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Enantioselective synthesis of α-hydroxy-β-amino acids from α-amino acids mediated by sulfoxides

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Abstract—The synthesis of the optically pure (2*S*,3*S*)- and (2*R*,3*S*)-3-amino-2-hydroxybutanoic acids from commercially available (*S*)-alanine derivatives is reported. The key step of the synthetic sequence is the conversion of γ-amino sulfoxides into γ-amino alcohols by treatment with TFAA and *sym*-collidine. The efficiency of this non-oxidative Pummerer reaction (NOPR) is dependent on the stereochemistry of the starting sulfoxide.

1. Introduction

α-Hydroxy-β-amino acids constitute an important class of substances that has received considerable attention because of the occurrence thereof in biologically active molecules.[1] For example, this entity is present in antitumor agents (paclitaxel[2]), aminopeptidase inhibitors (bestatin[3] and amastatin[4]), rennin inhibitors (KRI-1314[5]), angiotensin converting enzymes (microginin[6]), and antibacterial agents (dideoxy-kanamycin A[7]). In recent years, much effort has been devoted to the asymmetric synthesis of α-hydroxy-β-amino acid structural units and a large number of synthetic approaches thereto have been developed including, among others: (i) homologation of chiral amino acids,[8] (ii) Ojima's β-lactam ring opening methodologies,[9] (iii) asymmetric aminohydroxylation[10] or enantioselective epoxidation of olefins followed by nucleophilic ring opening of the resulting chiral epoxides,[11] (iv) electrophilic hydroxylation of chiral enolates,[12] and (v) addition of nucleophiles to chiral α-amino aldehydes[13] and imines.[14] Although satisfactory degrees of stereocontrol have been achieved for these processes, most of them involve multi-step reaction sequences, and therefore the search for new routes to synthesize both diastereoisomers of a given α-hydroxy-β-amino acid starting with a common precursor continues to be of considerable interest.

The non-oxidative Pummerer reaction is an interesting process allowing the stereoselective conversion of β-amino sulfoxides into the corresponding β-amino alcohols by reaction with TFAA and *sym*-collidine (Scheme 1). These reactions, which occur with inversion of configuration at the carbon bearing the sulfinyl group, were discovered and extensively used by Zanda's group.[15] To the best of our knowledge, however, the conversion of γ-amino sulfoxides into the corresponding γ-amino alcohols under analogous conditions has received little attention.[16] Given that these compounds are obvious precursors of β-amino acids, and that we have recently reported the synthesis of β-hydroxy-γ-amino sulfoxides (both epimeric hydroxyl compounds) starting from the readily available amino acid methyl ester hydrochlorides,[17] we chose to examine the behavior of such γ-amino sulfoxides under the conditions of the non-oxidative Pummerer reaction. The objectives of this study were to synthesize 3-amino-1,2-propanediols, precursors of α-hydroxy-β-amino acids (Scheme 1), to compare the behavior of the γ-amino sulfoxides with that of the β-amino derivatives, and to examine the influence of the stereochemistry of the starting materials on the reaction course. In this paper we report the results obtained in this study.

2. Results and discussion

The overall synthetic sequence is depicted in Scheme 2. The starting optically pure (3*S*,*R*s)-*N*-(*tert*-butoxycarbonyl)-3-amino-1-[(4-methylphenyl)sulfinyl]-2-butanone (**1a**) and

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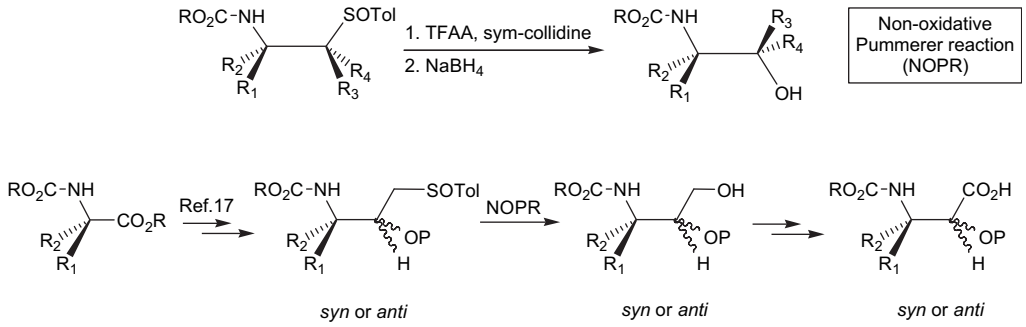
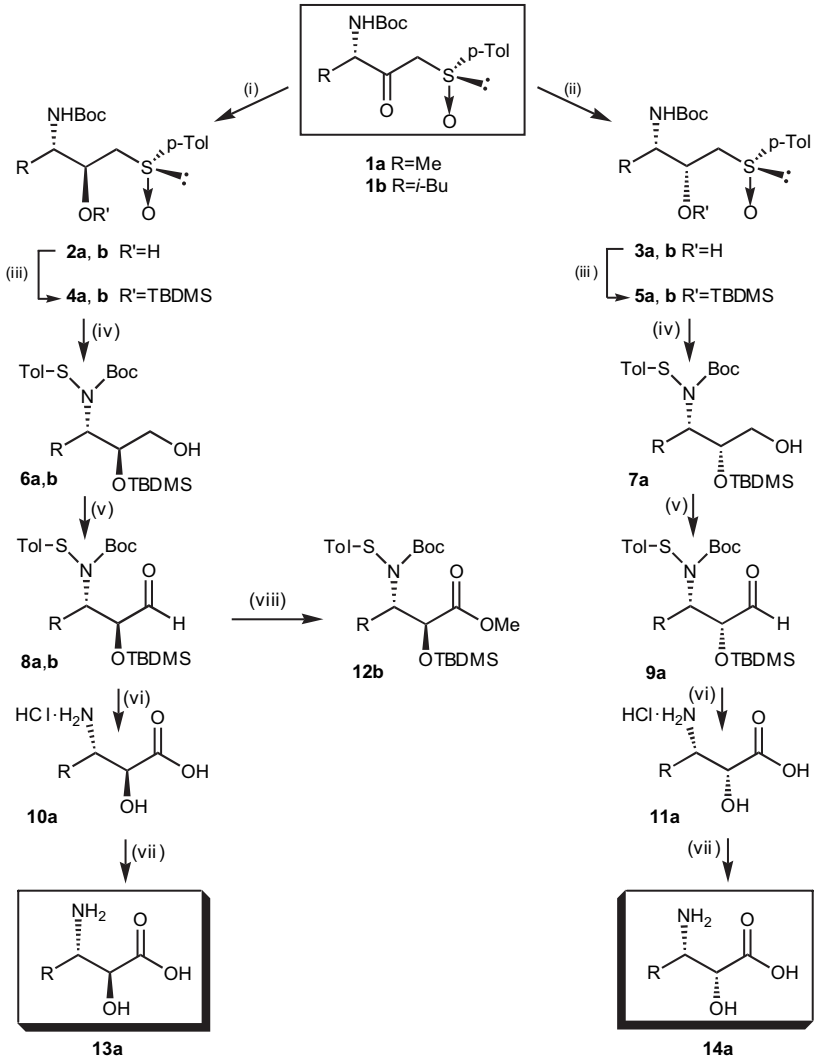


