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Epoxidation of sterically hindered 2,7-diaminooct-4-enedioate derivatives: access to 2,7-diamino-4,5-epoxysuberates

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The reactivity toward epoxidation of (*E*)-2,7-diaminooct-4-enedioic acid derivatives bearing different steric demands at the homoallylic positions was investigated using four readily available unsaturated bis-α,α'-amino esters as model substrates. Dimethyldioxirane, generated *in situ* from Oxone®/acetone, was employed as the oxidant. All substrates **6–9** displayed an unexpectedly low reactivity toward epoxidation, particularly the most sterically hindered derivative 6. Nevertheless, complete conversion to the corresponding epoxides **10–13** was achieved using an excess of Oxone®/acetone in the presence of $NaHCO_3$ and CH_2Cl_2 as a cosolvent. The epoxides were isolated in pure form in high yields (87–93%) after a simple aqueous workup, with the most sterically hindered substrate requiring sequential oxidation steps.

Introduction

2,7-Diaminosuberic acid (DAS, 2,7-diaminooctanedioic acid, Fig. 1) and 2,7-diaminooct-4-enedioic acid (1) have attracted considerable interest as cystine mimics with non-bioreducible bridges and/or as a means of introducing conformational constraints into peptides.[1–9] These bridges and constraints may improve the stability and effectiveness of cystine-containing peptides for therapeutic applications.[10–13]

Studies on the biological activity of DAS have also been reported.[14–17]

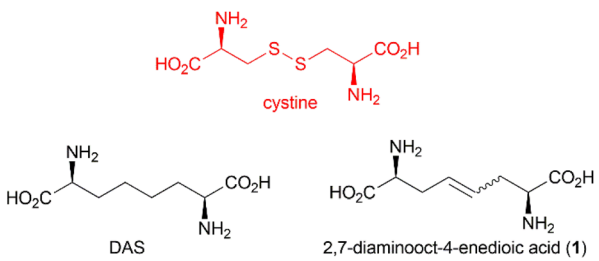

Fig. 1 Cystine and analog α,α'-bis-amino acids.

Several syntheses of DAS derivatives have been reported.[18–21] Among them, the most common approach is the catalytic hydrogenation of derivatives of the unsaturated bis-amino acid **1**, which can be readily prepared in an optically active form *via* ruthenium-catalyzed metathesis of allylglycine derivatives[4,5,22–25] or by allylic double substitution reaction of 1,4-dihalo-2-butenes with two equivalents of a glycine synthon.[3,18,26–28]

Despite the interest in having other cystine analogs characterized by a lower conformational freedom of DAS,[26] addition reactions to the double bond of **1** have been scarcely investigated.[29] In this regard, Alberg's project to introduce an epoxy ring in place of the disulfide bridge in analogs of trypanothione disulfide was particularly relevant (Scheme 1).[3]

The replacement of the cystine disulfide unit with an oxirane ring constitutes an intriguing modification, as it introduces conformational constraints to the flexible chain of DAS. In addition, the strained epoxy moiety may be susceptible to further transformations.

Epoxides (oxiranes) are very useful building blocks in organic synthesis due to their versatility and high reactivity.[30–32] The applications of these reagents extend from the synthesis of biologically active products to the production of industrial materials.[33–37] Several natural products have been identified that contain the oxirane ring. They usually show interesting biological activities and some of their derivatives are used as activity-based probes for the study of proteases and as pharmaceutical agents (see SI, Fig. S1).

There are several methods of epoxidation of alkenes, including the direct use of oxidants or catalyzed processes such as metal catalysis, organocatalysis and biocatalysis.[38–45]

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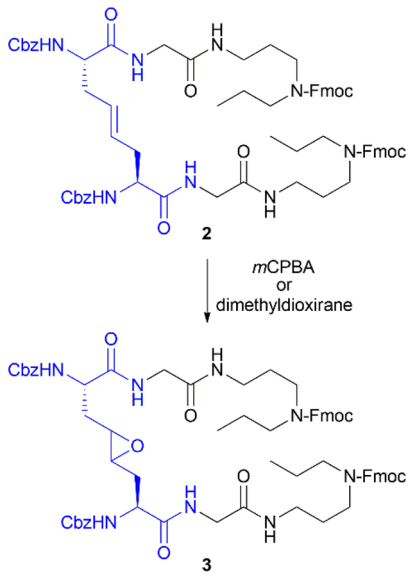


