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Asymmetric Diels−Alder Reactions of Chiral Cyclopropylidene Imide Dienophiles: Preparation of *gem*-Dimethyl- and Spirocyclopropane Norbornyl Carboxylic Acids

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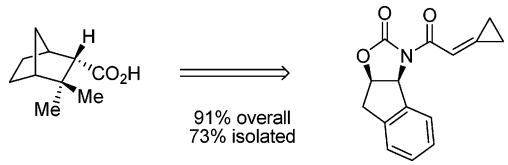
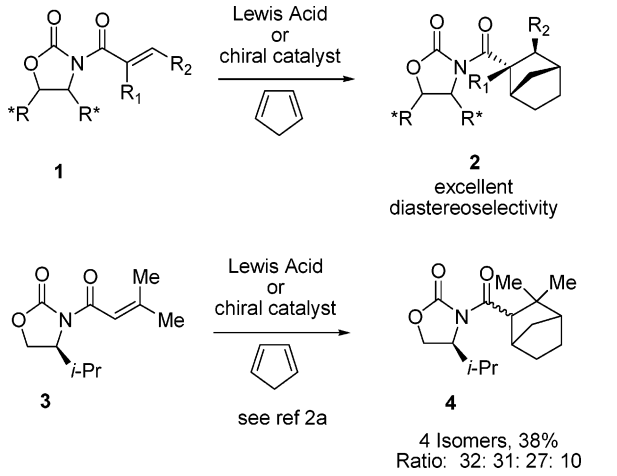


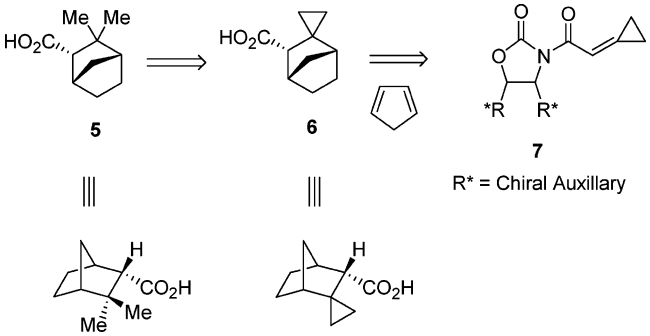
A highly efficient strategy has been developed for the rapid asymmetric synthesis of *gem*-dimethyl and spirocyclopropyl norbornyl carboxylic acids. The key transformation involved the unprecedented asymmetric Diels−Alder reaction of highly reactive β,β-cyclopropyl-α,β-unstaturated *N*-acyloxazolidinones with cyclopentadiene affording the adducts in high yield and de.

The Diels−Alder reaction provides a highly efficient and rapid means of constructing functionalized six-membered ring systems often with complete control of the regio-, diastereo-, and enantioselectivity. In particular, asymmetric Diels−Alder reactions are among the most powerful and versatile organic transformations in chemical synthesis.[1] The pioneering work of Evans[2] using oxazolidinones derived from amino alcohols as chiral auxiliaries has led to the discovery of a number of chiral Lewis acid catalytic variants.[1] In addition, recent developments employing organocatalysis have emerged as a remarkable means of controlling enantioselective catalytic cycloaddition reactions.[3,4] Due to the limited availability, cost, and high catalyst loading (typically 10−30 mol %) associated with most asymmetric catalytic Diels−Alder reactions, these methods have remained mainly academic. In recent years, auxiliary-based asymmetric Diels−Alder reactions have become particularly attractive since many oxazolidinone auxiliaries are inexpensive, commercially available in both optical antipodes, and can easily be recovered and recycled after nondestructive cleavage from the substrate. While monosubstituted (R_1 = H) and *E*-disubstituted ($R_1 \neq$ H) imide dienophiles **1** readily participate in both auxiliary-based and catalytic Diels−Alder reactions with various dienes, β,β-disubstituted imide dienophiles of type **3** exhibit poor reactivity and generally give a mixture of all four possible diastereomeric products (Scheme 1). Indeed, reaction of **3** with cyclopentadiene was reported to only proceed at rt to give **4** as a mixture of diastereomers in 38% combined yield.[2a] This poor reactivity was attributed to steric influences where the *Z*-substituent destabilizes the *S*-cis unsaturated carbonyl conformation.

