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Rapid Synthesis of the *epi*-Biotin Sulfone via Tandem *S,N*-Carbonyl Migration/aza-Michael/Spirocyclization and Haller−Bauer Reaction

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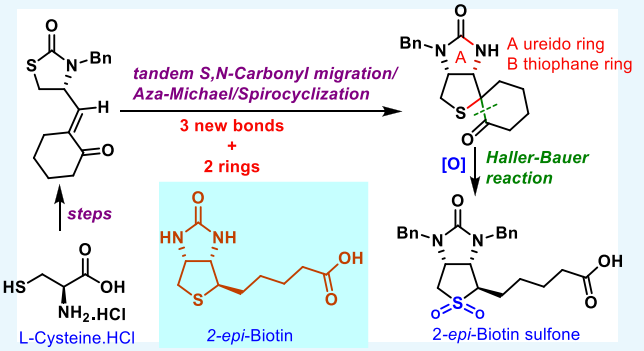
ABSTRACT: A synthesis of 2-*epi*-biotin sulfone was accomplished from commercially available L-cysteine. The synthesis features an unprecedented tandem *S,N*-carbonyl migration/aza-Michael/spirocyclization reaction from an L-cysteine-derived enone with aq. ammonia, in which three new sigma bonds and two rings are formed. In addition, the synthesis includes a highly diastereoselective late-stage Haller−Bauer reaction of sulfone for direct introduction of the carbon side chain.



INTRODUCTION

Stereoselective syntheses of molecules, both natural and designed, employing cascade reactions have emerged in recent years.[1] Cascade reactions which involve the formation of multiple bonds or multiple transformations in a one-pot operation are often associated with an environmentally benign, atom-economical, and efficient process. A well-designed cascade and its execution are effective solutions to access desired biologically important natural products. In this context, considerable effort has been invested to explore various strategies. The development of cascades to provide specific biologically important molecules of unique architecture and stereocontrol presents a remarkable challenge.

(+)-Biotin (**1**, Figure 1), known as vitamin H, has long attracted intense attention from the synthetic community

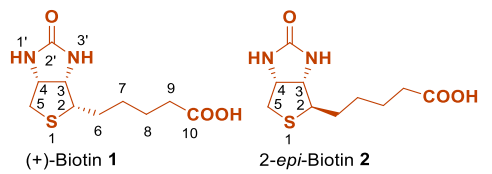


Figure 1. Structures of (+)-biotin and 2-*epi*-biotin.

because of its important biological function in the human diet and animal strength.[2] In addition, it is associated with an essential part of the metabolic cycle, resulting in catalytic fixation of carbon dioxide in the biosynthesis of organic molecules. From the pharmaceutical point of view, it is used as an additive and as an avidin complex in the field of drug delivery; biotinylation has allowed genomic and postgenomic eras[3] to detect and isolate the protein complement of cells. The scarcity of efficient fermentation methods[4] for biotin has drawn the attention of organic chemists toward its synthesis. The supply of (+)-biotin (**1**) required across the world has entirely relied on the synthetic method.

Additionally, biotin−(strept)avidin systems have been widely used for various applications including immunoassay, diagnostics, and localization.[5−7] However, major difficulties using biotinylation in the purification of protein are due to the strong affinity of biotin for avidin. Therefore, the synthesis of biotin analogues having a weak affinity for (strept)avidin is highly desirable.[1c,8]

To date, a number of synthetic approaches involving various strategies for the control of three contiguous stereogenic centers are reported.[9] However, to the best of our knowledge, the Goldberg and Sternbach approach developed by Hoffman−La Roche,[10] which was established about 60 years ago, is considered to be the most efficient and commercial approach. The Goldberg and Sternbach approach has been thoroughly modified for several years. With our ongoing interest and endeavors in the synthesis of biologically active compounds,[11] we were interested in exploring an efficient synthesis of (+)-biotin.

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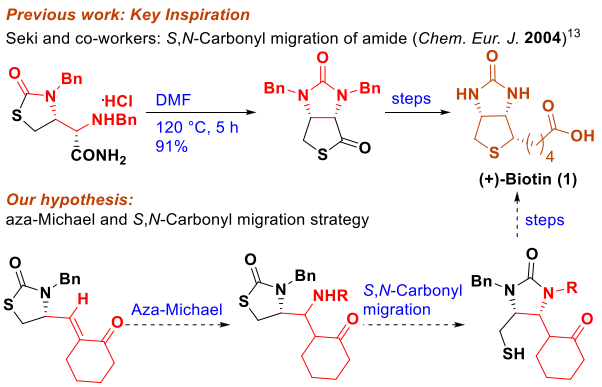
Of the several approaches reported toward (+)-biotin synthesis, cysteine[12] has attracted a great deal of attention because it possesses requisite stereochemistry and ready availability. On the basis of Seki's pioneering findings[13] (Scheme 1), the utility of *S,N*-carbonyl migration of amide

Scheme 1. Key Inspiration and Crucial *S,N*-Carbonyl Migration Reaction Involved in the Earlier Total Synthesis of Biotin and Our Hypothesis



has provided a powerful protocol to effect one-pot C−N and S−C bond formation to access the *cis*-[5−5]-fused ring system of the (+)-biotin skeleton. This has inspired us to develop the elegant synthesis of (+)-biotin, utilizing an aza-Michael reaction followed by *S,N*-carbonyl migration to generate the *cis*-[5−5]-fused ring system of the (+)-biotin skeleton with excellent stereocontrol. The proposed hypothesis using aza-Michael and *S,N*-carbonyl migration in the efficient syntheses of (+)-biotin (**1**) is shown in Scheme 1.

