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Expedient Preparation of All Isomers of 2-Aminocyclobutanecarboxylic Acid in Enantiomerically Pure Form

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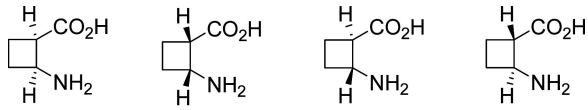

A short, convenient, gram scale protocol has been established to allow facile access to all four stereoisomers of 2-aminocyclobutanecarboxylic acid, each in enantiomerically pure form (ee >99%). Starting from the readily available cis racemate, the procedure combines efficient α-phenylethylamine derivative resolution and controlled cis-to-trans epimerization procedures, and proceeds with invariably high yields.

There is considerable interest in alicyclic β-amino acids as intermediates in synthetic chemistry, as structural features in biologically active compounds, and as valuable components for the design and synthesis of molecular architectures bestowed with local or long-ranging self-organizational ability.[1] Recently, cyclobutane β-amino acids have begun to show a potential that is comparable with that of their 5- and 6-membered congeners. A strong tendency for regular structuring in peptides containing this moiety has been demonstrated,[2] and very recently a cyclobutane β-tetrapeptide self-assembled to produce nanosized fibrils.[3] Furthermore, patent literature suggests that cyclobutane β-amino acid building blocks are increasingly a part of the molecular inventory for the construction of new biologically active materials.[4] Given this interest, a convenient access to the enantiomerically pure parent amino acids is of major importance.

While many elegant approaches have been described for the asymmetric synthesis of β-amino acids,[5] only a few of these are applicable for the preparation of cyclic compounds.[6] The synthesis of enantiomerically pure *cis*-cyclobutane β-amino acid was described by each of the groups of Ortuño[7] and Bolm,[8] using an approach based on the enantioselective desymmetrization of a derivative of *meso*-1,2-cyclobutanedicarboxylic acid.[9] Recently, we described an alternative approach based on the [2+2] photocycloaddition reaction of ethene with a nonracemic uracil derivative, which furnished both enantiomers of the cis compound.[10] A protocol for the transformation of each cis enantiomer into its corresponding trans isomer was also described.[10a] To date, this is the only published preparation of the trans compounds in enantiomerically pure form. However, due to the likely increase in demand for these materials for the above-stated reasons, we sought a more practical access to the title compound in its various stereochemical forms.

To this end, racemic *cis*-2-aminocyclobutanecarboxylic acid, (±)-*cis*-**1**, was considered a good entry point. Multigram quantities of this compound are readily available via a short photochemical route[11] or through conventional transformations of *meso*-cyclobutane-1,2-dicarboxylic acid derivatives.[7,8,12]

The first objective was to optimize the cis-to-trans isomerization procedure. This was a considerably more delicate operation than the corresponding transformation for the cyclopentane and cyclohexane congeners, generally done with carboxylic ester derivatives.[13] Indeed, basic treatment of an *N*-Boc methyl ester derivative of (±)-*cis*-**1** was previously shown to give 60% yield of the trans isomer at best;[10a] furthermore, the process is capricious and loss of material is a

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(1) Reviews: (a) Fülöp, F. *Chem. Rev.* **2001**, *101*, 2181–2204. (b) Kuhl, A.; Hahn, M. G.; Dumić, M.; Mittendorf, J. *Amino Acids* **2005**, *29*, 89–100. (c) Fülöp, F.; Martinek, T. A.; Tóth, G. *Chem. Soc. Rev.* **2006**, *35*, 323–334.

(2) (a) Izquierdo, S.; Rúa, F.; Sbai, A.; Parella, T.; Álvarez-Larena, Á.; Branchadell, V.; Ortuño, R. M. *J. Org. Chem.* **2005**, *70*, 7963–7971. (b) Izquierdo, S.; Kogan, M. J.; Parella, T.; Moglioni, A. G.; Branchadell, V.; Giralt, E.; Ortuño, R. M. *J. Org. Chem.* **2004**, *69*, 5093–5099.