Scheme 1.

(3*S*,*R*s)-*N*-(*tert*-butoxycarbonyl)-3-amino-5-methyl-1-[(4-methylphenyl)sulfinyl]-2-hexanone (**1b**) were obtained following a previously described synthetic route.[17a,c] The reduction of β-keto sulfoxide **1a** (or **1b**) with DIBAH or DIBAH/$ZnBr_2$ gave the γ-amino-β-hydroxy sulfoxides **2a** and **3a**[17a] (or **2b** and **3b**[17c]), respectively, as diastereoisomerically pure products. These compounds were converted into the corresponding *tert*-butyldimethylsilyl ethers **4a** and **4b** (**5a** and **5b**) and then reacted with TFAA (5–10.5 equiv) and *sym*-collidine in acetonitrile at room temperature. The reaction mixtures were then diluted with a large excess of saturated aqueous $NaHCO_3$[18] and left at ambient temperature. In this way the sulfenamides **6a** and **6b** were obtained in excellent yields (86 and 81% yields) after 48 and 22 h, respectively. In stark contrast, after 7 days, compound **7a** was produced in only 25% yield (substantial recovered **5a**) and



Scheme 2. *Reagents and conditions*: (i) DIBAH, THF, −78 °C; (ii) DIBAH–$ZnBr_2$, THF, −78 °C; (iii) TBDMSCl, imidazole; (iv) (1) TFAA, *sym*-collidine, 0→25 °C, (2) $NaHCO_3$–H_2O, 25 °C; (v) PCC, CH_2Cl_2, 25 °C; (vi) (1) $KMnO_4$–*t*-BuOH, pH 4, (2) HCl(g)–Et_2O, 25 °C; (vii) ion-exchange chromatography; (viii) (1) $Na_2Cr_2O_7$, H_2SO_4, −15→25 °C, (2) CH_2N_2, Et_2O.

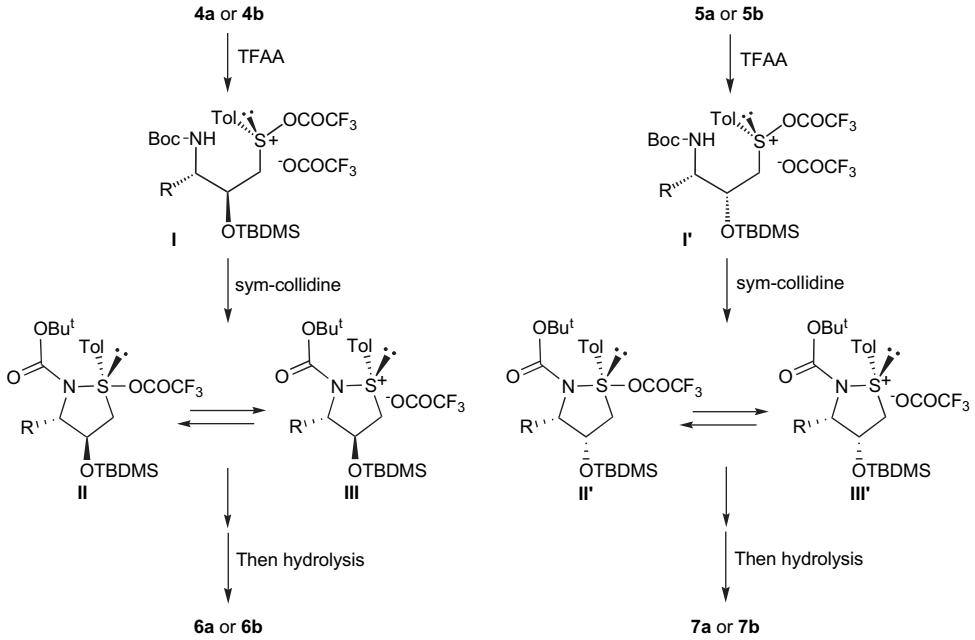
the conversion of **5b** to **7b** did not take place at all (**5b** is quantitatively recovered).[19]

