Synthesis of Chiral Benzosultams: 3-Functionalized 1,2-Benzisothiazoline 1,1-Dioxides

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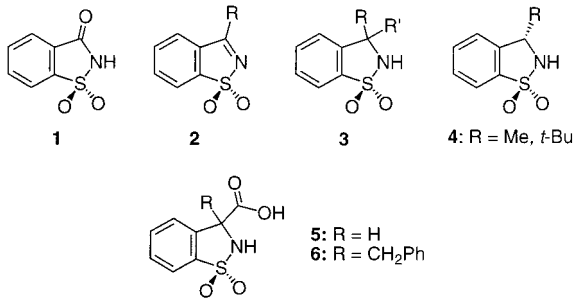
Introduction

1,2-Benzisothiazoline-3-one 1,1-dioxide (**1**), known as saccharin, has been frequently used as a key component of biologically active compounds.[1] Also, it is a cheap and versatile starting material for the synthesis of related heterocyclic derivatives. Among those derivatives, 3-substituted ones are readily accessible through direct nucleophilic additions to the carbonyl carbon using strong nucleophiles such as alkyl- and aryllithium reagents or corresponding Grignard reagents.[2] The substitution reactions proceed at monoaddition or diaddition stage depending on the reagents and reaction conditions. The monoaddition reactions lead to 3-substituted saccharins **2**, while the diadditions provide benzosultam analogues **3**.[3] Recently, we have devised an efficient and practical synthetic route to various enantiomeric 3-substituted benzosultams such as **4** starting from saccharin via the nucleophilic addition and subsequent catalytic reduction steps.[4] As a continuing study on the synthesis and application of chiral benzosultam derivatives, we have been interested in chiral 3-carboxy-substituted benzosultams.[5] Although the direct nucleophilic addition approaches are useful for the synthesis of 3-alkyl- or 3-aryl-substituted derivatives, we were unsuccessful in introducing directly a functional moiety such as cyano group.[6] To synthesize 3-functionalized saccharin derivatives, particularly 3-carboxy analogues **5** and **6**, we have studied two indirect approaches, an asymmetric approach and a racemic synthesis followed by chemical resolution approach. Herein, we report the synthetic results which provide some useful chemistry on the C-3 functionalization of saccharin and 3-carboxybenzosultams.



Results and Discussion

An Asymmetric Approach to 3-Carboxysultam 5 and Its Derivatives. The asymmetric route to sultam **5** was studied using an inexpensive starting material, sodium *o*-formylbenzenesulfonate (**7**). The results are depicted in Scheme 1. The key steps are the Sharpless asymmetric epoxidation[7] of *o*-(aminosulfonyl)-*trans*-cinnamyl alcohol (**10**) and a subsequent intramolecular epoxide opening by the sulfonamide group. An aqueous Wittig−Horner−Emmons reaction[8] of aldehyde **7** with triethyl phosphonoacetate readily afforded cinnamate **8**. After the azeotropic removal of water, **8** was directly converted to sulfonamide **9** in overall 45% yield by treatment with thionyl chloride followed by an aqueous ammonium hydroxide solution.[9] Reduction of the ester group of **9** was done with excess DIBALH, affording allylic alcohol **10** in 86% yield. Asymmetric epoxidation of allylic alcohol **10** was then carried out according to the Sharpless protocol.[7] Employing (+)-diisopropyl tartrate, *tert*-butyl hydroperoxide, titanium isopropoxide, and 4 Å activated molecular sieve at −15 to −20 °C, we were able to obtain the corresponding epoxy-alcohol **11** in 90% yield. Enantiopurity of the epoxide was determined to be 91%

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(6) Attempt at the preparation of 3-cyano-1,2-benzisothiazole 1,1-dioxide from 3-chloro-1,2-benzisothiazole 1,1-dioxide under various conditions was not successful.

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(9) During the drying stage of **8** with methanol by a rotary evaporator, transesterification was occurred to give the methyl ester.

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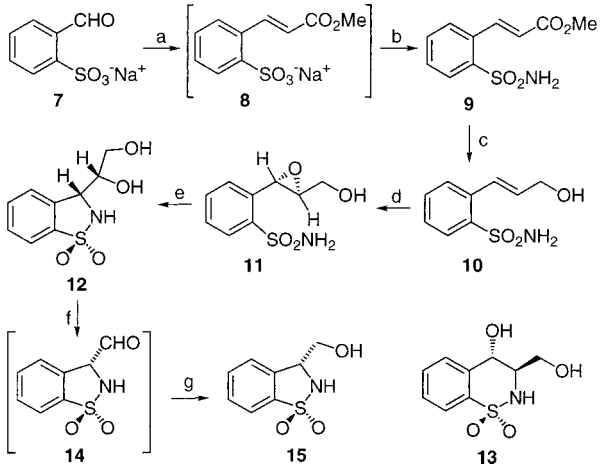
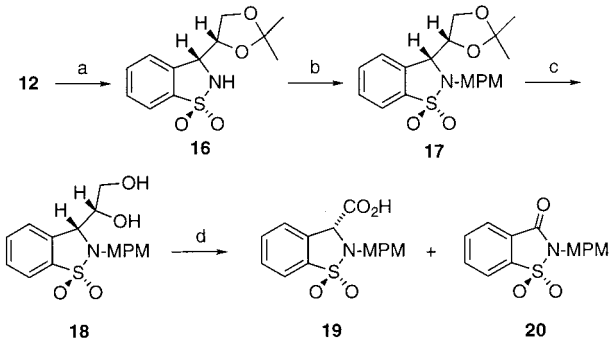
Scheme 1[a]



[a] Reagents and conditions: (a) $(EtO)_2P(O)CH_2CO_2Et$, aq K_2CO_3, 25 °C; (b) DMF, $SOCl_2$, reflux; aq NH_4OH, 0 °C; (c) DIBAL, THF, −78 °C; (d) ^tBuOOH, $Ti(O^iPr)_4$, (+)-DIPT, 4 Å molecular sieve, −10 °C; (e) $Ti(O^iPr)_4$, Et_3N, CH_2Cl_2, rt; (f) $NaIO_4$, aq MeOH, 0 °C; (g) $NaBH_4$, 0 °C.

ee by ^{19}F NMR analysis of its Mosher ester.[10] Thus, the presence of the sufonamide substituent in allylic alcohol **10** resulted in a slight decrease in the chiral induction of the epoxidation, compared to the case of cinnamyl alcohol.[7] The next key step, an intramolecular epoxide opening reaction of epoxy-alcohol **11**, was studied under several reaction conditions. The selectivity between the 5-*exo*-type opening (leading to diol **12**) and the 6-*endo*-type opening (leading to diol **13**) was ~1:1 when K_2CO_3 in DMF was used as the base system. The regioselectivity was increased to 3.5:1 when the base system was changed to 5 mol % NaOMe in MeOH.[11] The observed 6-*endo*-type opening might be caused by a ring strain, which would develop at the transition state of the 5-*exo*-type opening due to the benzene ring.[12] A complete regioselectivity was achieved by using the $Ti(O^iPr)_4-Et_3N$ system.[13] Under these conditions, the desired diol **12** was obtained in 83% yield, together with 12% yield of a side product after column chromatography. The enantiopurity of this diol **12** was determined to be 96% ee by ^{19}F NMR analysis of its Mosher ester, which excludes a possibility of epimerization during the ring opening. The side product was identified to be the C-3-opened diol by the isopropyloxy ion that must be transferred from the titanium reagent. The final step, oxidative conversion of the diol functionality in **12** to the carboxy group, was found to be difficult due to the instability of the reaction intermediate. Treatment of diol **12** with sodium periodate produced the corresponding aldehyde, and subsequent in situ oxidation with potassium permaganate[14] produced decomposed products instead of the desired 3-carboxysultam **5**. When