(3) Rúa, F.; Boussert, S.; Parella, T.; Díez-Pérez, I.; Branchadell, V.; Giralt, E.; Ortuño, R. M. *Org. Lett.* **2007**, *9*, 3643–3645.

(4) Recent patents: (a) Zenkoh, T.; Nozawa, E.; Matsuura, K.; Seo, R. *Chem. Abstr.* **2008**, *149*, 471824. (b) Barchuk, W. T.; Dunford, P. J.; Edwards, J. P.; Fourie, A. M.; Karlsson, L.; Quan, J. M. *Chem. Abstr.* **2008**, *149*, 268051. (c) Zahn, S. K.; Bister, B.; Boehmelt, G.; Guertler, U.; Mantoulidis, A.; Reiser, U.; Schoop, A.; Solca, F.; Tontsch-Grunt, U.; Treu, M. *Chem. Abstr.* **2008**, *148*, 11249.

(5) (a) *Enantioselective Synthesis of β-Amino Acids*, 2nd ed.; Juaristi, E., Soloshonok, V. A., Eds.; Wiley-VCH: Weinheim, Germany, 2005. (b) Liu, M.; Sibi, M. P. *Tetrahedron* **2002**, *58*, 7991–8035.

(6) For reviews which include particular mention of cyclobutane β-amino acids, see: (a) Ortuño, R. M.; Moglioni, A. G.; Moltrasio, G. Y. *Curr. Org. Chem.* **2005**, *9*, 237–259. (b) Ortuño, R. M. In *Enantioselective Synthesis of β-Amino Acids*, 2nd ed.; Juaristi, E., Soloshonok, V. A., Eds.; Wiley-VCH: Weinheim, Germany, 2005; Chapter 5, pp 117−137. (c) Avotins, F. M. *Russ. Chem. Rev.* **1993**, *62*, 897–906.

(7) (a) Martín-Vilà, M.; Muray, E.; Aguado, G. P.; Alvarez-Larena, A.; Branchadell, V.; Minguillón, C.; Giralt, E.; Ortuño, R. M. *Tetrahedron: Asymmetry* **2000**, *11*, 3569–3584. (b) Martín-Vilà, M.; Minguillón, C.; Ortuño, R. M. *Tetrahedron: Asymmetry* **1998**, *9*, 4291–4294.

(8) Bolm, C.; Schiffers, I.; Atodiresei, I.; Hackenberger, C. P. R. *Tetrahedron: Asymmetry* **2003**, *14*, 3455–3467.

(9) For a recent review on the desymmetrization of cyclic *meso*-anhydrides, see: Atodiresei, I.; Schiffers, I.; Bolm, C. *Chem. Rev.* **2007**, *107*, 5683–5712.

(10) (a) Fernandes, C.; Gauzy, C.; Yang, Y.; Pereira, E.; Faure, S.; Aitken, D. J. *Synthesis* **2007**, 2222–2232. (b) Gauzy, C.; Pereira, E.; Faure, S.; Aitken, D. J. *Tetrahedron Lett.* **2004**, *45*, 7095–7097.

(11) (a) Aitken, D. J.; Gauzy, C.; Pereira, E. *Tetrahedron Lett.* **2002**, *43*, 6177–6179. (b) Gauzy, C.; Saby, B.; Pereira, E.; Faure, S.; Aitken, D. J. *Synlett* **2006**, 1394–1398.

(12) Kennewell, P. D.; Matharu, S. S.; Taylor, J. B.; Westwood, R.; Sammes, P. G. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2563–2570.

(13) Davies, S. G.; Ichihara, O.; Lenoir, I.; Walters, I. A. S. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1411–1414.

