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Enantioselective Synthesis of Dihydro-1*H*-benzindoles

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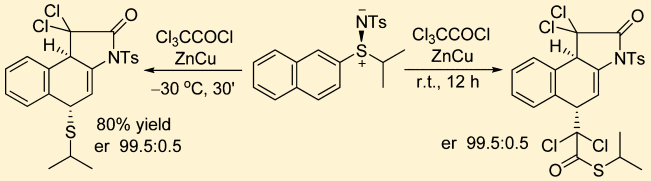
Supporting Information

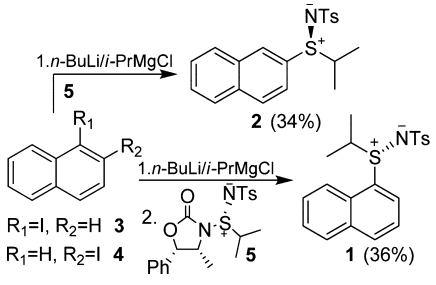
ABSTRACT: The first examples of dihydro-1*H*-benzindoles by enantioselective γ-lactamization reaction of naphthyl sulfilimines with trichloroacetyl chloride in the presence of ZnCu as catalyst (≥98:2 er and 65−80% yields) are described. Products are obtained by [3,3]-sigmatropic rearrangement of the azasulfonium enolate or followed by a second allylic rearrangement that transfers chirality. The absolute stereochemistry was confirmed by X-ray crystallography, which provides support for the mechanisms proposed.



Notwithstanding the structural similarity of the sulfilimine and the sulfoxides, sulfilimines have received less attention than sulfoxides as key intermediates in the synthesis of bioactive molecules.[1−4] Over the past three decades, our group has developed the reaction between chiral vinyl sulfoxides and dichloroketene as a versatile synthesis of γ-lactones.[5−8] This reaction was pivotal in the synthesis, by our group[9,10] and by others,[11−13] of various natural and medicinally useful compounds. As an extension of this reaction, we[14] and Padwa et al.[15,16] used vinylsulfilimines to prepare racemic γ-lactams. Herein we present the first example of the enantioselective synthesis of naphthyl-γ-lactams prepared through the reaction of naphthylsulfilimines with dichloroketene.

The naphthylsulfilimines[17] **1** and **2** were synthesized by the iodo exchange of 1- or 2-iodonaphthalene (**3** or **4**) with lithium isopropylmagnesate followed by the reaction of the magnesium ate complex[18] formed from (*R*)-*N*-tosylisopropyloxazolidinone sulfilimine **5** in 34% and 36% yields, respectively (Scheme 1).

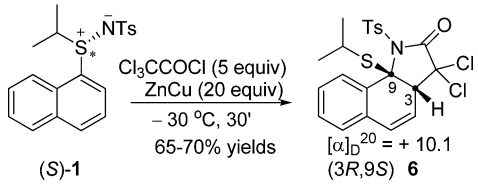
Scheme 1. Synthesis of Chiral Sulfilimines 1 and 2



Similar yields of sulfilimines **1** and **2** were obtained when this one-pot reaction was carried out on a 2−5 mmol scale. Compounds **1** and **2** were stored under argon at 4 °C for two weeks without any decomposition. The chiral center was assigned as being *S* by assuming that the sulfilimine is formed by an S_N2 mechanism.[17]

Then, (*S*)-sulfilimines **1** and **2** were separately evaluated as γ-lactamization reagents.[19] Reaction of the 1-naphthylsulfilimine **1** with trichloroacetyl chloride, in the presence of zinc−copper couple as catalyst, in dry THF (−30 °C, 30 min) gave the (3*R*,9*S*)-*S*-isopropylbenzo[*g*]indolone **6** in a 65−70% yields (Scheme 2). Crystallization of naphthyl-γ-lactam **6** by slow

Scheme 2. γ-Lactamization from Reaction of (*S*)-Sulfilimine 1 and Trichloroacetyl Chloride



evaporation of ethyl acetate/hexanes, at room temperature, furnished white granular crystals ($[\alpha]^{20}_D$ = +10.1; *c* = 3.65, CH_2Cl_2; er ≥99:1). X-ray analysis of these crystals confirmed the (3*R*,9*S*) stereochemistry depicted in Scheme 2.

In contrast, using the identical experimental conditions as for **1**, the same γ-lactamization reaction using (*S*)-sulfilimine **2** unexpectedly gave the (5*S*,9*R*)-benzo[*e*]indolone **7** as product in 77−80% yields (Scheme 3).[20] Chiral NMR shift reagent analysis demonstrated this γ-lactam $[\alpha]^{20}_D$ = +130; *c* = 1.6, $CHCl_3$) to have exceptional (er ≥99.5:0.5) enantiomeric purity.