Scheme 2[a]



[a] Reagents and conditions: (a) $(CH_3)_2C(OCH_3)_2$, PPTS cat, CH_3CN, 25 °C; (b) MPMCl, NaH, DMF, 0 °C; (c) 2 N HCl, THF, 25 °C; (d) $NaIO_4$, $RuCl_3(H_2O)$, $CCl_4-CH_3CN-H_2O$, 25 °C.

diol **12** was treated with sodium periodate followed by sodium borohydride, alcohol **15** was obtained in 96% yield. However, all attempts to oxidize alcohol **15** to 3-carboxysultam **5** with PDC, $KMnO_4$, or Ru(IV) reagents[15] did not give an appreciable amount of the desired product but instead produced decomposed compounds. During the preparation of alcohol **15** from diol **12**, we could observe an intermediate on TLC, which was believed to be **14**. However, the intermediate decomposed during the subsequent oxidation stage. When *N*-protected diol **18**, prepared from **12** in three steps, was subjected to the $RuCl_3-NaIO_4$ oxidation, the major product was not the desired carboxylic acid **19** (27%) but saccharine derivative **20** (50%) (Scheme 2). These results indicate that 3-formylsultam **14** and its *N*-protected derivatives have limited stability and may undergo deformylation under the oxidation conditions. Because we were not successful in converting diol **12** or alcohol **15** into the corresponding carboxylic acid, we turned our attention to a racemic route.

Racemic Routes to 3-Substituted Benzosultams 5 and 6. The introduction of a carboxy group at the 3-position of saccharin was carried out according to Scheme 3. The *p*-methoxyphenylmethyl (MPM) group was chosen as a protecting group for the sulfonamide of saccharin, because it can be deprotected under mild conditions. *N*-Protected saccharin **20** was treated with DIBALH to give semi aminal **21** in 88% yield. Conversion of the hydroxy group of **21** to the cyano group of **22** was cleanly done with TMSCN in the presence of $BF_3 \cdot OEt_2$ in 92% yield. Nitrile **22** was hydrolyzed to the corresponding methyl ester **23** in a methanolic hydrogen chloride solution in a quantitative yield. Deprotection of the MPM group of **23** with ceric ammonium nitrate (CAN) gave sultam **24** in 95% yield. Finally, hydrolysis of the ester group of **24** with LiOH in THF-water produced racemic 3-carboxysultam **5** in 80% yield. This racemic route from saccharin to 3-carboxysultam **5** involves six steps with an overall yield of 55%.

Similarly, we have studied the synthesis of (±)-3-benzyl-3-carboxysultam **6**, starting from ester **23**. The results of the synthesis are depicted in Scheme 4. Treatment of ester **23** with NaH in DMF followed by benzyl bromide gave 3-benzylated sultam **25** in 96% yield. Deprotection of the MPM group of **25** with CAN produced ester **26** in 95% yield. Finally, hydrolysis of the ester

(10) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

(11) The selectivity was determined by the analysis of ^1H NMR spectrum of the crude products. Because two products (**12** and **13**) were not easily separable by column chromatography, the mixture was treated in situ with sodium periodate to give chromatographically separable aldehyde **14** and unreacted **13**.

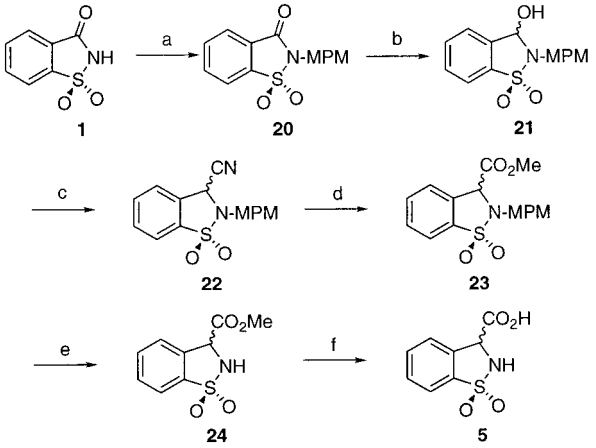
(12) It was originally suggested by Baldwin that the 5-exo-type opening of an unrestricted epoxide would be more favorable than the 6-endo-type opening, see: Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734.

(13) Caron, M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 1557.

(14) Abiko, A.; Roberts, J. C.; Takemasa, T.; Masamune, S. *Tetrahedron Lett.* **1986**, *27*, 4537.

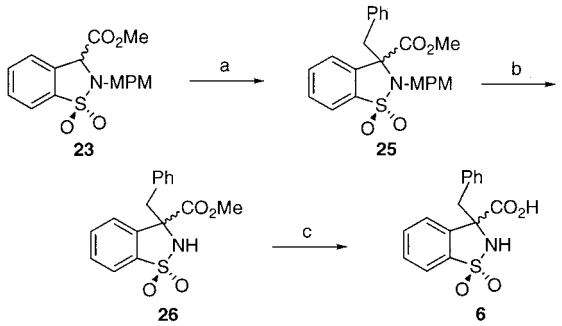
(15) Carlsen, P. H. J.; Katsuki, T.; Martin, V. C.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936.

Scheme 3[a]



[a] Reagents and conditions: (a) MPMCl, NaH, DMF, 110 °C, 5 h, 89%; (b) DlBALH, CH_2Cl_2, −78 °C, 1 h, 88%; (c) TMSCN, $BF_3{\cdot}OEt_2$, CH_2Cl_2, −78 °C, 1 h, 92%; (d) HCl-MeOH, 1,4-dioxane, 25 °C, 3 d, 100%; (e) CAN, CH_3CN-H_2O (3:1), 25 °C, 1 h, 95%; (f) LiOH, THF−H_2O (1:1), 25 °C, 10 min, 80%.

Scheme 4[a]



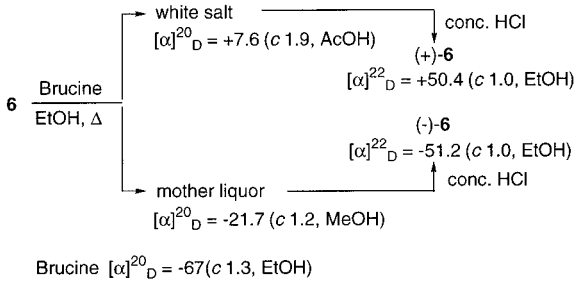
[a] Reagents and conditions: (a) BnBr, NaH, DMF, 0 °C, 2 h, 96%; (b) CAN, CH_3CN-H_2O (3:1), 25 °C, 2 h, 95%; (c) LiOH, THF−H_2O (1:1), 25 °C, 20 min, 96%.

