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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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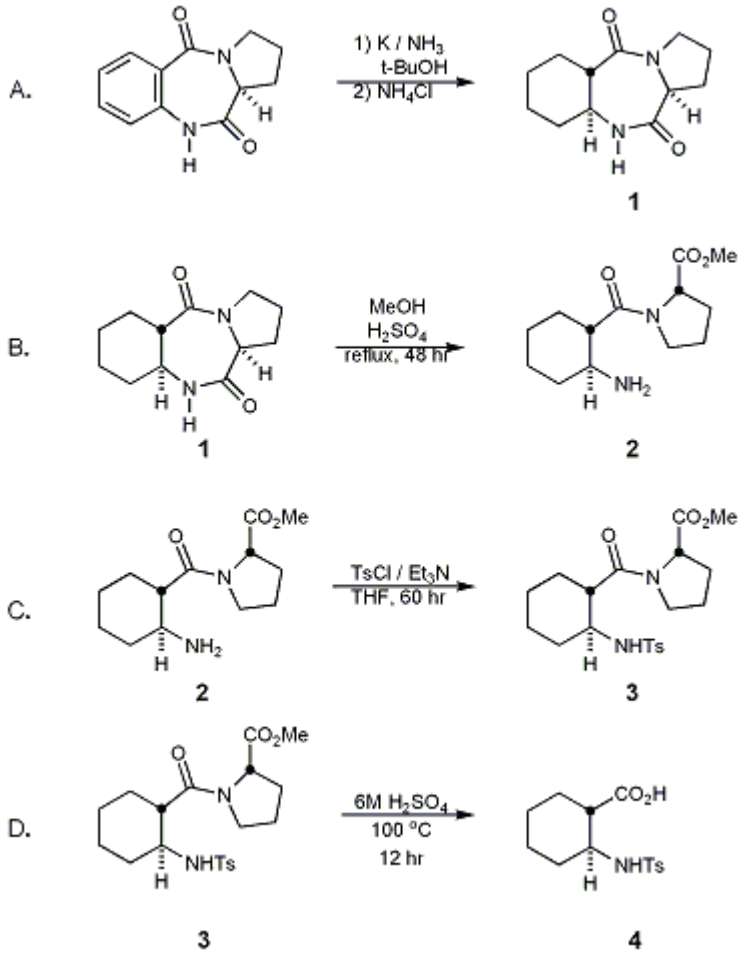
ASYMMETRIC SYNTHESIS OF trans-2-AMINOCYCLOHEXANECARBOXYLIC ACID DERIVATIVES FROM PYRROLOBENZODIAZEPINE-5,11-DIONES: (1S,2S)-2-(N-TOSYLAMINO)CYCLOHEXANECARBOXYLIC ACID



Submitted by Arthur G. Schultz and Carlos W. Alva[1].
Checked by Steven S. Henry and Albert I. Meyers.

1. Procedure

A. *(5aS,9aS,11aS)-Perhydro-5H-pyrrolo[2,1-c][1,4]benzodiazepine-5,11-dione* **(1)**. A 3-L, three-necked, round-bottomed flask, equipped with a mechanical stirrer bearing a glass paddle, a dry ice/acetone-cooled cold-finger condenser bearing a nitrogen inlet/outlet valve vented through a mineral oil bubbler, and a gas inlet (Note 1) is placed under a nitrogen atmosphere, and charged with 25.0 g (0.116 mol) of 99% pure (S)-(+)-2,3-dihydro-1H-pyrrolo[2,1-c][1,4]benzodiazepine-5,11(10H,11aH) dione (Note 2) and a solution of 42.2 g (0.570 mol) of tert-butyl alcohol in 150 mL of dry tetrahydrofuran (THF) (Note 3). The mixture is cooled to −78°C (dry ice/acetone bath) and 2 L of dry ammonia is distilled into the mixture (Note 4). After stirring is initiated, a total of 35.7 g (0.912 mol) of potassium metal is added to the reaction mixture in small chunks at −78°C, and the resulting blue-colored solution is stirred for 1 hr. The reaction is then carefully quenched at −78°C by the addition of 61 g (1.14 mol) of solid ammonium chloride (Note 5). The cooling bath and condenser are removed, and the ammonia is allowed to evaporate overnight. The residue is suction filtered, and the filter cake is washed with 100 mL of chloroform. The filtrate is diluted with 200 mL of water, transferred to a 1-L