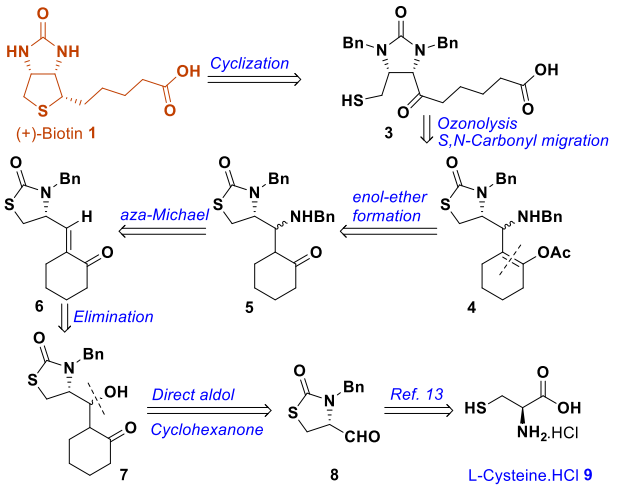
RESULTS AND DISCUSSION

The enone **6** appeared to be an ideal scaffold to study the aza-Michael reaction. The retrosynthetic analysis of (+)-biotin indicated that the stereogenic centers of **1** would be established by the aza-Michael reaction of enone **6**. The enone **6** can be obtained from aldol product **7** by a base-promoted elimination reaction. In turn, aldol adduct **7** can be accessed by aldol reaction of known α-amino aldehyde **8** with cyclohexanone. The α-amino aldehyde **8** could be derived from commercially available L-cysteine (**9**, Scheme 2). The side chain of **1** could be constructed through oxidative cleavage of enol-acetate **4**, and in turn **1** could be assembled from **4** by using *S,N*-carbonyl migration and cyclization.

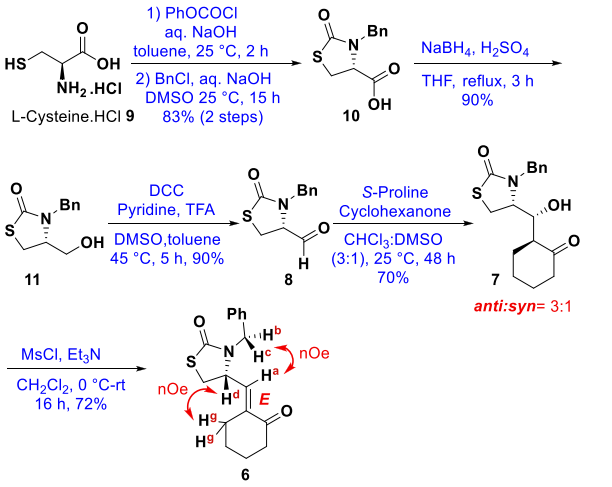
In this study, the synthesis of (+)-biotin (**1**) commenced with the synthesis of α-amino aldehyde **8** in 4 steps from L-cysteine (**9**) by following a known procedure.[13] The direct diastereoselective aldol reaction[4a,14b] of (*R*)-amino aldehyde **8** was carried out with 2 mol equiv of cyclohexanone as a donor in the presence of 20 mol % of (*S*)-proline at 0 °C to rt in $CHCl_3$−DMSO as the solvent to afford a mixture of (*anti-syn*)-aldol product **7** as a diastereomeric mixture in good yield (Scheme 3).

The *anti* selectivity of the direct proline-catalyzed aldol reaction may be accounted for by the Houk−List model proposed for cyclic ketone. Intermolecular hydrogen bonding between the cyclic enamine intermediate and α-amino aldehyde plays a critical role in providing *anti*-**7** stereoselectively.[14b,15] A mixture of *anti*-**7** and *syn*-**7** could be used for the subsequent transformation. The diastereomeric mixture

Scheme 2. Retrosynthetic Analysis



Scheme 3. Synthesis of Enone 6 and NOESY Correlation



of aldol product **7** was subjected to mesylation using mesyl chloride and excess triethylamine to afford corresponding enone **6**. The stereochemistry of enone **6** was confirmed by two-dimensional (2D) NOESY data, which supported the *E* configuration of olefin (Supporting Information).

The next task was the installation of a vicinal diamine moiety. We decided to introduce the second nitrogen by performing aza-Michael reaction[16a] on enone **6**. Various amines and catalysts were screened to achieve this transformation (Table 1). Thus, treatment of enone **6** with different amines (benzylamine/dibenzylamine/*N*-benzyl hydroxylamine)[16a] in the presence of catalysts (amberlyst-15/$CeCl_3{\cdot}7H_2O$, NaI, SiO_2)[16b,c] was unsuccessful. After careful screening, treatment of enone **6** with $TMSN_3$ and AcOH and catalyzed by triethyl amine[16d] did effect the aza-Michael adduct **12**, however in poor yield. Interestingly, enone **6** and aza-Michael adduct **12** appeared at the same R_f, rendering the purification a difficult task. After this disappointment, it was thought that aq. ammonia could be a better choice to access the aza-Michael adduct, based on significant rate acceleration of the aza-Michael reaction in water which was reported by Ranu and co-workers.[16e] Aza-Michael reaction of enone **6** with aq. NH_3 solution in ethanol at 140 °C in sealed tube was performed. Gratifyingly, a one-pot tandem *S,N*-carbonyl migration/aza-

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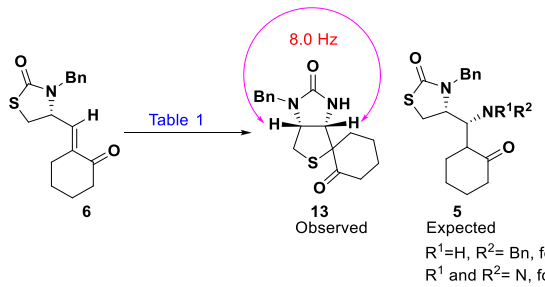
Table 1. Aza-Michael Reaction of Enone 6



entry	conditions	temp (°C)	yield (%)
1	$BnNH_2$, EtOH	0−rt	–
2	$BnNH_2$, amberlyst-15, solvent free	rt	–
3	BnNHOH, $CHCl_3$	0−rt	–
4	Bn_2NH, $CeCl_3{\cdot}7H_2O$, NaI, SiO_2	40	–
5	NaN_3, AcOH, THF	rt	trace
6	$TMSN_3$, AcOH, Et_3N	rt	trace of **12**
7	aq. NH_3 (30%), EtOH	140	65 of **13**

