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Design and Synthesis of Backbone-Fused, Conformationally Constrained Morpholine-Proline Chimeras

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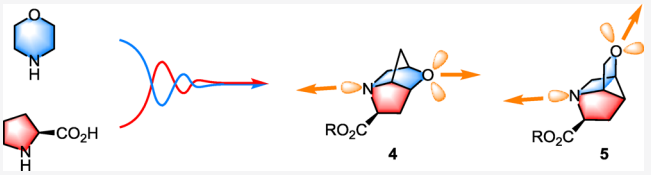
ABSTRACT: We report the synthesis of two novel bridged morpholine-proline chimeras **4** and **5**, which represent rigid conformationally locked three-dimensional structures wherein the lone pairs of electrons on oxygen and nitrogen are oriented in spatially different "east−west" and "north−west" directions, respectively. In combination with the presence of a carboxylic acid, the electronic features of these compounds may be useful in the context of peptidomimetic design of biologically relevant compounds. Quantitative estimates of the basicity of the nitrogen atoms were obtained using conceptual density functional theory analysis.



INTRODUCTION

Morpholine and its substituted congeners are among the most frequently exploited saturated six-membered heterocycles in medicinal chemistry.[1,2] Its chair-like flexible structure and the presence of a basic nitrogen offer structural and functional attributes that have been useful in the design and synthesis of a plethora of CNS-active compounds.[3] Currently, there are over 16 marketed drugs in which a morpholine unit is appended to the extremities of core structures.[4] The literature is richly documented with methods of synthesis of a variety of sp^3-substituted morpholines, many in optically pure form.[5−7] In contrast, morpholines are constituents of only a handful of natural products such as chelonin A, chelonin B, and acortatarin A.[8,9]

Introducing constrain in otherwise conformationally flexible saturated six-membered azaheterocycles creates a privileged topology wherein the spatial orientation of the lone pair of electrons on the tertiary nitrogen atom can be critical for recognition by biological receptors and enzymes. A historically relevant example is found in analgesics such as morphine[10] in which an *N*-methyl piperidine unit is appended to a tetracyclic core structure and in synthetic morphinomimetics derived from *N*-methyl isopavines.[11] Constraining the conformation of a morpholine can be achieved by bridging two ring carbon atoms with one or two methylene units across the ring. Appending such bridged morpholines to otherwise bioactive compounds can also modulate lipophilicity and potentiate their activity.[12] In this regard, bridged morpholines and their analogues can be considered as useful bioisosteres that have been used as a design strategy in the context of medicinally important compounds. Indeed, replacement of a morpholine by a bridged morpholine in several compounds has shown improved activity and selectivity against target proteins.[13] Among such bridged morpholines is the venerable 2-oxa-5-azabicyclo[2.2.1]heptane motif (**1**), originally reported by Portoghese and Sepp,[14] which is especially relevant in another context, since it constitutes the core structure of the alkaloid loline (**2**)[15,16] (Figure 1). Inspired by the structure of loline,

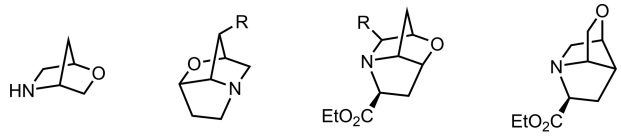


Figure 1. Structures of bridged morpholines and bridged morpholine-proline chimeras.

we envisaged that incorporating an ethano bridge in the core structure **1** would introduce a second element of constraint leading to a backbone-fused tricycle exemplified by structures **4** and **5**. We surmised that unlike **1**, which except for the basic tertiary nitrogen atom, is functionally inert, the presence of a carboxyl group as part of the backbone-fused chimeras between morpholine and proline would allow further diversification as well as the generation of quaternary salts by N-methylation with potential pharmacological effects.[17] It is of interest that N-terminal prolines are post-translationally methylated to *N*-methyl proline[18] and *N*,*N*-dimethyl proline[19] in a variety of proteins.[20] Compounds **4** and **5** represent

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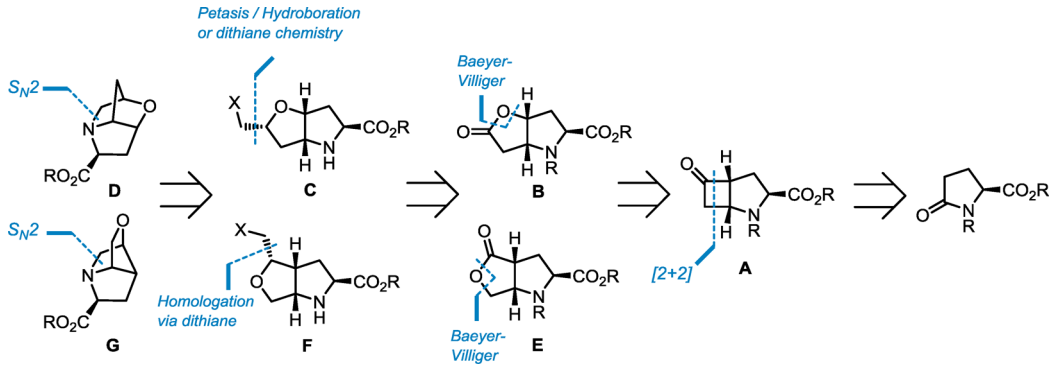
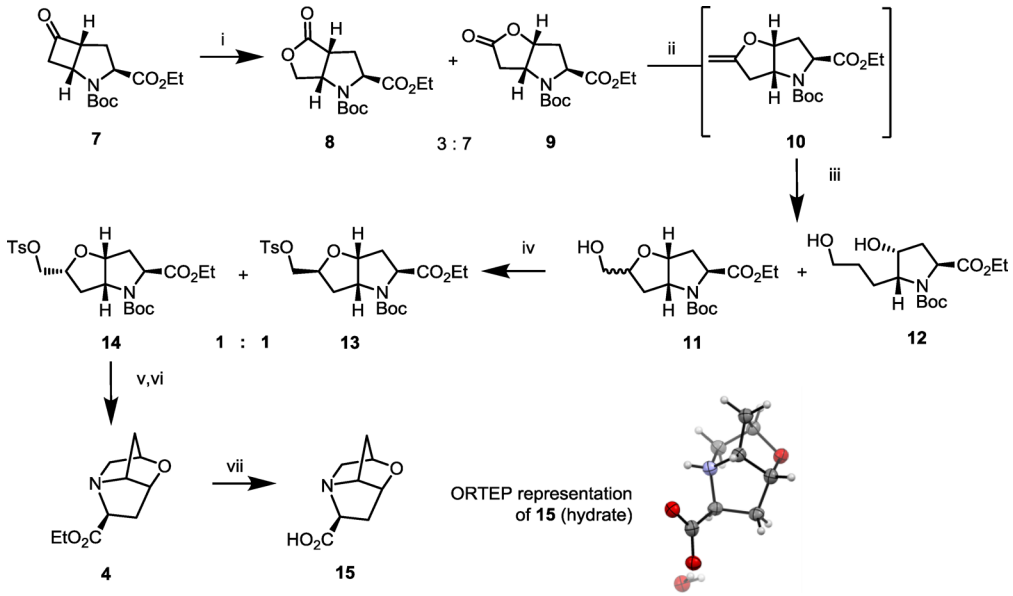
Scheme 1. Retrosynthetic Analysis of Bridged Morpholine-Proline Chimeras



Scheme 2. Synthetic Scheme for the Synthesis of the Bridged Morpholine-Proline Chimera 4[a]



[a]Petasis methylenation/hydroboration route: (i) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, 0 °C, 70% for **9** and 21% for **8**; (ii) Cp_2TiMe_2, toluene, 80 °C; (iii) $BH_3{\cdot}Me_2S$ then NaOH, H_2O_2, THF, 0 °C, 30% over 3 steps for **11** and 30% for **12**; (iv) TsCl, Et_3N, DMAP, CH_2Cl_2, 0 °C to r.t., 94%; (v) TFA, CH_2Cl_2; (vi) Et_3N, EtOH, 79% over 2 steps; (vii) LiOH, EtOH, 93%.

lipophilic mimics of N-terminal prolines that may find utility in further probing the enzymatic activity of methyl transferases in yeast and humans for example.[21] The conformational constraint imposed on compounds **4** and **5** is such that while the nitrogen atom remains in a fixed (westerly) position relative to the ether oxygen atoms, the lone pair on each of the oxygen atoms adopts spatially different orientations. These features may be useful in the context of the peripheral attachment of chimeras **4** and **5** to bioactive compounds as bulky amides possessing localized sites of electron density. We note that there are only a few reported examples of morpholines fused to other cyclic entities[22] and of bicyclic morpholino carboxylic acids[23] but none involving backbone-fused bridged morpholine-proline chimeras.[24,25]

RETROSYNTHETIC ANALYSIS

We set out to explore stereocontrolled methods toward the synthesis of the novel morpholine-proline chimeras **4** and **5**, as well as sp^3 ring-substituted variants such as **6**. The disconnective analysis in Scheme 1 shows discrete intermediates that can be derived from the known bicyclo[3:2:0]-azaheptanone carboxylic ethyl ester, itself readily prepared from L-pyroglutamic acid according to Correia and co-workers[26] (Scheme 1). In principle, lactone **B** derived from the Baeyer–Villiger oxidation of ketone **A** could be subjected to a Petasis olefination/hydroboration sequence to provide the [3.3.0] bicyclic intermediate **C**, which would undergo an intramolecular S_N2 displacement of a suitable leaving group to give the intended bridged morpholine-proline chimera **D**. An alternative strategy would involve a one-carbon extension with lithiodithiane from lactone **B**. A similar strategy starting with the lactone **E** would lead to intermediate **F** and ultimately to the isomeric bridged morpholine congener **G**.

