# Synthesis of *trans*-3,4-Dimethyl-4-(3-hydroxyphenyl)piperidine Opioid Antagonists: Application of the *Cis*-Thermal Elimination of Carbonates to Alkaloid Synthesis

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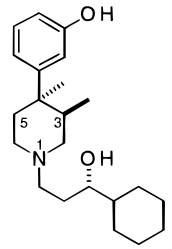
Improved syntheses of two *trans*-3,4-dimethyl-4-(3-hydroxyphenyl)piperidine opioid antagonists from 1,3-dimethyl-4-piperidinone are described. The 1,3-dimethyl-4-arylpiperidinol **23** was selectively dehydrated in a two step process to the 1,3-dimethyl-4-aryl-1,2,3,6-tetrahydropyridine **26** by the *cis*-thermal elimination of the corresponding alkyl carbonate derivative at 190 °C. In the presence of a basic nitrogen, the success of the elimination was found to be critically dependent upon the nature of the carbonate alkyl group, with Et, *i*-Bu, and *i*-Pr being preferred (90% yield). Alkylation of the metalloenamine, formed by deprotonation of **26** with *n*-BuLi, proceeded regio- and stereospecifically to give the *trans*-3,4-dimethyl-4-aryl-1,2,3,4-tetrahydropyridine **27**, which was converted in three steps to the common intermediate, (3*R*,4*R*)-3,4-dimethyl-4-(3-hydroxyphenyl)-piperidine. LY255582, a centrally-active opioid antagonist, and LY246736-dihydrate, a peripherally-active opioid antagonist, were prepared from 1,3-dimethyl-4-piperidinone in 11.8% yield (8 steps) and 6.2% yield (12 steps), respectively.

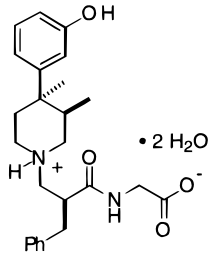
## Introduction

The *trans*-3,4-dimethyl-4-(3-hydroxyphenyl)piperidines are an important class of compounds exhibiting pure opioid antagonist activity as a result of the 3-methyl substituent.[1] Previously, all known opioid antagonists were polycyclic analogs having a morphine-like structure, such as naloxone and naltrexone. Endogenous opioids are known to play a key role in moderating various physiological functions, such as GI motility, appetite, pain sensitivity, and emotional state.[2] Thus, selective opioid antagonists may find uses in a number of therapeutic areas. An efficient synthetic approach to this class of antagonists should provide an opportunity for the further evaluation of these compounds.

LY255582 (**1**) and LY246736-dihydrate (**2**) are two examples of this class of opioid antagonists. LY255582 is a centrally-active antagonist which has a high affinity for both the $\mu$- and $\kappa$-opioid receptors ($K_i$ = 0.4 and 2 nM, respectively) and may prove useful in the treatment of obesity and eating disorders.[1c,3] This antagonist has been shown to promote weight loss in obese Zucker rats over an extended time without any tolerance observed.[4] It has recently been suggested that this anoretic effect may be linked to the selectivity of LY255582 for the $\kappa_{2b}$-binding site.[5] LY246736-dihydrate is a peripherally-active antagonist which has a high affinity for the $\mu$-opioid receptor in the lining of the gastrointestinal tract ($K_i$ < 1 nM) and may prove useful in the treatment of GI motility disorders.[6]




LY255582 (1)




LY246736-dihydrate (2)

Our successful efforts in developing an efficient synthesis of the (3*R*,4*R*)-3,4-dimethyl-4-(3-hydroxyphenyl)-piperidine nucleus allowed for the preparation of multikilogram quantities of both **1** and **2** to support clinical investigations and provided a key intermediate for further SAR studies. During the course of this work, the use of an alkyl carbonate for a *cis*-thermal elimination reaction *in the presence of a basic nitrogen* was demonstrated for the first time. This method should find application in alkaloid synthesis as a selective method for dehydration of amino alcohols at reasonable temperatures under neutral conditions.

## Results and Discussion

**Synthesis of the *trans*-3,4-Dimethyl-4-arylpiperidine Nucleus.** Establishing the *trans*-diaxial relation-

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(1) (a) Zimmerman, D. M.; Nickander, R.; Horng, J. S.; Wong, D. T. *Nature* **1978**, *275*, 332. (b) Zimmerman, D. M.; Leander, J. D.; Cantrell, B. E.; Reel, J. K.; Snoddy, J.; Mendelsohn, L. G.; Johnson, B. G.; Mitch, C. H. *J. Med. Chem.* **1993**, *36*, 2833. (c) Mitch, C. H.; Leander, J. D.; Mendelsohn, L. G.; Shaw, W. N.; Wong, D. T.; Cantrell, B. E.; Johnson, B. G.; Reel, J. K.; Snoddy, J. D.; Takemori, A. E.; Zimmerman, D. M. *J. Med. Chem.* **1993**, *36*, 2842.

(2) (a) Zimmerman, D. M.; Leander, J. D. *J. Med. Chem.* **1990**, *33*, 895. (b) Jaffe, J. H.; Martin, W. R. In *Goodman and Gilman's the Pharmacological Basis of Therapeutics*, 7th ed.; Gilman, A. G., Goodman, L. S., Rall, T. W., Murad, F., Eds.; Macmillan: New York, 1985; p 491.