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SCHEME 1. Epimerization Protocol for Racemic Amino Acid 1

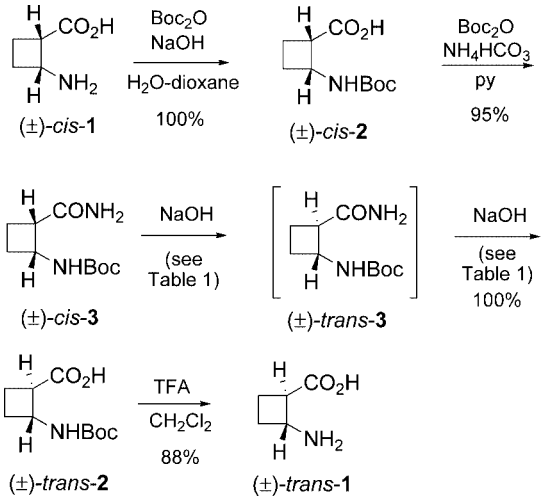


TABLE 1. Qualitative Evaluation of the Transformation of Racemic *cis*-3 under Basic Conditions[a]

			reflux	
entry	NaOH solution (molar equiv)	rt, 4 h	4 h	18 h
1	0.04 M (2 equiv)	*cis*-**3**	*cis*-**3**	*trans*-**3**
2	0.2 M (10 equiv)	*cis*-**3**	*trans*-**3**	*trans*-**2**
3	1.5 M (90 equiv)	*cis*-**3**	*trans*-**2**	*trans*-**2**

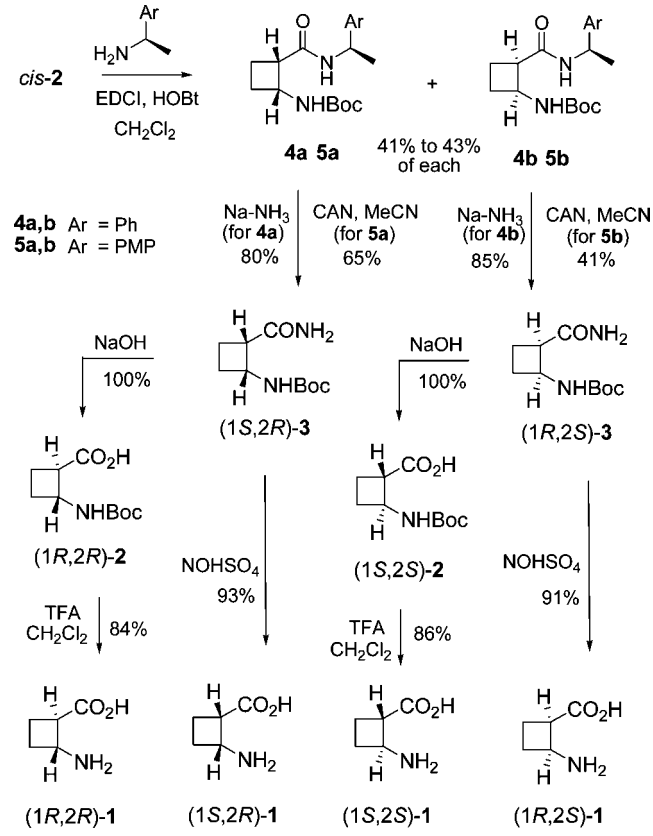
[a] Reactions were conducted with use of racemic material in aqueous methanol solution on a 0.2 mmol scale. For each entry, the sample was subjected successively to the conditions indicated in the three columns. The evolution of the reaction was examined at the end of each reaction period (by ^{1}H NMR); the major constituent (>80%) of the mixture is reported.

frequent problem, doubtless due to the push−pull ring opening propensity of the system.[2a,14] We reasoned that an alternative carboxylic acid derivative might be better suited for this operation for the cyclobutane skeleton, and after some unproductive experimentation with urea derivatives we focused on a primary carboxamide function.

Racemic *N*-Boc-amino carboxamide derivative (±)-*cis*-**3** was prepared easily from (±)-*cis*-**1** in two steps in 95% yield (Scheme 1). From the preliminary studies on the behavior of this material in the presence of NaOH in aqueous methanol, it soon became apparent that more than one process was operating. Various reaction conditions were investigated and the evolution of each reaction mixture was followed by NMR analysis of a small sample; the qualitative results of these analyses are summarized in Table 1.