RESULTS

Baeyer–Villiger oxidation of the known ketone **7**[26,27] resulted in a 3:7 mixture of lactones **8** and **9**, which were separated by column chromatography (Scheme 2). In view of its potential brevity, we first explored the Petasis/hydroboration route shown in the scheme toward the bridged morpholine **4**. Thus, treatment of **9** with Cp_2TiMe_2 according to Petasis and Bzowej protocol[28] led to the enol ether **10**, which was used directly in a hydroboration reaction followed by oxidation, which resulted in a 1:1 mixture of hydroxymethyl products **11** and **12**

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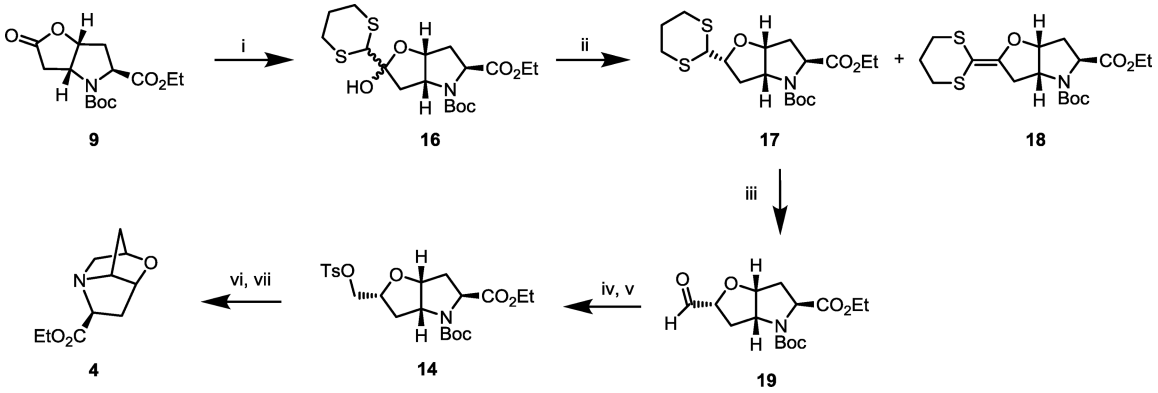
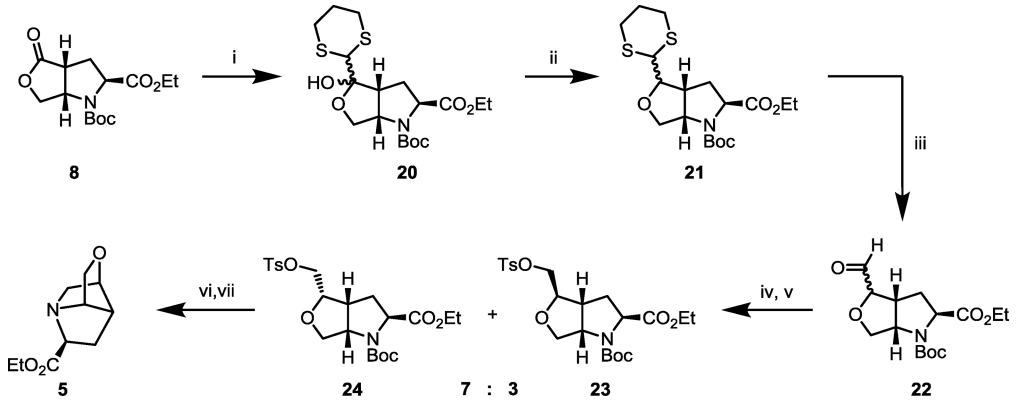
Scheme 3. Synthetic Scheme for the Synthesis of Bridged Morpholine-Proline Chimera 4[a]



[a]Dithiane route: (i) 1,3-dithiane, BuLi, THF, −78 °C, 63%; (ii) $BF_3{\cdot}Et_2O$, Et_3SiH, CH_2Cl_2, −78 °C, 59% for **17**, 20% for **18**; (iii) HgO, $BF_3{\cdot}Et_2O$, THF/H_2O (7/3), 55%; (iv) $NaBH_4$, EtOH, 0 °C to r.t.; (v) TsCl, Et_3N, DMAP cat., CH_2Cl_2, 0 °C to r.t., 62% over two steps; (vi) TFA, CH_2Cl_2; (vii) Et_3N, EtOH, 79% over two steps.

Scheme 4. Synthetic Scheme for the Synthesis of Morpholine-Proline Chimera 5[a]



[a](i) 1,3-Dithiane, BuLi, THF, −78 °C, 62%; (ii) $BF_3{\cdot}Et_2O$, Et_3SiH, CH_2Cl_2, −78 °C, 82%; (iii) HgO, $BF_3{\cdot}Et_2O$, THF/H_2O (7/3), 40%; (iv) $NaBH_4$, EtOH, 0 °C to r.t.; (v) TsCl, Et_3N, DMAP cat. CH_2Cl_2, 0 °C to r.t., 41% for **24** and 19% for **23**, over 2 steps; (vi) TFA, CH_2Cl_2; (vii) Et_3N, EtOH, 84% over two steps.

(Scheme 2). Tosylation of **11** led to the *syn*- and *anti*-tosylates **13** and **14**, which were separated chromatographically. Cleavage of the *N*-Boc group in what was assumed to be **14**, followed by intramolecular cyclization, led to the intended bridged morpholine-proline chimera **4** in an excellent yield over two steps. Cleavage of the ester group afforded the carboxylic acid **15**, which was characterized by an X-ray structure determination of its hydrate (Supporting Information), thus confirming the structure of **14.** The isomeric *syn*-tosylate was not further investigated since cyclization would not be geometrically possible.

In view of the low yield of the Petasis reaction with the lactone **9** and lack of selectivity in the hydroboration reaction, we explored a different approach to generate the intermediate **14,** since once obtained, its ring closure could be efficiently accomplished as shown in Scheme 3. Stereoselective addition of lithiodithiane to **9** led to the corresponding lactol **16**, as a mixture of anomers, presumably enriched in the "all syn-"isomer from a preferential attack on the more accessible convex face. The mixture of lactols was subjected to deoxygenation in the presence of $BF_3{\cdot}Et_2O/Et_3SiH$ to afford **17** as the major product in 59% yield, accompanied by the corresponding ketene dithioacetal **18** in 20% yield. The predominance of the α-oriented dithiane **17** can be explained by attack of the hydride ion from the less hindered convex face of the corresponding bicyclic oxocarbenium ion generated from the major "all syn-"isomer of lactol **16**. The formation of the ketene dithioacetal **18** may possibly arise from the minor isomer of lactol **16** by BF_3-mediated elimination of the anomeric tertiary alcohol. Under the same reaction conditions, the ketene dithioacetal was stable.

For treatment of the dithiane adduct **17** with HgO, $BF_3{\cdot}Et_2O$ led to the aldehyde **19**, which, upon reduction with $NaBH_4$ and tosylation of the resulting primary alcohol, gave the tosylate **14** whose structure and identity were previously established in the preceding synthesis (Scheme 2). Cleavage of the *N*-Boc group and exposure to Et_3N led to a smooth conversion to the intended amino acid ester **4** in 79% yield.[29]

The synthesis of the alternate bridged morpholine-proline chimera **5** was initiated with lactone **8** and processed essentially as described for **4** (Scheme 4). Thus, addition of lithiodithiane to **8** led to a mixture of anomeric lactols **20**, which was efficiently deoxygenated to a mixture of epimeric dithianes **21**. However, contrary to the analogous reaction in the above described synthesis of **18** (Scheme 3), none of the ketene dithioacetal was formed possibly due to a much more pronounced $A^{1,3}$-strain effect compared to **18**. Removal of the dithiane group led to a mixture of epimeric aldehydes **22**,

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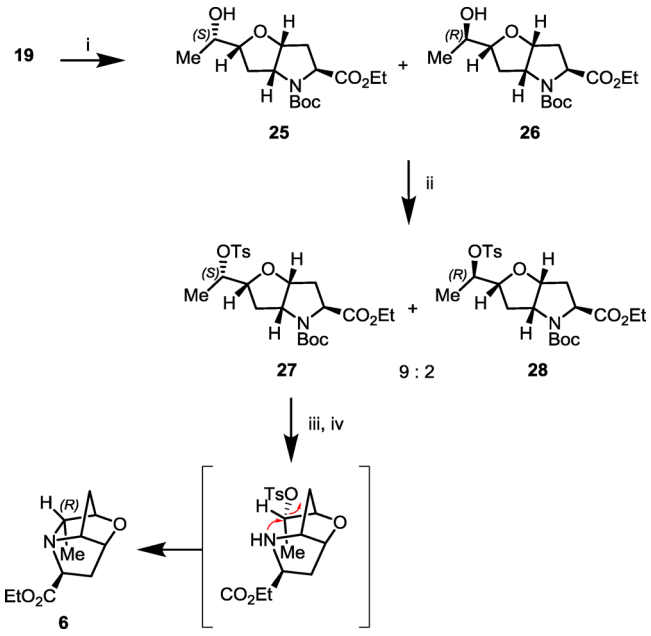
which, upon reduction and tosylation, led to the tosylates **23** and **24** as a 3:7 mixture. Cleavage of the *N*-Boc group in **24** and exposure to Et_3N led to the intended bridged morpholine-proline ethyl ester chimera **5**.

