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Stereoselective α-Hydroxylation of Amides Using Oppolzer's Sultam as Chiral Auxiliary

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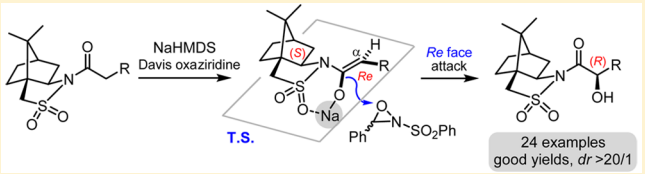
Supporting Information

ABSTRACT: An Oppolzer's sultam-based highly stereoselective α-hydroxylation of amides was developed to deliver the desired products in good yield and excellent diastereoselectivity (>20/1). The generally crystalline products and the recyclability of the chiral auxiliary illustrate the practicability and scalability of the current approach.

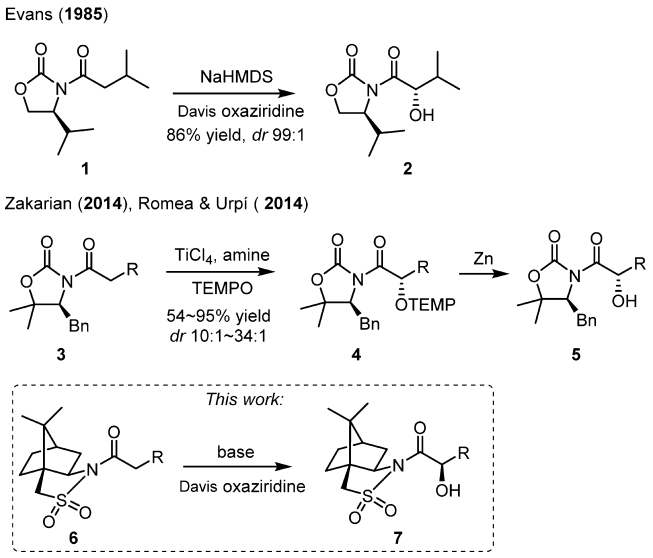


Optically pure α-hydroxy carboxylic acid derivatives are a recurring structural motif in numerous bioactive natural products and pharmaceuticals as well as for ligand design toward asymmetric catalysis.[1] In the past several decades, a plethora of methods have been developed for the asymmetric synthesis of α-hydroxy carboxylic acid derivatives, among which the regio- and stereoselective enolate oxidation was most extensively exploited.[2] Using various oxidants, enantioselective oxidation of an enolate (such as a metal or silyl enolate) was proven to be effective with a chiral auxiliary-based protocol as well as a chiral catalyst.

The concept of chiral auxiliaries has orchestrated an era of diastereoselective synthesis and remains an efficient approach in establishing chirality centers in a highly stereoselective manner.[3] A highly stereoselective hydroxylation of selected carboxylic acid derivatives was documented with *N*-acyl oxazolidinones as the auxiliary in Evans' seminal work three decades ago (Scheme 1).[4] However, this protocol was not fully appreciated until a recent renaissance from the Zakarian and Urpí groups, who independently disclosed the Davies oxazolidinones-based radical addition of Ti enolates with TEMPO ((2,2,6,6-tetramethylpiperidin-1-yl)oxyl).[5] In these latest investigations, however, a partial racemization was found in α-aryl substituted amides during the reductive cleavage of the N−O bond by a large excess of zinc powder in some circumstances. Comparable to Evans-type oxazolidinones, camphorsultam, well-known as Oppolzer's sultam, was also commercially available and has been widely applied in asymmetric reactions such as α-alkylation of carboxylic acid derivatives, Diels−Alder cycloaddition, and the aldol reaction.[6−9] To our surprise, camphorsultam has not been implemented to α-hydroxylation of amides despite that its derivatives have a great tendency to be crystalline for ease of enantioenrichment. Herein, we report our preliminary results on developing an efficient protocol using (1*S*)-(−)-2,10-camphorsultam as a chiral auxiliary giving products with high diastereoselectivity.

Accordingly, the α-hydroxylation of *N*-acyl sultam **6a** was achieved with *N*-sulfonyloxaziridine (Davis oxaziridine, **8**),

Scheme 1. α-Hydroxylation of Amides Using a Chiral Auxiliary Approach



whose racemic form could be readily synthesized with a one-pot protocol.[10] An initial screening of different bases revealed NaHMDS to be optimal, affording α-hydroxy product **7a** in 63% yield. Hydrolysis of the chiral auxiliary under basic conditions was detected as the major side reaction to form the corresponding acid (<15% yield) when an aqueous ammonium chloride solution was used to quench the reaction (entry 3 vs entries 1 and 2 in Table 1). Gratifyingly, the diastereoselectivity (*dr*) of **7a** was determined as 20/1 with comparison to two diastereoisomers derived from direct reduction of an α-keto amide.[11] Besides Evans' recommendation[4a] of using camphorsulfonic acid (CSA) as a protonic acid to quench the reaction, other acids were also examined, including chloroacetic acid,

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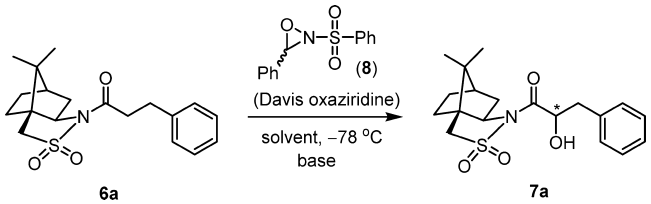
Table 1. Optimization of Sultam-Based α-Hydroxylation of Compound 6a[a]



6a 7a

entry	base	quenching reagents	solvents	conv. %[b]	yield %[c]	*dr*[d]
1	LiHMDS	NH_4Cl	THF	61	25	n.d.[e]
2	KHMDS	NH_4Cl	THF	69	27	n.d.[e]
3	NaHMDS	NH_4Cl	THF	89	63	20:1
4	NaHMDS	$CHCl_2CO_2H$	THF	49	5	
5	NaHMDS	CF_3CO_2H	THF	72	4	
6	NaHMDS	CH_3SO_3H	THF	93	6	
7	NaHMDS	CSA	THF	90	49	20:1
8	NaHMDS	CH_3CO_2H	THF	87	80	>20:1
9	NaHMDS	CH_3CO_2H	toluene	76	69	8:1
10	NaHMDS	CH_3CO_2H	Et_2O	68	10	17:1
11	NaHMDS	CH_3CO_2H	TBME	57	43	n.d.[e]
12	NaHMDS	CH_3CO_2H	DME	0	0	
13	NaHMDS	CH_3CO_2H	THF	100	0[f]	

[a]Reaction conditions: **6a** (0.3 mmol), base (1.2 equiv), Davis oxaziridine (**8**) (1.5 equiv), solvent (6 mL), −78 °C, quenching reagents (2.5 equiv), 5 min. [b]The conversion was determined by ^{1}H NMR (400 MHz, $CDCl_3$) spectroscopy. [c]Yield of isolated product. [d]The diastereoselectivity (*dr*) was determined by crude ^{1}H NMR (400 MHz, $CDCl_3$). [e]n.d.= not determined. [f]The reaction was quenched at room temperature. THF = tetrahydrofuran, Et_2O = diethyl ether, DME = dimethoxymethane, TBME = *tert*-butyl methyl ether.

trifluoroacetic acid, methanesulfonic acid, and acetic acid (entries 4−8). Although the addition of CSA gave a moderate yield and excellent diastereoselectivity (entry 7), the excess amount of this acid was problematic during the workup and product purification stage. The volatile acetic acid was the optimal proton source to provide the corresponding α-hydroxy product **7a** in 80% isolated yield and >20:1 *dr* (entry 8). Other solvents with less coordination ability to metal ion were then examined, and the conversion and diastereoselectivity were deteriorated (entries 9−11 vs 8). When a strong chelating ligand, dimethoxyethane (DME), was utilized as solvent, no transformation was found (entry 12). It was also found that keeping the whole process at −78 °C was crucial since significant cleavage of the chiral auxiliary and unidentified side products were detected if the reaction was quenched by addition of acetic acid at room temperature. Under that situation, no desired product was observed (entry 13).

Encouraged by the success of introducing *N*-acyl sultam **6a**, the substrate scope of the α-hydroxylation reaction was investigated under the optimal reaction conditions (entry 8 in Table 1). Good yields and excellent diastereoselectivity (*dr* > 20/1) were generally obtained whether electron-donating or electron-deficient groups were introduced on the arene (**7a**−**7i**) (Table 2). It is particularly noteworthy that, when the substrate bearing an oxidant-sensitive thiophene group (**6j**) was exposed to the reaction conditions, the desired **7j** was isolated in good yield and diastereoselectivity. For truncated substrates **7k**−**n**, high diastereoselectivity (>20:1) was also obtained with a comparison to a similar phenylacetic acid derivative in Evans' case (*dr* 90:10).[4a] Strong electron-deficient elements like fluorine in **7k** and **7l**, the electron-donating methyl group in **7m**, the 2,6-dimethyl substituted substance in **7n**, and the more strikingly thienyl group-embedded in **7o** were also tolerated with excellent outcomes. The crystalline nature of **7a**−**o** allows for further improvement of the diastereoselectivity if necessary. In contrast to previous investigations,[5,12] hydroxylated products **7k**−**o** were rather stable and no appreciable racemization was detected when they were stored in $CHCl_3$ at room temperature for 2 weeks. We speculated that the camphorsultam moiety would decrease the acidity of the α-proton of the corresponding amides, which, in turn, retards the propensity to racemization. The stereochemistry of hydroxyl compounds **7b** and **7i** was unambiguously established by X-ray analysis, and the absolute (*R*)-α-hydroxy stereochemistry was assigned.[13] The generality of this α-hydroxylation protocol offers a fair alternative to synthesize such valuable building blocks.

The substrate scope was further expanded to sterically flexible alkyl substituents (Table 3). Acyclic chains, such as methyl, homoallyl, pentyl, and protected 4-hydroxybutyl groups, were also effectively hydroxylated to provide the corresponding products in good yield and stereoselectivity (**7p**−**u**).[14] For those bulky alkyl groups in **7v**−**x**, the hydroxylation proceeded smoothly without deterioration in the isolated yield or diastereoselectivity. For alkylated α-hydroxyl products, with the exception of **7p** and **7s**−**u**, crystalline compounds were isolated and the workup was clearly superior to previous methods.[5,6]

Building on the general concept of camphorsultam-controlled asymmetric induction[15] as well as the X-ray structures of the corresponding products **7b** and **7i**, as shown in the possible transition state (**T.S.**),[15d] presumably the nucleophilic attack from the sterically less hindered orientation of the metal-chelated enolate with the electrophilic oxaziridine gives an (*R*)-configured α-hydroxy amide **7** (Scheme 2). Although oxaziridine **8** was used as a racemic form, the power of stereochemical control by Oppolzer's sultam overrides the potential of the *match-mismatch* problem.[16] Since the enantiomer of (1*R*)-(+)-2,10-camphorsultam was also commercially available, (*S*)-α-hydroxy amides could be thus readily prepared with the current protocol.

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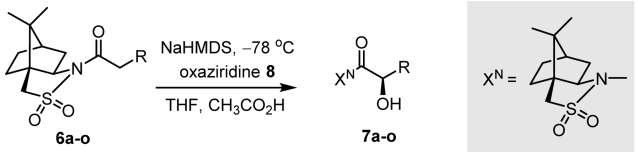
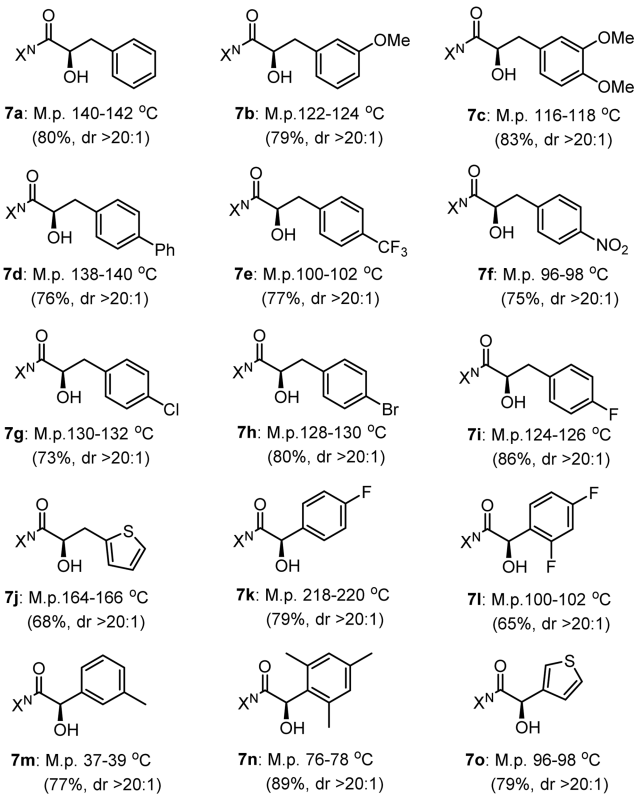
Table 2. Substrate Scope for Sultam-Based α-Hydroxylation[a,b,c]



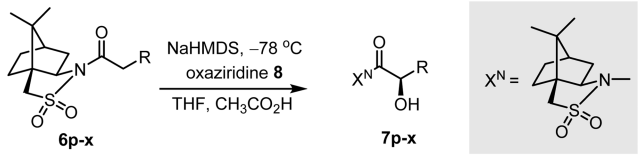


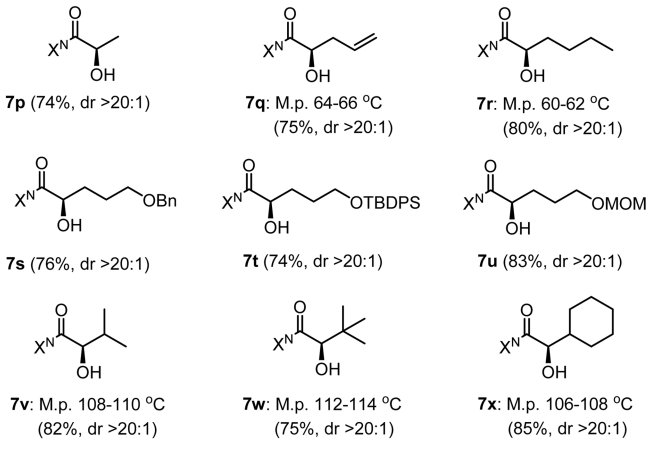
[a]Reaction conditions: **6** (0.3 mmol), NaHMDS (1.2 equiv), oxaziridine **8** (1.5 equiv), THF (6 mL), −78 °C, 5 min. [b]Yield of isolated product. [c]The diastereoselectivity (*dr*) was determined by crude ^{1}H NMR (400 MHz, $CDCl_3$).