The reaction of starting material (±)-*cis*-**3** produced first the epimer (±)-*trans*-**3**, which was in turn transformed into the *N*-Boc-amino acid (±)-*trans*-**2** (as its sodium salt until final acid workup). Base strength and reaction temperature determined the rapidity of this tandem process. The intermediate (±)-*trans*-**3** was isolated and characterized in one preparative run, while the two-step transformation of (±)-*cis*-**3** was optimized for preparative purposes by refluxing in 1.5 M NaOH (in aqueous MeOH) for 12 h, which provided (±)-*trans*-**2** in quantitative yield. This highly gratifying result warrants further comment. First, while an *N*-Boc group is generally reputed to be stable in

SCHEME 2. Resolution Protocols Leading to Enantiomerically Pure Amino Acids 1



basic medium, the entirely chemoselective alkaline hydrolysis of a primary carboxamide in the presence of a *tert*-butyl carbamate is noteworthy, since this operation is not often encountered in the literature.[15] Furthermore, no trace of (±)-*cis*-**2** was detected at any time, and it was verified in a separate control reaction that (±)-*cis*-**2** is completely stable in the basic reaction conditions. This implies the specific sequence of events presented in Scheme 1: compound (±)-*cis*-**3** reacts with NaOH by epimerizing to provide (±)-*trans*-**3**; this process may or may not be reversible, but only the latter isomer undergoes carboxamide hydrolysis to provide a carboxylate product. With this completely selective tandem operation secured, TFA-mediated *N*-Boc group cleavage of (±)-*trans*-**2** completed access to (±)-*trans*-**1** (Scheme 1). Overall, the transformation of *cis*-**1** to *trans*-**1** is remarkably efficient (84% overall yield).

We next sought to combine this operation with a practical resolution procedure to access all stereoisomers of the target amino acid. α-Phenylethylamine and some derivatives are commercially available and have an established portfolio as chiral reagents for the preparation of enantiomerically pure compounds.[16] One of the advantages of using these chiral agents is that their "easy-on-easy-off" resolution protocols can be combined with a net structural transformation. We felt that this class of reagent should be able to provide resolved *cis*-**3** from (±)-*cis*-**2** in only two steps, and indeed two complementary procedures were established to this end (Scheme 2).

(14) Aitken, D. J.; Gauzy, C.; Pereira, E. *Tetrahedron Lett.* **2004**, *45*, 2359–2361.

(15) For a precedent, see: Onoprienko, V. V.; Yelin, E. A.; Miroshnikov, A. I. *Russ. J. Bioorg. Chem.* **2000**, *26*, 361–368.

(16) (a) Juaristi, E.; Escalante, J.; León-Romo, J. L.; Reyes, A. *Tetrahedron: Asymmetry* **1998**, *9*, 715–740. (b) Juaristi, E.; León-Romo, J. L.; Reyes, A.; Escalante, J. *Tetrahedron: Asymmetry* **1999**, *10*, 2441–2495.

Condensation of (±)-*cis*-**2** with commercial (*R*)-α-phenylethylamine gave a mixture of diastereoisomers **4a** and **4b** which were completely separated by column chromatography. The isolated yield of each pure stereoisomer was reproducibly above 40%. Each was then treated with sodium in liquid ammonia to cleave the *N*-benzylic bond and furnish enantiomerically pure *cis*-**3** efficiently. As an alternative that avoids the Na/NH_3 procedure, diastereomeric amides **5a** and **5b** were prepared with (*R*)-α-(*p*-methoxyphenyl)ethylamine and were separated chromatographically, again with good isolated material recovery (above 40% for each isomer). Conversion of each compound into the corresponding *cis*-**3** enantiomer was achieved by using ceric ammonium nitrate. All of the above procedures can be reproduced on quantities up to gram scale.[17]

Each pure enantiomer of *cis*-**3** was easily transformed into either the cis or trans isomer of **1** (Scheme 2). For the trans isomers, the procedures which had been established above for racemic materials were reproduced successfully. In practice, stock samples of each enantiomer of the intermediate *trans*-**2** are prepared on several-hundred milligram scale, since this compound is completely stable. The final *N*-deprotection step is best performed only on such quantities of amino acid as are required, since this material is visibly less stable over time.