(3) For the synthesis of **1** see: Mitch, C. H.; Zimmerman, D. M.; Snoddy, J. D.; Reel, J. K.; Cantrell, B. E. *J. Org. Chem.* **1991**, *56*, 1660.

(4) For a recent reference see: Shaw, W. N. *Pharmacol. Biochem. Behav.* **1993**, *46*, 653.

(5) Rothman, R. B.; Xu, H.; Char, G. U.; Kim, A.; De Costa, B. R.; Rice, K. C.; Zimmerman, D. M. *Peptides* **1993**, *14*, 17.

(6) (a) Zimmerman, D. M.; Gidda, J. S.; Cantrell, B. E.; Schoepp, D. D.; Johnson, B. G.; Leander, J. D. *J. Med. Chem.* **1994**, *37*, 2262. (b) Zimmerman, D. M.; Gidda, J. S.; Cantrell, B. E.; Werner, J. A.; Parli, C. J.; Franklin, R. B.; Francis, P. C.; Means, J. R.; Pohland, R. C.; Leander, J. D. *Drugs of the Future* **1994**, *19*, 1078.

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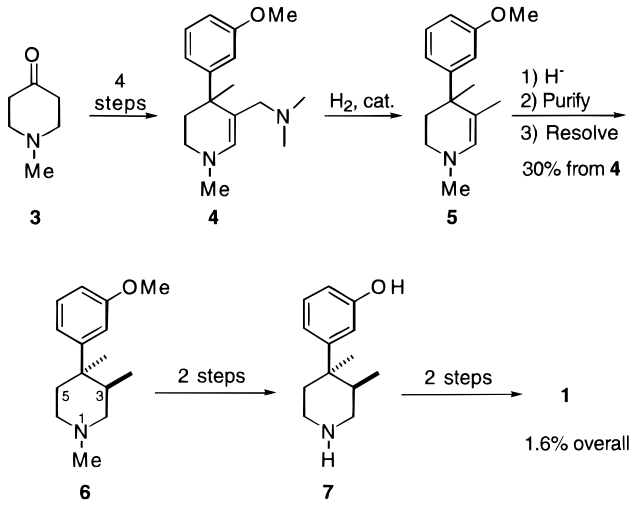
**Scheme 1. Literature Synthesis of 1**[3]

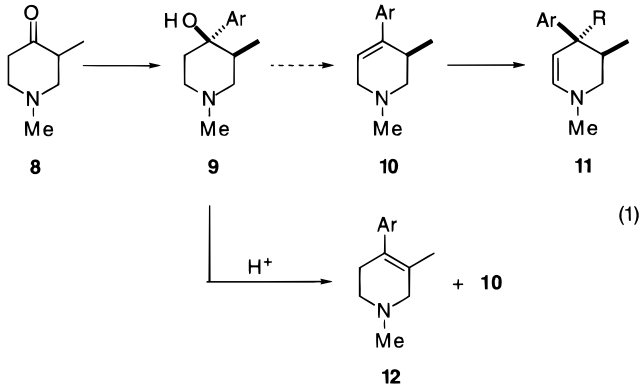



ship between the two methyl groups has been a major challenge in the synthesis of **7**. Mitch and co-workers[3] used a two-step reduction strategy to prepare piperidine **6** from the (dimethylamino)methyl enamine **4**[7] (Scheme 1). Hydrogenolysis of the dimethylamino group in **4**, followed by reduction of enamine **5** with $NaBH_3CN$ in MeOH, afforded racemic **6** in 94% yield as a 93:7 mixture of diastereomers. After separation of the diastereomers by recrystallization of the HBr salt (80%), (±)-6 was resolved with dibenzoyl-D-tartaric acid in 38% yield to give the *trans*-3,4-dimethylpiperidine **6**. The protecting groups on **6** were removed in two steps to complete the synthesis of the piperidine nucleus **7** (8.5% overall yield from **3**), which was then carried on to complete the synthesis of opioid antagonist **1** (1.6% overall yield from **3**).

This approach presents three major challenges for its safe implementation on a large scale. First, one of the synthetic intermediates, 1-methyl-4-(3-methoxyphenyl)-1,2,3,6-tetrahydropyridine causes neurotoxicity in mice similar to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)[8] (which leads to Parkinson's-like symptoms in animals and humans). Second, only moderate selectivity is achieved in controlling the relative stereochemistry of the *C*3-methyl group. And finally, the resolution occurs 6 steps into a 10-step synthesis, which critically impacts the efficient use of resources.

The neurotoxicity issue was solved by changing the nitrogen and oxygen protecting groups to ethyl and isopropyl, respectively. Substituents larger than methyl on either the piperidine nitrogen[9] or the aryl oxygen[10] are known to prevent the MPTP-like neurotoxicity in animals. *C*-Methyl substitution on the piperidine ring also eliminates all neurotoxicity.[11] This process was safely implemented on a pilot plant scale by modification of the literature procedures as summarized in the Supporting Information and afforded the piperidine nucleus **7** in 5.5% overall yield from *N*-ethyl-4-piperidinone.