To demonstrate the synthetic utility, a gram-scale synthesis of the side chain of lithospermic acid (**9**) was completed (Scheme 3). α-Hydroxy ester **10** was utilized in several syntheses of (+)-lithospermic acid (**9**), a potent and nontoxic anti-HIV agent.[17,18] Thus, 5 g of **6c** was subjected to α-hydroxylation under the optimized reaction conditions, and amide **7c** was obtained in 87% isolated yield and >20:1 *dr*. Mild esterification with in situ generated MeOMgBr resulted in (*R*)-α-hydroxyled methyl ester **10**, a known compound with an enantiomeric ratio of >99:1 (as determined by chiral HPLC).[19] The stereochemistry of **10** was consistent with the natural product, and it further confirmed the stereochemistry model of hydroxylation (Scheme 2). Moreover, the Oppolzer's sultam was readily recycled in excellent yield (94%).

In summary, a highly stereoselective α-hydroxylation of amides was developed with (1*S*)-(−)-2,10-camphorsultam as chiral auxiliary. Excellent diastereoselectivity values (>20/1) were generally achieved. Moreover, a gram-scale synthesis of the side chain of lithospermic acid was also exemplified without deterioration of *dr* or isolated yield. The generally crystalline products and the facile removal and recyclability[15c,20] of the chiral auxiliary indicate the practicability and scalability of the current approach. As (1*S*)-(−)-2,10-camphorsultam and (1*R*)-(+)-2,10-camphorsultam are both commercially available in large quantities, the method presented here would be a feasible

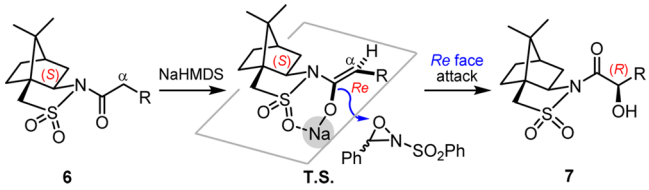
Table 3. Alkyl Substituted Substrates for Sultam-Based α-Hydroxylation[a,b,c]



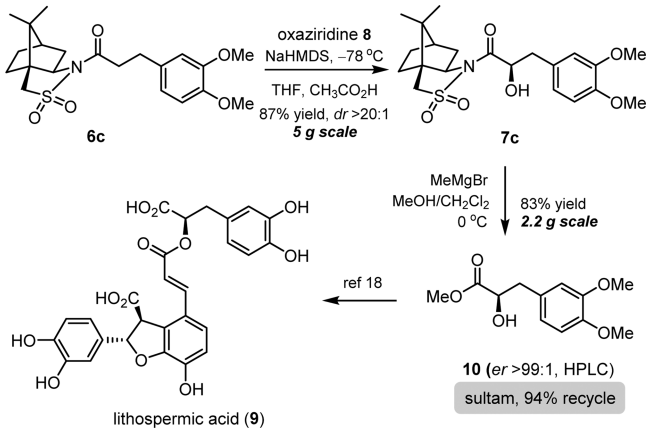


[a]Reaction conditions: **6** (0.3 mmol), NaHMDS (1.2 equiv), oxaziridine **8** (1.5 equiv), THF (6 mL), −78 °C, 5 min. [b]Yield of isolated product. [c]The diastereoselectivity (*dr*) was determined by crude ^{1}H NMR (400 MHz, $CDCl_3$).

Scheme 2. Stereochemistry Origin of α-Hydroxylation with Oppolzer's Sultam



Scheme 3. Gram-Scale Synthesis of the Side Chain of Lithospermic Acid (9)



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approach to deliver either stereochemistry of α-hydroxyl carboxylic acid derivatives as desired.

EXPERIMENTAL SECTION

All the reactions were carried out under a N_2 atmosphere unless otherwise stated. All the solvents utilized for reactions were dried using a standard procedure and distilled before use. All reagents were used after receiving, albeit with special treatment as indicated. ^{1}H NMR, ^{13}C NMR, and ^{19}F NMR were recorded on 400 MHz spectrometers in $CDCl_3$. ^{1}H NMR data were recorded as follows: multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet or unresolved, coupling constant (solid) in Hz, integration). IR spectra were recorded on a digital FT-IR spectrometer. Frequencies are given in reciprocal centimeters (cm^{-1}), and only selected absorbance is reported. Mass spectra were determined on LTQ FT Ultra mass spectrometers in DART positive mode, or FT mass spectrometers in electrospray ionization (ESI) mode. Microscopic melting apparatus was not calibrated.

General Procedure for Asymmetric α-Hydroxylation Reaction. Sodium bis(trimethylsilyl) amide (2.0 M in THF, 177 μL, 0.36 mmol) was slowly added to a solution of **6** (0.3 mmol) in THF (3 mL) at −78 °C. After the mixture was stirred for 30 min, a solution of Davis oxaziridine (133 mg, 0.5 mmol) in THF (3 mL) was added dropwise via syringe. A solution of CH_3COOH (48.0 mg, 0.8 mmol) in THF (5 mL) was cannulated into the flask after 5 min. Upon return to room temperature, the reaction mixture was diluted with Et_2O (15 mL) and washed with water (10 mL). The organic phase was separated, and the organic layer was washed with saturated aq. NH_4Cl (2 × 15 mL) and brine (15 mL). The combined aqueous phases were re-extracted with Et_2O (3 × 15 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash silica gel chromatography.

*(R)-1-((3aS,6R,7aR)-8,8-Dimethyl-2,2-dioxidohexahydro-1H-3a,6-methanobenzo[c]isothiazol-1-yl)-2-hydroxy-3-phenylpropan-1-one (**7a**).* The title compound was prepared by the general synthesis on a 0.20 mmol scale and obtained in 80% yield (58.4 mg) as a white solid after column chromatography (PE/EA = 6:1). *dr* > 20:1; $[\alpha]_D^{26}$ −72.0 ($CHCl_3$, *c* = 0.48); M.p. 140−142 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 7.31−7.27 (m, 4H), 7.25−7.20 (m, 1H), 4.83 (dd, *J* = 8.6, 3.8 Hz, 1H), 3.91 (dd, *J* = 7.7, 5.0 Hz, 1H), 3.53 (d, *J* = 13.8 Hz, 1H), 3.47 (d, *J* = 13.8 Hz, 1H), 3.25 (dd, *J* = 14.2, 3.9 Hz, 1H), 2.92 (dd, *J* = 14.2, 8.6 Hz, 1H), 2.27−2.17 (m, 1H), 2.09 (dd, *J* = 14.0, 7.9 Hz, 1H), 1.96−1.86 (m, 3H), 1.50−1.31 (m, 2H), 1.15 (s, 3H), 0.98 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 172.0, 137.2, 129.8, 128.5, 126.8, 71.9, 65.5, 53.0, 49.4, 48.1, 44.6, 39.1, 38.2, 32.9, 26.6, 20.8, 20.0; FT-IR: ν (cm^{-1}) 3498, 2959, 2881, 1685, 1496, 1455, 1328, 1134, 1083, 802, 700; HRMS-ESI: calcd. for $C_{19}H_{25}NNaO_4S$ [M + Na]$^+$: 386.1397, found: 386.1408.

*(R)-1-((3aS,6R,7aR)-8,8-Dimethyl-2,2-dioxidotetrahydro-3H-3a,6-methanobenzo[c]isothiazol-1(4H)-yl)-2-hydroxy-3-(3-methoxyphenyl)propan-1-one (**7b**).* The title compound was prepared by the general synthesis on a 0.27 mmol scale and obtained in 79% yield (82.5 mg) as a white solid after column chromatography (PE/EA = 5:1). *dr* > 20:1; $[\alpha]_D^{26}$ −68.4 ($CHCl_3$, *c* = 0.67); M.p. 122−124 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 7.21 (t, *J* = 7.9 Hz, 1H), 6.90−6.84 (m, 2H), 6.81−6.78 (dd, *J* = 8.0, 2.4 Hz, 1H), 4.83 (ddd, *J* = 8.7, 7.3, 3.9 Hz, 1H), 3.91 (dd, *J* = 7.8, 5.0 Hz, 1H), 3.79 (s, 3H), 3.53 (d, *J* = 13.8 Hz, 1H), 3.47 (d, *J* = 13.8 Hz, 1H), 3.22 (dd, *J* = 14.2, 3.8 Hz, 1H), 3.10 (d, *J* = 7.1 Hz, 1H), 2.89 (dd, *J* = 14.2, 8.7 Hz, 1H), 2.25−2.17 (m, 1H), 2.09 (dd, *J* = 13.8, 8.2 Hz, 1H), 1.98−1.83 (m, 3H), 1.49−1.31 (m, 2H), 1.15 (s, 3H), 0.97 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 171.9, 159.7, 138.8, 129.5, 122.1, 115.3, 112.4, 71.9, 65.4, 55.3, 53.0, 49.4, 48.1, 44.6, 39.1, 38.1, 32.9, 26.6, 20.8, 20.0; FT-IR: ν (cm^{-1}) 3505, 2959, 2836, 1691, 1602, 1584, 1488, 1438, 1331, 1265, 1135, 1055, 769; HRMS-DART: calcd. for $C_{20}H_{28}NO_5S$ [M + H]$^+$: 394.1683, found: 394.1678.

*(R)-3-(3,4-Dimethoxyphenyl)-1-((3aS,6R,7aR)-8,8-dimethyl-2,2-dioxidotetrahydro-3H-3a,6-methanobenzo[c]isothiazol-1(4H)-yl)-2-hydroxypropan-1-one (**7c**).* The title compound was prepared by the general synthesis on a 0.25 mmol scale and obtained in 83% yield (86.5 mg) as a white solid after column chromatography (PE/EA = 3:1). *dr* > 20:1; $[\alpha]_D^{26}$ −65.3 ($CHCl_3$, *c* = 1.08); M.p. 116−118 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 6.86−6.77 (m, 3H), 4.85−4.76 (m, 1H), 3.90 (dd, *J* = 7.9, 5.0 Hz, 1H), 3.87 (s, 3H), 3.85 (s, 3H), 3.53 (d, *J* = 13.8 Hz, 1H), 3.47 (d, *J* = 13.8 Hz, 1H), 3.19 (dd, *J* = 14.3, 3.9 Hz, 1H), 3.07 (d, *J* = 7.2 Hz, 1H), 2.86 (dd, *J* = 14.3, 8.5 Hz, 1H), 2.27−2.15 (m, 1H), 2.09 (dd, *J* = 14.0, 7.9 Hz, 1H), 1.97−1.82 (m, 3H), 1.49−1.32 (m, 2H), 1.15 (s, 3H), 0.97 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 172.0, 148.8, 147.9, 129.7, 121.7, 112.9, 111.2, 72.0, 65.4, 56.0, 55.9, 52.9, 49.3, 48.0, 44.5, 38.7, 38.1, 32.8, 26.5, 20.8, 20.0; FT-IR: ν (cm^{-1}) 3497, 2958, 2836, 1692, 1591, 1516, 1465, 1331, 1264, 1158, 1136, 1028, 760; HRMS-ESI: calcd. for $C_{21}H_{29}NNaO_6S$ [M + Na]$^+$: 446.1608, found: 446.1614.

*(R)-3-([1,1′-Biphenyl]-4-yl)-1-((3aS,6R,7aR)-8,8-dimethyl-2,2-dioxidotetrahydro-3H-3a,6-methanobenzo[c]isothiazol-1(4H)-yl)-2-hydroxypropan-1-one (**7d**).* The title compound was prepared by the general synthesis on a 1.18 mmol scale and obtained in 76% yield (395 mg) as a white solid after column chromatography (PE/EA = 7:1). *dr* > 20:1; $[\alpha]_D^{26}$ −67.7 ($CHCl_3$, *c* = 1.04). M.p. 138−140 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 7.61−7.56 (m, 2H), 7.53 (d, *J* = 8.2 Hz, 2H), 7.46−7.29 (m, 5H), 4.88 (ddd, *J* = 8.6, 7.4, 3.9 Hz, 1H), 3.93 (dd, *J* = 7.8, 5.0 Hz, 1H), 3.55 (d, *J* = 13.8 Hz, 1H), 3.48 (d, *J* = 13.8 Hz, 1H), 3.29 (dd, *J* = 14.2, 3.8 Hz, 1H), 3.12 (d, *J* = 7.3 Hz, 1H), 2.96 (dd, *J* = 14.2, 8.7 Hz, 1H), 2.29−2.19 (m, 1H), 2.11 (dd, *J* = 14.0, 7.9 Hz, 1H), 2.00−1.84 (m, 3H), 1.50−1.31 (m, 2H), 1.16 (s, 3H), 0.98 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 172.0, 141.2, 139.7, 136.3, 130.2, 128.8, 127.3, 127.2, 71.9, 65.5, 53.0, 49.4, 48.1, 44.6, 38.8, 38.2, 32.9, 26.6, 20.8, 20.0; FT-IR: ν (cm^{-1}) 3526, 2960, 2258, 1691, 1680, 1485, 1329, 1294, 1235, 1135, 1059, 909, 761; HRMS-DART: calcd. for $C_{25}H_{30}NO_4S$ [M + H]$^+$: 440.1890, found: 440.1887.

