Stereoselective Synthesis of *trans*-2-(Indol-3-yl)cyclopropylamines: Rigid Tryptamine Analogues

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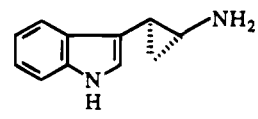
A procedure for the preparation of *trans*-2-(indol-3-yl)cyclopropylamines is reported. The key step in the sequence is a stereoselective palladium-catalyzed cyclopropanation of the indole-3-acryloyl derivative of Oppolzer's chiral sultam (bornane[10,2]sultam) with diazomethane, following by the purification of the resulting diastereomeric cyclopropanated sultams by recrystallization. Base hydrolysis of the pure crystalline diastereomers gave the resolved indolylcyclopropanecarboxylic acids. These could be converted into enantiomers of indolylcyclopropylamine by Curtius rearrangement, which did not affect the absolute configuration. In addition, single crystal X-ray crystallography of the cyclopropanated sultam was used to determine the absolute configuration of the intermediate indolylcyclopropanecarboxylic acid and thus to establish the configuration of the final compound.

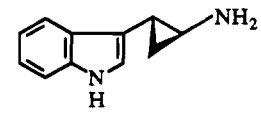
Introduction

A number of tryptamine derivatives have been obtained from natural sources or prepared by chemical synthesis and studied for their biological activity.[1–6] One of the more well known and studied of these, 5-hydroxytryptamine (5-HT, serotonin), is an important neurotransmitter with numerous physiological functions in the central and peripheral nervous systems. Other tryptamine derivatives such as *N,N*-dimethyl- and *N,N*-diethyltryptamine, psilocin, and psilocybin have psychotomimetic activity much like that of LSD.[7] Some of them, such as α-methyl- and α-ethyltryptamine, have activity as inhibitors of 5-HT uptake into rat hypothalamic synaptosomes.[3]

The conformations of drugs at their receptor sites is a topic of active research. Little is known regarding the mutual conformational changes that occur between the molecule and receptor during their interaction. One way to circumvent this uncertainty is to evaluate the relative pharmacological potencies of conformationally rigid analogues of natural substrates or agonists. Therefore, the study of conformationally restricted analogues of tryptamine might lead to a better understanding of how tryptamines bind to their receptor site(s). The use of a cyclopropane ring is an effective strategy to impart conformational rigidity to molecules containing an ethylamine moiety.[8–12] Thus, this report describes the synthesis of enantiomeric *trans*-2-(indol-3-yl)cyclopropylamines **1a** and **1b**.



(1*R*,2*S*)-**1a**



(1*S*,2*R*)-**1b**

Results and Discussion

Chemical resolution of racemic indolylcyclopropylamines by crystallization of diastereomeric salts with a chiral acid was considered as a possibility, but such procedures are usually tedious and low-yielding. In addition, racemic **1** quickly revealed itself to be a relatively unstable molecule quickly darkening, even under refrigeration, and it was considered possible that multiple recrystallizations might ultimately lead to complete decomposition of the product.

An attractive alternative method to prepare optically active *trans*-2-(indol-3-yl)cyclopropylamines is based on the method of Vallgårda and Hacksell.[13] The key step in this procedure is an initial derivatization of α,β-unsaturated carboxylic acids with Oppolzer's sultam (bornane[10,2]sultam; **6**), which functions as an easily removable, inexpensive, and efficient chiral auxiliary. Reaction of the resulting *N*-enoyl sultam with diazomethane in the presence of catalytic palladium diacetate produced predominantly one cyclopropanated stereoisomer. The advantage of this method is the availability of both enantiomers of **6**, allowing for the preparation of both enantiomeric cyclopropane carboxylic acids.