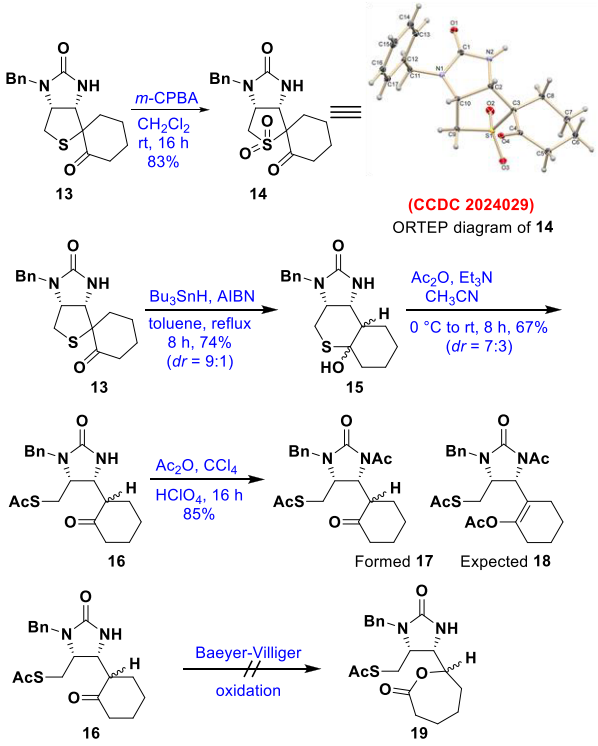
Michael/spirocyclization reaction allowed a facile entry to the requisite core of the biotin skeleton.

During the initial screening (entries 1−6) of various amines with enone **6**, the usual formation of the aza-Michael adduct was expected. However, unusual spiroketone **13** was observed in 65% yield as a single diastereomer (Table 1). The resultant high degree of diastereoselectivity may be due to the facial selectivity and the rigid framework of enone **6** (for the proposed mechanism, see the Supporting Information). The *cis* stereochemistry of vicinal diamine was confirmed by ^{1}H NMR coupling constants, J = 8.0 Hz, for product **13** (Supporting Information).

The introduction of a carbon side chain of biotin (**1**) was the next task of our investigation. Earlier, we successfully demonstrated the Baeyer−Villiger oxidation[17a] of cyclic ketones and oxidative cleavage of cyclohexene derivatives using ozonolysis employed in the side-chain construction of biotin.[17b,c] Accordingly, the initial choice was the Baeyer−Villiger oxidation of ketone **13** to obtain the desired lactone. The reaction of ketone **13** with *m*-CPBA led to the formation of sulfone **14** in 83% yield as a yellow solid, and the desired lactone could not be isolated in various conditions. The structure and relative stereochemistry of sulfone **14** were confirmed by single-crystal X-ray crystallography, wherein it was found to possess the desired *cis*-vicinal diamine moiety (Scheme 4).

In order to construct the side chain of biotin (**1**), it was thought that thioacetate (**16**, Scheme 4) could be an ideal precursor to perform Baeyer−Villiger oxidation or oxidative cleavage via formation of enol-acetate **18**. As the reactive sulfide was protected as its thioacetate, it was expected that the acetate group might remain intact in oxidation reaction conditions. Accordingly, the reductive cleavage[18] of spiroketone **13** with tributyltin hydride and AIBN as a radical initiator in refluxing toluene afforded thiohemiacetal **15** in 74% yield (dr = 9:1). Further, the chemoselective acetylation of **15** was carried out to access desired thioacetate **16** in 67% yield with dr = 7:3. Subsequently, a diastereomeric mixture of thioacetate **16** was subjected to acid-catalyzed enol acetate formation by using catalytic perchloric acid and acetic anhydride,[19] which led to the formation of *N*-acetate **17**, and desired enol acetate **18** was not formed, even after keeping the reaction for a

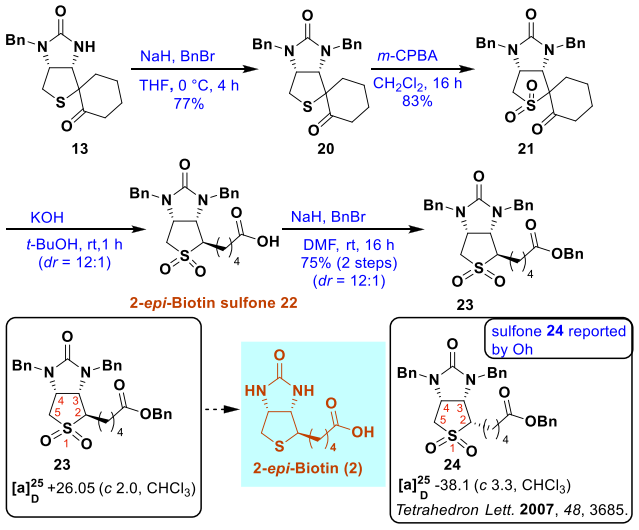
Scheme 4. Synthesis of Thioacetate 16



prolonged period. The Baeyer−Villiger oxidation of ketone **16** with *m*-CPBA was also unsuccessful.

After disappointing results in the oxidation of thioacetate substrate **16**, the Haller−Bauer reaction of sulfide **20** and sulfone **21** was planned (Scheme 5). It was envisioned that the

Scheme 5. Synthesis of 2-*epi*-Biotin Sulfone and Optical Rotation



base-induced cleavage Haller−Bauer reaction[20a] of ketone **20** should directly provide a biotin precursor. The reaction was tested by bases like NaOH, KOH, and $NaNH_2$; however, unfortunately, the reaction did not take place even after refluxing **20** in MeOH or toluene for a prolonged period of 48 h, and the starting material ketone **20** remained unreacted. Gratifyingly, it was understood that the oxidation of sulfide **20**

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to sulfone **21** by using *m*-CPBA is necessary for the success of Haller−Bauer reaction. In an effort to simplify the experimental procedure of the Haller−Bauer reaction, we investigated the use of powdered potassium hydroxide in *tert*-butyl alcohol, a base system previously employed by Marshall et al.[20b] for cleavage of cyclic α-diketone monothioketals. Under this condition, excellent results could be obtained using the KOH−*tert*-butyl alcohol system with a sulfone **21**. Optimum yields were realized when the temperature was near room temperature, and lower temperatures (−10 to 0 °C) prolonged the required reaction time. Accordingly, for quick access to acid **22** through KOH−*tert*-butyl alcohol[20b] mediated Haller−Bauer cleavage, reaction was performed to furnish the acid **22** with dr = 12:1. We believe that this is the first example of KOH−*tert*-butyl alcohol mediated Haller−Bauer reaction of sulfone where the transformation is executed under mild conditions.