The reaction of **6a**, **6b**, and **7a** with PCC at room temperature gave the aldehydes **8a**, **8b**, and **9a**, respectively. The oxidation of **8a** and **9a** using $KMnO_4$ in buffered (pH 4) aqueous *tert*-butyl alcohol produced the corresponding carboxylic acids. Although the yields of the crude products were high, these compounds are not very stable and suffer extensive degradation on attempted purification by silica gel chromatography. Therefore the crude carboxylic acids were dissolved in ether saturated with hydrogen chloride, which effected removal of both the protecting groups and sulfonamide cleavage, and generated the hydrochloride salts of **10a** and **11a** in 42 and 76% yields. The known free amino acids, (2*S*,3*S*)-alloisothreonine[20,21] (**13a**) and (2*R*,3*S*)-isothreonine[20–23] (**14a**) were generated from the hydrochloride salts by ion exchange using a SCX column. Unexpectedly, oxidation of aldehyde **8b** with $KMnO_4$ and subsequent hydrogen chloride treatment of the crude oxidation product, under conditions identical to those used for **8a** and **9a**, produced the corresponding hydrochloride as a mixture of C-2 epimers. In contrast, oxidation of **8b** with sodium dichromate in sulfuric acid at −15 °C and esterification of the crude product with diazomethane, gave the diasteriomerically pure methyl ester **12b** (74%).

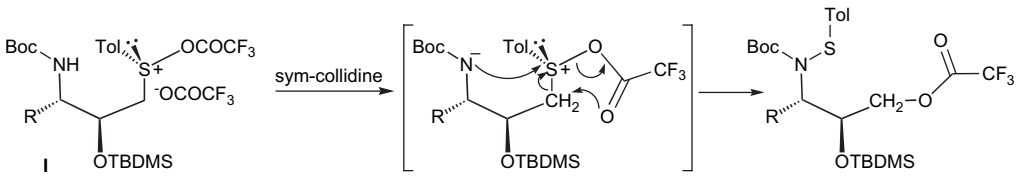
If the conversion of γ-amino sulfoxides into the corresponding amino diols by the non-oxidative Pummerer reaction proceeds by a mechanism analogous to that proposed by Zanda[15d] for the β-amino sulfoxide series, then the reaction sequence depicted in Scheme 3 would be expected. After the formation of the acyloxysulfonium salts (**I** and **I′**) by reaction of the sulfinyl oxygen with TFAA, the intramolecular attack of the amide anion (generated after adding *sym*-collidine) to the sulfur at these salts would yield the thiaazacyclopentane rings (**III** and **III′**), probably through the sulfurane intermediates (**II** and **II′**).[24] Finally, these intermediates would be opened by the trifluoroacetate anion affording compounds **6** and **7**. On the assumption that the five membered intermediates **II** or **III** might be sufficiently stable to be observable, we chose to follow the reaction by NMR spectroscopy. When **4a** was dissolved in CD_3CN containing 5 equiv of TFAA, substantial deshielding of the methylene hydrogens α- to sulfur was observed, as expected for the formation of the acyloxysulfonium salt **I**, but no signals attributable to **II** or **III** were ever seen.[25] Upon addition of *sym*-collidine to this solution, the only new absorptions, which appeared were those corresponding to the trifluoroacetate of **6a**, thus precluding to obtain any proof supporting the formation of the intermediates **II** or **III**.

It is remarkable that the conditions under which **4a** and **4b** are converted into **6a** and **6b** are either inefficient or ineffective for the generation of the corresponding products from **5a** or **5b**, respectively. The cause of this phenomenon must be associated with the sulfoxide stereochemistry, but the precise role, which it plays is not clear. It may be a consequence of the different easiness of the acyloxysulfonium salts to evolve into their corresponding sulfuranes or azasulfonium salt intermediates, that would be determined by the steric interactions of the nearly eclipsed conformation [for the C(1)–C(2) bond] that **I** and **I′** must adopt to be transformed into **II** and **II′** (much higher for **I′**) and/or by the higher stability of the *trans* intermediates (**II** and **III**) with respect to the *cis* ones (**II′** and **III′**).

Although the mechanism depicted in Scheme 3 seems to be appropriated to explain the most of the experimental results, some doubts subsist from the fact that intermediates **II** or **III** cannot be detected in our NMR experiments, despite of their presumable stability, which seriously put in question their existence. In such a case other mechanistic possibilities must be considered for these reactions. One of them assumes an almost concerted process, like that depicted in the Scheme 4, where the nitrogen attack produces the cleavage



Scheme 3.



Scheme 4.

of the S–$OCOCF_3$ bond and the simultaneous intramolecular attack of the leaving trifluoroacetate to the properly arranged carbon, resulting in the formation of trifluoroacetate derivative of **6** from **I**. The evolution of **I′** (derived from **5**) according to a similar route would involve a much more unstable TS due to the almost eclipsed (R/OTBDMS) interaction. This proposal would involve an intramolecular attack of the nucleophilic trifluoroacetate, thus contrasting with the intermolecular attack proposed in Scheme 3. Some information about these two possibilities could be obtained by studying the reaction in the presence of external nucleophiles, which would compete with $CF_3CO_2^-$ only for the intermolecular processes. Thus, we have performed the reaction of **4a** with TFAA and *sym*-collidine in the presence of tetrabutylammonium acetate (different concentrations were used). In all the cases, compound **6a** and their corresponding trifluoroacetate were exclusively formed, whereas the acetate of the alcohol **6a** was not detected in any experience. Taking into account that $CH_3CO_2^-$ has higher nucleophilic character than $CF_3CO_2^-$, the absence of the acetate in the reaction mixtures is not compatible with the intermolecular attack proposed in Scheme 3.

