *J* 2.8, 9.4 Hz, C*H*–CH=CH), 2.36–2.31 (1H, m, cyclohexyl–C*H*–N), 1.99–1.58 (5H, m, cyclohexyl), 1.42 (9H, s, C(CH_3)$_3$), 1.25 (3H, t, *J* 7.2 Hz, $COCH_2CH_3$), 1.22–1.07 (6H, m, cyclohexyl); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 165.7, 160.4, 144.2, 124.0, 81.7, 60.4, 50.4, 42.5, 39.7, 30.3, 29.8, 27.8, 26.0, 25.6, 25.4, 14.2; HRMS (ES Q-TOF): $[M+H]^+$, found 324.2179. $C_{18}H_{29}NO_4$ requires 324.2175.

4.2.4. General procedure for the LiBr/Amb15 ring opening reaction. LiBr (4 mmol, 260 mg) and Amberlyst15 (1 mmol, 212 mg) were added to 1 mmol of the appropriate substrate dissolved in 8 mL of acetone and the mixture stirred overnight. After filtration, the mixture was concentrated in vacuo and the residue taken up in 5 mL of ethyl acetate, neutralized and washed with 5 mL of brine. The organic layer was dried on Na_2SO_4 and the solvent evaporated under reduced pressure to give the desired product that was used without any purification.

4.2.4.1. (E)(4R,5S*)-Ethyl 4-bromo-5-hydroxyoct-2-enoate (**9a**).* Pale yellow oil (238 mg, 90% yield); IR (neat, cm^{-1}): 3315, 2915, 1720, 1245, 550; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.03 (1H, dd, *J* 9.9, 15.4 Hz, C*H*=CHCO), 5.99 (1H, d, *J* 15.4 Hz, C*H*CO), 4.59 (1H, dd, *J* 3.3, 9.9 Hz, C*H*–Br), 4.20 (2H, q, *J* 7.2 Hz, COCH_2CH$_3$), 3.96–3.80 (1H, m, C*H*–OH), 2.40 (1H, br s, O*H*), 1.61–1.39 (4H, m, $CH_2\times2$), 1.30 (3H, t, *J* 7.2 Hz, $COCH_2CH_3$), 0.92 (3H, t, *J* 7.3 Hz, $CH_2CH_2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 165.12, 141.9, 124.2, 73.6, 60.5, 57.1, 35.7, 18.7, 13.9, 13.5; HRMS (ES Q-TOF): $[M+H]^+$, found 265.0436. $C_{10}H_{17}BrO_3$ requires 265.0439.

4.2.4.2. (E)(4R,5S*)-Ethyl 4-bromo-5-cyclohexyl-5-hydroxypent-2-enoate (**9b**).* Pale yellow oil (289 mg, 95% yield); IR (neat, cm^{-1}): 3290, 2945, 1715, 1250, 685, 560; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.15 (1H, dd, *J* 10.2, 15.6 Hz, C*H*=CHCO), 6.02 (1H, d, *J* 15.6 Hz, CHCO), 4.79 (1H, dd, *J* 3.8, 10.2 Hz, C*H*–Br), 4.18 (2H, q, *J* 7.2 Hz, COCH_2CH$_3$), 3.64 (1H, dd, *J* 3.8, 7.7 Hz, C*H*–O*H*), 2.8 (1H, br s, OH), 1.8–0.93 (14H, m, cyclohexyl+$COCH_2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 165.6, 140.7, 125.6, 76.9, 64.7, 60.9, 39.8, 29.2, 28.1, 26.2, 25.9, 25.5, 14.2;

HRMS (ES Q-TOF): $[M+H]^+$, found 305.0750. $C_{13}H_{21}BrO_3$ requires 305.0753.

4.2.4.3. (E)(4R,5R*)-Ethyl 4-bromo-5-hydroxyoct-2-enoate (**15**).* Pale yellow oil (238 mg, 90% yield); IR (neat, cm^{-1}): 3310, 2915, 1720, 1240, 550; ^1H NMR (300 MHz, $CDCl_3$) δ: 6.90 (1H, dd, *J* 9.7, 15.4 Hz, C*H*=CHCO), 5.90 (1H, d, *J* 15.4 Hz, CHCO), 4.47 (1H, dd, *J* 5.1, 9.7 Hz, C*H*–Br), 4.20 (2H, q, *J* 7.2 Hz, COCH_2CH$_3$), 3.65–3.51 (1H, m, C*H*–OH), 2.96 (1H, br s, O*H*), 1.55–1.30 (4H, m, CH_2×2), 1.20 (3H, t, *J* 7.2 Hz, COCH$_2$CH_3), 0.80 (3H, t, *J* 6.7 Hz, CH$_2$CH$_2$CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 165.6, 143.4, 123.6, 73.0, 60.8, 58.6, 36.5, 18.7, 14.1, 13.8; HRMS (ES Q-TOF): $[M+H]^+$, found 265.0438. $C_{10}H_{17}BrO_3$ requires 265.0439.