In an effort to introduce additional functionality in the bridged morpholine-proline chimera **5**, we considered adding a substituent proximal to the tertiary nitrogen atom. The aldehyde function present in the intermediate **19** was treated with MeMgCl in the presence of $LaCl_3$·LiCl[30] to give a mixture of alcohols **25** and **26**, which could be separated by column chromatography after conversion to the corresponding tosylates **27** and **28** in a ratio of 9:2, respectively (Scheme 5). Intramolecular cyclization of the major isomer **27** led to the

Scheme 5. Synthetic Scheme for the *C*-Methyl-Bridged Morpholine-Proline Chimera 6[a]



[a](i) MeMgCl, $LaCl_3$·LiCl, 0 °C to r.t., 50%; (ii) TsCl, Et_3N, DMAP cat., CH_2Cl_2, 0 °C to r.t., 82%, only **27** can be isolated; (iii) TFA, CH_2Cl_2; (iv) Et_3N, EtOH, 66% over two steps.

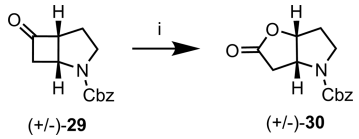
C-methyl analogue **6** in 66% yield. Its stereochemistry was determined by NOESY experiments (Supporting Information). It is noteworthy that the (*S*)-tosylate **27** was formed within 16 h, while the conversion of the (*R*)-tosylate **28** was much slower (30 h).

DISCUSSION

The formation of the lactone **8** as a minor isomer in the Baeyer–Villiger reaction of ketone **7** is of interest in the context of related precedents reported by Correia group[31] who reported similar results with the corresponding *t*-butyl ester. However, oxidation of the bicyclic ketone lacking the ester group **29** led only to the expected lactone **30** (Scheme 6).

As mentioned above, the Baeyer–Villiger oxidation of ketone **7** led to a 7:3 ratio of lactones **9** and **8** (Scheme 2). There appears to be a clear preference for the migratory insertion of the C5–C6 bond (Scheme 7-**A**) rather than the C6–C7 bond (Scheme 7-**B**) leading to the major lactone **9**, even though both bonds are equally well aligned with favorable primary and secondary stereoelectronic effects.[32] The more

Scheme 6. Formation of the Lactone 30 by Baeyer–Villiger Reaction with Ketone 29[a]



(+/-)-**29** (+/-)-**30**

[a](i) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, 0 °C, 90%.[28a]

electron-rich C5–C6 bond may benefit from a hyperconjugative effect favoring migration. It is also possible that intermediate **B** may be less favored due to a more pronounced repulsive *syn*-interaction of the ester and hydroxyl oxygen atoms. These past[31] and present observations warrant further study to explain the role of the ester group in these bicyclo[3:2:0]azaheptanones.

The formation of both diastereoisomers during the Grignard reaction with aldehyde **19** could be rationalized by various models.[33] We had expected that the addition of MeMgBr would proceed via a chelation-controlled mechanism involving the ring oxygen atom,[34] whereby the methyl group would be delivered from the Re face to give the *R*-configured secondary alcohol **26** (Scheme 8-**A**). However, the major product **25** resulted from a dipolar Felkin–Anh transition-state model (Scheme 8-**B**). Similar selectivities have also been reported in the literature for related reactions.[35,36]

To compare relative basicities of the tertiary nitrogen of the bridged morpholine-proline chimeras **4** and **5**, we conducted a DFT analysis using the *N*-methyl 2-oxa-5-azabicyclo[2.2.1]-heptane motif (**N-Me 1**) as a reference compound. Unlike the bridged morpholine-proline chimeras **4** and **5**, whose lone pair of electrons on nitrogen is spatially fixed by the introduction of an additional ring, the *N*-methyl group in the 2,5-bridged morpholine (**N-Me 1**) can adopt an equatorial or axial position with energies within 1 kcal·mol^{-1} between the two rapidly exchanging conformers at room temperature.

Atomic charges (q), electrophilic Fukui indices (f^-), and local softness (s^-) were calculated as a measure of the basicity of the N and O atoms (Figure 2).[37] We expect that a more negative charge, as well as higher positive values of f^- and s^-, would indicate higher basicity, bearing in mind that Fukui indices and local softness are better indicators than atomic charges. As anticipated, the nitrogen atom is largely more basic than the oxygen. Both f^- and s^- descriptors predict a decrease in basicity at the nitrogen in the order **N-Me 1**, **4**, and **5**. These reactivity descriptors rely entirely on electronic effects, reflecting the tendency of the nitrogen atom to share its lone pair with an acceptor, but without considering steric effects. In an attempt to include these global effects in a putative interaction with H-donors, we calculated formation energies of the complexes with water, hydrocyanic acid, and methanol (Figure 3). Considering the length of the hydrogen bonds, the calculations suggest that the hydrogen bond strengths decrease in the order **N-Me 1** > **4** > **5**, in accordance with the order of basicities. From the formation energies of the H-bonded entities, the ranking is shifted to **4** > **5** > **N-Me 1**, but this is most probably due to added stabilizing interactions from the ethyl ester, lowering the free energies of H-bond formation for **4** and **5**.

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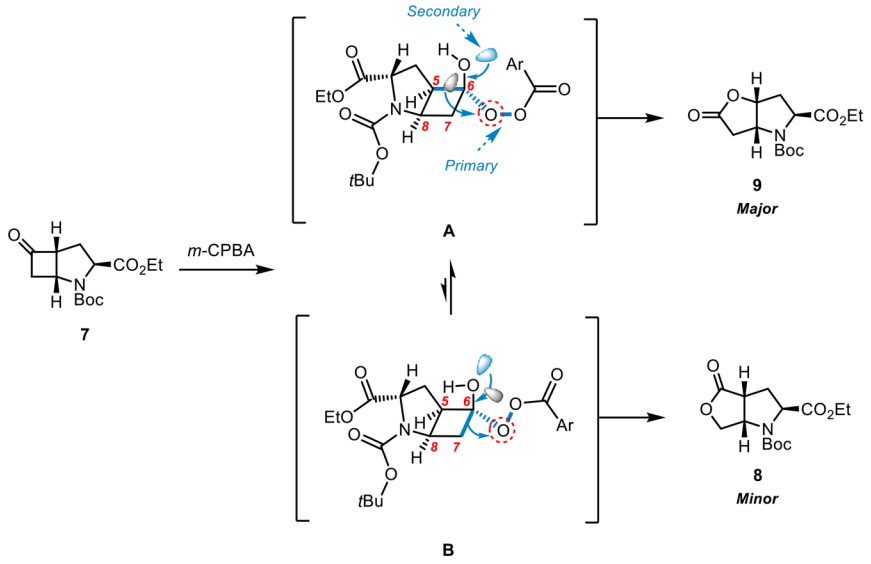
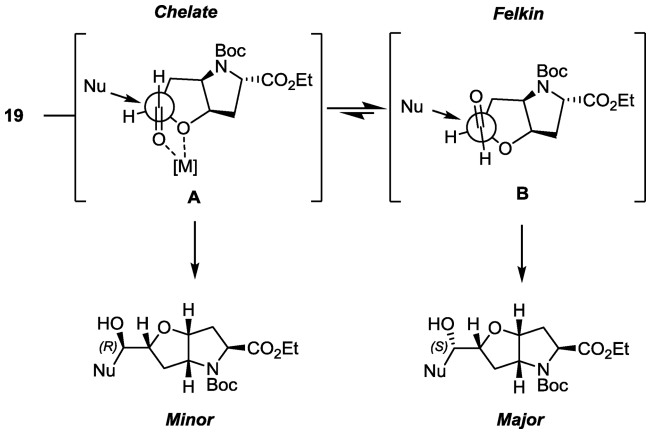
Scheme 7. Primary and Secondary Stereoelectronic Effects in Criegee Intermediates Leading to Both Regioisomers 8 and 9



Scheme 8. Selectivity of the Grignard Addition on Aldehyde 19



CONCLUSIONS

We have reported synthetic routes to two novel backbone-fused bridged morpholine-proline chimeras having rigid three-dimensional structures starting from the readily available bicyclo[3:2:0]azabicycloheptanone carboxylic acid ethyl ester.[26,27] A Baeyer−Villiger reaction gave access to two lactones, which could be individually manipulated to intermediates ultimately leading to the intended bridged morpholine-proline chimeric molecules that could accommodate functional groups on a stereogenic carbon atom vicinal to the bridgehead nitrogen atom. Mechanistic rationales for the formation of the lactones and the stereoselective Grignard addition to create a new stereogenic center adjacent to the bridgehead nitrogen atom were given. A DFT study allowed us to compare the basicities of our new chimeras, with that of the *N*-methyl 2-oxa-5-azabicyclo[2.2.1]heptane motif (**N-Me 1**), originally reported by Portoghese and Sepp.[14] The rigidity of the bridged morpholine-proline chimeras forces the electron pairs of the respective nitrogen and oxygen atoms to be directionally oriented. Coupled with the presence of a carboxylic acid, the bridged morpholine-proline chimeras could prove to be useful for the design of peptidomimetic molecules of medicinal importance.