*(R)-1-((3aS,6R,7aR)-8,8-Dimethyl-2,2-dioxidotetrahydro-3H-3a,6-methanobenzo[c]isothiazol-1(4H)-yl)-2-hydroxy-3-(4-(trifluoromethyl)phenyl)propan-1-one (**7e**).* The title compound was prepared by the general synthesis on a 0.24 mmol scale and obtained in 77% yield (79.7 mg) as a white solid after column chromatography (PE/EA = 8:1). *dr* > 20:1; $[\alpha]_D^{26}$ −63.3 ($CHCl_3$, *c* = 0.55); M.p. 100−102 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 7.55 (d, *J* = 8.1 Hz, 2H), 7.41 (d, *J* = 8.1 Hz, 2H), 4.85−4.80 (m, 1H), 3.91 (dd, *J* = 7.8, 5.0 Hz, 1H), 3.55 (d, *J* = 13.8 Hz, 1H), 3.48 (d, *J* = 13.8 Hz, 1H), 3.29 (dd, *J* = 14.2, 3.8 Hz, 1H), 3.18 (d, *J* = 7.2 Hz, 1H), 2.96 (dd, *J* = 12, 8.0 Hz, 1H), 2.28−2.17 (m, 1H), 2.09 (dd, *J* = 14.0, 7.9 Hz, 1H), 1.94−1.87 (m, 3H), 1.51−1.31 (m, 2H), 1.15 (s, 3H), 0.98 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 171.7, 141.3 (q, *J* = 1.3 Hz), 130.0, 128.9 (q, *J* = 32.4 Hz), 125.2 (q, *J* = 3.8 Hz), 124.3 (q, *J* = 271.8 Hz), 71.6, 65.4, 52.9, 49.5, 48.1, 44.5, 38.9, 38.1, 32.8, 26.6, 20.8, 20.0; ^{19}F NMR (376 MHz, $CDCl_3$) −62.47 (s); FT-IR: ν (cm^{-1}) 3502, 2960, 1693, 1618, 1456, 1325, 1236, 1164, 1109, 1066, 1019, 825, 769; HRMS-DART: calcd. for $C_{20}H_{25}NF_3O_4S$ [M + H]$^+$: 432.1451, found: 432.1448.

*(R)-1-((3aS,6R,7aR)-8,8-Dimethyl-2,2-dioxidotetrahydro-3H-3a,6-methanobenzo[c]isothiazol-1(4H)-yl)-2-hydroxy-3-(4-nitrophenyl)propan-1-one (**7f**).* The title compound was prepared by the general synthesis on a 0.27 mmol scale and obtained in 75% yield (273 mg) as a pale yellow solid after column chromatography (PE/EA = 6:1). *dr* > 20:1; $[\alpha]_D^{26}$ −34.9 ($CHCl_3$, *c* = 0.59); M.p. 96−98 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 8.15 (d, *J* = 8.6 Hz, 2H), 7.46 (d, *J* = 8.6 Hz, 2H), 4.84 (td, *J* = 7.9, 3.9 Hz, 1H), 3.90 (dd, *J* = 7.8, 5.0 Hz, 1H), 3.55 (d, *J* = 13.9 Hz, 1H), 3.49 (d, *J* = 13.9 Hz, 1H), 3.33 (dd, *J* = 14.2, 3.8 Hz, 1H), 3.24 (d, *J* = 7.2 Hz, 1H), 3.01 (dd, *J* = 14.2, 8.5 Hz, 1H), 2.27−2.16 (m, 1H), 2.09 (dd, *J* = 14.0, 7.9 Hz, 1H), 2.00−1.86 (m, 3H), 1.50−1.30 (m, 2H), 1.14 (s, 3H), 0.98 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 171.4, 147.0, 145.2, 130.7, 123.6, 71.3, 65.4, 52.9, 49.5, 48.1, 44.5, 38.9, 38.0, 32.8, 26.6, 20.8, 20.0; FT-IR: ν (cm^{-1}) 3506, 2961, 2885, 2262, 1692, 1603, 1519, 1346, 1236, 1166, 1136, 1060, 911, 733; HRMS-DART: calcd. for $C_{19}H_{25}N_2O_6S$ [M + H]$^+$: 409.1428, found: 409.1426.

*(R)-3-(4-Chlorophenyl)-1-((3aS,6R,7aR)-8,8-dimethyl-2,2-dioxidotetrahydro-3H-3a,6-methanobenzo[c]isothiazol-1(4H)-yl)-2-hydroxypropan-1-one (**7g**).* The title compound was prepared by the general synthesis on a 0.26 mmol scale and obtained in 73% yield (76.3 mg) as a white solid after column chromatography (PE/EA =

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8:1). *dr* > 20:1; $[\alpha]_D^{27}$ −60.0 ($CHCl_3$, *c* = 0.39); M.p. 130−132 °C; ^1H NMR (400 MHz, $CDCl_3$) 7.28−7.26 (m,, 1H), 7.25−7.20 (m, 3H), 4.78 (ddd, *J* = 8.3, 7.6, 4.0 Hz, 1H), 3.90 (dd, *J* = 7.8, 5.0 Hz, 1H), 3.54 (d, *J* = 13.8 Hz, 1H), 3.47 (d, *J* = 13.8 Hz, 1H), 3.20 (dd, *J* = 14.3, 3.9 Hz, 1H), 3.13 (d, *J* = 7.3 Hz, 1H), 2.88 (dd, *J* = 14.3, 8.5 Hz, 1H), 2.26−2.15 (m, 1H), 2.08 (dd, *J* = 14.0, 7.9 Hz, 1H), 1.96−1.85 (m, 3H), 1.49−1.32 (m, 2H), 1.14 (s, 3H), 0.97 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 171.8, 135.7, 132.6, 131.2, 128.6, 71.7, 65.4, 52.9, 49.4, 48.1, 44.5, 38.4, 38.1, 32.8, 26.6, 20.8, 20.0; FT-IR: *ν* (cm^{-1}) 3501, 2960, 2884, 1691, 1491, 1410, 1330, 1235, 1135, 1090, 1016, 810, 762; HRMS-DART: calcd. for $C_{19}H_{25}NClO_4S$ $[M + H]^+$: 398.1187, found: 398.1181.

*(R)-3-(4-Bromophenyl)-1-((3aS,6R,7aR)-8,8-dimethyl-2,2-dioxidotetrahydro-3H-3a,6-methanobenzo[c]isothiazol-1(4H)-yl)-2-hydroxypropan-1-one (**7h**).* The title compound was prepared by the general synthesis on a 0.24 mmol scale and obtained in 80% yield (83.0 mg) as a white solid after column chromatography (PE/EA = 7:1). *dr* > 20:1; $[\alpha]_D^{27}$ −49.4 ($CHCl_3$, *c* = 0.37); M.p. 128−130 °C; ^1H NMR (400 MHz, $CDCl_3$) 7.44−7.38 (m, 2H), 7.17 (d, *J* = 8.4 Hz, 2H), 4.82−4.73 (m, 1H), 3.90 (dd, *J* = 7.8, 5.0 Hz, 1H), 3.54 (d, *J* = 13.8 Hz, 1H), 3.47 (d, *J* = 13.8 Hz, 1H), 3.18 (dd, *J* = 14.3, 3.9 Hz, 1H), 3.13 (d, *J* = 7.3 Hz, 1H), 2.87 (dd, *J* = 14.2, 8.5 Hz, 1H), 2.30−2.15 (m, 1H), 2.08 (dd, *J* = 14.0, 7.9 Hz, 1H), 1.96−1.86 (m, 3H), 1.49−1.32 (m, 2H), 1.14 (s, 3H), 0.97 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 171.7, 136.2, 131.6, 131.5, 120.7, 71.6, 65.4, 52.9, 49.4, 48.1, 44.5, 38.5, 38.1, 32.8, 26.6, 20.8, 20.0; FT-IR: *ν* (cm^{-1}) 3503, 2959, 2884, 1692, 1487, 1456, 1330, 1293, 1235, 1135, 1060, 1012, 760; HRMS-DART: calcd. for $C_{19}H_{25}NBrO_4S$ $[M + H]^+$: 442.0682, found: 442.0677.

*(R)-1-((3aS,6R,7aR)-8,8-Dimethyl-2,2-dioxidotetrahydro-3H-3a,6-methanobenzo[c]isothiazol-1(4H)-yl)-3-(4-fluorophenyl)-2-hydroxypropan-1-one (**7i**).* The title compound was prepared by the general synthesis on a 0.27 mmol scale and obtained in 86% yield (89.1 mg) as a white solid after column chromatography (PE/EA = 6:1). *dr* > 20:1; $[\alpha]_D^{26}$ −74.3 ($CHCl_3$, *c* = 0.51); M.p. 124−126 °C; ^1H NMR (400 MHz, $CDCl_3$) 7.29−7.23 (m, 2H), 7.00−6.96 (m, 2H), 4.83−4.74(m, 1H), 3.91 (dd, *J* = 7.8, 5.0 Hz, 1H), 3.54 (d, *J* = 13.8 Hz, 1H), 3.47 (d, *J* = 13.8 Hz, 1H), 3.21 (dd, *J* = 14.3, 3.9 Hz, 1H), 3.08 (d, *J* = 7.3 Hz, 1H), 2.89 (dd, *J* = 14.3, 8.4 Hz, 1H), 2.28−2.16 (m, 1H), 2.09 (dd, *J* = 14.0, 7.9 Hz, 1H), 2.00−1.85 (m, 3H), 1.49−1.32 (m, 2H), 1.15 (s, 3H), 0.98 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 171.9, 161.9 (d, *J* = 248.5 Hz), 132.9 (d, *J* = 3.0 Hz), 131.3 (d, *J* = 8.1 Hz), 115.3 (d, *J* = 21.2 Hz), 71.9, 65.4, 53.0, 49.4, 48.1, 44.6, 38.3, 38.1, 32.9, 26.64, 20.8, 20.0; ^{19}F NMR (376 MHz, $CDCl_3$) −116.68 (s); FT-IR: *ν* (cm^{-1}) 3503, 2960, 1692, 1510, 1330, 1220, 1166, 1059, 816, 774; HRMS-ESI: calcd. for $C_{19}H_{24}FNNaO_4S$ $[M + Na]^+$: 404.1302, found: 404.1316.

*(R)-1-((3aS,6R,7aR)-8,8-Dimethyl-2,2-dioxidotetrahydro-3H-3a,6-methanobenzo[c]isothiazol-1(4H)-yl)-2-hydroxy-3-(thiophen-2-yl)-propan-1-one (**7j**).* The title compound was prepared by the general synthesis on a 1.42 mmol scale and obtained in 68% yield (358 mg) as a pale yellow solid after column chromatography (PE/EA = 8:1). *dr* > 20:1; $[\alpha]_D^{27}$ −79.0 ($CHCl_3$, *c* = 1.11); M.p. 164−166 °C; ^1H NMR (400 MHz, $CDCl_3$) 7.17 (dd, *J* = 4.8, 1.6 Hz, 1H), 6.96−6.91 (m, 2H), 4.80 (td, *J* = 7.7, 4.1 Hz, 1H), 3.91 (dd, *J* = 7.8, 5.0 Hz, 1H), 3.53 (d, *J* = 13.8 Hz, 1H), 3.47 (d, *J* = 13.8 Hz, 1H), 3.45−3.40 (m, 1H), 3.32 (d, *J* = 7.1 Hz, 1H), 3.21 (dd, *J* = 15.2, 7.9 Hz, 1H), 2.25−2.16 (m, 1H), 2.08 (dd, *J* = 14.0, 7.9 Hz, 1H), 1.95−1.85 (m, 3H), 1.49−1.30 (m, 2H), 1.15 (s, 3H), 0.97 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 171.4, 138.8, 126.9, 126.7, 124.6, 71.6, 65.4, 52.9, 49.4, 48.1, 44.6, 38.1, 33.2, 32.8, 26.6, 20.8, 20.0; FT-IR: *ν* (cm^{-1}) 3488, 3005, 2983, 2881, 1696, 1368, 1318, 1214, 1114, 1060, 994, 763, 716; HRMS-DART: calcd. for $C_{17}H_{24}NO_4S_2$ $[M + H]^+$: 370.1141, found: 370.1140.

*(R)-1-((3aS,6R,7aR)-8,8-Dimethyl-2,2-dioxidotetrahydro-3H-3a,6-methanobenzo[c]isothiazol-1(4H)-yl)-2-(4-fluorophenyl)-2-hydroxyethan-1-one (**7k**).* The title compound was prepared by the general synthesis on a 0.29 mmol scale and obtained in 79% yield (83.0 mg) as a white solid after column chromatography (PE/EA = 5:1). *dr* > 20:1; $[\alpha]_D^{26}$ −110.1 ($CHCl_3$, *c* = 0.64); M.p. 218−220 °C; ^1H NMR (400 MHz, $CDCl_3$) 7.44−7.37 (m, 2H), 7.09−7.01 (m, 2H), 5.66 (d, *J* = 7.2 Hz, 1H), 3.89 (dd, *J* = 7.9, 5.0 Hz, 1H), 3.65 (d, *J* = 7.7 Hz, 1H), 3.51 (d, *J* = 13.8 Hz, 1H), 3.41 (d, *J* = 13.8 Hz, 1H), 2.30−2.21 (m, 1H), 2.08 (dd, *J* = 14.0, 7.9 Hz, 1H), 1.93−1.85 (m, 3H), 1.46−1.30 (m, 2H), 1.17 (s, 3H), 0.97 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 171.1, 162.9 (d, *J* = 248.5 Hz), 133.0 (d, *J* = 3.0 Hz), 129.8 (d, *J* = 8.1 Hz), 115.4 (d, *J* = 21.2 Hz), 72.3, 65.4, 52.8, 49.2, 47.9, 44.4, 38.0, 32.7, 26.4, 20.6, 19.8; ^{19}F NMR (376 MHz, $CDCl_3$) −113.12 to −113.25 (m); FT-IR: *ν* (cm^{-1}) 3485, 2961, 2885, 2262, 1692, 1603, 1510, 1334, 1221, 1136, 1051, 911, 732; HRMS-DART: calcd. for $C_{18}H_{23}NFO_4S$ $[M + H]^+$: 368.1322, found: 368.1326.

*(R)-2-(2,4-Difluorophenyl)-1-((3aS,6R,7aR)-8,8-dimethyl-2,2-dioxidotetrahydro-3H-3a,6-methanobenzo[c]isothiazol-1(4H)-yl)-2-hydroxyethan-1-one (**7l**).* The title compound was prepared by the general synthesis on a 1.42 mmol scale and obtained in 65% yield (355 mg) as a white solid after column chromatography (PE/EA = 8:1). *dr* > 20:1; $[\alpha]_D^{26}$ −114.8 ($CHCl_3$, *c* = 1.04); M.p. 100−102 °C; ^1H NMR (400 MHz, $CDCl_3$) 7.49−7.43 (m, 1H), 6.91−6.87 (m, 1H), 6.84−6.78 (m, 1H), 5.87 (s, 1H), 3.93 (dd, *J* = 7.9, 4.9 Hz, 1H), 3.53 (d, *J* = 13.9 Hz, 1H), 3.45 (d, *J* = 13.9 Hz, 1H), 2.27−2.17 (m, 1H), 2.06 (dd, *J* = 14.0, 7.9 Hz, 1H), 1.98−1.82 (m, 3H), 1.47−1.29 (m, 2H), 1.17 (s, 3H), 0.97 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 169.8, 163.1 (dd, *J* = 268.7, 11.1 Hz), 160.7 (dd, *J* = 268.7, 11.1 Hz), 129.8 (dd, *J* = 13.4, 6.3 Hz), 120.8 (dd, *J* = 17.7, 5.1 Hz), 111.4 (dd, *J* = 26.5, 3.8 Hz), 103.9 (t, *J* = 26.3 Hz), 67.6, 65.5, 52.8, 49.5, 48.1, 44.5, 37.9, 32.7, 26.5, 20.7, 20.0; ^{19}F NMR (376 MHz, $CDCl_3$) −109.51 to −109.90 (m), −112.84 (dd, *J* = 17.8, 8.6 Hz); FT-IR: *ν* (cm^{-1}) 3492, 2961, 2890, 1692, 1619, 1504, 1432, 1336, 1269, 1220, 1167, 1138, 1053, 966, 850; HRMS-DART: calcd. for $C_{18}H_{22}NO_4F_2S$ $[M + H]^+$: 386.1232, found: 386.1231.