Having successfully introduced the side chain of the biotin sulfone skeleton, the next task was reduction of highly stable sulfone **22** to sulfide. Sulfone **22** was *O*-benzylated to obtain **23** in 75% yield over two steps (dr = 12:1). The absolute and relative stereochemistry of the side chain was established by comparison of specific rotation of *O*-benzyl ester **23** with known *O*-benzyl derivative **24**, which was reported by Oh.[21] It was found that the spectral as well as specific rotation data of **23** were significantly different, as shown in Scheme 5.

The stereocenter at C(2) on the thiophane ring was found to be *trans* with respect to the stereocenter at C(3) and C(4). The *O*-benzyl ester **23** could be converted to hydroxyl-sulfide by sulfone reduction using $LiAlH_4$.[22a] Finally, the chemoselective oxidation of the resultant primary hydroxyl sulfide can be converted to the corresponding *N*,*N*-benzyl 2-*epi*-biotin derivative via the stepwise Swern oxidation[22b] and PDC oxidation[22c] reaction sequence. The *N*,*N*-benzyl 2-*epi*-biotin derivative, upon the known debenzylation[17a] conditions, would lead to 2-*epi*-biotin. Hence, the present route constitutes an attempt toward the synthesis of 2-*epi*-biotin (**2**).

CONCLUSIONS

In summary, the synthesis of *N*,*N*′-dibenzyl 2-*epi*-biotin sulfone **22** using L-cysteine has been achieved. A direct proline-catalyzed aldol reaction, tandem *S*,*N*-carbonyl migration/aza-Michael/spirocyclization reaction, and late-stage Haller−Bauer reaction are the key steps in the synthesis. The tandem *S*,*N*-carbonyl migration/aza-Michael/spirocyclization reaction to access the required *cis*-[5−5]-fused ring system of the (+)-biotin skeleton was one of the key findings of this work. The direct, flexible, and versatile introduction of a side chain at C(2) of **21** to form **22** opened an avenue for the synthesis of biotin analogues. Especially by varying the bases at the Haller−Bauer reaction step, we can enable the synthesis of biotin analogues. The work in this direction is in progress in our laboratory and will be communicated in due course.

EXPERIMENTAL SECTION

General. All reactions were carried out in oven-dried glassware under a positive pressure of argon or nitrogen unless otherwise mentioned with magnetic stirring. Air-sensitive reagents and solutions were transferred via syringe or cannula and were introduced to the apparatus via a rubber septa. All reagents and solvents were used as received from the manufacturer. Solvents were dried over CaH_2 or sodium. Analytical TLC was carried out using precoated silica gel plates (Merck TLC silica gel 60 F_{254}), and visualization was accomplished with either UV light, with iodine adsorbed on silica gel, or by immersion in ethanolic solution of phosphomolybdic acid (PMA), *p*-anisaldehyde, 2,4-DNP, $KMnO_4$, or ninhydrin solution followed by heating with a heat gun for ∼15 s. Merck's flash silica gel (230−400 mesh) was used for column chromatography. IR spectra were recorded on a PerkinElmer 1615 FT infrared spectrophotometer using a NaCl cell. Melting points of solids were measured on a Buchi melting point apparatus. Optical rotation values were recorded on a P-2000 polarimeter at 589 nm. HRMS (ESI) were recorded on an ORBITRAP mass analyzer (Thermo Scientific, Q Exactive). Mass spectra were measured with ESI ionization in an MSQ LCMS mass spectrometer. ^1H and ^{13}C NMR spectra were recorded using a Bruker Advance (200, 400, and 500 MHz) spectrometer. Chemical shifts are reported in ppm relative to residual $CHCl_3$ (δ = 7.26) in $CDCl_3$ for ^1H NMR and $CDCl_3$ (δ = 77.0) for ^{13}C in the ^{13}C NMR spectra. Structural assignments were made with additional information from gCOSY, gNOESY, gHSQC, and gHMBC experiments.

(R)-3-Benzyl-4-((R)-hydroxy((S)-2-oxocyclohexyl)methyl)-thiazolidin-2-one (7). Pyridine (0.70 mL, 8.8 mmol), TFA (0.66 mL, 8.8 mmol), and DCC (10.9 g, 52 mmol) in toluene (20 mL) were successively added to a solution of **11** (10.0 g, 44 mmol) in DMSO (22 mL) at 25 °C, and the mixture was stirred at 45 °C for 5 h. Toluene (100 mL) was added to the mixture, which was then cooled in an ice bath and filtered. The filtrate was washed with brine and water, while the aqueous layer was extracted with EtOAc. The extracts were combined, dried over anhydrous Na_2SO_4, and filtered, and the solvent was evaporated to afford **8**[13] (8.9 g, 90%) as a viscous oil. The spectral data of aldehyde **8** matched well with the reported information.[13] The obtained crude aldehyde **8** was directly used for the next step without further purification. To a stirred solution of α-amino aldehyde **8** (4.0 g, 18.09 mmol) and cyclohexanone (3.77 mL, 36.18 mmol) in solvent $CHCl_3$−DMSO (3:1, 40 mL) was added 20 mol % of (*S*)-proline (0.41 g) at 0 °C. The reaction was stirred for 48 h at room temperature and monitored by TLC. After completion of the reaction, the solvent was removed *in vacuo*. The resulting residue was taken up in EtOAc (40 mL) and stirred with 10% $NaHCO_3$ solution (10 mL). The organic layer was separated and washed with brine solution, dried over anhydrous Na_2SO_4, filtered, and evaporated *in vacuo*. The crude residue was purified by flash chromatography on silica gel (230−400 mesh) with EtOAC−PE (40:60) to give the aldol product **7** (4.0 g, 70% yield) as a yellow viscous oil with diastereoselectivity (*anti*/*syn*) = 3:1 determined by ^1H NMR analysis. The *anti*-**7** stereoselectively may be confirmed by the proposed Houk−List model (Figure 2) for closely related proline-catalyzed direct aldol reaction of cyclohexanone and Garner's aldehyde reported in the literature.[14b]

