Supporting Information

Synthesis of β2,2-Amino Acids by Stereoselective Alkylation of Isoserine Derivatives Followed by Nucleophilic Ring-Opening of Quaternary Sulfamidates

Pablo Tovillas,†,a Claudio D. Navo,†,b Paula Oroz,a Alberto Avenoza,a Francisco Corzana,a María M. Zurbano,a Gonzalo Jiménez-Osés,b,c Jesús H. Busto,a,* and Jesús M. Peregrinaa,*

a Departamento de Química, Centro de Investigación en Síntesis Química, Universidad de La Rioja, 26006 Logroño, La Rioja, Spain.
b Center for Cooperative Research in Biosciences (CIC bioGUNE), Basque Research and Technology Alliance (BRTA), Bizkaia Technology Park, Building 800, 48160 Derio, Spain.
c Ikerbasque, Basque Foundation for Science, 48013 Bilbao, Spain.

* Email: jesusmanuel.peregrina@unirioja.es hector.busto@unirioja.es
†P.T. and C.D.N. contributed equally to this work.

Contents

1. Additional tables to follow the text of the manuscript ........................................... S02-S03
2. Diastereomeric purity determination ...................................................................... S04-S08
3. NMR spectra ........................................................................................................... S09-S62
4. Chromatogram for peptide 21 ................................................................................ S63
5. Computational details ............................................................................................. S64-S88
6. X-Ray diffraction analysis ...................................................................................... S89-S90
7. Enantiomeric purity determination of 7e and 8e by NMR chiral shift reagents .... S91-S93
1. Additional tables to follow the text of the manuscript

Table S1. Formation of chiral N,O-acetals 2, 3 and 4 from Boc-L-isoSer-OMe (1) and TMB.

| Entry | Solvent | Temperature | Time   | Acid (equiv) | mmol 1 | Yield 2+3 (%) | Ratio 2/3 | Yield 4 (%) |
|-------|---------|-------------|--------|--------------|-------|---------------|----------|------------|
| 1     | toluene | reflux      | 4 h    | TsOH·H2O (0.1) | 0.91  | 51            | 0.69/0.31 | 34         |
| 2     | toluene | reflux      | 24 h   | TsOH·H2O (0.1) | 0.46  | 64            | 0.64/0.36 | 27         |
| 3     | toluene | reflux      | 1 h    | TsOH·H2O (0.5) | 0.46  | 87            | 0.60/0.40 | 13         |
| 4     | toluene | reflux      | 1 h    | CSA·H2O (0.1)  | 0.91  | 57            | 0.72/0.28 | 29         |
| 5     | toluene | reflux      | 1 h    | CSA·H2O (0.2)  | 0.1   | 88            | 0.63/0.37 | 11         |
| 6     | toluene | 80 °C       | 1 h    | TsOH·H2O (0.2) | 0.46  | 86            | 0.62/0.38 | 14         |
| 7     | toluene | 80 °C       | 1 h    | CSA·H2O (0.2)  | 0.91  | 87            | 0.63/0.37 | 13         |
| 8     | toluene | 80 °C       | 1 h    | CSA·H2O (0.1)  | 0.91  | 57            | 0.74/0.26 | 29         |
| 9     | toluene | 80 °C       | 1 h    | BF3·Et2O (0.2) | 0.46  | 62            | 0.52/0.48 | 38         |
| 10    | toluene | 50 °C       | 1 h    | TsOH·H2O (0.2) | 0.46  | 58            | 0.79/0.21 | 25         |
| 11    | toluene | reflux      | 30 min | H2SO4 (2)     | 0.46  | 85            | 0.60/0.40 | 15         |
| 12    | xylene  | reflux      | 15 min | H2SO4 (2)     | 0.46  | 68            | 0.59/0.41 | 3          |
| 13    | xylene  | reflux      | 5 min  | H2SO4 (1)     | 0.46  | 91            | 0.66/0.34 | 9          |
| 14    | xylene  | 125 °C      | 30 min | TsOH·H2O (1)  | 0.46  | 62            | 0.79/0.21 | 38         |
| 15    | toluene | reflux      | 1 h    | CSA·H2O (0.2)  | 13.7  | 85            | 0.63/0.37 | 13         |

Only the conditions of entry 15 gave good results when we tried to scale up the reaction. For this reason, other entries such as 5, 7 and 13 were not considered.
**Table S2.** Diastereoselective alkylation of chiral bicyclic $N, O$-acetal 2.

![Diagrams of alkylation process]

| Entry | RX     | Base (equiv) | Solvent | Additive | Temperature | Time (min) | Ratio 5a-d/5’a-d | Yield 5a-d+5’a-d (%) |
|-------|--------|--------------|---------|----------|-------------|------------|------------------|---------------------|
| 1     | Mel    | LHMDS (2.0)  | THF     | HMPA     | -78 °C      | 5          | 5a/5’a          | 95                  |
| 2     | Mel    | KHDMS (2.0)  | THF     | -        | -78 °C      | 5          | 5a/5’a          | 55                  |
| 3     | Mel    | LHDMS (2.0)  | THF     | -        | -78 °C      | 60         | -               | -                   |
| 4     | Mel    | LHDMS (2.0)  | THF     | -        | -50 °C      | 60         | -               | -                   |
| 5     | Mel    | LHDMS (2.0)  | THF     | HMPA     | -90 °C      | 15         | 5a/5’a          | 95                  |
| 6     | Mel    | LHDMS (2.0)  | THF     | HMPA     | -90 °C      | 5          | 5a/5’a          | 95                  |
| 7     | Mel    | LHDMS (2.0)  | THF     | HMPA     | -90 °C      | 5          | 5a/5’a          | 84                  |
| 8     | Mel    | LHMDS (1.2)  | THF     | HMPA     | -78 °C      | 60         | 5a/5’a          | 62/17               |
| 9     | Allyl  | LHDMS (2.0)  | THF     | HMPA     | -78 °C      | 10         | 5d/5’d          | 93                  |
| 10    | BnBr   | LHDMS (2.0)  | THF     | HMPA     | -78 °C      | 10         | 5c/5’c          | 87/13               |
| 11    | BnI    | LHDMS (2.0)  | THF     | HMPA     | -78 °C      | 10         | 5c/5’c          | 73/18               |
| 12    | EtI    | LHDMS (2.0)  | THF     | HMPA     | -78 °C      | 60         | 5b/5’b          | 91                  |
| 13    | EtOTf  | LHDMS (2.0)  | THF     | HMPA     | -78 °C      | 10         | 5b/5’b          | 88/20               |
2. Diastereomeric purity determination

Purity of building blocks 2 and 3.

After an easy purification by column chromatography, compound 2 was used as starting material with a 98:2 diastereomeric ratio with respect to diastereomer 3. In the case of compound 3 the diastereomeric ratio after column chromatography was 99:1 with respect to diastereomer 2.

Figure S1. Overlapping of $^1$H NMR spectra corresponding to compounds 2 and 3.

Figure S2. $^1$H NMR zoom corresponding to spectra of starting materials after purification by column chromatography: compound 2 (A) and compound 3 (B).
Purity of alkylated compounds and derivatives.

1) The ratio of diastereoisomers for alkylation of compound 2 with methyl iodide to give 5a as a major compound is 83/17. In the same way, the ratio of diastereoisomers for alkylation of compound 3 with methyl iodide to give 6a (enantiomer of 5a) as the major compound is 82/18. In both cases, these ratios were measured by $^1$H NMR of the crude reaction mixture.

After purification by column chromatography, in the $^1$H NMR spectrum of compound 5a, the minor diastereomer was not observed. Therefore, its diastereomeric purity is >99:1. However, after purification, compound 6a showed some quantity of its diastereomer, which was integrated (98:2).

Figure S3. Ratio of diastereomers extracted from the $^1$H NMR spectra of the crude alkylation reaction mixtures of 2 (A) and 3 (B) with Mel.

Figure S4. Peaks extracted from the $^1$H NMR spectra showing in red the mixture of diastereomers from the crude alkylation reactions and in blue the pure compounds 5a (A) and 6a (B) after purification by column chromatography. (C) Integration of compound 6a.
Taking into account the starting purity of compound 2 (98% of 2 and 2% of 3), and that alkylation of the minor isomer (3) gives the enantiomer of the alkylated compound (6a), subsequent hydrolysis to obtain the amino acid gives compound 7a with an ee = 96%. Similar features occurred for amino acid 8a, which was obtained with an ee = 94%.