The probable mechanism for the formation of (+)-7 follows from previous studies.[5−8] A [3,3]-sigmatropic rearrangement of the azasulfonium enolate **8** sets the C-9 stereochemistry of the intermediate **9**. A second allylic rearrangement transfers the chirality of the isopropylmercaptan group of **9** to give **7** (Scheme 4).

For the purposes of reaction optimization and isolation of a racemate to verify enantiomeric purity, racemic γ-lactam **7** was prepared from the racemic sulfilimine (±)-**2**.[17] Unexpectedly,

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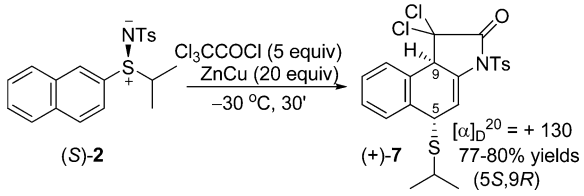
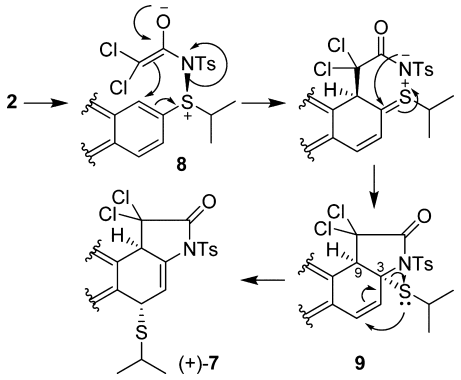
Scheme 3. Product of γ-Lactamization for the (*S*)-Sulfilimine 2 with Dichloroketene

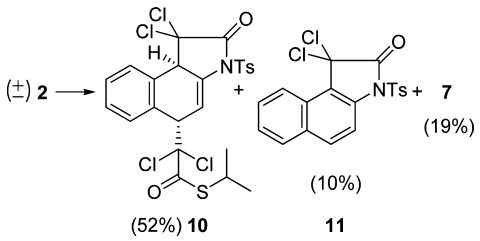


Scheme 4. Proposed Mechanism for Formation of the Chiral (5*S*,9*R*)-Benzoindolone 7



the use of longer reaction times and higher temperature (30 min at −30 °C, but allowing the reaction to warm overnight to room temperature) diminished the isolated yield of **7** to 19%, with the appearance of two new products. The major product of the two (isolated yield of 52%) was the *S*-isopropyl benzo[*e*]indolone (±)-**10**. The third and minor product (isolated yield 10%) was the aromatic γ-lactam **11** (Scheme 5).[21]

Scheme 5. Products Obtained for γ-Lactamization of (±)-2[a]

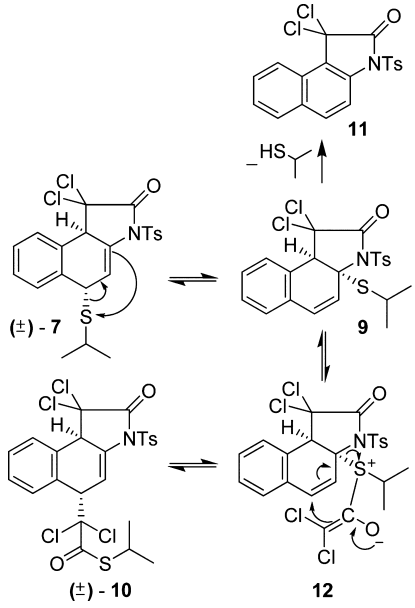


[a]Reaction conditions: trichloroacetyl chloride, ZnCu couple (5 and 20 equiv, respectively), THF dry, 16 h, rt.

These observations are consistent with an equilibrium between γ-lactams **7** and **9** and with **7** as the more stable isomer. Nonetheless, **9** is the pivotal intermediate leading from **7** to **10** and **11**. After the [3,3]-sigmatropic rearragement of the isopropylmercaptan, intermediate **9** reacts with a second molecule of dichloroketene resulting to a new [3,3]-sigmatropic rearrangement yielding benzoindolone **10**. Concurrently, intermediate **9** undergoes gradual aromatization by elimination of the isopropylmercaptan to give γ-lactam **11** as the overall themodynamic product (Scheme 6).