SCHEME 1



SCHEME 2



Recently, we required an efficient route for the construction of the *gem*-dimethylnorbornyl carboxylic acid **5**[5] (Scheme 2). We reasoned that an asymmetric Diels−Alder reaction between the highly reactive β,β-cyclopropyl-α,β-unsaturated *N*-acyloxy-

(1) For recent reviews of enantioselective Diels−Alder reactions, see: (a) Evans, D. A.; Johnson, J. S. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, 1999; Vol. 3, p 1177 and references therein. (b) Oppolzer, W. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: New York, 1991; Vol. 5. (c) Kagan, H. B.; Riant, O. *Chem. Rev.* **1992**, *92*, 1007. (d) Dias, L. C. *J. Braz. Chem. Soc.* **1997**, *8*, 289. (e) Corey, E. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 1650.

(2) (a) Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238. (b) Evans, D. A.; Chapman, K. T.; Bisaha, J. *Tetrahedron Lett.* **1984**, *25*, 4071. (c) Evans, D. A.; Chapman, K. T.; Hung, D. T.; Kawaguchi, A.; Bisaha, J. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1184.

(3) For reviews on organocatalysis, see: (a) Jarvo, E. R.; Miller, S. J. *Tetrahedron* **2002**, *58*, 2481. (b) List, B. *Tetrahedron* **2002**, *58*, 5573. (c) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138. (d) *Acc. Chem. Res.* **2004**, *37* (8) (special issue on organocatalysis). (e) Bolm, C.; Rantanen, T.; Schiffers, I.; Zani, L. *Angew. Chem., Int. Ed.* **2005**, *44*, 1758.

(4) For organocatalysis in asymmetric Diels−Alder reactions, see: (a) Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243. (b) Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 2458. (c) Kim, K. H.; Lee, S.; Lee, D.-W.; Ko, D.-H.; Ha, D.-C. *Tetrahedron Lett* **2005**, *46*, 5991.

(5) The enantiomer of acid **5** has been reported to have cytotoxic effects on cancer cell lines, see: Jaeger, W.; Paesler, B.; Buchgauer, G.; Chiba, P. *Pharmazie* **1995**, *50*, 619.

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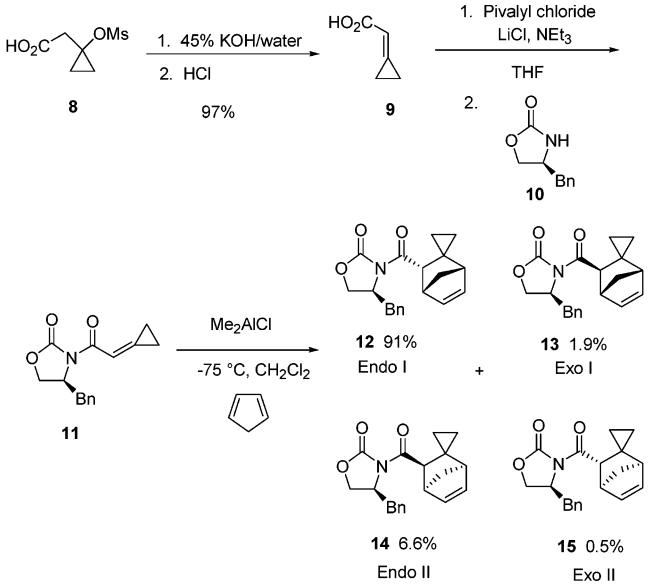
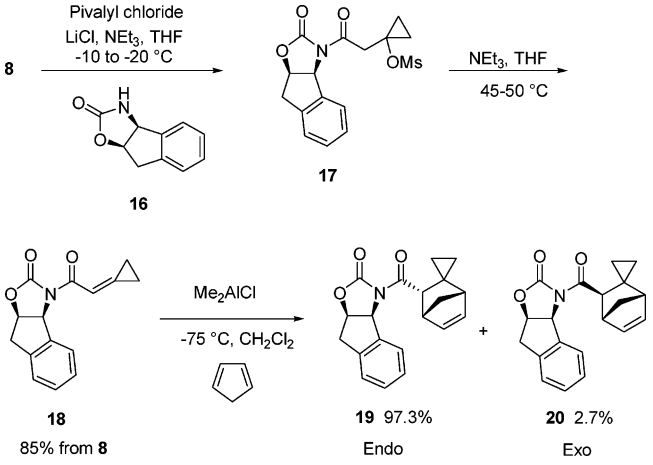
SCHEME 3