2) The diastereomeric ratio for alkylation reaction of compound 2 with ethyl triflate to give 5b is 85/15 measured by $^1$H NMR of the crude reaction mixture.

**Figure S5.** Ratio of diastereomers extracted from the $^1$H NMR spectrum of the crude alkylation reaction mixture of 2 with EtOTf.

After purification by column chromatography, the corresponding compound 5b has a diastereomeric purity of 95:5 with respect to the minor diastereomer.

**Figure S6.** A) In red the mixture 85:15 of diastereomers and in blue the purified compound 5b in 95:5 ratio. B) Integration of compound 5b after purification by a column chromatography.
Taking into account the starting purity of compound 2 (98% of 2 and 2% of 3), and that alkylation of the minor isomer (3) gives the enantiomer of the alkylated compound, subsequent hydrolysis to obtain the amino acid gives compound 7b with an ee = 86%.

3) The diastereomeric ratio for alkylation reaction of compound 2 with benzyl iodide to give 5c is 80/20. In the same way, the ratio of diastereoisomers for alkylation of compound 3 with benzyl iodide to give 6c (enantiomer of 5c) as the major compound is 80/20. In both cases, these ratios were measured by 1H NMR of the crude reaction mixtures.

After purification by column chromatography, in the 1H NMR spectrum of the corresponding compound 5c, used as starting material for sulfamidate chemistry, the minor diastereomer was not observed. In the same way, after purification by column chromatography the corresponding compound 6c was obtained in a 98:2 ratio respect to its diastereomer.

Figure S7. Ratio of diastereomers extracted from the 1H NMR spectra of the crude alkylation reaction mixture of 2 (A) and 3 (B) with BnI.

Figure S8. In red the mixture 80:20 of diastereoisomers. In blue the purified compounds 5c (A) and 6c (B). Compound 5b appears as a pure compound and 6c in a 98:2 ratio.
Taking into account the starting purity of compound 2 (98% of 2 and 2% of 3), and that alkylation of the minority isomer gives the enantiomer of the alkylated compound, enantiomeric excess of 5c is $\text{ee} = 96\%$. Subsequent hydrolysis to obtain the amino acid gives compound 7c with an $\text{ee} = 96\%$. The same enantiomeric excess was obtained for the sulfamidate 10 and the amino acid derivatives, which undergo reactions without loss of enantiomeric purity (ring-opening and hydrolysis reactions).

4) The diastereomeric ratio for alkylation reaction of compound 2 with allyl iodide to give 5e is 87/13 measured by $^1$H NMR of the crude reaction mixture.

![Diastereomer Ratio](image1.png)

**Figure S9. Ratio of diastereoisomers extracted from the $^1$H NMR spectrum of the crude alkylation reaction mixture of 2 with allyl iodide.**

After purification by column chromatography, in the $^1$H NMR spectrum of the corresponding compound 5d, the minor diastereomer was not observed.

![1H NMR Spectrum](image2.png)

**Figure S10. In red mixture 87:13 of diastereoisomers. In blue the pure compound 5d.**
4. NMR spectra

$^1$H NMR 400 MHz in CDCl$_3$

$^{13}$C{$_{^1}$H} NMR 100 MHz in CDCl$_3$
COSY in CDCl₃

edited-HSQC in CDCl₃ (color blue corresponds to CH₂ carbons and color red corresponds to CH₃ or CH carbons)
$^1$H NMR 400 MHz in CDCl$_3$

$^{13}$C($^1$H) NMR 100 MHz in CDCl$_3$
COSY in CDCl₃

edited-HSQC in CDCl₃ (color blue corresponds to CH₂ carbons and color red corresponds to CH₃ or CH carbons)
HMBC in CDCl₃

NOESY in CDCl₃
$^1$H NMR 400 MHz in CDCl$_3$

$^{13}$C($^1$H) NMR 100 MHz in CDCl$_3$
COSY in CDCl₃

edited-HSQC in CDCl₃ (color blue corresponds to CH₂ carbons and color red corresponds to CH₃ or CH carbons)
$^1$H NMR 400 MHz in CDCl$_3$

$^{13}$C($^1$H) NMR 100 MHz in CDCl$_3$
COSY in CDCl₃

Edited-HSQC in CDCl₃ (color blue corresponds to CH₂ carbons and color red corresponds to CH₃ or CH carbons)
$^1$H NMR 400 MHz in CDCl$_3$

$^{13}$C-$^1$H NMR 100 MHz in CDCl$_3$
COSY in CDCl₃

edited-HSQC in CDCl₃ (color blue corresponds to CH₂ carbons and color red corresponds to CH₃ or CH carbons)
$^1$H NMR 400 MHz in CDCl$_3$

$^{13}$C($^1$H) NMR 100 MHz in CDCl$_3$
COSY in CDCl$_3$

edited-HSQC in CDCl$_3$ (color blue corresponds to CH$_2$ carbons and color red corresponds to CH$_3$ or CH carbons)
$^1$H NMR 400 MHz in CDCl$_3$ (enantiomer of 5c)
$^1$H NMR 400 MHz in CDCl$_3$

$^{13}$C($^1$H) NMR 100 MHz in CDCl$_3$
COSY in CDCl₃

edited-HSQC in CDCl₃ (color blue corresponds to CH₂ carbons and color red corresponds to CH₃ or CH carbons)
$^1$H NMR 400 MHz in CDCl$_3$

Compound 6a is the enantiomer of 5a and its spectral data are in good agreement.

$^1$H NMR 400 MHz in CDCl$_3$

Compound 7a (α–MeisoSer) is the enantiomer of 8a and their spectral data are in good agreement and match with previously published data (reference 24 in the manuscript).
$^1$H NMR 400 MHz in D$_2$O

$^{13}$C($^1$H) NMR 100 MHz in D$_2$O
COSY in D$_2$O

edited-HSQC in D$_2$O (color blue corresponds to CH$_2$ carbons and color red corresponds to CH$_3$ or CH carbons)
$^1$H NMR 400 MHz in D$_2$O

$^{13}$C($^1$H) NMR 100 MHz in D$_2$O
COSY in D$_2$O

edited-HSQC in D$_2$O (color blue corresponds to CH$_2$ carbons and color red corresponds to CH$_3$ or CH carbons)
$^1$H NMR 400 MHz in D$_2$O (enantiomer of 7c)
\[ ^1H \text{ NMR} \ 400 \text{ MHz in CDCl}_3 \]

\[ ^{13}C\{^1H\} \text{ NMR} \ 100 \text{ MHz in CD}_2\text{Cl}_2 \]
COSY in CD$_3$Cl

edited-HSQC in CDCl$_3$ (color blue corresponds to CH$_2$ carbons and color red corresponds to CH$_3$ or CH carbons)
$^1$H NMR 400 MHz in CD$_3$Cl

$^{13}$C($^1$H) NMR 100 MHz in CDCl$_3$
COSY in CDCl₃

edited-HSQC in CDCl₃ (color blue corresponds to CH₂ carbons and color red corresponds to CH₃ or CH carbons)
$^1$H NMR 400 MHz in CDCl$_3$

$^{13}$C($^1$H) NMR 100 MHz in CDCl$_3$
COSY in CDCl₃

edited-HSQC in CDCl₃ (color blue corresponds to CH₂ carbons and color red corresponds to CH₃ or CH carbons)
$^1$H NMR 400 MHz in CDCl$_3$

$^{13}$C$^{[1]}$H NMR 100 MHz in CDCl$_3$
$^{1}H$ NMR 400 MHz in CDCl$_3$

$^{13}C\{^1H\}$ NMR 100 MHz in CDCl$_3$
COSY in CDCl₃

edited-HSQC in CDCl₃ (color blue corresponds to CH₂ carbons and color red corresponds to CH₃ or CH carbons)
$^1$H NMR 400 MHz in CDCl$_3$

$^{13}$C($^1$H) NMR 100 MHz in CDCl$_3$
COSY in CD$_3$Cl

Edited-HSQC in CDCl$_3$ (color blue corresponds to CH$_2$ carbons and color red corresponds to CH$_3$ or CH carbons)
$^1$H NMR 400 MHz in CDCl$_3$

![NMR Spectrum of Compound 14](image)

$^{13}$C{$_1^1$H} NMR 100 MHz in CDCl$_3$

![NMR Spectrum of Compound 14](image)
COSY in CDCl₃

edited-HSQC in CDCl₃ (color blue corresponds to CH₂ carbons and color red corresponds to CH₃ or CH carbons)
$^1$H NMR 400 MHz in CDCl$_3$

$^{13}$C($^1$H) NMR 100 MHz in CDCl$_3$
COSY in CDCl₃

edited-HSQC in CDCl₃ (color blue corresponds to CH₂ carbons and color red corresponds to CH₃ or CH carbons)
$^{19}$F{$^{1}$H} NMR 281.25 MHz in CDCl$_3$

$^1$H NMR 400 MHz in CDCl$_3$

Spectral data match with previously published data (reference 57 in the manuscript).