In summary, we have shown that both (2*S*,3*S*)- and (2*R*,3*S*)-3-amino-2-hydroxybutanoic acid (**13a**) and (**14a**) can be synthesized in high optical purity from the readily available β-keto sulfoxide **1a**, by a sequence involving five steps: stereodivergent reduction of **1a** with DIBAH or DIBAH/$ZnBr_2$, protection of the resulting hydroxy sulfoxides, non-oxidative Pummerer reactions, oxidation of the resulting primary alcohols into acids and final deprotection. The efficiency of the key step of the sequence, the non-oxidative Pummerer reaction, is strongly dependent on the stereochemistry of the starting γ-amino sulfoxides.

3. Experimental section

3.1. General methods

All moisture sensitive reactions were carried out in flame dried glassware under argon atmosphere and monitored by TLC. Flash chromatography was performed with silica gel 60 (230–400 mesh ASTM). Melting points were determined in a Culatti melting point apparatus in open capillary tubes and are uncorrected. The optical rotations were measured at room temperature (20–23 °C) using a Perkin–Elmer 343 polarimeter (concentration in g/100 mL). The IR spectra were recorded in a FTIR Bruker Tensor 27 spectrophotometer. The NMR spectra were determined in $CDCl_3$ solutions unless otherwise indicated at 200 (or 300) and 50.3 (or 75.5) MHz for ^1H and ^{13}C NMR, respectively. *J* values are given in hertz. The diastereoisomeric excesses were determined by 300 MHz ^1H NMR spectroscopy. Mass spectra were measured at 70 eV and 190 °C. All described compounds were over 97% pure by NMR analysis.

3.1.1. (2*S*,3*S*,*R*s) *tert*-Butyl-3-(*tert*-butyldimethylsilyloxy)-4-[(4-methylphenyl)sulfinyl]butan-2-ylcarbamate (4a). A mixture of hydroxy sulfoxide **2a**[17a] (0.96 g, 2.93 mmol, 1 equiv) *tert*-butyldimethylsilyl chloride (3 equiv), imidazole (6 equiv), and 1 mL of anhydrous DMF was stirred at room temperature for 48 h. Then, cold water (60 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (3×60 mL). The organic layers were combined, washed with brine, dried (Na_2SO_4), and evaporated. The crude product was purified by flash chromatography (hexane–ethyl acetate 80:20), to produce 1.15 g (89%,) of **4a** as a white sticky solid; $[\alpha]_D$ +118.0 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) ν_{max}: 3455, 1709, 1599, 1497, 1368, 1165 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 0.13 (s, 3H), 0.20 (s, 3H), 0.94 (s, 9H), 1.08 (d, 3H, *J* 6.9), 1.43 (s, 9H), 2.41 (s, 3H), 2.64 (dd, 1H, *J* 9.0 and 12.9), 2.86 (dd, 1H, *J* 3.3 and 12.9), 3.74 (br m, 1H), 4.21 (br m, 1H), 4.52 (br d, 1H, *J* 6.9), 7.32 and 7.54 (AA′BB′ system, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ −4.5, −4.4, 15.1, 18.2, 21.4, 25.9, 28.4, 50.7, 63.8, 69.3, 79.5, 123.9, 130.0, 141.4, 141.5, 155.0; EIMS *m*/*z* 442 (1%, M^++1), 384 (8), 368 (10), 328 (100), 310 (32), 246 (16), 206 (20), 144 (45), 139 (42), 123 (28), 88 (26), 57 (77). Anal. Calcd for $C_{22}H_{39}NO_4SSi$: C, 59.82; H, 8.90; N, 3.17. Found: C, 59.89; H, 8.87; N, 3.10.

3.1.2. (2*S*,3*S*,*R*s) *tert*-Butyl-2-(*tert*-butyldimethylsilyloxy)-5-methyl-1-[(4-methylphenyl)sulfinyl]hexan-3-ylcarbamate (4b). Following the same procedure used for the preparation of **4a**, and starting from 0.369 g (1 mmol) of **2b**,[17c] 0.417 g (92%) of **4b** was obtained. The product was purified by column chromatography (hexane–ethyl acetate 8:2), oil; $[\alpha]_D$ +92.2 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) ν_{max}: 3450, 1709, 1500, 1367, 1166 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 0.15 (s, 3H), 0.21 (s, 3H), 0.89 (d, 3H, *J* 6.6), 0.91 (d, 3H, *J* 6.9), 0.94 (s, 9H), 1.15–1.35 (m, 2H), 1.43 (s, 9H), 1.55–1.75 (m, 1H), 2.42 (s, 3H), 2.66 (dd, 1H, *J* 9.0 and 12.9), 2.83 (dd, 1H, *J* 2.1 and 13.2), 3.74 (br m, 1H), 4.17 (m, 1H), 4.31 (br d, 1H, *J* 9.3), 7.32 and 7.55 (AA′BB′ system, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ −4.5, −4.3, 18.2, 21.4, 21.6, 23.6, 24.6, 25.9, 28.3, 39.1, 53.1, 63.6, 69.6, 79.3, 123.9, 130.0, 141.3, 141.4, 155.3.