*(R)-1-((3aS,6R,7aR)-8,8-Dimethyl-2,2-dioxidotetrahydro-3H-3a,6-methanobenzo[c]isothiazol-1(4H)-yl)-2-hydroxy-2-(m-tolyl)ethan-1-one (**7m**).* The title compound was prepared by the general synthesis on a 0.29 mmol scale and obtained in 77% yield (80.7 mg) as a white solid after column chromatography (PE/EA = 5:1). *dr* > 20:1; $[\alpha]_D^{24}$ −136.4 ($CHCl_3$, *c* = 1.00); M.p. 37−39 °C; ^1H NMR (400 MHz, $CDCl_3$) 7.29−7.20 (m, 3H), 7.15 (d, *J* = 7.0 Hz, 1H), 5.64 (d, *J* = 7.8 Hz, 1H), 3.91 (dd, *J* = 7.9, 5.0 Hz, 1H), 3.59 (d, *J* = 7.9 Hz, 1H), 3.51 (d, *J* = 13.8 Hz, 1H), 3.41 (d, *J* = 13.8 Hz, 1H), 2.36 (s, 3H), 2.30−2.21 (m, 1H), 2.08 (dd, *J* = 14.0, 8.0 Hz, 1H), 1.95−1.85 (m, 3H), 1.45−1.29 (m, 2H), 1.18 (s, 3H), 0.98 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 171.5, 138.3, 137.2, 129.7, 128.5, 128.5, 125.1, 73.2, 65.6, 52.9, 49.4, 48.1, 44.6, 38.2, 32.9, 26.6, 21.6, 20.8, 20.0; FT-IR: *ν* (cm^{-1}) 3496, 2959, 2890, 1688, 1456, 1412, 1334, 1214, 1135, 1051, 912, 782; HRMS-DART: calcd. for $C_{19}H_{26}NO_4S$ $[M + H]^+$: 364.1577, found: 364.1575.

*(R)-1-((3aS,6R,7aR)-8,8-Dimethyl-2,2-dioxidotetrahydro-3H-3a,6-methanobenzo[c]isothiazol-1(4H)-yl)-2-hydroxy-2-mesitylethan-1-one (**7n**).* The title compound was prepared by the general synthesis on a 0.27 mmol scale and obtained in 89% yield (93.4 mg) as a white solid after column chromatography (PE/EA = 10:1). *dr* > 20:1; $[\alpha]_D^{26}$ −60.9 ($CHCl_3$, *c* = 1.23); M.p. 76−78 °C; ^1H NMR (400 MHz, $CDCl_3$) 6.84 (s, 2H), 5.86 (d, *J* = 5.2 Hz, 1H), 3.97 (dd, *J* = 7.7, 4.9 Hz, 1H), 3.91 (d, *J* = 5.3 Hz, 1H), 3.54 (d, *J* = 13.7 Hz, 1H), 3.45 (d, *J* = 13.8 Hz, 1H), 2.30 (s, 6H), 2.25 (s, 3H), 2.20−2.11 (m, 1H), 2.10−2.01 (m, 1H), 1.99−1.84 (m, 3H), 1.49−1.30 (m, 2H), 1.23 (s, 3H), 0.99 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 172.3, 138.1, 137.5, 131.0, 129.8, 71.3, 66.1, 53.1, 49.3, 48.1, 44.7, 38.2, 32.9, 26.6, 21.1, 20.9, 20.9, 20.0; FT-IR: *ν* (cm^{-1}) 3515, 2960, 1704, 1611, 1512, 1482, 1453, 1375, 1326, 1215, 1132, 1065, 980, 848, 732; HRMS-DART: calcd. for $C_{21}H_{30}NO_4S$ $[M + H]^+$: 392.1890, found: 392.1887.

*(R)-1-((3aS,6R,7aR)-8,8-Dimethyl-2,2-dioxidotetrahydro-3H-3a,6-methanobenzo[c]isothiazol-1(4H)-yl)-2-hydroxy-2-(thiophen-3-yl)-ethan-1-one (**7o**).* The title compound was prepared by the general synthesis on a 0.30 mmol scale and obtained in 79% yield (83.0 mg) as a pale yellow solid after column chromatography (PE/EA = 8:1). *dr* > 20:1; $[\alpha]_D^{26}$ −69.1 ($CHCl_3$, *c* = 0.55); M.p. 96−98 °C; ^1H NMR (400 MHz, $CDCl_3$) 7.38 (d, *J* = 2.8 Hz, 1H), 7.31 (dd, *J* = 4.9, 3.0 Hz, 1H), 7.14 (dd, *J* = 5.0, 0.9 Hz, 1H), 5.74 (s, 1H), 3.89 (dd, *J* = 7.9, 5.0 Hz, 1H), 3.52−3.39 (m, 3H), 2.26 (ddd, *J* = 10.7, 7.8, 3.7 Hz, 1H), 2.08 (dd, *J* = 14.0, 8.0 Hz, 1H), 1.96−1.84 (m, 3H), 1.49−1.30 (m, 2H), 1.16 (s, 3H), 0.97 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 171.3, 138.1, 126.9, 126.2, 124.8, 69.1, 65.5, 52.8, 49.4, 48.1, 44.6, 38.2, 32.8, 26.5,

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20.8, 20.0; FT-IR: ν (cm^{-1}) 3479, 2959, 2886, 1690, 1482, 1461, 1412, 1333, 1217, 1166, 1135, 1051, 988, 758; HRMS-DART: calcd. for $C_{16}H_{22}NO_4S_2$ $[M + H]^+$: 356.0985, found: 356.0980.

*(R)-1-((3aS,6R,7aR)-8,8-Dimethyl-2,2-dioxidotetrahydro-3H-3a,6-methanobenzo[c]isothiazol-1(4H)-yl)-2-hydroxypropan-1-one (**7p**).*[11b] The title compound was prepared by the general synthesis on a 3.69 mmol scale and obtained in 74% yield (785 mg) as a colorless oil after column chromatography (PE/EA = 6:1). *dr* > 20:1; $[\alpha]_D^{27}$ −84.9 ($CHCl_3$, *c* = 0.51); ^1H NMR (400 MHz, $CDCl_3$) 4.72 (td, *J* = 6.5 Hz, 1H), 3.89 (dd, *J* = 7.7, 5.0 Hz, 1H), 3.52 (d, *J* = 13.8 Hz, 1H), 3.45 (d, *J* = 13.8 Hz, 1H), 3.19 (d, *J* = 7.1 Hz, 1H), 2.24−2.14 (m, 1H), 2.07 (dd, *J* = 14.0, 7.9 Hz, 1H), 1.94−1.83 (m, 3H), 1.48−1.32 (m, 5H), 1.15 (s, 3H), 0.97 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 173.0, 67.3, 65.3, 52.9, 49.3, 48.0, 44.5, 38.1, 32.8, 26.6, 20.8, 20.0, 18.9; FT-IR: ν (cm^{-1}) 3502, 2960, 2360, 2340, 1698, 1456, 1374, 1331, 1269, 1219, 1135, 1060, 974, 774; HRMS-DART: calcd. for $C_{13}H_{22}NO_4S$ $[M + H]^+$: 288.1264, found: 288.1260.

*(R)-1-((3aS,6R,7aR)-8,8-Dimethyl-2,2-dioxidotetrahydro-3H-3a,6-methanobenzo[c]isothiazol-1(4H)-yl)-2-hydroxypent-4-en-1-one (**7q**).*[21] The title compound was prepared by the general synthesis on a 0.34 mmol scale and obtained in 75% yield (79.1 mg) as a white solid after column chromatography (PE/EA = 8:1). *dr* > 20:1; $[\alpha]_D^{25}$ −80.1 ($CHCl_3$, *c* = 0.76); M.p. 64−66 °C; ^1H NMR (400 MHz, $CDCl_3$) 5.92−5.79 (m, 1H), 5.24−5.09 (m, 2H), 4.66 (td, *J* = 7.5, 4.6 Hz, 1H), 3.90 (dd, *J* = 7.8, 5.0 Hz, 1H), 3.53 (d, *J* = 13.8 Hz, 1H), 3.46 (d, *J* = 13.8 Hz, 1H), 3.12 (d, *J* = 7.3 Hz, 1H), 2.69−2.58 (m, 1H), 2.53−2.42 (m, 1H), 2.25−2.16 (m, 1H), 2.08 (dd, *J* = 14.0, 7.9 Hz, 1H), 1.98−1.84 (m, 3H), 1.49−1.30 (m, 2H), 1.15 (s, 3H), 0.97 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 171.9, 133.2, 118.7, 70.4, 65.4, 53.0, 49.4, 48.1, 44.6, 38.1, 37.1, 32.9, 26.6, 20.8, 20.0; FT-IR: ν (cm^{-1}) 3512, 3096, 2960, 1692, 1459, 1332, 1283. 1236, 1166, 1135, 1059, 1040, 992; HRMS-DART: calcd. for $C_{15}H_{24}NO_4S$ $[M + H]^+$: 314.1421, found: 314.1417.

*(R)-1-((3aS,6R,7aR)-8,8-Dimethyl-2,2-dioxidotetrahydro-3H-3a,6-methanobenzo[c]isothiazol-1(4H)-yl)-2-hydroxyhexan-1-one (**7r**).*[22] The title compound was prepared by the general synthesis on a 1.03 mmol scale and obtained in 80% yield (263 mg) as a white solid after column chromatography (PE/EA = 8:1). *dr* > 20:1; $[\alpha]_D^{25}$ −86.2 ($CHCl_3$, *c* = 1.08); M.p. 60−62 °C; ^1H NMR (400 MHz, $CDCl_3$) 4.59−4.49 (m, 1H), 3.89 (dd, *J* = 7.8, 4.9 Hz, 1H), 3.52 (d, *J* = 13.8 Hz, 1H), 3.45 (d, *J* = 13.8 Hz, 1H), 3.02 (d, *J* = 7.3 Hz, 1H), 2.25−2.15 (m, 1H), 2.07 (dd, *J* = 14.0, 7.9 Hz, 1H), 1.92−1.82 (m, 3H), 1.69−1.55 (m, 2H), 1.52−1.30 (m, 6H), 1.14 (s, 3H), 0.97 (s, 3H), 0.90 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 172.8, 71.0, 65.4, 52.9, 49.3, 48.0, 44.5, 38.2, 32.8, 32.6, 27.4, 26.6, 22.6, 20.8, 20.0, 14.1; FT-IR: ν (cm^{-1}) 3509, 2958, 2873, 1695, 1457, 1332, 1269, 1166, 1135, 1061, 816, 780; HRMS-ESI: calcd. for $C_{16}H_{27}NNaO_4S$ $[M + Na]^+$: 352.1553, found: 352.1564.

*(R)-5-(Benzyloxy)-1-((3aS,6R,7aR)-8,8-dimethyl-2,2-dioxidotetrahydro-3H-3a,6-methanobenzo[c]isothiazol-1(4H)-yl)-2-hydroxypentan-1-one (**7s**).* The title compound was prepared by the general synthesis on a 0.33 mmol scale and obtained in 76% yield (105 mg) as a colorless oil after column chromatography (PE/EA = 6:1). *dr* > 20:1; $[\alpha]_D^{25}$ −65.6 ($CHCl_3$, *c* = 0.50); ^1H NMR (400 MHz, $CDCl_3$) δ 7.35−7.32 (m, 4H), 7.29−7.27 (m, 1H), 4.64−4.56 (m, 1H), 4.51 (s, 2H), 3.89 (dd, *J* = 9.2, 3.8 Hz, 1H), 3.54−3.42 (m, 4H), 3.34 (d, *J* = 7.4 Hz, 1H), 2.25−2.16 (m, 1H), 2.11−2.03 (m, 1H), 2.03−1.85 (m, 5H), 1.81−1.74 (m, 2H), 1.47−1.34 (m, 2H), 1.15 (s, 3H), 0.97 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 172.5, 138.6, 128.5, 127.8, 127.6, 73.0, 70.9, 70.1, 65.4, 53.0, 49.3, 48.0, 44.6, 38.2, 32.9, 29.9, 26.6, 25.6, 20.9, 20.0; FT-IR: ν (cm^{-1}) 3517, 2959, 2877, 1692, 1453, 1331, 1218, 1165, 1135, 1097, 1059, 771; HRMS-DART: calcd. for $C_{22}H_{32}NO_5S$ $[M + H]^+$: 422.1996, found: 422.1993.

*(R)-5-((tert-Butyldiphenylsilyl)oxy)-1-((3aS,6R,7aR)-8,8-dimethyl-2,2-dioxidotetrahydro-3H-3a,6-methanobenzo[c]isothiazol-1(4H)-yl)-2-hydroxypentan-1-one (**7t**).* The title compound was prepared by the general synthesis on a 0.18 mmol scale and obtained in 74% yield (76.1 mg) as a colorless oil after column chromatography (PE/EA = 8:1). *dr* > 20:1; $[\alpha]_D^{26}$ −46.8 ($CHCl_3$, *c* = 1.07); ^1H NMR (400 MHz, $CDCl_3$) 7.72−7.63 (m, 4H), 7.45−7.32 (m, 6H), 4.62−4.55 (m, 1H), 3.90 (dd, *J* = 7.7, 5.0 Hz, 1H), 3.69 (t, *J* = 5.4 Hz, 2H), 3.52 (d, *J* = 13.8 Hz, 1H), 3.45 (d, *J* = 13.8 Hz, 1H), 3.25 (d, *J* = 7.1 Hz, 1H), 2.25−2.16 (m, 1H), 2.12−1.96 (m, 2H), 1.95−1.84 (m, 3H), 1.84−1.63 (m, 3H), 1.48−1.31 (m, 2H), 1.16 (s, 3H), 1.04 (s, 9H), 0.97 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 172.5, 135.7, 134.0, 129.7, 127.8, 71.1, 65.4, 63.8, 53.0, 49.3, 48.0, 44.6, 38.2, 32.9, 29.6, 28.4, 27.0, 26.6, 20.8, 20.0, 19.3; FT-IR: ν (cm^{-1}) 3532, 3070, 2958, 2856, 1708, 1691, 1468, 1427, 1333, 1217, 1110, 1038, 822, 703, 536; HRMS-ESI: calcd. for $C_{31}H_{43}NNaO_5SSi$ $[M + Na]^+$: 592.2523, found: 592.2529.