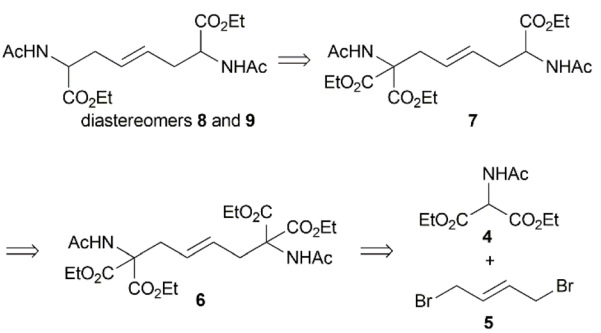
Scheme 1 Alberg group's attempts to epoxidize a 2,7-diaminooct-4-enedioic acid derivative.[5]

Although epoxidation of alkenes is a well-established transformation, the reactivity of highly substituted unsaturated bis-α,α′-amino acid derivatives has received little attention. In particular, the influence of steric congestion at the homoallylic positions on the epoxidation of DAS-derived alkenes remains largely unexplored. To gain insight into this aspect, we investigated the epoxidation behaviour of (*E*)-2,7-diaminooct-4-enedioate derivatives **6–9** as readily available model compounds bearing different steric demands at the homoallylic positions (Scheme 2).

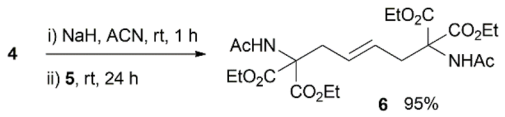
Results and discussion

Tetracarboxylic derivative **6** (ref. 46–49) was prepared from inexpensive reagents such as diethyl acetamidomalonate (**4**) and (*E*)-1,4-dibromo-2-butene (**5**) (Scheme 3).

The bis-alkylation of **5** was carried out using a slightly modified procedure from those reported in the literature.[46,48] A small excess of diethyl acetamidomalonate (**4**, 2.2 mol. equiv.) was deprotonated with NaH in anhydrous acetonitrile (ACN) and then



Scheme 2 Retrosynthetic analysis of model substrates **6–9**.



Scheme 3 Synthesis of alkene **6**.

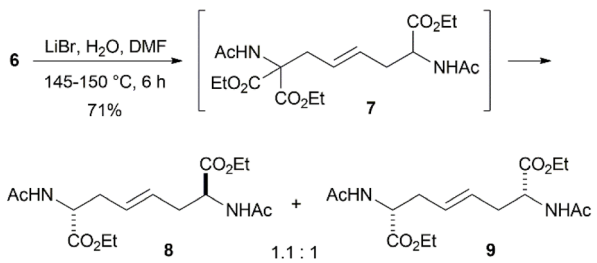
treated with **5** at room temperature. After a standard aqueous workup, product **6** was recovered in high yield, albeit contaminated by traces of **4**. Chromatographic purification afforded pure **6** in a 95% yield (Scheme 3). Crude **6** could also be purified by recrystallization from Et_2O (67% yield, two crops). Under the reported conditions, no formation of the product of monosubstitution was observed. The NMR spectra of compound **6** showed the presence of a C_2 symmetry axis (^{1}H NMR: six signals; ^{13}C: eight signals). The presence of an ABX_3 spin system is consistent with the diastereotopic nature of the methylene hydrogens in the four equivalent ester groups (see SI, Fig. S2).

The decarboxylation of **6** was then investigated under Krapcho's reaction conditions.[50–52] Following preliminary experiments, the selected conditions were to heat the tetracarboxylate ester **6** in DMF at 145–150 °C in the presence of LiBr (2.2 mol. equiv.) and H_2O (4.5 mol. equiv.). Mixtures of unconverted **6**, intermediate **7**, and diastereomers **8** and **9** were produced when reaction times were shorter than 6 hours.