![Chemical structure of (15b)]
$\text{H NMR 400 MHz in D}_2\text{O}$

$\text{C}_{\{^1\text{H}\}} \text{ NMR 100 MHz in D}_2\text{O}$
COSY in D$_2$O

edited-HSQC in D$_2$O (color blue corresponds to CH$_2$ carbons and color red corresponds to CH$_3$ or CH carbons)
$^1$H NMR 400 MHz in D$_2$O

$^{13}$C($^1$H) NMR 100 MHz in D$_2$O
COSY in D$_2$O

edited-HSQC in D$_2$O (color blue corresponds to CH$_2$ carbons and color red corresponds to CH$_3$ or CH carbons)
$^1$H NMR 400 MHz in D$_2$O

$^{13}$C{$^1$H} NMR 75 MHz in D$_2$O
COSY in D$_2$O

edited-HSQC in D$_2$O (color blue corresponds to CH$_2$ carbons and color red corresponds to CH$_3$ or CH carbons)
$^1$H NMR 400 MHz in D$_2$O

$^{13}$C($^1$H) NMR 100 MHz in D$_2$O

HCl · H$_2$N$^{(S)}$CO$_2$H

(19)
COSY in D$_2$O

edited-HSQC in D$_2$O (color blue corresponds to CH$_2$ carbons and color red corresponds to CH$_3$ or CH carbons)
$^{19}\text{F}^{1\text{H}}$ NMR 282 MHz in D$_2$O
$^1$H NMR 400 MHz in CDCl$_3$

$^{13}$C$[^1$H$]$ NMR 100 MHz in CDCl$_3$
COSY in CDCl₃

edited-HSQC in CDCl₃ (color blue corresponds to CH₂ carbons and color red corresponds to CH₃ or CH carbons)
$^1$H NMR 400 MHz in DMF-d$_7$

$^{13}$C($^1$H) NMR 100 MHz in DMF-d$_7$
COSY in DMF-d7

edited-HSQC in DMF-d7 (color blue corresponds to CH$_2$ carbons and color red corresponds to CH$_3$ or CH carbons)
4. Chromatogram for peptide 21

Semi-preparative RP-HPLC purification of peptide 21 using the following conditions:

Phenomenex Luna C18(2) column (10 μm, 250 mm × 21.2 mm) and a dual absorbance detector, with a flow rate of 20 mL/min. Retention time (Rt) = 34.02 min, using a gradient: acetonitrile/water+0.1% TFA (22.5:77.5) → (77.5:22.5), 37 min (λ = 212 nm).

**Figure S11. Chromatogram of peptide 21.**
5. Computational details

All possible conformers and ring isomers were investigated. Some structures converged to the same stationary point upon optimization; redundant isomers were discarded and only the unique structures were included in the Boltzmann distribution of Gibbs free energies, summarized in the following table. Bold entries are the minimum energy structures for each diastereomer. The index in last position of each structure names corresponds to the approximate value of dihedral angle formed between Me7-C7-O7-OMe7.

Table S3. Energies, enthalpies, free energies and entropies of all the conformers of diastereomers I-IV calculated with PCM(toluene)/M062x/6-31+G(d,p).

| Structure | E_{elec} (Hartree) | E_{elec + ZPE} (Hartree) | H (Hartree) | S (cal mol^{-1} K^{-1}) | Lowest freq. (cm^{-1}) | G (Hartree) | G (kcal mol^{-1}) | p (%) | cumulative p (%) |
|-----------|------------------|-------------------------|-------------|--------------------------|----------------------|--------------|-----------------|-------|-----------------|
| I-α-in-60 | -895.896008      | -895.634610             | -895.606992 | 148.3                    | 28.7                 | -895.695952  | 5.5             | 0.0              |                  |
| I-α-in-180| -895.900938      | -895.639530             | -895.611854 | 148.4                    | 24.2                 | -895.700896  | 2.4             | 1.6              |                  |
| I-α-in-300| -895.901896      | -895.640657             | -895.612855 | 149.6                    | 23.9                 | -895.702378  | 1.5             | 5.3              |                  |
| I-α-out-60| -895.897292      | -895.635821             | -895.608233 | 148.5                    | 22.9                 | -895.697173  | 4.7             | 0.1              |                  |
| I-α-out-180| -895.902043     | -895.640776             | -895.613019 | 148.7                    | 26.5                 | -895.702384  | 1.5             | 5.3              |                  |
| I-α-out-300| -895.903045     | -895.641726             | -895.613981 | 148.5                    | 33.0                 | -895.703487  | 0.8             | 13.1             |                  |
| II-α-in-60| -895.896364      | -895.634918             | -895.607300 | 148.7                    | 25.3                 | -895.696357  | 5.3             | 0.0              |                  |
| II-α-in-180| -895.896528     | -895.635212             | -895.607408 | 150.3                    | 23.9                 | -895.696817  | 5.0             | 0.1              |                  |
| II-α-in-300| -895.893544     | -895.632030             | -895.604432 | 149.2                    | 21.8                 | -895.693094  | 7.3             | 0.0              |                  |
| II-α-out-60| -895.897451      | -895.636006             | -895.608387 | 148.5                    | 27.3                 | -895.697534  | 4.5             | 0.1              |                  |
| II-α-out-180| -895.897857     | -895.636362             | -895.608733 | 148.6                    | 25.4                 | -895.697664  | 4.4             | 0.1              |                  |
| II-α-out-300| -895.894893     | -895.633425             | -895.605824 | 148.6                    | 25.1                 | -895.694680  | 6.3             | 0.0              |                  |
| II-β-in-60| -895.897568      | -895.636318             | -895.608583 | 149.3                    | 23.9                 | -895.697823  | 4.3             | 0.1              |                  |
| II-β-in-300| -895.894820     | -895.633599             | -895.605920 | 148.8                    | 29.2                 | -895.694767  | 6.2             | 0.0              |                  |
| II-β-out-60| -895.898160      | -895.637036             | -895.609264 | 149.3                    | 28.6                 | -895.698623  | 3.8             | 0.3              |                  |
| II-β-out-300| -895.895603     | -895.634384             | -895.606717 | 149.1                    | 21.1                 | -895.695565  | 5.8             | 0.0              |                  |
### II-α-in-60

| Energy Values |  |  |  |  |  |  |
|---------------|---|---|---|---|---|---|
| -895.905267   | -895.643851 | -895.616333 | 146.5 | 42.1 | -895.704741 | 0.0 | 36.4 |
| -895.904377   | -895.642780 | -895.615392 | 145.3 | 41.7 | -895.703225 | 1.0 | 10.6 |
| -895.899429   | -895.637991 | -895.610562 | 146.1 | 38.6 | -895.698714 | 3.8 | 0.3 |
| -895.904562   | -895.642967 | -895.615520 | 146.4 | 32.7 | -895.703877 | 0.5 | 18.0 |
| -895.903363   | -895.641982 | -895.614492 | 146.2 | 33.2 | -895.702807 | 1.2 | 7.5 |
| -895.898699   | -895.637295 | -895.609857 | 146.4 | 33.2 | -895.698107 | 4.2 | 0.2 |

### II-α-in-180

| Energy Values |  |  |  |  |  |  |
|---------------|---|---|---|---|---|---|
| -895.899139   | -895.637205 | -895.610169 | 142.3 | 50.9 | -895.697136 | 4.8 | 0.1 |
| -895.898320   | -895.636565 | -895.609328 | 144.1 | 47.7 | -895.697050 | 4.8 | 0.1 |
| -895.897193   | -895.635188 | -895.608222 | 142.5 | 46.0 | -895.694961 | 6.1 | 0.0 |
| -895.89649    | -895.637399 | -895.609794 | 148.2 | 16.5 | -895.698367 | 4.0 | 0.2 |