*(R)-1-((3aS,6R,7aR)-8,8-Dimethyl-2,2-dioxidotetrahydro-3H-3a,6-methanobenzo[c]isothiazol-1(4H)-yl)-2-hydroxy-5-(methoxymethoxy)pentan-1-one (**7u**).* The title compound was prepared by the general synthesis on a 0.17 mmol scale and obtained in 83% yield (53.5 mg) as a colorless oil after column chromatography (PE/EA = 6:1). *dr* > 20:1; $[\alpha]_D^{25}$ −33.6 ($CHCl_3$, *c* = 0.48); ^1H NMR (400 MHz, $CDCl_3$) 4.62 (s, 2H), 4.61−4.56 (m, 1H), 3.89 (dd, *J* = 7.8, 5.0 Hz, 1H), 3.57 (t, *J* = 6.1 Hz, 2H), 3.52 (d, *J* = 13.8 Hz, 1H), 3.45 (d, *J* = 13.8 Hz, 1H), 3.35 (s, 3H), 3.27−3.23 (m, 1H), 2.24−2.15 (m, 1H), 2.07 (dd, *J* = 14.0, 7.9 Hz, 1H), 2.03−1.95 (m, 1H), 1.95−1.84 (m, 3H), 1.84−1.68 (m, 3H), 1.47−1.32 (m, 2H), 1.15 (s, 3H), 0.97 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 172.5, 96.5, 70.8, 67.6, 65.4, 55.4, 52.9, 49.3, 48.0, 44.6, 38.2, 32.9, 29.8, 26.6, 25.5, 20.8, 20.0; FT-IR: ν (cm^{-1}) 3505, 2957, 1693, 1482, 1452, 1375, 1332, 1270, 1135, 1038, 916, 764; HRMS-DART: calcd. for $C_{17}H_{30}NO_6S$ $[M + Na]^+$: 376.1794, found: 376.1788.

*(R)-1-((3aS,6R,7aR)-8,8-Dimethyl-2,2-dioxidotetrahydro-3H-3a,6-methanobenzo[c]isothiazol-1(4H)-yl)-2-hydroxy-3-methylbutan-1-one (**7v**).* The title compound was prepared by the general synthesis on a 1.67 mmol scale and obtained in 82% yield (433 mg) as a white solid after column chromatography (PE/EA = 12:1). *dr* > 20:1; $[\alpha]_D^{25}$ −87.3 ($CHCl_3$, *c* = 0.97); M.p. 108−110 °C; ^1H NMR (400 MHz, $CDCl_3$) 4.32 (dd, *J* = 7.7, 5.8 Hz, 1H), 3.90 (dd, *J* = 7.9, 5.0 Hz, 1H), 3.51 (d, *J* = 13.8 Hz, 1H), 3.45 (d, *J* = 13.8 Hz, 1H), 2.96 (d, *J* = 7.7 Hz, 1H), 2.32−2.17 (m, 2H), 2.07 (dd, *J* = 14.0, 7.9 Hz, 1H), 1.97−1.82 (m, 3H), 1.48−1.30 (m, 2H), 1.14 (s, 3H), 1.01−0.93 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) 172.1, 75.5, 65.4, 53.0, 49.2, 48.0, 44.5, 38.1, 32.8, 30.0, 26.5, 20.8, 20.0, 19.5, 16.5; FT-IR: ν (cm^{-1}) 3511, 2962, 2880, 2253, 1692, 1468, 1413, 1392, 1331, 1268, 1236, 1166, 1135, 1061, 991, 819, 746; HRMS-DART: calcd. for $C_{15}H_{26}NO_4S$ $[M + H]^+$: 316.1577, found: 316.1576.

*(R)-1-((3aS,6R,7aR)-8,8-Dimethyl-2,2-dioxidotetrahydro-3H-3a,6-methanobenzo[c]isothiazol-1(4H)-yl)-2-hydroxy-3,3-dimethylbutan-1-one (**7w**).* The title compound was prepared by the general synthesis on a 0.96 mmol scale and obtained in 75% yield (235 mg) as a white solid after column chromatography (PE/EA = 6:1). *dr* > 20:1; $[\alpha]_D^{27}$ −77.1 ($CHCl_3$, *c* = 0.49); M.p. 112−114 °C; ^1H NMR (400 MHz, $CDCl_3$) 4.20 (d, *J* = 7.1 Hz, 1H), 3.91 (dd, *J* = 7.8, 4.9 Hz, 1H), 3.53 (d, *J* = 13.8 Hz, 1H), 3.46 (d, *J* = 13.8 Hz, 1H), 3.08 (d, *J* = 7.2 Hz, 1H), 2.21−2.12 (m, 1H), 2.05 (dd, *J* = 13.9, 7.8 Hz, 1H), 1.95−1.84 (m, 3H), 1.41 (dd, *J* = 9.2, 3.8 Hz, 2H), 1.16 (s, 3H), 1.07 (s, 9H), 0.97 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 170.5, 76.8, 65.3, 53.1, 48.9, 48.0, 44.6, 38.3, 34.7, 32.9, 26.6, 25.9, 20.9, 20.0; FT-IR: ν (cm^{-1}) 3531, 2958, 1707, 1483, 1461, 1326, 1268, 1206, 1132, 1057, 988, 771; HRMS-DART: calcd. for $C_{16}H_{28}NO_4S$ $[M + H]^+$: 330.1734, found: 330.1732.

*(R)-2-Cyclohexyl-1-((3aS,6R,7aR)-8,8-dimethyl-2,2-dioxidotetrahydro-3H-3a,6-methanobenzo[c]isothiazol-1(4H)-yl)-2-hydroxyethan-1-one (**7x**).* The title compound was prepared by the general synthesis on a 0.30 mmol scale and obtained in 85% yield (89.0 mg) as a white solid after column chromatography (PE/EA = 5:1). *dr* > 20:1; $[\alpha]_D^{26}$ −105.3 ($CHCl_3$, *c* = 0.89); M.p. 106−108 °C; ^1H NMR (400 MHz, $CDCl_3$) 4.34 (dd, *J* = 7.8, 6.2 Hz, 1H), 3.91 (dd, *J* = 7.9, 5.0 Hz, 1H), 3.52 (d, *J* = 13.8 Hz, 1H), 3.45 (d, *J* = 13.8 Hz, 1H), 2.85 (d, *J* = 7.8 Hz, 1H), 2.28−2.19 (m, 1H), 2.08 (dd, *J* = 14.0, 8.0 Hz, 1H), 2.01−1.85 (m, 4H), 1.84−1.70 (m, 3H), 1.69−1.59 (m, 2H), 1.48−1.33 (m, 2H), 1.33−1.04 (m, 8H), 0.97 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 172.0, 75.1, 65.5, 53.0, 49.2, 48.0, 44.6, 39.7, 38.2, 32.9, 29.7, 26.9, 26.5, 26.4. 26.2, 25.9, 20.8, 20.0; FT-IR: ν (cm^{-1}) 3501, 2926, 2852, 2262, 1691, 1680, 1461, 1450, 1330, 1236, 1135, 1061, 1039, 990, 733; HRMS-DART: calcd. for $C_{18}H_{30}NO_4S$ $[M + H]^+$: 356.1890, found: 356.1888.

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Gram-Scale Synthesis of 7c. To a solution of substrate **6c** (5.00 g, 12.3 mmol) in THF (150 mL) was slowly added sodium bis(trimethylsilyl)amide (2.0 M in THF, 7.4 mL, 14.7 mmol) at −78 °C under an Ar atmosphere. After being stirred at −78 °C for 30 min, the mixture was then dropwise added Davis oxaziridine (4.88 g, 18.4 mmol) in THF (150 mL) at −78 °C in 4 h. The reaction mixture was stirred for another 10 min and quenched with acetic acid (1.8 mL, 30.7 mmol) in THF (50 mL). The mixture was allowed to room temperature and extracted with ethyl acetate (3 × 100 mL). The combined organic layers were washed with saturated $NaHCO_3$ (aq.) and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was subjected to purification on silica gel chromatography (DCM/MeOH: 80/1) to provide the single detectable isomer (**7c**) as a white solid (4.50 g, 87% yield).

3-(3,4-Dimethoxy-phenyl)-2-hydroxy-propionic Acid Methyl Ester (10).[18a] To an ice-cooled MeOH solution (33 mL) was added methylmagnesium bromide (1.0 M in THF, 10.3 mL, 10.3 mmol). The mixture was stirred for 20 min. The above suspension was added to a solution of **7c** (2.17 g, 5.13 mmol) in CH_2Cl_2/MeOH (3/1, 48 mL) at 0 °C. The reaction mixture was stirred for another 10 min and quenched with 10% sodium sulfate (aq. 20 mL). The mixture was allowed to room temperature and concentrated under reduced pressure. The residue was added 10% sodium sulfate (aq. 200 mL) and extracted with isopropyl acetate (3 × 100 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was subjected to purification on silica gel chromatography (PE/EtOAc: 3/1−1/1) to provide the product (**10**) as a white solid (1.02 g, 83% yield, er > 99:1) and the camphorsultam as a white solid (1.04 g, 94% yield). The er value was determined by HPLC. HPLC, OD-H, hexane/IPA = 7:3, 0.7 mL/min, 214 nm, t_{minor} = 11.1 min, t_{major} = 13.1 min. $[\alpha]_D^{26}$ +6.9 (CH_2Cl_2, *c* = 1.03); M.p. 47−49 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 6.80 (d, *J* = 8.8 Hz, 1H), 6.75−6.73 (m 2H), 4.44−4.42 (m, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.77 (s, 3H), 3.07 (dd, *J* = 14, 4.4 Hz, 1H), 2.91 (dd, *J* = 14, 6.6 Hz, 1H), 2.71 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 174.7, 148.9, 148.2, 128.9, 121.6, 112.8, 111.3, 71.5, 56.0, 55.9, 52.6, 40.2; FT-IR: *ν* (cm^{-1}) 3392, 2948, 2833, 1726, 1516, 1462, 1362, 1157, 855, 790, 627; HRMS-DART: calcd. for $C_{12}H_{17}O_5$ $[M + H]^+$: 241.1071, found: 241.1070.

Substrate Preparation. *Preparation of **6a, 6p, 6r, 6v**.*[23] A solution of (−)-camphorsultam (5.0 g, 23.2 mmol) in distilled toluene (100 mL) was treated with NaH (60% dispersion in mineral oil) (1.4 g, 34.8 mmol) at room temperature for 30 min, and acyl chloride (34.8 mmol) was added dropwise. The reaction mixture was stirred at room temperature for 2 h, the reaction mixure was quenched by 10% HCl (aq.), and the resulting solution was partitioned between EtOAc and 10% HCl (aq.). The organic phase was washed with 10% HCl (aq.), 5% $NaHCO_3$ (aq.), and brine, then dried (Na_2SO_4), filtered, and concentrated, and the crude product was crystallized in MeOH to afford white crystals. (75−92% yield).

*1-((3aS,6R,7aR)-8,8-Dimethyl-2,2-dioxidohexahydro-1H-3a,6-methanobenzo[c]isothiazol-1-yl)-3-phenylpropan-1-one (**6a**).*[15c] The title compound was prepared on a 23.2 mmol scale and obtained in 75% yield (6..08 g) as a white solid after recrystallization. $[\alpha]_D^{22}$ −76.5 ($CHCl_3$, *c* = 1.01); M.p. 140−142 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 7.30−7.26 (m, 1H), 7.25−7.14 (m, 4H), 3.86 (t, *J* = 6.3 Hz, 1H), 3.48 (d, *J* = 13.8 Hz, 1H), 3.42 (d, *J* = 13.8 Hz, 1H), 3.12−2.92 (m, 4H), 2.08−2.01 (m, 2H), 1.90−1.80 (m, 3H), 1.43−1.29 (m, 2H), 1.09 (s, 3H), 0.95 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 171.2, 140.3, 128.6, 128.6, 126.3, 65.3, 53.1, 48.5, 47.9, 44.8, 38.6, 37.0, 33.0, 30.6, 26.6, 20.9, 20.0; FT-IR: *ν* (cm^{-1}) 3055, 2960, 2878, 1682, 1604, 1452, 1362, 1162, 770, 699; HRMS-DART: calcd. for $C_{19}H_{26}O_3NS$ $[M + H]^+$: 348.1633, found: 348.1629.

*1-((3aS,6R,7aR)-8,8-Dimethyl-2,2-dioxidohexahydro-1H-3a,6-methanobenzo[c]isothiazol-1-yl)propan-1-one (**6p**).*[15c] The title compound was prepared on a 23.2 mmol scale and obtained in 76% yield (4.76 g) as a white solid after column chromatography (PE/EA = 8:1). $[\alpha]_D^{24}$ −105.3 ($CHCl_3$, *c* = 1.20); M.p. 138−140 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 3.85 (dd, *J* = 7.5, 5.2 Hz, 1H), 3.48 (d, *J* = 13.8 Hz, 1H), 3.42 (d, *J* = 13.8 Hz, 1H), 2.83−2.64 (m, 2H), 2.17−2.02 (m, 2H), 1.96−1.82 (m, 3H), 1.46−1.28 (m, 2H), 1.22−1.08 (m, 6H), 0.96 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 172.7, 65.3, 53.0, 48.6, 47.9, 44.8, 38.6, 33.0, 29.0, 26.6, 20.9, 20.0, 8.5; FT-IR: *ν* (cm^{-1}) 2967, 2881, 1688, 1457, 1392, 1330, 1220, 1132, 1051, 968, 771; HRMS-DART: calcd. for $C_{13}H_{22}NO_3S$ $[M + H]^+$: 272.1315, found: 272.1311.

