JOC Article

Asymmetric Synthesis of 1,2,3-Trisubstituted Cyclopentanes and Cyclohexanes as Key Components of Substance P Antagonists

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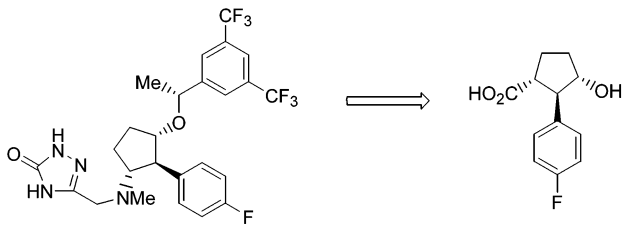
An efficient asymmetric synthesis of 1,2,3-trisubstituted cyclopentanes and cyclohexanes is described. Three methods were developed for the preparation of the 2,3-disubstituted cyclopentenones and cyclohexenones, which are key achiral building blocks. These intermediates are reduced catalytically with (*R*)-2-methyloxazaborolidine in high yield (82−98%) and excellent ee (89−96%). Directed reduction of the chiral allylic alcohols using Red-Al gives exclusively the 1,2-anti stereochemistry (>99:1). Epimerization of the ester center followed by saponification/crystallization affords the desired hydroxyacids in good yield (65−70%) and in high enantiomeric excess (>99%).

Introduction

Primarily associated with sensory neurons and located in specific areas of the central nervous system (CNS), neurokinin-1 (NK1) is a member of the seven-transmembrane G-protein-coupled receptor family. The natural ligand for NK1 is the tachykinin peptide Substance P and has been implicated in the pathophysiology of a wide range of conditions including anxiety, asthma, cystitis, depression, emesis, inflammatory bowel disease, migraine, movement disorders, pain, and psoriasis.[1] The search for potent, nonpeptide antagonists of the human neurokinin-1 (hNK-1) receptor is an intensive area of investigation.[2,3] Efforts to target potent, orally active hNK-1 antagonists have motivated further interest in the antidepressant activity exhibited by a neuropeptide antagonist being developed by Merck.[4−6] Recently, a series of cyclopentane-based compounds such as **1** have been identified to have significant binding affinity (subnanomolar) for the hNK-1 receptor.[7,8] Key to the success of the preparation of **1** is the asymmetric synthesis of the core hydroxy acid intermediate **2**. The challenging aspect of the synthesis of the *trans*,*trans*-cyclopentyl core of **2** is control of the relative and absolute stereochemistry. The enantioselective synthesis of **2** and model studies for the further extension to a cyclohexyl core are discussed.



1 hNK1 IC_{50} = 0.18 nM **2**

Results and Discussion

Substituted cyclopentanes and cyclohexanes comprise a large and diverse class of naturally occurring and pharmacologically important molecules.[9] Stereoselective

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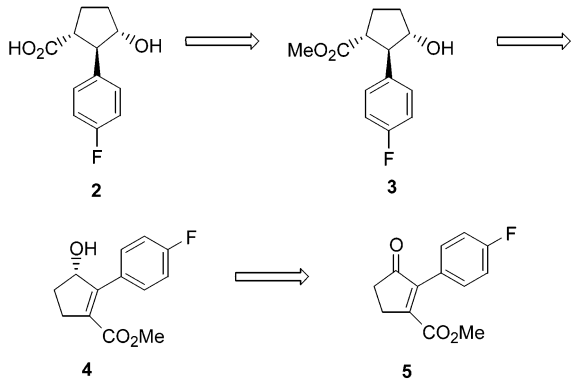
SCHEME 1. Retrosynthetic Approach to Hydroxyacid 2

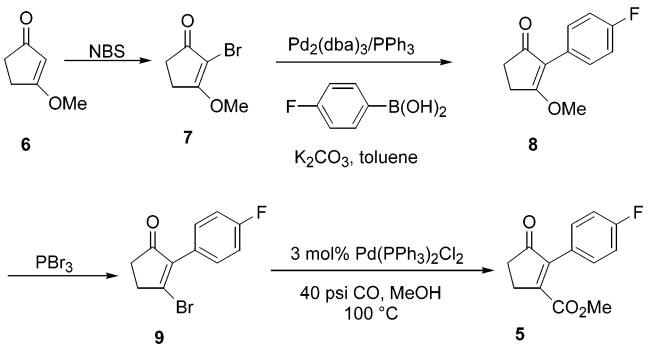


and enantioselective routes for the construction of these compounds have led to numerous methods for their synthesis.[9−12] Cyclopentenones and cyclohexenones often serve as precursors for the synthesis of their saturated counterparts. In addition, the cyclopentenone and cyclohexenone moieties are found in several biologically important compounds.[10] Therefore, the development of new synthetic processes that offer improved efficiency for the enantioselective preparation of these compounds remains a challenge.

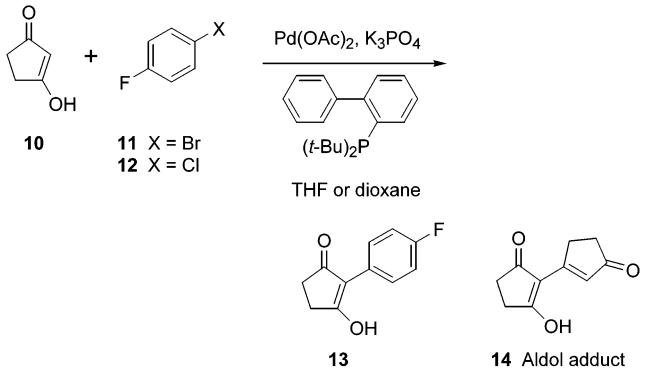
Our retrosynthetic approach to **2** involves the preparation of cyclopentenone **5**, which possesses all the features of **2** and requires an enantioselective reduction of the ketone followed by a hydroxyl-directed reduction of the α,β-unsaturated ester **4** (Scheme 1). Epimerization of the ester center gives the thermodynamically more stable *trans*,*trans*-cyclopentane **3**. Finally, saponification of **3** gives the required hydroxyacid **2**.

Preparation of Cyclopentenone 5. Cyclopentenone **5** was prepared by two different routes. Bromination of commercially available 3-methoxy-2-cyclopentenone **6** with *N*-bromosuccinimide provided 2-bromo-3-methoxycyclopentenone **7** in quantitative yield (Scheme 2).[13] Suzuki−Miyaura cross coupling[14] with 4-fluorophenylboronic acid afforded the coupled product **8** in 89% yield. Examination of workup conditions for the coupling reaction showed that quenching the cooled reaction mixture with aqueous K_3PO_4 significantly improved the purity of the isolated product by effectively removing excess boronic acid. Conversion of the methoxy group to the corresponding bromide was effected with phosphorus tribromide (PBr_3) in refluxing 1,2-dichloroethane, providing bromide **9** in 65% isolated yield.[15] Palladium-