3.1.3. (2*S*,3*R*,*R*s) *tert*-Butyl-3-(*tert*-butyldimethylsilyloxy)-1-[(4-methylphenyl)sulfinyl]butan-2-ylcarbamate (5a). Following the same procedure used for the preparation of **4a**, and starting from 0.96 g (2.93 mmol) of **3a**,[17a] 1.2 g (93%) of **5a** was obtained. The product was purified by column chromatography (hexane–ethyl acetate 75:25), mp 152–154 °C (CH_2Cl_2–hexane); $[\alpha]_D$ +117.0 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) ν_{max}: 3447, 1702, 1498, 1367, 1165 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) (major rotamer): δ 0.10 (s, 6H),

0.88 (s, 9H), 1.21 (d, 3H, *J* 6.9), 1.46 (s, 9H), 2.40 (s, 3H), 2.69–2.98 (m, 2H), 4.06–4.26 (br m, 2H), 4.69 (br d, 1H), 7.30 and 7.56 (AA′BB′ system, 4H); (minor rotamer): δ 0.17 (s, 3H), 0.26 (s, 3H), 0.95 (s, 9H), 1.13 (d, 3H, *J* 6.9), 1.41 (s, 9H), 2.41 (s, 3H), 2.69–2.98 (m, 2H), 4.06–4.26 (br m, 2H), 4.69 (br d, 1H), 7.32 and 7.51 (AA′BB′ system, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) (major rotamer): δ −4.8, −4.3, 17.9, 18.5, 21.4, 25.8, 28.4, 48.3, 63.6, 70.3, 79.4, 123.9, 129.9, 140.9, 141.4, 155.6; (minor rotamer): δ −4.8, −4.2, 17.9, 18.2, 21.4, 26.0, 28.4, 50.5, 63.8, 69.1, 79.4, 123.9, 130.0, 140.9, 141.4, 155.3. Anal. Calcd for $C_{22}H_{39}NO_4SSi$: C, 59.82; H, 8.90; N, 3.17. Found: C, 59.69; H, 8.98; N, 3.03.

3.1.4. (2*R*,3*S*,*R*s) *tert*-Butyl-2-(*tert*-butyldimethylsilyloxy)-5-methyl-1-[(4-methylphenyl)sulfinyl]hexan-3-ylcarbamate (5b). Following the same procedure used for the preparation of **4a**, and starting from 1.011 g (2.74 mmol) of **3b**,[17c] 1.225 g (93%) of **5b** was obtained. The product was purified by column chromatography (hexane–ethyl acetate 85:15), mp 81–82 °C (CH_2Cl_2–hexane); $[\alpha]_D$ +98.4 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) ν_{max}: 3446, 1701, 1499, 1367, 1166 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.10 (s, 6H), 0.87 (s, 9H), 0.95 (d, 6H, *J* 6.3), 1.20–1.75 (m, 3H), 1.45 (s, 9H), 2.39 (s, 3H), 2.74 (dd, 1H, *J* 3.0 and 12.9), 2.91 (dd, 1H, *J* 10.2 and 12.9), 4.05–4.20 (m, 2H), 4.62 (br d, 1H, *J* 9.6), 7.28 and 7.57 (AA′BB′ system, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ −4.7, −4.2, 17.9, 21.3, 22.1, 23.2, 24.9, 25.8, 28.4, 41.9, 50.8, 63.9, 69.8, 79.3, 123.9, 129.8, 141.1, 141.2, 156.0.

3.1.5. (2*S*,3*S*) *tert*-Butyl-3-(*tert*-butyldimethylsilyloxy)-4-hydroxybutan-2-yl-[(4-methylphenyl)sulfenyl]carbamate (6a). To a cooled solution of **4a** (0.93 g, 2.1 mmol, 1 equiv) in 30 mL of dry acetonitrile, *sym*-collidine (0.83 mL, 6.3 mmol, 3 equiv) and trifluoroacetic anhydride (1.48 mL, 10.5 mmol, 5 equiv) were added. The solution was allowed to reach room temperature and stirred for 48 h. Then 50 mL of 10% $NaHCO_3$ was added and the resulting mixture was vigorously stirred for 48 h. After the addition of water (50 mL), the mixture was extracted with Et_2O (4×50 mL). The organic phase was separated, washed with 5% HCl (50 mL), saturated $NaHCO_3$ (2×50 mL), brine (50 mL), dried, and concentrated. The residue was purified by column chromatography eluting with hexane–ethyl acetate 9:1 to produce 0.80 g (86%) of **6a** as a colorless oil; $[\alpha]_D$ −51.6 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) ν_{max}: 3485, 2929, 2857, 1700, 1679, 1460, 1368, 1299, 1163 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.08 (s, 3H), 0.09 (s, 3H), 0.90 (s, 9H), 1.21 (d, 3H, *J* 6.8), 1.48 (s, 9H), 2.32 (s, 3H), 3.43 (br d, 2H, *J* 2.3), 3.69 (td, 1H, *J* 2.7 and 8.7), 4.49 (qd, 1H, *J* 6.8 and 8.7), 7.11 and 7.19 (AA′BB′ system, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ −4.6, −4.3, 15.9, 18.1, 21.0, 25.9, 28.1, 56.5, 63.3, 74.4, 82.3, 126.1, 129.5, 136.2, 136.8, 157.6; EIMS *m*/*z* 442 (3%, M^++1), 441 (2), 386 (6), 368 (6), 328 (54), 284 (43), 166 (100), 123 (34), 57 (33). Anal. Calcd for $C_{22}H_{39}NO_4SSi$: C, 59.82; H, 8.90; N, 3.17. Found: C, 59.99; H, 8.97; N, 3.22.