4.2.5. General procedure for the nucleophilic substitution (Br–N_3). Under nitrogen atmosphere NaN_3 (4 mmol, 260 mg) was added to 1 mmol of the appropriate substrate dissolved in 1 mL of anhydrous DMF and the mixture left stirring at room temperature until complete consumption of the substrate. The mixture was then diluted with 3 mL of ethyl acetate and washed with 5 mL of brine. The organic layer was dried on Na_2SO_4 and the solvent evaporated under reduced pressure to give the desired product, which was used without any purification.

4.2.5.1. (E)(4S,5S*)-Ethyl 4-azido-5-hydroxyoct-2-enoate (**10a**).* Yellow oil (204 mg, 90% yield); IR (neat, cm^{-1}): 3305, 3050, 2890, 2125, 1720; ^1H NMR (300 MHz, $CDCl_3$) δ: 6.78 (1H, dd, *J* 7.2, 15.9 Hz, C*H*=CHCO), 6.01 (1H, d, *J* 15.9 Hz, CHCO), 4.20 (2H, q, *J* 7.2 Hz, COCH_2CH$_3$), 3.95–3.75 (1H, m, CHN$_3$), 3.60–3.45 (1H, m, C*H*–OH), 2.40 (1H, br s, O*H*), 1.61–1.11 (4H, m, CH_2×2), 1.30 (3H, t, *J* 7.2 Hz, COCH$_2$CH_3), 0.92 (3H, t, *J* 7.3 Hz, CH$_2$CH$_2$CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 165.34, 141.48, 124.41, 72.55, 67.31, 60.47, 35.17, 18.37, 13.80, 13.52; HRMS (ES Q-TOF): $[M+H]^+$, found 228.1345. $C_{10}H_{17}N_3O_3$ requires 228.1348.

4.2.5.2. (E)(4S,5S*)-Ethyl 4-azido-5-cyclohexyl-5-hydroxypent-2-enoate (**10b**).* Brown oil (254 mg, 95% yield); IR (neat, cm^{-1}): 3300, 3055, 2910, 2120, 1730; ^1H NMR (300 MHz, $CDCl_3$) δ: 6.83 (1H, dd, *J* 7.5, 15.8 Hz, C*H*=CHCO), 6.04 (1H, d, *J* 15.8 Hz, CHCO), 4.31–3.98 (3H, m, C*H*N$_3$+COCH_2CH$_3$), 3.28 (1H, dd, *J* 5.4 Hz, C*H*–OH), 2.65 (1H, br s, O*H*), 1.94–0.93 (14H, m, cyclohexyl+COCH$_2$CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 165.5, 141.9, 124.5, 77.2, 64.9, 60.7, 40.0, 29.6, 27.0, 26.0, 25.9, 25.7, 14.0; HRMS (ES Q-TOF): $[M+H]^+$, found 268.1663. $C_{13}H_{21}N_3O_3$ requires 268.1661.

4.3. General procedure for the dihydroxylation reaction

To a solution of 1 mmol of the appropriate substrate in 9 mL of acetone/water (8:1) were added 2 mmol (270 mg) of NMO and 0.63 mL of a 2.5% solution of OsO_4 in *tert*-butanol (0.05 mmol of OsO_4) and the mixture left stirring overnight at room temperature. The reaction was then quenched with 5 mL of a saturated solution of $Na_2S_2O_3$, the mixture left stirring for 1 h and then transferred in a separating funnel. The aqueous layer was extracted with 10 mL of ethyl acetate, the combined organic layers dried over Na_2SO_4 and the solvent removed under reduced pressure. The residue was then purified by chromatography on silica gel to give the mixture of the desired products.

The chromatographically inseparable mixtures **20a**/**20a′**, **20b**/**20b′**, **22a**/**22a′**, **24a**/**24a′**, **24b**/**24b′** were subsequently converted into the corresponding acetonides to allow a full characterization.

4.3.1. (2R,3S*,4S*,5S*)-Ethyl 4-azido-2,3,5-trihydroxyoctanoate (**16a**) (data given only for the major product).* Pale yellow oil (200 mg, 77% yield); IR (neat, cm^{-1}): 3290, 2905, 2125, 1725, 1780; ^1H NMR (300 MHz, $CDCl_3$) δ: 4.45 (1H, d, *J* 0.5 Hz, CHOH–CO), 4.2 (2H, q, *J* 7.2 Hz, COCH_2CH$_3$), 3.97–3.88 (1H, m, CH$_2$CHOH), 3.85 (1H, dd, *J* 0.5, 9.6 Hz, CHOH–CHOH), 3.62 (1H, dd, *J* 5.6, 9.6 Hz, CHN$_3$), 1.71–1.46 (7H, m, CH_2×2+O*H*×3), 1.3 (3H, t, *J* 7.2 Hz, COCH$_2$CH_3), 0.9 (3H, t, *J* 6.6 Hz, CH$_2$CH$_2$CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 173.3, 73.6, 73.2, 71.3, 65.9, 62.4, 34.7, 18.7, 14.2, 14.1; HRMS (ES Q-TOF): $[M+H]^+$, found 262.1406. $C_{10}H_{19}N_3O_5$ requires 262.1403.