separatory funnel, the organic phase is separated, and the aqueous phase is extracted three times with 100 mL of chloroform. The combined organic layers are dried over anhydrous sodium sulfate (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue is crystallized from ethyl acetate, and the mother liquor purified by chromatography (Note 6) to give a total of 17.8 g (69%) of **1** (R_f 0.31, EtOAc/MeOH, 9:1) as a colorless solid, mp 225–227°C, $[\alpha]_D^{23}$ +55° ($CHCl_3$, *c* 0.61) (Note 7) and (Note 8).

B. *(1S,2S)-2-Amino-1-[((2S)-2-carbomethoxypyrrolidinyl)carbonyl]cyclohexane* **(2)**. A 250-mL, single-necked, round-bottomed flask equipped with a condenser bearing a nitrogen inlet/outlet valve as above (Part A) and a magnetic stirring bar, is charged with a solution of 20.0 g (90.0 mmol) of **1**, 100 mL of anhydrous methanol, and 18.4 g (180 mmol) of concentrated sulfuric acid, placed under a nitrogen atmosphere, and heated at reflux (oil bath temperature at 80–85°C) for 48 hr or until TLC analysis indicates the disappearance of **1**. The solution is concd under reduced pressure, 100 mL of dichloromethane (CH_2Cl_2) is added, and the mixture is cooled to 0°C. A total of 150 mL of saturated aqueous sodium bicarbonate solution is added in small portions with good stirring, followed by 10–12 mL of concd ammonium hydroxide until a pH of 10 is reached (Note 9). After thorough mixing, the organic phase is separated and the aqueous phase is extracted twice with 50 mL of CH_2Cl_2. The combined organic phases are dried over Na_2SO_4, concentrated, and the resulting crude amine **2** used immediately in the next step (Note 10).

C. *(1S,2S)-2-(N-Tosylamino)-1-[((2S)-2-carbomethoxypyrrolidinyl)carbonyl] cyclohexane* **(3)**. Approximately 22.9 g (~90 mmol) of crude amine **2** (prepared above in part B), 13.66 g (135 mmol) of triethylamine, and 100 mL of dry THF are placed in a 300-mL, round-bottomed flask, equipped with a pressure-equalizing dropping funnel, a magnetic stirring bar, and a nitrogen inlet. The dropping funnel is charged with a solution of 18.9 g (99.1 mmol) of p-toluenesulfonyl chloride (Note 11) in 50 mL dry THF. The reaction mixture is cooled to 0°C with magnetic stirring, and the solution of p-toluenesulfonyl chloride is delivered dropwise over a 30-min period. The resulting cloudy solution is stirred for 60 hr at ambient temperature. After this time period, the reaction mixture is diluted with 50 mL of saturated sodium chloride solution and 50 mL of ethyl acetate, transferred to a 500-mL separatory funnel, mixed thoroughly, and the organic phase separated. The aqueous phase is extracted twice with 50 mL of ethyl acetate. The combined organic layers are dried (Na_2SO_4), filtered, concentrated under reduced pressure, and the resulting residue purified by chromatography (Note 12) to give 22.43 g (61% from **1**) of **3** (R_f 0.34, $CHCl_3$/EtOAc, 1:1) as a colorless solid, mp 144–146°C (Note 13).

D. *(1S,2S)-2-(N-Tosylamino)cyclohexanecarboxylic acid* **(4)**. A 250-mL round-bottomed flask, equipped with a water-cooled condenser, is charged with 28.8 g (70.5 mmol) of **3** and 120 mL of 6 M sulfuric acid. The resulting heterogeneous mixture is heated at reflux (oil bath temperature 110–115°C) for 14 hr. After several hours at reflux, suspended solids are observed. The mixture is cooled to room temperature, transferred to a 500-mL separatory funnel, and extracted three times with 100 mL of CH_2Cl_2. The combined organic layers are dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure to afford **4** as a colorless solid. Recrystallization of the crude solid **4** from CH_2Cl_2 and ethyl acetate affords 12.16 g (58%) of pure **4**(R_f ~0.29, $CHCl_3$/EtOAc, 1:1) as colorless needles, mp 175–177°C, $[\alpha]_D^{20}$ +35° ($CHCl_3$, *c* 0.50) (Note 14) and (Note 15).