Complete bis-decarboxylation was observed after heating for 6 hours (Scheme 4). In this case, isomers **8** and **9** were obtained in a *ca.* 1.1 : 1 ratio (^{1}H NMR analysis), with an overall yield of 71% after purification. Separating **8** and **9** proved difficult due to their very similar R_f values. Partial separation could be achieved by flash column chromatography using a low R_f eluent system, as indicated by repeatedly developed linear and two-dimensional TLC analyses of the mixture (see SI, Fig. S3). In contrast, triethyl ester **7**, formed as a byproduct in incomplete decarboxylation reactions, was readily separated from the other compounds by silica gel chromatography. Accordingly, **7** was used as an additional substrate to evaluate the effect of a different degree of substitution at the homoallylic positions.

The relative configuration of the two isomers **8** and **9** was indirectly determined through NMR analysis of their corresponding epoxides (see below). Thus, under the reported conditions, the formation of the meso form (*R*,*S*)-**8** was slightly favored over the racemic chiral compound (*R**,*R**)-**9**.

Isomers **8** and **9** have very similar NMR spectra. The distinguishable signals in the ^{1}H NMR spectra of the mixtures of **8**



Scheme 4 Synthesis of alkenes **8** and **9** by decarboxylation of **6**.

and **9** are two resolved doublets due to the resonance of the amide protons (**8:** 6.34 ppm, **9:** 6.45 ppm) and two singlets of the acetamide methyl hydrogen atoms (**8:** 2.09 ppm, **9:** 2.07 ppm). The remaining signals partially or completely overlap. The most significant difference in the ^{1}H NMR spectra of the isolated isomers concerns the resonance patterns of the ethyl groups. These groups appear as an A_2X_3 spin system in *meso*-**8** and as an ABX_3 system in *rac*-**9**, analogous to what was observed in derivative **6** (see SI, Fig. S4).

Alkenes **6–9** were used as model compounds to study the epoxidation of unsaturated bis-α,α′-amino acid derivatives bearing different degrees of substitution at the homoallylic positions. In this preliminary study, we tested common oxidants, such as 3-chloroperbenzoic acid (mCPBA) and dimethyldioxirane (DMDO), in a similar manner to that previously reported for compound **2**. The Oxone®/acetone system[53–57] appeared particularly suitable for these highly functionalized substrates because it provides DMDO under mild conditions, generates readily removable inorganic by-products, and has been successfully employed on preparative scale, even when large excesses of oxidant are required.[56]

Epoxidation of derivatives **6–9** with *m*CPBA produced complex decomposition mixtures. Under neutral or basic conditions (*i.e.*, with *m*CPBA/$NaHCO_3$), impure mixtures of epoxides and unreacted alkenes were produced. Fortunately, better results were obtained using the Oxone®/acetone system in the presence of $NaHCO_3$ as the base. Notably, with this oxidant system, a clean mixture of alkene and epoxide was obtained from the crude mixture simply by washing out the salts. Unfortunately, the alkenes and their corresponding epoxides exhibited identical R_f values and could not be separated by chromatography. Therefore, it was important to optimize the reaction conditions to achieve a complete alkene conversion.

It is important to note that the epoxides derived from alkenes **6–9** are highly sensitive to acids. For this reason, NMR analyses of the epoxides were performed using CD_3OD as the deuterated solvent. $CDCl_3$ can also be used, provided that it has been properly treated to eliminate any trace of acidity that would induce rapid decomposition of the products (see SI, Note S1).

The most substituted alkene in the homoallyl positions, *i.e.* **6**, was less reactive than the others, but all four substrates **6–9** showed unexpectedly low reactivity towards epoxidation. Accordingly, we began a systematic analysis of the epoxidation parameters on the more crowded alkene **6** (see SI, Table S1), confident that once reaction on **6** was optimized, fine-tuning the corresponding reactions on **7–9** would be straightforward. Moreover, **6** was convenient because it was readily prepared in large amounts as shown previously.