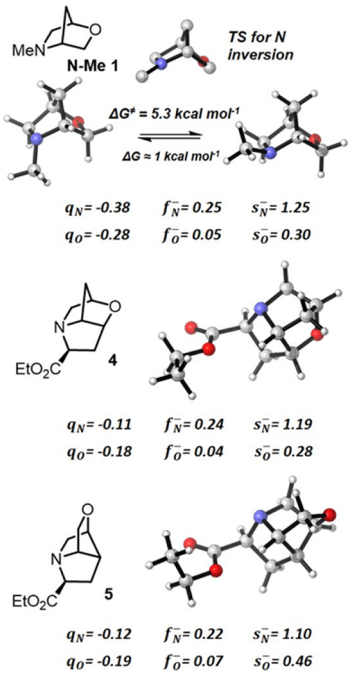


Figure 2. DFT-optimized geometries and reactivity indices.

EXPERIMENTAL SECTION

For physical data and spectroscopic measurements, NMR spectra were recorded on a Bruker 300 spectrometer (75 MHz for ^{13}C), a Bruker AVANCE 400 RG spectrometer (400 MHz for ^{1}H), and a Bruker AVANCE 500 Ultrashield Plus spectrometer (500 MHz for ^{1}H, 126 MHz for ^{13}C) in chloroform-*d* or methanol-*d*4. Data are reported as fellows: chemical shifts (δ) reported in parts per million (ppm), multiplicity, coupling constants (J) reported in Hertz (Hz), and integration. Accurate mass measurements were performed on an LC-TOF instrument from Agilent Technologies in a positive electrospray mode. Protonated molecular ions $(M + H)^+$ and/or sodium adducts $(M + Na)^+$ were used for empirical formula confirmation. Thin-layer chromatography (TLC) was performed on precoated Silicycle silica gel (250 μM, 60 Å) plates with an F-254

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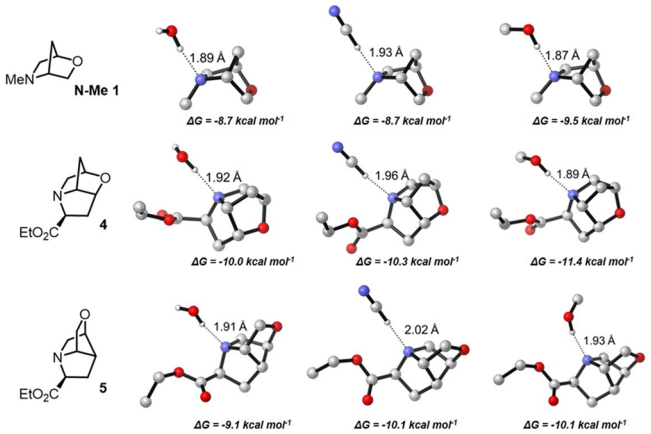

Figure 3. Counterpoise-corrected interaction energies with water, hydrocyanic acid, and methanol through hydrogen bonds.

indicator. Visualizing was performed with a UV light (254 nm) or with stains ($KMnO_4$, *p*-anisaldehyde, or ninhydrin). ZEO Prep 60 (0.040−0.063 mm) silica gel was used for all column chromatography.

4-(*tert*-Butyl) 5-Ethyl (3*aR*,5*S*,6*aR*)-2-Oxohexahydro-4*H*-furo[3,2-*b*]pyrrole-4,5-dicarboxylate (8) and 1-(*tert*-Butyl) 2-Ethyl (2*S*,3*aR*,6*aS*)-4-Oxohexahydro-1*H*-furo[3,4-*b*]pyrrole-1,2-dicarboxylate (9). To a solution of ketone 7 (6.39 g, 22.6 mmol) in CH_2Cl_2 (161 mL) were added $NaHCO_3$ (2.08 g, 24.8 mmol) and *m*-CPBA (5.56 g, 24.8 mmol) at 0 °C. The suspension was stirred at the same temperature for 1 h. The reaction mixture was transferred to a separatory funnel and washed with Na_2SO_3 and $NaHCO_3$ solutions. The organic phase was collected, dried over anhydrous $MgSO_4$, and filtered, and the solvent was evaporated in vacuo to give a colorless oil. NMR indicates a molar ratio **8**/**9** = 3:7. The resulting crude mixture was purified by flash chromatography (silica gel; 30% EtOAc/hexane) to give 4.7 g (70% yield) of the more polar regioisomer **9** and 1.4 g (21% yield) of the less polar regioisomer **8** as white solids. A fraction with a mixture of both isomers was also recovered (600 mg). Data for **8**: $[\alpha]_D^{23°C}$ = +119.0 (*c* = 0.80, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$, mixture of rotamers): δ 4.73−4.63 (m, 1.7H), 4.49 (dd, *J* = 10.5, 2.1 Hz, 0.3H), 4.44−4.35 (m, 1.3H), 4.30 (dd, *J* = 8.5, 6.4 Hz, 0.7H), 4.26−4.08 (m, 2H), 3.31−3.20 (m, 1H), 2.71 (ddd, *J* = 13.7, 8.6, 3.3 Hz, 0.7H), 2.62 (ddd, *J* = 13.2, 8.4, 4.6 Hz, 0.3H), 2.35−2.24 (m, 1H), 1.47 (s, 3H, minor Boc conformer), 1.41 (s, 6H, major Boc conformer), 1.33−1.21 (m, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$, mixture of rotamers): δ 177.5, 177.0, 172.3, 171.8, 153.8, 153.5, 81.8, 81.7, 72.7, 71.6, 61.7, 61.6, 60.4, 60.0, 6.71, 59.0, 43.7, 43.0, 31.9, 31.2, 28.5, 28.3, 14.3, 14.2. HRMS (ESI) *m*/*z*: $[M + K]^+$ calcd for $C_{14}H_{21}NO_6K$, 338.10005; found, 338.0998. Data for **9**: $[\alpha]_D^{23°C}$ = −149.4 (*c* = 1.70, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$, mixture of rotamers): δ 5.09−5.05 (m, 0.3H), 5.05−5.00 (m, 0.7H), 4.62 (t, *J* = 5.6 Hz, 0.7H), 4.59−4.55 (m, 0.3H), 4.43 (t, *J* = 7.7 Hz, 0.3H), 4.36 (t, *J* = 7.7 Hz, 0.7H), 4.26−4.08 (m, 2H), 3.07 (d, *J* = 18.8 Hz, 0.6H), 2.82 (dd, *J* = 19.0, 6.7 Hz, 1.4H), 2.63 (ddd, *J* = 14.4, 8.1, 1.5 Hz, 0.7H), 2.55 (ddd, *J* = 14.3, 8.0, 2.6 Hz, 0.3H), 2.32−2.21 (m, 1H), 1.46 (s, 3H, minor Boc conformer), 1.40 (s, 6H, major Boc conformer), 1.31−1.22 (m, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$, mixture of rotamers): δ 175.4, 175.0, 172.4, 172.0, 153.6, 153.5, 82.4, 81.7, 81.5, 61.7, 61.6, 59.3, 59.2, 58.4, 36.9, 35.8, 35.7, 35.0, 28.5, 28.3, 14.3, 14.2. HRMS (ESI) *m*/*z*: $[M + Na]^+$ calcd for $C_{14}H_{21}NO_6Na$, 322.1261; found, 322.1267.