Recrystallization of the benzoindolone (±)-**10** by slow evaporation, at room temperature, using 15% of ethyl acetate/hexanes gave rodlike/blocklike pale yellow crystals. To our surprise, the X-ray analysis showed that enantiomeric

Scheme 6. Proposed Mechanism for the Products 7, 10, and 11



pure crystals of **10** were obtained (38% yield, ≥99.5:0.5 er by chiral support HPLC and Eu(hfc)$_3$ shift reagent titration, ($[\alpha]^{20}_D$ = 8.9; *c* = 1.2, CH_2Cl_2), Figure 1. Thus, from the racemic mixture of compound (±)-**10**, both enatiomers (+)-**10** and (−)-**10** selectively crystallized (Scheme 7).

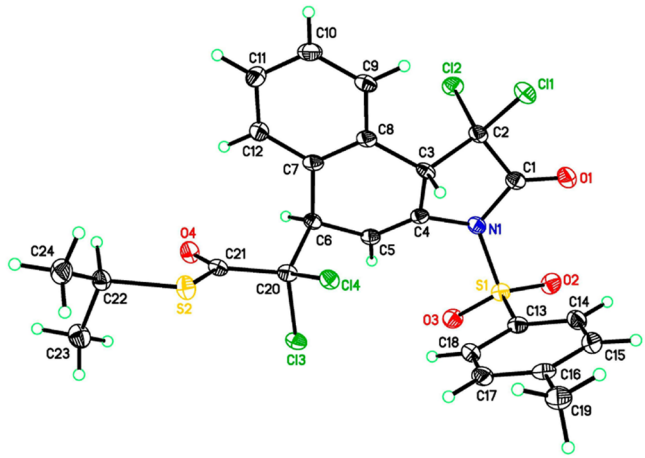
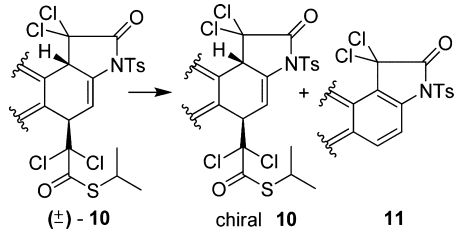


Figure 1. X-ray structure for the benzoindolone (5*R*,9b*S*)-**10**.

However, when the crystals of **10** were resolubilized in ethyl acetate/hexanes and the yellow solution was allowed to

Scheme 7. Spontaneous Chiral Crystallization of the Racemic Benzoindolone (±)-10



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evaporate at room temperature for more than 24 h a dark solution was formed indicating that elimination was occurring to furnish the thermodynamic product **11**.

Finally, the racemic sulfilimine (±)-**2** was reacted under standard lactamization conditions (quench after 30 min of reaction instead of allowing the reaction to warm overnight to room temperature) and the expected racemic γ-lactam (±)-**7** was obtained in 88% yield.

In conclusion, we have disclosed the first example of an enantioselective γ-lactamization reaction between naphthylsulfilimine isomers and trichloroacetyl chloride. We are currently exploring this reaction for the synthesis of natural products,[22,23] and our results will be reported in due course.

EXPERIMENTAL SECTION

Commercial grade reagents and solvents were used without further purification except as indicated below. Anhydrous tetrahydrofuran (THF) was distilled from sodium and benzophenone. Reactions were carried out in oven- or flame-dried glassware under an atmosphere of dry argon only when specified in the experimental details. All reactions were magnetically stirred and monitored by analytical thin-layer chromatography using silica gel 60 F-254 plates. Visualization was accomplished by UV light (256 nm), and phosphomolybdic acid 10% solution. Flash chromatography was performed by mixing the crude with silica gel 60 (230−400 mesh) in a proportion of 1:4 using a SimpliFlash with BSR pump system. ^{1}H NMR and ^{13}C NMR spectra were recorded at ambient temperature with the residual solvent and TMS peaks as internal standards. The line positions of multiplets are given in ppm (δ), and the coupling constants (*J*) are given as absolute values in hertz. Infrared spectra were recorded with an FT-IR spectrometer and reported as cm^{-1}. X-ray diffraction analysis of a single crystal was performed using a combination of ω- and φ-scans of 0.3°. Specific rotations were measured at 589 nm and 20 °C. All melting points were recorded uncorrected. High-resolution mass spectra (HRMS) were quantified with a LTQ-FT instrument using ES ionization. Enantiomeric ratios (er) were determined using chiral HPLC (0.02% of Et_2NH was added to the spectroscopic ethanol) with chiralcel OD column and detector at 235 nm or by Eu shift reagents. Yields refer to chromatographically and spectrographically pure compounds, unless otherwise noted.