4.3.2. (2S,3R*,4S*,5S*)-Ethyl 4-azido-2,3,5-trihydroxyoctanoate (**16a′**) (data given only for the signal(s) used to calculate the ratio between the two diastereomers).* ^1H NMR (300 MHz, $CDCl_3$) δ: 4.4 (1H, d, *J* 0.6 Hz, CHOH–CO).

4.3.3. (2R,3S*,4S*,5S*)-Ethyl 4-azido-5-cyclohexyl-2,3,5-trihydroxypentanoate (**16b**) (data given only for the major product).* Pale yellow oil (241 mg, 80% yield); IR (neat, cm^{-1}): 3300, 2910, 2120, 1720, 1770; ^1H NMR (300 MHz, $CDCl_3$) δ: 4.43 (1H, d, *J* 0.5 Hz, CHOH–CO), 4.28–4.05 (4H, m, COCH_2CH$_3$+CHOH–CHOH+cyclohexyl–CHOH), 3.65–3.63 (1H, m, CHN$_3$), 1.88–1.44 (8H, m, cyclohexyl+O*H*×3), 1.34–0.8 (9H, m, cyclohexyl+COCH$_2$CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 173.1, 83.4, 78.1, 74.7, 71.5, 62.2, 40.4, 30.1, 29.2, 26.4, 25.9, 25.6, 14.2; HRMS (ES Q-TOF): $[M+H]^+$, found 302.1711. $C_{13}H_{23}N_3O_5$ requires 302.1715.

4.3.4. (2S,3R*,4S*,5S*)-Ethyl 4-azido-5-cyclohexyl-2,3,5-trihydroxypentanoate (**16b′**) (data given only for the signal(s) used to calculate the ratio between the two diastereomers).* ^1H NMR (300 MHz, $CDCl_3$) δ: 4.39 (1H, d, *J* 0.4 Hz, CHOH–CO).

4.3.5. (2R,3S*,4R*,5S*)-Ethyl 4-azido-2,3,5-trihydroxyoctanoate (**18a**) (data given only for the major product).* Pale yellow oil (198 mg, 76% yield); IR (neat, cm^{-1}): 3280, 2910, 2120, 1720, 1780; ^1H NMR (300 MHz, $CDCl_3$) δ: 4.26 (1H, d, *J* 2.6 Hz, CHOH–CO), 4.2 (2H, q, *J* 7.2 Hz, COCH_2CH$_3$), 4.08 (1H, dd, *J* 2.6, 6.3 Hz, CHOH–CHOH), 3.78–3.70 (1H, m, CH$_2$CHOH), 3.38 (1H, dd, *J* 2.4, 6.3 Hz, CHN$_3$), 1.67–1.33 (7H, m, CH_2×2+O*H*×3), 1.27 (3H, t, *J* 7.2 Hz, COCH$_2$CH_3), 0.9 (3H, t, *J* 7.3 Hz, CH$_2$CH$_2$CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 173.4, 71.4, 71.1, 70.4, 65.5, 62.3, 36.3, 19.2, 14.2, 13.9; HRMS (ES Q-TOF): $[M+H]^+$, found 262.1400. $C_{10}H_{19}N_3O_5$ requires 262.1403.

4.3.6. (2S,3R*,4R*,5S*)-Ethyl 4-azido-2,3,5-trihydroxyoctanoate (**18a′**) (data given only for the signal(s) used to calculate the ratio between the two diastereomers).* ^1H NMR (300 MHz, $CDCl_3$) δ: 4.41 (1H, d, *J* 1.5 Hz, CHOH–CO).

4.3.7. (2R,3S*,4R*,5S*)-Ethyl 4-azido-5-cyclohexyl-2,3,5-trihydroxypentanoate (**18b**) (data given only for the major product).* Pale yellow oil (236 mg, 78% yield); IR (neat, cm^{-1}): 3290, 2910, 2120, 1725, 1780; ^1H NMR (300 MHz, $CDCl_3$) δ: 4.36 (1H, d, *J* 2.6 Hz, CHOH–CO), 4.33–4.21 (3H, m, COCH_2CH$_3$+CHOH–CHOH), 3.69 (1H, dd, *J* 2.0, 6.7 Hz, cyclohexyl–CHOH), 3.45 (1H, dd, *J* 2.0, 8.4 Hz, CHN$_3$), 2.0–1.50 (8H, m, cyclohexyl+O*H*×3), 1.34–0.8 (9H, m, cyclohexyl+COCH$_2$CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 172.8, 75.9, 73.9, 71.0, 64.6, 62.5, 41.2, 29.1, 26.3, 25.9, 25.8, 25.5, 14.2; HRMS (ES Q-TOF): $[M+H]^+$, found 302.1717. $C_{13}H_{23}N_3O_5$ requires 302.1715.

