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An improved synthesis of aziridine-2,3-dicarboxylates via azido alcohols—epimerization studies

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Abstract—The reasons for epimerization of 3-azido-2-hydroxysuccinates observed during the ring opening of epoxides or cyclic sulfites with sodium azide is now clarified. It is caused by the high acidity of the proton at the 3-position. This is proven by a proton deuterium exchange in assays with either D_2O or DCl containing solvents. The *anti*-3-azido-2-hydroxysuccinates serve as intermediates for enantiomerically pure *trans*-aziridine-2,3-dicarboxylates for which an optimized synthetic pathway is presented. The first example of an enantiomerically pure mixed diester of the aziridine-2,3-dicarboxylic acid the synthesis of the allyl ethyl ester is reported herein.

1. Introduction

Over the last few years, the interest in inhibitors of cysteine proteases has increased strongly.[1–3] Since these proteases play essential roles in various pathological processes, low molecular weight inhibitors could be useful therapeutic agents. One class of inhibitors comprises of peptides containing an epoxide[4–13] or aziridine[14–19] ring.[20] These three-membered heterocycles act as electrophilic head groups which can be attacked by the cysteine residue of the enzyme's active site thus leading to irreversible enzyme alkylation and inactivation. In connection with the development of new inhibitors containing aziridine-2,3-dicarboxylic acid as an electrophilic building block, we investigated synthetic strategies for the stereoselective synthesis of symmetrical and mixed diesters of this dicarboxylic acid.

There are several synthetic routes to aziridine-2,3-dicarboxylates described in the literature. First of all, the (*S*,*S*)-dicarboxylic acid as natural product[21] can be obtained by fermentation using a *Streptomyces* strain.[22] Esterification of this diacid can be performed only after protection of the aziridine nitrogen.[22] The Cromwell synthesis with 2,3-dibromo succinates and ammonia leads to the *trans*-racemates in low yields accompanied by *cis*-aziridines, open chain enamines and aziridine-2,3-carboxamides.[23,24] Similar results are obtained by Michael addition of diphenylsulfimine to fumarates.[17,25] Other main products of this reaction are enamines, aziridines which formed in a 25–35% yield as *trans*-racemates.

The ex-chiral pool synthesis (Scheme 1) of the enantiomerically pure *trans*-(2*S*,3*S*)- and -(2*R*,3*R*)-diethyl aziridine-2,3-dicarboxylates **7b** starts from the reversed configured tartrates **1b**, which are converted within a three step synthesis into (2*R*,3*R*)- and (2*S*,3*S*)-diethyl epoxysuccinates **2b**, respectively.[26–28] These intermediates then have to be purified by distillation. Subsequent ring opening with sodium azide or trimethylsilyl azide leads to (2*R*,3*S*)-*anti*-3-azido-2-hydroxysuccinate **6b** in the case of the (*R*,*R*)-configured epoxide **2b** and to (2*S*,3*R*)-*anti*-3-azido-2-hydroxysuccinate **6b** in the case of the (*S*,*S*)-configured one. With NaN_3, the diastereomers of these azido alcohols, the (2*R*,3*R*)-*syn*- and (2*S*,3*S*)-*syn*-3-azido-2-hydroxysuccinates **6b** are formed as by-products which have to be separated by column chromatography, otherwise, the following ring closure to *trans*-(2*S*,3*S*)- and *trans*-(2*R*,3*R*)-aziridine-2,3-dicarboxylate **7b**, respectively, with triphenylphosphine would be accompanied by formation of the *cis*-(2*S*,3*R*)-aziridine.[14,29,30] The maximum overall yield of this five step aziridine synthesis is about 30%. The reasons for complete epimerization using NaN_3 as azide donor and an appropriate alcohol as solvent[14,29] during the ring opening of the epoxide, however, remained unclear.

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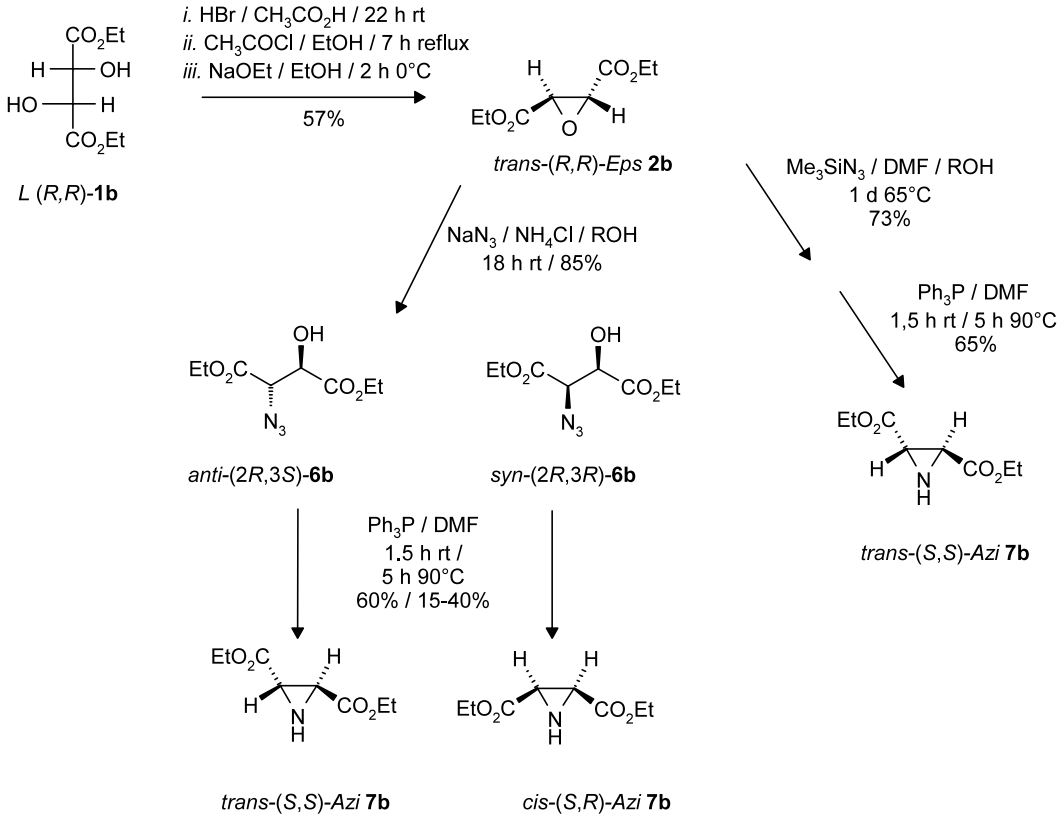


Scheme 1. Ex-chiral pool synthesis of (2*S*,3*S*)-aziridine-2,3-dicarboxylates **7** via the epoxide route.

Other possibilities for obtaining the azido alcohols **6** are nucleophilic ring openings of the appropriate cyclic sulfites **3**,[31–35] sulfates **4**,[37] carbonates,[35] and thionocarbonates **5**[36,38,39] with NaN_3. In references describing these reactions, epimerization of the azido alcohols is not mentioned. During our research to improve the syntheses of aziridine-2,3-dicarboxylates **7** we decided to investigate the epimerization tendency of the mentioned ring opening reactions with NaN_3 on dependency of the starting material (epoxide, cyclic sulfite, cyclic sulfate), addition of NH_4Cl as the proton source, the solvent (ROH, DMF, acetone, DMSO) and the water content of the solvent.

Another goal of our work was the synthesis of enantiomerically pure, unsymmetrically substituted diesters to allow orthogonal peptide chemistry reactions. Until now mixed diesters of aziridine-2,3-dicarboxylic acid have only been prepared as *trans*-racemates starting from the mixed fumarates by the above mentioned diphenylsulfimine route.[17]

2. Results and discussion

2.1. Investigations on epimerization tendency

To investigate the epimerization tendency of the ring opening of the above mentioned heterocycles we carried out the reaction with NaN_3 in different solvents. The results are shown in Tables 1 and 3 (epoxide ring

Table 1. Ratios of *anti*-(2*R*,3*S*)- and *syn*-(*R*,*R*)-azido alcohols **6** obtained by the ring opening of epoxides **2** in protic solvents

Entry	Substrate	Solvent/reagents	Time (h)	*anti*/*syn*
1[29]	(*R*,*R*)-**2a**	MeOH/NH_4Cl	18	**1**/**1**
2	(*R*,*R*)-**2b**	$EtOH_{abs}$/NH_4Cl[c]	18[a]	1/0.7
3	(*R*,*R*)-**2b**	EtOH 98%/NH_4Cl[c]	18–24[a]	1/0.4–1[d]
4	(*R*,*R*)-**2b**	DMSO 85%/NH_4Cl[c]	20[a]	1/1.33
5	(*R*,*R*)-**2b**	EtOH 80%[e]	20[a]	1/0.26
6	(*R*,*R*)-**2b**	EtOH 85%[e]	20 (60%)[b]	1/0.17
7	(*R*,*R*)-**2b**	$EtOH_{abs.}$[e]	20 (10%)[b]	1/0.09
8	(*R*,*R*)-**2b**	DMF 80%[e]	0.25 (13%)[b]	1/0.014
			1 (43%)[b]	1/0.11
			24 (100%)[b]	1/0.46
9	(*R*,*R*)-**2b**	DMSO 80%[e]	20[a]	1/1
10	(*R*,*R*)-**2b**	DMSO 90%[e]	17[a]	1/0.4
11	(*R*,*R*)-**2b**	Acetone 85%[e]	20[a]	1/0.2

[a] Reaction time, during this time the epoxide was completely consumed unless otherwise indicated.
[b] % Conversion of epoxide to azido alcohol.
[c] 2–3 Equiv. NaN_3, 2–3 equiv. NH_4Cl.
[d] Three reactions performed.
[e] 2 Equiv. NaN_3, no NH_4Cl, aqueous work-up after the reaction time indicated.