azolidinones of type **7** and cyclopentadiene could offer a rapid method for the preparation of spirocyclopropyl norbornyl carboxylic acid **6**.[6,7] Since the cyclopropane ring can be considered as a *gem*-dimethyl surrogate, this approach was particularly attractive and would circumvent the poor diastereoselective Diels−Alder reaction of **3**. In this paper, we document a practical and highly efficient synthesis of **5** and **6** via the unprecedented asymmetric Diels−Alder reactions of chiral cyclopropylidene imide dienophiles **7** with cyclopentadiene.

Our first challenge was preparation of the required cyclopropylidene imide dienophile (Scheme 3). Reaction of the known mesyl acid **8**[8] with oxalyl chloride followed by treatment with the lithium salt of oxazolidinone **10** under standard conditions[2a] afforded the desired cyclopropylidene imide dienophile **11** in <30% isolated yield. No acylated intermediates bearing a mesyloxy group were identified in the crude reaction mixture. Elimination of the mesyl group of **8** by treatment with 45% KOH in water followed by an extractive workup gave cyclopropenyl acid **9** in 97% isolated yield. Treatment of the acid chloride of acid **9** with the lithium salt of oxazolidinone **10** was equally unsuccessful, giving **11** in <30% yield. In each of these cases, significant unidentified impurities resulting from apparent ring-opening of the cyclopropyl group were observed. Reaction of **9** with pivaloyl chloride in the presence of LiCl, NEt_3, and oxazolidinone **10** afforded the desired **11** in an unoptimized 75% yield.[9] The product was conveniently obtained by direct crystallization from the crude reaction mixture. The Diels−Alder reaction of **11** with cyclopentadiene was conducted by slow addition of 1.4 equiv of Me_2AlCl (1 M in hexanes) to a mixture of **11** and 1.6 equiv of cyclopentadiene at −75 °C. HPLC analysis of the crude reaction mixture revealed the formation of 4 diastereomeric products in a ratio of 91:1.9:6.6:0.5 (**12**/**13**/**14**/**15**) and in a combined yield of 97%.[10] The desired *endo* adduct **12** was obtained in diastereomerically pure form (> 99:1, 80% isolated yield) by recrystallization of the crude reaction mixture from either *n*-heptane or cyclohexane. The relative and absolute stereochemistry of **12** was unambiguously established by single-crystal X-ray analysis.[11] It should also be noted that the use of Me_2AlCl in either heptane or hexanes gave slightly higher de than Et_2AlCl solutions, and the use of either of these Lewis acids as solutions in toluene resulted in a substantial erosion in de.

SCHEME 4



Inspired by previous reports from these laboratories,[12] we examined the Diels−Alder reaction of the conformationally constrained cyclopropylidene imide dienophile **18**. Dienophile **18** was prepared in excellent overall yield by the procedure outlined in Scheme 4. After considerable optimization, it was discovered that slow addition of NEt_3 to a mixture of mesyl acid **8**, LiCl, pivalyl chloride, and aminoindanone **16** in THF at −10 to −20 °C followed by the addition of water afforded the highly crystalline intermediate **17** in 88% yield. Subsequent reaction with NEt_3 in THF at 45−50 °C gave **18** in 85% overall yield. This two-step process eliminated undesired Michael addition products resulting from the addition of either chloride or pivalic acid to the reactive cyclopropenyl imide double bond.[6,13] The Diels−Alder reaction of **18** was conducted below −70 °C with 1.4 equiv of Me_2AlCl in the presence of 1.6 equiv of cyclopentadiene and provided a mixture of *endo* product **19** and *exo* product **20** as the exclusive products in a 97.3:2.7 ratio in near-quantitative yield. There were no detectable amounts of any other diastereomeric products by either proton NMR or HPLC analysis of the crude reaction mixture. Attempts to upgrade the diastereomeric ratio of **19** by crystallization from a number of solvent systems only resulted in a net upgrade of the undesired *exo* product **20**, and this mixture was used crude without purification.