### II-α-in-300

| Energy Values |  |  |  |  |  |  |
|---------------|---|---|---|---|---|---|
| 72.9

### IV-α-in-60

| Energy Values |  |  |  |  |  |  |
|---------------|---|---|---|---|---|---|
| -895.895947   | -895.634462 | -895.607036 | 146.7 | 31.9 | -895.694992 | 6.1 | 0.0 |
| -895.89342    | -895.637800 | -895.610273 | 147.3 | 34.3 | -895.698383 | 4.0 | 0.2 |
| -895.898115   | -895.636612 | -895.609161 | 147.2 | 30.7 | -895.697279 | 4.7 | 0.1 |
| -895.892875   | -895.631549 | -895.604019 | 148.0 | 24.2 | -895.692288 | 7.8 | 0.0 |
| -895.898651   | -895.637154 | -895.609618 | 147.4 | 29.4 | -895.697974 | 4.2 | 0.1 |
| -895.896251   | -895.634948 | -895.607360 | 149.2 | 24.0 | -895.695874 | 5.6 | 0.0 |
| -895.899139   | -895.637205 | -895.610169 | 142.3 | 50.9 | -895.697136 | 4.8 | 0.1 |
| -895.898320   | -895.636565 | -895.609328 | 144.1 | 47.7 | -895.697050 | 4.8 | 0.1 |
| -895.897193   | -895.635188 | -895.608222 | 142.5 | 46.0 | -895.694961 | 6.1 | 0.0 |
| -895.89649    | -895.637399 | -895.609794 | 148.2 | 16.5 | -895.698367 | 4.0 | 0.2 |

### IV-α-in-180

| Energy Values |  |  |  |  |  |  |
|---------------|---|---|---|---|---|---|
| 0.8

### IV-α-in-300

| Energy Values |  |  |  |  |  |  |
|---------------|---|---|---|---|---|---|
| aEnergy values calculated with PCM(toluene)/M06-2X/6-31+G(d,p). 1 Hartree = 627.51 kcal mol⁻¹. bThermal corrections at 388.15 K.

| Energy Values |  |  |  |  |  |  |
|---------------|---|---|---|---|---|---|
| aEnergy values calculated with PCM(toluene)/M06-2X/6-31+G(d,p). 1 Hartree = 627.51 kcal mol⁻¹. bThermal corrections at 388.15 K.
Acid-catalyzed elimination to form enecarbamates 4

Protonation at O1 in all the conformers calculated for I (compound 3) and III (compound 2) led to the spontaneous cleavage of the O1-C7a bond and formation of enammonium cations (4H) upon optimization of the corresponding structures. Only one structure of each diastereoisomers (2H and 3H) kept these atoms bonded to each other. Potential energy scan along the O1-C7a bond revealed a barrierless (ΔE‡ ≤ 0.2 kcal mol⁻¹) and highly exergonic process (ΔE = -15.0 kcal mol⁻¹) for both diastereomers.

![Figure S12](image)

**Figure S12.** A) Lowest-energy structures for the protonated bicyclic scaffolds (2H and 3H) and the corresponding enammonium cations (4H) formed upon cleavage of the O1-C7a bond. B) Potential energy scan along the O1-C7a bond calculated with PCM(toluene)/M06-2X/6-31+G(d,p).

| Structure | E_{elc} (Hartree)ᵃ | E_{elc} + ZPE (Hartree)ᵃ | H (Hartree)ᵇ | S (cal mol⁻¹ K⁻¹)ᵇ | G (Hartree)ᵃᵇ | Lowest freq. (cm⁻¹) | # of imaginary frequencies |
|-----------|-------------------|--------------------------|--------------|-------------------|----------------|-------------------|--------------------------|
| 2H        | -896.263391       | -895.989469              | -895.961270  | 148.9             | -896.051515    | 43.3              | 0                       |
| 3H        | -896.263619       | -895.990495              | -895.962321  | 147.9             | -896.052205    | 45.7              | 0                       |
| (2S',5'R)-4H | -896.286615      | -896.012925              | -895.983912  | 152.1             | -896.076140    | 40.5              | 0                       |
| (2S',5'S)-4H | -896.285306      | -896.012075              | -895.982940  | 153.1             | -896.075134    | 37.3              | 0                       |

ᵃEnergy values calculated with PCM(toluene)/M06-2X/6-31+G(d,p). 1 Hartree = 627.51 kcal mol⁻¹.
ᵇThermal corrections at 388.15 K.
Table S5. Energies, enthalpies, free energies and entropies of the lowest-energy structures for the alkylation reaction of enolates 2' and 3' with bromomethane calculated with PCM(THF)/M06-2X/6-31+G(d,p).

| Structure          | E_{elec} (Hartree) | E_{elec} + ZPE (Hartree) | H (Hartree) | S (cal mol^{-1} K^{-1}) | G (Hartree) | Lowest freq. (cm^{-1}) | # of imag freq |
|--------------------|--------------------|----------------------------|-------------|--------------------------|-------------|--------------------------|---------------|
| 2'                 | -895.385429        | -895.139171                | -895.130778 | 105.8                    | -895.162455 | 32.6                     | 0             |
| 2'_TSinv           | -895.383295        | -895.137343                | -895.129284 | 102.7                    | -895.160568 | -49.7                    | 1             |
| 2'_epi             | -895.386465        | -895.140164                | -895.131624 | 106.5                    | -895.163771 | 44.4                     | 0             |
| MeBr               | -2611.678064       | -2611.640379               | -2611.637871 | 54.8                     | -2611.654906 | 619.7                    | 0             |
| 2'_preTSMeBr       | -3507.079438       | -3506.794090               | -3506.783029 | 131.1                    | -3506.819923 | 14.6                     | 0             |
| 2'_TSMeBr          | -3507.072730       | -3506.787764               | -3506.777132 | 125.9                    | -3506.813518 | -533.6                   | 1             |
| 5a_epi             | -935.213258        | -934.924431                | -934.915493 | 108.1                    | -934.948056 | 39.5                     | 0             |
| 2'_epi_preTSMeBr   | -3507.082843       | -3506.797538               | -3506.786279 | 129.4                    | -3506.823998 | 26.7                     | 0             |
| 2'_epi_TSMeBr      | -3507.074239       | -3506.789171               | -3506.778460 | 126.9                    | -3506.814996 | -546.4                   | 1             |
| 5a                 | -935.210622        | -934.922044                | -934.912860 | 110.9                    | -934.945962 | 31.1                     | 0             |
| 3'                 | -895.386465        | -895.140164                | -895.131624 | 106.5                    | -895.163771 | 44.4                     | 0             |
| 3'_TSinv           | -895.383295        | -895.137343                | -895.129284 | 102.7                    | -895.160568 | -49.7                    | 1             |
| 3'_epi             | -895.385429        | -895.139171                | -895.130778 | 105.8                    | -895.162455 | 32.6                     | 0             |
| 3'_preTSMeBr       | -3507.082843       | -3506.797538               | -3506.786279 | 129.4                    | -3506.823998 | 26.7                     | 0             |
| 3'_TSMeBr          | -3507.074239       | -3506.789171               | -3506.778460 | 126.9                    | -3506.814996 | -546.4                   | 1             |
| 6a                 | -935.210622        | -934.922044                | -934.912860 | 110.9                    | -934.945962 | 31.1                     | 0             |
| 3'_epi_preTSMeBr   | -3507.079438       | -3506.794090               | -3506.783029 | 131.1                    | -3506.819923 | 14.6                     | 0             |
| 3'_epi_TSMeBr      | -3507.072730       | -3506.787764               | -3506.777132 | 125.9                    | -3506.813518 | -533.6                   | 1             |
| 6a_epi             | -935.213258        | -934.924431                | -934.915493 | 108.1                    | -934.948056 | 39.5                     | 0             |
| Br                 | -2571.959141       | -2571.959141               | -2571.957596 | 36.9                     | -2571.969074 | 0                        | 0             |

*Energy values calculated with PCM(THF)/M06-2X/6-31+G(d,p). 1 Hartree = 627.51 kcal mol^{-1}. *bThermal corrections at 195.15 K.
Figure S13. Minimum-energy pathways for the alkylation reaction of enolate 3' with bromomethane calculated with PCM(THF)/M06-2X/6-31+G(d,p). Free Gibbs energies (ΔG) calculated at 195 K are given in kcal mol⁻¹.
Figure S14. Lowest-energy structures for the alkylation reaction of enolates 2’ with bromomethane calculated with PCM(THF)/M06-2X/6-31+G(d,p).
**Figure S15.** Lowest-energy structures for the alkylation reaction of enolates 3' with bromomethane calculated with PCM(THF)/M06-2X/6-31+G(d,p).
Cartesian coordinates of the lowest-energy calculated structures.