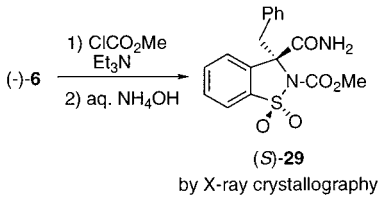
group of **26** produced the desired sultam **6** in 96% yield. Overall, our synthesis of racemic sultam **6** from saccharin involves seven steps with an overall yield of 63%.

With racemic 3-carboxysultams **5** and **6** at hand, we studied their chemical resolution. We have found that 3-benzyl-3-carboxysultam **6** can be efficiently resolved with a readily available resolving agent (−)-brucine, as described in Scheme 5. Two diastereomeric salts were separated into a white salt and an ethanol solution. The sultams regenerated from both the white salt and the ethanol solution, when treated with concentrated HCl, exhibited almost the same specific rotation but of opposite sign.

In contrast to the successful resolution of benzyl-substituted carboxylic acid **6**, we were unable to resolve 3-carboxysultam **5** using (−)-brucine or (−)-α-methylbenzylamine as the resolving agent. Therefore, we studied a derivatization approach, as depicted in Scheme 6. 3-Carboxysultam **19**, prepared from ester **23** in 77% yield by hydrolysis with aqueous LiOH, was coupled with (*S*)-(−)-α-methylbenzylamine by a mixed anhydride method to give a 1:1 mixture of diastereomeric amide **27** in 90% yield. The two diastereomers of amide **27** were not separable on SiO_2. However, after deprotecting the MPM group, we could readily separate both diastereomeric (+)-**28** and (−)-**28** by SiO_2 column chromatography.

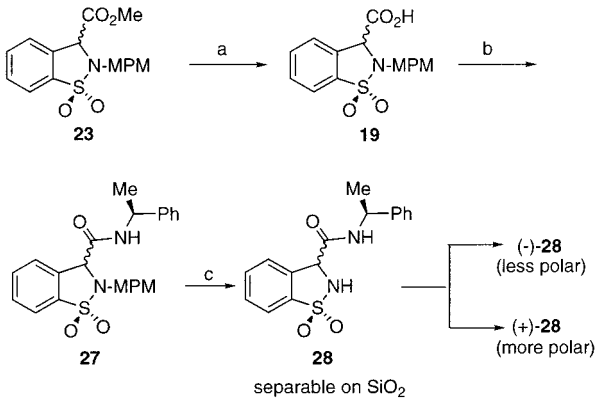
Scheme 5





(*S*)-**29**
by X-ray crystallography

Scheme 6[a]



[a] Reagents and conditions: (a) LiOH, THF-H_2O (1:1), 25 °C, 77%; (b) *i*-BuOCOCl, 4-methylmorpholine, (*S*)-(−)-α-methylbenzylamine, CH_2Cl_2, −10 → 25 °C, 5 h, 90% (c) CAN, CH_3CN-H_2O (3:1), 25 °C, 1 h, 80%.

X-ray Crystallographic Studies on the Benzosultams. To confirm the absolute stereochemistry of product **12**, we made an effort and could get the single crystals suitable for X-ray crystallography in the case of its derivative **16**. The crystal structure of **16** confirms the absolute stereochemistries of diol **12** as (*R*,*R*),[16] which is also inferred from the chiral induction mechanism of the Sharpless epoxidation process.[17] In the case of 3-benzyl-substituted carboxylic acid **6**, we could not get crystals suitable for X-ray crystallography. However, finally we succeeded in obtaining single crystals from its amide derivative (−)-**29**, which was prepared by treatment with ethyl chloroformate followed by an ammonium hydroxide solution. The X-ray crystallography of (−)-**29** provided its absolute stereochemistry as (*S*).[16] In the case of amides (−)-**28** and (+)-**28**, we have not succeeded in getting suitable single crystals, and their absolute stereochemistries are not known at present.

(16) The authors have deposited atomic coordinates for (*R*,*R*)-**16** (CCDC 149844) and (*S*)-**29** (CCDC 149893) with the Cambridge Crystallographic Data Centre. The coordination can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK; e-mail: deposit@ccdc.cam.ac.uk. For ORTEP plots of (*R*,*R*)-**16** and (*S*)-**29**, see the Supporting Information.

(17) Finn, M. G.; Sharpless, K. B. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1985; Vol. 5, Chapter 8, p 247.

In summary, we have established an asymmetric and racemic routes to 3-functionalized 1,2-benzisothiazoline 1,1-dioxides. Both routes consist of all high-yielding steps amenable to a large scale. Racemic benzosultam **6** has been efficiently resolved with (−)-brucine, while benzosultam **5** can be separated after derivatization to a diastereomeric mixture. Single-crystal X-ray crystallography for benzosultams **16** and **29** established their absolute stereochemistries. The established chemistry throughout the syntheses would be useful for the synthesis of related benzosultam derivatives, which are important heterocyclic compounds in pharmaceutical research and asymmetric synthesis.

Experimental Section

General Procedures. All reagents were commercial products and were used without further purification. All reactions involving air-sensitive agents were conducted under an argon atmosphere. Column chromatography was performed on Merck silica gel 60 (230−400 mesh). Melting points are uncorrected. Elemental and high-resolution mass analyses were performed by Seoul Branch Analytical Laboratory of Korea Basic Science Institute. NMR spectral data are reported as follows: chemical shift in ppm from internal Me_4Si on the delta scale, multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet, dd = doublet of doublet, br s = broad singlet), integration, and coupling constant.

Methyl *o*-Aminosulfonyl-*trans*-cinnamate (9). A solution of 2-formylbenzenesulfonic acid sodium salt dihydrate (**7**, 75% purity, 50.0 g, 180 mmol), K_2CO_3 (49.8 g, 360 mmol), and $(EtO)_2P(O)CH_2COOEt$ (35.7 mL, 180 mmol) in water (120 mL) was stirred at 25 °C for 6 h. MeOH (120 mL) was added to the reaction mixture, and it was further stirred for 30 min. The reaction mixture was filtered through a Büchner funnel to remove precipitates, and the filtrate was concentrated under reduced pressure to remove most of MeOH and water (at this stage, transesterification from ethyl ester to methyl ester occurred), and the remaining solvent was thoroughly dried using a freeze-drying apparatus to give a white solid. To this hygroscopic Wittig−Horner−Emmons reaction product (**8**) was added dropwise $SOCl_2$ (120 mL) at 0 °C using a dropping funnel, followed by DMF (5 mL). The resulting mixture was refluxed at 80 °C for 2 h. (The evolved gas was trapped by an aqueous KOH solution). The heterogeneous mixture was cooled to 25 °C, and excess $SOCl_2$ was distilled off using an aspirator pump. The resulting mixture was diluted with CH_2Cl_2 and was stirred for 30 min, and the precipitates were filtered off. The filtrate was concentrated, redissolved in THF (120 mL), and was treated slowly with an aqueous ammonium hydroxide solution (60 mL) at 0 °C. After being stirred for 10 min, the mixture was first acidified to pH = 7 with concentrated HCl and then to pH = 2 with 2 N aqueous HCl. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate three times. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified first by passing through a short pad of silica gel (eluant: 30% ethyl acetate in hexanes) and then by recrystallizing from ethyl acetate−hexanes to give cinnamate **9** (19.5 g, 45% yield): R_f = 0.63 (ethyl acetate/hexanes = 1/1); mp 138.1−139.2 °C; IR (KBr pellet, cm^{-1}) 3330, 3248, 1697, 1633, 1344, 1205, 1159; ^1H NMR (300 MHz, acetone-d_6) δ 8.48 (d, 1H, J = 15.7 Hz), 8.00 (d, 1H, J = 6.4 Hz), 7.7 (d, 1H, J = 7.2 Hz), 7.58−7.43 (m, 2H), 6.35 (d, 1H, J = 15.7 Hz), 3.72 (s, 3H), 6.43 and 2.73 (br s and s, 2H, $-SO_2NH_2$); ^{13}C NMR (75 MHz, acetone-d_6) δ 166.5, 142.0, 141.4, 133.4, 132.6, 128.8, 128.6, 128.2, 122.2, 51.6; MS (EI) m/z (rel intensity) 241 (M^+, 12).