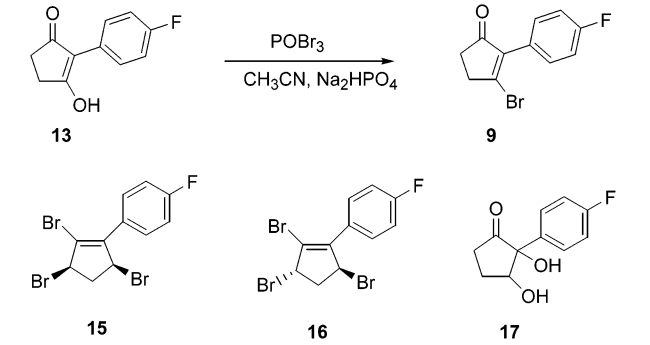
SCHEME 2



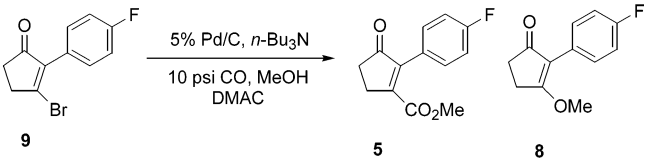
SCHEME 3



SCHEME 4



SCHEME 5



catalyzed carbonylation (40 psi CO, 100 °C, MeOH, 3 mol % $Pd(PPh_3)_2Cl_2$) provided the key intermediate **5** in 90% isolated yield.[16] Use of the protocols outlined in Schemes 2−5 allowed a series of variously substituted cyclopentenones and cyclohexenones to be prepared (Table 1).[17]

(9) (a) *The Total Synthesis of Natural Products*; ApSimon, J., Ed.; Wiley: New York,1981; Vol. 1−4 and references therein. (b) Harre, M.; Raddatz, P.; Walenta, R.; Winterfeldt, E. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 480. (c) Noyori, R.; Suzuki, M. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 847. (d) Taylor, R. J. K.; Pyke, S. G.; Pyke, S. M. In *Second Supplements to the 2nd Edition of Rodd's Chemistry of Carbon Compounds;* Sainsbury, M., Ed.; Elsevier: Amsterdam, 1992; pp 221−282. (e) Gribble, G. W. In *Second Supplements to the 2nd Edition of Rodd's Chemistry of Carbon Compounds*; Sainsbury, M., Ed.; Elsevier: Amsterdam, 1992; Vols. IIA and IIB(partial), pp 375−4452 and references therein.

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(16) Schoenberg, A.; Bartoletti, I.; Heck, R. F. *J. Org. Chem.* **1974**, *39*, 3318.

(17) Complete experimental procedures and characterization data for all intermediates used in the synthesis of the cyclopentenones and cyclohexenones listed in Table 1 can be found in Supporting Information.

While the chemistry outlined in Scheme 2 provided bromide intermediate **9**, a more streamlined approach to **5** was developed and is outlined in Schemes 3−5. In an extension of the chemistry developed by Buchwald,[19] heating dione **10** in the presence of 1-bromo-4-fluorobenzene (**11**), K_3PO_4, $Pd(OAc)_2$ (1 mol %), and 2-(di-*tert*-butylphosphino)biphenyl (2 mol %) in refluxing 1,4-dioxane gave **13** in 85% yield (HPLC).[20] This reaction can also be carried out with the corresponding aryl chloride (**12**) and has been optimized in terms of the catalyst/ligand loading with the chloride. Potassium phosphate (K_3PO_4, powdered, anhydrous) was found to be the best base, giving the most consistent results. Other bases screened gave either no product or significant amounts of aldol adduct **14**.[21] The reaction was carried out by sequentially charging the $Pd(OAc)_2$, ligand, 1,3-cyclopentanedione, and K_3PO_4. The solids were degassed (three times) with vacuum/nitrogen backfill cycles, and the 1,4-dioxane was added followed by 1-chloro-4-fluorobenzene. The reaction mixture was again degassed (three times) with vacuum/nitrogen backfill. It was particularly important that the degassing of both the solids and the reaction mixture was carried out prior to heating the reaction mixture. When these degassing procedures were not carried out, low conversion to product was noted (<30%). The addition of more catalyst and ligand at this point failed to bring about any further conversion. The heterogeneous mixture was then heated at reflux for 12−14 h and cooled to room temperature. The workup was simply a matter of dilution with water, which gave a homogeneous solution, and acidification with concentrated HCl, which precipitated the product **13** as a solid in 92% yield.

Due to the toxicity of 1,4-dioxane, a change in the reaction solvent from 1,4-dioxane to THF was necessary. When the reagents were added together as described above and heated to reflux in THF, low conversion (<35%) to **13** was noted. However, when the reaction was conducted in a pressurized vessel (RC1 Reaction Calorimeter)[22] at 100 °C (25 psi), a 73% yield was obtained with 12% remaining starting material. Increasing the internal temperature to 105 °C (30 psi) resulted in an increase in the yield for **13** to 83% with 3−5% remaining starting material. Optimal results were obtained by heating the reaction at 110 °C (36 psi) and afforded **13** in 87−90% yield. Upon dilution of the mixture with water, the THF was removed by distillation in order to obtain a high recovery of the product. Addition of 6 N HCl at 50 °C resulted in a crystalline, free-flowing product that was filtered to give **13** in 86% isolated yield.

Bromination conditions utilized for **8** (PBr_3 in refluxing 1,2-dichloroethane) gave bromide **9** in 65% yield. While the reaction proceeded to completion, the significant byproduct of this reaction was dione **13**. Bromination of **13** with PBr_3 in refluxing 1,2-dichloroethane gave **9** in 78% yield (the remainder was starting material). Prolonged reaction times and the addition of excess PBr_3 to these reactions failed to drive the reactions to the complete formation of **9**. Switching from PBr_3 to Ph_3PBr_2 as the brominating reagent in MeCN at 60 °C resulted in clean transformation of **13** to **9** in 96% yield (HPLC); however, a significant problem was the generation of triphenylphosphine oxide, which was difficult to remove without resorting to chromatography. Bromination with phosphorus oxybromide ($POBr_3$) gave better results with bromide **9** obtained in 96% yield (HPLC). Optimal conditions involved treatment of dione **13** with 0.75 equiv of $POBr_3$ in MeCN with 0.5 equiv of Na_2HPO_4 at 65 °C for 1.5 h. The workup involved cooling the reaction mixture to room temperature, quenching with 1 N KOH, and separating the bottom aqueous layer. Concentration of the acetonitrile layer and addition of water precipitated the product, which was isolated in 92% yield. Upon completion of the reaction, it was discovered that approximately 4% of tribromide impurities **15** and **16** (6:1 by HPLC) were present in the crude reaction mixture. During the course of the KOH quench, it was noted that **15** and **16** were converted to a new impurity with a molecular weight determined by LCMS to be 210. We have tentatively assigned the structure of this impurity as **17**. These impurities were effectively removed during the crystallization step.

Having developed a practical process for the preparation of bromide **9**, we revisited the carbonylation reaction. To eliminate the need for chromatography, improvements were needed over the initial carbonylation conditions. In addition, significant amounts (∼5−8%, HPLC) of **8** were formed under the reaction conditions. After experimentation with a variety of catalyst systems and solvents, the best conditions involved running the reaction in dimethylacetamide (1 M in **9**) with 5 equiv of MeOH, 2 equiv of *n*-Bu_3N, 1 mol % of 5 wt % Pd/C at 60 °C at 10 psi CO for 12 h.[23] These conditions eliminated the formation of **8** and resulted in the formation of **5** in 96% yield (HPLC). Filtration of the catalyst and removal of the MeOH by distillation were followed by precipitation of the methyl ester by addition of 1−1.3 volumes of 1 N HCl and afforded **5** in 90% yield.