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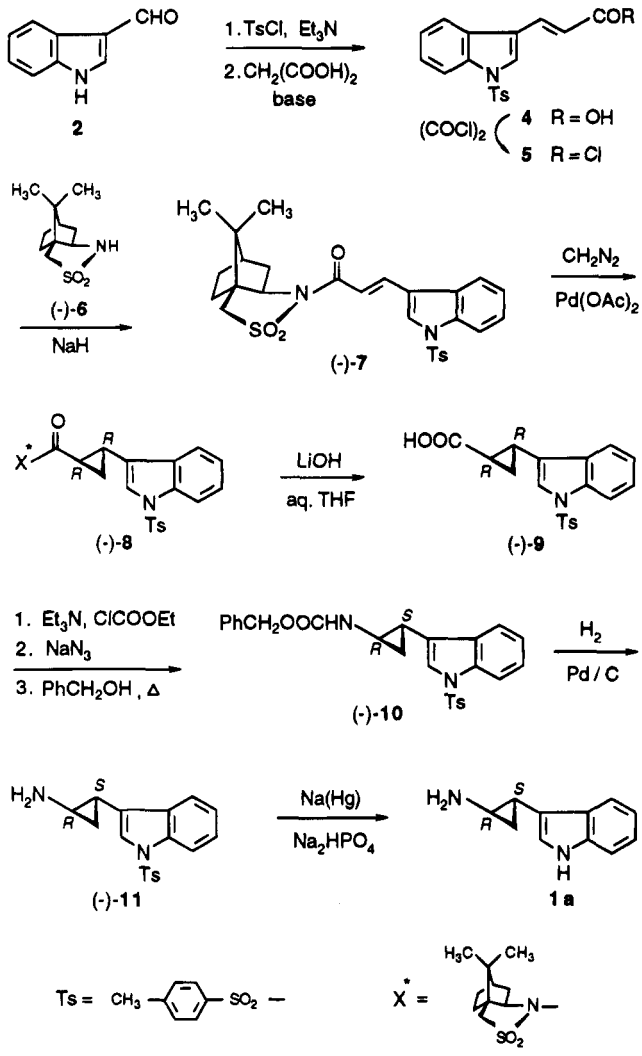
Scheme 1



The total stereoselective synthesis of **1a** is detailed in Scheme 1. Transformation of acid **4** to its acid chloride **5** followed by treatment with (−)-bornane[10,2]sultam (−)-**6** gave *N*-enoyl sultam **7**, which underwent cyclopropanation with diazomethane in the presence of catalytic palladium diacetate to afford stereoisomeric cyclopropanated sultam **8**. The major diastereomer could be isolated in pure form by recrystallization from ethanol. Single crystal X-ray crystallography of **8** was used to determine its absolute configuration and thus to establish the configuration of the final compound. Hydrolysis of **8** with LiOH gave enantiomeric acid **9**. Curtius rearrangement, treatment of the isocyanate with benzyl alcohol, followed by catalytic hydrogenation, and detosylation gave optically pure (1*R*,2*S*)-*trans*-2-(indol-3-yl)-cyclopropylamine (**1a**). The optically pure (1*S*,2*R*) enantiomer **1b** could be obtained by the same procedure using (+)-bornane[10,2]sultam, (+)-**6**.

Conclusions

Cyclopropanation of the indole-3-acryloyl derivative of Oppolzer's chiral sultam with diazomethane at 0 °C produces the stereoisomeric cyclopropanated sultams in ratios of about 70:30, determined by HPLC. The chromatographic properties of the two diastereomers are so similar that they could not be completely separated by chromatography; however, the major diastereomer was isolated in pure form (greater than 99% de, by HPLC analysis) by recrystallization. Thus, through this series of reactions we have prepared, for the first time, optically active *trans*-2-(indol-3-yl)cyclopropylamines, rigid tryptamine analogues.

Experimental Section

Melting points were determined with a Thomas-Hoover Meltemp apparatus and are uncorrected, except where indicated. ^{1}H NMR spectra were recorded on a Varian VXR-500S 500-MHz instrument. Chemical shifts are reported in δ values (parts per million, ppm) relative to an internal standard of tetramethylsilane (TMS) in $CDCl_3$, except where noted. Abbreviations used in NMR analysis are as follows: br s = broad singlet, d = doublet, dd = doublet of doublets, m = multiplet, q = quartet, s = singlet, t = triplet. Analytical thin-layer chromatography (TLC) was performed on Baker-flex silica gel 1B2-F plastic plates. The chemical ionization mass spectra (CIMS) were determined on a Finnigan 4000 quadrupole mass spectrometer, using isobutane as the reagent gas and are reported as *m/e* (relative intensity). The fast-atom bombardment mass spectra (FABMS) were determined on a Kratos MS-50 spectrometer. Elemental analyses were obtained from Galbraith Laboratories, Inc., and were within 0.4% of the calculated values, unless otherwise noted. Optical rotations were measured using a Perkin-Elmer Model 241 digital polarimeter. A Parr apparatus was used for all low pressure hydrogenations. The X-ray structural analysis was done using an Enraf-Nonius CAD4 computer-controlled κ axis diffractometer equipped with a graphite crystal, incident beam monochromator. The structure was solved using the structure solution program SHELX-86. All of the reagents are Aldrich products.