***o*-Aminosulfonyl-*trans*-cinnamyl Alcohol (10).** To a solution of ester **9** (9.3 g, 38.6 mmol) in THF (130 mL) at −78 °C was added dropwise neat DIBALH (31 mL, 174 mmol) under an argon atmosphere, and the reaction mixture was stirred for 1 h. The reaction was carefully quenched with an aqueous sodium potassium tartrate solution (30%, 150 mL), and the resulting mixture was vigorously stirred at 25 °C overnight. The mixture was extracted with ethyl acetate, dried over $MgSO_4$, concentrated under reduced pressure. The residue was purified by recrystallization from CH_2Cl_2 to afford the allylic alcohol **10** as a white solid (6.8 g, 86%). **10**: R_f = 0.42 (ethyl acetate/hexanes = 4/1); mp 125.3−126.1 °C; IR (KBr pellet, cm^{-1}) 3344, 3243, 2862, 1531, 1466, 1301, 1153, 1122; ^1H NMR (300 MHz, acetone-d_6) δ 7.92 (d, 1H, J = 7.9 Hz), 7.58 (d, 1H, J = 7.9 Hz), 7.49−7.38 (m, 2H), 7.30 (t, 1H, J = 6.6 Hz), 6.37−6.28 (m, 1H), 4.26 (dd, 2H, J = 1.8, 5.0 Hz), 6.18 and 3.14 (each br s, 3H, SO_2NH_2 and OH); ^{13}C NMR (75 MHz, acetone-d_6) δ 140.7, 136.3, 135.3, 132.4, 128.2, 127.7, 127.3, 126.2, 62.8; MS (EI) m/z (rel intensity) 213 (M^+, 22); Anal. Calcd for $C_9H_{11}NO_4S$: C, 50.69; H, 5.20; N, 6.57. Found: C, 50.45; H, 5.25; N, 6.41.

(1*S*,2*S*)-*o*-(3-Hydroxy-1,2-epoxypropan-1-yl)benzenesulfonamide (11). An oven-dried flask was charged with 1.5 g of 4 Å powdered, activated molecular sieves and 350 mL of dry CH_2Cl_2. After being cooled to −25 °C, to the mixture were added L-(+)-diisopropyl tartrate (0.408 mL, 2.1 mmol) and $Ti(O\text{-}i\text{-}Pr)_4$ (0.524 mL, 1.76 mmol) sequentially by a hypodermic syringe with stirring. The reaction mixture was stirred at −25 °C for 10 min, and *t*-BuOOH (77.6 mmol, 13.0 mL, 5,97 M in toluene) was added at a moderate rate (over ca. 3 min). The resulting mixture was stirred at −20 °C for 30 min. The allylic alcohol **10** (7.49 g, 35.1 mmol), dissolved in 18 mL of THF, was then added dropwise over a period of 10 min, being careful to maintain the reaction temperature between −20 to −15 °C. The mixture was stirred for an additional 1 h at −20 °C, and the reaction temperature was slowly raised to −15 °C and stirred for 4 h. When the reaction was complete, to the reaction mixture was added 370 mg (1.76 mmol) of citric acid monohydrate dissolved in 48 mL of 10% acetone in ethyl ether. The cooling bath was removed, and the mixture was stirred for 20 min before filtering through a pad of Celite. The filtrate was concentrated under reduced pressure, and the residue was subjected to column chromatography (eluant: 50% ethyl acetate in hexanes) to give the epoxy alcohol **11** (7.24 g, 90%). The enantiopurity of this compound was determined to be 91% ee by ^1H and ^{19}F NMR analysis of the corresponding Mosher ester prepared with (+)-Mosher's acid chloride. **11**: R_f = 0.45 (ethyl acetate/hexanes = 4/1); mp 125.3−126.1 °C; $[\alpha]^{24}_D$ −69.7 (*c* 1.01, MeOH); IR (KBr pellet, cm^{-1}) 3344, 3259, 1557, 1448, 1329, 1156; ^1H NMR (300 MHz, acetone-d_6) δ 7.96−7.93 (m, 1H), 7.63−7.56 (m, 1H), 7.49−7.44 (m, 2H), 6.79 (br s, 2H), 4.50 (s, 1H), 4.37−4.33 (m, 1H), 3.88−3.83 (m, 1H), 3.76−3.69 (m, 1H), 3.01−2.97 (m, 1H), 2.85−2.83 (m, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 140.7, 134.7, 131.4, 126.7, 126.5, 124.7, 61.3, 61.0, 52.8; MS (FAB) m/z (rel intensity) 252 (MNa^+, 12).

3(*R*)-{1(*R*),2-Dihydroxyethan-1-yl}-1,2-benzisothiazoline 1,1-Dioxide (12). To a suspension of epoxy-alcohol **11** (6.15 g, 26.8 mmol) in dichloromethane (134 mL) was added titanium(IV) isopropoxide (8.8 mL, 29.5 mmol). When the mixture became a solution, triethylamine (4.1 mL, 29.5 mmol) was added dropwise under an argon atmosphere at the same temperature. The reaction temperature was raised to 25 °C and stirred for 1 h. The mixture was cooled to 0 °C and acidified to pH = 2 with 1 M aqueous HCl. After being stirred vigorously for 1 h, the mixture was extracted with ethyl acetate five times, and the extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (ethyl acetate/hexane = 1:1) to give the diol **12** (5.12 g, 83%) as a white solid and the side product (see the text, 947 mg, 12%) as an oil. The enantiopurity of the major product was determined to be 96% ee by ^1H NMR analysis of the corresponding Mosher ester prepared with (+)-Mosher's acid chloride. **12**: R_f = 0.38 (ethyl acetate); mp (CH_2Cl_2−MeOH, 20:1) 130−131 °C; $[\alpha]^{24}_D$ +24.7 (*c* 1.0, MeOH); IR (KBr pellet, cm^{-1}) 3471, 3228, 1619, 1474, 1398, 1280, 1161; ^1H NMR (300 MHz, CD_3OD) δ 7.76−7.55 (m, 4H), 4.76 (s, 3H, OH and NH), 4.65 (d, 1H, J = 6.2 Hz), 3.74−3.64 (m, 3H); ^{13}C NMR (75 MHz, CH_3OH-d_4) δ 140.3, 137.5, 133.7, 130.4, 127.8, 121.6, 75.4, 64.6, 59.8; MS (FAB) m/z (rel intensity) 252 (MNa^+, 22), 230 (M + 1, 48).