While the bromide **9** was contaminated with small amounts of **15**−**17**, these impurities remained either unreactive (**17**) or decomposed under the reaction conditions (**15** or **16**). In addition, these impurities were removed during the crystallization of **5**.

Conversion of 5 to Hydroxyacid 2. The conversion of **5** to hydroxyacid **2** involved a series of transformations where acid **2** was the only isolated product. The enantioselective reduction of ketone **5** was achieved by addition of **5** to a preformed mixture of (*R*)-2-methyloxazaborolidine **18** (10 mol %) and BH_3·SMe_2 (0.6 equiv) in toluene at −20 °C (Scheme 6).[24,25] The chiral allylic alcohol **4** was formed in >95% yield (HPLC) with 92−94% ee. The use of BH_3·SMe_2 was significant since the use of BH_3·THF

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(19) Fox, J. M.; Huang, X.; Chieffi, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 1360.

(20) The HPLC yields refer to quantitative HPLC analysis of crude reaction mixtures using an analytically pure standard.

(21) Eskola, S. *Suom. Kemistil.* **1957**, *30B*, 34; *Chem. Abstr.* **1957**, *53*, 16014f.

(22) The internal temperature and pressure were monitored by a Mettler-Toledo RC1 Reaction Calorimeter.

(23) Davies, I. W.; Matty, L.; Hughes, D. L.; Reider, P. J. *J. Am. Chem. Soc.* **2001**, *123*, 10139.

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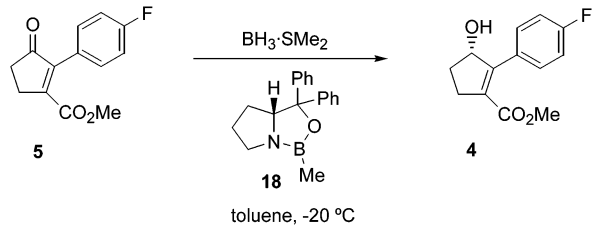
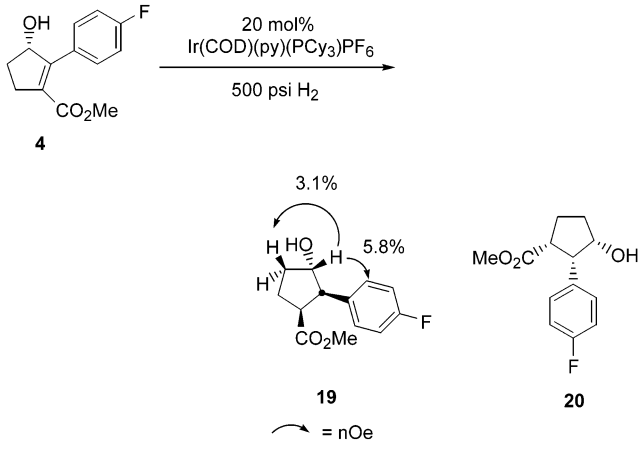
SCHEME 6



resulted in significant erosion in ee (56−84% ee). When BH_3·$NHMe_2$ was used as the reductant, the starting material was recovered unchanged. Once the reaction was complete (2 h), the reaction mixture was quenched with 6 equiv of MeOH and allowed to warm to 20 °C. After being washed with 1 N HCl, the toluene solution was azeotropically dried for the stereoselective reduction of the double bond.

With an efficient synthesis of allylic alcohol **4** in hand, our attention turned to the selective reduction of the double bond. Since a high degree of stereocontrol has been achieved by transition-metal-catalyzed hydrogenations directed by proximal hydroxyl groups, these catalyst systems were screened.[26] Crabtree reduction[27] (20 mol % Ir(COD)(py)(PCy_3)PF_6, 500 psi, 12 h) of **4** gave a 63% yield (the remainder was starting material) of **19** as a single isomer (>99:1) where the stereochemistry was confirmed by NOE studies (Scheme 7). The rhodium

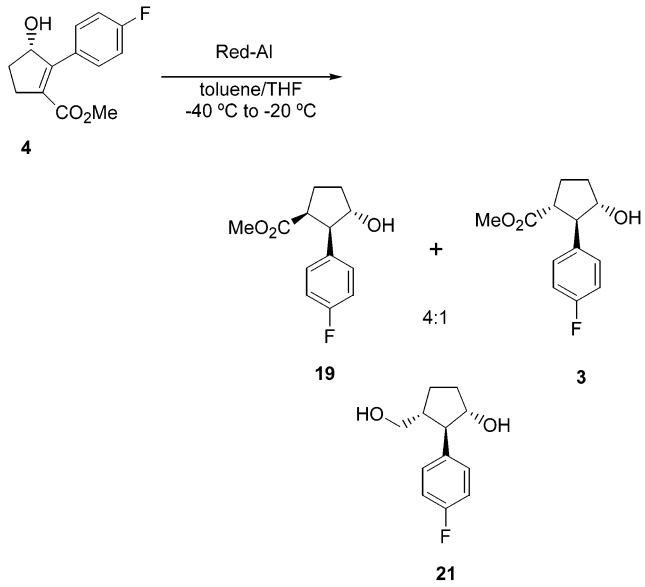
SCHEME 7



catalysts Rh(COD)(dppb)PF_6 and Rh(C_7H_8)(dppb)PF_6 were also examined.[28] Although these reactions proceeded to completion, they were generally nonselective and gave varying amounts of **19** and the all-cis isomer **20**. Due to incomplete reductions and the expense of Crabtree's catalyst, alternative methods for the stereoselective reduction of **4** were examined. Using the more stable iridium−carbene complexes recently described by Nolan (chlorobenzene, 80 °C, 50 psi H_2) gave excellent stereoselectivity (>99.9% **19**); however, the catalyst only survived three turnovers.[29]

After experimenting with a number of reducing agents for the reduction of **4** to either **19** or **3**, we discovered that reaction with Red-Al resulted in clean reduction and gave the desired 1,2-anti stereochemistry exclusively.[30,31] There was no evidence of any of the 1,2-syn product **20** being formed in the reaction resulting from anti addition of hydride. Optimal conditions involved addition of 1.5 equiv of Red-Al to a solution of **4** in 3:2 toluene/THF at −40 °C (Scheme 8). Warming the reaction mixture to −25

SCHEME 8

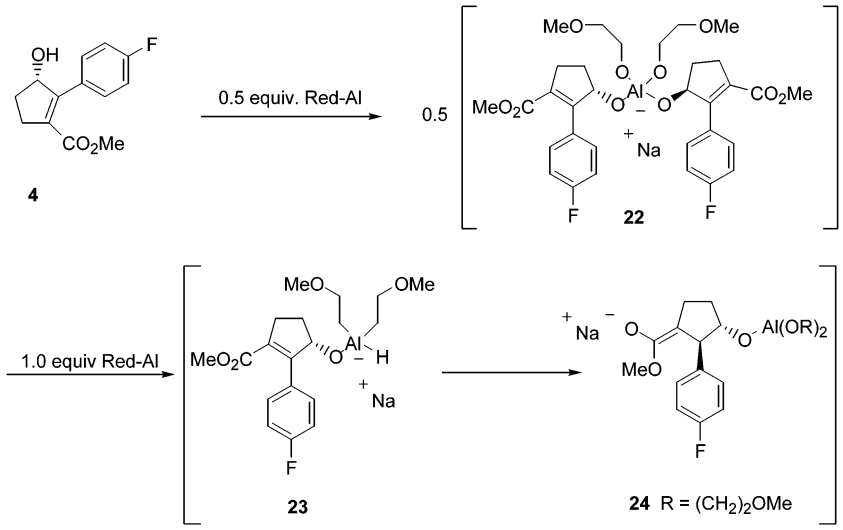


°C drives the reaction to completion. The use of THF as a cosolvent was important since it helps solubilize the Red-Al at low temperatures. When Red-Al was added to **4** in toluene alone at low temperatures, the Red-Al was slow to solubilize and the reaction took considerably longer to go to completion. Inverse addition of the reaction mixture to a 2 M solution of $NaHSO_4$ afforded approximately a 4:1 mixture of **19**:**3** in 83% yield together with 5−8% over-reduction byproduct **21**.