1-(*p*-Toluenesulfonyl)indole-3-carboxaldehyde (3). A mixture of indole-3-carboxaldehyde (**2**) (1.50 g, 10.3 mmol) and *p*-toluenesulfonyl chloride (3.00 g, 15.7 mmol) in triethylamine (25 mL) was heated at 90−95 °C for 1 h. The reaction mixture was poured into ice-cold water (35 mL), stored in a refrigerator for 1 h, and then filtered. The insoluble solid was washed with water and air-dried to yield a brown solid. Recrystallization from ethyl acetate gave pure **3** (2.47 g, 80%) as a white powder: mp 148−150 °C, lit.[14] 148−150 °C; ^{1}H NMR ($CDCl_3$) δ 10.09 (s, 1H), 8.26 (m, 1H), 8.22 (s, 1H), 7.96 (m, 1H), 7.85 (d, 2H, J = 8.6 Hz), 7.38 (m, 2H), 7.30 (d, 2H, J = 8.6 Hz), 2.38 (s, 3H); CIMS 300 (MH^+).

***trans*-β-[1-(*p*-Toluenesulfonyl)indol-3-yl)]acrylic Acid (4).** Following the modified method of Moffatt,[15] a solution of **3** (2.00 g, 6.68 mmol) and malonic acid (2.25 g, 21.62 mmol) in pyridine (8 mL) containing piperidine (8 drops) was heated at 75−80 °C under nitrogen for 3 h. The solution was poured into ice-cold water (50 mL) and acidified with 5 N hydrochloric acid. After the mixture had been stored in the refrigerator overnight, the precipitate was filtered and washed with water to afford a pale brown solid. Recrystallization from methanol gave pure **4** (2.00 g, 87%) as a white powder: mp 243−244 °C; ^{1}H NMR (DMSO-d_6) δ 12.40 (br s, 1H), 8.43 (s, 1H), 7.96 (d, 1H, J = 8.3 Hz), 7.92 (d, 1H, J = 8.3 Hz), 7.90 (d, 2H, J = 8.4 Hz), 7.74 (d, 1H, J = 16.2 Hz), 7.41 (t, 1H, J = 8.3 Hz), 7.39 (d, 2H, J = 8.4 Hz), 7.34 (t, 1H, J = 8.2 Hz), 6.57 (d, 1H, J = 16.2 Hz), 2.30 (s, 3H); CIMS 342 (MH^+). Anal. Calcd for $C_{18}H_{15}NO_4S$: C, 63.33; H, 4.43; N, 4.10. Found: C, 63.65; H, 4.44; N, 4.22.

***trans*-β-[1-(*p*-Toluenesulfonyl)indol-3-yl]acryloyl Chloride (5).** Oxalyl chloride (1.0 mL 11.0 mmol) was added dropwise to a solution of acid **4** (1.68 g, 4.92 mmol) in dry methylene chloride (20 mL). The reaction mixture was stirred under nitrogen at room temperature for 1 h. Solvent removal under vacuum gave a pale brown solid that was briefly placed under high vacuum and immediately used for the next reaction without further purification.

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(−)-*N*-[(*E*)-3-[1-(*p*-Toluenesulfonyl)indol-3-yl]-2-propenoyl]bornane-10,2-sultam [(−)-7]. Following the modified method of Vallgårda and Hacksell,[13] a solution of bornane-[10,2]sultam (−)-**6**[16,17] (1.08 g, 5.02 mmol) in dry toluene (15 mL) was added dropwise to a suspension of NaH (60% dispersion in mineral oil; 480 mg, 12.0 mmol) in dry toluene (10 mL). The mixture was stirred under nitrogen at room temperature for 1 h. A freshly prepared solution of acryloyl chloride **5** in dry toluene (10 mL) was slowly added, and the mixture was stirred under nitrogen overnight. The reaction mixture was poured into ice-cold water (20 mL) and extracted with ethyl acetate (4 × 15 mL). The combined organic phases were dried ($MgSO_4$) and filtered, and the solvent was removed to yield 2.22 g (83%) of crude product. After washing with methanol, pure **7** was obtained as a white powder: mp 235–237 °C; ^{1}H NMR ($CDCl_3$) δ 7.99 (d, 1H, J = 6.9 Hz), 7.89 (s, 1H), 7.88 (d, 1H, J = 15.6 Hz), 7.86 (d, 1H, J = 6.8 Hz), 7.79 (d, 2H, J = 8.3 Hz), 7.36 (m, 2H), 7.30 (d, 1H, J = 15.6 Hz), 7.25 (d, 2H, J = 8.3 Hz), 4.01 (dd, 1H, J = 7.6 and 5.1 Hz), 3.55 and 3.49 (AB quartet, 2H, J = 13.8 Hz), 2.35 (s, 3H), 2.17 (m, 2H), 1.93 (m, 3H), 1.45 (m, 2H), 1.21 (s, 3H), 1.00 (s, 3H); CIMS 539 (MH^+). Anal. Calcd for $C_{28}H_{30}N_2O_5S_2$: C, 62.43; H, 5.61; N, 5.20. Found: C, 62.22; H, 5.80; N, 5.14. $[\alpha]_D$ = −62.0° (CH_2Cl_2, c = 0.4).