3.1.6. (2*S*,3*S*) *tert*-Butyl-2-(*tert*-butyldimethylsilyloxy)-1-hydroxy-5-methylhexan-3-yl-[(4-methylphenyl)sulfenyl]-carbamate (6b). To a cooled solution of **4b** (1.164 g, 2.4 mmol, 1 equiv) in 120 mL of dry acetonitrile, *sym*-collidine (3 mL, 22.7 mmol, 9.5 equiv) and trifluoroacetic anhydride (3.5 mL, 25.2 mmol, 10.5 equiv) were added. The solution was allowed to reach room temperature and stirred for 22 h. Then 60 mL of 10% $NaHCO_3$ was added and the resulting mixture was vigorously stirred for 20 h. The mixture was extracted with Et_2O (4×50 mL). The organic phase was separated, washed with 5% HCl (50 mL), saturated $NaHCO_3$ (2×50 mL), brine (50 mL), dried, and concentrated. The product was purified by column chromatography (hexane–ethyl acetate 85:15) to produce 0.946 g (81%) of **6b** as a colorless oil; $[\alpha]_D$ −45.3 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) ν_{max}: 3500, 2956, 2860, 1704, 1675, 1468, 1367, 1296, 1163, 1118 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.06 (s, 3H), 0.09 (s, 3H), 0.83 (d, 6H, *J* 6.3), 0.90 (s, 9H), 1.30–1.80 (m, 3H), 1.53 (s, 9H), 2.33 (s, 3H), 3.35 (br s, 2H), 3.54–3.80 (m, 2H), 4.43 (br t, 1H. *J* 9.6), 7.12 and 7.38 (AA′BB′ system, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ −4.6, −4.2, 18.1, 21.1, 21.3, 23.5, 24.7, 25.9, 28.1, 38.2, 58.8, 63.3, 73.6, 82.3, 129.3, 129.6, 135.5, 138.2, 158.1.

3.1.7. (2*S*,3*R*) *tert*-Butyl-3-(*tert*-butyldimethylsilyloxy)-4-hydroxybutan-2-yl-[(4-methylphenyl)sulfenyl]carbamate (7a). To a cooled solution of **5a** (0.93 g, 2.1 mmol, 1 equiv) in 30 mL of dry acetonitrile, *sym*-collidine (0.83 mL, 6.3 mmol, 3 equiv) and trifluoroacetic anhydride (1.48 mL, 10.5 mmol, 5 equiv) were added. The solution was allowed to reach room temperature and stirred for 7 days. Then 50 mL of 10% $NaHCO_3$ was added and the resulting mixture was vigorously stirred for 48 h. After the addition of water (50 mL), the mixture was extracted with Et_2O (4×50 mL). The organic phase was separated, washed with 5% HCl (50 mL), saturated $NaHCO_3$ (50 mL), brine (50 mL), dried, and evaporated. The product was purified by column chromatography (hexane–ethyl acetate 8:2) to produce 0.232 g (25%) of **7a** as colorless oil; $[\alpha]_D$ −77.6 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) ν_{max}: 3478, 2930, 2858, 1702, 1671, 1469, 1368, 1311, 1162 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.08 (s, 3H), 0.11 (s, 3H), 0.93 (s, 9H), 1.24 (d, 3H, *J* 6.9), 1.42 (s, 9H), 2.31 (s, 3H), 3.36 (dd, 1H, *J* 7.5 and 11.9), 3.49 (dd, 1H, *J* 4.2 and 11.9) 3.74 (dt, 1H, *J* 4.1 and 7.6), 4.69 (dq, 1H, *J* 4.1 and 6.9), 7.08 (A_2B_2 system, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ −4.8, −4.4, 15.8, 18.0, 21.0, 25.8, 28.0, 54.8, 63.1, 75.5, 82.2, 124.0, 129.3, 135.6, 137.4, 158.4. Anal. Calcd for $C_{22}H_{39}NO_4SSi$: C, 59.82; H, 8.90; N, 3.17. Found: C, 59.72; H, 8.65; N, 3.28.

3.1.8. (2*S*,3*S*) *tert*-Butyl-3-(*tert*-butyldimethylsilyloxy)-4-oxobutan-2-yl-[(4-methylphenyl)sulfenyl]carbamate (8a). To a solution of **6a** (0.441 g, 1 mmol, 1 equiv) in 15 mL of CH_2Cl_2, freshly prepared pyridinium chlorochromate (0.323 g, 1.5 mmol, 1.5 equiv) was added. The mixture was stirred at room temperature for 30 h. After filtration the solvent was removed under vacuum. The product was purified by column chromatography (hexane–ethyl acetate 95:5) to produce 0.337 g (77%) of **8a** as colorless oil; $[\alpha]_D$ −43.4 (*c* 0.5, $CHCl_3$); IR (film) ν_{max}: 2932, 2859, 1733, 1701, 1468, 1368, 1298, 1163 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.05 (s, 3H), 0.08 (s, 3H), 0.92 (s, 9H), 1.21 (d, 3H, *J* 6.7), 1.45 (s, 9H), 2.31 (s, 3H), 4.00 (dd, 1H, *J* 2.3 and 6.7), 4.66 (qd, 1H, *J* 6.7 and 6.7), 7.13 (A_2B_2 system, 4H), 9.55 (d, 1H, *J* 2.3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ −5.0, −4.7, 14.7, 18.1, 21.0, 25.7, 28.0, 57.8, 79.2, 82.2, 125.2, 129.5, 136.4 (2C), 156.7, 202.1; EIMS *m*/*z* 439 (1%, M^+), 384 (5), 326 (15), 298 (14), 166 (100), 123

(34), 57 (33). Anal. Calcd for $C_{22}H_{37}NO_4SSi$: C, 60.10; H, 8.48; N, 3.19. Found: C, 59.97; H, 8.77; N, 3.11.