To gain mechanistic insight into the formation of **19** and **3**, the reaction was monitored by measuring hydrogen evolution and by ReactIR.[32] The addition of 0.5 equiv of Red-Al resulted in the evolution of 2 mol of H_2 and the formation of intermediate **22** (Scheme 9).[33] Figure 1 shows the cumulative evolution of hydrogen (mmol) and the cumulative amount (mmol) of Red-Al added vs time. The hydrogen evolution abruptly stops after 0.5 equiv of Red-Al is added, and the molar rate of hydrogen release

(26) For a review of directed hydrogenations, see: Brown, J. M. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 190.
(27) (a) Stork, G.; Kahne, D. E. *J. Am. Chem. Soc.* **1983**, *105*, 1072. (b) Crabtree, R. H.; Davies, M. W. *Organometallics* **1983**, *2*, 681.
(28) Evans, D. A.; Morrissey, M. M. *J. Am. Chem. Soc.* **1984**, *106*, 3866.
(29) Lee, H. M.; Jiang, T.; Stevens, E. D.; Nolan, S. P. *Organometallics* **2001**, *20*, 1255.
(30) For the reduction of α,β-unsaturated ester using Red-Al, see: (a) SarKar, A.; Rao, B. R.; Konar, M. M. *Synth. Commun.* **1989**, *19*, 2313. (b) Malek, J. *Org. React.* **1988**, *36*, 249.
(31) For the reduction of α,β-unsaturated ester using Red-Al and copper (I) bromide, see: (a) Semmelhack, M. F.; Stauffer, R. D.; Yamashita, A. *J. Org. Chem.* **1977**, *42*, 3180. (b) Semmelhack, M. F.; Stauffer, R. D. *J. Org. Chem.* **1975**, *40*, 3619.
(32) ReactIR refers to the real-time, in situ monitoring of the IR spectrum of the reaction with a ReactIR 4000 Reaction Analysis System available from ASI Applied Systems.
(33) (a) Malek, J. *Org. React.* **1988**, *36*, 249 and references therein. (b) Malek, J. *Org. React.* **1985**, *34*, 1.

SCHEME 9



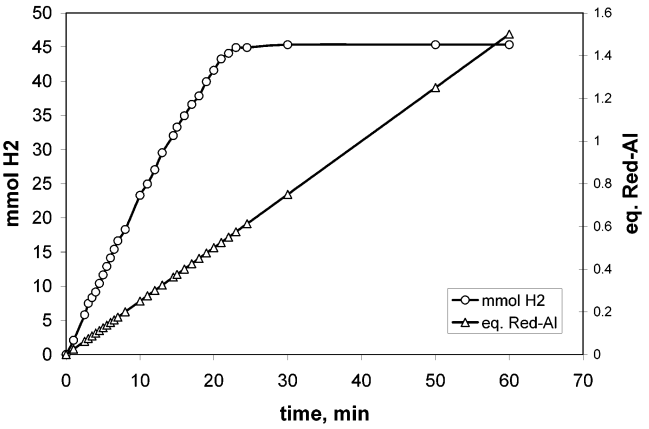


FIGURE 1. Amount (mmol) of H_2 evolved and equiv of Red-Al added vs time.

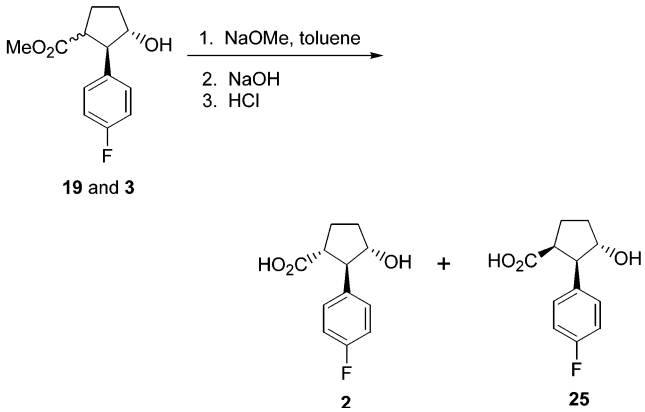
is approximately 2 times the molar rate of Red-Al added. The IR shows the complete disappearance of the OH stretch of **4** after 0.5 equiv of Red-Al was added. Quenching the intermediate at this stage resulted only in the recovery of starting material. However, the addition of additional Red-Al to **22** led to the rapid formation of **19** and **3**. We speculate that addition of 1.0 equiv of Red-Al leads to the formation of intermediate **23**,[34,35] where intramolecular hydride delivery occurs diastereoselectively from the α-face to give the observed 1,2-anti stereochemistry. The formation of intermediate **24** was monitored by IR where the disappearance of the carbonyl absorption of the ester of **22** (1722 cm^{-1}) and the formation of the enolate (1690 cm^{-1}) of **24** was observed.

Epimerization of the crude toluene solution containing **19** and **3** was conducted by adding 0.4 equiv of NaOMe to the dry toluene solution from the Red-Al reduction at 50 °C and then further heating the reaction mixture at 75 °C for 1 h where the diastereomeric ratio was >17:1

(34) Casensky, B.; Machacek, J.; Abrham, K. *Collect. Czech. Chem. Commun.* **1971**, *36*, 2648.

(35) The addition of less than 1.5 total equiv of Red-Al results in incomplete conversion of starting material to products, while the addition of more than 1.5 equiv of Red-Al results in significantly more over-reduction product **21**.

SCHEME 10



(**3**:**19**) (Scheme 10). There was a small amount (<1.0%, HPLC) of hydroxyacid **2** that formed under the reaction conditions. Saponification of the mixture by the direct addition of 6 N NaOH (3.5 equiv), water, and MeOH (2.6 equiv) to the toluene solution and vigorous stirring for 3 h at 20 °C gave **2**. In addition, small amounts of **25** were present in the reaction mixture. Aqueous workup and crystallization from 3:1 heptane/isopropyl acetate gave **2** in 65% overall yield from **4**. The crystallization not only completely removed **25** but also increased the ee of **2** from 92 to 94% ee to >99.9% ee.