*1-((3aS,6R,7aR)-8,8-Dimethyl-2,2-dioxidohexahydro-1H-3a,6-methanobenzo[c]isothiazol-1-yl)hexan-1-one (**6r**).*[24] The title compound was prepared on a 21.8 mmol scale and obtained in 92% yield (6.28 g) as colorless oil after column chromatography (PE/EA = 10:1). $[\alpha]_D^{24}$ −81.7 ($CHCl_3$, *c* = 1.12); ^{1}H NMR (400 MHz, $CDCl_3$) 3.86 (dd, *J* = 7.4, 5.3 Hz, 1H), 3.49 (d, *J* = 13.8 Hz, 1H), 3.42 (d, *J* = 13.8 Hz, 1H), 2.78−2.62 (m, 2H), 2.16−2.02 (m, 2H), 1.95−1.83 (m, 3H), 1.72−1.61 (m, 2H), 1.44−1.28 (m, 6H), 1.15 (s, 3H), 0.96 (s, 3H), 0.88 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 172.3, 65.4, 53.1, 48.5, 47.9, 44.8, 38.7, 35.6, 33.0, 31.3, 26.6, 24.3, 22.5, 21.0, 20.0, 14.0; FT-IR: *ν* (cm^{-1}) 2958, 2877, 1693, 1237, 1377, 1331, 1134, 1060, 987, 805, 772; HRMS-ESI: calcd. for $C_{16}H_{27}NNaO_3S$ $[M + Na]^+$: 336.1609, found: 336.1604.

*1-((3aS,6R,7aR)-8,8-Dimethyl-2,2-dioxidohexahydro-1H-3a,6-methanobenzo[c]isothiazol-1-yl)-3-methylbutan-1-one (**6v**).*[25] The title compound was prepared on a 4.64 mmol scale and obtained in 90% yield (1.26 g) as a white solid after column chromatography (PE/EA = 12:1). $[\alpha]_D^{25}$ −91.9 ($CHCl_3$, *c* = 1.10); M.p. 110−112 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 3.87 (t, *J* = 6.3 Hz, 1H), 3.49 (d, *J* = 13.8 Hz, 1H), 3.42 (d, *J* = 13.8 Hz, 1H), 2.66 (dd, *J* = 15.7, 7.1 Hz, 1H), 2.51 (dd, *J* = 15.7, 6.9 Hz, 1H), 2.29−2.17 (m, 1H), 2.09 (d, *J* = 7.1 Hz, 2H), 1.96−1.82 (m, 3H), 1.46−1.29 (m, 2H), 1.15 (s, 3H), 1.00−0.93 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) 171.7, 65.4, 53.2, 48.4, 47.9, 44.8, 44.4, 38.8, 33.0, 26.6, 25.7, 22.5, 22.4, 21.0, 20.0; FT-IR: *ν* (cm^{-1}) 2960, 2877, 1695, 1466, 1387, 1216, 1137, 1110, 991, 831, 773; HRMS-DART: calcd. for $C_{15}H_{26}NO_3S$ $[M + H]^+$: 300.1628, found: 300.1625.

*Preparation of Sultams **6b−o, 6q, 6w−x**.*[26] To a solution of the corresponding acid (5.6 mmol) and triethylamine (0.9 mL, 6.5 mmol) in THF (10 mL) was slowly added pivaloyl chloride (0.7 mL, 5.6 mmol) at −78 °C under an atmosphere of dry argon. The mixture was stirred at this temperature for 5 min and then for 1 h at 0 °C. In a second flask, a solution of the corresponding (2*S*)-bornane-10,2-sultam (1.0 g, 4.6 mmol) in THF (15 mL) was cooled to −78 °C and ^{n}BuLi (2.1 mL, 2.4 M in hexanes, 5.1 mmol) was added via syringe. The solution was then stirred for 30 min at −78 °C. The first solution was recooled to −78 °C, and then the cold solution of the lithium salt of the sultam was added rapidly. Stirring was continued at this temperature for 15 min and then at 0 °C until the starting material was fully consumed, as indicated by TLC. The reaction was quenched by addition of water (15 mL). The aqueous layer was extracted with EA, and the combined organic extracts were dried with $MgSO_4$, filtered, and evaporated. The residue was purified by flash chromatography on silica using PE/EA mixtures as the eluent. (58−88% yield).

*1-((3aS,6R,7aR)-8,8-Dimethyl-2,2-dioxidohexahydro-1H-3a,6-methanobenzo[c]isothiazol-1-yl)-3-(3-methoxyphenyl)propan-1-one (**6b**).* The title compound was prepared on a 4.64 mmol scale and obtained in 81% yield (1.41 g) as a white solid after column chromatography (PE/EA = 10:1). $[\alpha]_D^{23}$ −65.4 ($CHCl_3$, *c* = 1.31); M.p. 128−130 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 7.18 (t, *J* = 7.8 Hz, 1H), 6.86−6.69 (m, 3H), 3.86 (t, *J* = 6.2 Hz, 1H), 3.79 (s, 3H), 3.48 (d, *J* = 13.8 Hz, 1H), 3.42 (d, *J* = 13.8 Hz, 1H), 3.14−2.91 (m, 4H), 2.12−1.99 (m, 2H), 1.96−1.81 (m, 3H), 1.46−1.29 (m, 2H), 1.09 (s, 3H), 0.96 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$) 171.2, 159.8, 141.8, 129.5, 121.0, 114.1, 112.0, 65.4, 55.3, 53.1, 48.6, 47.9, 44.8, 38.6, 37.0, 33.0, 30.7, 26.6, 20.9, 20.0; FT-IR: *ν* (cm^{-1}) 3010, 2974, 2996, 2838, 1936, 2689, 1601, 1589, 1493, 1466, 1388, 1327, 1234, 1170, 1053, 988, 793; HRMS-DART: calcd. for $C_{20}H_{28}NO_4S$ $[M + H]^+$: 378.1734, found: 378.1731.

*3-(3,4-Dimethoxyphenyl)-1-((3aS,6R,7aR)-8,8-dimethyl-2,2-dioxidohexahydro-1H-3a,6-methanobenzo[c]isothiazol-1-yl)-propan-1-one (**6c**).* The title compound was prepared on a 15.6 mmol scale and obtained in 76% yield (4.83 g) as a white solid after recrystallization. $[\alpha]_D^{24}$ −56.2 ($CHCl_3$, *c* = 1.45); M.p. 126−128 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 6.76 (s, 3H), 3.87−3.84 (m, 7H), 3.47 (d, *J*

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= 13.8 Hz, 1H), 3.41 (d, J = 13.8 Hz, 1H), 3.12−2.91 (m, 4H), 2.09−1.98 (m, 2H), 1.93−1.81 (m, 3H), 1.44−1.31 (m, 2H), 1.05 (s, 3H), 0.95 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 171.3, 148.9, 147.6, 132.8, 120.5, 111.9, 111.3, 65.3, 56.1, 55.9, 53.1, 48.5, 47.9, 44.8, 38.6, 37.2, 33.0, 30.4, 26.6, 20.7, 20.0; FT-IR: ν (cm^{-1}) 3014, 2959, 1687, 1586, 1516, 1462, 1387, 1328, 1213, 1027, 867, 813, 767; HRMS-ESI: calcd. for $C_{21}H_{29}NNaO_5S$ $[M + Na]^+$: 430.1659, found: 430.1670.

*3-([1,1′-Biphenyl]-4-yl)-1-((3aS,6R,7aR)-8,8-dimethyl-2,2-dioxidohexahydro-1H-3a,6-methanobenzo[c]isothiazol-1-yl)propan-1-one (**6d**).* The title compound was prepared on a 4.05 mmol scale and obtained in 74% yield (1.26 g) as a white solid after column chromatography (PE/EA = 12:1). $[\alpha]_D^{25}$ −56.6 ($CHCl_3$, c = 1.14); M.p. 104−106 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 7.60 (d, J = 7.4 Hz, 2H), 7.54 (d, J = 8.0 Hz, 2H), 7.45 (t, J = 7.6 Hz, 2H), 7.37−7.33 (m, 3H), 3.88 (t, J = 6.2 Hz, 1H), 3.49 (d, J = 13.8 Hz, 1H), 3.43 (d, J = 13.8 Hz, 1H), 3.24−3.00 (m, 4H), 2.16−2.05 (m, 2H), 1.96−1.76 (m, 3H), 1.44−1.26 (m, 2H), 1.11 (s, 3H), 0.94 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 171.2, 141.2, 139.4, 139.3, 129.1, 128.8, 127.3, 127.2, 127.2, 65.4, 53.1, 48.6, 47.9, 44.8, 38.6, 37.0, 33.0, 30.3, 26.6, 20.9, 20.0; FT-IR: ν (cm^{-1}) 3010, 2989, 2959, 2877, 1681, 1485, 1455, 1411, 1339, 1207, 1109, 989, 778; HRMS-DART: calcd. for $C_{25}H_{30}NO_3S$ $[M + H]^+$: 424.1941, found: 424.1937.

*1-((3aS,6R,7aR)-8,8-Dimethyl-2,2-dioxidohexahydro-1H-3a,6-methanobenzo[c]isothiazol-1-yl)-3-(4-(trifluoromethyl)phenyl)-propan-1-one (**6e**).* The title compound was prepared on a 3.82 mmol scale and obtained in 64% yield (1.01 g) as a white solid after column chromatography (PE/EA = 5:1). $[\alpha]_D^{24}$ −67.7 ($CHCl_3$, c = 1.23); M.p. 130−132 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 7.53 (d, J = 7.9 Hz, 2H), 7.34 (d, J = 7.9 Hz, 2H), 3.85 (t, J = 6.2 Hz, 1H), 3.49 (d, J = 13.8 Hz, 1H), 3.42 (d, J = 13.8 Hz, 1H), 3.17−2.96 (m, 4H), 2.12−1.98 (m, 2H), 1.97−1.81 (m, 3H), 1.45−1.28 (m, 2H), 1.05 (s, 3H), 0.95 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 170.7, 144.2 (q, J = 1.3 Hz), 128.9, 128.6 (q, J = 32.4 Hz), 125.3 (q, J = 3.8 Hz), 124.3 (q, J = 271.8 Hz), 65.3, 53.0, 48.6, 47.8, 44.7, 38.5, 36.4, 32.9, 30.3, 26.5, 20.8, 19.9; ^{19}F NMR (376 MHz, $CDCl_3$) −62.43 (s); FT-IR: ν (cm^{-1}) 3020, 2966, 2933, 2886, 1931, 1684, 1618, 1454, 1223, 1107, 1068, 990, 866; HRMS-DART: calcd. for $C_{20}H_{25}NO_3F_3S$ $[M + H]^+$: 416.1502, found: 416.1497.

*1-((3aS,6R,7aR)-8,8-Dimethyl-2,2-dioxidohexahydro-1H-3a,6-methanobenzo[c]isothiazol-1-yl)-3-(4-nitrophenyl)propan-1-one (**6f**).* The title compound was prepared on a 4.64 mmol scale and obtained in 67% yield (1.23 g) as a pale yellow solid after column chromatography (PE/EA = 8:1). $[\alpha]_D^{25}$ −76.2 ($CHCl_3$, c = 1.03); M.p. 132−134 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 8.13 (d, J = 8.4 Hz, 2H), 7.39 (d, J = 8.4 Hz, 2H), 3.85 (t, J = 6.2 Hz, 1H), 3.50 (d, J = 13.8 Hz, 1H), 3.43 (d, J = 13.8 Hz, 1H), 3.17−3.04 (m, 4H), 2.08−1.94 (m, 2H), 1.97−1.81 (m, 3H), 1.46−1.29 (m, 2H), 1.06 (s, 3H), 0.96 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 170.2, 148.1, 146.7, 129.5, 123.7, 65.3, 52.9, 48.6, 47.8, 44.7, 38.4, 36.0, 32.9, 30.2, 26.5, 20.8, 19.9; FT-IR: ν (cm^{-1}) 3016, 2966, 2876, 1681, 1603, 1514, 1455, 1386, 1326, 1218, 1135, 1069, 989; HRMS-DART: calcd. for $C_{19}H_{25}N_2O_5S$ $[M + H]^+$: 393.1479, found: 393.1474.

*3-(4-Chlorophenyl)-1-((3aS,6R,7aR)-8,8-dimethyl-2,2-dioxidohexahydro-1H-3a,6-methanobenzo[c]isothiazol-1-yl)propan-1-one (**6g**).* The title compound was prepared on a 4.64 mmol scale and obtained in 65% yield (1.15 g) as a white solid after column chromatography (PE/EA = 8:1). $[\alpha]_D^{23}$ −69.3 ($CHCl_3$, c = 1.23); M.p. 156−158 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 7.23 (d, J = 8.4 Hz, 2H), 7.15 (d, J = 8.4 Hz, 2H), 3.84 (t, J = 6.3 Hz, 1H), 3.48 (d, J = 13.8 Hz, 1H), 3.41 (d, J = 13.8 Hz, 1H), 3.11−2.90 (m, 4H), 2.08−1.98 (m, 2H), 1.95−1.81 (m, 3H), 1.42−1.27 (m, 2H), 1.06 (s, 3H), 0.95 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 170.8, 138.6, 132.0, 130.0, 128.6, 65.2, 53.0, 48.5, 47.8, 44.7, 38.5, 36.7, 32.9, 29.9, 26.5, 20.8, 19.9; FT-IR: ν (cm^{-1}) 3017, 2994, 2963, 2876, 1901, 1681, 1493, 1328, 1135, 1092, 1070, 818, 772; HRMS-DART: calcd. for $C_{19}H_{25}NO_3SCl$ $[M + H]^+$: 382.1238, found: 382.1233.

*3-(4-Bromophenyl)-1-((3aS,6R,7aR)-8,8-dimethyl-2,2-dioxidohexahydro-1H-3a,6-methanobenzo[c]isothiazol-1-yl)propan-1-one (**6h**).* The title compound was prepared on a 4.64 mmol scale and obtained in 70% yield (1.38 g) as a white solid after column chromatography (PE/EA = 8:1). $[\alpha]_D^{23}$ −64.1 ($CHCl_3$, c = 1.01); M.p. 150−152 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 7.38 (d, J = 8.4 Hz, 2H), 7.10 (d, J = 8.4 Hz, 2H), 3.84 (t, J = 6.3 Hz, 1H), 3.48 (d, J = 13.8 Hz, 1H), 3.41 (d, J = 13.8 Hz, 1H), 3.10−2.90 (m, 4H), 2.07−1.97 (m, 2H), 1.95−1.79 (m, 3H), 1.44−1.27 (m, 2H), 1.05 (s, 3H), 0.95 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 170.8, 139.2, 131.5, 130.4, 120.1, 65.3, 53.0, 48.5, 47.8, 44.7, 38.5, 36.6, 32.9, 30.0, 26.5, 20.8, 20.0; FT-IR: ν (cm^{-1}) 3017, 2993, 2961, 2877, 1682, 1489, 1452, 1327, 1218, 1135, 1070, 1014, 814; HRMS-DART: calcd. for $C_{19}H_{25}NO_3SBr$ $[M + H]^+$: 426.0733, found: 426.0729.