2. Notes

1. All glassware is flame dried and cooled under a stream of anhydrous nitrogen. All reactions are carried out under a positive pressure of nitrogen except for step D.
2. (S)-(+)-2,3-Dihydro-1H-pyrrolo[2,1-c][1,4]benzodiazepine-5,11(10H,11aH)-dione was purchased from the Aldrich Chemical Company, Inc. Other reagents, solvents, and drying agents were obtained from either Aldrich Chemical Company, Inc. or Fisher Scientific Company.
3. tert-Butyl alcohol is distilled prior to use. THF is distilled immediately before use from sodium benzophenone ketyl.
4. The ammonia is dried thoroughly over sodium metal before distillation into the reaction flask. If this step is not performed, a mixture of products may be obtained.[2]
5. Ammonium chloride is introduced as rapidly as possible, but with great care to avoid splashing and violent evaporation of the ammonia. The coloration of the reaction mixture will change from dark blue

to colorless within 5–10 min.
6. As much product as possible is crystallized from the residue obtained from the organic extracts. The mother liquor from the crystallization is chromatographed on a column filled with neutral alumina (available from J. T. Baker Chemical Company, powder, Brockmann Activity Grade 1) using 20 g of alumina per gram of residue (elution with $CHCl_3$/EtOAc, 1:1). Chromatography removes an impurity that makes crystallization difficult. Material purified by chromatography is also crystallized from ethyl acetate.
7. TLC analyses were performed on Macherey-Nagel Polygram SIL G UV/254 plates that were stained with a solution of phosphomolybdic acid in 95% ethanol.
8. Purified **1** has the following spectral data: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.18–1.43 (m, 4 H), 1.69–1.93 (m, 4 H), 1.95–2.08 (m, 2H), 2.19 (dt, 1 H, J = 11.3, 3.3), 2.43–2.53 (m, 1 H), 2.58 (m, 1 H), 3.46–3.69 (m, 3 H), 4.54 (t, 1 H, J = 6.8), 5.95 (s (br), 1 H); ^{13}H NMR (75 MHz, $CDCl_3$) δ: 22.2, 25.0, 25.6, 27.9, 29.7, 32.4, 48.8, 51.7, 52.5, 56.2, 170.9, 171.2; IR (KBr) cm^{-1}: 3215, 1678, 1587; chemical ionization mass spectrum, m/z (relative intensity) $M^+ + 1$ (100). Anal. Calcd for $C_{12}H_{18}N_2O_2$: C, 64.85; H, 8.15. Found: C, 64.74; H, 8.14.
9. The aqueous layer must be strongly alkaline to enable extraction of the amine.
10. The free amine cyclizes to the diamide **1** upon standing.
11. p-Toluenesulfonyl chloride is recrystallized from chloroform prior to use.
12. Column chromatography is performed using 30 g of silica per gram of residue and $CHCl_3$/EtOAc (1:1) as the eluent. The resulting clear solution is concentrated and the product crystallizes slowly upon standing.
13. The N-tosylamino derivative **3** has the following spectral data: ^{1}H NMR (300 MHz, $CDCl_3$) (≃ 4:1 mixture of rotamers) δ: 1.05–1.27 (m, 2 H), 1.35–1.54 (m, 1 H), 1.59–1.78 (m, 4 H), 1.80–2.34 (m, 5 H), 2.39 (s, 3 H), 2.61 (dt, 1 H, J = 11.5, 3.2), 3.05 (m, 1 H), 3.49 (m, 1 H), 3.71 (s, 0.6 H, minor rotamer), 3.78 (s, 2.4 H, major rotamer), 3.89 (m, 1 H), 4.48 (dd, 0.8 H, J = 8.5, 4.4, major rotamer), 4.53 (d, 0.2 H, J = 8, exchanges with D_2O, minor rotamer), 4.80 (dd, 0.2 H, J = 8.5, 3.0, minor rotamer), 5.41 (d, 0.8 H, J = 2, exchanges with D_2O, major rotamer), 7.25 (d, 2 H, J = 8, overlapping minor and major rotamers), 7.69 (d, 0.4 H, J = 8 minor rotamer), 7.74 (d, 1.6 H, J = 8, major rotamer); IR (KBr) cm^{-1}: 3260, 1740, 1611, 1417; chemical ionization mass spectrum, m/z (relative intensity) $M^+ + 1$ (100). Anal. Calcd for $C_{20}H_{28}N_2O_5S$: C, 58.82; H, 6.90. Found: C, 58.92; H, 6.92.
14. The submitters obtained yields of **4** as high as 92% after recrystallization in some runs.
15. The carboxylic acid **4** has the following spectral data: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.08–1.30 (m, 4 H), 1.48 (dd, 1 H, J = 24.5, 11.8), 1.56–1.68 (m, 3 H), 1.88–2.00 (m, 2 H), 2.28 (dt, 1 H, J = 11.1, 3.7), 2.38 (m, 4 H), 3.34 (m, 1 H), 5.27 (d, 1 H, J = 8, exchanges with D_2O), 7.26 (d, 2 H, J = 8), 7.70 (s (br), 1 H, exchanges with D_2O), 7.73 (d, 2 H, J = 8); IR (KBr) cm^{-1}: 3310, 1674, 1152; chemical ionization mass spectrum, m/z (relative intensity) 298 ($M^+ + 1$, 30), 280 (100). Anal. Calcd for $C_{14}H_{19}NO_4S$: C, 56.56; H, 6.44. Found: C, 56.60; H, 6.42.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