We also expanded the reduction methodology to the preparation of a number of substituted cyclopentanes and cyclohexanes. Enantioselective reduction of ketones **26a**−**f** proceeded in good to excellent yield and in high ee (Scheme 11, Table 1). There was no significant loss in enantioselectivity going from a five- to a six-membered ring. In addition, the substituent at the 2-position of the enone was observed to have no detrimental effect on the yield or ee. Reduction of **27a**−**c** with Red-Al afforded the anti-syn products **28a**−**c** and anti-anti cyclopentanes **29a**−**c** as a 4:1 mixture of diastereomers. Epimerization of the crude reaction mixtures with NaOMe followed by saponification of the methyl ester gave the corresponding hydroxy acids **30a**−**c** in good yield and in >99% ee. Interestingly, reduction of the six-membered ring ana-

SCHEME 11

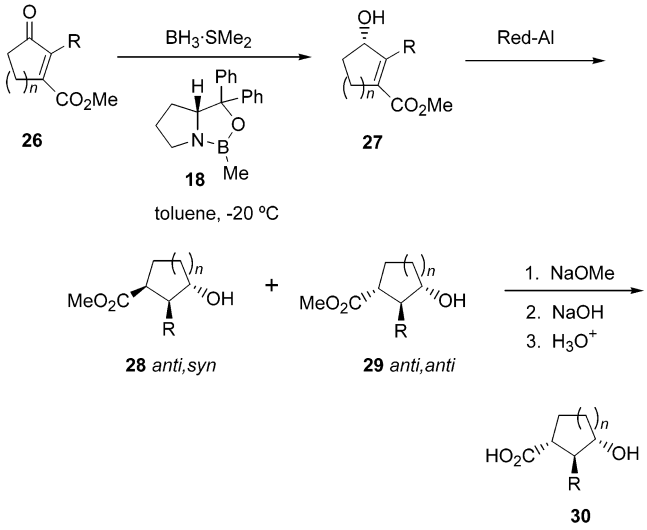


TABLE 1

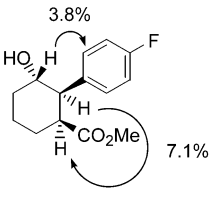
		27		**30**
ketone **26**	R	yield (%)[a]	ee (%)[b]	yield (%)[c]
a $n = 1$[d]	Me	82	96	67
b $n = 1$	Ph	94	90	68
c $n = 1$	*o*-tolyl	98	90	60
d $n = 2$	Me	92	90	70
e $n = 2$	Ph	89	91	60
f $n = 2$	4-F-Ph	84	89	66

[a] Isolated yield after column chromatography. [b] Enantiomeric excess was determined by chiral supercritical fluid chromatography on either the Chiralcel OJ or Chiralcel OF chiral stationary phase (4.6 × 250 mm) using a standard gradient of 4−40% methanol in carbon dioxide at a flow rate of 1.5 mL/min at a pressure of 300 bar with a column temperature of 30 °C and UV detection at 215 nm. [c] Isolated yield after crystallization. [d] See ref 37.

logues **27d**−**f** gave the anti-syn cyclohexanes **28d**−**f** as the major products (**28**:**29** > 20:1) where the stereochemistry was confirmed by NOE experiments on **28f**.[36] Epimerization with NaOMe and saponification afforded hydroxyacids **30d**−**f** in good yield and in >99% ee.

In conclusion, a practical method for the synthesis of 2-substituted cyclopentenone and cyclohexenones has been developed. Asymmetric reduction of the enone leads to cyclic allylic alcohols, which in conjunction with Red-Al and epimerization/saponification allows for a highly stereoselective synthesis of anti,anti-1,2,3-trisubstituted cyclopentanes and cyclohexanes. These systems can be elaborated to novel NK1 receptor antagonists.[7,8]

(36) Observed NOE data for compound **28f**:



28f

(37) Newman, M. S.; McPherson, J. L. *J. Org. Chem.* **1954**, *19*, 1717.

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−hexane mixture as the eluent unless specified otherwise. Elemental analyses were performed by Quantitative Technologies, Inc., Whitehouse, NJ. The water content (KF) was determined by Karl Fisher titration.

Preparation of 3-Methoxy-2-(4-fluorophenyl)-2-cyclopenten-1-one (8). To a solution of 10.0 g (52.4 mmol) of **7**, 14.5 g (105.0 mmol) of anhydrous K_2CO_3, and 9.52 g (68.1 mmol) of 4-fluorophenylboronic acid suspended in 100 mL of toluene were added 0.479 mg (0.524 mmol) of $Pd_2(dba)_3$ and 274 mg (1.05 mmol) of PPh_3. The resulting mixture was heated at reflux for 12 h, cooled to 20 °C, and then washed with 75 mL of 0.33 M K_3PO_4. The resulting toluene layer was then concentrated under reduced pressure, and the residue was purified by flash silica gel chromatography to provide 9.61 g (89%) of **8** as a white solid: mp 91−92 °C (MTBE/hexane); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.59 (m, 2H), 2.80 (m, 2H), 4.02 (s, 3H), 7.05 (t, 2H, J = 8.9 Hz), 7.75 (dd, 2H, J = 8.9 and 5.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.7, 33.9, 57.1, 115.0 (d, J = 20 Hz), 117.8, 127.0, 130.1, 161.8 (d, J = 240 Hz), 184.8, 203.0. Anal. Calcd for $C_{12}H_{11}FO_2$: C, 69.89; H, 5.38. Found: C, 69.77; H, 5.46.

General Procedure for Coupling of 1,3-Cyclopentanediones and 1,3-Cyclohexanediones with Aryl Chlorides. Method A in 1,4-Dioxane. To a 100 mL round-bottom flask were sequentially added $Pd(OAc)_2$ (0.25 mmol), 2-(di-*tert*-butylphosphino)biphenyl (0.55 mmol), the appropriate 1,3-dione (25.24 mmol), and powdered K_3PO_4 (50.5 mmol). The resulting mixture was degassed (three times) by vacuum/N_2 backfills. The vessel was then charged with 26 mL of 1,4-dioxane and the appropriate aryl chloride (32.8 mmol). The vessel was degassed (three times) with vacuum/N_2 backfills. The resulting slurry was heated to reflux for 12 h and cooled to room temperature, and water (75 mL) was added. To the homogeneous solution was added concentrated HCl to adjust the pH to 1 and the slurry stirred for 2.5 h. The slurry was then filtered and the cake washed with 1 bed volume of water and 1 bed volume of toluene. The solid was then dried under vacuum at 60 °C for 48 h. An analytical sample was obtained by recrystallization from acetone/hexane.

Method B in THF. To a solution of THF (41 mL) were added sequentially powdered K_3PO_4 (50.5 mmol), the appropriate 1,3-dione (25.24 mmol), 2-(di-*tert*-butylphosphino)-biphenyl (0.55 mmol), $Pd(OAc)_2$ (0.25 mmol), and the appropriate aryl chloride (32.78 mmol). The sides of the flask were washed with an additional 10 mL of THF, and the reaction vessel was purged (three times) with vacuum/N_2 backfills. The heterogeneous reaction mixture was stirred at 110 °C for 12 h, cooled to room temperature, and diluted with 75 mL of water. The resulting homogeneous solution was distilled to remove THF and then heated to 50 °C. The aqueous solution was then slowly acidified with 6 N HCl until a final pH of 1. The slurry was cooled to room temperature and filtered. The wet cake was washed with 1 bed volume of water, 1 bed volume of toluene, and dried under vacuum at 60 °C for 48 h.