(4*R*,5*S*)-3-(Isopropylthio)-4-methyl-5-phenyloxazolidin-2-one (13). To a solution of 2.5 g of the Evan's oxazolidinone[24] (14.1 mmol) in 40 mL of dry THF at 0 °C was slowly added 1 equiv of *n*-BuLi. The color of the solution turned from colorless to dark red. After the reaction mixture was allowed to react for 30 min at 0 °C, a solution of 2.5 g of *S*-isopropyl isopropanesulfonothioate[25] (14.4 mmol) in 40 mL of dry THF was added by cannula, at once, and the reaction was allowed to stir overnight at room temperature. The white mixture was quenched with 50 mL of saturated NH_4Cl and extracted with 50 mL of ethyl acetate. The organic layer was washed with 50 mL of H_2O and brine, dried with $MgSO_4$, and then filtered.[26] The solvent was removed via rotovap, and the colorless oil was purified through flash chromatography with elution by 1:9 ethyl acetate/hexanes to provided 2.51 g of the oxazolidine sulfide **13** (73% yield) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 0.87 (d, *J* = 6.70 Hz, 3 H), 1.27 (d, *J* = 6.94 Hz, 3 H), 1.32 (d, *J* = 6.70 Hz, 3 H), 3.36 (spt, *J* = 6.70 Hz, 1 H), 4.08−4.19 (m, 1 H), 5.65 (d, *J* = 7.89 Hz, 1 H), 7.23− 7.29 (m, 2 H), 7.31−7.44 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 15.6, 20.6, 21.3, 41.1, 60.5, 79.0, 126.1, 128.8, 128.8; HRMS (ESI) *m*/*z* calcd for $C_{13}H_{17}NO_2S$ 251.0980, found 251.0985.

***N*-[(1*E*)-Ethyl[(4*R*,5*S*)-4-phenyl-5-methyl-2-oxo-1,3-oxazolidin-3-yl](1-methylethyl)-λ^4-sulfanylidene]-4-methylbenzenesulfonamide ((*R*)- and (*S*)-5).** To a solution of 7.54 g of the oxazolidinone sulfide **13** (30 mmol) in 150 mL of CH_3CN was added 10.15 g of chloramine-T (1.2 equiv), and the reaction mixture was allowed to stir overnight at room temperature. A white solid was formed on the bottom of the round flask. The reaction was quenched with H_2O and extracted with 25 mL of ethyl acetate. The organic layer was washed with 25 mL of brine, dried with $MgSO_4$, and then filtered. The solvent was removed under rotovap, and the colorless oil was purified through flash chromatography with elution by 4:6 ethyl acetate/hexanes. The less polar fraction afforded 5.55 g of the (*S*)-sulfilimine **5** (44% yield) as white crystals, and the more polar fraction gave 4.79 g of the (*R*)-sulfilimine **5** (38% yield) as colorless bricklike crystals by slow evaporation of the mixture of solvents at room temperature.

(*R*)-**5**: mp = 123−124 °C; $[\alpha]^{20}_D$ = −391 (*c* = 0.68, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 0.90 (d, *J* = 6.46 Hz, 3 H), 1.27 (d, *J* = 7.04 Hz, 3 H), 1.37 (d, *J* = 7.04 Hz, 3 H), 2.42 (s, 3 H), 4.56−4.61 (m, 1 H), 4.64 (spt, *J* = 7.04 Hz, 1 H), 5.49 (d, *J* = 7.92 Hz, 1 H), 7.18 (m, 2 H), 7.29 (m, 2 H), 7.37−7.43 (m, 3 H), 7.83 (d, *J* = 8.22 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 16.3, 17.0, 17.3, 21.3, 51.4, 56.6, 80.4, 80.6, 125.8, 126.3, 128.2, 128.5, 128.9, 129.3, 133.0, 140.0, 142.4, 153.6; HRMS (ESI) *m*/*z* calcd 421.1250 for $C_{20}H_{24}N_2O_4S_2$, found 421.1256.

(*S*)-**5**: mp = 147−148 °C; $[\alpha]^{20}_D$ = −198.5 (*c* = 0.85, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 0.90 (d, *J* = 6.80 Hz, 3 H), 1.29 (d, *J* = 6.80 Hz, 3 H), 1.35 (d, *J* = 6.97 Hz, 3 H), 2.41 (s, 3 H), 3.41 (spt, *J* = 6.80 Hz, 1 H), 4.74 (pt, *J* = 7.13 Hz, 1 H), 5.45 (d, *J* = 8.13 Hz, 1 H), 7.22 (dd, *J* = 7.46, 1.82 Hz, 2 H), 7.32 (d, *J* = 7.96 Hz, 2 H), 7.37−7.44 (m, 3 H), 7.84 (d, *J* = 8.29 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 16.5, 17.4, 17.5, 20.1, 21.7, 50.6, 54.2, 82.1, 85.5, 126.1, 126.2, 127.0, 129.0, 129.2, 129.3, 129.8, 133.6, 139.4, 143.2, 158.4; HRMS (ESI) *m*/*z* calcd 421.1250 for $C_{20}H_{24}N_2O_4S_2$, found 421.1254.