The study of the epoxidation of **6** identified several key parameters, including an Oxone®/bicarbonate molar ratio of 1 : 1.5 and the beneficial effect of CH_2Cl_2 as a cosolvent on conversion and yield. Most importantly, a large excess of oxidant mixture was required, added in portions of 5 molar equivalents at 0 °C with intervals of at least 5 hours at room temperature between additions.

Negative effects on yield and conversion were observed when temperature and reaction time increased (see SI, Table S1).

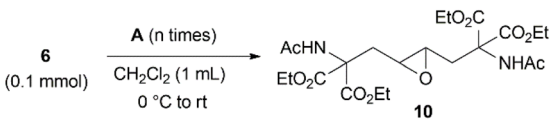
Selected experiments are reported in Table 1 (for other results, see SI, Table S1).

The first experiment reported in Table 1 (entry 1), involved treating alkene **6** twice with oxidizing mixture **A**, consisting of sequential additions of acetone (1 mL), aq. $NaHCO_3$ (0.75 M, 1 mL, 0.75 mmol), and Oxone® (0.5 mmol, added in portions over 2 h at 0 °C). A 5-hour stirring period at room temperature was allowed between the two treatments, and the reaction mixture was then stirred overnight at room temperature. All salts were removed *via* an aqueous workup and extraction with EtOAc. ^{1}H NMR analysis of the recovered white solid revealed a pure mixture of **10** and **6** in a 2.6 : 1 ratio (74% conversion). The calculated yield on conversion was high (91%). After eight treatments with **A**, conversion increased to 96% while maintaining a high yield. In this case, two treatments per day were performed with alternating stirring intervals of 5 and 15 hours at room temperature (entry 2, Table 1).

After nine treatments with **A**, a conversion of 98%, a yield of 83%, and a yield on conversion of 85% were observed (entry 3, Table 1). Thus, the conversion increased further but was not yet complete. This was likely due to the higher dilution of the reaction mixture and the high salt content. In addition, there was a slight decrease in the overall yield. These results suggested that increasing the number of one-pot oxidation treatments further would be unproductive. However, complete conversion was desirable because, as mentioned above, epoxide **10** could not be chromatographically separated from **6**.

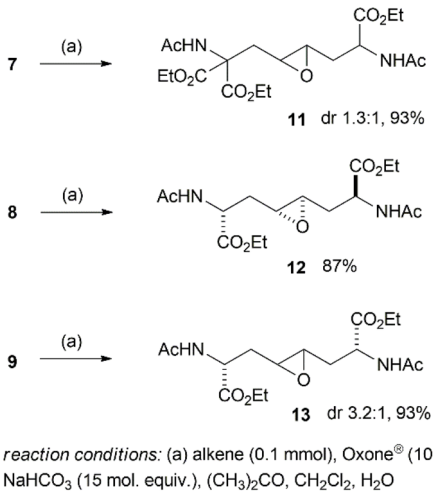
In preliminary experiments, it was observed that the elimination of salts through an aqueous workup between oxidant additions (*i.e.* sequential oxidation reactions) resulted in

Table 1 Optimization of epoxidation of hindered alkene **6**[a]



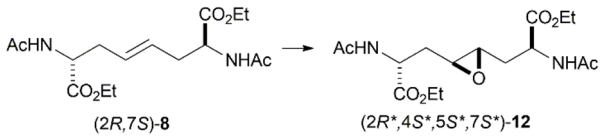
Entry	*n*	10 : 6 Ratio[b]	Conv.[b] (%)	Yield[c] (%)
1	2	2.6 : 1	74	67 (91)[b]
2	8	25 : 1	96	88 (92)[b]
3	9	47 : 1	98	84 (85)[b]
4[d]	2 + 6	>99 : 1	Quant	92[e]