For direct access to enantiomerically pure *cis*-**1**, we found after some experimentation that commercial nitrosylsulfonic acid solution[18] was a very convenient reagent for the one-pot combined cleavage of the *N*-Boc group and controlled diazotization of the carboxamide of *cis*-**3** (Scheme 2). This operation was complete within 2 h at ambient temperature, with no significant over-reaction (diazotization of the amine) and no trace of epimerization. Thus each enantiomer of *cis*-**3** can be converted smoothly into the corresponding *cis*-**1** enantiomer in a single, high-yielding reaction (>90%).

In conclusion, we have established a short and efficient protocol, combining resolution and controlled epimerization, to provide access to all the stereoisomers of the title cyclobutane amino acid from a single parent racemate. This approach highlights the use of a carboxamide rather than an ester function for the epimerization step, and has several advantages over the only other previous route to the trans isomers of the target amino acid in enantiomerically pure form. Although we have applied the process to obtain hundred-milligram quantities of intermediates (sufficient for our requirements), the procedures appear amenable to larger scale preparations. By extension, they should also have useful applications in the configuration control and functional group manipulation of other β-amino acid derivatives.

Experimental Section

Carboxamides 4a and 4b. To a solution of (±)-*cis*-**2** (1.98 g, 9.20 mmol) in dry CH_2Cl_2 (170 mL) at 0 °C under argon were added 1-hydroxybenzotriazole monohydrate (1.96 g, 12.8 mmol) and (*R*)-α-phenylethylamine (1.22 g, 10.1 mmol). After 10 min, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (2.63 g, 13.7 mmol) was added and the cooling bath was removed; the mixture was stirred at rt for 12 h, then washed with 5% citric acid solution (170 mL) then with saturated $NaHCO_3$ solution (170 mL). The organic layer was dried with $MgSO_4$, filtered, and evaporated. Flash chromatography (EtOAc/cyclohexane 15:85) of the residue furnished **4a** (1.26 g, 43%) and **4b** (1.23 g, 42%).

Carboxamides 5a and 5b. To a solution of (±)-*cis*-**2** (2.50 g, 11.6 mmol) in dry CH_2Cl_2 (210 mL) at 0 °C under argon were added 1-hydroxybenzotriazole monohydrate (2.19 g, 16.2 mmol) and (*R*)-α-(*p*-methoxyphenyl)ethylamine (1.86 g, 12.7 mmol). After 10 min, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (3.33 g, 17.4 mmol) was added and the cooling bath was removed; the mixture was stirred at rt for 12 h, then washed with 5% citric acid solution (210 mL) then saturated $NaHCO_3$ solution (210 mL). The organic layer was dried with $MgSO_4$, filtrated, and evaporated. Flash chromatography (EtOAc/cyclohexane 15:85) of the residue furnished **5a** (1.70 g, 42%) and **5b** (1.66 g, 41%).

(+)-(1*S*,2*R*)-2-(*tert*-Butyloxycarbonylamino)cyclobutanecarboxamide, (+)-(1*S*,2*R*)-3. Method A: Sodium (0.50 g, 21.7 mmol) was added under a stream of argon to liquid ammonia (50 mL) at −40 °C. A solution of amide **4a** (1.00 g, 3.14 mmol) in THF (30 mL) was added, and the mixture was stirred at −40 °C for 1 h then quenched by addition of solid NH_4Cl (1.76 g, 32.9 mmol) and allowed to warm to rt as the ammonia evaporated. Water (30 mL) was added to the residual solution, then 1 M HCl was added slowly until pH 7. The mixture was extracted with CH_2Cl_2 (3 × 45 mL), and combined organic extracts were dried with anhydrous $MgSO_4$, filtered, and evaporated. Flash chromatography (EtOAc/cyclohexane 50:50) provided the title compound as a white powder (0.54 g, 80%).