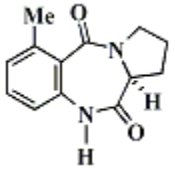
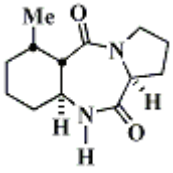
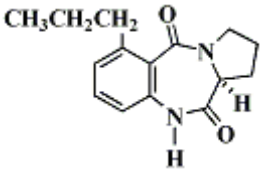
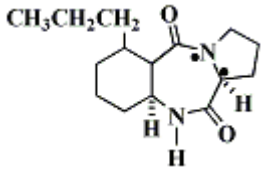
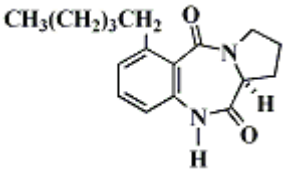
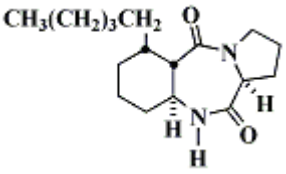
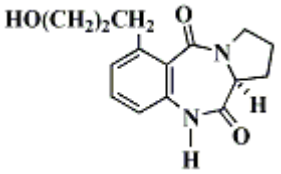
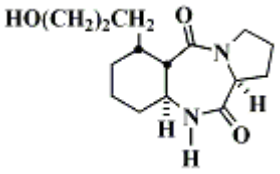
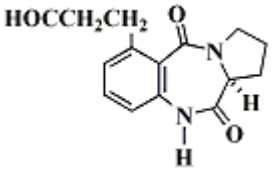
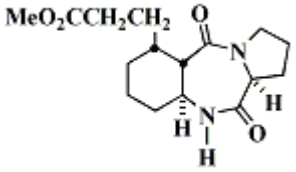
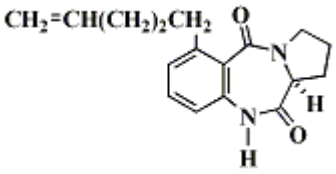
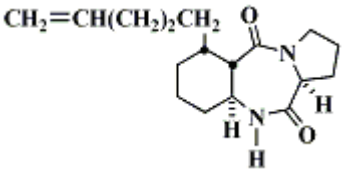
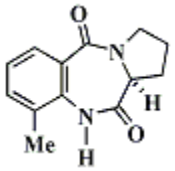
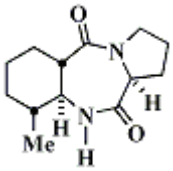
3. Discussion