4(*S*)-Hydroxy-3(*R*)-hydroxymethyl-3,4-dihydro-2*H*-1,2-benzthiazine 1,1-Dioxide (13). This compound was Isolated as a byproduct during the epoxide opening (**11** → **12**, see the text): mp 201.5−202.5 °C; $[\alpha]^{20}_D$ +20.1 (*c* 1.02, MeOH); IR (KBr pellet, cm^{-1}) 3518, 3218, 2934, 1420, 1342, 1311, 1260, 1171; ^1H NMR (300 MHz, DMSO-d_6) δ 7.71−7.59 and 7.48−7.43 (m, 4H), 5.94 (d, 1H, J = 8.1 Hz, NH), 4.82 (br s, OH), 4.61 (dd, 1H,

J = 9.3, 8.7 Hz), 3.80−3.66 (m, 2H, CH_2), 3.56−3.50 (m, 1H); ^{13}C NMR (75 MHz, acetone-d_6) δ 140.2, 137.7, 132.5, 128.5, 128.2, 123.1, 64.4, 61.0, 60.9; MS (EI) m/z (rel intensity) 229 (M^+, 4), 198 [M^+ − 31(CH_2OH), 27].

3(*R*)-Hydroxymethyl-1,2-benzisothiazoline 1,1-Dioxide (15). To a solution of $NaIO_4$ (1.67 g, 7.8 mmol) in water (12 mL) at 0 °C was added diol **12** (1.49 g, 6.5 mmol) in MeOH (22 mL), and the mixture was stirred for 10 min. To this mixture was added $NaBH_4$ (295 mg, 7.7 mmol), and the resulting solution was stirred for 10 min at 0 °C. The reaction mixture was neutralized with 1 N aqueous HCl and evaporated under reduced pressure, and the residue was subjected to column chromatography (50% ethyl acetate in hexanes) to afford 3-hydroxy-sultam **15** (1.24 g, 96% yield). This product was found to be essentially enantiopure by ^{19}F NMR analysis of the corresponding Mosher ester prepared with (+)-Mosher's acid chloride. **15**: mp 116.5−117.8 °C; $[\alpha]^{24}_D$ +34.5 (*c* 1.1, MeOH); IR (KBr pellet, cm^{-1}) 3506, 3218, 1470, 1390, 1269, 1159, 1130; ^{1}H NMR (300 MHz, acetone-d_6) δ 7.77−7.57 (m, 4H), 6.62 (br s, 1H), 4.78 (dd, 1H, J = 11.2, 5.6 Hz), 4.24 (t, 1H, J = 5.6 Hz), 3.88 (m, 2H); ^{13}C NMR (75 MHz, acetone-d_6) δ 138.3, 137.0, 132.3, 129.0, 125.1, 120.3, 64.1, 58.8; MS (FAB) m/z (rel intensity) 222 (MNa^+, 87), 200 (M + 1, 90).

3(*R*)-{1(*R*),2-*O*-Isopropylidene-1,2-dihydroxyethan-1-yl}-1,2-benzisothiazoline 1,1-Dioxide (16). To a solution of diol **12** (2.02 g, 8.8 mmol) in acetonitrile (44 mL) at 25 °C was added 2,2-dimethoxypropane (2.6 mL, 21 mmol) followed by pyridinium *p*-toluenesulfonate (88 mg, 0.35 mmol). After being stirred at the same temperature for 2 h, the reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography (50% ethyl acetate in hexanes) to give acetonide **16** (2.37 g, 100%): R_f = 0.42 (ethyl acetate/hexanes = 2/3); mp 167.2−168.0 °C; $[\alpha]^{20}_D$ −2.9 (*c* 1.05, $CHCl_3$); IR (NaCl, cm^{-1}) 3278, 2988, 1453, 1378, 1292, 1170, 1088; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, 1H, J = 7.5 Hz), 7.65−7.53 (m, 3H), 5.20 (br s, 1H), 4.73 (dd, 1H, J = 5.6, 6.8 Hz), 4.32 (dd, 1H, J = 6.8, 12.5 Hz), 4.02 (dd, 1H, J = 6.2, 8.9 Hz), 3.91 (dd, 1H, J = 5.0, 9.4 Hz), 1.55 (s, 3H), 1.37 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.6, 136.4, 133.8, 130.5, 126.5, 122.1, 111.1, 78.3, 67.1, 59.3, 27.5, 25.7; MS (EI) m/z (rel intensity) 269 (M^+, 60); Anal. Calcd for $C_{12}H_{15}NO_4S$: C, 53.52; H, 5.61; N, 5.20. Found: C, 53.66; H, 5.74; N, 5.23.

3(*R*)-{1(*R*),2-Dihydroxyethan-1-yl}-2-(4-methoxyphenyl) Methyl-1,2-benzisothiazoline 1,1-Dioxide (18). To a solution of sultam **16** (2.3 g, 8.5 mmol) in DMF (43 mL) at 0 °C was added NaH (372 mg, 9.3 mmol, 60% dispersion in mineral oil) followed by *p*-methoxybenzyl chloride (1.3 mL, 9.3 mmol), and the mixture was stirred for 4 h. The reaction was quenched with a small amount of water, and the mixture was extracted with ethyl acetate. The extracts were washed with water, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. This crude *N*-protected sultam (**17**) was subjected to next step without further purification.

To a solution of **17** in THF (14 mL) was added 2 N HCl (14 mL), and the resulting solution was stirred at 25 °C for 12 h. Most of THF was evaporated under reduced pressure, and the residue was extracted with ethyl acetate. The extracts were washed with brine, dried over $MgSO_4$, and filtered. The residue was purified by column chromatography (50% ethyl acetate in hexanes) to give diol **18** (2.73 g, overall 92%). R_f = 0.5 (ethyl acetate/hexanes = 4/1); $[\alpha]^{24}_D$ +82.7 (*c* 1.0, $CHCl_3$); IR (Nalco, cm^{-1}) 3453, 2926, 1611, 1586, 1512, 1457, 1272, 1171, 1044; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78−7.75 (m, 1H), 7.57−7.47 (m, 2H), 7.36−7.26 (m, 3H), 6.86−6.81 (m, 2H), 4,64−4.47 (m, 3H), 3.99 (br s, −OH), 3.75 (s, 3H), 3.60 (dd, 1H, J = 6.2, 11.2 Hz), 3.47 (d (overlapped dd), 1H, J = 11.2 Hz), 3.20 (d, 1H, J = 4.4 Hz), 2.54 (br s, −OH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.1, 136.1, 135.8, 133.3, 130.2, 127.8, 125.9, 121.9, 114.7, 74.4, 62.9, 62.8, 55.9, 49.1; MS (EI) m/z (rel intensity) 349 (M^+, 48).