General Preparation of Chiral 1- and 2-Naphthylsulfilimines. *n*-BuLi (1.26 mL, 2.54 M in hexanes, 3.2 mmol) was added to 0.82 mL of *i*-PrMgCl (1.95 M in THF, 1.6 mmol) at −5 °C, and the mixture was allowed to stir until the Mg−ate complex was formed (15−30 min). The ate complex was cooled to −20 °C, and 1.6 mmol of iodide in 4 mL of dry THF was transferred by cannula. The reaction mixture was allowed to stir for another 30 min at −5 °C and recooled to −30 °C. Then, 420 mg of the sulfilimine chiral auxiliary **5** (0.7 equiv) in 10 mL of THF was added to the naphthyl Mg−ate complex. After 30 min of reaction at −30 °C the mixture was quenched with 5 mL of saturated NH_4Cl and extracted with 15 mL of ethyl acetate. The organic layer was washed with 10 mL of brine. Purification by flash column chromatography with elution by ethyl acetate/hexanes 10−60% provided a mixture of the desired product and Evan's auxiliary in a proportion of 55:45. Second purification of the mixture by flash chromatography with elution by ethyl acetate/hexanes 30−60% gave the desired product. Alternatively, the solid can be recrystallized by slow evaporation at room temperature in a mixture of ethyl acetate/hexanes.

(S)-Isopropyl(4-methylphenylsulfonamido)(naphthalen-2-yl)-sulfonium (1): 134 mg (36% yield); mp = 146−147 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.15 (d, *J* = 6.70 Hz, 3 H), 1.21 (d, *J* = 6.70 Hz, 3 H), 2.27 (s, 3 H), 3.37 (sept, *J* = 6.70 Hz, 1 H), 7.07 (d, *J* = 8.61 Hz, 2 H), 7.54−7.66 (m, 3 H), 7.72 (d, *J* = 8.61 Hz, 2 H), 7.90−7.96 (m, 1 H), 8.00 (d, *J* = 8.61 Hz, 2 H), 8.06−8.12 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 15.1, 21.6, 53.7, 122.0, 125.8, 126.5, 128.3, 128.7, 129.4, 132.8, 135.2, 141.7; HRMS (ESI) *m*/*z* calcd for $C_{20}H_{22}NO_2S_2$ 372.1086, found 372.1086.

(S)-Isopropyl(4-methylphenylsulfonamido)(naphthalen-1-yl)-sulfonium (2). Chiral assay for **2** indicated ≥98:2% er according to HPLC analysis with a Chiralpak OD column using EtOH/hexanes 15% (*t* = 12.4−14.0 min).

(*R*)-**2**: $[\alpha]^{20}_D$ = +227 (*c* = 3.46, $CHCl_3$); 126 mg (34% yield). (*S*)-**2**: $[\alpha]^{20}_D$ = −170 (*c* = 2.57, $CHCl_3$); 119 mg (32% yield); mp = 129−130 °C; ^{1}H NMR (300 MHz, $CDCl_3$) ppm 1.18 (d, *J* = 6.70 Hz, 3 H), 1.23 (d, *J* = 6.70 Hz, 3 H), 2.26 (s, 3 H), 3.28 (d, *J* = 6.70 Hz, 1 H), 7.09 (d, *J* = 8.61 Hz, 2 H), 7.53−7.66 (m, 3 H), 7.71−7.78 (m, 2 H), 7.81−7.96 (m, 3 H), 8.15 (d, *J* = 1.67 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 15.5, 16.9, 21.5, 54.5, 121.9, 126.4, 126.4, 127.8, 128.1, 128.8, 128.8, 129.2, 129.6, 129.6, 130.1, 132.7, 141.6; HRMS (ESI) *m*/*z* calcd for $C_{20}H_{22}NO_2S_2$ 372.1086, found 372.1086.