Table 2. Ratios of *anti*-(2*R*,3*S*)- and *syn*-(*R*,*R*)-azido alcohols **6** obtained by the ring opening of cyclic sulfites **3** and sulfates **4** in protic solvents; amounts of tartrate **1** formed during ring opening

Entry	Substrate	Solvent/reagents	Time (h)	*anti*/*syn*	**6**/**1**[f]
1	(*R*,*R*)-**3b**	DMSO 80%/NH_4Cl[a]	18[c]	1/0	1/0.6
2	(*R*,*R*)-**3b**	EtOH 80%[b]	14[c]	–/–[e]	0/1
3	(*R*,*R*)-**3b**	$EtOH_{abs.}$[b]	14 (33%)[d]	1/0.8	1/0.26
4	(*R*,*R*)-**3b**	DMF 80%[b]	14[c]	1/0.63	1/0.34
5	(*R*,*R*)-**3b**	DMSO 96%[b]	24 (70%)[d]	1/0	1/0.1
			48 (100%)[d]	1/0	1/0.1
6	(*R*,*R*)-**3b**	DMSO 80%[b]	30[c]	1/0	1/0.26
7	(*R*,*R*)-**3b**	DMSO 80%[b]	3 (91%)[d]	1/0	1/0.29
8	(*R*,*R*)-**3d**	DMSO 80%[b]	24[c]	1/0	1/0.3
9	(*R*,*R*)-**3c**	Acetone 85%[b]	12[c]	1/0.4	1/0.4
10	(*R*,*R*)-**3d**	Acetone 85%[b]	12 (83%)[d]	1/0.25	1/0.47
11	(*R*,*R*)-**4c**	Acetone 85%[b]	2[c]	1/0	1/0

[a] 2 Equiv. NaN_3, 2 equiv. NH_4Cl.
[b] 2 Equiv. NaN_3, no NH_4Cl, aqueous work-up after the reaction time indicated.
[c] Reaction time, after this time complete consumption of the starting material unless otherwise indicated
[d] % Consumption of cyclic sulfite.
[e] Complete transformation to tartrate **1**.
[f] Determined by integration of the signal for the protons at the 2- and 3-position of **1**, s at 4.55 ppm, 2H.

Table 3. Ratios of *anti*-(2*R*,3*S*)- and *syn*-(*R*,*R*)-azido alcohols **6** obtained by the ring opening of epoxide (*R*,*R*)-**2b** in aprotic solvents

Entry	Solvent/reagents	Time	*anti*/*syn*
1	$DMF_{abs.}/NH_4Cl$[c]	20 h[a]	1/1.64
2	$DMF_{abs.}$[d]	0.25 h (2%)[b]	1/0
		1 h (10%)[b]	1/0.1
		24 h (84%)[b]	1/1.5
3	$DMSO_{abs.}$[d]	20 h[a]	1/2
4	$Acetone_{abs.}$[d]	20 h (0%)[b]	–/–[e]

[a] Reaction time, during this time the epoxide was completely consumed unless otherwise indicated.
[b] % Conversion of epoxide to azido alcohol.
[c] 2 Equiv. NaN_3, 2 equiv. NH_4Cl.
[d] 2 Equiv. NaN_3, no NH_4Cl, aqueous work-up after the reaction time indicated.
[e] No reaction.

opening) and Tables 2 and 4 (ring opening of cyclic sulfites and sulfate). The ratios of the diastereomeric *anti*-(2*R*,3*S*)- and *syn*-(2*R*,3*R*)-3-azido-2-hydroxysuccinates **6** have been determined by ^1H NMR spectra taken directly from the reaction mixtures after aqueous work-up and evaporation of the solvents using the integrals of the signals for the protons at the 2- or 3-position (d, $J=2.8$ Hz, at 4.62 ppm for the protons at the 2-position of the *anti*-epimer and at 4.73 ppm for the *syn*-epimer of the diethyl ester **6b**; 4.64 ppm (*anti*) and 4.75 ppm (*syn*) for the dimethyl esters **6a**; 4.57 ppm (*anti*) and 4.70 (*syn*) ppm for the dibenzyl esters **6c**; 4.39 ppm (*anti*) and 4.27 ppm (*syn*) for the protons in 3-position of the epimeric diallyl esters **6d**).

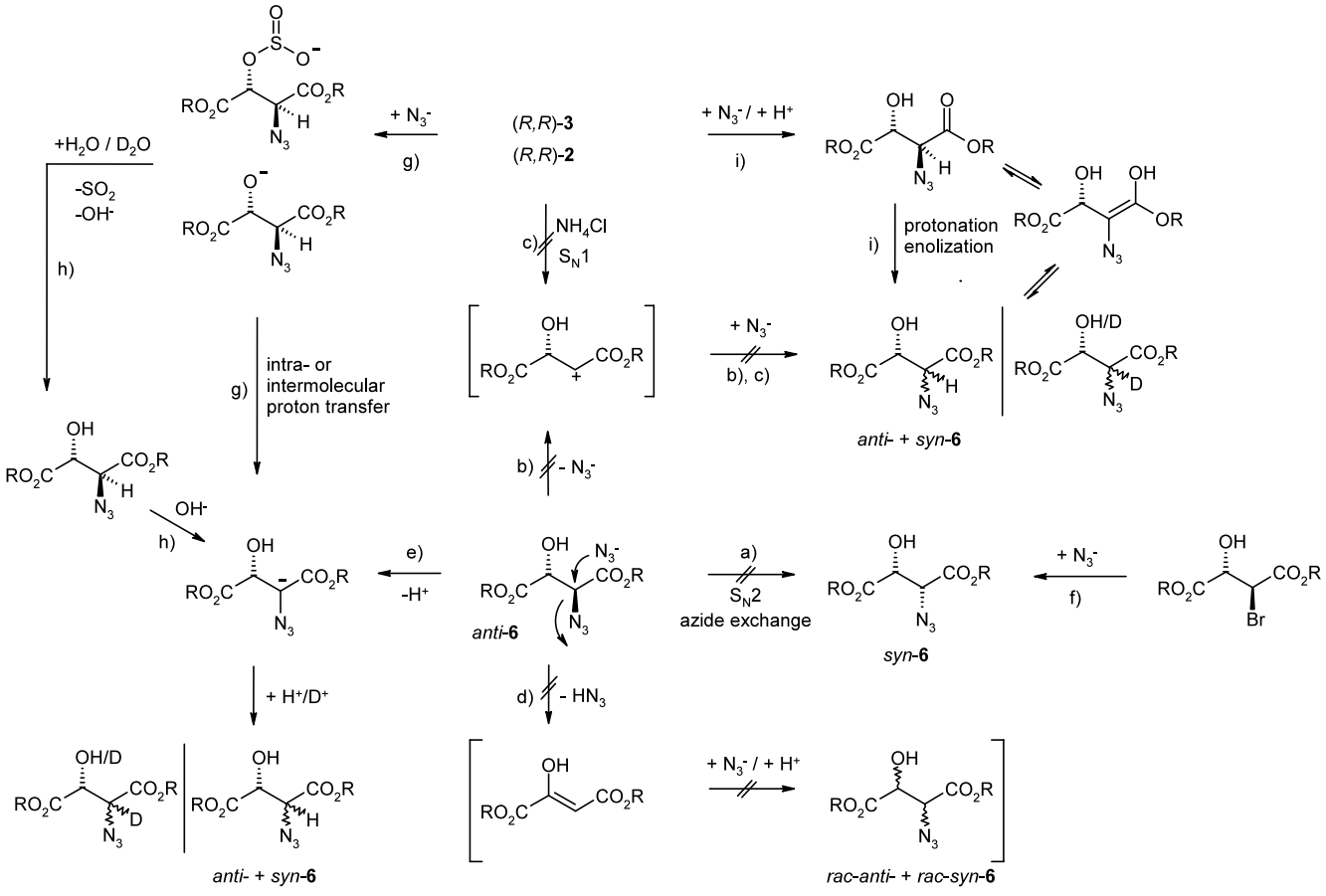
These results show clearly that the epoxide ring opening with NaN_3 is accompanied by epimerization independent from the solvent, the water content of the solvent, either neutral or acidic conditions and the azide concentration (Table 1, protic solvents, and Table 3, aprotic solvents). The best conditions to avoid epimerization during ring opening of cyclic sulfites are absolute DMF in the absence of NH_4Cl (Table 4, entries 2, 5, 6). The small amounts of *syn*-epimer found in some of these reactions is probably caused by traces of water, since an increased water content leads to a higher epimerization tendency (Table 2, entry 4). The use of absolute acetone or DMSO is also possible (Table 4, entries 3, 4, 7), but longer reaction times are needed for complete conversion to the azido alcohols in acetone with the work-up procedure in DMSO being more intricate than that in DMF. In contrast, no epimerization is seen using with the cyclic sulfate **4c** as the starting material in acetone 85% (Table 2, entry 11).