However, an alternative synthetic strategy is required to address the second and third issues mentioned above; namely, the moderate selectivity in controlling the relative stereochemistry of the *C*3-methyl group and the late resolution. Starting with 1,3-dimethyl-4-piperidinone (**8**) would solve both of these problems (eq 1). Introduction of the *C*3-methyl group from the start potentially allows the resolution to be conducted after step 1 instead of step 6. Furthermore, it should also provide a control element for establishing the relative stereochemistry between the two methyl groups. Barnett[7] has demonstrated that the metalloenamine derived from deprotonation of **10** (Ar = 3-$MeOC_6H_4$) with *n*-BuLi can be alkylated with complete regio- and stereocontrol with propyl bromide to give **11** (R = Pr, Ar = 3-$MeOC_6H_4$) in 93% yield.




(1)

Implementation of this strategy requires the unprecedented regiospecific dehydration of **9** to **10**. The acid-promoted dehydration of **9** is well precedented and gives a 2.3:1.0 mixture of olefins **10** and **12**.[7,12] Upon acid equilibration, the more substituted alkene **12** predominates in a 1:9 mixture. Thus, acid-promoted dehydration is not a viable solution because it gives low yields of **10** and would involve a difficult purification. Also, if **12** is present as a contaminant, both strategic advantages from starting with **8** are lost as deprotonation of **12** would give a planar metalloenamine, which upon methylation would produce enamine **5**.

A "*cis*-dehydration" of alcohol **9** is required to achieve the regiospecific elimination to **10**. This has been accomplished by Portoghese[13] through the use of a two-step procedure: formation of the propionate ester followed by thermal elimination at 300 °C in mineral oil for 1 h. This afforded **10** (Ar = Ph) in 62% yield. We chose to use a similar strategy, the thermal *cis*-elimination of an acyl derivative, but needed to identify a derivative that would undergo elimination at a significantly lower temperature and in higher yield.

Carbonate esters were selected as the acyl group to be examined for the *cis*-thermal elimination. They are known to eliminate at lower temperatures than carboxylic esters, 150−300 vs 250−400 °C, and produce neutral byproducts upon elimination ($CO_2$ and alcohol).[14] Xanthate esters were not examined because of our concern about quaternization of the piperidine nitrogen during their formation.

(7) Prepared in four steps using methodology adapted from Barnett's synthesis of picenadol, a *cis*-3,4-dialkyl-4-arylpiperidine: Barnett, C. J.; Copley-Merriman, C. R.; Maki, J. *J. Org. Chem.* **1989**, *54*, 4795.

(8) For a review of the pharmacology of MPTP and related analogs see: Markey, S. P.; Schmuff, N. R. *Med. Res. Rev.* **1986**, *6*, 389.

(9) Zimmerman, D. M.; Cantrell, B. E.; Reel, J. K.; Hemrick-Luecke, S. K.; Fuller, R. W. *J. Med. Chem.* **1986**, *29*, 1517 and references cited therein.

(10) Fuller, R. W., Eli Lilly and Company. Unpublished results, May 21, 1986.

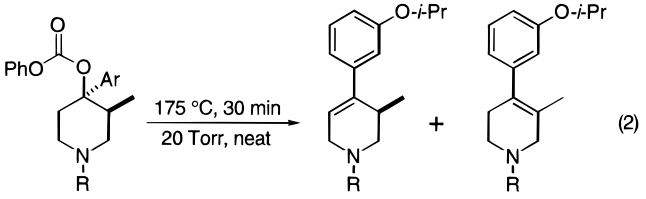
(11) Fries, D. S.; de Vries, J.; Hazelhoff, B.; Horn, A. S. *J. Med. Chem.* **1986**, *29*, 424.

(12) Casy, A. F.; Beckett, A. H.; Iorio, M. A. *Tetrahedron* **1967**, *23*, 1405 and references therein.

(13) (a) Larson, D. L.; Portoghese, P. S. *J. Med. Chem.* **1973**, *16*, 195. (b) The analogous reaction in a seven-membered ring nitrogen heterocycle (75%, 280−300 °C) has been reported: Diamond, J.; Bruce, W. F.; Tyson, F. T. *J. Med. Chem.* **1964**, *7*, 57.

(14) For a review of pyrolytic *cis*-eliminations see: DePuy, C. H.; King, R. W. *Chem. Rev.* **1960**, 431.

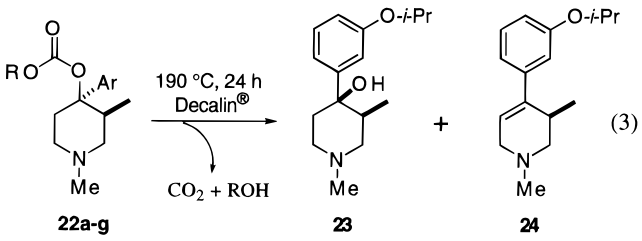
The thermal elimination of carbonates has been used for some time in carbocyclic systems,[14] but to the best of our knowledge, it is *unprecedented with alkaloids.* The dramatic effect that the basic nitrogen can have is illustrated in eq 2. Thermal decomposition of the *N*-ethyl analog **13** at 175 °C (with a slight vacuum to remove phenol as it is formed) gives the desired olefin **14** in 21% yield and 1.5% of the corresponding piperidinol (weight percent analysis by capillary GC) along with a multitude of other products (analysis by $^1$H NMR). Heating the hydrochloride salt **16** under the same conditions gives a mixture of the two olefin isomers, **17** (25%) and **18** (38%), and 1.5% of the piperidinol. We suspect that the carbonate is undergoing an acid-promoted solvolysis to give the mixture of elimination products since the less substituted product **17** does not undergo isomerization when subjected to the reaction conditions. Removal of the basic nitrogen has a dramatic impact on the success of the thermal elimination process. Carbamate **19**, which is prepared in 87% yield by treating **13** with phenyl chloroformate in refluxing toluene, gives olefin **20** in 92% yield upon heating.[15] Apparently the basic nitrogen is responsible for the decomposition of phenyl carbonate **13**, and at 175 °C, decomposition occurs more readily than does elimination. Unfortunately, we were unable to characterize the decomposition products. We suspected that an alkyl carbonate derivative might be more stable than the phenyl carbonate derivative in the presence of the basic amine, particularly if it was somewhat sterically hindered.