General Procedure to Prepare the Racemic Sulfilimines 1 and 2. *Isopropyl(4-methylphenylsulfonamido)(naphthalen-2-yl)-sulfonium ((±)-2).* To a solution of 577 mg of the naphthyl isopropyl

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sulfide[27] (2.85 mmol) in 25 mL of CH_3CN, at room temperature, was added 1.2 g of chloramine-T (1.5 equiv), and the reaction mixture was allowed to stir overnight. The mixture was diluted with 20 mL of H_2O, and the organic phase was extracted with 25 mL of ethyl acetate and washed with 20 mL of brine. The solvent was removed under rotovap, and the colorless oil was purified through flash chromatography with elution by (30−60% ethyl acetate/hexanes) to give 930 mg of the naphthyl sulfilimine **2** (88% yield) as a white solid.

General Lactamization Procedure. To 480 mg of zinc powder (7.35 mmol) in a dry flask equipped with a magnetic stir bar and a condenser was added 728 mg of CuCl (7.35 mmol) and 4 mL of anhydrous THF. The reaction mixture was refluxed under nitrogen until the formation of a dark gray solid (1.5−2 h). The reaction was cooled to the temperature indicated. To the zinc−copper mixture was added 0.37 mmol of the respective naphthylsulfilimine in 3 mL of dry THF by cannula and allowed to stir for 15 min. Finally, 205 μL of trichloroacetyl (1.84 mmol) chloride was added via syringe pump during 30 min. After the reaction mixture was allowed to stir for the indicated time, it was filtered through a Celite pad into 5 mL of sodium bicarbonate solution, followed by extraction with 20 mL of ethyl acetate. The organic layer was washed with 10 mL of brine and dried over magnesium sulfate. The solvent was removed via rotovap, and the crude was purified by silica gel chromatography with ethyl acetate/hexanes to give the desired lactam.

*(3aR,9bS)-3,3-Dichloro-9b-(isopropylthio)-1-tosyl-3,3a-dihydro-1H-benzo[g]indol-2(9bH)-one (**6**).* Using standard (reaction time of 30 min, reaction temperature of −30 °C) lactamization conditions, purification by flash column chromatography with elution by ethyl acetate/hexanes provided 116−125 mg of **6** as a colorless solid (65−70% yields). Recrystallization by slow evaporation of ethyl acetate/hexanes at room temperature gave white granular crystals which were used to have the structure solved by X-ray crystallography with Flack parameter = 0.01(3). Chiral assay indicated 98:2 er according to HPLC analysis with a Chiralcel OD column using 3% EtOH/hexanes (t = 9.6−10.6 min): mp = 143−144 °C dec; $[\alpha]^{20}_D$ = +10.1 (c = 3.65, CH_2Cl_2); IR 1754, 1371, 1225, 1174. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.45 (d, J = 6.80 Hz, 3 H), 1.30 (d, J = 7.13 Hz, 3 H), 2.48 (s, 3 H), 3.17 (spt, J = 6.97 Hz, 1 H), 3.26 (dd, J = 5.89, 0.75 Hz, 1 H), 6.03 (dd, J = 9.79, 5.80 Hz, 1 H), 6.90 (d, J = 9.79 Hz, 1 H), 7.16 (dd, J = 7.46, 1.33 Hz, 1 H), 7.35 (td, J = 7.46, 1.33 Hz, 1 H), 7.39 (d, J = 8.46 Hz, 2 H), 7.41−7.45 (m, 1 H), 8.04 (d, J = 7.80 Hz, 1 H), 8.25 (d, J = 8.46 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 22.0, 23.3, 24.5, 39.1, 59.1, 76.9, 77.2, 77.6, 118.3, 127.7, 128.0, 129.5, 129.5, 129.7, 130.2, 131.0, 131.4, 133.1, 135.1, 145.9, 164.9; HRMS (ESI) m/z calcd for $C_{22}H_{21}Cl_2NNaO_3S_2$ 504.0238, found 504.0232.

*(5S,9bR)-1,1-Dichloro-5-(isopropylthio)-3-tosyl-5,9b-dihydro-1H-benzo[e]indol-2(3H)-one (**7**).* Using standard (reaction time of 30 min, reaction temperature of −30 °C) lactamization conditions, purification by flash column chromatography with elution by 15% ethyl acetate/hexanes provided 137−143 mg (77−80% yields) of **7** as colorless needle crystals, er ≥99.5:0.5 using Eu(FOD) + Ag(FOD).