Structure I-α-in-180

| Atom | X     | Y     | Z     |
|------|-------|-------|-------|
| O    | -0.529474 | -0.279341 | 0.885654 |
| N    | 0.595225   | 0.773956   | -0.786735 |
| H    | 4.281069   | -1.922726   | 0.418124 |
| H    | 4.450318   | -0.173241   | 0.059771 |
| H    | 4.580889   | -1.375439   | -1.249070 |
| C    | 4.080026   | -1.132985   | -0.312495 |
| C    | 0.454792   | -0.423831   | -0.242506 |
| C    | -0.925029  | 1.365867    | -0.816147 |
| H    | -0.918200  | -1.419418   | -1.546068 |
| H    | 0.803268   | -1.606625   | -2.004720 |
| C    | 0.098926   | -1.561434   | -1.175436 |
| C    | 1.888629   | 0.599742    | 0.605913 |
| H    | 4.822009   | -1.856844   | 1.734451 |
| C    | 1.845168   | -1.173759   | 2.001740 |
| H    | 0.066797   | -2.571996   | -0.327874 |
| H    | -0.841405  | -1.514402   | -1.416412 |
| C    | -0.753147  | 1.322335    | -0.849796 |
| C    | 1.545280   | 1.556906    | -0.119768 |
| C    | -1.362480  | 0.796564    | 0.484504 |
| H    | 0.720970   | 2.409458    | -0.907437 |
| C    | -1.347138  | 1.571084    | 1.256499 |
| H    | -1.275380  | 0.921318    | -1.721448 |
| C    | -2.814129  | 0.386263    | 0.289932 |
| O    | -3.733630  | 1.144373    | 0.483288 |
| C    | -2.942246  | -0.853415   | -0.178121 |
| C    | -4.288447  | -1.276987   | -0.436900 |
| C    | -4.874600  | -1.236164   | 0.482439 |
| H    | -4.208720  | -2.299585   | 0.798658 |
| C    | -4.745774  | -0.632230   | -1.189304 |

Structure I-α-in-60

| Atom | X     | Y     | Z     |
|------|-------|-------|-------|
| O    | -0.529474 | -0.279341 | 0.885654 |
| N    | 0.595225   | 0.773956   | -0.786735 |
| H    | 4.281069   | -1.922726   | 0.418124 |
| H    | 4.450318   | -0.173241   | 0.059771 |
| H    | 4.580889   | -1.375439   | -1.249070 |
| C    | 4.080026   | -1.132985   | -0.312495 |
| C    | 0.454792   | -0.423831   | -0.242506 |
| C    | -0.925029  | 1.365867    | -0.816147 |
| H    | -0.918200  | -1.419418   | -1.546068 |
| H    | 0.803268   | -1.606625   | -2.004720 |
| C    | 0.098926   | -1.561434   | -1.175436 |
| C    | 1.888629   | 0.599742    | 0.605913 |
| H    | 4.822009   | -1.856844   | 1.734451 |
| C    | 1.845168   | -1.173759   | 2.001740 |
| H    | 0.066797   | -2.571996   | -0.327874 |
| H    | -0.841405  | -1.514402   | -1.416412 |
| C    | -0.753147  | 1.322335    | -0.849796 |
| C    | 1.545280   | 1.556906    | -0.119768 |
| C    | -1.362480  | 0.796564    | 0.484504 |
| H    | 0.720970   | 2.409458    | -0.907437 |
| C    | -1.347138  | 1.571084    | 1.256499 |
| H    | -1.275380  | 0.921318    | -1.721448 |
| C    | -2.814129  | 0.386263    | 0.289932 |
| O    | -3.733630  | 1.144373    | 0.483288 |
| C    | -2.942246  | -0.853415   | -0.178121 |
| C    | -4.288447  | -1.276987   | -0.436900 |
| C    | -4.874600  | -1.236164   | 0.482439 |
| H    | -4.208720  | -2.299585   | 0.798658 |
| C    | -4.745774  | -0.632230   | -1.189304 |

Structure I-α-in-300

| Atom | X     | Y     | Z     |
|------|-------|-------|-------|
| O    | -0.518740 | -0.317141 | 0.806685 |
| O    | 2.236931  | 0.901179 | 0.502887 |
| O    | 1.474622  | 2.882001 | -0.250103 |
| N    | 0.449508  | 0.887715 | -0.862885 |
| O    | 2.691644  | -1.058795 | -0.618837 |
| C    | 1.883241  | -0.488920 | 0.358774 |
| C    | 0.098926  | -1.561434 | -1.175435 |
| H    | 0.803268  | -1.606625 | -2.004720 |
| H    | 0.128384  | -2.503196 | -0.621257 |
| H    | -0.918200 | -1.419418 | -1.546068 |
| C    | -0.925029 | 1.365867 | -0.816147 |
| C    | 1.397328  | 1.682241 | -0.211760 |
| C    | 0.454792  | -0.423831 | -0.242506 |
| C    | 4.080026  | -1.132985 | -0.312495 |
| H    | 4.580889  | -1.375439 | -1.249070 |
| C    | 4.450318  | -0.173241 | 0.059771 |

Structure I-α-out-180

| Atom | X     | Y     | Z     |
|------|-------|-------|-------|
| O    | -0.387924 | -0.541535 | 0.883383 |
| O    | 2.295330  | 0.843835 | 0.751452 |
Structure I-α-out-300

Structure I-α-out-60

Structure I-α-out-180

Structure II-α-in-180
Structure II-α-out-60

Structure II-β-in-300

Structure II-α-out-300
| Structure III-α-out-180 |  |
|------------------------|--|---|---|---|
| O  | -0.125305 | 1.498756 | 0.559117 |
| O  | 1.021626 | -1.429460 | 0.284257 |
| O  | 3.030682 | -0.323441 | 0.574227 |
| O  | -0.406790 | -2.012095 | -1.356680 |
| N  | 0.430034 | 0.150148 | -1.206010 |
| C  | -0.792423 | 0.844683 | -1.598080 |
| C  | 1.002265 | 0.895072 | -0.101768 |
| H  | 1.951441 | 2.009302 | -0.495278 |
| H  | 2.817096 | 1.634546 | -1.039953 |
| H  | 1.417327 | 2.733908 | -1.147772 |
| H  | 2.296348 | 2.516962 | 0.408766 |
| C  | 0.275341 | -1.185522 | -0.809434 |
| C  | 1.400937 | -0.087880 | 2.248140 |
| H  | 1.845839 | 0.845092 | 2.603014 |
| H  | 0.328213 | -0.079443 | 2.437316 |
| H  | 1.875082 | -0.927923 | 2.758503 |
| C  | -1.293184 | 1.339839 | -0.219698 |
| C  | 1.652941 | -0.230390 | 0.767159 |
| O  | 3.479848 | -0.900863 | -0.648022 |
| C  | 4.550578 | -0.703343 | -0.694781 |
| C  | 3.307573 | -1.979250 | -0.651537 |
| H  | 2.991842 | -0.453399 | -1.521881 |
| H  | -1.828757 | 2.290180 | -0.826210 |
| H  | -0.552302 | 1.681386 | -2.255306 |
| C  | -1.476789 | 0.162471 | -2.102373 |
| C  | -2.199337 | 0.291588 | 0.418174 |
| O  | -1.860980 | -0.467289 | 1.298219 |
| O  | -3.403821 | 0.300453 | -0.156447 |
| C  | -4.312475 | -0.715611 | -0.294667 |
| H  | -5.222930 | -0.571536 | -0.282396 |
| H  | -3.884899 | -1.702243 | 0.108546 |
| H  | -4.506066 | -0.595053 | 1.361641 |