*1-((3aS,6R,7aR)-8,8-Dimethyl-2,2-dioxidohexahydro-1H-3a,6-methanobenzo[c]isothiazol-1-yl)-3-(4-fluorophenyl)propan-1-one (**6i**).* The title compound was prepared on a 2.01 mmol scale and obtained in 70% yield (513 mg) as a white solid after column chromatography (PE/EA = 10:1). $[\alpha]_D^{25}$ −74.9 ($CHCl_3$, c = 1.16); M.p. 150−152 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 7.18 (dd, J = 8.7, 5.5 Hz, 2H), 6.97−6.93 (m, 2H), 3.85 (t, J = 6.3 Hz, 1H), 3.48 (d, J = 13.8 Hz, 1H), 3.41 (d, J = 13.8 Hz, 1H), 3.11−2.89 (m, 4H), 2.09−2.01 (m, 2H), 1.96−1.80 (m, 3H), 1.44−1.28 (m, 2H), 1.07 (s, 3H), 0.95 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 171.0, 161.6 (d, J = 244.4 Hz), 135.9 (d, J = 3.0 Hz), 130.1 (d, J = 8.1 Hz), 115.3 (d, J = 21.2 Hz), 65.4, 53.1, 48.6, 47.9, 44.8, 38.6, 37.1, 33.0, 29.8, 26.6, 20.9, 20.0; ^{19}F NMR (376 MHz, $CDCl_3$) −117.25 (s); FT-IR: ν (cm^{-1}) 3019, 2964, 1892, 1681, 1598, 1511, 1373, 1327, 1218, 1160, 1071, 991.12, 766; HRMS-ESI: calcd. for $C_{19}H_{24}O_3FNSNa$ $[M + Na]^+$: 388.1353, found: 388.1373.

*1-((3aS,6R,7aR)-8,8-Dimethyl-2,2-dioxidohexahydro-1H-3a,6-methanobenzo[c]isothiazol-1-yl)-3-(thiophen-2-yl)propan-1-one (**6j**).* The title compound was prepared on a 4.64 mmol scale and obtained in 58% yield (956 mg) as a pale yellow solid after column chromatography (PE/EA = 10:1). $[\alpha]_D^{24}$ −80.7 ($CHCl_3$, c = 1.03); M.p. 128−130 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 7.11 (dd, J = 5.0, 0.8 Hz, 1H), 6.93−6.87 (m, 1H), 6.86−6.81 (m, 1H), 3.87 (t, J = 6.2 Hz, 1H), 3.50 (d, J = 13.8 Hz, 1H), 3.43 (d, J = 13.8 Hz, 1H), 3.28−3.18 (m, 2H), 3.17−3.02 (m, 2H), 2.15−2.04 (m, 2H), 1.96−1.83 (m, 3H), 1.45−1.31 (m, 2H), 1.12 (s, 3H), 0.97 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 170.7, 142.8, 126.9, 125.0, 123.6, 65.4, 53.1, 48.6, 47.9, 44.8, 38.6, 37.2, 33.0, 26.6, 24.6, 20.9, 20.0; FT-IR: ν (cm^{-1}) 3109, 3009, 2959, 2877, 1686, 1457, 1383, 1332, 1212, 1070, 989, 716; HRMS-DART: calcd. for $C_{17}H_{24}NO_3S_2$ $[M + H]^+$: 354.1192, found: 354.1187.

*1-((3aS,6R,7aR)-8,8-Dimethyl-2,2-dioxidohexahydro-1H-3a,6-methanobenzo[c]isothiazol-1-yl)-2-(4-fluorophenyl)ethanone (**6k**).*[27] The title compound was prepared on a 4.64 mmol scale and obtained in 75% yield (1.23 g) as a white solid after column chromatography (PE/EA = 10:1). $[\alpha]_D^{23}$ −113.2 ($CHCl_3$, c = 1.12); M.p. 70−72 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 7.31−7.17 (m, 2H), 6.98−6.94 (m, 2H), 4.01 (d, J = 16.0 Hz, 1H), 3.94 (d, J = 16.0 Hz, 1H), 3.85 (t, J = 6.1 Hz, 1H), 3.51 (d, J = 14.0 Hz, 1H), 3.44 (d, J = 14.0 Hz, 1H), 2.07−1.93 (m, 2H), 1.91−1.73 (m, 3H), 1.42−1.22 (m, 2H), 1.09 (s, 3H), 0.92 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 169.9, 162.2 (d, J = 246.4 Hz), 131.5 (d, J = 8.1 Hz), 129.1 (d, J = 3.0 Hz), 115.4 (d, J = 21.2 Hz), 65.54, 53.2, 48.6, 47.9, 44.7, 41.2, 38.5, 33.0, 26.6, 20.9, 20.09; ^{19}F NMR (376 MHz, $CDCl_3$) −115.83 (s); FT-IR: ν (cm^{-1}) 3073, 3007, 2966, 2885, 1694, 1589, 1507, 1458, 1392, 1315, 1133, 1012, 939; HRMS-DART: calcd. for $C_{18}H_{23}NO_3FS$ $[M + H]^+$: 352.1377, found: 352.1374.

*2-(2,4-Difluorophenyl)-1-((3aS,6R,7aR)-8,8-dimethyl-2,2-dioxidohexahydro-1H-3a,6-methanobenzo[c]isothiazol-1-yl)ethanone (**6l**).* The title compound was prepared on a 4.64 mmol scale and obtained in 65% yield (1.10 g) as a white solid after column chromatography (PE/EA = 10:1). $[\alpha]_D^{23}$ −90.6 ($CHCl_3$, c = 1.08); M.p. 80−82 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 7.24−7.18 (m, 1H), 6.87−6.77 (m, 2H), 4.10 (d, J = 17.1 Hz, 1H), 4.02 (d, J = 17.1 Hz, 1H), 3.90 (dd, J = 7.7, 5.0 Hz, 1H), 3.55 (d, J = 13.8 Hz, 1H), 3.48 (d, J = 13.8 Hz, 1H), 2.19−2.10 (m, 1H), 2.04 (dd, J = 13.9, 7.9 Hz, 1H), 1.98−1.83 (m, 3H), 1.47−1.29 (m, 2H), 1.19 (s, 3H), 0.99 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 168.6, 162.4 (dd, J = 248.0, 11.8 Hz), 161.2 (dd, J = 249.2, 11.9 Hz), 132.5 (dd, J = 10.1, 6.1 Hz), 116.9 (dd, J = 16.2, 3.5 Hz), 111.3 (dd, J = 21.2, 4.0 Hz), 104.0 (t, J = 26.2 Hz), 65.6, 53.1, 48.8, 48.0, 44.8, 38.5, 35.2, 33.0, 26.6, 21.0, 20.0; ^{19}F NMR (376 MHz,

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$CDCl_3$) −111.32 (s), −112.14 (s); FT-IR: ν (cm^{-1}) 2992, 2953, 2884, 1698, 1623, 1602, 1504, 1311, 1197, 1085, 961, 851, 771; HRMS-DART: calcd. for $C_{18}H_{22}NO_3F_2S$ $[M + H]^+$: 370.1283, found: 370.1279.

*1-((3aS,6R,7aR)-8,8-Dimethyl-2,2-dioxidohexahydro-1H-3a,6-methanobenzo[c]isothiazol-1-yl)-2-(m-tolyl)ethanone (**6m**).* The title compound was prepared on a 4.64 mmol scale and obtained in 72% yield (1.16 g) as a white solid after column chromatography (PE/EA = 10:1). $[\alpha]_D^{26}$ −106.4 ($CHCl_3$, c = 0.66); M.p. 88−90 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23−7.18 (m, 1H), 7.13−7.04 (m, 3H), 4.04 (d, J = 15.9 Hz, 1H), 3.96 (d, J = 15.9 Hz, 1H), 3.90 (dd, J = 7.4, 5.3 Hz, 1H), 3.55 (d, J = 13.8 Hz, 1H), 3.48 (d, J = 13.8 Hz, 1H), 2.33 (s, 3H), 2.11−1.97 (m, 2H), 1.97−1.81 (m, 3H), 1.46−1.27 (m, 2H), 1.14 (s, 3H), 0.97 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 170.2, 138.2, 133.3, 130.7, 128.5, 128.0, 136.9, 65.6, 53.2, 48.6, 47.9, 44.8, 42.0, 38.5, 32.9, 26.6, 21.5, 20.9, 20.0; FT-IR: ν (cm^{-1}) 3009, 2934, 2874, 1955, 1700, 1613, 1455, 1352, 1325, 1132, 1060, 989, 773; HRMS-DART: calcd. for $C_{19}H_{26}NO_3S$ $[M + H]^+$: 348.1628, found: 348.1624.

*1-((3aS,6R,7aR)-8,8-Dimethyl-2,2-dioxidohexahydro-1H-3a,6-methanobenzo[c]isothiazol-1-yl)-2-mesitylethanone (**6n**).* The title compound was prepared on a 4.64 mmol scale and obtained in 80% yield (1.40 g) as a white solid after column chromatography (PE/EA = 12:1). $[\alpha]_D^{23}$ −129.2 ($CHCl_3$, c = 1.35); M.p. 174−176 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 6.85 (s, 2H), 4.12 (d, J = 17.7 Hz, 1H), 4.03 (d, J = 17.7 Hz, 1H), 3.92 (dd, J = 7.6, 5.0 Hz, 1H), 3.56 (d, J = 13.8 Hz, 1H), 3.49 (d, J = 13.8 Hz, 1H), 2.25 (s, 3H), 2.22 (s, 6H), 2.17−2.07 (m, 1H), 2.02 (dd, J = 14.0, 7.8 Hz, 1H), 1.98−1.82 (m, 3H), 1.47−1.30 (m, 2H), 1.22 (s, 3H), 1.00 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 169.7, 137.1, 136.8, 128.9, 128.3, 65.6, 53.2, 48.8, 48.0, 44.8, 38.7, 36.0, 33.0, 26.6, 21.1, 21.0, 20.3, 20.0; FT-IR: ν (cm^{-1}) 3008, 2959, 2912, 1707, 1615, 1578, 1464, 1373, 1220, 1112, 1062, 986, 820; HRMS-DART: calcd. for $C_{21}H_{30}NO_3S$ $[M + H]^+$: 376.1941, found: 376.1936.

*1-((3aS,6R,7aR)-8,8-Dimethyl-2,2-dioxidohexahydro-1H-3a,6-methanobenzo[c]isothiazol-1-yl)-2-(thiophen-3-yl)ethanone (**6o**).* The title compound was prepared on a 4.64 mmol scale and obtained in 84% yield (1.32 g) as a pale yellow oil after column chromatography (PE/EA = 15:1). $[\alpha]_D^{25}$ −113.2 ($CHCl_3$, c = 1.11); ^{1}H NMR (400 MHz, $CDCl_3$) 7.27 (dd, J = 4.9, 3.2 Hz, 1H), 7.21−7.18 (m, 1H), 7.06 (dd, J = 4.9, 1.2 Hz, 1H), 4.11 (d, J = 16.2 Hz, 1H), 4.01 (d, J = 16.2 Hz, 1H), 3.89 (dd, J = 7.2, 5.5 Hz, 1H), 3.53 (d, J = 13.8 Hz, 1H), 3.46 (d, J = 13.8 Hz, 1H), 2.11−1.98 (m, 2H), 1.96−1.81 (m, 3H), 1.46−1.28 (m, 2H), 1.11 (s, 3H), 0.96 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 169.4, 132.8, 128.9, 125.6, 123.7, 65.5, 53.1, 48.6, 47.9, 44.7, 38.5, 36.8, 33.0, 26.6, 20.9, 20.0; FT-IR: ν (cm^{-1}) 3109, 2959, 2894, 1697, 1453, 1329, 1217, 1132, 1063, 988, 772; HRMS-DART: calcd. for $C_{16}H_{22}NO_3S_2$ $[M + H]^+$: 340.1036, found: 340.1030.

*1-((3aS,6R,7aR)-8,8-Dimethyl-2,2-dioxidohexahydro-1H-3a,6-methanobenzo[c]isothiazol-1-yl)pent-4-en-1-one (**6q**).*[15c] The title compound was prepared on a 9.29 mmol scale and obtained in 57% yield (1.64 g) as a white solid after column chromatography (PE/EA = 15:1). $[\alpha]_D^{22}$ −98.1 ($CHCl_3$, c = 1.03); M.p. 72−74 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 5.90−5.80 (m, 1H), 5.13−4.95 (m, 2H), 3.87 (dd, J = 7.3, 5.3 Hz, 1H), 3.49 (d, J = 13.8 Hz, 1H), 3.43 (d, J = 13.8 Hz, 1H), 2.92−2.74 (m, 2H), 2.43 (dd, J = 13.8, 7.3 Hz, 2H), 2.16−2.02 (m, 2H), 1.97−1.82 (m, 3H), 1.45−1.28 (m, 2H), 1.16 (s, 3H), 0.97 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 171.3, 136.6, 115.8, 65.4, 53.1, 48.6, 47.9, 44.8, 38.6, 34.7, 33.0, 28.5, 26.6, 21.0, 20.0; FT-IR: ν (cm^{-1}) 3010, 2959, 2876, 1691, 1644, 1457, 1361, 1165, 924, 776; HRMS-DART: calcd. for $C_{15}H_{24}O_3NS$ $[M + H]^+$: 298.1471, found: 298.1468.