An S_N2 nucleophilic azide exchange (Scheme 2(a)) or slow release and subsequent fast addition of azide via a carbocation (Scheme 2(b)) have been proposed to be the most likely reasons for epimerization during epoxide ring opening.[29] However, a carbocation vicinal to the positively polarized ester carbon is supposed to be unfavourable. The same reason also excludes an S_N1 ring opening mechanism (Scheme 2(c)). S_N2, like an azide exchange at the azido alcohol step, (Scheme 2(a)) can be excluded because our own results showed that no epimerization takes place if the *anti*-azido alcohol **6b** is stirred with 2 equiv. of NaN_3 for 24 h in ethanol, $DMF_{abs.}$ and DMF 90%. Release of HN_3 to an enole (Scheme 2(d)) seems to be unlikely due to the fact that no racemization takes place at the 2-position. If NH_4Cl is used as proton source, the deprotonation step to a carbanion (Scheme 2(e)) cannot occur due to the slightly acidic conditions. If water or an aqueous work-up is used as proton source instead of NH_4Cl, the azide anion may of course act as a base in the aqueous solvents leading to deprotonation (Scheme 2(e)). However, in these reactions we could not observe any differences if the reaction mixture containing NaN_3 was extracted with an organic solvent for the isolation of the azido alcohol immediately after water addition or if it was stirred with water for 20 h.

Table 4. Ratios of *anti*-(2*R*,3*S*)- and *syn*-(*R*,*R*)-azido alcohols **6** obtained by ring opening of cyclic sulfites **3** in aprotic solvents; amounts of tartrate **1** formed during ring opening

Entry	Substrate	Solvent/reagents	Time (h)	*anti*/*syn*	**6**/**1**[f]
1	(*R*,*R*)-**3b**	$DMF_{abs.}/NH_4Cl$[a]	18[c]	1/0.43	1/0.16
2	(*R*,*R*)-**3b**	$DMF_{abs.}$[b]	14[c]	1/0–0.08[d]	1/0–0.09[d]
3	(*R*,*R*)-**3b**	$DMSO_{abs.}$[b]	30[c]	1/0.03	1/0.05
4	(*R*,*R*)-**3d**	$DMSO_{abs.}$[b]	24[c]	1/0.04	1/0.02
5	(*R*,*R*)-**3c**	$DMF_{abs.}$[b]	12[c]	1/0	1/0.09
6	(*R*,*R*)-**3d**	$DMF_{abs.}$[b]	12[c]	1/0.02[e]	1/0[e]
7	(*R*,*R*)-**3d**	$Acetone_{abs.}$[b]	7 days[c]	1/0.16	1/0

[a] 2 Equiv. NaN_3, 2 equiv. NH_4Cl.
[b] 2 Equiv. NaN_3, no NH_4Cl, aqueous work-up after the reaction time indicated.
[c] Reaction time, after this time, complete consumption of the starting material.
[d] Four reactions performed.
[e] Two reactions performed.
[f] Determined by the integration of the signal for the protons at the 2- and 3-position of **1**, s at 4.55 ppm, 2H.



Scheme 2. Possible pathways of the epimerization of *anti*-(*R*,*S*)-azido alcohols **6**.

The appearance of *syn*-(*R*,*R*)-azido alcohol (ca. 10%) using $TMSN_3$ (in $DMF_{abs.}$, ROH, DMAP) as an azide donor in the epoxide ring opening has been to shown to be caused by an impurity of the epoxide synthesis, namely (2*S*,3*S*)-2-bromo-3-hydroxysuccinate (Scheme 2(f)).[27] This impurity reacts in a S_N2 reaction with the azide donor giving small amounts of the diastereomeric *syn*-azido alcohol. This may well be the reason for partial epimerization with NaN_3. However, since the ring opening of the epoxide leads exclusively to the *anti*-diastereomer at the beginning of the reaction (Table 1, entry 8; Table 3, entry 2) and the amount of the *syn*-diastereomer increases during reaction (as also observed by Lecters et al.)[29] this impurity is only responsible for a small part of the epimerization product observed. Additionally, our own results showed that the reaction of (2*S*,3*S*)-2-bromo-3-hydroxysuccinate with NaN_3 leads to a mixture of *syn*- and *anti*-azido alcohols as well.

Particularly in the aprotic solvents DMF and DMSO, the percentage of the *syn*-epimer exceeds that of the *anti*-epimer during the epoxide ring opening (Table 3, entries 2 and 3). If no proton source is present the ring opening will, at first, lead to an alcoholate. This intermediate (Scheme 2(g)) can then act as a strong base. Inter- or intramolecular proton transfer leads to a resonance stabilized carbanion the protonation of which produces the *syn*- and *anti*-azido alcohol. The amount of alcoholate increased with reaction time, which explains the high increase of *syn*-epimer at the end of the reaction. This pathway to epimerization is not possible via the ring opening of cyclic sulfites due to the much weaker basicity of the β-sulfite produced as the intermediate. The intermediate β-sulfate produced by the ring opening of the cyclic sulfate **4c** was insoluble in the reaction media and as a result was no longer available for subsequent reactions.

According to this hypothesis a strong base added to the *anti*-azido alcohol should lead to epimerization. Thus, we performed assays with azido alcohol *anti*-**6b** with equimolar amounts of sodium ethanolate and did indeed observe total epimerization.

If water-containing solvents without NH_4Cl were used, protonation of the intermediate β-sulfite and alcoholate by water led to the elimination of SO_2 and formation of azido alcohol (Scheme 2(h)). Hydroxide ions produced by this pathway also led to deprotonation at the 3-position of the azido alcohol (Scheme 2(h)).

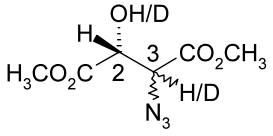
To prove that the proton at the 3-position of the azido alcohol was acidic enough to be deprotonated we performed ring opening assays in DMF/D_2O, DMSO/D_2O and acetone/D_2O with the dimethyl esters (*R*,*R*)-**3a** (Table 6, entries 2, 3, 4) and (*R*,*R*)-**2a** (Table 5, entries 3, 4, 5). The dimethyl esters were chosen to facilitate integration of the signals for the protons at the 3-position of *syn*- and *anti*-**6a**. The ^1H NMR spectra taken after ring opening of (*R*,*R*)-**3a** showed that after 19 h in DMF/D_2O, 8% of the protons in 3-position of both the *syn*- and *anti*-epimer of **6a** were exchanged against deuterium (Table 6, entry 2). After 2 days 37% of the protons had exchanged. Similar results were also obtained in acetone/D_2O (Table 6, entry 4). In DMSO/D_2O, only 2% exchange was detected (Table 6, entry 3). Analogous results were obtained with the epoxide **2a** (Table 5: 59% exchange in DMF/D_2O, 45% in DMSO/D_2O, and 18% in acetone/D_2O) This was consistent with the epimerization rates observed for both the epoxides and the cyclic sulfites in these solvents (Tables 5 and 6). This high acidity of the proton at the 3-position, mainly caused by the second ester group, also explained the differences to oxirane-2-carboxylic acid derivatives, which did not show any epimerization.[40]

If NH_4Cl was used as the proton source protonation and the subsequent deprotonation via an enole at the azido alcohol step (Scheme 2(i)) could be considered as the reasons for epimerization. To investigate the epimerization mechanism under slightly acidic conditions we studied the reaction of *anti*-(3*R*,2*S*)-**6b** with NaN_3 and NH_4Cl in different solvents and indeed observed epimerization to 18–20% *syn*-**6b** within 72 h. In addition, we also performed ring opening assays with (*R*,*R*)-**3a** (Table 6, entries 1 and 2) and (*R*,*R*)-**2a** (Table 5, entry 1) and used DCl instead of NH_4Cl. Again, we found an exchange of the protons at the 3-position of both the *syn*- and the *anti*-epimer against deuterium proving pathway (i) (Scheme 2(i)).

In summary, the epimerization observed in all cases, either acidic or basic, is due to the relatively high acidity of the proton at the 3-position of the azido alcohols.