(6) For a review on the synthesis of various alkylidenecyclopropanes, see: Brandi, A.; Goti, A. *Chem. Rev.* **1998**, *98*, 589.

(7) For the use of alkylidenecyclopropanes as dienophiles in racemic Diels−Alder reactions, see: (a) Heiner, T.; Michalski, S.; Gerke, K.; Kuchta, G.; Buback, M.; de Meijere, A. *Synlett* **1995**, 355. (b) Seyed-Mahdavi, F.; Teichmann, S.; De Meijere, A. *Tetrahedron Lett.* **1986**, *27*, 6185. (c) Spitzner, D.; Engler, A.; Wagner, P.; de Meijere, A.; Bengtson, G.; Simon, A.; Peters, K.; Peters, E.-M. *Tetrahedron* **1987**, *43*, 3213. (d) Hadjiarapoglou, L.; Klein, I.; Spitzner, D.; de Meijere, A. *Synthesis* **1996**, 525.

(8) Limbach, M.; Dalai, S.; de Meijere, A. *Adv. Synth. Catal.* **2004**, *346*, 760.

(9) Ho, G.-J.; Mathre, D. J. *J. Org. Chem.* **1995**, *60*, 2271.

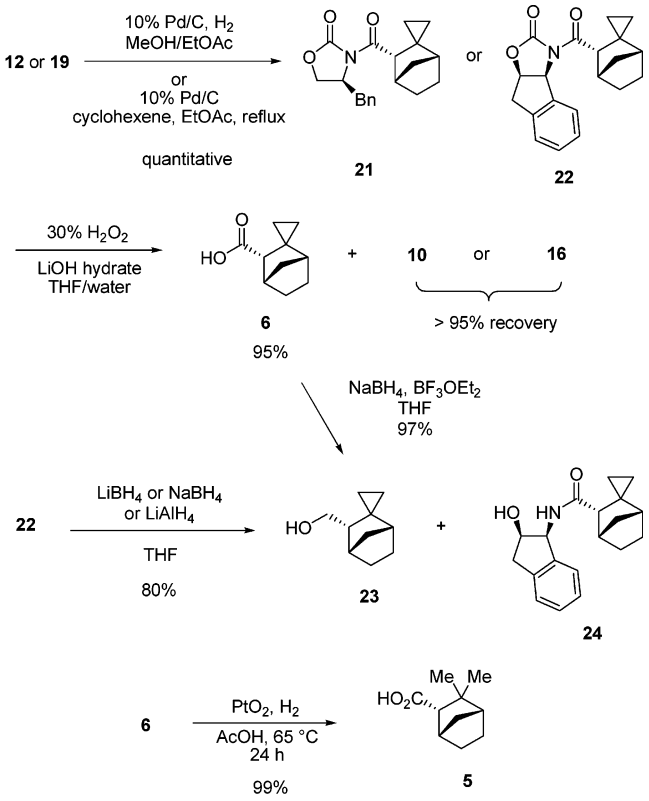
(10) The assignment of products **13**−**15**, which were not isolated, was based on NMR experiments on the crude reaction mixture.

(11) See the Supporting Information.

(12) Davies, I. W.; Senanayake, C. H.; Castonguay, L.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J. *Tetrahedron Lett.* **1995**, *36*, 7619.

(13) For catalytic hydrogenation of a similar spirocyclopropyl norbornyl system, see: Gream, G. E.; Pincombe, C. F. *Aust. J. Chem.* **1974**, *27*, 543.