3(*R*)-Carboxy-2-(4-methoxyphenyl)methyl-1,2-benzisothiazoline 1,1-Dioxide (19). See the experimental of (±)-**19** in Scheme 6 for the physical and spectroscopic data: $[\alpha]^{24}_D$ −24.0 (*c* 1.0, $CHCl_3$).

2-(4-Methoxyphenyl)methyl-3-oxo-1,2-benzisothiazoline 1,1-Dioxide (20). To a solution of NaH (1.2 g, 30 mmol, 60% dispersion in mineral oil) in DMF (50 mL) at 0 °C under an argon atmosphere was added a solution of saccharin (5.0 g, 27.3 mmol) in DMF (20 mL) through a cannula, followed by *p*-methoxybenzyl chloride (4.0 mL, 30.0 mmol) dropwise. The resulting mixture was warmed to 25 °C, and the reaction flask was equipped with a reflux condenser and was heated to reflux (bath temperature 110 °C) for 5 h. After being cooled to 25 °C, the reaction was quenched with water, and the resulting mixture was extracted with ethyl acetate. The extracts were washed with water three times and finally with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give **20**. Recrystallization of the crude product from CH_2Cl_2−hexanes afforded **20** as a colorless crystalline solid (7.37 g, 89% yield): R_f = 0.42 (ethyl acetate/hexanes = 3/7); mp 153.1−154.0 °C; IR (NaCl, cm^{-1}) 1730, 1612, 1514, 1461, 1333, 1249, 1180, 1034; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03−7.80 (m, 4H), 7.49−7.46 (m, 2H), 6.91−6.88 (m, 2H), 4.87 (s, 2H), 3.80 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.9, 159.3, 138.1, 135.2, 134.7, 130.8, 127.7, 127.0, 125.6, 121.4, 114.4, 55.7, 42.7; MS (EI) m/z (rel intensity) 303 (M^+, 44).

(±)-3-Hydroxy-2-(4-methoxyphenyl)methyl-1,2-benzisothiazoline 1,1-dioxide (21). To a solution of sultam **20** (7.0 g, 23.0 mmol) in CH_2Cl_2 (77 mL) at −78 °C under an argon atmosphere was added dropwise DIBALH (25.4 mL, 25.4 mmol, 1.0 M solution in hexanes), and the mixture was stirred for 1 h. The reaction was carefully quenched with 30% aqueous solution of Rochelle's salt, and the resulting mixture was vigorously stirred at 25 °C for 3 h. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was recrystallized from ethyl acetate−hexanes to give 3-hydroxysultam **21** (6.24 g, 88% yield): R_f = 0.56 (ethyl acetate/hexanes = 3/2); mp 108.2−108.8 °C; IR (KBr pellet, cm^{-1}) 3377, 1614, 1519, 1437, 1347, 1285, 1249, 1170, 1045; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77−7.52 (m, 4H), 7.40 (d, 2H, J = 8.4 Hz). 6.89 (d, 2H, J = 8.4 Hz), 5.53 (d, 1H, J = 11.1 Hz), 4.60 (d, 1H, J = 14.7 Hz), 4.32 (d, 1H, J = 14.7 Hz), 3.80 (s, 3H), 3.29 (d, OH, J = 11.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.8, 136.7, 135.3, 133.8, 131.3, 130.9, 127.0, 125.8, 121.4, 114.5, 80.3, 55.7, 43.2; MS (EI) m/z (rel intensity) 305 (M^+, 72).

(±)-3-Cyano-2-(4-methoxyphenyl)methyl-1,2-benzisothiazoline 1,1-Dioxide (22). To a solution of 3-hydroxysultam **21** (22.3 g, 73 mmol) in CH_2Cl_2 (360 mL) at −78 °C (dry ice−acetone bath) under an argon atmosphere was added boron trifluoride etherate (9.0 mL, 73.0 mmol) followed by trimethylsilyl cyanide (18.3 mL, 146.0 mmol) dropwise, and the resulting mixture was stirred for 1 h. The dry ice−acetone bath was replaced with an ice−water bath, and the reaction was quenched with a saturated aqueous $NaHCO_3$ solution. The separated organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was recrystallized from CH_2Cl_2−hexanes to give nitrile compound **22** (21.1 g, 92% yield): R_f = 0.53 (ethyl acetate/hexanes = 1/1); mp 153.4−154.0 °C; IR (NaCl, cm^{-1}) 2932, 2352, 1611, 1513, 1456, 1311, 1249, 1175, 1130, 1036; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92−7.56 (m, 4H), 7.78−7,52 (m, 4H), 7.44 (d, 2H, J = 8.1 Hz), 6.95 (d, 2H, J = 8.5 Hz), 5.06 (s, 1H), 4.84 (d, 1H, J = 14.3 Hz), 4.32 (d, 1H, J = 14.3 Hz), 3.84 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.5, 135.0, 134.2, 131.8, 131.2, 129.1, 125.2, 124.9, 122.4, 115.0, 114.0, 55.9, 49.0, 45.8; MS (EI) m/z (rel intensity) 314 (M^+, 70); Anal. Calcd for $C_{15}H_{13}N_2O_3S$: C, 61.13; H, 4.49; N, 8.91. Found: C, 61.01; H, 4.58; N, 8.88.

(±)-3-Methoxycarbonyl-2-(4-methoxyphenyl)methyl-1,2-benzisothiazoline 1,1-Dioxide (23). To a solution of nitrile **22** (21.0 g, 67.0 mmol) in dry dioxane (100 mL) at 0 °C was added dry MeOH (220 mL) followed by acetyl chloride (40.0 mL, 558.0 mmol) dropwise, and the resulting mixture was warmed to 25 °C and was stirred for 3 days. The mixture was treated with water and extracted with ethyl acetate. The combined organic phase was washed sequentially with an aqueous saturated $NaHCO_3$ solution, water, and brine, and then it was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give ester **23** as a colorless oil (23.37 g, 100%): R_f = 0.40 (ethyl acetate/hexanes = 2/3); IR (NaCl, cm^{-1}) 2846, 1750, 1612, 1513, 1453, 1300, 1249, 1175, 1132, 1061; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87−7.84 (m, 1H), 7.62−7.51 (m, 3H), 7.31 (d, 2H, J = 8.6 Hz), 6.89 (d, 3H, J = 8.6 Hz), 4.86 (s, 1H), 4.76 (d, 1H, J = 14.5 Hz), 4.40 (d, 1H, J = 14.5 Hz), 3.81 (s, 3H), 3.73 (s, 3H); ^{13}C

NMR (75 MHz, $CDCl_3$) δ 168.5, 160.1, 134.8, 133.5, 131.4, 131.0, 130.7, 126.3, 125.1, 122.0, 114.6, 60.8, 55.7, 53.6, 45.5; MS (EI) *m*/*z* (rel intensity) 347 (M^+, 63); HRMS Calcd for $C_{17}H_{17}NO_5S$: 347.082745. Found: 347.082886.