(−)-*N*-[(1*R*,2*R*)-*trans*-2-[1-(*p*-Toluenesulfonyl)indol-3-yl]cycloprop-1-yl]carbonyl]bornane-10,2-sultam [(−)-8]. Following the modified method of Vallgårda and Hacksell,[13] an azeotrope of diazomethane and ether [prepared by slowly adding a solution of *N*-nitroso-*N*-methyl-4-toluenesulfonamide (5.23 g, 24.4 mmol) in ether (30 mL) to a heated mixture of potassium hydroxide (1.40 g, 25.0 mmol), ether (3 mL), water (3 mL), and 2-(2-ethoxyethoxy)ethane (8 mL)] was continuously distilled into a cold (ice-salt bath) stirred solution of *N*-enoyl sultam **7** (3.78 g, 7.0 mmol) in ether (20 mL) and dichloromethane (4 mL), containing palladium diacetate (18 mg). The reaction mixture was kept at −10 to −5 °C (bath temperature) until all diazomethane had been distilled. The cooling was discontinued after 2 h, and the reaction mixture was filtered. The insoluble solid was washed with excess dichloromethane. The filtrate and washing were evaporated to afford 2.80 g (72.1%) of crude product with 64.8% de, determined by HPLC. Recrystallization from ethanol gave pure **8** (38%) as colorless crystals with diastereomeric purity of >99% de (determined by HPLC): mp 206–208 °C; ^{1}H NMR ($CDCl_3$) δ 7.94 (d, 1H, J = 8.1 Hz), 7.74 (d, 2H, J = 8.2 Hz), 7.61 (d, 1H, J = 7.9 Hz), 7.46 (s, 1H), 7.30 (t, 1H, J = 7.9 Hz), 7.23 (t, 1H, J = 8.0 Hz), 7.20 (d, 2H, J = 8.2 Hz), 3.94 (dd, 1H, J = 7.6 and 4.9 Hz), 3.55 and 3.49 (AB quartet, 2H, J = 13.7 Hz), 2.60 (m, 1H), 2.50 (m, 1H), 2.32 (s, 3H), 2.10 (m, 2H), 1.92 (m, 3H), 1.77 (m, 1H), 1.40 (m, 2H), 1.30 (m, 1H), 1.20 (s, 3H), 1.00 (s, 3H); CIMS 553 (MH^+). Anal. Calcd for $C_{29}H_{32}N_2O_5S_2$: C, 63.02; H, 5.84; N, 5.07. Found: C, 62.72; H, 5.97; N, 4.98. $[\alpha]_D$ = −124.1° (CH_2Cl_2, c = 0.4). X-ray crystallography shows that it has the 1*R*,2*R* stereochemistry.[21]

(1*R*,2*R*)-(−)-*trans*-2-[1-(*p*-Toluenesulfonyl)indol-3-yl]-cyclopropanecarboxylic Acid [(−)-9]. A mixture of cyclopropanated sultam **8** and LiOH·H_2O (1.32 g, 31.5 mmol) in THF/H_2O (2:1, 24 mL)[18] was stirred at room temperature for 6 h at which time TLC (5% EtOAc in CH_2Cl_2) showed complete reaction. Water (30 mL) was added, and the reaction mixture was extracted with methylene chloride (4 × 10 mL), dried ($MgSO_4$), and filtered, and the solvent was removed in vacuo to give 670 mg (85%) of the recovered sultam. The aqueous phase was acidified (pH 2–3) with 1 N hydrochloric acid, saturated with NaCl, and extracted with CH_2Cl_2 (4 × 10 mL). Drying ($MgSO_4$), filtration, and evaporation of the solvent gave the carboxylic acid (−)-**9** (1.04 g, 80%) as a white solid: mp 150–152 °C; ^{1}H NMR ($CDCl_3$) δ 7.97 (d, 1H, J = 8.3 Hz), 7.75 (d, 2H, J = 8.3 Hz), 7.58 (d, 1H, J = 7.1 Hz), 7.34 (t, 1H, J = 8.3), 7.29 (s, 1H), 7.26 (t, 1H, J = 7.1 Hz), 7.23 (d, 2H, J = 8.4 Hz), 2.58 (m, 1H), 2.33 (s, 3H), 1.88 (m, 1H), 1.66 (m, 1H), 1.40 (m, 1H); CIMS 356 (MH^+). Anal. Calcd for $C_{19}H_{17}NO_4S$: C, 64.21; H, 4.82; N, 3.94. Found: C, 64.09; H, 4.95; N, 4.11. $[\alpha]_D$ = −107.4° (CH_2Cl_2, c = 0.4).