2-(4-Fluorophenyl)-1,3-cyclopentanedione (13). White solid (92%): mp 243−244 °C (THF/hexane); ^{1}H NMR ($(CD_3)_2$-CO, 400 MHz) δ 2.57 (s, 4H), 7.05 (m, 2H), 7.97 (m, 2H), 12.5 (br s, 1H); ^{13}C NMR ($(CD_3)_2CO$, 100 MHz) δ 30.3, 113.9, 114.3 (d, J = 21 Hz), 128.4, 129.5, 161.1 (d, J = 243 Hz), 209.1. Anal. Calcd for $C_{11}H_9FO_2$: C, 68.74; H, 4.72. Found: C, 68.63; H, 4.60.

General Procedure for Bromination of 3-Alkoxy-2-substituted Cyclopenten-1-ones and 3-Alkoxy-2-substituted Cyclohexen-1-ones. To a solution of the appropriate 3-alkoxy-2-substituted cyclopenten-1-one or cyclohexen-1-one (10 mmol) in 20 mL of 1,2-dichloroethane was added PBr_3 (15 mmol). The resulting mixture was heated to reflux for 1 h, cooled to 20 °C, and poured over cracked ice. The organic layer

was separated, washed with saturated aqueous $NaHCO_3$, and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue purified over a plug of silica gel.

3-Bromo-2-(4-fluorophenyl)-2-cyclopenten-1-one (9). White solid (65%): mp 57−58 °C (MTBE/hexane); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.72 (m, 2H), 3.10 (m, 2H), 7.13 (m, 2H), 7.51 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 35.8, 36.3, 115.4 (d, J = 20 Hz), 126.1, 131.0, 142.1, 156.0, 162.9 (d, J = 250 Hz), 202.2. Anal. Calcd for $C_{11}H_8BrFO$: C, 51.79; H, 3.16. Found: C, 51.72; H, 3.25.

General Procedure for the Bromination of 2-Substituted 1,3-Cyclopentanediones and 2-Substituted 1,3-Cyclohexanediones. To a slurry of the appropriately substituted cyclopentanedione or cyclohexanedione (10 mmol) and solid Na_2HPO_4 (5 mmol) in 15 mL of dry CH_3CN was added dropwise $POBr_3$ (7.5 mmol) in 5 mL of dry CH_3CN. The resulting mixture was heated to 65 °C for 1 h and cooled to room temperature. To the mixture was added slowly 1 N KOH until a final pH of 6.5−7.5 was obtained. The bottom aqueous layer was separated and the CH_3CN layer concentrated to a final volume of 15 mL. To the solution was added 37.5 mL of water, which precipitated the product. The product was collected by filtration.

***cis*-1-Fluoro-4-(2,3,5)-tribromocyclopent-1-enylbenzene (15).** Light yellow solid: mp 71−72 °C (MTBE/hexane); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.04 (d, 1H, J = 16.4 Hz), 3.32 (dt, 1H, J = 16.4 and 6.9 Hz), 5.13 (d, 1H, J = 6.2 Hz), 6.28 (d, 1H, J = 6.2 Hz), 7.14 (m, 2H), 7.64 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 43.8, 51.8, 56.7, 115.7 (d, J = 20 Hz), 124.6, 128.4, 130.4, 143.7, 163.2 (d, J = 250 Hz). Anal. Calcd for $C_{11}H_8Br_3F$: C, 33.12; H, 2.02. Found: C, 33.02; H, 1.70.

***trans*-1-Fluoro-4-(2,3,5)-tribromocyclopent-1-enyl-benzene (16).** Unstable brown oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.24 (m, 2H), 5.22 (m, 1H), 5.34 (m, 1H), 7.11 (m, 2H), 7.58 (m, 2H).

General Procedure for Carbonylation of 3-Bromo-2-substituted Cyclopenten-1-ones and 3-Bromo-2-substituted Cyclohexen-1-ones. Method A. A solution of the corresponding bromide (10 mmol), $Pd(PPh_3)_2Cl_2$ (0.30 mmol), and *n*-tributylamine (20 mmol) in 20 mL of MeOH was heated at 60 °C under 40 psi CO for 16 h. The mixture was cooled to room temperature; the catalyst was filtered over Celite, and the MeOH was removed under reduced pressure. The residue was redissolved in 35 mL of EtOAc and washed with 35 mL of 1 N HCl. The organic layer was dried over $MgSO_4$ and the solvent removed under reduced pressure. The residue was purified by chromatography on silica gel.

Method B. A solution of the corresponding bromide (10 mmol), 5% Pd/C (0.10 mmol), and *n*-tributylamine (20 mmol) in 20 mL of dimethylacetamide was heated at 60 °C under 10 psi CO for 12 h. The mixture was cooled to room temperature; the catalyst was filtered over Celite, and the MeOH was removed under reduced pressure. The mixture was slowly titrated with 1 N HCl (20 mL) while keeping the temperature below 25 °C. The product was then collected by filtration, washed with water until the filtrate pH was >5, and dried.

Methyl 2-(4-Fluorophenyl)-3-oxo-1-cyclopent-1-enecarboxylate (5). Colorless solid: mp 70−71 °C (MTBE/hexane); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.67 (m, 2H), 2.94 (m, 2H), 3.77 (s, 3H), 7.09 (t, 2H, J = 8.9 Hz), 7.35 (dd, 2H, J = 8.9 and 5.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.2, 34.7, 52.5, 115.3 (d, J = 20 Hz), 126.2, 131.2, 145.6, 156.5, 163.3 (d, J = 250 Hz), 166.2. Anal. Calcd for $C_{13}H_{11}FO_3$: C, 66.66; H, 4.73. Found: C, 66.47; H, 4.92.

Methyl 2-Phenyl-3-oxocyclopent-1-enecarboxylate (26b). White solid: mp 56−57 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.67 (m, 2H), 2.95 (m, 2H), 3.75 (s, 3H), 7.33 (m, 2H), 7.40 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.1, 34.6, 52.2, 128.0, 128.9, 129.0, 130.2, 146.4, 156.4, 207.2. Anal. Calcd for $C_{13}H_{12}O_3$: C, 72.21; H, 5.59. Found: C, 72.20; H, 5.34.

Methyl 2-(2-Tolyl)-3-oxocyclopent-1-enecarboxylate (26c). Colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.12 (s, 3H), 2.67 (m, 2H), 2.98 (m, 2H), 3.68 (s, 3H), 6.98 (d, 1H, J = 7.6 Hz), 7.25 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.0, 27.2, 34.7, 52.4, 125.5, 128.7, 128.9, 130.1, 131.0, 136.1, 149.3, 157.4, 165.7, 207.6.

Methyl 2-Methyl-3-oxo-1-cyclohex-1-enecarboxylate (26d). Colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.94 (t, 3H, J = 2.1 Hz), 2.20 (m, 2H), 2.47 (m, 2H), 2.57 (m, 2H), 3.82 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 12.9, 22.4, 27.5, 35.4, 38.0, 52.3, 137.5, 144.4, 169.1, 199.6.

Methyl 2-Phenyl-3-oxo-1-cyclohex-1-enecarboxylate (26e). White solid: mp 44−45 °C (MTBE/hexane); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.18 (m, 2H), 2.62 (t, 2H, J = 6.7 Hz), 2.73 (t, 2H, J = 6.0 Hz), 3.48 (s, 3H), 7.10 (m, 2H), 7.32 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.2, 27.7, 38.2, 51.9, 127.8, 123.0, 129.0, 134.4, 139.4, 147.5, 169.0, 197.8. Anal. Calcd for $C_{14}H_{14}O_3$: C, 73.03; H, 6.13. Found: C, 73.14; H, 5.99.