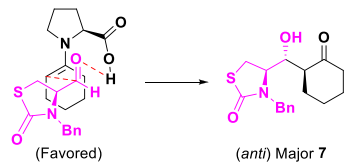

Figure 2. Houk−List model for diastereoselective aldol reaction.

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R_f: 0.5 (EtOAc−PE = 50:50). IR ($CHCl_3$): ν_{max} 3399, 1720, 1660, 1495, 1446, 1221 cm^{-1}. [α] −27.33 (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) mixture of diastereomers was observed: δ 7.26−7.15 (m, 5H), 5.95 (s, 1H), 5.25−5.05 (m, 2H), 4.45 (d, *J* = 8.5 Hz, 1H), 3.94−3.92 (m, 1H), 2.31−2.25 (m, 2H), 2.0−1.96 (m, 3H), 1.61−1.56 (m, 4H), 1.09−1.02 (m, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) mixture of diastereomers was observed: δ 212.3, 171.6, 135.7, 129.0 (2C), 128.2, 128.0 (2C), 67.4, 65.7, 56.6, 47.3, 42.5, 37.6, 28.1, 25.5, 24.5. HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{22}NO_3S$: 320.1315, found: 320.1312.

*(R,E)-3-Benzyl-4-((2-oxocyclohexylidene)methyl)-thiazolidin-2-one (**6**).* To a solution of aldol **7** (mixture of *anti*/*syn*) (2.0 g, 6.26 mmol) in anhydrous dichloromethane (20 mL) was added Et_3N (9 mL, 62.6 mmol) at 0 °C followed by $MeSO_2Cl$ (2.4 mL, 31.34 mmol) dropwise. After 1 h, the ice bath was removed, and the reaction was stirred for 16 h at room temperature, the reaction being followed by TLC. After completion of the reaction (monitored by TLC), the reaction was quenched with water (5 mL), and the organic layer was washed with aq. $NaHCO_3$ (2%, 10 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by flash chromatography on silica gel (230−400 mesh) with EtOAC-PE (30:70) to give the enone **6** (1.35 g, 72%) as a yellowish solid. The stereochemistry of enone **6** was confirmed by two-dimensional (2D) NOESY data which supported the *E* configuration of olefin. R_f: 0.5 (EtOAc−PE= 30:70). MP: 85−87 °C. IR ($CHCl_3$): ν_{max} 2933, 1694, 1651, 1631, 1261, 756 cm^{-1}. [α] −32.2 (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.35−7.27 (m, 3H), 7.18 (d, *J* = 7.3 Hz, 2H), 6.44 (d, *J* = 9.8 Hz, 1H), 5.04 (d, *J* = 14.6 Hz, 1H), 4.40−4.33 (m, 1H), 3.83 (d, *J* = 14.6 Hz, 1H), 3.27 (dd, *J* = 7.9, 11.0 Hz, 1H), 3.01 (dd, *J* = 7.3, 11.0 Hz, 1H), 2.50−2.46 (m, 2H), 2.20−2.17 (m, 2H), 1.87−1.79 (m, 2H), 1.71−1.56 (m, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 200.2, 172.0, 140.5, 135.7, 132.7, 128.7 (2C), 128.2 (2C), 127.9, 55.3, 47.0, 40.4, 30.2, 26.9, 23.4, 23.2. HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{20}NO_2S$: 302.1209, found: 302.1205.

*(3a′S,6a′R)-1′-Benzyltetrahydrospiro[cyclohexane-1,4′-thieno[3,4-d]imidazole]-2,2′(1′H)-dione (**13**).* A 30 mL sealed screw-capped glass pressure reaction tube was charged with enone **6** (300 mg, 0.99 mmol) and aq. ammonia (30%, 5 mL) in ethanol (5 mL). The tube was sealed carefully and placed in a metal bomb (Note: outer metal bomb was used for safety purposes), and then the reaction was heated at 140 °C for 16 h. After that, the reaction mixture was cooled carefully to room temperature. The solvent was evaporated *in vacuo*. The purification of the obtained residue by silica gel (230−400 mesh) column chromatography using EtOAC−PE (60:40) afforded pure **13** (200 mg, 65%) as a thick yellowish oil as a single diastereomer by ^1H NMR. R_f: 0.5 (EtOAc−PE = 70:30). IR ($CHCl_3$): ν_{max} 3283, 1706, 1689, 1550, 1449, 1252 cm^{-1}. [α] +11.2 (*c* 1.0, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ 7.36−7.28 (m, 5H), 5.90 (br s, 1H), 4.68 (d, *J* = 15.6 Hz, 1H), 4.43 (d, *J* = 8.0 Hz, 1H), 4.37 (dd, *J* = 5.0, 8.0 Hz, 1H), 4.15 (d, *J* = 15.6 Hz, 1H), 3.18 (dt, *J* = 6.3, 14.4 Hz, 1H), 2.74 (d, *J* = 13.0 Hz, 1H), 2.52 (dd, *J* = 5.0, 13.0 Hz, 1H), 2.38 (d, *J* = 13.7 Hz, 1H), 2.25 (d, *J* = 13.7 Hz, 1H), 2.08−2.05 (m, 1H), 1.96−1.94 (m, 2H), 1.66−1.62 (m, 2H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 206.2, 161.5, 136.9, 128.7 (2C), 127.9 (2C), 127.6, 69.1, 64.5, 61.1, 45.5, 36.3, 35.3, 32.9, 25.9, 23.6. HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{21}N_2O_2S$: 317.1318, found: 317.1321.