1-(*tert*-Butyl) 2-Ethyl (2*S*,4*R*,5*R*)-4-Hydroxy-5-(3-hydroxypropyl)pyrrolidine-1,2-dicarboxylate (12), 4-(*tert*-Butyl) 5-Ethyl (2*S*,3*aR*,5*S*,6*aR*)-2-((Tosyloxy)methyl)-hexahydro-4*H*-furo[3,2-*b*]pyrrole-4,5-dicarboxylate (13), and 4-(*tert*-Butyl) 5-Ethyl (2*R*,3*aR*,5*S*,6*aR*)-2-((Tosyloxy)methyl)-hexahydro-4*H*-furo[3,2-*b*]pyrrole-4,5-dicarboxylate (14). The lactone **9** (730 mg, 2.42 mmol) was dissolved in toluene (19 mL), then a freshly prepared Petasis reagent was added (3.1 mL, 3.6 mmol, 1.2 M), and the solution was stirred in a sealed tube at 80 °C using an oil bath for 5 h. The reaction mixture was poured in pentane, the yellow precipitate was removed by filtration, and the solvent was removed under vacuum to give the crude enol ether as an orange oil, which was directly dissolved in THF (1.3 mL). $BH_3{\cdot}SMe_2$ solution (1.2 mL, 2.4 mmol, 2 M) was added dropwise at 0 °C, and the mixture was stirred at the same temperature until complete consumption of the starting material. The reaction was quenched with 15% $NaOH_{aq}$ (1.6 mL) and 30% H_2O_{2aq} (1.6 mL). The mixture was stirred at room temperature for 1.5 h, followed by quenching with saturated NH_4Cl. The whole was extracted with Et_2O, and the extract was washed with brine and dried over Na_2SO_4. The filtrate was concentrated under reduced pressure to give an oil, which was purified by column chromatography (hexanes/EtOAc, 1:1) to afford the side product **12** (more polar compound) as a colorless oil (229 mg, 30%) and the desired alcohol **11** as a colorless oil (229, 725umol 30%, R_f: 0.5 (hexanes/EtOAc, 1:1)), which was dissolved in CH_2Cl_2 (1.6 mL). *p*-Toluenesulfonyl chloride (311 mg, 1.63 mmol), 4-dimethylaminopyridine (0.9 mg, 7.28 μmol), and triethylamine (306 μL, 2.19 mmol) were added successively at 0 °C, and the mixture was stirred for 16 h at r.t. The solvent was removed under vacuum to give an oil, which was purified by column chromatography (hexanes/EtOAc, 7:3) to afford the less polar tosylate **13** as a colorless oil (154 mg, 47%) and the more polar tosylate **14** as a colorless oil (156 mg, 47%). Data for **12**: R_f: 0.3 (hexanes/EtOAc, 1:1), $[\alpha]_D^{23°C}$ = −34.2 (*c* = 0.81, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$, mixture of rotamers): δ 4.57−4.48 (m, 1H), 4.28−4.07 (m, 3H), 4.07−4.00 (m, 0.7H), 3.95−3.91 (m, 0.3H), 3.76−3.61 (m, 2H), 3.57 (bs, 0.7H), 3.38 (bs, 0.3H), 2.26−2.03 (m, 2H), 1.99 (bs, 0.5H), 1.88−1.54 (m, 3.5H), 1.45 (s, 3H), 1.38 (s, 6H), 1.30−1.21 (m, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 173.3, 154.3, 80.6, 80.5, 77.4, 77.2, 76.9, 70.3, 69.6, 62.8, 61.3, 59.5, 59.3, 57.6, 57.0, 53.6, 35.7, 35.1, 29.8, 29.0, 28.5, 28.4, 26.3, 25.9, 14.4, 14.3. HRMS (ESI) *m*/*z*: $[M + Na]^+$ calcd for $C_{15}H_{27}NO_6Na$, 340.17306; found, 340.17395. Data for **13**: R_f: 0.40 (hexanes/EtOAc, 7:3), $[\alpha]_D^{23°C}$ = −57.6 (*c* = 2.21, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, mixture of rotamers): δ 7.79 (d, *J* = 8.3 Hz, 2H), 7.34 (d, *J* = 8.2 Hz, 2H), 4.72−4.54 (m, 1H), 4.43 (dt, *J* = 12.6, 5.7 Hz, 1H), 4.38−4.04 (m, 5H), 3.97 (ddd, *J* = 13.9, 10.5, 5.2 Hz, 1H), 2.56−2.43 (m, 1H), 2.45 (s, 3H), 2.38−2.14 (m, 1H), 2.16−1.95 (m, 1H), 1.97−1.70 (m, 1H), 1.46 (s, 3H), 1.39 (s, 6H), 1.30−1.21 (m, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, mixture of rotamers): δ 172.9, 158.3, 145.1, 133.0, 130.0, 128.1, 126.3, 82.7, 81.9, 80.9, 77.4, 76.0, 75.8, 71.1, 70.9, 63.9, 63.3, 61.3, 60.5, 60.4, 60.2, 36.3, 35.9, 35.5, 34.6, 29.8, 28.5, 28.3, 21.8, 21.2, 14.3, 14.3. HRMS (ESI) *m*/*z*: $[M + Na]^+$ calcd for $C_{22}H_{31}NO_8SNa$ 492.1663; found, 492.1673. Data for **14**: R_f: 0.22 (hexanes/EtOAc, 7:3), $[\alpha]_D^{23°C}$ = +62.9 (*c* = 0.55, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, mixture of rotamers): δ 7.78 (d, *J* = 8.3 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 4.51−4.43 (m, 1H), 4.43−4.35 (m, 1H), 4.25−4.09 (m, 4H), 4.09−4.01 (m, 1H), 3.99−3.85 (m, 1H), 2.44 (s, 3H), 2.40−2.18 (m, 2H), 2.10−1.92 (m, 2H), 1.43 (s, 3H, minor Boc rotamer), 1.39 (s, 6H, major Boc rotamer), 1.25 (m, *J* = 7.0 Hz, 3H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, mixture of rotamers): δ 172.8, 172.2, 153.8, 153.6, 145.1, 145.0, 133.0, 132.9, 130.0, 130.0, 128.1, 128.1, 83.2, 82.7, 80.8, 80.7, 77.9, 77.8, 71.3, 71.0, 63.8, 63.2, 61.3, 61.2, 60.0, 59.9, 36.8, 35.5, 34.9, 34.7, 28.5, 28.3, 21.8, 14.3, 14.2. HRMS (ESI) *m*/*z*: $[M + Na]^+$ calcd for $C_{22}H_{31}NO_8SNa$, 492.1663; found, 492.1664. Only compound **14** could be cyclized to **4**.

Ethyl (1*R*,3*S*,6*R*,7*aS*)-Hexahydro-1*H*-1,6-epoxypyrrolizine-3-carboxylate (4). To a solution of tosylate **14** (138 mg, 294 μmol) in CH_2Cl_2 (5.14 mL) was added trifluoroacetic acid (450 μL, 5.88 mmol). After 1 h, the solvent was evaporated, and the residue was dried overnight under high vacuum to give the TFA salt. The salt was then dissolved in EtOH (3.05 mL), triethylamine (124 μL, 882 μmol) was added at r.t., and the solution was stirred for 16 h. The solvent was evaporated, sat. Na_2CO_3 was added, and the resulting mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phases were dried with anhydrous $MgSO_4$, the mixture was filtered, and the

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solvent was removed under vacuum to give the morpholine-proline chimera **4** as an orange colored oil (46.0 mg, 79%). $[\alpha]_D^{23°C}$ = +7.0 (*c* = 2.32, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 4.39 (dd, *J* = 4.0, 1.7 Hz, 1H), 4.29 (d, *J* = 2.7 Hz, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 3.85 (dd, *J* = 9.2, 4.3 Hz, 1H), 3.79 (s, 1H), 3.37 (d, *J* = 11.3 Hz, 1H), 2.53−2.45 (m, 2H), 2.20−2.11 (m, 2H), 1.99−1.92 (m, 1H), 1.30−1.22 (m, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 174.0, 82.6, 74.2, 69.5, 68.2, 65.7, 61.2, 38.1, 37.4, 14.3. HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{10}H_{16}NO_3$, 198.1125; found, 198.1128.

(1*R*,3*S*,6*R*,7*aS*)-Hexahydro-1*H*-1,6-epoxypyrrolizine-3-carboxylic Acid (15). To a solution of ethyl ester **4** (28.8 mg, 146 μmol) in EtOH/H_2O (1:1, 10 mL) was added LiOH (14.2 mg, 5.94 μmol) as a solid. The mixture was acidified with HCl to reach pH = 2, and the solvent was evaporated. The resultant oil was further purified by elution, using water then NH_4OH solution (1 M) by ion exchange chromatography (Dowex 50WX8, mesh 200, freshly regenerated with 1 N hydrochloric acid and water). The product **15** was obtained as a white amorphous powder (23 mg, 93%). $[\alpha]_D^{23°C}$ = +1.6 (*c* = 1.40, H_2O); ^1H NMR (300 MHz, CD_3OD): δ 4.71 (s, 1H), 4.60 (d, *J* = 3.3 Hz, 2H), 4.37 (dd, *J* = 9.9, 5.0 Hz, 1H), 3.71 (d, *J* = 12.1 Hz, 1H), 3.27 (d, *J* = 12.2 Hz, 1H), 2.73 (dd, *J* = 15.2, 9.8 Hz, 1H), 2.42 (dt, *J* = 15.2, 4.8 Hz, 1H), 2.32−2.25 (m, 2H). $^{13}C\{^1H\}$ NMR (75 MHz, CD_3OD): δ 230.6, 80.6, 73.6, 70.3, 69.8, 63.7, 35.9, 35.1. HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_8H_{12}NO_3$, 170.0812; found, 170.0810. Upon standing at r.t. for several weeks, the ester **4** was hydrolyzed to the amorphous acid, which was obtained as the crystalline acid **15** hydrate (Supporting Information).