(1*R*,2*S*)-(−)-*trans*-2-[1-(*p*-Toluenesulfonyl)indol-3-yl]-1-[(benzyloxycarbonyl)amino]cyclopropane [(−)-10]. Following the modified method of Weinstock,[19] the cyclopropane carboxylic acid (−)-**9** (1.50 g, 4.22 mmol) was suspended in water (0.8 mL), and sufficient acetone was added to effect solution. This mixture was cooled to 0 °C (ice-salt bath), and a solution of triethylamine (0.8 mL, 5.74 mmol) in acetone (6 mL) was added. While maintaining the temperature at 0 °C, a solution of ethyl chloroformate (0.7 mL, 7.32 mmol) in acetone (3 mL) was slowly added. The mixture was stirred for 1 h at this temperature. A solution of sodium azide (1.00 g, 15.38 mmol) in water (4 mL) was then added dropwise, and stirring was continued for 2 h. The reaction mixture was poured into ice–water (20 mL), extracted with toluene (4 × 10 mL), dried ($MgSO_4$), and filtered. The toluene filtrate was heated at gentle reflux with dry benzyl alcohol (3 mL, 28.85 mmol) for 10 h. The solvent and excess benzyl alcohol were removed in vacuo. Purification of the crude reaction product by flash chromatography (1% EtOAc in CH_2Cl_2) provided the *N*-carbobenzoxy derivative (−)-**10** (1.35 g, 69.6%) as a yellow oil that crystallized on cooling: mp 86–88 °C; ^{1}H NMR ($CDCl_3$) δ 7.95 (d, 1H, J = 8.4 Hz), 7.72 (d, 2H, J = 8.2 Hz), 7.32 (m, 9), 7.20 (d, 2H, J = 8.1 Hz), 5.14 (s, 2H), 5.11 (br s, 1H), 2.71 (m, 1H), 2.33 (s, 3H), 2.06 (m, 1H), 1.18 (m, 2H); CIMS 461 (MH^+). Anal. Calcd for $C_{26}H_{24}N_2O_4S$: C, 67.81; H, 5.25; N, 6.08. Found: C, 68.00; H, 5.33; N, 6.10. $[\alpha]_D$ = −31.4° (CH_2Cl_2, c = 0.4).

(1*R*,2*S*)-(−)-*trans*-2-[1-(*p*-Toluenesulfonyl)indol-3-yl]-cyclopropylamine Oxalate, (−)-11. In a 500-mL hydrogenation bottle were placed 500 mg of 10% palladium on charcoal and absolute ethanol (30 mL). A solution of (−)-**10** (1.13 g, 2.45 mmol) in absolute ethanol (30 mL) was added. The mixture was shaken on a Parr apparatus for 12 h under 50 psig hydrogen. The catalyst was removed by filtration and washed with ethanol. The combined filtrate and washing were evaporated to give the crude product which was purified via centrifugal rotary chromatography (chromatotron) to give the pure amine (−)-**11** (585 mg, 73%) as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 7.95 (d, 1H, J = 7.4 Hz), 7.72 (d, 2H, J = 8.4 Hz), 7.59 (d, 1H, J = 7.4 Hz), 7.31 (t, 1H, J = 7.4 Hz), 7.25 (t, 1H, J = 7.4 Hz), 7.20 (d, 2H, J = 8.4 Hz), 7.11 (s, 1H), 2.51(m, 1H), 2.33 (s, 3H), 1.84 (m, 1H), 1.74 (br s, 2H), 1.02 (m, 1H), 0.95 (m, 1H); CIMS 327 (MH^+). Anal. Calcd for $C_{18}H_{18}N_2O_2S$: C, 66.23; H, 5.56; N, 8.58. Found: C, 66.10; H, 5.79; N, 8.67.

The oxalate salt was prepared using 1 equiv of oxalic acid in ether. Recrystallization from ethanol–petroleum ether gave an analytical sample: mp 163-164 °C dec; $[\alpha]_D$ = −25.3° (CH_3OH, c = 0.4).