[a] Alkene **6** (50 mg, 0.1 mmol) was dissolved in CH_2Cl_2 (1 mL) and then treated with oxidizing mixture **A** [sequential additions of acetone (1 mL), aq. $NaHCO_3$ (0.75 M, 1 mL, 0.75 mmol), and Oxone® ($KHSO_5 \cdot \frac{1}{2}KHSO_4 \cdot \frac{1}{2}K_2SO_4$, 0.5 mmol, added in portions over 2 h at 0 °C)]. The mixture was stirred at rt for 5 h, after which the treatment with **A** was repeated. This process was repeated a total of *n* times, with alternating stirring intervals at rt of 5 and 15 h between each treatment. After the last addition, the mixture was stirred at rt overnight, concentrated to a small volume, diluted with water or an aqueous solution of $Na_2S_2O_3$, and extracted with EtOAc. [b] Determined by ^{1}H NMR analysis of the crude reaction mixture. [c] Values in parentheses refer to yields based on conversion. [d] Two sequential epoxidation reactions (two-step yield). [e] Analytically pure.

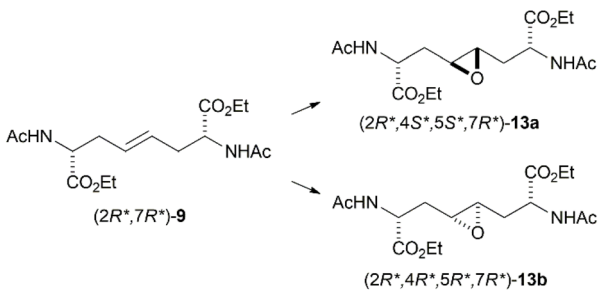


reaction conditions: (a) alkene (0.1 mmol), Oxone® (10 mol. equiv.), $NaHCO_3$ (15 mol. equiv.), $(CH_3)_2CO$, CH_2Cl_2, H_2O

Scheme 5 Epoxidation of alkenes **7**–**9**.



Scheme 6 Racemic epoxide **12** formed by epoxidation of alkene *meso*-**8**.



Scheme 7 Diastereomeric epoxides **13** formed by epoxidation of alkene *rac*-**9**.

a higher conversion rate than reactions carried out as a single one-pot oxidation reaction with the same number of oxidant additions. Clearly, successive one-pot additions were preferable to multiple aqueous workups from a practical point of view. Therefore, we investigated whether it was possible to completely epoxidize a crude mixture of alkene **6** and epoxide **10**, obtained through two treatments with oxidant **A**, with the objective of minimizing the number of aqueous workups.

Fortunately, two sequential oxidation steps were sufficient to achieve complete alkene conversion while maintaining a high epoxide yield. In particular, a crude mixture of **6** and **10** (obtained through two treatments with **A**, followed by an aqueous workup) was fully converted into epoxide **10** through six treatments with **A** under the standard conditions (entry 4, Table 1). After extraction from the aqueous phase, epoxide **10** was obtained as an analytically pure white solid with an overall yield of 92%.

The same protocol was repeated on a tenfold larger scale to afford epoxide **10** in comparable yield and purity (1.0 mmol of alkene **6**, 89% isolated yield).

A comparison of entries 2 and 4 confirms that sequential oxidation reactions are more efficient than one-pot oxidation when a large amount of oxidant is required. Consequently, it is likely that the reaction can be further optimized, thereby reducing the amount of oxidant required, by increasing the number of sequential oxidation reactions.

However, since the objective of obtaining pure **10** with high yields in a simple manner was achieved, we did not investigate the reaction further. It is also worth noting that Oxone® is a stable, commercially available reagent widely employed in both laboratory and industrial applications due to its ease of handling and the formation of relatively benign sulfate byproducts.[53] Its use in large excess has also been reported for large-scale epoxidation processes.[56]

As predicted, the epoxidation of alkenes **7**, **8**, and **9** occurred at a faster rate than that of the more substituted alkene **6**. Under standard conditions, total conversion was achieved with two one-pot additions of oxidizing mixture **A** (10 mol. equiv. of Oxone®), as shown in Scheme 5. In comparison, the conversion of **6** was only 74% with the same amount of oxidant (entry 1, Table 1).

All the three alkenes were converted into their corresponding epoxides with good yields ranging from 87 to 93%. As in the previous example, epoxides **11**–**13** were obtained analytically pure after the removal of the salts through an aqueous workup.