Methyl 2-(4-Fluorophenyl)-3-oxo-1-cyclohex-1-enecarboxylate (26f). White solid: mp 51−52 °C (MTBE/hexane); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.19 (m, 2H), 2.61 (t, 2H, J = 6.7 Hz), 2.72 (t, 2H, J = 6.1 Hz), 3.46 (s, 3H), 7.18 (m, 2H), 7.21 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.3, 27.5, 38.2, 51.9, 115.1 (d, J = 20 Hz), 119.6, 129.3, 132.4, 136.0, 161.5 (d, J = 240 Hz), 197.5. Anal. Calcd for $C_{14}H_{13}FO_3$: C, 67.73; H, 5.28. Found: C, 67.77; H, 5.29.

General Procedure for the Preparation of (1*R*,2*R*,3*S*)-2-Substituted 3-Hydroxycyclopentane-1-carboxylic Acids and (1*R*,2*R*,3*S*)-2-Substituted 3-Hydroxycyclohexane-1-carboxylic Acids. To a solution of (*R*)-2-methyl-CBS-oxazaborolidine (**18**, 10 mmol) in 75 mL of toluene was added 60 mmol of $BH_3{\cdot}SMe_3$ (60 mmol). The resulting mixture was cooled to −20 °C, and the appropriate ketone (100 mmol) in 360 mL of toluene was added dropwise while maintaining the internal temperature below −15 °C. After 2 h, the mixture was quenched with 60 mmol of MeOH and allowed to warm to room temperature. The resulting mixture was washed with 234 mL of 1 N HCl and the toluene layer azeotropically dried to a KF < 120 and a final volume of 250 mL. An analytical sample can be obtained by removal of the toluene under reduced pressure and purification of the residue by silica gel chromatography.

To the above dry toluene stream was added 170 mL of THF and the mixture cooled to −40 °C. To the cooled solution was added dropwise over 15 min 70% Red-Al (150 mmol) in toluene while maintaining the internal temperature at <−35 °C. The reaction mixture was allowed to slowly warm to −25 °C over 2.5 h and then added to a solution of 300 mL of 2 M $NaHSO_4$. The organic layer was then washed with 300 mL of water and azeotropically dried to a KF < 130 and a final volume of 250 mL. An analytical sample can be obtained by removal of the solvent under reduced pressure and purification of the residue by silica gel chromatography.

To the above toluene solution was added 25 wt % NaOMe in MeOH (40 mmol) and the mixture heated to 75 °C for 1 h. The reaction was cooled to 50 °C; to the cooled mixture were added 6 N NaOH (350 mmol), 300 mL of water, and MeOH (300 mmol), and the mixture was stirred at room temperature for 3 h. The layers were allowed to separate, and the aqueous layer was washed with 230 mL of MTBE. The aqueous layer was then made acidic (pH ∼1−1.5) with concentrated HCl and extracted with 610 mL of isopropyl acetate. The isopropyl acetate solution was treated with activated carbon, filtered, and concentrated to a final volume of 220 mL and KF < 200. To the isopropyl acetate solution was added 640 mL of heptane. The slurry was cooled to −10 °C and filtered, and the wet cake was washed with 1:5 isopropyl acetate/heptane and then heptane.

Methyl (3*S*)-2-(4-Fluorophenyl)-3-hydroxycyclopent-1-enecarboxylate (4). White solid (94%): $[\alpha]_D$ −186.6 (*c* 0.01, MeOH); mp 43−44 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.72 (br s, 1H), 1.89 (m, 1H), 2.45 (m, 1H), 2.67 (m, 1H), 2.92 (m, 1H), 3.63 (s, 3H), 5.14 (m, 1H), 7.04 (t, 2H, J = 8.9 Hz), 7.35 (dd, 2H, J = 8.9 and 5.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 31.6,

32.0, 51.5, 80.6, 115.1 (d, $J = 20$ Hz), 130.1, 130.7, 131.4, 152.3, 162.6 (d, $J = 250$ Hz), 166.3. Anal. Calcd for $C_{13}H_{13}FO_3$: C, 66.09; H, 5.55. Found: C, 65.81; H, 5.61.

Methyl (1*S*,2*R*,3*S*)-2-(4-Fluorophenyl)-3-hydroxycyclopentane-1-carboxylate (19). Colorless oil: $[\alpha]_D$ +74.9 (*c* 0.0064, MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.71 (m, 2H), 2.10 (m, 2H), 2.37 (m, 1H), 3.30 (s, 3H), 3.32 (m, 2H), 4.62 (q, 1H, $J = 6.9$ Hz), 7.01 (m, 2H), 7.19 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.9, 48.1, 51.3, 56.0, 77.0, 115.2 (d, $J = 30$ Hz), 129.7 (d, $J = 10$ Hz), 134.7, 161.7 (d, $J = 240$ Hz), 174.7. Anal. Calcd for $C_{13}H_{15}FO_3$: C, 65.53; H, 6.35. Found: C, 65.58; H, 6.30.

Methyl (1*S*,2*S*,3*S*)-2-(4-Fluorophenyl)-3-hydroxycyclopentane-1-carboxylate (20). Colorless oil: $[\alpha]_D$ −45.6 (*c* 0.0026, MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.05 (m, 2H), 2.07−2.18 (m, 2H), 3.35 (m, 1H), 3.45 (m, 1H), 3.50 (s, 3H), 3.74 (d, 1H, $J = 10.6$ Hz), 4.55 (m, 1H), 6.99 (m, 2H), 7.36 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.4, 35.5, 47.1, 52.0, 52.1, 74.7, 115.0 (d, $J = 20$ Hz), 130.5, 133.4, 161.6 (d, $J = 240$ Hz), 178.3. Anal. Calcd for $C_{13}H_{15}FO_3$: C, 65.53; H, 6.35. Found: C, 65.42; H, 6.26.

Methyl (1*R*,2*R*,3*S*)-2-(4-Fluorophenyl)-3-hydroxycyclopentane-1-carboxylate (3). Colorless oil: $[\alpha]_D$ −103.3 (*c* 0.01, MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.83 (m, 1H), 1.95 (br s, 1H), 2.13 (m, 3H), 2.91 (q, 1H, $J = 8.5$ Hz), 3.22 (dd, 1H, $J =$ 18.2 and 8.5 Hz), 3.62 (s, 3H), 4.17 (m, 1H), 7.01 (m, 2H), 7.21 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 26.3, 33.1, 49.3, 51.9, 56.7, 79.6, 115.5 (d, $J = 20$ Hz), 129.0, 136.7, 161.8 (d, $J =$ 240 Hz), 175.6. Anal. Calcd for $C_{13}H_{15}FO_3$: C, 65.53; H, 6.35. Found: C, 65.15; H, 6.05.