4-(*tert*-Butyl) 5-Ethyl (3*aR*,5*S*,6*aR*)-2-(1,3-Dithian-2-yl)-2-hydroxyhexahydro-4*H*-furo[3,2-*b*]pyrrole-4,5-dicarboxylate (16). To a solution of 1,3-dithiane (663 mg, 5.51 mmol) in THF (24.2 mL) was added butyl lithium solution (2.20 mL, 5.51 mmol, 2.5 M in hexane) dropwise at −78 °C. The solution was stirred at the same temperature for 30 min. Then the lithiodithiane solution was transferred by cannula to a solution of lactone **9** (1.50 g, 5.01 mmol) in THF (18.6 mL) dropwise at −78 °C. The resultant mixture was allowed to warm to r.t. and then stirred for 2 h. The reaction mixture was quenched with NH_4Cl and extracted with CH_2Cl_2 (2 × 20 mL), and the combined organic phases were dried with anhydrous $MgSO_4$. The solution was filtered, and the solvent was removed under vacuum to give an oil, which was purified by column chromatography (hexanes/EtOAc, 7:3) to afford a mixture of lactol **16** (1.46 g, 63%) as a light yellow oil and 510 mg (34%) of the starting material. ^1H NMR (400 MHz, $CDCl_3$, mixture of rotamers and diastereoisomers): δ 4.94−4.82 (m, 1H), 4.67−4.57 (m, 1H), 4.57−4.31 (m, 1H), 4.31−4.10 (m, 2H), 3.77−3.65 (m, 1H), 3.29−3.14 (m, 2H), 2.89−2.35 (m, 5H), 2.23−1.96 (m, 3H), 1.53−1.39 (m, 9H), 1.36−1.24 (m, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$, mixture of rotamers and diastereoisomers): δ 175.4, 173.1, 172.8, 172.7, 172.4, 172.3, 154.0, 153.6, 153.5, 110.5, 110.4, 109.8, 84.2, 83.3, 82.3, 81.7, 81.7, 81.5, 80.6, 80.6, 80.5, 65.5, 63.4, 63.3, 62.7, 62.6, 61.3, 61.2, 61.2, 61.1, 60.5, 60.3, 60.1, 59.8, 59.7, 59.2, 58.4, 49.7, 49.5, 48.9, 43.1, 42.0, 41.9, 40.2, 37.7, 36.9, 35.8, 35.7, 35.3, 35.1, 34.8, 31.1, 30.7, 28.6, 28.5, 28.4, 28.4, 28.3, 28.30, 28.3, 27.4, 27.1, 27.1, 27.0, 26.9, 26.8, 26.7, 25.1, 25.0, 19.2, 19.2, 14.3, 14.3, 14.2, 13.8. HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{18}H_{30}NO_6S_2$, 420.1509; found, 420.1500.

4-(*tert*-Butyl) 5-Ethyl (2*R*,3*aR*,5*S*,6*aR*)-2-(1,3-Dithian-2-yl)-hexahydro-4*H*-furo[3,2-*b*]pyrrole-4,5-dicarboxylate (17) and 4-(*tert*-Butyl) 5-Ethyl (3*aR*,5*S*,6*aR*)-2-(1,3-Dithian-2-ylidene)-hexahydro-4*H*-furo[3,2-*b*]pyrrole-4,5-dicarboxylate (18). To a solution of lactol **16** (4.20 g, 10.0 mmol) in CH_2Cl_2 (71.1 mL) were added dropwise at −78 °C triethylsilane (6.40 mL, 40.0 mmol) and boron trifluoride diethyl etherate (4.93 mL, 39.9 mmol). The solution was stirred for 45 min and then quenched with water, the resulting mixture was extracted with CH_2Cl_2 (3 × 20 mL), and the combined organic phases were dried with anhydrous $MgSO_4$. The solution was filtered, and the solvent was removed under vacuum to give a colorless oil, which was purified by column chromatography (hexanes/EtOAc, 8:2) to afford the major dithiane adduct **17** as a colorless oil (2.40 g, 59%) and a fraction with the mixture of **17** and its epimer as a colorless oil (406 mg, 10% yield). The less polar ketendithioacetal **18** was also isolated as a white solid (802 mg, 20% yield). Data for **17**: R_f: 0.54 (hexanes/EtOAc, 7:3), $[\alpha]_D^{23°C}$ = +133.4 (*c* = 2.33, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, mixture of rotamers): δ 4.58−4.36 (m, 3H), 4.24−4.09 (m, 4H), 2.85 (pt, *J* = 10.7, 4.8 Hz, 4H), 2.55−2.28 (m, 3H), 2.22−1.86 (m, 3H), 1.46 (s, 3H, minor Boc conformer), 1.39 (s, 6H, major Boc conformer), 1.25 (td, *J* = 7.2, 4.5 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$, mixture of rotamers): δ 171.9, 171.4, 152.9, 152.6, 82.2, 81.6, 81.4, 81.3, 79.5, 62.7, 62.2, 60.2, 60.1, 59.0, 58.9, 50.1, 49.9, 37.0, 35.8, 34.6, 34.0, 28.9, 28.7, 28.6, 27.5, 27.4, 25.0, 25.0, 13.3, 13.2. HRMS (ESI) *m*/*z*: $[M + Na]^+$ calcd for $C_{18}H_{29}NO_5S_2Na$, 426.1379; found, 426.1374. Data for **18**: R_f: 0.61 (hexanes/EtOAc, 7:3), $[\alpha]_D^{23°C}$ = −112.2 (*c* = 3.33, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$, mixture of rotamers): δ 5.04−4.93 (m, 1H), 4.55 (t, *J* = 5.8 Hz, 1H), 4.47 (t, *J* = 6.1 Hz, 1H), 4.38 (t, *J* = 7.6 Hz, 1H), 4.32 (t, *J* = 7.7 Hz, 1H), 4.28−4.09 (m, 2H), 3.35 (d, *J* = 18.4 Hz, 1H), 3.24 (d, *J* = 17.9 Hz, 1H), 3.01−2.65 (m, 5H), 2.65−2.51 (m, 1H), 2.13 (dd, *J* = 7.4, 4.4 Hz, 3H), 1.48 (s, 4H), 1.40 (s, 5H), 1.26 (ddd, *J* = 9.5, 7.3, 3.7 Hz, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$, mixture of rotamers): δ 172.6, 172.1, 159.2, 158.7, 153.7, 153.5, 92.5, 92.3, 86.4, 85.5, 81.1, 61.8, 61.4, 61.4, 61.1, 59.6, 59.5, 37.3, 36.4, 35.9, 35.3, 31.3, 31.0, 30.9, 29.8, 28.5, 28.3, 26.4, 26.4, 14.3, 14.2. HRMS (ESI) *m*/*z*: $[M + Na]^+$ calcd for $C_{18}H_{27}NO_5S_2Na$, 424.1223; found, 424.1219.

4-(*tert*-Butyl) 5-Ethyl (2*R*,3*aR*,5*S*,6*aR*)-2-Formylhexahydro-4*H*-furo[3,2-*b*]pyrrole-4,5-dicarboxylate (19). Dithiane **17** (1.78 g, 4.41 mmol) was dissolved in a mixture of THF-H_2O (9:1, 100 mL), a mixture of red HgO (1.93 g, 8.82 mmol) and $BF_3{\cdot}Et_2O$ (1.09 mL, 8.82 mmol) in THF (30 mL) was added, and the resulting mixture was stirred at room temperature for 48 h. The reaction mixture was then diluted with water and extracted with EtOAc (3 × 20 mL), and the combined organic phases were dried with anhydrous $MgSO_4$. The solution was filtered, and the solvent was removed under vacuum to give an oil, which was purified by column chromatography (hexanes/EtOAc, 5:5) to afford the aldehyde **19** as a colorless oil (764 mg, 55% yield) and 304 mg (17%) of the starting material. $[\alpha]_D^{23°C}$ = +12.1 (*c* = 1.53, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$, mixture of rotamers): δ 9.65 (s, 0.3H, minor Boc rotamer), 9.60 (s, 0.6H, major Boc rotamer), 4.73−4.67 (m, 1H), 4.46−4.35 (m, 2H), 4.34−4.28 (m, 1H), 4.23−4.09 (m, 2H), 2.92 (dd, *J* = 14.1, 2.1 Hz, 0.6H), 2.64−2.50 (m, 1.4H), 2.47−2.34 (m, 1H), 2.10−2.01 (m, 1H), 1.45 (s, 3H, minor Boc rotamer), 1.38 (s, 6H, major Boc rotamer), 1.27 (q, *J* = 6.9 Hz, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, CDCl3, mixture of rotamers): δ 202.7, 201.9, 172.9, 172.4, 153.5, 84.8, 84.0, 83.8, 83.7, 81.2, 81.2, 63.5, 63.1, 61.4, 61.4, 60.1, 60.0, 36.6, 35.9, 35.0, 34.8, 28.5, 28.3, 14.3, 14.2. HRMS (ESI) *m*/*z*: $[M + Na]^+$ calcd for $C_{15}H_{23}NO_6Na$, 336.1418; found, 336.1516.