Method B: A solution of amide **5a** (0.75 g, 2.15 mmol) and CAN (5.86 g, 10.7 mmol) in acetonitrile (75 mL) and water (20 mL) was stirred at rt until TLC analysis showed no remaining starting material (approximately 1 h). The mixture was diluted with water (20 mL) and extracted with EtOAc (3 × 20 mL). The combined extracts were washed successively with saturated $NaHCO_3$ solution (6 mL) and water (10 mL), dried with $MgSO_4$, then evaporated to give crude product. Flash chromatography (EtOAc/cyclohexane 50:50) provided the title compound as a white powder (0.30 g, 65%).

(−)-(1*R*,2*S*)-2-(*tert*-Butyloxycarbonylamino)cyclobutanecarboxamide, (−)-(1*R*,2*S*)-3. Method A: Sodium (0.33 g, 14.3 mmol) was added under a stream of argon to liquid ammonia (35 mL) at −40 °C. A solution of amide **4b** (0.67 g, 2.10 mmol) in THF (23 mL) was added, and the mixture was stirred at −40 °C for 1 h then quenched by addition of solid NH_4Cl (1.17 g, 21.9 mmol) and allowed to warm to rt as the ammonia evaporated. Water (20 mL) was added to the residual solution, then 1 M HCl was added slowly until pH 7. The mixture was extracted with CH_2Cl_2 (3 × 30 mL), and combined organic extracts were dried with anhydrous $MgSO_4$, filtered, and evaporated. Flash chromatography (EtOAc/cyclohexane 50:50) provided the title compound as a white powder (0.38 g, 85%).

Method B: A solution of amide **5b** (0.48 g, 1.38 mmol) and CAN (3.84 g, 7.00 mmol) in acetonitrile (60 mL) and water (15 mL) was stirred at rt until TLC analysis showed no remaining starting material (approximately 1 h). The mixture was diluted with water (15 mL) and extracted with EtOAc (3 × 15 mL). The extracts were washed successively with saturated $NaHCO_3$ solution (3 mL) and water (5 mL), dried with $MgSO_4$, then evaporated to give crude product. Flash chromatography (EtOAc/cyclohexane 50:50) provided the title compound as a white powder (0.12 g, 41%).

(+)-(1*R*,2*R*)-2-(*tert*-Butyloxycarbonylamino)cyclobutanecarboxylic Acid, (+)-(1*R*,2*R*)-2. A solution of (+)-(1*S*,2*R*)-**3** (0.46 g, 2.15 mmol) in MeOH (90 mL) was treated with 6.25 M aqueous NaOH solution (30 mL) and the mixture was heated at reflux for 12 h. The methanol was then removed by careful evaporation under reduced pressure and the residual aqueous phase was washed with EtOAc (3 × 40 mL). The aqueous phase was then cooled at −5 °C, while concd HCl was added slowly until pH 2. The aqueous phase was then extracted with EtOAc (3 × 80 mL) and the combined organic extracts were dried with $MgSO_4$ and concentrated under vacuum. Flash chromatography (EtOAc/HOAc 99.7:0.3)

(17) The possibility of epimerization of **4** or **5** to give trans-isomers was considered. In a series of tests, however, **4a/4b** mixtures were recovered completely unreacted from basic aqueous conditions, or extensively degraded when treated with *t*-BuOK/THF at reflux. For a related use of these latter conditions, see: Priego, J.; Flores, P.; Ortiz-Nava, C.; Escalante, J. *Tetrahedron: Asymmetry* **2004**, *15*, 3545–3549.

(18) Wade, L. G.; Silvey, W. B. *Org. Prep. Proced. Int.* **1982**, *14*, 357–359.

provided the title compound as a white powder (0.46 g, 100%). $[\alpha]^{27}_{D}$ +44 (*c* 0.50, $CHCl_3$). Other physical and spectral data for this compound were identical with those reported previously.[10a]