**13**, R = Et **14**, 21% **15**, 0%
**16**, R = Et•HCl **17**, 25% **18**, 38%
**19**, R = $CO_2$Ph **20**, 92% **21**, 0%

In screening a number of alkyl carbonates, we found that thermal elimination of primary alkyl carbonates with some steric hindrance and secondary alkyl carbonates cleanly gave elimination, while a tertiary alkyl carbonate gave predominately carbinol **23** (Table 1).[16,17] The thermal eliminations were conducted under two sets of conditions: (1) method A, 225 °C, 1 h, neat: (2) method B, 190 °C, 24 h, refluxing Decalin. Similar results were obtained with both procedures. The data from method B are summarized in Table 1. The primary alkyl carbonates (entries 1−4) give high yields only when there is some additional steric hindrance around the carbonyl group, as with the ethyl and isobutyl carbonates. The methyl and benzyl carbonates provide **24**, in moderate yields of 68% and 75%, respectively. The lower yields are due both to the formation of other byproducts (GC analysis) and to the alcoholysis of the carbonate group by the liberated ROH, as evidenced by the formation of alcohol **23** in 4.4−13.7% yield. The secondary alkyl carbonate (entry 5, R = *i*-Pr) undergoes clean elimination, while the phenyl carbonate (entry 7) undergoes predominantly decomposition (poor mass balance and many products by $^1$H NMR, as observed with **13** above).

**Table 1. Thermal Elimination of Carbonates in Decalin**




| entry | R | substrate | **23** (%)[a] | **24** (%)[a] |
|---|---|---|---|---|
| 1 | Me | **22a** | 13.7 | 68 |
| 2 | Et | **22b** | 0.5 | 91 |
| 3 | *i*-Bu | **22c** | 0.1 | 92 |
| 4 | Bn | **22d** | 4.4 | 75 |
| 5 | *i*-Pr | **22e** | 0.6 | 90 |
| 6 | *t*-Bu | **22f** | 86.4 | 13 |
| 7 | Ph | **22g** | 0.5 | 41 |

[a] GC yields using naphthalene as an internal standard. Conditions: column; DB-wax (30 m × 0.32 i.d. × 0.25 $\mu$m film), cool on-column injection, oven, 35 °C (1.5 min) to 225 °C (15 min) at 15 deg/min; detector, 260 °C; carrier, He (1.7 mL/min). $t_R$ = 12.0 min (naphthalene), 18.5 min (**24**), 25.2 min (**23**).

Two factors are responsible for the successful elimination with the ethyl, isobutyl, and isopropyl carbonates. First, those carbonates are sufficiently stable in the presence of the basic nitrogen to permit elimination to occur. Second, the R-groups are primary or secondary alkyl groups, which are known to undergo elimination at slower rates than tertiary alkyl groups (such as the piperidinyl group).[14] Thus, thermal elimination gives exclusively tetrahydropyridine **24**. When both alkyl groups are tertiary (entry 6, R = *t*-Bu), elimination occurs at comparable rates, and a statistical mixture of elimination products is obtained, **24** and isobutene (with an equal amount of alcohol **23**).

Application of this methodology to the synthesis of the piperidine nucleus **7** is shown in Scheme 2. Treatment of 1,3-dimethyl-4-piperidinone (**8**) with the aryllithium derived from 3-(isopropoxy)bromobenzene using literature conditions[7] gives a 9:1 mixture of diastereomeric alcohols. Recrystallization from heptane affords **23** as a single diastereomer in 69% yield. Alcohol **23** can be resolved with (+)-3-bromocamphor-8-sulfonic acid;[18] however, upon scale up the results are highly variable and the salt is difficult to filter.

Acylation of alcohol **23** with ethyl chloroformate in EtOAc gives carbonate (±)-**25**, which is efficiently resolved with (+)-di-*p*-toluoyl-D-tartaric acid (DTTA) in ethanol as a 1:1 salt. Unlike the resolution of alcohol **23**, the resolution of (±)-**25** is extremely reproducible on all scales. Recrystallization of the salt from ethanol gives the enriched salt as a 95:5 mixture in 41% yield.[19] Furthermore, any unreacted **23** is also removed during the process.

(15) Alkylation of the metalloenamine formed by deprotonation of **20** using the conditions described in Table 2 gave only a 30% yield of the desired *trans*-$\gamma$-alkylation product along with significant amounts of *N*-deprotected starting material. Therefore, a method for effecting the elimination in the presence of the basic amine was required.