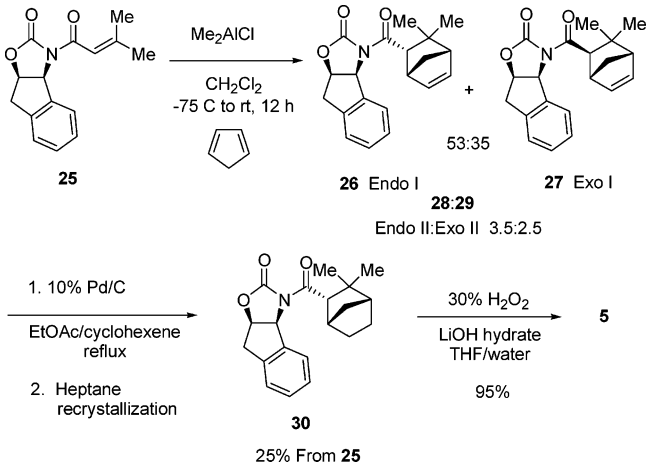
SCHEME 5



Reduction of the double bond in the Diels−Alder adducts **12** and **19** was accomplished by either catalytic hydrogenation over 10% Pd/C or transfer hydrogenation over 10% Pd/C employing cyclohexene (Scheme 5). In both cases, reduced compounds **21** and **22** were obtained in quantitative yield. Under these reaction conditions, no detectable amounts of over-reduction of the cyclopropane ring to the *gem*-dimethyl analogues was observed, even upon prolonged reaction. At this stage, the diastereomeric purity of **22** could be upgraded to >99:1 by crystallization from heptane (80% overall yield from **18**). The relative and absolute stereochemistry of **22** was unambiguously established by single-crystal X-ray analysis.[11] Hydrolysis of either **21** or **22** was performed with LiOOH, prepared from 2 equiv of LiOH and 3 equiv of H_2O_2 in a THF/water solvent system.[2] Upon reaction completion, the excess peroxide was quenched with sodium sulfite, and THF was removed under reduced pressure leaving an aqueous slurry of the auxiliary which could be isolated by filtration in >95% recovered yield and in analytically pure form. The resulting aqueous layer was made acidic with concentrated HCl and crystalline acid **6** was obtained in 95% yield and in analytically pure form after filtration and drying. Finally, catalytic hydrogenation of acid **6** over PtO_2 in acetic acid for 24 h gave the desired *gem*-dimethylnorbornyl carboxylic acid **5** in 99% yield.[13] Interestingly, reduction of **22** under a number of standard conditions including $LiBH_4$, $NaBH_4$, or $LiAlH_4$ provided a mixture of alcohol **23** (80%) and amide **24** (20%) where reduction of the oxazolidinone carbonyl was competitive with reduction of the *N*-acyl carbonyl. Similar results were also observed for **21**. On the other hand, in situ borane reduction of **6** gave alcohol **23** in 97% yield.

We also thought it worth investigating the Diels−Alder reaction of dimethyl imide **25** as a more direct approach to **5**

SCHEME 6



(Scheme 6). Treatment of **25** with Me_2AlCl in the presence of cyclopentadiene at low temperature resulted in no reaction. Upon warming to rt and stirring for 12 h, conversion to adducts **26**−**29** was noted. The reaction afforded the expected mixture of diastereomers **26**−**29** in a 53:35:3.5:2.5 ratio and 79% combined yield.[14] This result demonstrated that the conformationally constrained *cis*-aminoindanone auxiliary provided a bias for approach of the dienophile, although no real facial selectivity was observed. Transfer hydrogenation of the crude reaction mixture (Pd/C, cyclohexene, reflux) followed by fractional crystallization from heptane gave the major product **30** in 25% overall yield from **25**. Hydrolysis of **30** with lithium peroxide gave **5** in 95% isolated yield.

In summary, we have outlined a highly efficient and practical asymmetric method for the preparation of both *gem*-dimethyl and spirocyclopropyl norbornyl carboxylic acids **5** and **6** with complete control of both the regio- and absolute stereochemistry. This protocol provides enantiopure **5** in just six synthetic steps from readily available mesyl acid **8**, requires no chromatographic separations, and the chiral auxiliary can be recovered and recycled. The unprecedented selectivity of the highly reactive β,β-cyclopropyl-α,β-unsaturated *N*-acyloxazolidinones **11** and **18** in the Diels−Alder reactions with cyclopentadiene offer their use in the asymmetric preparation of other novel carbo- and heterocyclic systems.