4-(*tert*-Butyl) 5-Ethyl (2*R*,3*aR*,5*S*,6*aR*)-2-((Tosyloxy)methyl)-hexahydro-4*H*-furo[3,2-*b*]pyrrole-4,5-dicarboxylate (14). The aldehyde **19** (225 mg, 713 μmol) was dissolved in EtOH (4.50 mL), and $NaBH_4$ (157 mg, 4.31 mmol) was added at 0 °C. After stirring at r.t. for 1 h, the reaction mixture was quenched carefully with sat. NH_4Cl (5 mL) at 0 °C, the resulting mixture was extracted with EtOAc (3 × 20 mL), and the combined organic phases were washed with sat. NaCl. The organic phase was dried with anhydrous $MgSO_4$, filtered, and the solvent was removed under vacuum to give the crude alcohol as an oil, which was dissolved in CH_2Cl_2 (2.25 mL). *p*-Toluenesulfonyl chloride (301 mg, 1.58 mmol), 4-dimethylaminopyridine (877 μg, 7.18 μmol), and triethylamine (300 μL, 2.15 mmol) were added successively at 0 °C, and the mixture was stirred for 16 h at r.t. The solvent was removed under vacuum to give an oil, which was purified by column chromatography (hexanes/EtOAc, 7:3) to afford the tosylate **14** as a colorless oil (209 mg, 62%). This compound was found to be identical with the one obtained from the tosylation of **11** and separation as evidenced by NMR spectroscopy and optical rotation.

1-(*tert*-Butyl) 2-Ethyl (2*S*,3*aR*,6*aS*)-4-(1,3-Dithian-2-yl)-4-hydroxyhexahydro-1*H*-furo[3,4-*b*]pyrrole-1,2-dicarboxylate (20). To a solution of 1,3-dithiane (512 μL, 4.78 mmol) in THF (21 mL) was added buthyllithium solution (1.97 mL, 4.78 mmol, 2.41 M

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in hexane) dropwise at −78 °C. The solution was stirred at the same temperature for 30 min. Then, the lithiodithiane solution was transferred by a cannula to a solution of lactone **8** (1.30 g, 4.34 mmol) in THF (16.2 mL) dropwise at −78 °C. The resultant mixture was allowed to warm to r.t. and stirred for 2 h. The reaction mixture was quenched with NH_4Cl and extracted with CH_2Cl_2 (2 × 20 mL), and the combined organic phases were dried with anhydrous $MgSO_4$. The solution was filtered, and the solvent was removed under vacuum to give an oil, which was purified by column chromatography (hexanes/EtOAc, 7:3) to afford the lactol **20** (1.24 g, 62%) as a light yellow oil and 370 mg (29%) of the starting material. ^{1}H NMR (300 MHz, $CDCl_3$, mixture of rotamers and diastereoisomers): δ 4.67−4.41 (m, 2H), 4.38−3.99 (m, 4H), 3.97−3.83 (m, 1H), 3.60 (d, J = 5.7 Hz, 0.5H), 3.49−3.37 (m, 0.5H), 3.26−2.74 (m, 3H), 2.60−2.23 (m, 3H), 2.22−1.80 (m, 3H), 1.43 (s, 4H), 1.38 (s, 5H), 1.31−1.20 (m, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$, mixture of rotamers and diastereoisomers): δ 173.1, 172.7, 172.7, 172.4, 154.0, 153.7, 107.8, 107.7, 107.3, 107.2, 80.6, 80.6, 80.4, 77.4, 73.5, 73.0, 63.4, 62.8, 62.5, 62.4, 62.2, 61.8, 61.4, 61.1, 61.0, 60.9, 51.9, 50.7, 49.9, 49.1, 48.7, 48.3, 31.8, 31.0, 30.1, 29.2, 28.5, 28.4, 28.3, 26.8, 26.8, 26.7, 26.6, 25.2, 25.0, 14.3, 14.2. HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{18}H_{29}NO_6S_2Na$, 442.1329; found, 442.1342.

1-(*tert*-Butyl) 2-Ethyl (2*S*,3a*R*,6a*S*)-4-(1,3-Dithian-2-yl)-hexahydro-1*H*-furo[3,4-*b*]pyrrole-1,2-dicarboxylate (21). To a solution of lactol **20** (1.79 g, 4.27 mmol) in CH_2Cl_2 (30.3 mL) were added dropwise at −78 °C triethylsilane (2.73 mL, 17.1 mmol) and boron trifluoride diethyl etherate (2.10 mL, 17.0 mmol). The solution was stirred for 45 min and then quenched with water. The resulting mixture was extracted with CH_2Cl_2 (3 × 10 mL), the combined organic phases were dried with anhydrous $MgSO_4$ filtered, and the solvent was removed under vacuum to give a colorless oil, which was purified by column chromatography (hexanes/EtOAc, 8:2) to afford the dithianes **21** as a colorless oil (1.41 g, 82%). ^{1}H NMR (400 MHz, $CDCl_3$, mixture of rotamers and diastereoisomers): δ 4.58−4.30 (m, 2H), 4.26−3.91 (m, 3H), 3.87−3.66 (m, 1H), 3.25−2.95 (m, 2H), 2.93−2.77 (m, 4H), 2.63−2.32 (m, 1H), 2.31−1.82 (m, 4H), 1.43 (s, 3H), 1.39 (s, 6H), 1.31−1.18 (m, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$, mixture of rotamers and diastereoisomers): δ 172.3, 172.0, 153.8, 153.7, 80.6, 80.5, 80.1, 76.9, 74.0, 73.8, 62.9, 62.4, 60.8, 60.8, 60.7, 60.5, 45.8, 45.4, 44.9, 43.8, 29.0, 28.9, 28.6, 28.4, 28.2, 28.1, 28.0, 27.9, 25.19, 25.2, 13.9, 13.8. HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{18}H_{29}NO_5S_2Na$, 426.1379; found, 426.1382.

1-(*tert*-Butyl) 2-Ethyl (2*S*,3a*R*,6a*S*)-4-Formylhexahydro-1*H*-furo[3,4-*b*]pyrrole-1,2-dicarboxylate (22). Dithianes **21** (1.08 g, 2.68 mmol) was dissolved in a mixture of THF-H_2O (9:1, 60 mL), a mixture of red HgO (1.17 g, 5.35 mmol) and BF_3 etherate (661 μL, 5.35 mmol) in THF (20 mL) were added, and the resulting mixture was stirred at room temperature for 48 h. The reaction mixture was then diluted with water and extracted with EtOAc (3 × 20 mL), and the combined organic phases were dried with anhydrous $MgSO_4$. The solution was filtered, and the solvent was removed under vacuum to give an oil, which was purified by column chromatography (hexanes/EtOAc, 5:5) to afford the aldehyde **22** as a colorless oil (333 mg, 40%) and 233 mg (22%) of the starting material. ^{1}H NMR (400 MHz, $CDCl_3$, mixture of rotamers and diastereoisomers): δ 9.80 (d, J = 2.5 Hz, 1H), 4.65−4.31 (m, 2H), 4.28−4.08 (m, 3H), 4.08−3.59 (m, 2H), 3.32−3.17 (m, 0.3H), 3.00 (bs, 0.7H), 2.39−1.95 (m, 2H), 1.51−1.36 (m, 9H), 1.33−1.22 (m, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$, mixture of rotamers and diastereoisomers): δ 199.5, 199.4, 171.4, 171.1, 153.3, 153.1, 83.8, 83.8, 79.9, 73.6, 73.2, 62.6, 62.1, 60.6, 60.5, 60.4, 43.9, 42.9, 29.9, 29.0, 27.5, 27.3, 27.3, 27.2, 13.4, 13.2. HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{15}H_{23}NO_6Na$, 336.1418; found, 336.1510.