3.1.9. (2*S*,3*S*) *tert*-Butyl-2-(*tert*-butyldimethylsilyloxy)-5-methyl-1-oxohexan-3-yl-[(4-methylphenyl)sulfenyl]carbamate (8b). Following the same procedure used for the preparation of **8a**, and starting from 0.460 g (0.95 mmol) of **6b**, 0.340 g (74%) of **8b** was obtained. The product was purified by column chromatography (hexane–ethyl acetate 85:15). Colorless oil; $[\alpha]_D$ −52.0 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) ν_{max}: 2932, 2861, 1730 (sh), 1704, 1468, 1368, 1297, 1163 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 0.04 (s, 3H), 0.07 (s, 3H), 0.83 (d, 3H, *J* 6.0), 0.90 (d, 3H, *J* 6.0), 0.91 (s, 9H), 1.22–1.75 (m, 3H), 1.47 (s, 9H), 2.31 (s, 3H), 3.89 (dd, 1H, *J* 2.4 and 7.5), 4.63 (br t, 1H. *J* 7.8), 7.09 and 7.29 (AA′BB′ system, 4H), 9.55 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ −5.0, −4.7, 18.1, 21.1, 21.7, 23.0, 24.6, 25.7, 28.1, 37.7, 61.7, 78.3, 82.1, 127.5, 129.5, 135.5, 137.4, 157.3, 202.0; EIMS *m*/*z* 481 (1%, M^+), 368 (26), 308 (11), 200 (100), 185 (17), 123 (19), 117 (13), 73 (20), 57 (48).

3.1.10. (2*S*,3*R*) *tert*-Butyl-3-(*tert*-butyldimethylsilyloxy)-4-oxobutan-2-yl-[(4-methylphenyl)sulfenyl]carbamate (9a). Following the same procedure used for the preparation of **8a**, and starting from 0.236 g (0.53 mmol) of **7a**, 0.083 g (35%) of **9a** was obtained. The product was purified by column chromatography (hexane–ethyl acetate 9:1). White crystals, mp 80–81 °C (CH_2Cl_2–hexane); $[\alpha]_D$ −14.3 (*c* 1, $CHCl_3$); IR (film) ν_{max}: 2931, 2858, 1736, 1703, 1470, 1368, 1295, 1164 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 0.07 (s, 3H), 0.12 (s, 3H), 0.93 (s, 9H), 1.15 (d, 3H, *J* 6.9), 1.45 (s, 9H), 2.31 (s, 3H), 4.01 (dd, 1H, *J* 2.7 and 6.9), 4.68 (qd, 1H, *J* 6.9 and 6.9), 7.11 (s, 4H), 9.58 (d, 1H, *J* 2.7); ^{13}C NMR ($CDCl_3$, 75 MHz): δ −4.9, −4.4, 15.2, 18.1, 21.0, 25.7, 28.1, 56.3, 79.9, 82.0, 124.7, 129.5, 136.1, 136.8, 156.8, 201.8. Anal. Calcd for $C_{22}H_{37}NO_4SSi$: C, 60.10; H, 8.48; N, 3.19. Found: C, 60.24; H, 8.53; N, 3.17.

3.1.11. (2*S*,3*S*)-3-Amino-2-hydroxybutanoic acid hydrochloride (10a). To a stirred mixture of the aldehyde **8a** (0.337 g, 0.77 mmol, 1 equiv), 2-methyl-2-propanol (5 mL) and a 5% aqueous solution of NaH_2PO_4 (3 mL) a 1 M aqueous solution of $KMnO_4$ (4.5 mL, 4.5 mmol, 5.8 equiv) was added at room temperature. After 10 min, the excess of $KMnO_4$ was decomposed by adding 10% Na_2SO_3 solution, the mixture was cooled at 0 °C and acidified with 10% HCl until pH 4–5. The reaction mixture was extracted with Et_2O (4×15 mL). The combined organic extracts were washed with brine, dried, and concentrated under vacuum, to give 0.327 g of the corresponding crude acid. Without further purification, to this crude product a saturated ethereal hydrogen chloride solution (20 mL) was added. The starting deep yellow solution was becoming pale as small white crystalline product was settling down in the ethereal layer. After 6 h, the crystals were filtered, washed with anhydrous ether, and dried at vacuum to produce 0.050 g (42%) of hygroscopic white crystals; $[\alpha]_D$ −16.0 (*c* 0.5, H_2O); IR (KBr) ν_{max}: 3700–2300, 1735, 1585, 1481, 1202 cm^{-1}; ^1H NMR (D_2O positioned at 4.67 ppm, 300 MHz): δ 1.14 (d, 3H, *J* 6.6), 3.73 (dq, 1H, *J* 3.3 and 6.6), 4.40 (d, 1H, *J* 3.6); ^{13}C NMR (D_2O, dioxane as external reference at 67.4 ppm, 75 MHz): δ 12.6, 49.8, 70.8, 174.9; HRMS (FAB^+) $C_4H_{10}NO_3$ requires: 120.0660. Found: 120.0658.

3.1.12. (2*R*,3*S*)-3-Amino-2-hydroxybutanoic acid hydrochloride (11a). Following the same procedure used for the preparation of **10a**, and starting from 0.107 g (0.24 mmol) of **9a**, 0.029 g (76%,) of **11a** was obtained as a white gummy solid. ^1H NMR (D_2O positioned at 4.78 ppm, 300 MHz): δ 1.37 (d, 3H, *J* 6.6), 3.65–3.76 (m, 1H), 4.31 (d, 1H, *J* 5.1).