Experimental Section

Melting points are uncorrected. All solvents and reagents were used as received from commercial sources. Analytical samples were obtained by chromatography on silica gel using an ethyl acetate−hexanes mixture as the eluent unless otherwise specified.

(3*S*,8a*R*)-3-(3′*R*,4′*S*,6′*S*)-5′,1″-Spirocyclopropane(bicyclo[2.2.1]-hepten-4′-yl)carbonyl-3,3a,8,8a-tetrahydroindeno[1,2-*d*]oxazol-2-one (19). To a −75 °C solution of 40.0 g (157 mmol) of **18** in 300 mL of CH_2Cl_2 was added 16.6 g (249 mmol) of freshly distilled cyclopentadiene. To the resulting mixture was added dropwise 218 mL (218 mmol) of a 1 M solution of Me_2AlCl in hexane at such a rate that the internal temperature was maintained below −67 °C. After 30 min, the reaction mixture was quenched by being poured slowly into 300 mL of 1 M HCl, the biphasic solution was mixed well for 30 min, and the layers were separated. The aqueous layer

(14) No attempt was made to isolate the individual diastereomers, and structural assignments were based on NMR experiments and analogy to products **13**−**15**.

was extracted with 50 mL of CH_2Cl_2. The combined extracts were concentrated under reduced pressure to give 49.1 g (97%) of a 97.3:2.7 mixture of **19**/**20** which was used in the next reaction without further purification. An analytical sample could be obtained by recrystallization from cyclohexane to give **19** as a white solid: mp 139−140 °C (cyclohexane); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.58 (m, 1H), 0.70 (m, 3H), 1.57 (d, 1H, J = 8.2 Hz), 1.91 (d, 1H, J = 8.2 Hz), 2.13 (s, 1H), 3.28 (s, 1H), 3.36 (d, 2H, J = 3.4 Hz), 4.19 (d, 1H, J = 3.4 Hz), 5.22 (m, 1H), 5.88 (d, 1H, J = 6.9 Hz), 5.99 (m, 1H), 6.45 (m, 1H), 7.29 (m, 3H), 7.56 (d, 1H, J = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 9.2, 11.9, 28.6, 38.1, 48.9, 49.7, 49.9, 53.1, 63.2, 77.9, 125.3, 127.1, 128.2, 129.8, 133.1, 137.7, 139.6, 139.7, 152.9, 173.7. Anal. Calcd for $C_{20}H_{19}NO_2$: C, 74.75; H, 5.96; N, 4.36. Found: C, 74.79; H, 5.94; N, 4.31.

(3*S*,8a*R*)-3-(3′*S*,4′*S*,6′*R*)-5′,1″-Spirocyclopropane(bicyclo[2.2.1]-heptan-4′-yl)carbonyl-3,3a,8,8a-tetrahydroindeno[1,2-*d*]oxazol-2-one (22). To a solution of 49.1 g (151.12 mmol) of crude **19** in 150 mL of EtOAc was added 159 mL (1.57 mol) of cyclohexene followed by 5.00 g of 10% Pd/C (wet, Degussa type E101 NE/W). The mixture was then heated to reflux for 1.5 h, cooled to rt, and filtered through a pad of Celite. The solvent was removed under reduced pressure, and the residue (HPLC assay 49.4 g, 100%) was suspended in 275 mL of heptane. The mixture was heated to reflux and then cooled to 45 °C, at which point the product began to crystallize. The resulting slurry was reheated to 50 °C and stirred for 30 min, cooled to 45 °C and stirred for 30 min, and then allowed to cool to rt. After being stirred for 2 h at rt, the solid was collected by filtration to give 43.8 g (89%) of a 98:2 mixture of **22** and the corresponding *exo* isomer. The resulting solid was slurried in 220 mL of heptane and heated to reflux and then allowed to cool slowly to rt. The resulting solid was then collected by filtration and was washed with 25 mL of cold heptane to afford 39.5 g (80% overall) of **22** as a diastereomerically pure white solid: mp 88−89 °C (heptane); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.26 (m, 1H), 0.59 (m, 1H), 0.69 (m, 1H), 0.80 (m, 1H), 1.30 (m, 1H), 1.31−1.57 (m, 4H), 1.75 (m, 1H), 1.90 (m, 1H), 2.75 (m, 1H), 3.36 (m, 2H), 3.89 (m, 1H), 5.22 (m, 1H), 5.92 (m, 1H), 7.28 (m, 3H), 7.68 (d, 1H, J = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 9.1, 16.5, 23.9, 26.5, 28.4, 38.1, 39.9, 42.8, 47.3, 50.9, 63.3, 76.8, 125.2, 127.2, 128.2, 129.8, 139.6, 152.8, 173.9.