4.3.8. (2S,3R*,4R*,5S*)-Ethyl 4-azido-5-cyclohexyl-2,3,5-trihydroxypentanoate (**18b′**) (data given only for the signal(s) used to calculate the ratio between the two diastereomers).* ^1H NMR (300 MHz, $CDCl_3$) δ: 4.41 (1H, d, *J* 2.0 Hz, CHOH–CO).

4.3.9. (2R,3S*)-Ethyl 3-((2S*,3R*)-3-propylaziridin-2-yl)-2,3-dihydroxy propanoate (**27a/27a′**) (data given for the inseparable mixture).* Pale brown oil (153 mg, 70% yield); IR (neat, cm^{-1}): 3300, 2920, 2415, 1725; ^1H NMR (300 MHz, $CDCl_3$) δ: 4.32–4.20 (6H, m, CHOH–CO×2+COCH_2CH$_3$×2), 3.73 (1H, dd, *J* 2.1, 4.8 Hz, CHOH–-CHOH), 3.65 (1H, dd, *J* 2.3, 4.9 Hz, CHOH–CHOH), 2.8–2.3 (4H, br s,

O*H*×4), 2.12–2.0 (2H, m, CH_2CH×2), 1.95–1.83 (2H, m, C*H*–CHOH×2), 1.54–1.37 (8H, m, CH_2×4), 1.35–1.20 (6H, m, $COCH_2CH_3$×2), 0.98–0.83 (6H, m, $CH_2CH_2CH_3$×2); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 172.7, 73.5, 72.8, 72.7, 71.9, 61.8, 39.1, 38.6, 35.7, 35.5, 35.4, 34.9, 20.8, 14.2, 13.9.

4.3.10. (2R,3S*)-Ethyl 3-((2S*,3R*)-3-cyclohexylaziridin-2-yl)-2,3-dihydroxy propanoate (**27b/27b′**) (data given for the inseparable mixture).* Brown oil (180 mg, 70% yield); IR (neat, cm^{-1}): 3295, 2920, 2410, 1725; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.33–4.14 (6H, m, C*H*OH–CO×2+$COCH_2CH_3$×2), 3.69 (1H, dd, *J* 4.5 Hz, C*H*OH–CHOH), 3.60 (1H, dd, *J* 2.2, 4.8 Hz, C*H*OH–CHOH), 3.4–2.9 (4H, br s, O*H*×4), 2.4–2.3 (2H, m, C*H*×2), 2.2–2.1 (2H, m, C*H*–CHOH×2), 1.9–1.5 (10H, m, cyclohexyl), 1.4–0.9 (18H, m, cyclohexyl+$COCH_2CH_3$×2); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 172.4, 73.9, 73.5, 73.2, 72.9, 62.1, 39.8, 39.0, 35.9, 35.8, 35.6, 34.9, 20.8, 14.2, 13.9.

4.3.11. (2R,3S*)-Ethyl 3-((2S*,3R*)-3-propyl-(N-ethoxycarbonyl) aziridin-2-yl)-2,3-dihydroxy propanoate (**28a**) (data given only for the major product).* Pale brown oil (182 mg, 63% yield); IR (neat, cm^{-1}): 3280, 2925, 1740; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.37 (1H, d, *J* 1.7 Hz, C*H*OH–CO), 4.27 (2H, q, *J* 7.2 Hz, $COCH_2CH_3$), 4.16 (2H, q, *J* 7.2 Hz, $NCOCH_2CH_3$), 3.99 (1H, dd, *J* 1.7, 4.9 Hz, C*H*OH–CHOH), 2.63–2.56 (1H, m, CH_2CH), 2.49 (1H, dd, *J* 3.4, 4.9 Hz, C*H*–CHOH), 2.1 (2H, br s, O*H*×2), 1.81–1.4 (4H, m, CH_2×2), 1.35–1.20 (6H, m, $COCH_2CH_3$×2), 0.9 (3H, t, *J* 7.4 Hz, $CH_2CH_2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 165.1, 160.7, 71.9. 69.1 62.1, 60.13, 45.4, 43.2, 32.7, 19.8, 14.1, 13.9, 13.2; HRMS (ES Q-TOF): $[M+H]^+$, found 290.1600. $C_{13}H_{23}NO_6$ requires 290.1604.

4.3.12. (2S,3R*)-Ethyl 3-((2S*,3R*)-3-propyl-(N-ethoxycarbonyl) aziridin-2-yl)-2,3-dihydroxy propanoate (**28a′**) (data given only for the significant signals).* ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.34 (1H, d, *J* 1.5 Hz, C*H*OH–CO).