The amount of tartrate **1** formed during the ring opening reactions of the cyclic sulfites also depends on the solvent (Tables 2 and 4). In EtOH/water, **3b** is quanti-

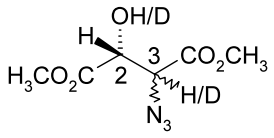
Table 5. Ratios of H-2/H-3 of azido alcohol **6a** after reactions of (*R*,*R*)-**2a** in D_2O- or DCl-containing solvents



Entry	Solvent/reagents	Time (h)	*anti*/*syn*	H-2/H-3[e]	H→D[f] (%)
1	$DMF_{abs.}$/DCl[a]	18 (28%)[d]	1/0.12	1/0.92	8
2	$MeOD_{d4}$/DCl[a]	18 (30%)[d]	1/0.12	1/0.85	15
3	DMF/D_2O 80%[b]	19[c]	1/0.33	1/0.41	59
4	DMSO/D_2O 80%[b]	19 (90%)[d]	1/0.25	1/0.55	45
5	Acetone/D_2O 80%[b]	19 (88%)[d]	1/0.09	1/0.82	18

[a] 2 Equiv. NaN_3, 2 equiv. DCl (solution in D_2O).
[b] 2 Equiv. NaN_3, aqueous work-up after the reaction time indicated.
[c] Reaction time, during this time the epoxide was completely consumed unless otherwise indicated.
[d] % Conversion of epoxide to azido alcohol.
[e] Determined by the integration of the signals for the protons at the 2- and 3-position of *syn*- and *anti*-**6a**, d at 4.75 (*syn*-H-2), 4.64 (*anti*-H-2), 4.33 (*anti*-H-3), 4.21 (*syn*-H-3).
[f] % Proton deuterium exchange at the 3-position.

Table 6. Ratios of H-2/H-3 of azido alcohol **6a** after reactions of (*R*,*R*)-**3a** in either D_2O- or DCl-containing solvents; amounts of tartrate **1** formed during ring opening



Entry	Solvent/reagents	t[a] (h)	*anti*/*syn*	**6**/**1**[d]	H-2/H-3[e]	H→D[f] (%)
1	$DMF_{abs.}/DCl$[b]	19	1/0.16	1/0.6	1/0.89	11
2	DMF/D_2O 80%[c]	19	1/0.9	1/0.36	1/0.92	8
		2 days	1/0.94	1/0.55	1/0.63	37
3	$DMSO/D_2O$ 80%[c]	19	1/0.1	1/0.1	1/0.98	2
4	$Acetone/D_2O$ 80%[c]	20	1/0.11	1/1	1/0.92	8
		120	1/0.28	1/0.8	1/0.8	20

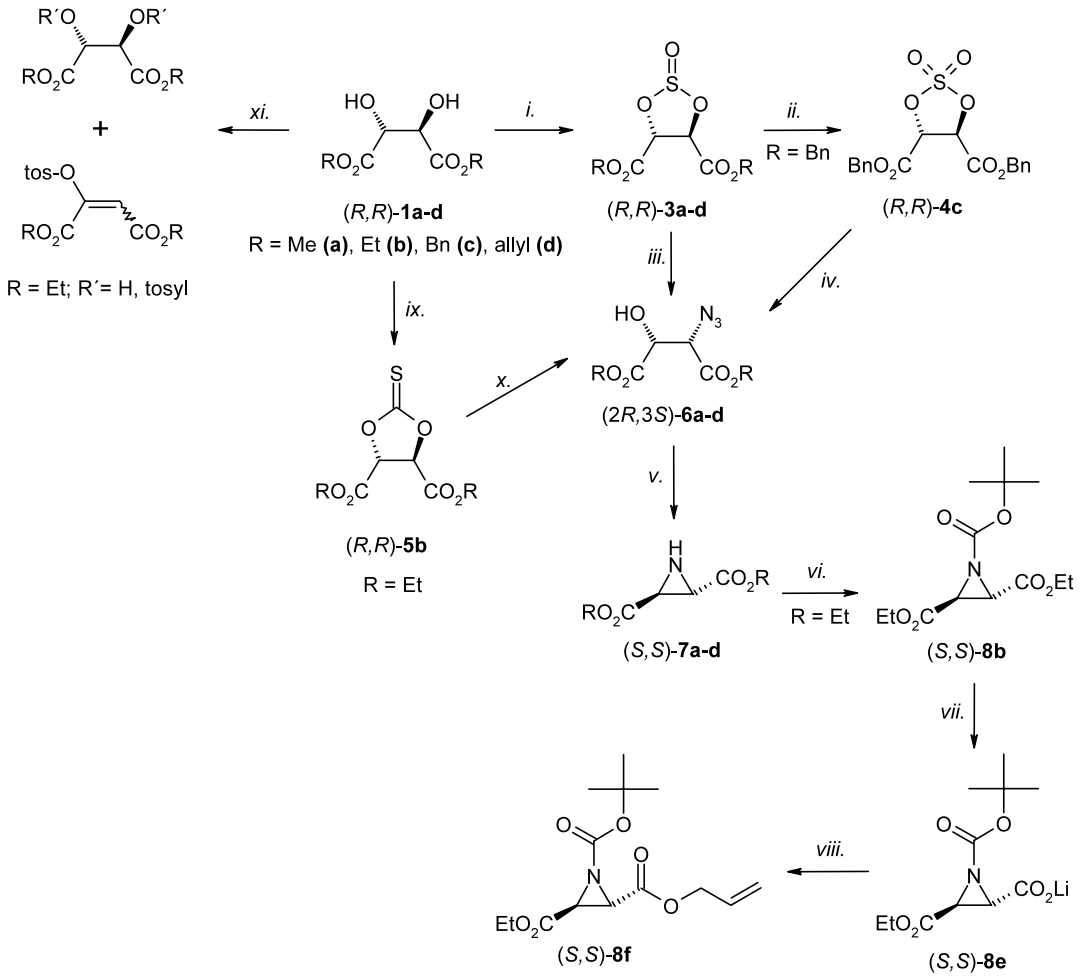
[a] Reaction time, after this time complete consumption of the starting material.
[b] 2 Equiv. NaN_3, 2 equiv. DCl (solution in D_2O).
[c] 2 Equiv. NaN_3, aqueous work-up after the reaction time indicated.
[d] Determined by the integration of the signal for the protons at the 2- and 3-position of **1**, s at 4.55 ppm, 2H.
[e] Determined by the integration of the signals for the protons at the 2- and 3-position of *syn*- and *anti*-**6a**, d at 4.75 (*syn*-H-2), 4.64 (*anti*-H-2), 4.33 (*anti*-H-3), 4.21 (*syn*-H-3).
[f] % Proton deuterium exchange at the 3-position.

tatively converted to tartrate (Table 2, entry 2). In the protic solvent EtOH (Table 2, entry 3) in either DMF/water (Table 2, entry 4) or DMSO/water (Table 2, entries 5, 6, 7, 8), the amount of tartrate formed is much higher than that in absolute DMF or DMSO (Table 4, entries 2–6) indicating base- or acid-mediated sulfite hydrolysis. Water-mediated hydrolysis of the cyclic esters only caused small amounts of tartrate since the cyclic sulfite **3b** was only partially hydrolysed to tartrate **1b** (ca. 7%) in a 20 h reaction in EtOH/water without NaN_3 and NH_4Cl.

2.2. Improved stereoselective synthesis of dimethyl, diethyl, dibenzyl and diallyl aziridine-2,3-dicarboxylates

The improved synthesis of both single *trans*-enantiomers of dimethyl **7a**, diethyl **7b**, dibenzyl **7c** and dially **7d** aziridine-2,3-dicarboxylates starts from the reversed configured tartrates **1a**–**d** (Scheme 3), which are prepared in high yields from tartaric acid, the respective alcohols, and *p*-toluene sulfonic acid. The different ester moieties were introduced on the tartrate step because of the transesterification on the epoxide or sulfite step being either very difficult or impossible.[46] Since the ring opening reactions of the epoxides with NaN_3 lead to epimerization in all cases we preferred, the sulfite route. The intermediate 2-oxo-1,3,2-dioxathiolanes **3a**–**d** were obtained with thionyl chloride in pyridine or with catalytic amounts of DMF (Scheme 3(*i*)). Since the work-up procedure was easier with DMF, the latter procedure was preferred. Ring opening of the cyclic sulfites **3a**–**d** with NaN_3 in $DMF_{abs.}$ yielded exclusively the *anti*-azido alcohols **6a**–**d**, only seldom accompanied by small amounts of *syn*-epimer (see Table 2) (Scheme 3(*iii*)). In the case of the dibenzyl esters, the oxidation of the sulfite to the sulfate **4c** with $NaIO_4/RuCl_3$, prior to ring opening, led to higher yields of the azido alcohol 6c (Scheme 3(*ii*, *iv*)). The initially formed β-sulfate had to be hydrolysed with H_2SO_4.

Another possible pathway to the azido alcohols **6** was the introduction and subsequent substitution of a tosylate as a good leaving group for the azide exchange (Scheme 3(*xi*)). However, the reaction of (*R*,*R*)-tartrate **1b** with tosyl chloride and pyridine or diisopropylethyl amine led to a mixture of the elimination product, tartrate, mono- and ditosylate, the separation of the latter by column chromatography being rather difficult. In addition, the synthesis of the azido alcohols was possible by starting from the cyclic thionocarbonate **5b**, which could be obtained from tartrate **1b** and thiophosgene (Scheme 3(*ix*)). This intermediate proved to be more reactive than the cyclic carbonate[35] and only slightly less reactive than the cyclic sulfate.[36] No further hydrolysis of the initially formed β-thiocarbonate was required. However, due to the toxicity of thiophosgene (which could be replaced by thiocarbonyldiimidazole),[41] we preferred the sulfite and sulfate route. The last step of the aziridine synthesis is the well known ring closure with triphenylphosphine in DMF (Scheme 3(*v*)). Attempts to use DMSO as a solvent for the ring closure led to quantitative formation of enamines. To improve the yields of the dibenzyl and diallyl aziridine-2,3-dicarboxylates **7c**,**d** it was necessary to add catalytic amounts of acetic acid after addition of PPh_3. This is proposed to catalyze the transformation of the 1,3,2-oxazaphospholidines and 2-hydroxy iminophosphoranes, which are valence tautomeric intermediates of the aziridine ring closure reactions.[42] The reaction mixture should also be heated immediately after addition of PPh_3 with longer stirring at rt to be avoided in the case of the dibenzyl and diallyl derivatives.