3.1.13. (2*S*,3*S*)-Methyl 3-[*tert*-butoxycarbonyl-[(4-methylphenyl)sulfenyl]amino]-5-methylhexanoate (12b). A stirred solution of the aldehyde **8b** (0.336 g, 0.70 mmol) in 3 mL of acetone at −15 °C was treated with 1.5 mL of Jones reagent. After being stirred at this temperature for 1 h and at room temperature for 24 h, the mixture was diluted with water and extracted with ether (4×10 mL). The organic layer was washed with brine (3×10 mL), dried, and concentrated. The residue was treated with an excess of ethereal solution of diazomethane. The crude product was purified by preparative thin layer chromatography (hexane–ethyl acetate 95:5) to produce 0.265 g (74%) of **12b**. $[\alpha]_D$ −46.0 (*c* 0.4, $CHCl_3$); IR (film) ν_{max}: 2955, 2931, 2860, 1738, 1705, 1469, 1367, 1294, 1162 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 0.04 (s, 3H), 0.06 (s, 3H), 0.52 (br d, 3H), 0.80 (d, 3H, *J* 6.5), 0.91 (s, 9H), 1.20–1.40 (m, 2H), 1.50 (s, 9H), 1.72 (m, 1H), 2.32 (s, 3H), 3.63 (s, 3H), 4.29 (d, 1H, *J* 8.0), 4.51 (m, 1H), 7.10 and 7.30 (AA′BB′ system, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ −5.3, −5.1, 18.2, 21.1, 21.5, 23.1, 24.6, 25.7, 28.1, 37.7, 51.7, 61.8, 73.6, 81.9, 128.0, 129.3, 136.1, 137.2, 157.2, 172.6. Anal. Calcd for $C_{26}H_{45}NO_5SSi$: C, 61.02; H, 8.90; N, 2.74. Found: C, 60.76; H, 8.95; N, 2.70.

3.1.14. (2*S*,3*S*)-3-Amino-2-hydroxybutanoic acid (13a). Prepared from **10a** (0.040 g, 0.26 mmol), using a Varian Bond Elut SCX column and a 2 M solution of NH_3 in methanol as eluant. Further purification was performed by silica gel chromatography using methanol–isopropanol–ammonium hydroxide 1:1:0.5, to produce 0.030 g (96%) of **13a**. Amorphous white solid, mp 239–241 °C (lit.[20] 242–243 °C; lit.[21] 240–241 °C); $[\alpha]_D$ −25.2 (*c* 1, H_2O) [(lit.[20] −26.15 (*c* 1.1, H_2O); lit.[21] −25.7 (*c* 1.1, H_2O)]; ^1H NMR (D_2O, DSS, 300 MHz): δ 1.20 (d, 3H, *J* 6.6), 3.71 (m, 1H), 4.20 (d, 1H, *J* 3.3); ^{13}C NMR (D_2O, DSS, 75 MHz): δ 14.7, 52.4, 74.3, 179.5.

3.1.15. (2*R*,3*S*)-3-Amino-2-hydroxybutanoic acid (14a). Prepared from **11a** (0.029 g, 0.18 mmol), using a Varian Bond Elut SCX column and a 2 M solution of NH_3 in methanol as eluant. Further purification was performed by silica gel chromatography using methanol–isopropanol–ammonium hydroxide 1:1:0.5, to produce 0.021 g (97%) of **14a**. Amorphous white solid; $[\alpha]_D$ +22.0 (*c* 0.5, H_2O) [(lit.[20] +22.2 (*c* 0.46, H_2O); lit.[21] +21.6 (*c* 1.1, H_2O); lit.[22] +22.6 (*c* 0.5, H_2O); lit.[23] +23.5 (*c* 2, H_2O)]; ^1H NMR (D_2O positioned at 4.68 ppm, 300 MHz): δ 1.16 (d, 3H, *J* 6.6), 3.39 (dq, 1H, *J* 4.8 and 6.6), 3.85 (d, 1H, *J* 4.8); ^{13}C NMR (D_2O, dioxane as external reference at 67.4 ppm, 75 MHz): δ 15.3, 50.6, 73.5, 177.9.

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18. The use of a stronger base such as K_2CO_3 to cleave the trifluoroacetates, favors TBDMS 3,4-migration, which suggests that $NaHCO_3$ is too weakly basic to form the alkoxide from the primary alcohol, which should be the required intermediate for the TBDMS migration.
19. The normal Pummerer products were not detected in any of these reactions, may be due to the smooth conditions used.
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24. Amide oxygen attack on sulfur resulting in the formation of a six-membered ring intermediate has also been suggested as the second step in the evolution of β-amino sulfoxides (see García Ruano, J. L.; Alemán, J.; Prado, M.; Fernández, I. *J. Org. Chem.* **2004**, *69*, 4454) as alternative to the amide nitrogen attack resulting in the azathiacyclobutane suggested by Zanda in Ref. 15d. This proposal was based on the higher stability of a 6-membered over a 4-membered cyclic systems. The attack of the nitrogen to the sulfur is the only able to explain the results obtained from the γ-amino sulfoxides described in this work because the attack of the oxygen would not explain the formation of compounds **6** or **7**, bearing the S–N bond. Taking into account that Zanda et al. have also isolated the sulfenamides from the NOPR of (Ref. 15d), an azathiacyclobutane intermediate resulting in the nitrogen attack seem to be the most probable intermediate also for β-amino sulfoxides.
25. Similar results were obtained starting from **5a**.