4.3.13. (2R,3S*)-Ethyl 3-((2S*,3R*)-3-cyclohexyl(N-ethoxycarbonyl) aziridin-2-yl)-2,3-dihydroxypropanoate (**28b**) (data given only for the major product).* Pale yellow oil (217 mg, 66% yield); IR (neat, cm^{-1}): 3295, 2920, 2410; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.32 (1H, d, *J* 0.5 Hz, C*H*OH–CO), 4.29–4.06 (5H, m, $COCH_2CH_3$×2+C*H*OH–CHOH), 2.5 (1H, dd, *J* 3.6 Hz, C*H*N), 2.4 (1H, dd, *J* 3.6, 6.0 Hz, C*H*N), 2.21 (2H, br s, O*H*×2), 2.01–1.56 (5H, m, cyclohexyl), 1.36–0.96 (12H, m, cyclohexyl+$COCH_2CH_3$×2); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 172.8, 172.7, 72.4, 69.7, 62.3, 62.2, 45.4, 43.0, 39.5, 30.8, 30.0, 26.3, 25.8, 25.6, 14.4, 14.2; HRMS (ES Q-TOF): $[M+H]^+$, found 330.1914. $C_{16}H_{27}NO_6$ requires 330.1917.

4.3.14. (2S,3R*)-Ethyl 3-((2S*,3R*)-3-cyclohexyl(N-ethoxycarbonyl) aziridin-2-yl)-2,3-dihydroxypropanoate (**28b′**) (data given only for the signal(s) used to calculate the ratio between the two diastereomers).* ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.29 (1H, d, *J* 0.8 Hz, C*H*OH–CO).

4.3.15. (2R,3S*)-Ethyl 3-((2S*,3R*)-3-propyl-(N-tert-butoxycarb onyl)aziridin-2-yl)-2,3-dihydroxy propanoate (**29a**) (data given only for the major product).* Pale brown oil (190 mg, 60% yield); IR (neat, cm^{-1}): 3300, 2920, 1735; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.38 (1H, d, *J* 0.5 Hz, C*H*OH–CO), 4.2 (2H, q, *J* 7.2 Hz, $COCH_2CH_3$), 3.88 (1H, dd, *J* 0.5, 5.2 Hz, C*H*OH–CHOH), 2.58–2.50 (1H, m, CH_2CHN), 2.45 (1H, dd, *J* 3.3, 5.2 Hz, C*H*–CHOH), 2.3 (2H, br s, O*H*×2), 1.78–1.39 (13H, m, CH_2×2+C(CH_3)$_3$), 1.29 (3H, t, *J* 7.2 Hz, $COCH_2CH_3$), 0.95 (3H, t, *J* 7.4 Hz, $CH_2CH_2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 165.2, 159.2, 80.9, 71.9, 69.1, 60.5, 45.8, 43.1, 33.1, 31.2, 27.9, 14.4, 14.0; HRMS (ES Q-TOF): $[M+H]^+$, found 318.1917. $C_{15}H_{27}NO_6$ requires 318.1917.

4.3.16. (2S,3R*)-Ethyl 3-((2S*,3R*)-3-propyl-(N-tert-butoxycarbonyl)aziridin-2-yl)-2,3-dihydroxy propanoate (**29a′**) (data given only for the signal(s) used to calculate the ratio between the two diastereomers).* ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.7 (1H, dd, *J* 1.6, 6.6 Hz, C*H*OH–CHOH).

4.3.17. (2R,3S*)-Ethyl 3-((2S*,3R*)-3-cyclohexyl-(N-tert-butoxycarbonyl)aziridin-2-yl)-2,3-dihydroxy propanoate (**29b**) (data given only for the major product).* Pale yellow oil (233 mg, 65% yield); IR (neat, cm^{-1}): 3295, 2920, 1740; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.38 (1H, d, *J* 0.5 Hz, C*H*OH–CO), 4.25 (2H, q, *J* 7.2 Hz, $COCH_2CH_3$), 3.97 (1H, dd, *J* 5.0, 1.8 Hz, C*H*OH–CHOH), 2.5 (1H, dd, *J* 3.5, 5.0 Hz, C*H*–CHOH), 2.36 (1H, dd, *J* 3.5, 7.5 Hz, cyclohexyl–C*H*), 2.05–1.59 (7H, m, cyclohexyl+O*H*×2), 1.4 (9H, s, C(CH_3)$_3$), 1.34–1.00 (9H, m, cyclohexyl+$COCH_2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 172.9, 161.1, 81.2, 72.4, 70.8, 62.2, 46.4, 42.7, 41.0, 39.7, 30.3, 28.0, 26.3, 25.8, 25.6, 14.2; HRMS (ES Q-TOF): $[M+H]^+$, found 358.2225. $C_{18}H_{31}NO_6$ requires 358.2229.