(16) Werner, J. A.; Cerbone, L. R. Poster presentation at the 203rd National Meeting of the American Chemical Society, San Francisco, CA, April 1992; paper ORGN 409.

(17) As expected, an ester gives only a low yield of the elimination product at this temperature. Heating the propionate ester of **23** at 190 °C for 24 h (method B) affords tetrahydropyridine **24** in only 12% yield, along with unreacted starting material (85%) and an uncharacterized impurity (3%).

(18) Resolution results: 22% yield, 96% ee, 4 recrystallizations from *i*-PrOH at 200 mg/mL. The diastereomeric enrichment of the initial crystallization varies from 2:1 to 1:1.

**Scheme 2**

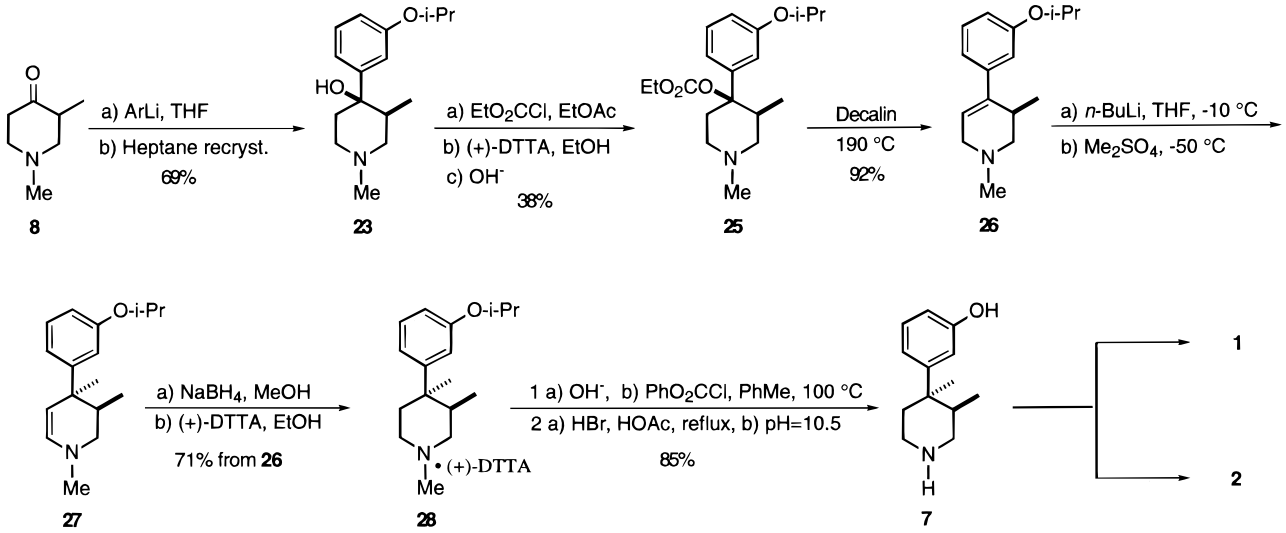
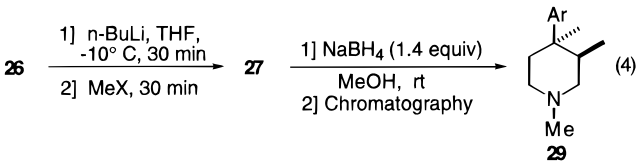



**Table 2. Metalloenamine Alkylation and Enamine Reduction**




| entry | MeX | equiv | temp (°C) | **29** (%) | purity (%)[a] |
|---|---|---|---|---|---|
| 1 | MeI | 1.2 | −50 | 69[b] | 71 |
| 2 | MeBr | 1.5 | −28 | 56[b] | 87 |
| 3 | $Me_2SO_4$ | 1.1 | −50 | 72[b] | 97 |
| 4 | $Me_2SO_4$ | 1.02 | −50 | 80 | 99 |

[a] HPLC area % after silica gel chromatography. [b] Yields corrected for purity of **26** (90% by HPLC).

Thermal elimination of the free base **25**, as described above, cleanly gives the desired olefin **26** in 92% yield after 24 h in refluxing Decalin. None of the isomeric elimination product can be detected by $^1$H NMR, and the crude product is used without further purification.

Methylation of the metalloenamine[20] with dimethyl sulfate (1.02 equiv) at −50 °C gives the desired *trans*-3,4-dimethyl enamine **27** in excellent yield. The alkylation reaction was examined extensively, and a brief summary is shown in Table 2 of our results with three different methylating agents under optimized conditions for each. Dimethyl sulfate is by far the superior methylating agent giving **29** in 80% yield after chromatography. However, due to the reactivity of this reagent, dimethyl sulfate must be used in stoichiometric amounts, and the reaction mixture must be quenched into aqueous ammonium hydroxide to prevent *N*-methylation (compare entries 3 and 4).[21] Methyl bromide appears to give clean alkylation (by $^1$H NMR), but a significant amount of a byproduct is produced upon reduction of crude **27** with $NaBH_4$. We were unable to characterize the byproduct and could not prevent the formation of this compound by modification of the MeBr stoichiometry. Methyl iodide gives a number of impurities in the alkylation step.