Scheme 3. Synthesis of symmetric and mixed diesters of aziridine-2,3-dicarboxylic acid. *Reagents and conditions*: *i*. 1.1. equiv. $SOCl_2$, $DMF_{cat.}$, 0.5 h 0°C, 1 h rt, 1 h 50°C, quant.; *ii*. $RuCl_3{\cdot}H_2O$, $NaIO_4$, H_3CCN 80%, 69%; *iii*. 1. 2.0 equiv. NaN_3, $DMF_{abs.}$, 20 h rt, 2. H_2O, CH_2Cl_2 0.25–20 h, 70–80%; *iv*. 1. NaN_3, acetone 85%, 2 h, 2. H_2SO_4, diethyl ether, 6 h, 82%; *v*. 1.05 equiv. PPh_3, $DMF_{abs.}$, 0.5 h 0°C, 1.5 h rt, 4–6 h, 90°C, 70–75%; *vi*. 3.0 equiv. $(BOC)_2O$, 1.0 equiv. DMAP, $CH_2Cl_{2abs.}$, 2 h 0°C, 2 days rt, 31%; *vii*. 0.95 equiv. $LiOH{\cdot}H_2O$, $EtOH_{abs.}$, 1 h 0°C, 3 days rt; *viii*. 2.0 equiv. allyl iodide, 2.0 equiv. $AgNO_3$, $H_3CCN_{abs.}$, 12-c-4, 2 days rt, 44%; *ix*. $CSCl_2$, pyr, DMAP, 82%; *x*. NaN_3, DMF, 48 h rt, 74%; *xi*.0.95 equiv. *p*-TS-Cl, 1.2 equiv. pyr, 2 h 0°C, 20 h rt, 20 h 40°C.

2.3. Synthesis of mixed aziridine-2,3-dicarboxylic diesters

Mixed diesters of aziridine-2,3-dicarboxylic acid have until now only been prepared as *trans*-racemates.[17] The transesterification of one of the ester groups of the diethyl tartrate needs protection of the diol groups as acetal e.g. with benzaldehyde or acetone. The monohydrolysis of the cyclic sulfite followed by the subsequent esterification led to a mixture of the elimination product, diethyl and monoethyl tartrate.[46] Thus we decided to introduce the second ester via the transesterification of diethyl aziridine-2,3-dicarboxylate (Scheme 3(*vi–viii*)). Esterification of the *N*-unprotected half ester, which can be obtained by hydrolysis with LiOH in EtOH, to the mixed esters failed using mild esterification procedures (DCC, DMAP, ROH; DPPA, TEA, ROH; Cbz-Cl, DMAP, TEA; tos-Cl, pyridine, ROH; BOOPCl, TEA, ROH). The DPPA procedure led to the highest with 20% of the desired mixed diester. Thus we introduced BOC as an *N*-protecting group to allow alkylation of the free acid group with the respective alkyl halogenide (Scheme 3(*vi*)). This reaction also led to alkylation of the aziridine-nitrogen if the unprotected half ester was used.[17] The mono-Li-salt **8e** resulting from hydrolysis of BOC-protected aziridine **8b** was esterified with allyl iodide/$AgNO_3$ to yield the allyl ethyl ester **8f** as the first example of an enantiomerically pure *trans*-configured mixed aziridine-2,3-dicarboxylic diester (Scheme 3(*vii*, *viii*)). Addition of crown ether (12-crown-4) increased the yield of this reaction. Deprotection of this mixed diester was easily and quantitatively possible with TFA/CH_2Cl_2.

3. Summary

The epimerization tendency of azido alcohols obtained by nucleophilic ring opening of epoxides or epoxide equivalent heterocycles with sodium azide has not been studied systematically so far. We have clarified that it depends mainly on the leaving group produced during

ring opening (alcoholate or β-sulfite) and the protic property of the solvent. Protic (ROH) or water containing solvents led to significantly higher amounts of *syn*-epimer in the case of the cyclic sulfite with the epoxid converted to both epimeric azido alcohols in all solvents used. Without NH_4Cl base-mediated carbanion formation as a result of the high acidity of the proton at the 3-position of the azido alcohol was proven by exchange against deuterium in assays with D_2O containing solvents. This also proved to be the reason for epimerization under slightly acidic conditions since ring opening with NaN_3/DCl led to proton deuterium exchange at the 3-position as well.

The most favourable pathway to the pure *anti*-azido alcohols is ring opening of the cyclic sulfite or sulfate with NaN_3 and $DMF_{abs.}$ as solvent. With this reaction we were able to optimise the yields of both *trans*-enantiomers of dimethyl, diethyl, dibenzyl and diallyl esters of aziridine-2,3-dicarboxylic acid which could be obtained by subsequent ring closure of the azido alcohols with PPh_3 under acid catalysis. The mixed ethyl allyl ester of this diacid could be obtained as a single enantiomer and diastereomer by transesterification after BOC-protection of the aziridine nitrogen.

4. Experimental

All solvents were purified by distillation and dried by standard procedures. Chemicals were reagent grade and were used after standard purification. Physico-chemical data and spectra were determined with the following apparatus: melting points on a Büchi apparatus type 510, values uncorrected; IR spectra with a Perkin–Elmer type 681 spectrometer; optical rotation values with a Perkin–Elmer polarimeter type 241; NMR spectra with a Bruker Avance 400 spectrometer, mass spectra on a Varian MAT-CH 7 and a Finnigan MAT 8200 spectrometer. Analytical TLC was performed on Merck aluminium sheets (silica gel 60 F_{254}). Compounds that were not visualized by UV light were detected by spraying with Ehrlich's reagent (1 g *p*-dimethylamino benzaldehyde, 25 mL HCl conc., 75 mL MeOH) followed by heating. Preparative flash column chromatography was performed using silica gel 60, 40–63 μm, from Merck. Preparative hydrostatic column chromatography was performed using silica gel 60, 63–200 μm, from Merck. ^{1}H NMR chemical shifts are reported in ppm relative to the $CHCl_3$ peak at $\delta = 7.26$ with $CDCl_3$ as the solvent and the DMSO peak ($\delta = 2.49$) with DMSO-d_6 as the solvent. ^{13}C NMR chemical shifts are reported in ppm relative to the $CHCl_3$ peak ($\delta = 77.00$) with $CDCl_3$ as the solvent. All ^{1}H NMR assignments were supported by homonuclear decoupling experiments or by 2-D COSY experiments. All ^{13}C NMR assignments were supported by 2-D HETCOR experiments. Coupling constants (J) are reported in hertz.

4.1. Epimerization assays

The assays were performed with 1 mmol epoxide, cyclic sulfite, and cyclic sulfate in 1 mL of the solvent and with the equivalents of NaN_3 and NH_4Cl indicated in the tables.

4.2. Tartrates 1

The tartrates (*R*,*R*)-**1a**, (*S*,*S*)-**1a**, (*R*,*R*)-**1b** and (*S*,*S*)-**1b** are commercially available. The tartrates (*R*,*R*)-**1c** and (*S*,*S*)-**1c** were prepared according to literature, with their analytical data corresponding to literature values.[43]

4.3. Procedure for the synthesis of tartrates 1d

Allyl alcohol (23 g, 400 mmol) and *p*-toluene sulfonic acid (1.8 g, 10% equiv.) were added to a suspension of (*R*,*R*)- and (*S*,*S*)-tartaric acid (15.0 g, 100 mmol) in 100 mL toluene. The mixture was refluxed in a flask equipped with a Dean–Stark apparatus for 10 h until water evolution ceased. Toluene was removed in vacuo, the residue diluted with 100 mL diethyl ether, and extracted with sat. $NaHCO_3$. After drying over Na_2SO_4 the solvent was removed.

4.3.1. (*R*,*R*)-Diallyl tartrate (*R*,*R*)-1d. 90% as a colourless oil; TLC cyclohexane:ethylacetate 3:1, $R_f = 0.26$; $[\alpha]_D^{20} = +18.4$ (*c* 1.0, MeOH); IR (film): $\tilde{\nu} = 3449$ (m, br), 3088 (s), 2947 (m), 1738 (s, C=O), 16541 (s), 1368 (m), 1278 (m), 1189 (m), 1128 (s), 1082 (s), 986 (m), 926 (m), 820 (m), 711 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400.13 MHz): $\delta = 3.04$ (br s, 2H, 2 OH), 4.62 (s, 2H, 2 CH), 4.75 (dd, 4H, -C*H*$_2$-CH=, $J = 4.55$ Hz, $J = 1.27$ Hz), 5.30 (dd, 2H, C*H*$_2$=CH-, $J = 1.01$ Hz, $J_{cis} = 10.61$ Hz), 5.38 (dd, 2H, C*H*$_2$=CH-, $J = 1.27$ Hz, $J_{trans} = 17.18$ Hz), 5.89–6.01 (m, 2H, 2 CH$_2$=C*H*-) ppm; ^{13}C NMR ($CDCl_3$, 100.62 MHz): $\delta = 67.21$ (2 -CH-*C*H$_2$-), 72.49 (2 *C*H), 119.68 (2 *C*H$_2$=CH-), 131.52 (2 CH$_2$=*C*H-), 171.60 (2 C=O) ppm; $C_{10}H_{14}O_6$ (230.21), calcd C, 52.17; H, 6.13; found: C, 52.25; H, 6.07%.