*1-((3aS,6R,7aR)-8,8-Dimethyl-2,2-dioxidohexahydro-1H-3a,6-methanobenzo[c]isothiazol-1-yl)-3,3-dimethylbutan-1-one (**6w**).* The title compound was prepared on a 4.64 mmol scale and obtained in 80% yield (1.17 g) as a white solid after column chromatography (PE/EA = 12:1). $[\alpha]_D^{24}$ −67.5 ($CHCl_3$, c = 1.28); M.p. 64−66 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 3.83 (t, J = 6.3 Hz, 1H), 3.46 (d, J = 13.8 Hz, 1H), 3.39 (d, J = 13.8 Hz, 1H), 2.70 (d, J = 14.9 Hz, 1H), 2.36 (d, J = 14.9 Hz, 1H), 2.07−1.95 (m, 2H), 1.92−1.76 (m, 3H), 1.41−1.29 (m, 2H), 1.11 (s, 3H), 1.01 (s, 9H), 0.92 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 171.2, 65.5, 53.4, 48.1, 47.9, 47.8, 44.9, 39.0, 33.1, 32.0, 29.8, 26.7, 21.0, 20.1; FT-IR: ν (cm^{-1}) 2990, 2953, 1688, 1465, 1340, 1130, 1034, 986, 871, 768; HRMS-DART: calcd. for $C_{16}H_{28}NO_3S$ $[M + H]^+$: 314.1784, found: 314.1780.

*2-Cyclohexyl-1-((3aS,6R,7aR)-8,8-dimethyl-2,2-dioxidohexahydro-1H-3a,6-methanobenzo[c]isothiazol-1-yl)ethanone (**6x**).* The title compound was prepared on a 4.64 mmol scale and obtained in 82% yield (1.29 g) as a white solid after column chromatography (PE/EA = 15:1). $[\alpha]_D^{24}$ −79.7 ($CHCl_3$, c = 1.08); M.p. 78−80 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 3.83 (t, J = 6.3 Hz, 1H), 3.46 (d, J = 13.8 Hz, 1H), 3.39 (d, J = 13.8 Hz, 1H), 2.60 (dd, J = 15.7, 7.2 Hz, 1H), 2.45 (dd, J = 15.7, 6.7 Hz, 1H), 2.09−1.97 (m, 2H), 1.94−1.77 (m, 4H), 1.73−1.53 (m, 5H), 1.42−1.27 (m, 2H), 1.27−1.15 (m, 2H), 1.15−1.06 (m, 4H), 1.04−0.94 (m, 2H), 0.92 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 171.7, 65.4, 53.2, 48.4, 47.9, 44.8, 43.1, 38.8, 34.9, 33.1, 33.0, 32.9, 27.2, 26.6, 26.3, 26.2, 21.0, 20.0; FT-IR: ν (cm^{-1}) 2925, 2853, 1685, 1483, 1392, 1358, 1221, 1037, 938, 771; HRMS-DART: calcd. for $C_{18}H_{30}NO_3S$ $[M + H]^+$: 340.1941, found: 340.1937.

*Preparation of Sultams **6s−u**. 5-(Benzyloxy)-1-((3aS,6R,7aR)-8,8-dimethyl-2,2-dioxidohexahydro-1H-3a,6-methanobenzo[c]-isothiazol-1-yl)pentan-1-one (**6s**).* To a solution of freshly distilled δ-valeralactone (2.10 g, 22.6 mmol) and benzyl bromide (5.0 mL, 42.1 mmol) dissolved in toluene (21.0 mL) was added solid potassium hydroxide (4.78 g, 85.2 mmol). The solution was stirred at reflux for 24 h. Once at 23 °C, water (20 mL) and diethyl ether (20 mL) were added and the layers separated. The organic layer was washed with aqueous sodium hydroxide (1.0 M, 3 × 20 mL). The combined aqueous layers were acidified by dropwise addition of 6.0 M HCl (pH ∼ 2). The aqueous layer was extracted with diethyl ether (3 × 20 mL). The combined organic layers were washed with brine, dried over magnesium sulfate, filtered through sodium sulfate, and concentrated in vacuo. The resulting white solid was submitted to the next reaction without further purification.

Oxalyl chloride (3.9 mL, 45.2 mmol) was added to a solution of the crude carboxylic acid and dimethylformamide (25.0 μL) in dichloromethane (8 mL) at 0 °C. After 10 min, the solution was warmed to 23 °C and stirred an additional 1.5 h (until all bubbling had stopped). The solution was concentrated in vacuo. In a second flask, n-butyllithium (6.7 mL, 16.0 mmol, 2.4 M in hexanes) was added to a solution of (2S)-bornane-10,2-sultam (3.2 g, 14.9 mmol) in THF (30.0 mL) at −78 °C under argon. The solution was stirred for 30 min at −78 °C. A solution of the crude acyl chloride in THF (9.0 mL total with rinses) was added dropwise at −78 °C. After stirring at −78 °C for 2 h, the reaction mixture was quenched with saturated ammonium chloride. The aqueous layer was extracted with ethyl acetate (3 × 15 mL). The combined organic layers were washed with brine, dried with sodium sulfate, and concentrated in vacuo. The resultant oil was purified by column chromatography (silica gel, PE:EA = 3:1) to afford compound **6s** as a colorless oil (1.8 g, 4.4 mmol, 27% yield). $[\alpha]_D^{27}$ −65.4 ($CHCl_3$, c = 1.05); ^{1}H NMR (400 MHz, $CDCl_3$) 7.39−7.20 (m, 5H), 4.49 (s, 2H), 3.86 (dd, J = 7.2, 5.4 Hz, 1H), 3.52−3.38 (m, 4H), 2.83−2.65 (m, 2H), 2.14−2.03 (m, 2H), 1.96−1.83 (m, 3H), 1.83−1.72 (m, 2H), 1.73−1.68 (m, 2H), 1.44−1.29 (m, 2H), 1.15 (s, 3H), 0.96 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 171.9, 138.7, 128.5, 127.8, 127.6, 73.0, 70.0, 65.4, 53.1, 48.5, 47.9, 44.8, 38.7, 35.3, 33.0, 29.1, 26.6, 21.3, 21.0, 20.0; FT-IR: ν (cm^{-1}) 2958, 2878, 1697, 1454, 1330, 1213, 1165, 1134, 1058, 772; HRMS-DART: calcd. for $C_{22}H_{32}NO_4S$ $[M + H]^+$: 406.2047, found: 406.2041.

*5-((tert-Butyldiphenylsilyl)oxy)-1-((3aS,6R,7aR)-8,8-dimethyl-2,2-dioxidohexahydro-1H-3a,6-methanobenzo[c]isothiazol-1-yl)-pentan-1-one (**6t**).* **6s** (1.3 g, 3.2 mmol) was dissolved in MeOH (15 mL) in the presence of 10% Pd/C (131 mg). The suspension was stirred under a hydrogen atmosphere until the uptake of hydrogen ceased (approximately 12 h). After filtration through Celite, followed by removal of the solvent in vacuo, the resultant oil was purified by short column chromatography (silica gel, PE:EA = 2:1) to afford the free alcohol compound as a pale yellow oil (674 mg, 2.1 mmol, 66% yield).

A solution of the above alcohol compound (150.0 mg, 0.5 mmol), imidazole (72.0 mg, 1.1 mmol), and TBDPSCl (140.0 μL, 0.5 mmol) in dichloromethane (1.5 mL) was stirred at room temperature for 16

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h. The reaction mixture was diluted with EtOAc (10 mL) and water (5 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with water (2 × 10 mL) and brine (10 mL), and then dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (PE:EA = 10:1) to provide **6t** (236 mg, 89%) as a colorless oil. $[\alpha]_D^{26}$ −53.1 ($CHCl_3$, c = 0.85); ^{1}H NMR (400 MHz, $CDCl_3$) 7.71−7.64 (m, 4H), 7.46−7.33 (m, 6H), 3.87 (dd, J = 7.2, 5.4 Hz, 1H), 3.67 (t, J = 6.2 Hz, 2H), 3.50 (d, J = 13.8 Hz, 1H), 3.43 (d, J = 13.8 Hz, 1H), 2.84−2.64 (m, 2H), 2.18−2.02 (m, 2H), 1.98−1.84 (m, 3H), 1.84−1.73 (m, 2H), 1.71−1.55 (m, 2H), 1.47−1.28 (m, 2H), 1.16 (s, 3H), 1.05 (s, 9H), 0.97 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 172.0, 135.7, 134.1, 129.6, 127.7, 65.4, 63.6, 53.1, 48.5, 47.9, 44.8, 38.7, 35.4, 33.0, 32.0, 27.0, 26.6, 21.1, 21.0, 20.0, 19.3; FT-IR: ν (cm^{-1}) 3079, 2957, 2857, 1697, 1461, 1427, 1332, 1058, 703; HRMS-ESI: calcd. for $C_{31}H_{43}NNaO_4SSi$ $[M + Na]^+$: 576.2574, found: 576.2581.

*1-((3aS,6R,7aR)-8,8-Dimethyl-2,2-dioxidohexahydro-1H-3a,6-methanobenzo[c]isothiazol-1-yl)-5-(methoxymethoxy)pentan-1-one (**6u**).* To a stirred solution of the above alcohol (250 mg, 0.8 mmol) in dry dichloromethane (3 mL) at 0 °C were added DIPEA (0.3 mL, 1.4 mmol) and MOMCl (0.1 mL, 1.4 mmol). The mixture was stirred for 12 h at 40 °C and then diluted with 1 M $NaHCO_3$ (aq.). The mixture was extracted with CH_2Cl_2 (3 × 50 mL), and the combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The crude product was purified by flash column chromatography on silica gel (PE:EA = 10:1) to furnish MOM ether **6u** as a colorless oil (220 mg, 77% yield). $[\alpha]_D^{27}$ −67.6 ($CHCl_3$, c = 0.88); ^{1}H NMR (400 MHz, $CDCl_3$) 4.60 (s, 2H), 3.86 (dd, J = 7.4, 5.3 Hz, 1H), 3.52 (t, J = 6.4 Hz, 2H), 3.47 (d, J = 13.8 Hz, 1H), 3.42 (d, J = 13.8 Hz, 1H), 3.34 (s, 3H), 2.83−2.66 (m, 2H), 2.15−2.00 (m, 2H), 1.96−1.82 (m, 3H), 1.82−1.70 (m, 2H), 1.69−1.63 (m, 2H), 1.45−1.28 (m, 2H), 1.14 (s, 3H), 0.96 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 171.8, 96.5, 67.4, 65.3, 55.3, 53.1, 48.5, 47.9, 44.8, 38.7, 35.2, 33.0, 29.1, 26.6, 21.3, 21.0, 20.0; FT-IR: ν (cm^{-1}) 2955, 2883, 1696, 1460, 1330, 1215, 1134, 1041, 917, 776; HRMS-ESI: calcd. for $C_{17}H_{29}NNaO_5S$ $[M + Na]^+$: 382.1659, found: 382.1672.

Synthesis of (*S*)-hydroxy product **7a**. A mixture of (*R*)-**7a** (100 mg, 0.3 mmol) and Dess−Martin periodinane (175 mg, 0.45 mmol) in CH_2Cl_2 (1.5 mL) was stirred for 2 h at room temperature. The reaction was stopped by addition of $NaHCO_3$ (aq.) (5 mL). The organic phase was separated, and the aqueous phase was extracted with diethyl ether (3 × 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography using PE−EA mixtures as the eluent to afford the desired product (53.5 mg, 54% yield). To a solution of the above product (39 mg, 0.107 mmol) in MeOH (1 mL) was added $NaBH_4$ (6 mg, 0.161 mmol). The mixture was stirred at room temperature for 30 min, 1.0 N aqueous HCl solution was added, and the mixture was extracted with EtOAc for three times. The organic phase was dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by flash chromatography using PE−EA mixtures as the eluent to afford compound (*S*)-**7a** as a white solid (12.6 mg, 41% yield; (*S*):(*R*) = 5:1). $[\alpha]_D^{25}$ −59.9 ($CHCl_3$, c = 0.50); M.p. 154−156 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 7.29 (m, 4H), 7.25−7.20 (m, 1H), 4.98 (td, J = 8.0, 4.0 Hz, 1H), 3.92 (m, 1H), 3.53 (d, J = 13.8 Hz, 1H), 3.47 (d, J = 13.8 Hz, 1H), 3.26 (dd, J = 13.6, 4.0 Hz, 1H), 2.94 (d, J = 7.7 Hz, 1H), 2.82 (dd, J = 13.6, 8.3 Hz, 1H), 2.08 (dd, J = 13.8, 7.8 Hz, 1H), 2.03−1.84 (m, 4H), 1.48−1.31 (m, 2H), 1.12 (s, 3H), 0.99 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 174.2, 136.6, 129.8, 128.5, 127.0, 72.2, 65.2, 53.1, 49.1, 48.0, 44.7, 42.0, 38.2, 32.9, 26.6, 20.9, 20.0; FT-IR: ν (cm^{-1}) 3498, 2959, 2881, 1685, 1496, 1455, 1328, 1134, 1083, 802, 700; HRMS-DART: calcd. for $C_{19}H_{26}NO_4S$ $[M + H]^+$: 364.1577, found: 364.1575.

Synthesis of *rac*-**10** for the determination of the enantiomeric excess of (+)-**10** derived from α-hydroxylation of amide **6c**: To a solution of (+)-**10** (100 mg, 0.417 mmol) in CH_2Cl_2 (8 mL) were successively added $NaHCO_3$ (solid) (175 mg, 2.08 mmol) and Dess−Martin periodinane (185 mg, 0.437 mmol) at 0 °C. The suspended mixture was stirred at 0 °C for 4 h and quenched with saturated $NaHCO_3$ (aq., 1 mL) and saturated $Na_2S_2O_3$ (aq., 1 mL). The aqueous phase was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was subjected to purification on short silica gel chromatography (PE/EtOAc: 4/1) to provide the unstable oxidized product as a pale yellow solid (74.2 mg, 75% yield). To a solution of the above product (27.6 mg, 0.116 mmol) in MeOH (1.5 mL) was added $NaBH_4$ (4.4 mg, 0.116 mmol) at 0 °C, and the mixture was stirred for 1 h. The reaction was quenched with water and concentrated under reduced pressure. To the obtained residue was added ethyl acetate/water (5 mL/5 mL), and the aqueous phase was extracted with ethyl acetate (3 × 5 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was subjected to purification on silica gel chromatography (PE/EtOAc: 3/1) to provide the product (*rac*-**10**) as a white solid (19.1 mg, 69% yield).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00068.

Full experimental details and analytical data including NMR spectra and X-ray of compounds **7b** and **7i** (PDF)
Crystallographic data for **7b** (CCDC 1426692) (CIF)
Crystallographic data for **7i** (CCDC 1426693) (CIF)

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Notes

The authors declare no competing financial interest.

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