Alkylation of the metalloenamine is regiospecific at the $\gamma$-position and occurs exclusively *trans* to the *C*3-methyl substituent, as anticipated from the Barnett[7] precedent. Apparently the *C*3-methyl group occupies a pseudoaxial position in the flattened metalloenamine, thus blocking alkylation from the $\beta$-face. The stereochemistry of the alkylation was determined by preparing an authentic sample of the *cis*-3,4-dimethyl analog of **29**[22] and comparing the $^1$H NMR spectra of the crude alkylation/reduction reaction mixtures (**29**, methyl doublet at 0.80 ppm; 3,4-*cis*-isomer, methyl doublet at 0.61 ppm). None of the *cis*-isomer could be detected although small quantities (3−5%) of the *C*4-desmethyl analog, resulting from protonation of the metalloenamine, were observed.

Purification of **29** by crystallization of the (+)-DTTA salt **28** proceeds in 65% overall yield from **25**, reduces all impurities to less than 1%, and increases the enantiomeric purity to 99.8% ee. It also provides a stable crystalline intermediate.

Demethylation of the free base of **29** with phenyl chloroformate in refluxing toluene followed by removal of both the *N*- and *O*-protecting groups with HBr in refluxing HOAc completes the synthesis of the key intermediate **7** (85% yield from **28**). Preparation of the *trans*-3,4-dimethylpiperidine nucleus **7** from **8** in seven steps and 14.4% overall yield represents a significant improvement over the strategy shown in Scheme 1.

**Synthesis of LY255582 (1).** The *N*-alkyl substituent of **1** is prepared in two steps from (*S*)-phenylpropane-1,3-diol (**30**),[23] Scheme 3. Reduction of the phenyl ring proceeds in 92% yield. The primary alcohol in **31** is readily derivatized to give the hydroxy brosylate **32** in

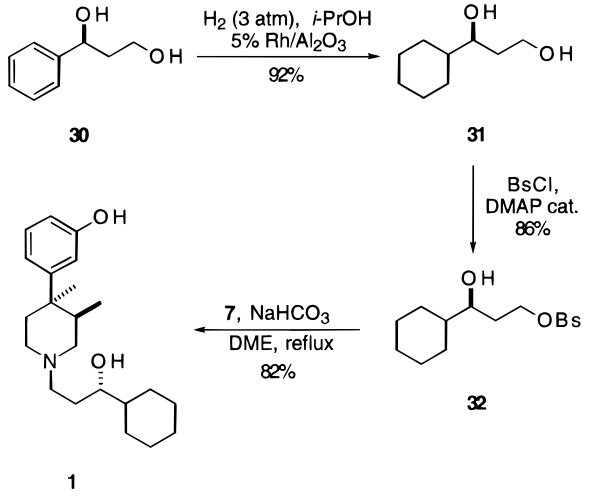
(19) (a) The "recrystallization" was conducted by heating a heterogeneous mixture at reflux for 2 h as described in the Experimental Section. This process gives superior yields and equivalent enrichment to those obtained by a true recrystallization from a homogeneous solution. (b) The absolute stereochemistry was confirmed by comparing the optical rotation of **7** with that reported previously: $[\alpha]^{25}_{365}$ +383° (*c* 1.01, MeOH) (lit.[3] $[\alpha]^{25}_{365}$ +361° (*c* 1.1, MeOH)). The (+)-DTTA salt was the only crystalline salt obtained from the 12 chiral acids examined.

(20) The introduction of an alkyl substituent at the 4-position of a piperidine ring by alkylation of a metalated enamine was first described by: Evans, D. A.; Mitch, C. H.; Thomas, R. C.; Zimmerman, D. M.; Robey, R. L. *J. Am. Chem. Soc.* **1980**, *102*, 5955.

(21) If excess dimethyl sulfate is present, the tertiary *N*-methyl signal of **26** at 2.37 ppm disappears, and two quaternary *N*-methyl signals at 3.55 and 3.59 ppm appear in the $^1$H NMR spectrum.

(22) The *cis*-3,4-dimethyl isomer of **29** was prepared from the *cis*-dimethyl isomer recovered from the purification of **45b** (see Scheme 5 in the Supporting Information). The *N*-ethyl substituent was converted to the *N*-methyl substituent by dealkylation with phenyl chloroformate followed by reduction of the phenyl carbamate with Red-Al.

**Scheme 3. Synthesis of LY255582 (1)**



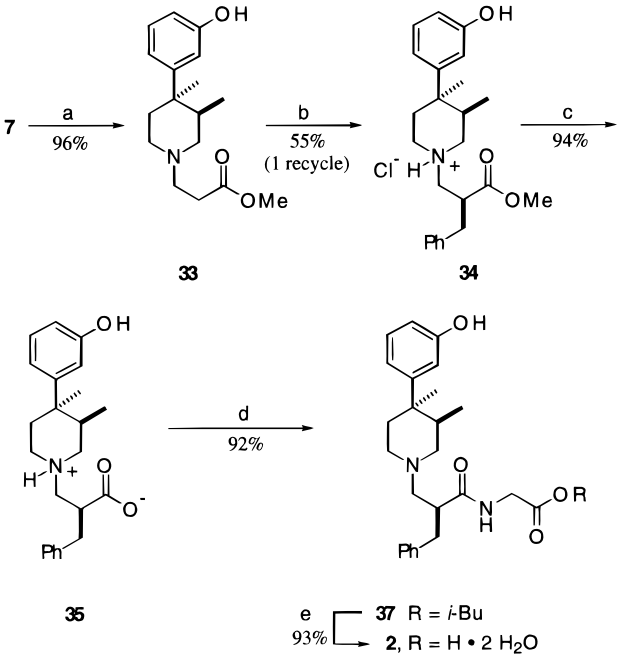

86% yield and greater than 90% ee[24] after recrystallization from toluene/cyclohexane.