4.3.2. (*S*,*S*)-Diallyl tartrate (*S*,*S*)-1d. 90% as a colourless oil with the same IR, ^{1}H NMR, and ^{13}C NMR data as (*R*,*R*)-**1d**; $[\alpha]_D^{20} = -18.9$ (*c* 1.0, MeOH); $C_{10}H_{14}O_6$ (230.21), calcd C, 52.17; H, 6.13; found: C, 51.99; H, 6.18%.

4.4. Epoxides 2

The epoxides **(*R*,*R*)-2a** and **(*R*,*R*)-2b** were prepared by well known methods.[26–28,32] All analytical data corresponds to literature values.

4.5. Cyclic sulfites 3

The analytical data of the cyclic sulfites (*R*,*R*)-**3a**, (*S*,*S*)-**3a**, (*R*,*R*)-**3b**, and (*R*,*R*)-**3c** correspond to the data described in the literature.[31,33,37,44]

4.6. General procedure for the synthesis of cyclic sulfites 3

$SOCl_2$ (3.90 mL, 50 mmol) was added dropwise at 0°C to a solution of tartrate (43 mmol) **1** in CH_2Cl_2 (20 mL), followed by addition of a catalytic amount of DMF (10 drops). In the case of liquid tartrates no CH_2Cl_2 was used. The reaction mixture was allowed to warm up to

rt and then heated at 50°C for 30 min. The excess of $SOCl_2$ and evolved HCl were removed with a fine N_2 stream. Residual $SOCl_2$ was removed in vacuo (50°C, 25 mbar).

4.6.1. (*S*,*S*)-Diethyl-1,3,2-dioxathiolane-2-oxo-4,5-dicarboxylate (*S*,*S*)-3b. 95% as a colourless liquid; $[\alpha]_D^{20}=+186.5$ (*c* 2.28, MeOH); IR (film): $\tilde{\nu}=3520$ (m, br), 3000 (s), 2960 (s), 1745 (s, br, C=O), 1685 (m), 1645 (m), 1475 (m), 1450 (m), 1375 (s), 1220 (s, br), 1060 (s, S=O), 1020 (s), 940 (m), 855 (m), 825 (m), 730 (s, br) cm^{-1}; ^1H NMR ($CDCl_3$, 400.13 MHz): $\delta=1.35$ (t, 6H, 2 CH_3 $J=7.0$ Hz), 4.30 (q, 4H, 2 CH_3, $J=7.0$ Hz), 5.22 (d, 1H, CH, $J=4.3$ Hz), 5.69 (d, 1H, CH, $J=4.3$ Hz) ppm; $C_8H_{12}O_7S$ (252.24), calcd C, 38.09; H, 4.80; found: C, 38.17; H, 4.93%.

4.6.2. (*S*,*S*)-Dibenzyl-1,3,2-dioxathiolane-2-oxo-4,5-dicarboxylate (*S*,*S*)-3c. 95% as a yellowish oily liquid; TLC cyclohexane:ethylacetate 3:1, $R_f=0.41$; $[\alpha]_D^{20}=+71.8$ (*c* 1.16, MeOH); IR (film): $\tilde{\nu}=3495$ (m, br), 3034 (s), 2959 (s, C-H), 1742 (s, br, C=O), 1661 (m), 1496 (m), 1454 (m), 1382 (m), 1261 (s), 1209 (s, br), 1058 (s, S=O), 1003 (s), 960 (m), 792 (m), 735 (m), 695 (s, br) cm^{-1}; ^1H NMR ($CDCl_3$, 400.13 MHz): $\delta=5.17$ (d, 4 H, 2 CH_2), 5.18 (d, 1H, 2 CH_2, $J=4.3$ Hz), 5.68 (d, 1H, CH, $J=4.3$ Hz), 7.25–7.32 (m, 10H, 2 C_6H_5) ppm; ^{13}C NMR ($CDCl_3$, 100.62 MHz): $\delta=68.98$ (CH_2), 69.05 (CH_2), 79.65 (*C*H), 80.17 (*C*H), 129.10 (C_6H_5), 134.60 (q*C*), 134.73 (qC), 166.62 (C=O), 166.74 (C=O) ppm; $C_{18}H_{16}O_7S$ (376.38), calcd C, 57.44; H, 4.28; found: C, 57.56; H, 4.35.

4.6.3. (*R*,*R*)-Diallyl-1,3,2-dioxathiolane-2-oxo-4,5-dicarboxylate (*R*,*R*)-3d. 95% as a yellowish liquid; TLC cyclohexane:ethylacetate 3:1, $R_f=0.42$; $[\alpha]_D^{20}=-173.5$ (*c* 1.07, MeOH); IR (film): $\tilde{\nu}=3501$ (m, br), 3090 (s), 2958 (s), 1742 (s, br, C=O), 1647 (m), 1450 (m), 1369 (m), 1275 (m), 1203 (m), 1056 (s, S=O), 990 (m), 937 (m), 804 (m), 733 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 400.13 MHz): $\delta=4.75$ (dt, 2H, -CH_2-CH=, $J=6.07$ Hz), 4.76 (dt, 2H, -CH_2-CH=, $J=6.07$ Hz), 5.30 (d, 1H, C*H*, $J=4.29$ Hz), 5.31 (dd, 1H, CH_2=CH-, $J=1.26$ Hz, $J_{cis}=10.36$ Hz), 5.33 (dd, 1H, CH_2=CH-, $J=1.01$ Hz, $J_{cis}=10.36$ Hz), 5.38 (dd, 1H, CH_2=CH-, $J=1.26$ Hz, $J_{trans}=17.18$ Hz), 5.40 (dd, 1H, CH_2=CH-, $J=1.26$ Hz, $J_{trans}=17.18$ Hz), 5.75 (d, 1H, C*H*, $J=4.29$ Hz), 5.88–5.99 (m, 2H, -C*H*=CH$_2$) ppm; ^{13}C NMR ($CDCl_3$, 100.62 MHz): $\delta=67.78$ (CH_2-CH), 67.82 (CH_2-CH), 79.59 (*C*H), 80.15 (*C*H), 120.21 (CH_2=CH), 120.54 (CH_2=CH), 130.85 (CH_2=*C*H), 130.98 (CH_2=*C*H), 166.47 (C=O), 166.57 (C=O) ppm; $C_{10}H_{12}O_7S$ (276.26), calcd C, 43.48; H, 4.38; found: C, 43.59; H, 4.42.

4.6.4. (*S*,*S*)-Diallyl-1,3,2-dioxathiolane-2-oxo-4,5-dicarboxylate (*S*,*S*)-3d. 95% as a yellowish liquid with the same IR, ^1H NMR and ^{13}C NMR data as (*R*,*R*)-**3d**; $[\alpha]_D^{20}=+167.0$ (*c* 1.12 in MeOH); $C_{10}H_{12}O_7S$ (276.26), calcd C, 43.48; H, 4.38; found: C, 43.51; H, 4.35.

4.7. Cyclic sulfates 4c

The dibenzyl-1,3,2-dioxathiolane-2,2-dioxo-4,5-dicarboxylate (*R*,*R*)-**4c** was synthesized according to literature.[37] The analytical data corresponds to literature values.

4.7.1. (*S*,*S*)-Dibenzyl-1,3,2-dioxathiolane-2,2-dioxo-4,5-dicarboxylate (*S*,*S*)-4c. A solution of (*S*,*S*)-**3c** (15 g, 40.0 mmol)in acetonitrile/water (1:1) was treated with $NaIO_4$ (9.6 g, 45.0 mmol) and catalytic amounts of $RuCl_3 \cdot 3\ H_2O$. The mixture was stirred for 1 h at rt and then extracted with 3×100 mL diethyl ether. The organic layer was washed with sat. $NaHCO_3$, 20% $Na_2S_2O_3$, water, and brine. After evaporation of the solvent the crude product was used without further purification. Yield: 73% as colourless oily liquid; TLC cyclohexane:ethyl acetate 3:1, $R_f=0.45$; $[\alpha]_D^{20}=+161.9$ (*c* 1.02, MeOH); ^1H NMR ($CDCl_3$, 400.13 MHz, TMS): $\delta=5.29$ (s, 4H, 2 CH_2), 5.45 (d, 1H, CH, $J=4.3$ Hz), 7.31–7.39 (m, 10H, 2 C_6H_5) ppm; ^{13}C NMR ($CDCl_3$, 100.62 MHz): $\delta=69.20$ (2×CH_2), 76.94 (2×*C*H), 128.90 (C_6H_5), 133.71 (q.*C*), 164.11 (C=O) ppm; $C_{18}H_{16}O_8S$ (392.38).