*(3a′S,6a′R)-1′-Benzyltetrahydrospiro[cyclohexane-1,4′-thieno[3,4-d]imidazole]-2,2′(1′H)-dione 5′,5′-dioxide (**14**).* To a stirred solution of sulfide ketone **13** (100 mg, 0.31 mmol) in dry dichloromethane (10 mL) at 0 °C was added a *meta*-chloroperbenzoic acid (100 mg, 0.63 mmol, 70% w/w) portionwise. The reaction was stirred for 16 h at room temperature and quenched with aqueous sodium bicarbonate. The reaction mixture was partitioned between dichloromethane and brine and extracted using dichloromethane (20 mL × 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by silica gel (230−400 mesh) column chromatography using EtOAC−PE (60:40) to give a sulfone **14** (92 mg, 83%) as yellow solid. R_f: 0.5 (EtOAc−PE = 60:40). MP: 155−157 °C. IR ($CHCl_3$): ν_{max} 3360, 1702, 1689, 1594, 1449, 1038 cm^{-1}. [α] −3.52 (*c* 1.0, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): 7.39−7.28 (m, 5H), 6.81 (br s, 1H), 4.69 (d, *J* = 15.3 Hz, 2H), 4.41 (t, *J* = 8.0 Hz, 1H), 4.20 (d, *J* = 15.6 Hz, 1H), 3.13 (d, *J* = 14.1 Hz, 1H), 3.00 (dd, *J* = 6.7, 14.1 Hz, 1H), 2.92−2.89 (m, 2H), 2.58 (d, *J* = 16.0 Hz, 1H), 2.02−1.99 (m, 2H), 1.85−1.68 (m, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 205.9, 160.8, 135.8, 129.0 (2C), 128.0 (3C), 73.4, 55.9, 52.9, 49.2, 45.9, 40.6, 27.4, 25.0, 20.6. HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{21}N_2O_4S$: 349.1222, found: 349.1226.

*(3aR,9bR)-3-Benzyl-5a-hydroxydecahydrothiochromeno-[3,4-d]imidazol-2(3H)-one (**15**).* In a flame-dried round-bottomed flask equipped with a reflux condenser, a solution of keto-sulfide **13** (200 mg, 0.63 mmol) in toluene (7 mL) was taken, and tri-*n*-butyltin hydride (0.25 mL, 0.94 mmol) was added followed by 10 mg (0.06 mmol) of azobis-(isobutyronitrile). The reaction mixture was refluxed for 8 h. After that, the reaction mixture was cooled slowly to room temperature. The solvent was evaporated *in vacuo*. The residue was purified by silica gel (230−400 mesh) column chromatography using EtOAC−PE (40:60) to afford thio-hemiacetal **15** (150 mg, 74%) as a viscous liquid in nonseparable diastereomers (dr = 9:1) determined by ^1H NMR analysis. R_f: 0.5 (EtOAc−PE = 60:40). IR ($CHCl_3$): ν_{max} 3445, 3360, 1691, 1594, 1459, 1048 cm^{-1}. [α] +11.09 (*c* 1.0, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) mixture of diastereomers was observed: δ 7.37−7.30 (m, 5H), 4.86 (d, *J* = 15.3 Hz, 1H), 4.77 (br s, 1H), 4.30 (s, 1H), 4.03 (d, *J* = 15.3 Hz, 1H), 3.72−3.70 (m, 1H), 3.63−3.59 (m, 1H), 3.00 (dd, *J* = 10.3, 14.1 Hz, 1H), 2.73 (dd, *J* = 5.3, 14.1 Hz, 1H), 2.07−1.98 (m, 2H), 1.91−1.85 (m, 2H), 1.60−1.55 (m, 3H), 1.40−1.37 (m, 2H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) mixture of diastereomers was observed: δ 161.5, 136.6, 128.8 (2C), 128.0 (2C), 127.8, 81.0, 55.6, 54.0, 45.7, 44.8, 38.6, 26.9, 26.0, 24.1, 21.7. LCMS (ESI): *m*/*z* 319.1 (M + H)$^+$.

*S-(((4R,5R)-3-Benzyl-2-oxo-5-(2-oxocyclohexyl)-imidazolidin-4-yl)methyl)ethanethioate (**16**).* To a diastereomeric mixture of thioacetal **15** (150 mg, 0.47 mmol) in 5 mL of dry acetonitrile were added acetic anhydride (0.066 mL, 0.70 mmol) and Et_3N (0.11 mL, 0.80 mmol) at room temperature. The reaction was stirred for 8 h and then quenched with 5% HCl. The aqueous phase was extracted with dichloromethane. The organic layer was washed with 5% HCl twice and then once with 1 M NaOH. The organic phase was dried over anhydrous Na_2SO_4 and filtered, and the solvent was evaporated *in vacuo*. The residue was purified by silica gel

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(230−400 mesh) column chromatography using EtOAC−PE (50:50) to give (115 mg, 67%) pure thio-acetate **16** as a viscous oil in nonseparable diastereomers (dr = 7:3) by ^{1}H NMR analysis. R_f: 0.5 (EtOAc−PE = 40:60). IR ($CHCl_3$): ν_{max} 3381, 1723, 1608, 1447, 1228, 1128, 755 cm^{-1}. [α] −2.21 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) mixture of diastereomers was observed: δ 7.36−7.27 (m, 5H), 5.31 (br s, 1H), 5.01 (d, *J* = 15.3 Hz, 1H), 4.83 (d, *J* = 15.3 Hz, 1H), 3.94−3.90 (m, 2H), 3.71 (t, *J* = 7.9 Hz, 1H), 3.60−3.56 (m, 1H), 3.38 (dd, *J* = 4.3, 14.0 Hz, 1H), 2.95−2.83 (m, 2H), 2.58−2.51 (m, 2H), 2.36 (s, 3H), 1.97−1.87 (m, 2H), 1.78−1.68 (m, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) mixture of diastereomers was observed: δ 212.0, 211.6, 195.0, 194.3, 161.6, 161.5, 137.0, 136.8, 128.6, 128.1, 128.0, 127.5, 56.1, 55.3, 54.8, 53.5, 51.2, 50.9, 44.9, 42.3, 31.6, 31.4, 30.7, 29.6, 28.2, 27.9, 26.8, 26.6, 24.7, 24.4. HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{25}N_2O_3S$ 361.1580, found 361.1584.