| Structure III-α-out-60 |  |
|------------------------|--|---|---|---|
| O  | 0.158458 | 1.233184 | -1.000621 |
| O  | 1.077466 | -1.281137 | 0.472753 |
| O  | -3.001195 | -0.091320 | 0.056625 |
| O  | 0.468969 | -1.315261 | 2.109477 |
| C  | -0.219675 | -0.703929 | 1.335125 |
| C  | -1.584070 | -0.779950 | -1.812454 |
| C  | -2.076566 | -0.065610 | -2.477930 |
| C  | -0.530346 | -0.865148 | -2.076551 |
| H  | -2.058987 | -1.757539 | -1.914358 |
| H  | -3.884899 | -1.702243 | 0.108546 |
| C  | -1.697463 | -0.298230 | -0.382863 |
| H  | -3.882515 | -1.202055 | -0.066628 |
| H  | -4.761626 | -0.954598 | 0.527602 |
| H  | -4.182902 | -1.353829 | -1.108039 |
| H  | -3.421956 | -2.112602 | 0.327743 |
| H  | 1.972970 | 2.148063 | -0.662280 |
| H  | 0.901837 | 2.409307 | 1.495243 |
| C  | 1.733115 | 0.868547 | 1.842185 |
| C  | 2.186985 | 0.009005 | -0.593290 |
| C  | 1.724439 | -0.996760 | -1.073355 |
| C  | 3.450368 | 0.143300 | -0.184571 |
| C  | 4.266964 | -1.031883 | -0.299816 |
| H  | 5.242527 | -0.749994 | 0.089454 |
| H  | 3.832625 | -1.842880 | 0.287108 |
| H  | 4.339047 | -1.334002 | -1.345817 |

| Structure III-α-out-360 |  |
|------------------------|--|---|---|---|
| O  | 0.010238 | 1.067463 | -1.052972 |
| O  | -0.902427 | 1.400862 | 0.702224 |
| O  | -2.941506 | -0.546900 | 0.379309 |
| O  | 0.747491 | -1.156646 | 2.214066 |
| N  | -0.230691 | 0.685058 | 1.193103 |
| C  | 0.983460 | 1.479378 | 1.047524 |
| C  | -0.981330 | 0.833171 | -0.037418 |
| C  | -1.939833 | 2.007561 | -0.031711 |
| H  | -2.723380 | 1.862102 | 0.711888 |
| H  | -1.384500 | 2.920901 | 0.195969 |
| H  | -2.383602 | 2.125981 | -1.023492 |
| C  | -0.048413 | -0.678134 | 1.448172 |
| C  | -1.574484 | -1.161649 | -1.575199 |
| H  | -2.072222 | -0.519637 | -2.306391 |
| H  | -0.521784 | -1.251135 | -1.841605 |
| H  | -2.040598 | -2.149444 | -1.575304 |
| C  | 1.274730 | 1.286292 | -0.460887 |
| C  | -1.659953 | -0.507699 | -0.185195 |

| Structure IV-α-in-180 |  |
|------------------------|--|---|---|---|
| O  | 0.023863 | -0.617555 | -1.239086 |
| O  | 1.063122 | 1.042640 | 1.089132 |
| O  | 1.920055 | 1.433688 | -0.037401 |
| O  | -0.458414 | 0.255120 | 2.552396 |
Structure IV-a-in-60

Structure IV-a-in-300

Structure IV-a-out-180
Structure IV-α-out-300

| C   | -0.066433  | -0.582762  | -1.347025 |
| C   | 1.170871   | 0.794088   | 1.180222  |
| O   | -0.549882  | 0.177643   | 2.496595  |
| N   | 0.255745   | -1.227229  | 0.829576  |
| O   | 1.880958   | 1.164518   | -0.994909 |
| C   | 1.877148   | 0.252476   | 0.032909  |
| C   | 1.752319   | -2.148017  | -0.943738 |
| H   | 2.470162   | -2.540384  | -0.222797 |
| H   | 2.274044   | -1.847290  | -1.855868 |
| H   | 1.043409   | -2.937622  | -1.203917 |
| C   | -1.035210  | -1.766596  | 0.417534  |
| O   | 0.209067   | -0.047669  | 1.598882  |
| C   | 0.992108   | -0.956428  | -0.391342 |
| C   | 2.603241   | 2.368694   | -0.763071 |
| H   | 2.321335   | 3.041017   | -1.570491 |
| C   | 3.684462   | 2.198735   | -0.795928 |
| C   | 2.320006   | 2.813529   | 0.195366  |
| C   | 3.263099   | -0.134362  | 0.527851  |
| H   | 3.732320   | 0.728662   | 1.003480  |
| H   | 3.885462   | -0.472895  | -0.307711 |
| H   | 3.187253   | -0.928967  | 1.273470  |
| C   | -1.287282  | -0.959239  | -0.883720 |
| H   | -1.782622  | -1.602728  | 1.193928  |
| H   | -1.804233  | -1.551377  | -1.643489 |
| H   | -0.946891  | -2.834486  | 0.212832  |
| C   | -2.112449  | 0.282936   | -0.567442 |
| O   | -1.667182  | 1.388580   | -0.395957 |
| C   | -3.405771  | -0.042166  | -0.450601 |
| C   | -4.274848  | 1.024450   | -0.044760 |
| H   | -4.257097  | 1.823628   | -0.787612 |

Structure IV-β-in-300

| O   | 0.363774   | -1.019450  | -1.510376 |
| C   | 1.145441   | 0.811575   | 1.334981  |
| O   | 0.200963   | 1.386702   | -0.692344 |
| O   | -0.033718  | -0.460601  | 2.785358  |
| N   | 0.686714   | -1.286087  | 0.740921  |
| C   | -0.390006  | -2.189220  | 0.356116  |
| C   | 1.272368   | -0.710648  | -0.465487 |
| C   | 2.610139   | -1.333375  | -0.816754 |
| H   | 3.331975   | -1.179829  | -0.012209 |
| H   | 2.463949   | -2.406564  | -0.956804 |
| H   | 2.999650   | -0.906405  | -1.749373 |
| C   | 0.515791   | -0.331214  | 1.722767  |
| C   | 2.607618   | 1.557834   | -0.397760 |
| H   | 2.572087   | 2.556769   | 0.040348  |
| C   | 3.461499   | 1.036398   | 0.033801  |
| H   | 2.740087   | 1.644298   | -1.479016 |
| Atom | X       | Y       | Z       |
|------|---------|---------|---------|
| H    | -4.514941 | -2.113695 | -0.343522 |
| H    | -2.871675  | -2.437183  | 0.302143 |
| H    | -4.098440  | -1.643589  | 1.338469 |
| H    | -1.266785  | 1.835589   | 1.546850 |
| Structure (2S,5'S)-4H |
| O    | -1.002155  | 2.040492   | 1.124331 |
| O    | 1.288418   | -1.372609  | -0.636405 |
| O    | 2.309388   | -0.368213  | 1.86106  |
| O    | -0.838520  | -1.493075  | -1.418405 |
| Structure 2' |
| H    | 0.132282   | -0.910353  | -1.01758 |
| O    | 3.414557   | -0.314615  | -1.010158 |
| H    | 3.861788   | -1.309322  | -0.979144 |
| H    | 3.173219   | -0.077272  | -2.048649 |
| Structure 2'_TSinv |
| H    | 4.124462   | 0.417710   | -0.619539 |
| C    | -1.844047  | 1.491705   | 0.152899 |
| C    | 2.153203   | -0.296968  | -0.169968 |
| C    | 3.133857   | -1.441048  | 1.673532 |
| C    | 3.006825   | -1.431596  | 2.573461 |
| H    | 2.793306   | -2.396539  | 1.267796 |
| O    | 4.181632   | -1.263203  | 1.421555 |
| H    | -2.701196  | 2.124549   | -0.05941 |
| H    | -0.739530  | 2.330696   | -1.521323 |
| C    | -1.621281  | 0.828290   | 1.925880 |
| C    | -2.343162  | 0.120289   | 0.605189 |
| O    | -1.834235  | -0.457500  | 1.537281 |
| O    | -3.317347  | -0.332065  | -0.157842 |
| C    | -3.777267  | -1.669430  | 0.129816 |
| H    | -4.569909  | -1.861372  | 0.580867 |
| H    | -2.951748  | -2.370080  | -0.001658 |
| C    | -4.154085  | -1.713931  | 1.151896 |
| H    | -0.984836  | 1.438796   | 1.887761 |
| H    | 0.992000   | 3.054555   | -0.283121 |
| C    | 1.991075   | 2.306278   | 0.986782 |
| H    | 2.668606   | 2.493867   | -0.631980 |
| Structure 2'_TSinv |
| H    | 4.181632   | -1.263203  | 1.421555 |
| O    | -2.951748  | 2.124549   | -0.05941 |
| O    | -4.154085  | 1.713931   | -1.151896 |
| C    | -0.984836  | -1.438796  | 1.887761 |
| C    | 0.992000   | 3.054555   | -0.283121 |
| C    | 1.991075   | 2.306278   | 0.986782 |
| H    | 2.668606   | 2.493867   | -0.631980 |
| Structure 2' |
| O    | 0.138091   | 0.542770   | -1.541420 |
| O    | -1.107730  | -0.621739  | 1.244700 |
| O    | -2.987669  | -2.263277  | -0.072970 |
| O    | 0.237501   | 0.508960   | 2.653910 |
| C    | -0.334088  | 1.382301   | 0.562340 |
| N    | 0.303896   | 1.834740   | 0.147660 |
| N    | -0.938618  | 0.807921   | -0.642010 |
| C    | -1.889831  | 1.763172   | -1.337420 |
| H    | -2.723467  | 2.032163   | -0.689650 |
| H    | -1.327917  | 2.659291   | 1.612210 |
| H    | -2.723467  | 2.032163   | -0.689650 |
| C    | -0.342809  | 0.442191   | 1.574280 |
| C    | 1.234201   | -1.751269  | -0.859130 |
| H    | 1.668191   | -1.714528  | -1.862540 |
| H    | -0.146611  | -1.804829  | -0.947890 |
| Structure 2'_TSinv |
| O    | 0.375272   | -0.521911  | 0.883879 |
| O    | -2.310528  | 0.894919   | 0.564219 |
| O    | -2.728448  | -0.851491  | -0.874201 |
Structure 5a_epi