(1*R*,2*S*)-(−)-*trans*-2-(Indol-3-yl)cyclopropylamine Oxalate (1a). Following the modified method of Boyles and Nichols,[20] the N-(1)-protected cyclopropylamine free base (−)-**11** (585 mg, 1.79 mmol) and anhydrous disodium hydrogen phosphate (1.01 g, 7.16 mmol) were stirred magnetically in dry methanol (25 mL) at room temperature under nitrogen. To the suspension was added all at once pulverized 6% sodium amalgam (3.60 g). Stirring was continued until the reaction was complete as indicated by TLC (about 45 min). The mixture was poured into water (50 mL) and extracted with ether (5 × 10 mL). The organic extract was dried ($MgSO_4$), filtered, and concentrated to afford a yellow oil that was purified via centrifugal rotary chromatography (chromatotron). This provided 156 mg (50%) of pure amine **1a** as a viscous yellow oil: ^{1}H NMR ($CDCl_3$) δ 7.95 (br s, 1H), 7.71(d, 1H, J = 8.1 Hz), 7.33 (d, 1H, J = 8.1 Hz), 7.19 (t, 1H, J = 8.1 Hz), 7.13

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(t, 1H, J = 8.1 Hz), 6.82 (d, 1H, J = 2.1 Hz), 2.52 (m, 1H), 1.96 (m, 1H), 1.77 (br s, 2H), 0.96 (m, 2H); CIMS 173 (MH^+).

The oxalate salt was prepared using 1 equiv of oxalic acid in ether. Recrystallization from ethanol–petroleum ether gave an analytical sample: mp 154–155 °C dec; ^{1}H NMR (CD_3OD) δ 7.65 (d, 1H, J = 7.8 Hz), 7.32 (d, 1H, J = 8.2 Hz), 7.11 (t, 1H, J = 8.2 Hz), 7.03 (t, 1H, J = 7.8 Hz), 7.02 (s, 1H), 2.74 (m, 1H), 2.40 (m, 1H), 1.34 (m, 1H), 1.27 (m, 1H); HRFABMS calcd for $C_{11}H_{12}N_2$ 173.1079, found 173.1080; $[\alpha]_D$ = −3.8° (CH_3OH, c = 0.4).

(+)-*N*-[(*E*)-3-[1-(*p*-Toluenesulfonyl)indol-3-yl]-2-propenoyl]bornane-10,2-sultam [(+)-7]. Using the procedure described for (−)-**7**, acylation of (+)-bornane[10,2]sultam with acyl chloride **5** afforded (+)-**7** (85%) as a white powder: mp 234–236 °C; ^{1}H NMR ($CDCl_3$) δ 7.99 (d, 1H, J = 7.4 Hz), 7.89 (s, 1H), 7.88 (d, 1H, J = 15.5 Hz), 7.86 (d, 1H, J = 7.3 Hz), 7.79 (d, 2H, J = 8.3 Hz), 7.36 (m, 2H), 7.30 (d, 1H, J = 15.5 Hz), 7.25 (d, 2H, J = 8.3 Hz), 4.01 (dd, 1H, J = 7.6 and 5.1 Hz), 3.55 and 3.49 (AB quartet, 2H, J = 13.7 Hz), 2.35 (s, 3H), 2.17 (m, 2H), 1.93 (m, 3H), 1.45 (m, 2H), 1.21 (s, 3H), 0.99 (s, 3H); CIMS 539 (MH^+); $[\alpha]_D$ = +63.3° (CH_2Cl_2, c = 0.4).

(+)-*N*-[(1*S*,2*S*)-*trans*-2-[1-(*p*-Toluenesulfonyl)indol-3-yl]cycloprop-1-ylcarbonyl]bornane-10,2-sultam [(+)-8]. Following a procedure identical to that for (−)-**8**, cyclopropanation of the *N*-enoyl sultam (+)-**7** afforded the cyclopropanated sultam (+)-**8** (85% crude yield, with 77.54% de. The diastereomeric purity of the final product was 98.5% de determined by HPLC after recrystallization from ethanol yield 30.8%) as colorless crystals: mp 203–204 °C; ^{1}H NMR ($CDCl_3$) δ 7.94 (d, 1H, J = 8.2 Hz), 7.74 (d, 2H, J = 8.3 Hz), 7.60 (d, 1H, J = 8.3 Hz), 7.46 (s, 1H), 7.30 (t, 1H, J = 8.2 Hz), 7.23 (t, 1H, J = 8.2 Hz), 7.20 (d, 2H, J = 8.3 Hz), 3.94 (dd, 1H, J = 7.7 and 4.9 Hz), 3.54 and 3.49 (AB quartet, 2H, J = 13.8 Hz), 2.60 (m, 1H), 2.50 (m, 1H), 2.32 (s, 3H), 2.10 (m, 2H), 1.92 (m, 3H), 1.77 (m, 1H), 1.40 (m, 2H), 1.29 (m, 1H), 1.22 (s, 3H), 0.99 (s, 3H); CIMS 553 (MH^+); $[\alpha]_D$ = +122.1° (CH_2Cl_2, c = 0.5).