(1*S*,2*S*,3*R*)-2-(4-Fluorophenyl)-3-hydroxymethylcyclopentanol (21). Colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.72 (m, 2H), 1.96 (m, 3H), 2.10 (m, 1H), 2.12 (m, 1H), 2.64 (dd, 1H, $J = 9.5$ and 7.4 Hz), 3.50 (dd, 1H, $J = 10.6$ and 6.2 Hz), 3.59 (dd, 1H, $J = 10.6$ and 6.2 Hz), 4.12 (q, 1H, $J = 6.8$ Hz), 7.01 (m, 2H), 7.18 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.2, 33.2, 47.2, 56.5, 65.2, 80.4, 115.5 (d, $J = 20$ Hz), 138.1, 161.7 (d, $J = 240$ Hz). Anal. Calcd for $C_{12}H_{15}FO_2$: C, 68.55; H, 7.19. Found: C, 68.42; H, 7.10.

(1*R*,2*R*,3*S*)-2-(4-Fluorophenyl)-3-hydroxycyclopentane-1-carboxylic Acid (2). White solid: $[\alpha]_D$ −67.0 (*c* 0.01, MeOH); mp 142−143 °C (isopropyl acetate/heptane); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.89 (m, 1H), 2.01 (2.10 br s, 1H), 2.17 (m, 3H), 2.96 (m, 1H), 3.23 (dd, 1H, $J = 9.8$ and 7.6 Hz), 4.19 (q, 1H, $J = 7.0$ Hz), 7.03 (m, 2H), 7.22 (m, 2H), 10.9 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.9, 33.2, 49.0, 56.7, 79.2, 115.0 (d, $J = 20$ Hz), 129.5, 138.0, 161.7 (d, *J* 240 Hz), 176.3. Anal. Calcd for $C_{12}H_{13}FO_3$: C, 64.28; H, 5.84. Found: C, 64.00; H, 6.04.

(1*R*,2*R*,3*S*)-2-Methyl-3-hydroxycyclopentane-1-carboxylic Acid (30a). White solid: $[\alpha]_D$ −15.26 (*c* 0.0019, MeOH); mp 87−88 °C (isopropyl acetate/heptane); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.12 (t, 3H, $J = 6.9$ Hz), 1.77 (m, 1H), 1.95−2.29 (m, 5H), 2.44 (q, 1H, $J = 8.0$ Hz), 3.83 (q, 1H, $J = 5.6$ Hz), 11.3 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 17.7, 25.9, 33.4, 49.4, 51.9, 79.7, 176.3; Anal. Calcd for $C_7H_{12}O_3$: C, 58.32; H, 8.39. Found: C, 58.30; H, 8.45.

(1*R*,2*R*,3*S*)-2-Phenyl-3-hydroxycyclopentane-1-carboxylic Acid (30b). White solid: $[\alpha]_D$ −30.3 (*c* 0.001, MeOH); mp 98−99 °C (isopropyl acetate/heptane); ^{1}H NMR (CD_3CN, 400 MHz) δ 1.73 (m, 1H), 2.09 (m, 3H), 2.11 (br s, 1H), 2.91 (m, 1H), 3.05 (m, 1H), 4.12 (q, 1H, $J = 7.0$ Hz), 7.31 (m 5H), 9.00 (br s, 1H); ^{13}C NMR (CD_3CN, 100 MHz) δ 26.2, 33.5, 49.1, 57.7, 79.3, 126.6, 127.8, 128.4, 138.0, 162.0. Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 69.82; H, 6.67.

(1*R*,2*R*,3*S*)-2-(2-Tolyl)-3-hydroxycyclopentane-1-carboxylic Acid (30c). White solid: $[\alpha]_D$ −9.00 (*c* 0.002, MeOH); mp 198−199 °C (isopropyl acetate/heptane); ^{1}H NMR ($(CD_3)_2SO$, 400 MHz) δ 1.61 (m, 1H), 1.96 (m, 3H), 2.29 (s, 3H), 2.73 (q, 1H, $J = 8.6$ Hz), 3.35 (t, 1H, $J = 8.7$ Hz), 3.95 (m, 1H), 4.75 (m, 1H), 7.12 (m, 3H), 7.19 (d, 1H, $J = 7.6$ Hz), 11.9 (s, 1H); ^{13}C NMR ($(CD_3)_2SO$, 100 MHz) δ 20.2, 27.2, 34.6, 50.4, 52.8, 80.3, 126.1, 126.6, 130.2, 137.1, 142.0, 176.8. Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.87; H, 7.33. Found: C, 70.47; H, 7.50.

(1*R*,2*R*,3*S*)-2-Methyl-3-hydroxycyclohexane-1-carboxylic Acid (30d). White solid: $[\alpha]_D$ −8.4 (*c* 0.004, MeOH); mp 139−140 °C (isopropyl acetate/hexane); ^{1}H NMR (CD_3CN, 400 MHz) δ 0.96 (d, 3H, $J = 6.4$ Hz), 1.25−1.45 (m, 5H), 1.65 (br s, 1H), 1.75 (m, 2H), 1.85 (m, 1H), 1.95 (m, 1H), 3.05 (ddd, 1H, $J = 10.0$ and 4.1 Hz); ^{13}C NMR (CD_3CN, 100 MHz) δ 16.6, 24.7, 30.6, 36.0, 42.5, 50.5, 75.0, 176.9. Anal. Calcd for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 60.82; H, 9.18.

(1*R*,2*R*,3*S*)-2-Phenyl-3-hydroxycyclohexane-1-carboxylic Acid (30e). White solid: $[\alpha]_D$ −12.73 (*c* 0.0033, MeOH); mp 176−177 °C (isopropyl acetate/hexane); ^{1}H NMR ($(CD_3)_2CO$, 400 MHz) δ 1.35−1.61 (m, 4H), 1.85 (m, 1H), 1.94 (m, 1H), 2.06 (m, 1H), 2.66 (m, 2H), 3.67 (m, 1H), 7.12 (m, 1H), 7.23 (m, 4H), 11.9 (br s, 1H); ^{13}C NMR ($(CD_3)_2CO$, 100 MHz) δ 23.8, 30.1, 35.3, 49.1, 54.4, 72.9, 126.2, 127.9, 128.8, 142.0, 174.6. Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 70.89; H, 7.32. Found: C, 70.75; H, 7.43.

(1*R*,2*R*,3*S*)-2-(4-Fluorophenyl)-3-hydroxycyclohexane-1-carboxylic Acid (30f). White solid: $[\alpha]_D$ −16.0 (*c* 0.002, MeOH); mp 137−138 °C (EtOAc/hexane); ^{1}H NMR ($(CD_3)_2CO$, 400 MHz) δ 1.51 (m, 4H), 1.83 (m, 1H), 1.96 (m, 1H), 2.02 (m, 1H), 2.65 (m, 2H), 3.65 (m, 1H), 6.96 (m, 2H), 7.26 (m, 2H), 11.1 (br s, 1H); ^{13}C NMR ($(CD_3)_2CO$, 100 MHz) δ 23.7, 30.0, 35.3, 49.1, 53.7, 72.8, 114.3 (d, $J = 30$ Hz), 130.3 (d, $J = 10$ Hz), 138.2, 161.5 (d, $J = 20$ Hz), 174.4. Anal. Calcd for $C_{13}H_{15}FO_3$: C, 65.54; H, 6.35. Found: C, 65.23; H, 6.23.

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Supporting Information Available: Characterization data for synthetic intermediates used in the synthesis of **26b**−**f**, ^{1}H NMR data for **16**, and ^{1}H and ^{13}C NMR data for compounds **26c**, **d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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