(5S,9bR)-**7** from (*S*)-**2**: $[\alpha]^{20}_D$ = +130 (c = 0.85, $CHCl_3$). (5R,9bS)-**7** from (*R*)-**2**: $[\alpha]^{20}_D$ = −137 (c = 1.6, $CHCl_3$); IR 1755, 1371, 1173. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.11 (d, J = 6.80 Hz, 3 H), 1.33 (d, J = 6.97 Hz, 3 H), 2.46 (s, 3 H), 3.44 (d, J = 6.80 Hz, 1 H), 4.00 (s, 1 H), 6.57−6.65 (m, 2 H), 7.26 (dd, 1 H), 7.33−7.45 (m, 4 H), 7.48 (dd, J = 7.30, 0.83 Hz, 1 H), 8.12 (d, J = 8.11 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ ppm 22.0, 24.3, 25.2, 36.1, 59.8, 74.8, 123.0, 126.5, 127.9, 128.7, 129.2, 129.7, 129.7, 129.8, 130.0, 132.0, 134.9, 146.1, 164.2; HRMS (ESI) m/z calcd for $C_{22}H_{21}Cl_2NO_3S_2$ 481.0340, found 481.0340.

*S-Isopropyl 2,2-Dichloro-2-(1,1-dichloro-2-oxo-3-tosyl-2,3,5,9b-tetrahydro-1H-benzo[e]indol-5-yl)ethanethioate ((±)-**10**).* Using nonstandard (reaction time of 16 h, reaction temperature of 25 °C) lactamization conditions, purification by flash column chromatography with elution by 15% ethyl acetate/hexanes provided 114 mg of the product (±)-**10** as a yellow solid.

*S-Isopropyl 2,2-Dichloro-2-((5R,9bS)-1,1-dichloro-2-oxo-3-tosyl-2,3,5,9b-tetrahydro-1H-benzo[e]indol-5-yl)ethanethioate (**10**).* The yellow solid (±)-**10** was dissolved in a mixture of 15% ethyl acetate/hexanes, and the solvents were slowly evaporated at room temperature during 18 h to give 42 mg (19% yield) of (+)-**10** and 42 mg (19% yield) of (−)-**10** as rodlike/blocklike pale yellow crystals. The compound spontaneously chirally resolves upon crystallization. The sample randomly selected was assigned as the (5R,9bS) enantiomer by X-ray crystallography with Flack parameter = 0.02(3). An assay of chirality indicated er ≥99.5:0.5 according to HPLC analysis with a Chiralcel OD column using 3% EtOH/hexanes and $Eu(hfc)_3$ shift reagent titration: mp = 170 °C; $[\alpha]_D^{20}$ = 8.9 (c = 1.2, CH_2Cl_2); IR 3115, 2978, 1785, 1700, 1653, 1392, 1189, 1172; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.40 (d, J = 6.97 Hz, 3 H), 1.42 (d, J = 6.97 Hz, 3 H), 2.46 (s, 3 H), 3.71 (spt, J = 6.91 Hz, 1 H), 4.46 (t, J = 2.65 Hz, 1 H), 4.81 (dd, J = 6.05, 2.74 Hz, 1 H), 6.74 (dd, J = 6.05, 2.74 Hz, 1 H), 7.34−7.40 (m, 3 H), 7.41−7.48 (m, 2 H), 7.89 (d, J = 7.63 Hz, 1 H), 8.01 (d, J = 8.62 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 22.1, 22.6, 37.7, 51.6, 52.8, 82.0, 95.1, 107.7, 126.8, 128.1, 128.5, 130.3, 130.9, 131.4, 131.6, 134.2, 136.0, 146.9, 164.2, 195.0; HRMS (ESI) m/z calcd for $C_{24}H_{21}Cl_4NNaO_4S_2$ 613.9564, found 613.9558.

*1,1-Dichloro-3-tosyl-1H-benzo[e]indol-2(3H)-one (**11**).* Using nonstandard (reaction time of 16 h, reaction temperature of 25 °C) lactamization conditions, purification by flash column chromatography with elution by 30% ethyl acetate/hexanes gave 15 mg (10% yield) of the product **11** as dark green oil: IR 1771, 1574, 1518, 1378, 1262, 1178, 1089, 815; ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 2.45 (s, 3 H), 7.04 (ddd, J = 8.51, 7.04, 1.47 Hz, 1 H), 7.30−7.31 (m, 1 H), 7.31−7.33 (m, 2 H), 7.69 (d, J = 8.51 Hz, 1 H), 7.76 (d, J = 9.10 Hz, 1 H), 7.78 (d, J = 8.22 Hz, 1 H), 7.83 (d, J = 8.80 Hz, 1 H), 7.84−7.85 (m, 1 H), 7.85−7.87 (m, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ ppm 21.8, 105.0, 112.5, 124.2, 125.2, 127.0, 128.3, 128.7, 129.5, 129.8, 131.4, 133.8, 134.4, 138.2, 145.9, 168.1; HRMS (ESI) m/z calcd for $C_{19}H_{13}Cl_2NO_3S$ 406.0066, found 406.0066.