Alkali metal in ammonia reductions of pyrrolobenzodiazepine-5,11-diones give trans-2-aminocyclohexanecarboxylic acid derivatives (e.g., **4**) in enantiomerically pure form.[2,3] A method for preparation of cis-2-aminocyclohexanecarboxylic acids related to **4** is based on the enantioselective hydrolysis of symmetrical diesters with pig liver esterase.[4] cis-2-Aminocyclohexane derivatives have been used for syntheses of aminocyclitol antibiotics.[4,5] 6-Alkyl-cis-2-aminocyclohexanecarboxylic acids can be prepared by alkali metal in ammonia reduction of pyrrolobenzodiazepine-5,11-diones followed by olefin hydrogenation; the cis-decahydroquinoline alkaloid (+)-pumiliotoxin C has been prepared by this methodology.[2]

The preparation of **4** described here can be modified to provide a range of substitution patterns as shown in the Table. Some of the derivatives have been used for enantioselective syntheses of poison frog alkaloids that possess the trans-decahydroquinoline ring system.[3,6] The 6-alkyl substituted

pyrrolobenzodiazepine-5,11-diones shown in the Table were prepared by metallation of the 6-methylpyrrolobenzodiazepine-5,11-dione with 2 equiv of butyllithium followed by addition of the appropriate alkylation reagent.[3,6] The highly stereoselective alkali metal in ammonia reductions of pyrrolobenzodiazepine-5,11-diones are a special application of a quite general method for enantioselective synthesis of chiral cyclohexanes from benzoic acid derivatives.[7]

TABLE
CHIRAL CYCLOHEXANE DERIVATIVES

Substrate	Product	Yield (%)
		91[a]
		83[b]
		90[c]
		92[d]
		52[e,f]
		90[c]
		80[a]

[a]See ref. [2]. [b]See ref. [3]. [c]See ref. [4]. [d]Unpublished work of C. Alva. [e]Unpublished work

of L. Waykole. [f]The alkali metal in ammonia reduction product was treated with diazomethane.

References and Notes

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

amine

sodium benzophenone ketyl

pyrrolobenzodiazepine-5,11-diones

6-methylpyrrolobenzodiazepine-5,11-dione

ethanol (64-17-5)

sulfuric acid (7664-93-9)

ammonia (7664-41-7)

ethyl acetate (141-78-6)

methanol (67-56-1)

ammonium chloride (12125-02-9)

chloroform (67-66-3)

sodium bicarbonate (144-55-8)

sodium chloride (7647-14-5)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

sodium (13966-32-0)

ammonium hydroxide (1336-21-6)

potassium (7440-09-7)

dichloromethane (75-09-2)

magnesium sulfate (7487-88-9)

butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

triethylamine (121-44-8)

tert-butyl alcohol (75-65-0)

phosphomolybdic acid (51429-74-4)

p-Toluenesulfonyl chloride (98-59-9)

(1S,2S)-2-(N-Tosylamino)cyclohexanecarboxylic acid (110456-11-6)

(5aS,9aS,11aS)-Perhydro-5H-pyrrolo[2,1-c][1,4]benzodiazepine-5,11-dione (110419-86-8)

(S)-(+)-2,3-dihydro-1H-pyrrolo[2,1-c][1,4]benzodiazepine-5,11(10H,11aH)dione,
(S)-(+)-2,3-Dihydro-1H-pyrrolo[2,1-c][1,4]benzodiazepine-5,11(10H,11aH)-dione

(1S,2S)-2-Amino-1-[((2S)-2-carbomethoxypyrrolidinyl)carbonyl]cyclohexane (174624-00-1)

(1S,2S)-2-(N-Tosylamino)-1-[((2S)-2-carbomethoxypyrrolidinyl)carbonyl] cyclohexane (110419-91-5)