Treatment of the piperidine nucleus **7** with brosylate **32** in refluxing 1,2-dimethoxyethane (DME) in the presence of $NaHCO_3$ for 8 h affords **1** in 82% yield (98% purity)[25] after crystallization from EtOAc. The synthesis of **1** from 1,3-dimethyl-4-piperidinone (**8**) in 8 steps and 11.8% yield (on a multikilo scale) offers an attractive alternative to the previously reported synthesis[3] (1.6% yield, 10 steps from *N*-methyl-4-piperidinone).

**Synthesis of LY246736-dihydrate (2).**[26] LY246736-dihydrate (**2**) was first prepared by the Michael addition of **7** to 3-phenyl-2-(ethoxycarbonyl)-1-propene in methanol.[6a] The reaction required 10 days at room temperature and afforded a 1:1 mixture of diastereomeric esters (60:40 mix of Me and Et esters) in 85% yield. The diastereomeric mixture was carried on (hydrolysis and peptide coupling) and was purified by a very difficult preparative HPLC purification of isobutyl ester **37**. Hydrolysis (6 N HCl), extraction of the triethylammonium salt into butanol/toluene (3:1), and silica gel chromatography (EtOAc:MeOH (9:1) to 100% MeOH) completed the synthesis of **2** with an overall yield of 4% from **7**. We desired a synthetic strategy that not only could be efficiently scaled up but would also provide an opportunity for the diastereoselective introduction of the benzyl substituent on the side chain.[27]

The alkylation-based approach shown in Scheme 4 meets both of these criteria. It permits the separation of the diastereomeric alkylation products by recrystallization of the hydrochloride salt **34** and also allows us to examine diastereoselective alkylations by replacing the methyl ester in **33** with a chiral auxiliary.

**Scheme 4** [a] **Synthesis of LY246736-dihydrate (2)**




[a] Conditions: (a) methyl acrylate, THF, 40 °C, 3 h; (b) LDA (2 equiv), −30 °C; BnBr (2 equiv), −20 °C; HCl, MeOH; (c) NaOH, $H_2O$−MeOH (1:1), rt, 3 h; HCl, pH = 6; (d) DCC, 1-hydroxybenzotriazole, $Et_3N$, $TsO^-H_3N^+CHCH_2CO_2$-*i*-Bu (**36**), THF, 48 h; rt; (e) NaOH, EtOH/$H_2O$ (2:1), rt, 30 min; HCl, pH = 6.

The Michael addition of **7** to methyl acrylate proceeds smoothly in either methanol (15 min, rt) or THF (4 h, 40 °C), giving a 96% yield of **33**. The difference in reaction times is probably due to the increased solubility of **7** in methanol.

Alkylation of the dianion of **33** proceeds in 97% yield, giving a 47:53 mixture of the desired (3*R*,4*R*,α*S*)-isomer and the undesired (3*R*,4*R*,α*R*)-isomer, respectively, which are readily separated by recrystallization of their hydrochloride salts from methanol to give **34** in 34% yield. Deprotonation of ester **33** with LDA (2.05 equiv,[28] THF, −30 °C) gives a slightly soluble dianion. The alkylation with benzyl bromide must be conducted between −30 and −15 °C. No reaction occurs below −30 °C, and the dianion is unstable at temperatures above −15 °C (retro-Michael). Due to the moderate reactivity of benzyl bromide, 2 equiv must be used for complete conversion of starting material. Use of less than 1.5 equiv gives only 80% conversion and does not change with the addition of a catalytic amount of LiI (2.5 mol %). No reaction occurs with benzyl chloride. Methyl iodide (1.05 equiv, −25 °C) gives a 1:1 mixture of alkylation products in 97% yield, thereby demonstrating that the low conversion is likely a function of the reactivity of benzyl bromide. The hydrochloride salt **34** must be formed prior to removing the solvent to prevent *N*- or *O*-alkylation by the excess benzyl bromide. Once the piperidine nitrogen is protonated by the addition of anhydrous HCl, the mixture can be concentrated without overalkylation. Upon the addition of methanol to the crude product, **34** precipitates

(23) Diol **30** is prepared in two steps from cinnamyl alcohol (Sharpless asymmetric epoxidation followed by Red-Al reduction): Gao, Y.; Sharpless, K. B. *J. Org. Chem.* **1988**, *53*, 4081.

(24) The enantiomeric purity of **32** varies from 90 to 99% ee depending on the reaction conditions of the hydrogenation step, the scale of the reduction, and whether or not **32** is recrystallized. Presumably the decrease in optical purity is due to the occurrence of a small amount of benzylic oxidation, via a catalytic dehydrogenation process, followed by a nonselective reduction back to diol **31**.

(25) The largest impurity was the *C*4-desmethyl isomer (0.6%), which was characterized by GC/MS: Murphy, A. T.; Breau, A. P.; Werner, J. A.; Robbins, D. K. Structural Investigation of Impurities in Synthesis of LY255582. Presented at the 41st American Society for Mass Spectrometry Conference, San Francisco, CA, May 1993.