4.8. Cyclic thionocarbonate (*R*,*R*)-5b

The cyclic thionocarbonate (*R*,*R*)-**5b** was synthesized according to Ref. 36. The analytical data corresponds to the literature values.

4.9. Azido alcohols 6

The analytical data of the azido alcohols (2*R*,3*S*)-**6a**, (2*S*,3*R*)-**6a**, (2*R*,3*S*)-**6b**, (2*S*,3*R*)-**6b,** and (2*R*,3*S*)-**6c** corresponds to the data described in literature.[30,37,44,45]

4.10. General procedure for the synthesis of azido alcohols 6a,b,d from cyclic sulfites

NaN_3 (6.5 g, 100 mmol) was added to a solution of 36 mmol of the appropriate cyclic sulfite **3** in $DMF_{abs.}$ (20 mL) and stirred for 24 h. The reaction was followed by TLC. After completion of the reaction, CH_2Cl_2 (50 mL) and water (30 mL) were added and the mixture stirred for 2 h. The aqueous phase was extracted with CH_2Cl_2 and the combined organic phases washed with water and dried with Na_2SO_4. The solvent was removed in vacuo.

4.11. General procedure for the synthesis of azido alcohols 6c from cyclic sulfates 4c

Cyclic sulfate (25.0 mmol) was dissolved in acetone/water mixture (4:1) at which point NaN_3 (3.2 g, 2 equiv.; 50.0 mmol) was added. The reaction mixture was stirred for 1 h and the white crystalline precipitate filtered off and washed excessively with diethyl ether (100 mL) yielding the ring open β-sulfate. Yield: 81% as a colourless solid; ^1H NMR (DMSO-d_6, 400.13 MHz): $\delta=4.97$ (d, 1H, CH, $J=4.0$ Hz), 4.99–5.09 (m, 4H, 2 CH_2), 5.10 (d, 1H, CH, $J=4.0$ Hz), 7.26–7.38 (m, 10H, 2 C_6H_5) ppm; ^{13}C NMR (DMSO-d_6, 100.62 MHz): $\delta=63.06$ (*C*H), 66.40 (CH_2), 66.98 (CH_2) 74.10 (*C*H), 128.09 (C_6H_5), 135.44 (q.*C*), 135.67 (q.*C*), 167.11 (C=O), 167.64 (C=O) ppm.

The β-sulfate was hydrolysed subsequently with 20% H_2SO_4 (100 mL) and diethyl ether (100 mL) for 4 h. The organic layer was dried and evaporated in vacuo.

4.11.1. (2*S*,3*R*)-Dibenzyl-3-azido-2-hydroxy succinate (2*S*,3*R*)-6c. 82% as colourless crystals; mp: 33–34°C; TLC cyclohexane:ethyl acetate 3:1, $R_f=0.45$; $[\alpha]_D^{20}=-37.1$ (*c* 1.02, MeOH); IR (film): $\tilde{\nu}=3412$ (m, br), 3062 (s), 3034 (s), 2105 (s), 1747 (s, br, C=O), 1713 (s), 1498 (m), 1456 (m), 1384 (m), 1294 (m), 1268 (m), 1099 (s), 1019 (m), 969 (m), 870 (m), 743 (m), 694 (s, br) cm^{-1}; ^1H NMR ($CDCl_3$, 400.13 MHz): $\delta=3.30$ (s, 1H, O*H*), 4.26 (d, 1H, C*H*, $J=2.8$ Hz), 4.57 (d, 1H, CH, $J=2.8$ Hz), 4.93 (t, 2H, CH_2), 4.98 (t, 2H, CH_2), 7.25–7.32 (m, 10H, 2 C_6H_5) ppm; ^{13}C NMR ($CDCl_3$, 100.62 MHz): $\delta=64.84$ (*C*H), 68.52 (*C*H_2), 68.79 (*C*H_2), 72,58 (*C*H), 129.06 (C_6H_5), 134.82 (q*C*), 134.98 (qC), 167.30 (C=O), 171.03 (C=O) ppm; $C_{18}H_{17}N_3O_5$ (355.34), calcd C, 60.84; H, 4.82; N, 11.83; found: C, 60.96; H, 4.78; N, 11.80%.

4.11.2. (2*R*,3*S*)-Diallyl-3-azido-2-hydroxy succinate (2*R*,3*S*)-6d. 60% as a colourless oily liquid; TLC cyclohexane:ethyl acetate 3:1, $R_f=0.38$; $[\alpha]_D^{20}=+30.4$ (*c* 2.005, MeOH); IR (film): $\tilde{\nu}=3412$ (m, br), 3062 (s), 3034 (s),2105 (s), 1747 (s, br, C=O), 1713 (s), 1498 (m), 1456 (m), 1384 (m), 1294 (m), 1268 (m), 1099 (s), 1019 (m), 969 (m), 870 (m), 743 (m), 694 (s, br) cm^{-1}; ^1H NMR ($CDCl_3$, 400.13 MHz): $\delta=3.33$ (s, 1H, O*H*), 4.39 (d, 1H, C*H*, $J=2.8$ Hz), 4.71 (d, 1H, CH, $J=2.8$ Hz), 5.32 (dd, 2H, -CH=CH_2, $J=0.76$ Hz, $J_{cis}=10.61$ Hz), 5.38 (dd, 2H, -CH=CH_2, $J=1.27$ Hz, $J_{trans}=17.18$ Hz), 5.86–5.99 (m, 2H, 2 C*H*=CH_2) ppm; ^{13}C NMR ($CDCl_3$, 100.62 MHz): $\delta=64.87$ (*C*H), 67.27 (*C*H_2), 67.61 (*C*H_2), 72,49 (*C*H), 120.05 (-CH=*C*H_2), 120.15 (-CH=*C*H_2), 131.23 (-*C*H=CH_2), 131.34 (-*C*H=CH_2), 167.08 (C=O), 170.83 (C=O) ppm; $C_{10}H_{13}O_5N_3$ (255.23), calcd C, 47.06; H, 5.13; N, 16.46; found: C, 46.91; H, 5.25; N, 16.58%.

4.11.3. (2*S*,3*R*)-Diallyl-3-azido-2-hydroxy succinate (2*S*,3*R*)-6d. 60% as a colourless oily liquid with the same IR, ^1H and ^{13}C NMR data as (2*R*,3*S*)-**6d**); $[\alpha]_D^{20}=-30.7$ (*c* 1.06, MeOH); $C_{10}H_{13}O_5N_3$ (255.23), calcd C, 47.06; H, 5.13; N, 16.46; found: C, 47.22; H, 5.01; N, 16.35.

4.12. Aziridines 7, 8

The analytical data of the aziridines (*S*,*S*)-**7a**, (*R*,*R*)-**7a**, (*S*,*S*)-**7b**, (*R*,*R*)-**7b** corresponds to the reported literature values.[14,29,44]

4.13. General procedure for the synthesis of the aziridines 7

A solution of 10 mmol of the appropriate azido alcohol **6** in DMF (50 mL) was cooled at 0°C. PPh_3 (18 mmol) was added over a period of 30 min in five portions. The solution was stirred at rt for 1.5 h and then heated at 80°C for another 4.5 h. In the case of the dibenzyl and diallyl derivatives, the solution was heated immediately after the addition of PPh_3 and catalytic amounts of acetic acid were added. DMF was removed in vacuo and the crude product purified by column chromatography on silica gel with diethyl ether:petrol ether 40–60 (1:3).

4.13.1. (*S*,*S*)-Dibenzyl aziridine-2,3-dicarboxylate (*S*,*S*)-7c. 38% as colourless crystals; mp: 59–60°C; TLC cyclohexane:ethyl acetate 3:1, $R_f=0.34$; $[\alpha]_D^{20}=+79.3$ (*c* 1.02 in, MeOH); IR (film): $\tilde{\nu}=3159$ (m, br), 2946 (s), 2889 (s), 1728 (s, br, C=O), 1496 (s), 1455 (m), 1383 (m), 1340 (m), 1271 (m), 1168 (m), 1004 (s), 958 (m), 910 (m), 865 (m), 831 (m), 744 (s), 698 cm^{-1}; ^1H NMR ($CDCl_3$, 400.13 MHz): $\delta=1.84$ (s, 1H, N*H*), 2.94 (s, 2H, C*H*), 5.20 (t, 4H, 2 CH_2), 7.36 (m, 10H, 2 C_6H_5) ppm; ^{13}C NMR ($CDCl_3$, 100.62 MHz): $\delta=35.47$ (*C*H), 36.21 (*C*H), 67.46 (*C*H_2), 68.02 (*C*H_2), 128.65 (C_6H_5), 134.85 (2 *C*), 168.43 (C=O), 169.83 (C=O) ppm; $C_{18}H_{17}O_4N$ (311.33), calcd C, 69.44; H, 5.50; N, 4.5; found: C, 69.51; H, 5.49; N, 4.39%.