4.3.18. (2S,3R*)-Ethyl 3-((2S*,3R*)-3-cyclohexyl-(N-tert-butoxy carbonyl)aziridin-2-yl)-2,3-dihydroxy propanoate (**29b**) (data given only for the signal(s) used to calculate the ratio between the two diastereomers).* ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.9 (1H, dd, *J* 1.6, 9.5 Hz, C*H*OH–CHOH).

4.4. General procedure for the acetonide formation

Appropriate substrate of 1 mmol was dissolved in 10 mL of acetone. To the mixture 2,2-dimethoxypropane (1.4 mmol, 0.17 mL) and a catalytic amount of *p*-toluensulfonic acid were added and the mixture left stirring at room temperature until complete consumption of the substrate. The reaction crude was diluted with 10 mL of Et_2O and filtered through a basic alumina pad; the solvent was then removed under reduced pressure and the residue purified by chromatography on silica gel to give the mixture of the desired products.

To obtain 1,2-acetonides the reaction needs to be carried out at −20 to 0 °C (kinetic control conditions) whereas at room temperature for 1,3-acetonides (thermodynamic control conditions).

4.4.1. (R)-Ethyl 2-((4S*,5S*,6S*)-5-azido-2,2-dimethyl-6-propyl-1,3-dioxan-4-yl)-2-hydroxyacetate (**17a**).* Pale yellow oil (271 mg, 90% yield); IR (neat, cm^{-1}): 3280, 2925, 2125, 1735; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.37 (1H, d, *J* 1.9 Hz, C*H*OH), 4.2 (2H, q, *J* 7.2 Hz, $COCH_2CH_3$), 3.89 (1H, dd, *J* 1.9, 10.0 Hz, C*H*–CHOH), 3.6 (1H, ddd, *J* 2.5, 8.0, 10.0 Hz, CH_2CH), 3.35 (1H, dd, *J* 10.0 Hz, C*H*N_3), 2.53 (1H, br s, O*H*), 1.82–1.41 (4H, m, CH_2×2), 1.37 (3H, s, CCH_3), 1.33 (3H, s, CCH_3), 1.28 (3H, t, *J* 7.2 Hz, $COCH_2CH_3$), 0.9 (3H, t, *J* 7.4 Hz, $CH_2CH_2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 172.1, 98.9, 73.5, 71.8, 70.0, 61.8, 58.6, 35.0, 29.2, 19.2, 18.1, 14.3, 13.9; HRMS (ES Q-TOF): $[M+H]^+$, found 302.1719. $C_{13}H_{23}N_3O_5$ requires 302.1716.

4.4.2. (R)-Ethyl 2-((4S*,5S*,6S*)-5-azido-2,2-dimethyl-6-cyclohexyl-1,3-dioxan-4-yl)-2-hydroxyacetate (**17b**).* Colourless oil (317 mg, 93% yield); IR (neat, cm^{-1}): 3290, 2920, 2120, 1735; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.43 (1H, dd, *J* 1.8, 9.0 Hz, C*H*OH), 4.2 (2H, q, *J* 7.2 Hz, $COCH_2CH_3$), 3.9 (1H, dd, *J* 1.8, 9.4 Hz, C*H*–CHOH), 3.65–3.45 (2H, m, C*H*–CHN_3+C*H*N_3), 2.9 (1H, d, *J* 9.0 Hz, O*H*), 1.84–1.57 (5H, m, cyclohexyl), 1.39–1.11 (15H, m, cyclohexyl+C(CH_3)$_2$+$COCH_2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 165.8, 99.0, 75.8, 73.7, 70.3, 61.9, 54.9, 39.1, 30.0, 29.3, 26.8, 26.5, 26.4, 25.7, 19.2, 14.0; HRMS (ES Q-TOF): $[M+H]^+$, found 342.2023. $C_{16}H_{27}N_3O_5$ requires 342.2029.

4.4.3. (R)-Ethyl 2-((4S*,5R*,6S*)-5-azido-2,2-dimethyl-6-propyl-1,3-dioxan-4-yl)-2-hydroxyacetate (**19a**).* Yellow oil (277 mg, 92% yield); IR (neat, cm^{-1}): 3285, 2920, 2125, 1735; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.44–4.11 (3H, m, $COCH_2CH_3$+C*H*OH), 3.91 (1H, dd, *J* 1.7, 10.0 Hz, C*H*–CHOH), 3.6 (1H, ddd, *J* 2.5, 7.9, 10.0 Hz, CH_2CH), 3.38

(1H, dd, *J* 10.0 Hz, C*H*N$_3$), 2.5 (1H, br s, O*H*), 1.82–1.41 (4H, m, CH_2×2), 1.37 (3H, s, CCH_3), 1.33 (3H, s, CCH_3), 1.28 (3H, t, *J* 7.2 Hz, COCH$_2$CH_3), 0.9 (3H, t, *J* 7.4 Hz, CH$_2$CH$_2$CH_3); ^{13}C NMR (75 MHz, CDCl$_3$) *δ*: 172.1, 98.9, 73.6, 71.9, 70.0, 61.8, 58.6, 35.1, 29.8, 19.2, 18.2, 14.4, 13.9; HRMS (ES Q-TOF): [M+H]$^+$, found 302.1719. $C_{13}H_{23}N_3O_5$ requires 302.1716.