(−)-(1*S*,2*S*)-2-(*tert*-Butyloxycarbonylamino)cyclobutanecarboxylic Acid, (−)-(1*S*,2*S*)-2. A solution of (−)-(1*R*,2*S*)-**3** (0.10 g, 0.47 mmol) in MeOH (20 mL) was treated with 6.25 M aqueous NaOH (7 mL) and the mixture was heated at reflux for 12 h. The methanol was then removed by careful evaporation under reduced pressure and the residual aqueous phase was washed with EtOAc (3 × 20 mL). The aqueous phase was then cooled at −5 °C, while concd HCl was added slowly until pH 2. The aqueous phase was then extracted with EtOAc (3 × 40 mL) and the combined organic extracts were dried with $MgSO_4$ and concentrated under vacuum. Flash chromatography (EtOAc/HOAc 99.7:0.3) provided the title compound as a white powder (0.10 g, 100%). $[\alpha]^{27}_{D}$ −44 (*c* 0.50, $CHCl_3$). Other physical and spectral data for this compound were identical with those reported previously.[10a]

(+)-(1*S*,2*R*)-2-Aminocyclobutanecarboxylic Acid, (+)-(1*S*,2*R*)-1. Commercial nitrosylsulfuric acid (40% solution in concd H_2SO_4; 0.45 mL) was added cautiously to water (0.18 mL) that was chilled in an ice bath. Solid amide (+)-(1*S*,2*R*)-**3** (50 mg, 0.23 mmol) was added, and the mixture was allowed to warm to rt over 2 h while being stirred. The reaction mixture was poured over crushed ice (1.2 g). After warming to rt, the solution was applied to an ion exchange column; elution provided the title compound as a white powder (25 mg, 93%). $[\alpha]^{27}_{D}$ +70 (*c* 0.50, H_2O). Chiral HPLC analysis: >99% ee. Other physical and spectral data for this compound were identical with those reported previously.[2a,10a]

(−)-(1*R*,2*S*)-2-Aminocyclobutanecarboxylic Acid, (−)-(1*R*,2*S*)-1. Commercial nitrosylsulfuric acid (40% solution in concd H_2SO_4; 0.45 mL) was added cautiously to water (0.18 mL) that was chilled in an ice bath. Solid amide (−)-(1*R*,2*S*)-**3** (50 mg, 0.23 mmol) was added, and the mixture was allowed to warm to rt over 2 h while being stirred. The reaction mixture was poured over crushed ice (1.2 g). After warming to rt, the solution was applied to an ion exchange column; elution provided the title compound as a white powder (24.5 mg, 91%). $[\alpha]^{27}_{D}$ −70 (*c* 0.55, H_2O). Chiral HPLC analysis: >99% ee. Other physical and spectral data for this compound were identical with those reported previously.[2a,8,10a]

(−)-(1*R*,2*R*)-2-Aminocyclobutanecarboxylic Acid, (−)-(1*R*,2*R*)-1. TFA (0.42 mL) was added dropwise to a solution of (+)-(1*R*,2*R*)-**2** (40 mg, 0.19 mmol) in dry CH_2Cl_2 (1.2 mL) at rt. The mixture was stirred for 30 min then evaporated under vacuum to leave a brown residue. This material was taken up in water and purified on an ion exchange column to provide the title compound as a white solid (18 mg, 84%). $[\alpha]^{27}_{D}$ −99 (*c* 0.55, H_2O). Chiral HPLC analysis: >99% ee. Other physical and spectral data for this compound were identical with those reported previously.[10a]

(+)-(1*S*,2*S*)-2-Aminocyclobutanecarboxylic Acid, (+)-(1*S*,2*S*)-1. TFA (0.40 mL) was added dropwise to a solution of (−)-(1*S*,2*S*)-**2** (37 mg, 0.17 mmol) in dry CH_2Cl_2 (1.0 mL) at rt. The mixture was stirred for 30 min then evaporated under vacuum to leave a brown residue. This material was taken up in water and purified on an ion exchange column to provide the title compound as a white solid (17 mg, 86%). $[\alpha]^{27}_{D}$ +99 (*c* 0.45, H_2O). Chiral HPLC analysis: >99% ee. Other physical and spectral data for this compound were identical with those reported previously.[10a]

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Supporting Information Available: Full experimental procedures, characterization, and copies of NMR spectra of all compounds and copies of chiral hplc chromatograms of each stereoisomer of the title compound. This material is available free of charge via the Internet at http://pubs.acs.org.

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