| Element | X    | Y    | Z    |
|---------|------|------|------|
| H       | 2.537719 | -0.021083 | 1.040511 |
| H       | 2.131248  | -1.167943 | -0.344859 |
| Br      | 4.671018  | -1.058755 | 0.032451 |

Structure 2'_epi_preTSMeBr

| Element | X    | Y    | Z    |
|---------|------|------|------|
| Br      | 4.063688 | 0.572816 | -0.952911 |

Structure 2'_epi_TSMeBr

| Element | X    | Y    | Z    |
|---------|------|------|------|
| Br      | 4.063688 | 0.572816 | -0.952911 |

Structure 2'_epi_TSMeBr

| Element | X    | Y    | Z    |
|---------|------|------|------|
| Br      | 4.063688 | 0.572816 | -0.952911 |
**Structure 5a**

- **H** 3.089320 3.549731 -0.693811
- **H** 2.026440 4.153081 -1.999221
- **H** 1.778860 4.687061 -0.310561
- **C** 2.174860 -0.433089 0.025719
- **H** 2.207520 0.133911 -0.892631
- **H** 2.601380 0.012581 0.912049
- **H** 1.362170 -1.134869 0.147199
- **Br** 3.771020 -1.854549 -0.400731

- **O** 0.294159 -0.480860 0.798271
- **O** -2.276921 1.033270 0.353591
- **O** -2.957571 -0.930320 -0.639439
- **O** -1.275111 2.847220 -0.522819
- **N** -0.489821 0.705270 -0.967299
- **C** 0.937269 1.000060 -0.946249
- **C** -0.664681 -0.552500 -0.258339
- **C** -0.438101 -1.785110 -1.108039
- **H** -1.123341 -1.796650 -1.954339
- **H** 0.594909 -1.801820 -1.462729
- **H** -0.598221 -2.676910 -0.497009
- **C** -1.338351 1.648990 -0.395859
- **C** -2.298891 -0.943020 1.712371
- **H** -2.224121 -2.033340 1.693351
- **H** -1.534291 -0.540280 2.375371
- **H** -3.287611 -0.652620 2.087691
- **C** 1.383899 0.346010 0.404881
- **C** -2.097631 -0.401010 0.217751
- **C** -0.129828 1.318061 1.348761
- **H** 0.693558 1.085221 2.251871
- **H** -0.940882 1.219511 1.542901
- **H** -0.335858 2.348951 1.050181
- **C** 1.365838 -1.740149 -0.076279
- **C** 2.217358 1.324921 -1.465379
- **H** 2.043348 2.374621 -1.214279
- **C** 3.527838 1.027161 -2.543191
- **H** 3.242848 1.203281 -1.819759
- **C** -1.520972 -0.249649 -0.522309
- **C** 1.979378 0.468191 -0.240369

**Structure 3'_TSinv**

- **O** -0.375272 0.521911 -0.883879
- **O** 2.310528 -0.894919 -0.564219
- **O** 2.728448 0.851491 0.874201
- **O** 1.443079 -2.939429 -0.230759
- **N** 0.373718 -1.040129 0.572431
- **C** -1.031662 -1.438999 0.279151
- **C** 0.503358 0.378461 0.217751

**Structure 3'_TSinv**

- **O** -0.292369 1.230111 -0.217309
- **O** -1.497243 -1.014112 0.918284
- **O** -3.129362 0.157510 -0.205359
- **O** -0.191103 -2.723566 0.273468
- **N** -0.397999 -0.810515 -1.031565
- **H** -2.221961 0.749516 -2.370781
- **H** -0.584050 1.412604 -2.643933
- **H** -1.729401 2.281158 -1.606812
- **C** -0.639642 -1.620266 0.062157
- **H** -1.853501 1.266125 1.557258
- **H** -2.204795 2.240507 1.207137
- **H** -0.831853 1.365284 1.922267
- **C** -1.391099 1.288913 -1.917287
- **C** 1.038019 -0.670233 -1.413612
- **C** -0.44086 0.543149 -0.714291
- **C** -1.91099 1.288913 -1.917287
- **C** 1.449092 0.445052 -0.506909
- **C** -1.882874 0.278371 0.411698
- **C** -4.219155 -0.156456 0.653559
- **H** -5.046680 -0.437337 0.002343
- **H** -4.513043 0.710413 1.253751

**Structure 3'_TSinv**

- **O** 3.026440 4.153081 -1.999221
- **H** 1.778860 4.687061 -0.310561
- **C** 2.174860 -0.433089 0.025719
- **H** 2.207520 0.133911 -0.892631
- **H** 2.601380 0.012581 0.912049
- **H** 1.362170 -1.134869 0.147199
- **C** 3.771020 -1.854549 -0.400731

**Structure 5a**

- **C** 0.129828 1.318061 1.348761
- **H** 0.693558 1.085221 2.251871
- **H** -0.940882 1.219511 1.542901
- **C** 1.368538 -1.740149 -0.076279
- **C** 2.217358 1.324921 -1.465379
- **H** 2.043348 2.374621 -1.214279
- **C** 3.527838 1.027161 -2.543191
- **H** 3.242848 1.203281 -1.819759
- **C** -1.520972 -0.249649 -0.522309
Structure 3'_epi

O  -0.138091  -0.542770  1.541420
H  1.107730   0.621739  -1.244700
O   2.987669   0.263277   0.027970
O  -0.237501  -0.508960  -2.635910
N   0.334088  -1.382301  -0.562340
C  -1.038962  -1.834740  -0.147660
C   0.938618  -0.807921   0.642010
C   1.889948  -1.763172   1.337420
H   2.723467  -2.032163   0.689650
H   1.327917  -2.659291   1.612210
H   2.278358  -1.294002  2.248290
C   0.342809  -0.442191  -1.574280
C   1.234201   1.751269   0.859130
H   1.668191   1.714528   1.862540
H   0.146611   1.804829   0.947890
H   1.605551   2.634578   0.334720
C   0.868591  -1.433636   0.499373
C   0.982994  1.574019
H   5.103991   0.402253   1.089798