1-(*tert*-Butyl) 2-Ethyl (2*S*,3a*R*,4*R*,6a*S*)-4-((Tosyloxy)methyl)-hexahydro-1*H*-furo[3,4-*b*]pyrrole-1,2-dicarboxylate (23) and 1-(*tert*-Butyl) 2-Ethyl (2*S*,3a*R*,4*S*,6a*S*)-4-((Tosyloxy)methyl)-hexahydro-1*H*-furo[3,4-*b*]pyrrole-1,2-dicarboxylate (24). The aldehyde **17** (290 mg, 925 μmol) was dissolved in EtOH (20 mL), and $NaBH_4$ (214 mg, 5.55 mmol) was added at 0 °C. After stirring at r.t. for 1 h, the reaction mixture was quenched carefully with sat. NH_4Cl (5 mL) at 0 °C. The resulting mixture was extracted with EtOAc (3 × 10 mL), and the combined organic phases were washed with sat. NaCl. The organic phase was dried with anhydrous $MgSO_4$, the solution was filtered, and the solvent was removed under vacuum to give the crude alcohol as an oil, which was dissolved in CH_2Cl_2 (2 mL). *p*-Toluenesulfonyl chloride (397 mg, 2.08 mmol), 4-dimethylaminopyridine (1.13 mg, 9.29 μmol), and triethylamine (390 μL, 2.79 mmol) were added successively at 0 ° C, and the mixture was stirred for 16 h. The solvent was removed under vacuum to give an oil, which was purified by column chromatography (hexanes/EtOAc, 7:3) to afford the more polar tosylate **24** as a colorless oil (179 mg, 41%) and the less polar tosylate **23** as a colorless oil (82.9 mg, 19%). Data for **23**: R_f: 0.44 (hexanes/EtOAc, 7:3), $[\alpha]_D^{23°C}$ = −48.3 (c = 2.25, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, mixture of rotamers): δ 7.81−7.73 (m, 2H), 7.39−7.30 (m, 2H), 4.53−4.30 (m, 2H), 4.28−4.05 (m, 3H), 4.05−3.64 (m, 4H), 2.86−2.67 (m, 1H), 2.44 (s, 3H), 2.22−2.00 (m, 2H), 1.42 (s, 3H), 1.38 (s, 6H), 1.35−1.20 (m, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$, mixture of rotamers): δ 172.5, 172.1, 154.1, 154.0, 145.3, 132.7, 132.6, 130.1, 130.1, 128.1, 128.1, 127.9, 127.2, 81.2, 81.2, 80.8, 80.7, 77.4, 74.8, 74.0, 69.7, 63.7, 63.2, 61.4, 61.3, 45.2, 44.2, 34.2, 33.2, 28.4, 28.3, 21.8, 14.4, 14.2. HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{22}H_{31}NO_8SNa$, 492.1663; found, 492.1682. Data for **24**: R_f: 0.25 (hexanes/EtOAc, 7:3), $[\alpha]_D^{23°C}$ = −65.2 (c = 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, mixture of rotamers): δ 7.76 (d, J = 8.3 Hz, 2H), 7.33 (d, J = 8.0 Hz, 2H), 4.54−4.35 (m, 1H), 4.35−4.26 (m, 1H), 4.24−4.01 (m, 4H), 4.00−3.78 (m, 2H), 3.69 (t, J = 6.0 Hz, 0.6H), 3.65 (t, J = 5.9 Hz, 0.4H), 2.98−2.84 (m, 1H), 2.43 (s, 3H), 2.13−1.76 (m, 2H), 1.41 (s, 4H), 1.36 (s, 5H), 1.25 (t, J = 7.2, 1.7H), 1.23 (t, J = 7.2, 1.3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$, mixture of rotamers): δ 172.4, 172.2, 154.2, 154.0, 145.3, 145.3, 132.5, 132.5, 130.0, 130.0, 128.0, 80.6, 77.4, 77.1, 74.4, 74.2, 67.9, 67.9, 63.5, 63.1, 61.5, 61.3, 61.3, 61.2, 44.5, 43.4, 29.2, 28.4, 28.3, 28.3, 21.7, 14.4, 14.2. HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{22}H_{31}NO_8SNa$, 492.1663; found, 492.1682.

Ethyl (2*S*,3a*R*,4*S*,6a*R*)-Hexahydro-1,4-methanofuro[3,4-*b*]-pyrrole-2-carboxylate (5). To a solution of tosylate **24** (112 mg, 239 μmol) in CH_2Cl_2 (4 mL) was added trifluoroacetic acid (369 μL, 4.77 mmol). After 1 h, the solvent was evaporated, and the sample was dried overnight under high vacuum to give the TFA salt. The salt was then dissolved in EtOH (2.4 mL), triethylamine (101 μL, 716 μmol) was added at r.t., and the solution was stirred for 16 h. The solvent was evaporated, sat. Na_2CO_3 was added, the resulting mixture was extracted with CH_2Cl_2 (3 × 20 mL), the combined organic phases were dried with anhydrous $MgSO_4$ and filtered, and the solvent was removed under vacuum to give **5** as an orange colored oil (47 mg, 84%). $[\alpha]_D^{23°C}$ = +52.9 (c = 0.70, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.19 (qd, J = 7.1, 1.2 Hz, 2H), 4.14 (t, J = 2.7 Hz, 1H), 3.94−3.84 (m, 2H), 3.54−3.48 (m, 1H), 3.35 (dd, J = 8.8, 3.2 Hz, 1H), 2.99 (d, J = 12.9 Hz, 1H), 2.54−2.47 (m, 1H), 2.33 (dt, J = 12.8, 2.5 Hz, 1H), 2.11 (ddd, J = 13.6, 5.0, 3.1 Hz, 1H), 1.74 (dd, J = 13.5, 8.8 Hz, 1H), 1.27 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 172.3, 79.1, 68.7, 68.7, 66.8, 61.4, 59.1, 44.5, 24.3, 14.3. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{10}H_{16}NO_3$, 198.1125; found, 198.1118.

4-(*tert*-Butyl) 5-Ethyl (2*R*,3a*R*,5*S*,6a*R*)-2-((*S*)-1-(Tosyloxy)-ethyl)hexahydro-4*H*-furo[3,2-*b*]pyrrole-4,5-dicarboxylate (27). To a solution of aldehyde **19** (400 mg, 1.28 mmol) in THF (12.8 mL) were added dropwise at 0 °C $LaCl_3$·LiCl solution (638 μL, 383 μmol, 0.6 M) and then methyl magnesium chloride (468 μL, 1.4 mmol) dropwise at the same temperature. The solution was stirred for 15 min at 0 °C and then warmed to r.t. for 16 h. Saturated NH_4Cl (10 mL) was added, the resulting solution was extracted with EtOAc (3 × 10 mL), and the combined organic phases were dried with anhydrous $MgSO_4$. The solution was filtered, and the solvent was removed under vacuum to give an oil, which was purified by column chromatography (hexanes/EtOAc, 1:1) to afford a mixture of inseparable alcohols **25** and **26** (212 mg, 644 μmol, 50%) as a colorless oil, which was dissolved in CH_2Cl_2 (2.5 mL). *p*-Toluenesulfonyl chloride (275 mg,

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1.42 mmol), 4-dimethylaminopyridine (1 mg, 8.2 μmol), and triethylamine (270 μL, 1.93 mmol) were added successively at 0 °C, and the mixture was stirred for 30 h. The solvent was removed under vacuum to give an oil, which was purified by column chromatography (hexanes/EtOAc, 7:3) to afford the pure (*S*)-tosylate **27** (more polar isomer) as a colorless oil (118 mg, 38%) and a mixture of tosylates **27** and **28** (NMR ratio 4/2, 138 mg, 44%) as a colorless oil. Data for **27**: R_f: 0.25 (hexanes/EtOAc, 7:3), ^{1}H NMR (400 MHz, $CDCl_3$, mixture of rotamers): δ 7.77 (d, *J* = 8.1 Hz, 2H), 7.31 (d, *J* = 7.9 Hz, 2H), 4.74−4.61 (m, 1H), 4.47−4.31 (m, 2H), 4.26−4.06 (m, 4H), 3.97−3.85 (m, 1H), 2.42 (s, 3H), 2.34−2.19 (m, 2H), 2.07−1.90 (m, 1H), 1.43 (s, 3H), 1.38 (s, 6H), 1.30−1.18 (m, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$, mixture of rotamers): δ 172.8, 172.3, 153.9, 153.6, 144.7, 144.7, 134.6, 134.5, 129.9, 129.8, 127.9, 82.7, 82.3, 82.2, 82.0, 80.7, 80.6, 79.8, 79.2, 63.4, 62.9, 61.2, 61.1, 59.9, 59.9, 36.1, 35.3, 34.7, 33.8, 28.5, 28.3, 17.0, 16.7, 14.3, 14.2; HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{23}H_{34}NO_8S$, 484.2000; found, 484.2015. Data for **28**: R_f: 0.30 (hexanes/EtOAc, 7:3).

Ethyl (1*R*,3*S*,5*R*,6*R*,7a*S*)-5-Methylhexahydro-1*H*-1,6-epoxypyrrolizine-3-carboxylate (6). To a solution of tosylate **27** (69 mg, 143 μmol) in CH_2Cl_2 (2.5 mL) was added trifluoroacetic acid (219 μL, 2.85 mmol). After 1 h, the solvent was evaporated, and the residue was dried overnight under high vacuum to give the TFA salt. The salt was then dissolved in EtOH (1.5 mL), triethylamine (40 μL, 285 μmol) was added at r.t., and the solution was stirred for 16 h. The solvent was evaporated, sat. Na_2CO_3 was added, the resulting solution was extracted with CH_2Cl_2 (3 × 10 mL), the combined organic phases were dried with anhydrous $MgSO_4$ and filtered, and the solvent was removed under vacuum to give **6** as an orange colored oil (20 mg, 66%). $[\alpha]_D^{23°C}$ = −62.7 (*c* = 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.35 (dd, *J* = 4.0, 1.6 Hz, 1H), 4.16 (qd, *J* = 7.1, 1.9 Hz, 2H), 3.98 (d, *J* = 2.7 Hz, 1H), 3.92 (dd, *J* = 9.2, 4.0 Hz, 1H), 3.77 (d, *J* = 2.2 Hz, 1H), 3.47 (q, *J* = 6.9 Hz, 1H), 2.27 (ddd, *J* = 14.6, 9.1, 1.0 Hz, 1H), 2.18−2.11 (m, 2H), 1.90 (dd, *J* = 10.5, 2.7 Hz, 1H), 1.30−1.22 (m, 3H), 1.09 (d, *J* = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 174.5, 83.0, 77.5, 69.2, 63.6, 61.0, 61.0, 38.6, 35.4, 29.7, 14.2, 11.9; HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{11}H_{18}NO_3$, 212.1281; found, 212.1288.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.9b03413.

^{1}H and ^{13}C NMR spectra of all the synthetic compounds (PDF)

X-ray details for **15** (hydrate) (CIF)

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Author Contributions

S.H. performed the chemistry, and G.B. performed the DFT calculations.

Notes

The authors declare no competing financial interest.

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