4.4.4. (R)-Ethyl 2-((4S*,5R*,6S*)-5-azido-2,2-dimethyl-6-cyclohexyl-1,3-dioxan-4-yl)-2-hydroxyacetate (**19b**).* colourless oil (325 mg, 95% yield); IR (neat, cm^{-1}): 3280, 2920, 2120, 1740; ^{1}H NMR (300 MHz, CDCl$_3$) *δ*: 4.45 (1H, dd, *J* 4.3, 7.4 Hz, C*H*OH), 4.2 (2H, q, *J* 7.2 Hz, COCH_2CH$_3$), 3.80 (1H, dd, *J* 3.0, 7.4 Hz, C*H*–CHOH), 3.60 (1H, dd, *J* 4.8 Hz, C*H*–CHN$_3$), 3.35 (1H, dd, *J* 3.0, 4.8 Hz, C*H*N$_3$), 2.6 (1H, d, *J* 4.3 Hz, O*H*), 1.84–1.57 (5H, m, cyclohexyl), 1.39–1.11 (15H, m, cyclohexyl+C(CH_3)$_2$+COCH$_2$CH_3); ^{13}C NMR (75 MHz, CDCl$_3$) *δ*: 170.8, 99.0, 75.8, 73.7, 70.3, 61.9, 54.9, 40.0, 30.0, 29.3, 26.8, 26.5, 26.4, 25.7, 19.2, 14.3; HRMS (ES Q-TOF): [M+H]$^+$, found 342.2023. $C_{16}H_{27}N_3O_5$ requires 342.2029.

4.4.5. (R)-Ethyl 2-((4R*,5S*,6S*)-5-bromo-2,2-dimethyl-6-propyl-1,3-dioxan-4-yl)-2-hydroxyacetate (**21a**).* Light orange oil (229 mg, 68% yield); IR (neat, cm^{-1}): 3300, 2920, 1750, 550; ^{1}H NMR (300 MHz, CDCl$_3$) *δ*: 4.57 (1H, dd, *J* 1.7, 9.2 Hz, C*H*OH), 4.41–4.14 (3H, m, C*H*–Br+COCH_2CH$_3$), 3.95–3.86 (2H, m, C*H*–O×2), 2.85 (1H, d, *J* 9.2 Hz, O*H*), 1.82–1.41 (4H, m, CH_2×2), 1.37 (3H, s, CCH_3), 1.33 (3H, s, CCH_3), 1.28 (3H, t, *J* 7.2 Hz, COCH$_2$CH_3), 0.9 (3H, t, *J* 7.4 Hz, CH$_2$CH$_2$CH_3); ^{13}C NMR (75 MHz, CDCl$_3$) *δ*: 172.3, 98.9, 75.5, 73.4, 70.7, 61.8, 48.3, 35.4, 29.4, 19.3, 18.1, 14.5, 13.9; HRMS (ES Q-TOF): [M+H]$^+$, found 339.0805. $C_{13}H_{23}BrO_5$ requires 339.0807.

4.4.6. (S)-Ethyl 2-((4S*,5S*,6S*)-5-bromo-2,2-dimethyl-6-propyl-1,3-dioxan-4-yl)-2-hydroxyacetate (**21a′**) (data given only for the signal(s) used to calculate the ratio between the two diastereomers).* ^{1}H NMR (300 MHz, CDCl$_3$) *δ*: 4.50 (1H, dd, *J* 1.5, 8 Hz, C*H*OH).

4.4.7. (R)-Ethyl 2-((4R*,5S*,6R*)-5-bromo-2,2-dimethyl-6-propyl-1,3-dioxan-4-yl)-2-hydroxyacetate (**23**).* Pale brown oil (237 mg, 70% yield); IR (neat, cm^{-1}): 3290, 2920, 1745, 560; ^{1}H NMR (300 MHz, CDCl$_3$) *δ*: 4.54 (1H, dd, *J* 4.2, 8.4 Hz, C*H*–Br), 4.41 (1H, dd, *J* 1.2 Hz, C*H*OH), 4.34–4.13 (3H, m, C*H*–CHOH+COCH_2CH$_3$), 3.76 (1H, ddd, *J* 4.2, 8.0, 12.2 Hz, CH$_2$–C*H*), 2.45 (1H, br s, O*H*), 1.71–1.19 (13H, m, CH_2×2+C(CH_3)$_2$+COCH$_2$CH_3), 0.9 (3H, t, *J* 7.4 Hz, CH$_2$CH$_2$CH_3); ^{13}C NMR (75 MHz, CDCl$_3$) *δ*: 172.3, 101.8, 76.4, 74.5, 69.0, 62.0, 54.9, 35.9, 23.9, 23.6, 18.8, 14.3, 13.9; HRMS (ES Q-TOF): [M+H]$^+$, found 339.0809. $C_{13}H_{23}BrO_5$ requires 339.0807.