(±)-3-Methoxycarbonyl-1,2-benzisothiazoline 1,1-Dioxide (24). To an acetonitrile solution (99 mL) of sultam **23** (2.87 g, 8.26 mmol) at 25 °C was ceric ammonium nitrate (18.11 g, 33.04 mmol) dissolved in water (33 mL). After being stirred for 1 h at the same temperature, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic phase was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Column chromatography of the crude product (30% ethyl acetate in hexanes) gave deprotected sultam **24** (1.78 g, 95%): R_f = 0.38 (ethyl acetate/hexanes = 1/1); mp 98.5−99.4 °C; IR (NaCl, cm^{-1}) 3273, 2958, 1749, 1455, 1297, 1108, 1067; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82−7.62 (m, 4H), 5.56 (br s, NH), 5.32 (d, 1H, J = 4.02 Hz), 3.94 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.8, 135.5, 133.9, 131.0, 126.3, 125.6, 122.0, 58.7, 54.4; MS (EI) *m*/*z* (rel intensity) 227 (M^+, 63); Anal. Calcd for $C_9H_9NO_4S$: C, 47.57; H, 3.99; N, 6.16. Found: C, 47.59; H, 4.10; N, 6.09.

(±)-3-Carboxy-1,2-benzisothiazoline 1,1-Dioxide (5). To a solution of ester **24** (1.56 g, 6.86 mmol) in THF (17 mL) at 25 °C was added $LiOH{\cdot}H_2O$ (630 mg, 15.0 mmol) followed by water (17 mL), and the mixture was stirred for 10 min. The reaction mixture was concentrated under reduced pressure to remove most of THF, and the residue was washed with diethyl ether to remove organic side products. The mixture was acidified to pH = 2 with 2 N HCl, and it was extracted with ether. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was recrystallized from ethyl acetate−hexanes to produce 3-carboxysultam **5** as a white solid (1.17 g, 80% yield): R_f = 0.34 (methanol/ethyl acetate = 1/4); mp 164.1−165.0 °C; IR (KBr pellet, cm^{-1}) 3264, 2945, 1723, 1597, 1433, 1288, 1162, 1091; ^{1}H NMR (300 MHz, methanol-d_4) δ 7.74−7.53 (m, 4H), 5.30 (s, 1H), 4.92 (br s, 2H, NH and COOH); ^{13}C NMR (75 MHz, methanol-d_4) δ 171.4, 136.4, 135.8, 134.6, 131.5, 126.9, 122.0, 59.6; MS (EI) *m*/*z* (rel intensity) 213 (M^+, 48). Anal. Calcd for $C_8H_7NO_4S$: C, 45.07; H, 3.31; N, 6.57. Found: C, 44.85; H, 3.54; N, 6.32.

(±)-3-Benzyl-3-methoxycarbonyl-2-(4-methoxyphenyl) Methyl-1,2-benzisothiazoline 1,1-Dioxide (25). To a solution of NaH (632 mg, 15.8 mmol, 60% dispersion in mineral oil) in DMF (40 mL) at 0 °C under argon atmosphere was added a solution of ester **23** (4.6 g, 13.2 mmol) in DMF (26 mL) through a cannula followed by benzyl bromide (1.7 mL, 14.5 mmol) dropwise, and the mixture was stirred for 2 h. The reaction was carefully quenched with water, and the resulting mixture was extracted with ethyl acetate. The extracts were washed three times with water and then with brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (20% ethyl acetate in hexanes) to give benzylated sultam **25** (5.48 g, 95%): R_f = 0.55 (ethyl acetate/hexanes = 2/3); mp 147.9−148.7 °C; IR (NaCl, cm^{-1}) 3023, 1738, 1514, 1452, 1297, 1247, 1176, 1138, 1044; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76−7.74 (m, 1H), 7.54−7.44 (m, 4H), 7.14−7.07 (m, 4H), 6.91−6.83 (m, 4H), 4.64 and 4.56 (AB q, 2H, J_{AB}= 15.7 Hz), 3.81 (s, 3H), 3.80 (d, 1H, J = 14.6 Hz), 3.48 (d, 1H, J = 14.6 Hz), 3.37 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.5, 159.8, 135.7, 134.4, 134.1, 132.8, 131.4, 130.8, 130.4, 128.5, 127.6, 127.2, 124.9, 121.9, 114.2, 71.5, 55.7, 53.4, 44.4, 39.5; MS (EI) *m*/*z* (rel intensity) 437 (M^+, 50), 113 (75), 99 (80), 85 (90), 71 (90).

(±)-3-Benzyl-3-methoxycarbonyl-1,2-benzisothiazoline 1,1-Dioxide (26). Deprotection of the MPM group of **25** (3.91 g, 8.9 mmol) with ceric ammonium nitrate in CH_3CN−water (3:1) afforded **26** in a yield of 95% (2.68 g) after purification by column chromatography (20% ethyl acetate in hexanes): R_f = 0.55 (ethyl acetate/hexanes = 2/3); mp 122.9−123.7 °C; IR (NaCl, cm^{-1}) 3286, 3030, 1740, 1495, 1450, 1376, 1304, 1254, 1204, 1167, 1134, 1035; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94−7.61 (m, 4H), 7.32 (s, 5H), 5.58 (br s, −NH), 3.83 (s, 3H), 3.61(d, 1H, J = 13.5 Hz), 3.20 (d, 1H, J = 13.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.0, 138.2, 135.9, 134.0, 131.0, 130.7, 128.9, 128.1, 126.3, 125.6, 121.9, 70.2, 54.2, 46.7; MS (EI) *m*/*z* (rel intensity) 318 (M + 1, 57).

(±)-3-Benzyl-3-carboxy-1,2-benzisothiazoline 1,1-Dioxide (6). Hydrolysis of ester **26** (2.89 g, 9.1 mmol) with LiOH in THF−water afforded **6** in a yield of 96% (2.64 g): R_f = 0.47 (methanol/ethyl acetate = 1/4); mp 164.2−165.1 °C; IR (KBr pellet, cm^{-1}) 3337, 1714, 1456, 1427, 1367, 1281, 1236, 1160, 1120, 1066; ^{1}H NMR (300 MHz, acetone-d_6) δ 8.08 (d, 1H, J = 7.8 Hz), 7.87−7.73 (m, 3H), 7.40−7.24 (m, 5H), 6.49 (s, −NH), 3.70 (d, 1H, J = 13.6 Hz), 3.22 (d, 1H, J = 13.6 Hz); ^{13}C NMR (75 MHz, acetone-d_6) δ 170.6, 138.5, 136.4, 135.6, 133.7, 131.0, 128.4, 127.6, 126.3, 126.0, 121.3, 69.8, 45.6; MS (EI) *m*/*z* (rel intensity) 303 (M^+, 60).