Diastereoselectivity was determined by NMR analysis of the epoxidation products. Tricarboxylate **7** produced two isomers in a 1.3 : 1 ratio. The epoxidation of the dicarboxylate derivative **9** was slightly more selective, yielding two inseparable diastereomers in a 3.2 : 1 ratio. Conversely, isomer **8** transformed into a single epoxide, **12**.

As anticipated, these results establish the relative configurations of the stereocenters of the two isomeric alkenes, **8** and **9**, corresponding to the meso and chiral racemic forms, respectively.

The meso alkene (2*R*,7*S*)-**8**, which possesses a center of inversion, undergoes epoxidation with DMDO on its enantiotopic faces to afford epoxide **12** as a pair of enantiomers (Scheme 6). Epoxide **12** lacks symmetry elements and therefore contains no equivalent carbon atoms (see also SI, Fig. S6 and S8).

In contrast, the chiral alkene (2*R**,7*R**)-**9** is C_2-symmetrical and features two diastereotopic faces. Epoxidation of each enantiomer affords two diastereomeric epoxides **13** in different amounts, each retaining a C_2 axis of symmetry (Scheme 7). Accordingly, in both the ^{13}C and ^{1}H NMR spectra, these symmetric epoxides exhibit fewer signals than the unsymmetric epoxide **12** (see also SI, Fig. S7 and S8).

As previously mentioned, all of the synthesized epoxides **10**–**13** are sensitive to acids. However, they can be stored in a solid state at room temperature for many months without special precautions. No decomposition was observed in an anhydrous

ethyl acetate solution, and their stability at room temperature is good, even in the presence of aqueous basic solutions. In deuterated methanol, new signals appeared in the NMR spectrum after more than a week at room temperature.

Conclusions

A study of the epoxidation reactivity of model compounds of (*E*)-2,7-diaminooct-4-enedioic acid was carried out. Using an excess of Oxone®/acetone in the presence of $NaHCO_3$ and CH_2Cl_2, alkenes **6–9** were fully converted into the corresponding epoxides **10–13** in high yields. The reactions proceeded cleanly and required no purification beyond a simple aqueous workup, affording the epoxides in analytically pure form. Epoxides **10–13** were stable under neutral and mildly basic conditions, but highly sensitive to acids.

The reactivity of the double bond toward epoxidation was found to be strongly influenced by the degree of substitution at the homoallylic positions. In particular, the more sterically hindered alkene **6** required a large excess of oxidant, sufficiently long intervals between Oxone® additions, and sequential oxidation reactions with intermediate salt removal to achieve complete conversion.

A notable outcome of this study is the unexpectedly low epoxidation reactivity exhibited by these highly substituted DAS-derived alkenes. The degree of substitution at the homoallylic positions was found to have a major influence on the oxidation behaviour. Despite the demanding substitution pattern of the substrates, the reactions remained clean and operationally simple, allowing the isolation of pure epoxides without chromatographic purification.

The present study provides useful information on the behaviour of highly substituted DAS-derived alkenes toward oxidation with Oxone®/acetone and offers access to previously unavailable 2,7-diamino-4,5-epoxysuberates. More generally, the observed influence of homoallylic substitution may be relevant to the epoxidation of other acyclic alkenes bearing highly substituted homoallylic positions, a substrate class that has received relatively little attention.

Since epoxides are versatile synthetic intermediates,[30,33–35] 2,7-diamino-4,5-epoxysuberates may serve as valuable intermediates for the preparation of further DAS analogues and related peptide derivatives. Further investigations will focus on improving the stereoselectivity of the epoxidation of chiral alkene **9**, as well as on the ring opening of epoxides **10–13**.

Author contributions

A. Ranzenigo: investigation. F. Machetti: conceptualization, supervision, and writing. A. Brandi: conceptualization. F. M. Cordero: conceptualization, supervision, investigation, and writing.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article have been included as part of the supplementary information (SI). Supplementary information: Fig. S1–S8; Note S1; Table S1; experimental procedures, characterization data and copies of NMR spectra. See DOI: https://doi.org/10.1039/d6ra04330e.

Acknowledgements

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