4.4.8. (S)-Ethyl 2-((4S*,5S*,6R*)-5-bromo-2,2-dimethyl-6-propyl-1,3-dioxan-4-yl)-2-hydroxy acetate (**23′**) (data given only for the signal(s) used to calculate the ratio between the two diastereomers).* ^{1}H NMR (300 MHz, CDCl$_3$) *δ*: 4.49 (1H, dd, *J* 4.0, 8.9 Hz, C*H*–Br).

4.4.9. (4R,5S*)-Ethyl 2,2-dimethyl-5-((2R*,3S*)-3-propyloxiran-2-yl)-1,3-dioxolane-4-carboxylate (**25a**).* Colourless oil (147 mg, 57% yield); IR (neat, cm^{-1}): 2915, 1750, 880; ^{1}H NMR (300 MHz, CDCl$_3$) *δ*: 4.44 (1H, d, *J* 7.7 Hz, C*H*–COOEt), 4.2 (2H, q, *J* 7.2 Hz, COCH_2CH$_3$), 4.02 (1H, dd, *J* 5.0, 7.7 Hz, C*H*–CHCOOEt), 2.99 (1H, ddd, *J* 2.2, 5.2, 7.4 Hz, CH–O–C*H*–CH), 2.93 (1H, dd, *J* 2.2, 5.0 Hz, CH$_2$–C*H*), 1.64–1.48 (4H, m, CH_2×2), 1.46 (3H, s, CCH_3), 1.43 (3H, s, CCH_3), 1.28 (3H, t, *J* 7.2 Hz, COCH$_2$CH_3), 0.9 (3H, t, *J* 7.4 Hz, CH$_2$CH$_2$CH_3); ^{13}C NMR (75 MHz, CDCl$_3$) *δ*: 170.4, 112.2, 78.9, 76.3, 61.7, 57.7, 56.1, 33.8, 26.7, 25.9, 19.4, 14.3, 14.0; HRMS (ES Q-TOF): [M+H]$^+$, found 259.1549. $C_{13}H_{22}O_5$ requires 259.1545.

4.4.10. (4S,5S*)-Ethyl 2,2-dimethyl-5-((2S*,3S*)-3-propyloxiran-2-yl)-1,3-dioxolane-4-carboxylate (**25a′**) (data given only for the signal(s) used to calculate the ratio between the two diastereomers).* ^{1}H NMR (300 MHz, CDCl$_3$) *δ*: 4.35 (1H, d, *J* 7.0 Hz, C*H*–COOEt).

4.4.11. (4R,5S*)-Ethyl 2,2-dimethyl-5-((2R*,3S*)-3-cyclohexyloxiran-2-yl)-1,3-dioxolane-4-carboxylate (**25b**).* Colourless oil (155 mg, 52% yield); IR (neat, cm^{-1}): 2920, 1750, 880; ^{1}H NMR (300 MHz, CDCl$_3$) *δ*: 4.44 (1H, d, *J* 7.7 Hz, C*H*–CO), 4.2 (2H, q, *J* 7.2 Hz, COCH_2CH$_3$), 4.02 (1H, dd, *J* 5.0, 7.7 Hz, C*H*–CHCO), 2.99 (1H, dd, *J* 2.2, 5.0 Hz, CH–O–C*H*), 2.93 (1H, dd, *J* 2.2, 5.4 Hz, cyclohexyl–C*H*), 1.84–1.57 (5H, m, cyclohexyl), 1.46 (3H, s, CCH_3), 1.43 (3H, s, CCH_3), 1.39–1.11 (9H, m, cyclohexyl+COCH$_2$CH_3); ^{13}C NMR (75 MHz, CDCl$_3$) *δ*: 170.4, 112.2, 79.3, 76.4, 61.7, 60.3, 56.7, 39.7, 29.8, 29.4, 26.3, 25.7, 25.6, 14.3; HRMS (ES Q-TOF): [M+H]$^+$, found 299.1854. $C_{16}H_{26}O_5$ requires 299.1858.

4.4.12. (4S,5S*)-Ethyl 2,2-dimethyl-5-((2S*,3S*)-3-cyclohexyl oxiran-2-yl)-1,3-dioxolane-4-carboxylate (**25b′**) (data given only for the signal(s) used to calculate the ratio between the two diastereomers).* ^{1}H NMR (300 MHz, CDCl$_3$) *δ*: 4.3 (1H, d, *J* 8.2 Hz, C*H*–CO).

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10. For the substrates with R=cyclohexyl the appropriate alcohol **1b** is not commercially available and it was synthesized from the cyclohexanecarboxaldehyde. A Horner–Emmons reaction, followed by a reduction of the ester using DIBAL, led to alcohol **1b** with an overall yield of 97%.
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