Structure 3'_preTSMeBr

O  -0.799347  -0.444280  -0.531389
H  0.041817   2.328571   0.391497
O  -2.009506   2.927715  -0.461788
O   0.676012   1.684813   2.447562
N  -1.142456   0.969354   1.391943
C  -0.906500  -0.708041  1.826731
C  -1.540223   0.612544  -1.133280
C  -3.030393   0.452499  -0.223680
H  -3.600245   1.212307   0.310384
H  -3.302378  -0.541345   0.139218
C  -3.262130   0.512368  -1.290577
C  -0.847999  1.568319  1.512155
C  -0.353941  1.909085  -1.936927
H  -1.133481  1.735278  -2.683483
H   0.356148   1.083321  -1.966179
H   0.166974   2.840045  -2.169262
H -2.07520  -0.133911   0.892631
H -2.601380  -0.012581  -0.912049
H -1.362170   1.134869  -0.147199
Br -3.771020   1.854549  0.400731

Structure 6a
O -0.294159   0.480860  -0.798271
O  2.276921  -1.033270  -0.353591
O  2.957571   0.930320   0.639439
O  1.275111  -2.847220   0.522819
N  0.489821  -0.705270   0.967299
C -0.937269  -1.000060   0.946249
C  0.664681   0.552500   0.258339
C  0.438101   1.785110   1.108039
H  1.123341   1.796650   1.954339
H -0.594909   1.801820   1.462729
O  2.957571   0.930320   0.639439
C -0.937269  -1.000060   0.946249
Structure 3'_epi_preTSMeBr
O  0.438101   1.785110   1.108039
H  1.123341   1.796650   1.954339
H -0.594909   1.801820   1.462729
O  2.276921  -1.033270  -0.353591
C -0.937269  -1.000060   0.946249

Structure 3'_epi_TSMeBr
O  0.294159   0.480860  -0.798271
O  2.276921  -1.033270  -0.353591
O  2.957571   0.930320   0.639439
O  1.275111  -2.847220   0.522819
N  0.489821  -0.705270   0.967299
C -0.937269  -1.000060   0.946249
C  0.664681   0.552500   0.258339
C  0.438101   1.785110   1.108039
H  1.123341   1.796650   1.954339
H -0.594909   1.801820   1.462729
O  2.957571   0.930320   0.639439
C -0.937269  -1.000060   0.946249

Structure 3'_epi_preTSMeBr
O  0.296432   0.699831  -0.519691
O  3.191561  -0.544611   0.234869
O  3.722122   1.650939  -0.194151
O  2.490910   1.788820   1.963939
N  1.435311  -0.283599   1.558299
C  0.029801  -0.283599   1.558299
6. X-Ray diffraction analysis

Details of the X-ray analyses are summarized in Table S6. Compound 2 was dissolved in dichloromethane and n-hexane was added carefully creating an interphase. The colourless crystal block was obtained by slow diffusion at 4 °C. Compound 10 was dissolved in dichloromethane and crystal needle was obtained at 4 °C. The formed crystals were analysed by X-ray diffraction.

The diffraction data were collected using graphite-monochromatic Mo-Kα radiation with a Bruker APEX-II diffractometer at a temperature of 298 K using the APEX3 software. The absorption correction was performed using MULTI-SCAN. The structures were solved with the WINGX program suite and refined by full-matrix least squares with SHELXL. Hydrogen atoms were located by mixed methods (electron-density maps and theoretical positions).

Mercury diagram of compounds 2 and 10 are represented in the Figure S16.

[S1] Blessing, R. H. Acta Crystallogr. 1995, A51, 33.
[S2] Farrugia, L. J. Appl. Crystallogr. 2012, 45, 849.
[S3] Sheldrick, G. Acta Crystallogr., Sect. C 2015, 71, 3.

\[\text{Figure S16. Mercury diagram of compounds 2 and 10 along with their 2D-ChemDraw structures.}\]
Table S6. X-ray Crystallographic Data for 2 and 10.

|                  | 2                      | 10                     |
|------------------|------------------------|------------------------|
| **Empirical formula** | C₁₀ H₁₅ N O₆          | C₁₆ H₂₁ N O₇ S        |
| **F₀**           | 245.23                 | 371.40                 |
| **T (K)**        | 298(2)                 | 298(2)                 |
| **Wavelength (Å)** | 0.71076               | 0.71076               |
| **Crystal system** | Orthorhombic          | Orthorhombic           |
| **Space group**  | P 2₁ 2₁ 2₁            | P 2₁ 2₁ 2₁            |
| **Crystal size (mm³)** | 0.2 x 0.1 x 0.07    | 0.27 x 0.19 x 0.1 |
| **a (Å)**        | 9.145(5)               | 6.6726(2)             |
| **b (Å)**        | 11.368(6)              | 12.7039(4)            |
| **c (Å)**        | 11.977(7)              | 21.7090(7)            |
| **α (°)**        | 90                     | 90                     |
| **β (°)**        | 90                     | 90                     |
| **γ (°)**        | 90                     | 90                     |
| **V (Å³)**       | 1245.2(12)             | 1840.23(10)           |
| **Z**            | 4                      | 4                      |
| **D_{calcd} (Mg/m3)** | 1.308                 | 1.341                 |
| **Absorption coefficient (mm⁻¹)** | 0.109                 | 0.212                 |
| **F(000)**       | 520                    | 784                    |
| **θ range for data collection (deg)** | 2.859 to 28.106 | 3.240 to 27.928 |
| **Index ranges** | -11<=h<=11, -15<=k<=14, -15<=l<=15 | -8<=h<=8, -16<=k<=16, 28<=l<=28 |
| **Reflections collected** | 84726                 | 88056                 |
| **Independent reflections** | 2988 [R(int) = 0.0657] | 4374 [R(int) = 0.0403] |
| **Data / restraints/ parameters** | 2988 / 0 / 155 | 4374 / 0 / 226 |
| **Goodness-of-fit on F²ᵃ** | 1.149                 | 1.054                  |
| **Final R index** | R₁ = 0.0594           | R₁ = 0.0340            |
| **[I > 2σ(I)]ᵃ** | wR₂ = 0.1364          | wR₂ = 0.1010           |
| **R indexes (all data)ᵃ** | R₁ = 0.0742, wR₂ = 0.1439 | R₁ = 0.0374, wR₂ = 0.1040 |
| **Largest diff. peak and hole (e. Å⁻³)** | 0.194 and -0.141 | 0.234 and -0.202 |

ᵃ R₁ = Σ[|F_o| - |F_c|]/Σ|F_o|; wR₂ = [Σw(F_o² - F_c²)²/ΣwF_o²]¹/²; goodness of fit = {Σ[w(F_o² - F_c²)²]/(N_{obs} - N_{param})}¹/²; w = [α²(F_o) + (g₁P)² + g₂P]⁻¹; P = [max(F_o²;0 + 2F_c²)]/3.
7. Enantiomeric purity determination of 7c and 8c by NMR chiral shift reagents

Following a recent but slightly modified procedure, the corresponding β-amino acid 7c, 8c or a mixture of known amounts of both was dissolved in D2O to generate a 0.05 M solution. The pH of these three solutions was adjusted to 10 using 1 M KOH solution in D2O. Then, a solution of 8 mg/mL of samarium(III) complex with (S,S)-ethylenediamine-N,N'-disuccinate in D2O was prepared and 0.2 mL of this solution were added to each of the corresponding NMR tubes containing 0.5 mL of a solution of the amino acids 7c, 8c or the mixture of both. The 1H NMR experiments were registered in a 400 MHz spectrometer.

[S4] Aizawa, S.-I.; Okano, M.; Kidani, T. Chirality 2017, 29, 273–281.

[S5] Aizawa, S.-I.; Okano, M. Magn. Reson. Chem. 2020, 58, 941–948.

Figure S17. 1H NMR 400 MHz in D2O corresponding to a mixture of amino acids 8c and 7c (78:22) with samarium(III) complex.
**Figure S18.** $^1$H NMR 400 MHz in D$_2$O corresponding to amino acid 8c with samarium(III) complex.

**Figure S19.** $^1$H NMR 400 MHz in D$_2$O corresponding to amino acid 7c with samarium(III) complex.
Figure S20. Aligned and expanded regions corresponding to CH$_2$H$_2$Ph signal (doublet) extracted from the $^1$H NMR (400 MHz) spectra in D$_2$O at 298 K of A) a mixture prepared by addition of amino acids (R)-α-benzyl-isoSer $7c$ and (S)-α-benzyl-isoSer $8c$ (enantiomers) in a 22:78 ratio, B) amino acid $8c$ and C) its enantiomer: amino acid $7c$. All spectra were recorded in the presence of a chiral samarium(III) complex at pH 10 ([Sm(III) complex]/[amino acid] = 0.2).