*S-(((4R,5R)-1-Acetyl-3-benzyl-2-oxo-5-(2-oxocyclohexyl)-imidazolidin-4-yl)methyl)ethanethioate (**17**).* To a diastereomeric mixture of keto-thioacetate **16** (100 mg, 0.27 mmol) in $CC1_4$ (5 mL) were added acetic anhydride (0.05 mL, 0.55 mmol) and two drops of 60% $HClO_4$ aqueous solution at 0 °C, and the mixture was stirred overnight at room temperature. The solution was diluted with dichloromethane (30 mL), washed with saturated $NaHCO_3$ aqueous solution, dried over anhydrous Na_2SO_4, and filtered, and after evaporation, the residue was purified by flash column chromatography and EtOAC−PE (40:60) to afford *N*-acetate **17** (95 mg, 85%) as a colorless oil in a nonseparable diastereomeric mixture (dr = 7:3) determined by ^{1}H NMR analysis. R_f: 0.5 (EtOAc−PE = 30:70). IR ($CHCl_3$): ν_{max} 2937, 1729, 1689, 1409, 1378, 909, 732 cm^{-1}. [α] −15.20 (*c* 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) mixture of diastereomers was observed: δ 7.36−7.27 (m, 5H), 4.94 (dd, *J* = 2.9, 7.8 Hz, 1H), 4.64 (d, *J* = 15.3 Hz, 1H), 4.50 (d, *J* = 15.3 Hz, 1H), 3.83 (dt, *J* = 3.8, 7.9 Hz, 1H), 3.29 (dd, *J* = 3.8, 14.5 Hz, 1H), 3.15−3.11 (m, 1H), 2.76−2.74 (m, 1H), 2.55 (s, 3H), 2.48−2.42 (m, 2H), 2.33 (s, 3H), 1.95−1.93 (m, 2H), 1.69−1.55 (m, 4H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) mixture of diastereomers was observed: δ 209.9, 194.7, 170.6, 156.2, 136.7, 128.7, 127.9, 127.7, 60.4, 58.1, 54.1, 52.1, 50.1, 46.1, 45.3, 41.6, 38.6, 30.3, 29.7, 28.7, 28.2, 27.6, 26.7, 25.9, 25.0, 24.3, 21.0, 20.4, 14.2. LCMS (ESI): *m*/*z* 403.2 (M + H)$^+$.

*(3a′S,6a′R)-1′,3′-Dibenzyltetrahydrospiro[cyclohexane-1,4′-thieno[3,4-d]imidazole]-2,2′(1′H)-dione (**20**).* To a stirred solution of sulfide **13** (150 mg, 0.47 mmol) in dry THF (10 mL) at 0 °C was added sodium hydride (16 mg, 0.71 mmol) portionwise over 3 min. The resulting mixture was stirred for 30 min at the same temperature. After that, benzyl bromide (0.08 mL, 0.71 mmol) was added. The resulting mixture was stirred at room temperature for 4 h. Water was added to quench the reaction, and the reaction mixture was diluted with ethyl acetate. The mixture was partitioned between EtOAc and brine and extracted using EtOAc (5 mL × 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel EtOAC−PE (30:70) as eluent to give the benzyl-protected sulfide **20** as a yellowish syrup (150 mg, 77%). R_f: 0.5 (EtOAc−PE = 70:30). IR ($CHCl_3$): ν_{max} 1709, 1690, 1550, 1449, 1252, 770 cm^{-1}. [α] −30.0 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32−7.25 (m, 10H), 5.14 (d, *J* = 15.5 Hz, 1H), 4.85 (d, *J* = 15.4 Hz, 1H), 4.20−4.18 (m, 1H), 4.11−4.07 (m, 2H), 3.93 (d, *J* = 15.4 Hz, 1H), 3.14 (ddd, *J* = 6.6, 13.8, 15.2 Hz, 1H), 2.77 (d, *J* = 13.0 Hz, 1H), 2.46−2.38 (m, 2H), 2.24−2.19 (m, 1H), 2.10−1.99 (m, 2H), 1.79−1.70 (m, 2H), 1.66−1.58 (m, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 206.1, 161.8, 136.8, 136.5, 128.7 (2C), 128.6 (2C), 128.2 (2C), 128.0 (2C), 127.6 (2C), 70.7, 62.7, 62.5, 49.1, 46.1, 36.4, 34.2, 33.7, 26.1, 23.7. HRMS (ESI): *m*/*z* [M + H] calcd for $C_{24}H_{27}N_2O_2S$: 407.1788, found: 407.1790.

*(3a′S,6a′R)-1′,3′-Dibenzyltetrahydrospiro[cyclohexane-1,4′-thieno[3,4-d]imidazole]-2,2′(1′H)-dione 5′,5′-dioxide (**21**).* To a stirred solution of sulfide ketone **20** (100 mg, 0.24 mmol) in dry dichloromethane (5 mL) at 0 °C was added a *meta*-chloroperbenzoic acid (127 mg, 0.72 mmol, 70% w/w) portionwise. The reaction was stirred for 16 h at room temperature and quenched with aqueous sodium bicarbonate. The reaction mixture was partitioned between dichloromethane and brine and extracted using dichloromethane (20 mL × 3). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by silica gel (230−400 mesh) column chromatography using EtOAC−PE (50:50) to give a sulfone **21** (90 mg, 83%) as a colorless syrup. R_f: 0.5 (EtOAc−PE = 30:70). IR ($CHCl_3$): ν_{max} 2930, 1702, 1689, 1594, 1449, 1038, 777 cm^{-1}. [α] −90.86 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): 7.35−7.24 (m, 10H), 4.86 (d, *J* = 10.1 Hz, 1H), 4.80 (d, *J* = 15.0 Hz, 1H), 4.65 (d, *J* = 15.0 Hz, 1H), 4.20 (d, *J* = 15.0 Hz, 1H), 4.06−4.00 (m, 1H), 3.97 (d, *J* = 15.0 Hz, 1H), 3.19−3.08 (m, 2H), 2.65−2.63 (m, 2H), 2.40−2.28 (m, 2H), 2.13−2.07 (m, 1H), 1.89−1.85 (m, 2H), 1.49−1.42 (m, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 201.8, 160.5, 136.5, 135.4, 129.0 (2C), 128.7 (4C), 128.4 (2C), 128.3, 127.9, 74.7, 57.0, 51.3, 50.5, 48.0, 47.6, 41.6, 29.3, 25.7, 19.7. HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{24}H_{27}N_2O_4S$: 439.1697, found: 439.1699.