(1*S*,2*S*)-(+)-*trans*-2-[1-(*p*-Toluenesulfonyl)indol-3-yl]cyclopropanecarboxylic Acid [(+)-9]. Following an identical procedure to that for (−)-**9**, alkaline hydrolysis of cyclopropanated sultam (+)-**8** afforded the carboxylic acid (+)-**9** (80%) as a white solid: mp 154–155 °C; ^{1}H NMR ($CDCl_3$) δ 7.97 (d, 1H, J = 8.3 Hz), 7.75 (d, 2H, J = 8.3 Hz), 7.58 (d, 1H, J = 7.8 Hz), 7.34 (t, 1H, J = 7.8 Hz), 7.29 (s, 1H), 7.26 (t, 1H, J = 8.0 Hz), 7.22 (d, 2H, J = 8.3 Hz), 2.58 (m, 1H), 2.34 (s, 3H), 1.88 (m, 1H), 1.66 (m, 1H), 1.40 (m, 1H); CIMS 356 (MH^+); $[\alpha]_D$ = +111.2° (CH_2Cl_2, c = 0.4).

(1*S*,2*R*)-(+)-*trans*-2-[1-(*p*-Toluenesulfonyl)indol-3-yl]-1-[(benzyloxycarbonyl)amino]cyclopropane [(+)-10]. Using the conditions described for (−)-**10**, the carboxylic acid (+)-**9** afforded (+)-**10** (71%) as a yellow oil that crystallized on cooling: mp = 82–84 °C; ^{1}H NMR ($CDCl_3$) δ 7.95 (d, 1H, J =8.6 Hz), 7.72 (d, 2H, J = 8.1 Hz), 7.30 (m, 9H), 7.20 (d, 2H, J = 8.1 Hz), 5.14 (s, 2H), 5.11 (br s, 1H), 2.72 (m, 1H), 2.33 (s, 3H), 2.07 (m, 1H), 1.28 (m, 1H), 1.15 (m, 1H); CIMS 461 (MH^+); $[\alpha]_D$ = +28.9° (CH_2Cl_2, c = 0.4).

(1*S*,2*R*)-(+)-*trans*-2-[1-(*p*-Toluenesulfonyl)indol-3-yl]-cyclopropylamine Oxalate [(+)-11]. Catalytic hydrogenation of (+)-**10** by a method similar to that described for (−)-**10** afforded the cyclopropylamine (+)-**11** (50%) as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 7.95 (d, 1H, J = 8.0 Hz), 7.72 (d, 2H, J = 8.4 Hz), 7.59 (d, 1H, J = 7.8 Hz), 7.31 (t, 1H, J = 8.0 Hz), 7.24 (t, 1H, J = 7.8 Hz), 7.20 (d, 2H, J = 8.4 Hz), 7.10 (s, 1H), 2.51(m, 1H), 2.33 (s, 3H), 1.84 (m, 1H), 1.68 (br s, 2H), 1.02 (m, 1H), 0.95 (m, 1H); CIMS 327 (MH^+).

The oxalate salt was prepared by using 1 equiv of oxalic acid in ether. Recrystallization from ethanol–petroleum ether gave an analytical sample: mp 160–162 °C dec; $[\alpha]_D$ = +26.9° (CH_3OH, c = 0.4).

(1*S*,2*R*)-(+)-*trans*-2-(Indol-3-yl)cyclopropylamine Oxalate (1b). Using the procedure described for **1a**, detosylation of (+)-**11** with sodium amalgam afforded the cyclopropylamine **1b** (50%) as a yellow oil; ^{1}H NMR δ 7.95 (br s, 1H), 7.71 (d, 1H, J = 8.0 Hz), 7.33 (d, 1H, J = 8.0 Hz), 7.19 (t, 1H, J = 7.5 Hz), 7.13 (t, 1H, J = 7.5 Hz), 6.82 (d, 1H, J = 2.0 Hz), 2.52 (m, 1H), 1.96 (m, 1H), 1.77 (br s, 2H), 0.96 (m, 2H); CIMS 173 (MH^+).