Resolution of (±)-**6**. Ethanol was added dropwise to a heterogeneous mixture of (±)-carboxylic acid **6** (938 mg, 3.0 mmol) and brucine hydrate (1.2 g, 3.0 mmol) in a small amount of ethanol at reflux temperature until the mixture became a homogeneous solution. The resulting solution was allowed to cool to room temperature whereupon a solid precipitated. The precipitate was filtered and dried in vacuo, which exhibited $[\alpha]^{25}_D$ = +7.8 (*c* 1.2, AcOH). The solid, which was obtained from the filtrate, after evaporating the solvent and drying in vacuo, exhibited $[\alpha]^{25}_D$ = −21.7 (*c* 1.2, MeOH). Each salt was treated with concentrated HCl and was subjected to extractive workup with diethyl ether to afford the corresponding resolved carboxylic acid **6**. From the (+)-salt, (+)-**6** was obtained, which exhibited $[\alpha]^{22}_D$ = +50.4 (*c* 1.0, EtOH); and from the (−)-salt, (−)-**6** was obtained, which exhibited $[\alpha]^{22}_D$ = −51.2 (*c* 1.0, EtOH).

(±)-3-Carboxy-2-(4-methoxyphenyl)methyl-1,2-benzisothiazoline 1,1-Dioxide (19). Hydrolysis of ester **23** (5.2 g, 14.9 mmol) with LiOH in THF−water afforded **19** in a yield of 77% (3.82 g): R_f = 0.50 (methanol/ethyl acetate = 1/4); mp 129.7−130.5 °C; IR (NaCl, cm^{-1}) 3157, 1742, 1611, 1514, 1459, 1293, 1248, 1174, 1128, 1061, 1032; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.59 (br s, −COOH), 7.87 (m, 1H), 7.67−7.60 (m, 3H), 7.31 (d, 2H, J = 8.4 Hz), 6.88 (d, 2H, J = 8.4 Hz), 4.87 (s, 1H), 4.84 (d, 1H, J = 14.5 Hz), 4.37 (d, 1H, J = 14.5 Hz), 3.80 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.7, 160.1, 134.7, 133.7, 131.1, 130.8, 126.3, 126.0, 125.5, 122.1, 114.8, 60.2, 55.7, 45.5; MS (EI) *m*/*z* (rel intensity) 333 (M^+, 48). Anal. Calcd for $C_{16}H_{15}NO_5S$: C, 57.65; H, 4.53; N, 4.20, Found: C, 57.44; H, 4.64; N, 4.11.

2-(4-Methoxyphenyl)methyl-3(*R*/*S*)-{(*S*)-(1-phenyl)-ethylamino}carbonyl-1,2-benzisothiazoline 1,1-Dioxide (27). To a solution of acid **19** (2.25 g, 6.75 mmol) in CH_2Cl_2 (34 mL) at −10 °C under an argon atmosphere was added isobutyl chloroformate (0.92 mL, 6.75 mmol) followed by 4-methylmorpholine (0.68 mL, 6.75 mmol), and the mixture was stirred for 10 min. To the mixture was added (*S*)-(−)-α-methylbenzylamine (0.82 mL, 6.75 mmol), and the reaction temperature was slowly raised to 25 °C and was further stirred for 5 h. The reaction mixture was filtered through a short pad of Celite to remove precipitates, and the filtrate was washed sequentially with 1 N HCl, a saturated aqueous $NaHCO_3$ solution, and water. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (40% ethyl acetate in hexanes) to give a diastereomeric mixture of **27** in a yield of 90% (2.65 g). The two diastereomers were hardly separable on SiO_2, but they exhibited separate ^{13}C NMR peaks: R_f = 0.62 (ethyl acetate/hexanes = 3/2); IR (NaCl, cm^{-1}) 3316, 2994, 1675, 1611, 1522, 1453, 1296, 1248, 1175, 1130; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83−6.73 (m, 14H, 13 aromatic and one NH protons), 4.93−4.34 (m, 4H), 3.83 and 3.78 (s, 3H; s, 3H, from each diastereomer), 1.30 (d, 3H, J = 6.9 Hz) and 1.25 (d, 3H, J = 7.0 Hz) from each diastereomer; ^{13}C NMR (75 MHz, $CDCl_3$) δ (167.2, 167.1), (160.5, 160.3), (143.1, 142.9), (134.2, 134.0), (133.9,133.7), (131.2, 131.0), (130.7, 130.6), (129.3, 129.0), (128.1, 127.7), (126.9, 126.7), (126.4, 126.0), (125.7, 125.5), (121.8, 121.7), (115.1, 115.0), (65.6, 65.0), (55.9, 55.7), (50.0, 49.6), (49.3, 49.2), (22.8, 22.1); MS (FAB) *m*/*z* (rel intensity) 459 (MNa^+, 45), 437 (M + 1, 16).

3(*R*/*S*)-{(*S*)-1-(Phenyl)ethylamino}carbonyl-1,2-benzisothiazoline 1,1-Dioxide (28). Deprotection of the MPM group of **27** (350 mg, 0.8 mmol) afforded a diastereomeric mixture of **28**. Each diastereomer can be separated by SiO_2 column chromatography: (−)-**28** (107 mg, 43% yield); R_f = 0.47 (ethyl acetate/hexanes = 2/3); mp 165.7−166.5 °C; $[\alpha]^{24}_D$ −63.7 (*c* 1.0, $CHCl_3$); IR (NaCl, cm^{-1}) 3174, 1668, 1528, 1454, 1305, 1168, 1130, 1063; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86−7.57 (m, 4H), 7.33−7.24 (m, 6H), 5.71 (d, J = 7.0 Hz, SO_2NH), 5.04 (d, J

= 7.0 Hz, 1H), 5.00−4.90 (m, 1H), 1.73 (br s, 1H), 1.38 (d, 3H, J = 7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.6, 143.0, 135.6, 134.5, 134.2, 130.7, 129.2, 127.8, 126.8, 126.2, 121.6, 60.0, 49.9, 23.1; MS (EI) m/z (rel intensity) 316 (M^+, 50). (+)-**28** (95 mg, 37%); R_f = 0.37 (ethyl acetate/hexanes = 2/3); mp 167.8−168.7 °C; $[\alpha]^{24}_D$ +10.1 (c 1.875, $CHCl_3$); IR (NaCl, cm^{-1}) 3227, 1668, 1526, 1452, 1382, 1304, 1167. 1130. 1064; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76−7.72 (m, 2H), 7.60−7.55 (m, 2H), 7.19−7.07 (m, 6H), 5.86 (d, $-SO_2NH$-, J = 6.8 Hz), 5.15 (d, 1H, J = 6.8 Hz), 5.05−4.95 (m, 1H), 1.70 (br s, 1H), 1.48 (d, 3H, J = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.6, 142.9, 135.6, 134.5, 134.2, 130.7, 129.2, 127.8, 126.8, 126.2, 121.6, 60.0, 49.9, 23.1; MS (EI) m/z (rel intensity) 317 (M + 1, 76).

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Supporting Information Available: Copies of ^{1}H NMR spectra for compounds **5**, **6**, **9**−**13**, **15**−**28** and ORTEP plots of (*R*,*R*)-**16** and (*S*)-**29**. This material is available free of charge via the Internet at http://pubs.acs.org.

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