*5-((3aS,6aR)-1,3-Dibenzyl-5,5-dioxido-2-oxohexahydro-1H-thieno[3,4-d]imidazol-4-yl)pentanoic Acid (**22**).* To keto sulfone **21** (100 mg, 0.22 mmol) in *t*-butyl alcohol (5 mL) was added 38 mg (0.68 mmol) of powdered potassium hydroxide at room temperature. The reaction was monitored by TLC, and after completion of the reaction, the solvent was evaporated *in vacuo*. While cooling with ice water, the mixture was carefully acidified to pH 1 with 2 N aq. HCl and then extracted with EtOAc. The extracts were washed twice with water, dried over anhydrous Na_2SO_4, and filtered. Concentrations of the organic layer *in vacuo* furnished acid **22** (94 mg, crude) as a viscous oil in nonseparable diastereomers (dr = 12:1) by ^{1}H NMR analysis. R_f: 0.5 (EtOAc−PE = 90:10). IR ($CHCl_3$): ν_{max} 3422, 2866, 1720, 1690, 1502, 1330 cm^{-1}. [α] +12.58 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) mixture of diastereomers was observed: δ 7.41−7.27 (m, 10H), 4.72 (dd, *J* = 6.7, 15.3 Hz, 2H), 4.42 (d, *J* = 15.3 Hz, 1H), 4.28 (d, *J* = 15.3 Hz, 1H), 4.14−4.08 (m, 1H), 3.77 (dd, *J* = 5.5, 9.2 Hz, 1H), 3.17−3.03 (m, 3H), 2.38−2.29 (m, 2H), 1.91−1.83 (m, 1H), 1.66 (br s, 1H), 1.35−1.22 (m, 4H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) mixture of diastereomers was observed: δ 178.7, 159.0, 136.1, 135.8, 133.5, 130.1, 129.8, 129.1 (3C), 128.3 (2C), 127.7 (2C), 63.4, 59.4, 53.0, 51.2, 47.4, 47.2, 33.4, 27.1, 26.0, 24.1. HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{24}H_{29}N_2O_5S$: 457.1797, found: 457.1795.

*Benzyl 5-((3aS,6aR)-1,3-Dibenzyl-5,5-dioxido-2-oxohexahydro-1H-thieno[3,4-d]imidazol-4-yl)pentanoate (**23**).* To a stirred solution of *epi*-biotin sulfone **22** (100 mg, 0.21 mmol) in dry dimethylformamide (5 mL) at room temperature was

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added sodium hydride (10 mg, 0.43 mmol) portionwise over 3 min. The resulting mixture was stirred for 30 min at room temperature. After cooling the mixture to room temperature, benzyl bromide (0.04 mL, 0.32 mmol) was added. The resulting mixture was stirred for 16 h at room temperature. While cooling with ice water, water was added to quench the reaction, and the reaction mixture was diluted with ethyl acetate. The mixture was partitioned between ethyl acetate and brine and extracted using ethyl acetate (10 mL × 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluent 30:70 EtOAC−PE) to give the sulfone ester **23** as a thick syrup (100 mg, 75% over two steps) in nonseparable diastereomers (dr = 12:1) by ^{1}H NMR analysis. R_f: 0.5 (EtOAc−PE = 20:80). IR ($CHCl_3$): ν_{max} 3031, 2942, 1700, 1496, 1449, 1357, 1311, 1235, 1142, 1111, 1076, 740, 698 cm^{-1}. [α] + 26.05 (*c* 2.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) mixture of diastereomers was observed: δ 7.42−7.27 (m, 15H), 5.15 (s, 2H), 4.72 (dd, *J* = 3.6, 15.6 Hz, 2H), 4.37 (d, *J* = 15.6 Hz, 1H), 4.29 (d, *J* = 14.9 Hz, 1H), 4.13−4.08 (m, 1H), 3.75−3.74 (m, 1H), 3.16 (dd, *J* = 7.1, 13.5 Hz, 1H), 3.06−2.97 (m, 2H), 2.31 (t, *J* = 7.1 Hz, 2H), 1.91−1.83 (m, 1H), 1.57−1.49 (m, 4H), 1.23−1.20 (m, 1H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) mixture of diastereomers was observed: δ 172.9, 158.9, 136.2, 135.9, 129.0 (2C), 128.6 (2C), 128.3, 128.2 (4C), 128.0 (4C), 127.7 (3C), 66.2, 63.4, 59.3, 53.0, 51.2, 47.3, 47.2, 33.6, 27.1, 26.1, 24.4. HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{31}H_{35}N_2O_5S$: 547.2261, found: 547.2263.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.2c01030.

Proposed mechanism for compounds **13** and **22**, characterization of compounds including copies of ^{1}H and ^{13}C NMR spectra for compounds **6**, **7**, **13**−**17**, and **20**−**23**, and 2D NMR spectra of **6** (PDF)

X-ray crystal data and structural refinement for compound **14** (CIF)

Accession Codes

CCDC 2024029 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: + 44 1223 336033.

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Notes

The authors declare no competing financial interest.

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