The oxalate salt was prepared by using 1 equiv of oxalic acid in ether. Recrystallization from ethanol–petroleum ether gave an analytical sample: mp 153–155 °C dec; ^{1}H NMR (CD_3OD) δ 7.65 (d, 1H, J = 7.8 Hz), 7.33 (d, 1H, J = 8.1 Hz), 7.11 (t, 1H, J = 7.6 Hz), 7.04 (t, 1H, J = 7.6 Hz), 7.02 (s, 1H), 2.74 (m, 1H), 2.40 (m, 1H), 1.34 (m, 1H), 1.28 (m, 1H); FABMS 173 (MH^+); $[\alpha]_D$ = +3.7° (CH_3OH, c = 0.4).

X-ray Crystallography of (−)-*N*-[(1*R*,2*R*)-*trans*-2-[1-(*p*-toluenesulfonyl)indol-3-yl]cycloprop-1-yl]carbonyl]bornane-10,2-sultam [(−)-8].[21] The absolute configuration of this compound was clearly established on the basis of the known (*S*)-stereochemistry of (−)-bornane[10,2]sultam used to prepare (−)-**8**.

Crystal data: $C_{29}H_{32}N_2O_5S$; formula weight = 552.72; colorless rhombic; space group $P2_12_12_1$ (no. 19); Z = 4; a = 10.715 (1) Å, b = 12.771 (1) Å, c = 19.978 (1) Å, V = 2733.8 Å^3; calculated density = 1.34 g/cm^3; absolute coefficient μ = 0.78 cm^{-1}. Data collection was performed with Cu Kα radiation (λ = 1.54184 Å) on an Enraf-Nonius CAD4 computer-controlled κ axis diffractometer equipped with a graphite crystal, incident beam monochromator. The data were collected at a temperature of 293 ± 1 K using the ω–2θ scan technique. The scan rate varied from 1 to 16°/min (in ω). The variable scan rate allows rapid data collection for intense reflections where a fast scan rate is used and assures good counting statistics for weak reflections where a slow scan rate is used. Data were collected to a maximum 2θ of 130.0°. The scan range (in degrees) was determined as a function of θ to correct for the separation of the Kα doublet; the scan width was calculated as follows: ω scan width = 0.38 + 0.150 tan θ. Moving-crystal moving-counterbackground counts were made by scanning an additional 25% above and below this range. Thus, the ratio of peak counting time to background counting time was 2:1. The counteraperture was also adjusted as a function of θ. The horizontal aperture width ranged from 1.7 to 2.6 mm; the vertical aperture was set at 4.0 mm. The diameter of the incident beam collimator was 0.7 mm, and the crystal to detector distance was 21 cm. For intense reflections, an attenuator was automatically inserted in front of the detector; the attenuator factor was 25.6.

A total of 2669 reflections were collected, of which 2669 were unique. Lorentz and polarization corrections were applied to the data. The linear absorption coefficient is 20.6/cm for Cu Kα radiation. The structure was solved using the structure solution program SHELX-86 (G. M. Sheldrick, Institut fur Anorganische Chemie der Universitat Gottingen, F.R.G.). The remaining atoms were located in succeeding difference Fourier syntheses. Hydrogen atoms were located and added to the structure factor calculations but their positions were not refined. The structure was refined in full-matrix least-squares where the function minimized was $\sum w(|F_o| - |F_c|)^2$ and the weight w is defined as per the Killean and Lawrence method with term of 0.020 and 1.0.[22]

Scattering factors were taken from Cromer and Waber.[23] Anomalous dispersion effects were included in F_c;[24] the values for f' and f'' were those of Cromer.[25] Only the 2164 reflections having intensities greater than 3.0 times their standard deviation were used in the refinements. The final cycle of

(21) The author has deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge, Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

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refinement included 343 variable parameters and converged (largest parameter shift was 0.00 times its esd) with unweighted and weighted agreement factors of:

$$R1 = \sum|F_o - F_c|/\sum F_o = 0.041$$

$$R2 = SQRT\left(\sum w(F_o - F_c)^2/\sum wF_o^2\right) = 0.051$$

The standard deviation of an observation of unit weight was 1.32. There were no correlation coefficients greater than 0.50. The highest peak in the final difference Fourier had a height of 0.18 e/Å^3 with an estimated error based on δF^{26} of 0.04. The refined values for the other absolute structure are $R = 0.048$, $Rw = 0.060$ and the estimated standard deviation of an observation of unit weight = 1.557. Plots of $\sum w(|F_o| - |F_c|)^2$ versus $|F_o|$, reflection order in data collection, sin θ/λ, and various classes of indices showed no unusual trends. All calculations were performed on a VAX computer and refinement was done using MolEN.[27]

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