4.13.2. (*R*,*R*)-Dibenzyl aziridine-2,3-dicarboxylate (*R*,*R*)-7c. 35% of colourless crystals with the same mp, IR, ^1H and ^{13}C NMR data as (*S*,*S*)-**7c**; $[\alpha]_D^{20}=-79.8$ (*c* 1.04, MeOH); $C_{18}H_{17}O_4N$ (311.33), calcd C, 69.44; H, 5.50; N, 4.50; found: C, 69.41; H, 5.56; N, 4.41.

4.13.3. (*S*,*S*)-Diallyl aziridine-2,3-dicarboxylate (*S*,*S*)-7d. 42% as a yellowish oily liquid, TLC cyclohexane:ethylacetate 3:1, $R_f=0.32$; $[\alpha]_D^{20}=+131.5$ (*c* 1.16, MeOH); IR (film): $\tilde{\nu}=3159$ (m, br), 2946 (s), 2889 (s), 1728 (s, br, C=O), 1496 (s), 1455 (m), 1383 (m), 1340 (m), 1271 (m), 1168 (m), 1004 (s), 958 (m), 910 (m), 865 (m), 831 (m), 744 (s), 698 cm^{-1}; ^1H NMR ($CDCl_3$, 400.13 MHz): $\delta=1.85$ (s, 1H, N*H*), 2.92 (s, 2H, C*H*), 4.66 (dt, 4 H, 2 CH_2-CH=), 5.28 (dd, 2H, -CH=CH_2, $J=1.01$ Hz, $J_{cis}=10.61$ Hz), 5.34 (dd, 2H, -CH=CH_2, $J=1.27$ Hz, $J_{trans}=17.18$ Hz), 5.87–5.99 (m, 2H, CH_2=C*H*-) ppm; ^{13}C NMR ($CDCl_3$, 100.62 MHz): $\delta=36.16$ (2 *C*H), 66.90 (2 *C*H_2-CH=), 119.73 (2 -CH=*C*H_2), 131.60 (2 -*C*H=CH_2), 169.62 (2 C=O) ppm; $C_{10}H_{13}O_4N$ (211.21), calcd C, 56.86; H, 6.20; N, 6.63; found: C, 56.97; H, 6.12; N, 6.61%.

4.13.4. (*R*,*R*)-Diallyl aziridine-2,3-dicarboxylate (*R*,*R*)-7d. 43% as a yellowish oily liquid, IR, ^1H and ^{13}C NMR data as (*S*,*S*)-**7d**; $[\alpha]_D^{20}=-130.8$ (*c* 1.02 in MeOH); $C_{10}H_{13}O_4N$ (211.21), calcd C, 56.86; H, 6.20; N, 6.63; found: C, 56.98; H, 6.15; N, 6.57%.

4.13.5. (*S*,*S*)-1-*tert*-Butyl-2,3-diethyl aziridine-1,2,3-tricarboxylate (*S*,*S*)-8b. Aziridine (1.31 g, 7.0 mmol) (*S*,*S*)-**7b** was dissolved in $CH_2Cl_{2abs.}$ (60 mL) and cooled at 0°C. Di-*tert*.-butyl dicarbonate (4.58 g, 21.0 mmol) and DMAP (855 mg, 7.0 mmol) were added and the solution stirred at 0°C for 2 h and then at rt for 2 days. The solution was concentrated and then washed with water and saturated NH_4Cl solution. The organic layer was dried with Na_2SO_4 and the residue remaining after evaporation of the solvent in vacuo purified by column chromatography on silica gel with cyclohexane:ethyl acetate 2:1. Yield: 31% as a yellowish viscous oil; $[\alpha]_D^{20}=+14.8$ (*c* 1.37, EtOH); IR (film): $\tilde{\nu}=2984$, 1744 (s, C=O), 1395, 1371 cm^{-1}; ^1H NMR ($CDCl_3$,

400.13 MHz): $\delta = 1.30$ (t, 6H, CH_2CH_3, $J = 7.0$ Hz), 1.44 [s, 9H, $C(CH_3)_3$], 3.33 (s, 2H, aziridine-H), 4.23 (m_c, 4H, CH_2) ppm; ^{13}C NMR ($CDCl_3$, 100.62 MHz): $\delta = 14.93$ (CH_2CH_3), 28.69 [$C(CH_3)_3$], 41.15 (2 aziridine-C), 63.05 (OCH_2CH_3), 64.91 (CH_2), 83.70 [$C(CH_3)_3$], 157.7 (NC=O), 167.4 (2 C=O) ppm; MS (CI, C_4H_{10}): m/z (%) = 287 (100) [M^+]; $C_{13}H_{21}NO_6$·EtOAc (287.31·EtOAc), calcd C, 54.39; H, 7.79; N, 3.73; found: C, 54.35; H, 7.36; N, 3.96%.

4.13.6. (*S*,*S*)-Lithium-1-*tert*.-butyl-3-ethyl aziridine-1,2,3-tricarboxylate (*S*,*S*)-8e. Aziridine (632.5 mg, 2.1 mmol) (*S*,*S*)-**8b** was dissolved in $EtOH_{abs.}$ (25 mL) and cooled at 0°C. LiOH monohydrate (86.4 mg, 2.06 mmol) was added and the suspension stirred at 0°C for 2 h and then at rt for 3 days. The solution was evaporated in vacuo and the crude yellowish solid half ester used without further purification.

4.13.7. (*S*,*S*)-2-Allyl-1-*tert*-butyl-3-ethyl aziridine-1,2,3-tricarboxylate (*S*,*S*)-8f. Aziridine (*S*,*S*)-**8e** (122.5 mg, 462 μmol) was dissolved at rt in acetonitrile (3 mL). 12-Crown-4 (81.4 mg, 462 μmol, 73.3 μL) was added and the solution stirred for 45 min. Allyl iodide (155.2 mg, 924 μmol, 84.8 μL) and $AgNO_3$ (155.1 mg, 924 μmol) suspended in acetonitrile (1 mL) were added and the suspension stirred for 2 d at rt. The suspension was filtered off over Celite and the residue washed with CH_2Cl_2. The organic layer was evaporated in vacuo and the crude product purified by column chromatography with silica gel and a cyclohexane:ethyl acetate 1:0–2:1 gradient. Yield: 44% as a yellow-orange viscous liquid; $[\alpha]_D^{20} = +9.0$ (*c* 1.06, MeOH); TLC cyclohexane:ethyl acetate 2:1, $R_f = 0.65$; $[\alpha]_D^{20} = +9.0$ (*c* 1.06, MeOH); IR (film): $\tilde{\nu} = 3060$ (s, C-H), 3010 (s, C-H), 1752 (s, C=O), 1650 (m, C=C), 1425 (m), 1375 (s), 1330 (s), 1310 (s), 1265 (s), 1195 (s), 1150 (s), 1097 (m), 1032 (m), 895 (m), 850 (m), 745 (s), 700 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 400.13 MHz): $\delta = 1.30$ (t, 3 H, CH_2CH_3, $J = 7.0$ Hz), 1.44 [s, 9 H, $C(CH_3)_3$], 3.34, 3.36 (d, d, je 1H, aziridine-H, $J = 2.2$ Hz), 4.24 (q, 2H, OCH_2CH_3, $J = 7.0$ Hz), 4.63, 4.70 (ddt, ddt, je 1H, $CHCH_2O$, $J = 28.0$ Hz, $J = 5.8$ Hz, $J = 1.3$ Hz), 5.28 (dd, 1H, CH_2CH, $J = 1.2$ Hz, $J_{cis} = 10.6$ Hz), 5.35 (dd, 1H, CH_2CH, $J = 1.2$ Hz, $J_{trans} = 17.5$ Hz), 5.86–5.96 (m, 1H, CH_2CHCH_2) ppm; ^{13}C NMR ($CDCl_3$, 100.62 MHz): $\delta = 12.34$ (CH_2CH_3), 26.17 [$C(CH_3)_3$], 38.63 (aziridine-C), 38.47 (aziridine-C), 60.50 (OCH_2CH_3), 64.91 (OCH_2CH), 81.20 [$C(CH_3)_3$], 117.7 ($CHCH_2$), 129.3 ($CHCH_2$), 155.0 (NC=O), 164.5 (2 C=O) ppm; MS (EI, 70 eV): m/z (%) = 225 (1) [M^+–$(CH_3)_3CO^+$], 169 (7), 73 (9) [$C_2H_5OOC^+$], 71 (11), 59 (8), 57 (21) [$CH_2CHCH_2O^+$], 55 (9), 43 (17) [$CH_2NCH_2^{\cdot +}$], 42 (7), 41 (100) [$CH_2CHCH_2^+$], 39 (16); $C_{14}H_{21}NO_6$ (299.32).

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46. Due to the very low solubility of the oxirane-2,3-dicarboxylic acid the following esterification methods failed: BnCl or BnBr, LiI, crown ether, different solvents; BnOH, DCC, different solvents; BnOH, *p*-TSOH; PCl_5, BnOH; $SOCl_2$, BnOH. Only the reaction of diisopropyl-*O*-benzyl isourea yielded 5% of the desired dibenzyl ester. Transesterification at the sulfite step also failed due to the formation of elimination products during ester hydrolysis.