(1*S*,3*R*,6*S*)-2,1′-Spirocyclopropane(bicyclo[2.2.1]heptane)-1′-carboxylic Acid (6). To a 0 °C solution of 25.0 g (77 mmol) of **22** in 125 mL of THF was added 26.3 g (232 mmol) of a 30% solution of H_2O_2. To the resulting solution was added 4.87 g (116 mmol) of lithium hydroxide hydrate in 30 mL of water at such a rate that the internal temperature did not rise above 5 °C. The resulting mixture was stirred at 5 °C for 1.5 h, allowed to warm to rt, and quenched by slowly pouring the reaction mixture into a solution of 39.0 g (309 mmol) of Na_2SO_3 in 130 mL of water at 10 °C. The mixture was stirred for 30 min, and the THF was removed under reduced pressure. The resulting slurry was stirred at rt for 12 h and filtered. The wet cake was washed with water and dried under vacuum/N_2 sweep for 12 h to provide 13.0 g (95%) of **16** as an analytically pure white solid. The filtrate was transferred to a 500 mL flask and made acidic (pH = 1) with concd HCl. The slurry of the crystalline acid **6** was stirred for 1 h at rt and filtered. The wet cake was washed with water and dried under vacuum/N_2 sweep for 12 h to provide 12.3 g (95%) of **6** as a white solid: mp 73−74 °C; $[\alpha]^{23}_D$ +67.4 (*c* 0.024, EtOH); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.30 (m, 1H), 0.51 (m, 1H), 0.61 (m, 1H), 0.96 (m, 1H), 1.44 (m, 5H), 1.75 (m, 2H), 2.67 (s, 1H), 2.78 (m, 1H), 11.8 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 7.8, 15.6, 23.7, 26.7, 27.6, 39.3, 52.6, 46.7, 51.7, 179.8. Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.27; H, 8.74.

(1*S*,3*R*,6*S*)-3,3-Dimethylbicyclo[2.2.1]heptane-2-carboxylic Acid (5). To a solution of 5.00 g (30.1 mmol) of **6** in 35 mL of acetic acid was added 200 mg of PtO_2. The resulting mixture was stirred at 65 °C at 40 psi H_2 for 24 h and then cooled to rt. The reaction mixture was filtered through Celite eluting with EtOAc. The solvent was removed under reduced pressure, and the crude product was recrystallized from MeOH/H_2O to provide 5.01 g (99%) of **5** as a colorless solid: mp 46−47 °C; $[\alpha]^{23}_D$ + 10.1 (*c* 0.0203, EtOH); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.05 (s, 3H), 1.13 (s, 3H), 1.25−1.44 (m, 3H), 1.68 (m, 2H), 1.86 (m, 1H), 1.97 (m, 1H), 2.37 (m, 1H), 2.44 (m, 1H), 12.0 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.5, 22.9, 24.6, 32.0, 37.6, 38.5, 40.9, 49.1, 56.2, 180.7. Anal. Calcd for $C_{10}H_{16}O_2 \cdot {}^1/_4\ H_2O$: C, 69.53; H, 9.63. Found: C, 69.82; H, 9.66.

Acknowledgment. We thank Lisa DiMichele and Peter G. Dormer of Merck & Co., Inc., for valuable NMR assistance.

Supporting Information Available: Experimental details, characterization data for all new compounds, X-ray crystallographic data, and ORTEP diagrams for **12** and **22**. This material is available free of charge via the Internet at http://pubs.acs.org.

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