■ ASSOCIATED CONTENT

Supporting Information

X-ray tables and discussions for (*R*)-**5**, (3R,9S)-**6**, and (5R,9bS)-**10**, ^{1}H and ^{13}C NMR for the new compounds herein presented, as well as chiral HPLC data for (*S*)-**2**, (3R,9S)-**6**, and (5R,9bS)-**10**.] This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Urban, C.; Macé, Y.; Cadoret, F.; Blazejewski, J.-C.; Magnier, E. *Adv. Synth. Catal.* **2010**, *352*, 2805.

(2) Collet, F.; Dodd, R. H.; Dauban, P. *Org. Lett.* **2008**, *10*, 5473.

(3) Ruano, J. L. G.; Alemparte, C.; Clemente, F. R.; Gutierrez, L. G.; Gordillo, R.; Castro, A. M. M.; Ramos, J. H. R. *J. Org. Chem.* **2002**, *67*, 2919.

(4) Takada, H.; Nishibayashi, Y.; Ohe, K.; Uemura, S. *J. Org. Chem.* **1997**, *62*, 6512.

(5) Marino, J. P.; Neisser, M. *J. Am. Chem. Soc.* **1981**, *103*, 7687.
(6) Marino, J. P.; Perez, A. D. *J. Am. Chem. Soc.* **1984**, *106*, 7643.
(7) Marino, J. P.; Laborde, E.; Paley, R. S. *J. Am. Chem. Soc.* **1988**, *110*, 966.
(8) Marino, J. P. *Pure Appl. Chem.* **1993**, *65*, 667.
(9) Marino, J. P.; Bogdan, S.; Kimura, K. *J. Am. Chem. Soc.* **1992**, *114*, 5566.
(10) Marino, J. P.; Rubio, M. B.; Cao, G.; de Dios, A. *J. Am. Chem. Soc.* **2002**, *124*, 13398.
(11) Kosugi, H.; Mirura, Y.; Kanna, H.; Uda, H. *Tetrahedron: Asymmetry* **1993**, *4*, 1409.
(12) Burke, S. D.; Shankaran, K.; Helber, M. J. *Tetrahedron Lett.* **1991**, *32*, 4655.
(13) Bravo, P.; Arnone, A.; Bandiera, P.; Bruche, L.; Ohashi, Y.; Ono, T.; Sekine, A.; Zanda, M. *Eur. J. Org. Chem.* **1999**, 111.
(14) Marino, J. P.; Zou, N. *Org. Lett.* **2005**, *7*, 1915.
(15) Wang, Q.; Nara, S.; Padwa, A. *Org. Lett.* **2005**, *7*, 839.
(16) Wang, Q.; Nara, S.; Padwa, A. *J. Org. Chem.* **2005**, *70*, 8538.
(17) Celentano, G.; Colonna, S.; Gaggero, N.; Richelmi, C. *Chem. Commun.* **1998**, 701.
(18) Inoue, A.; Kitagawa, K.; Shinokubo, H.; Oshima, K. *J. Org. Chem.* **2001**, *66*, 4333.
(19) The presence of Evan's chiral auxiliary as a side product with the sulfilimines **1** and **2** did not change the course of the lactamization reaction.
(20) (−)-Benzo[*e*]indolone (5*R*,9b*S*)-**7** (enantiomer of (+)-**7**) was obtained from (*R*)-naphthylsulfilimine **2** under the same reaction conditions.
(21) The same reaction gave a 1:1 mixture of products **10** and **7** after 8 h. Compound **11** was not observed.
(22) Zhao, R. Y.; Erickson, H. K.; Leece, B. A.; Reid, E. E.; Goldmacher, V. S.; Lambert, J. M.; Chari, R. V. J. *J. Med. Chem.* **2012**, *55*, 766.
(23) Song, X.; Crider, A. M.; Cruse, S. F.; Ghosh, D.; Klein-Stevens, C.; Liang, L.; Scheideler, M. A.; Varming, A.; Søtofte, I. *Eur. J. Med. Chem.* **1999**, *34*, 487.
(24) Davies, S. G.; Doisneau, G. J. M. *Tetrahedron: Asymmetry* **1993**, *4*, 2513.
(25) Derbesy, G.; Harpp, D. N. *J. Org. Chem.* **1995**, *60*, 4468.
(26) Silveira, G. P.; Carvallho, C. B.; Oliver, A. *Acta Crystallogr.* **2012**, *E68*, o2048.
(27) Node, M.; Nishide, K.; Ohta, K.; Fuji, K.; Fujita, E.i; Hori, H.; Inayama, S. *Chem. Pharm. Bull.* **1983**, *31*, 545.

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