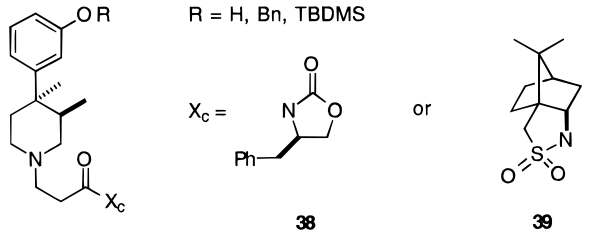
(26) This synthesis has been previously disclosed in communication format. See ref 6b.

(27) (a) For a recent review of synthetic approaches to β-amino acids see: Cole, D. C. *Tetrahedron* **1994**, *50*, 9517. (b) For a general review of diastereoselective alkylation strategies see: Evans, D. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press, Inc.: New York, 1984; Vol. 3, pp 2−110.

(28) Excess LDA must be avoided because it rapidly reacts with benzyl bromide to give bromodiphenylethane (even at −70 °C). See: Bazukis, P.; Dynak, J. N.; Wenkert, E. *Syn. Commun.* **1979**, *9*, 11.

as a crystalline solid. After a single recrystallization[19a] in hot methanol, the (3*R*,4*R*,α*S*)-isomer **34** is isolated in 34% yield as a 97:3 mixture of diastereomers. Epimerization (3 equiv LDA, −30 °C, THF; $H_2O$) and recycling of the (3*R*,4*R*,α*R*)-isomer increase the overall yield of the benzylation step from 34% to 55%.

We have been unsuccessful to date in our attempts to carry out a diastereoselective benzylation. Neither the sodium nor the lithium enolates of various *O*-protected oxazolidinone derivatives, **38**, are sufficiently nucleophilic to undergo alkylation with benzyl bromide. No reaction occurs at −30 °C. Upon warming the reaction mixture to 0 °C, acid **35** is isolated upon workup. Presumably the acid is formed by hydrolysis of the ketene, which results from the enolate undergoing elimination of the chiral auxiliary. The lithium enolate of the sultam[29] derivatives **39** are also unreactive toward benzyl bromide (−78 to 0 °C, THF). Alternative strategies for the diastereoselective introduction of the benzyl group are under investigation and will be reported separately.




Saponification of ester **34** proceeds in 94% yield with 1 N NaOH without epimerization. Amino acid **35** can be isolated in one of two ways: precipitation of the zwitterion (isoelectric point, pH = 6) from MeOH/$H_2O$ (1:1)[30] in 94% yield as the monohydrate or extraction of the zwitterion into chloroform/2-propanol (3:1) in 95% yield as the anhydrate. X-ray crystal structures were obtained for the monohydrate of **35** and the ester hydrochloride **34** and showed the α-carbon to have the (*S*)-configuration.

Condensation of amino acid **35** (as the *O*-acyl derivative of 1-hydroxybenzotriazole) with the isobutyl ester[31] of glycine gives ester **37** in 92% yield, which can either be carried on crude or purified as a salt. Two crystalline salts have been identified to date: the sesquimalate salt using L-malic acid (90% yield, EtOAc/acetone (12.5:1)) and the HCl•(acetone) salt (85% yield, acetone). Saponification of crude **37** with 1 N NaOH is very rapid in 2:1 EtOH/$H_2O$ (15 min, 25 °C), and the crystalline dihydrate **2** is isolated directly upon neutralization with hydrochloric acid in 93% yield. Opioid antagonist **2** was successfully prepared in 5 steps and 42% yield from the piperidine nucleus **7** and in 12 steps and 6.2% yield from 1,3-dimethyl-4-piperidinone (**8**).

## Conclusions

Alkylation of the metalloenamine derived from a *C*3-substituted 1,2,3,6-tetrahydropyridine is a very efficient method for the stereospecific preparation of the *trans*-3,4-dimethyl-4-arylpiperidine family of opioid antagonists. Preparation of the required tetrahydropyridine from the 4-aryl-4-piperidinol is readily accomplished in greater than 90% yield by a two-step procedure involving formation and thermal elimination of an alkyl carbonate derivative. The steric requirements of the alkyl group are critically important to the success of the elimination *in the presence of a basic nitrogen*, with Et, *i*-Bu, and *i*-Pr being preferred. In the first application of this methodology to the synthesis of alkaloids, the centrally-active opioid antagonist LY255582 (**1**) was prepared in 8 steps and 11.8% yield, and the peripherally-active opioid antagonist LY246736-dihydrate (**2**) was prepared in 12 steps and 6.2% yield, from 1,3-dimethyl-4-piperidinone (**8**) without any chromatographic purifications. This methodology should find general application in the synthesis of other alkaloids of this type, as it has been used successfully on a pilot plant scale to prepare 50 kg of the key intermediate **7** in 13.1% overall yield (cf. 14.4% laboratory yield).

## Experimental Section

**General.** All reactions were run under a nitrogen atmosphere. Reagents were used as received unless otherwise noted. Tetrahydrofuran (THF) was analyzed by Karl Fischer titration and dried if the water content was greater than 0.03% (either stored over 4 Å molecular sieves or distilled from a sodium benzophenone ketyl solution). 1,3-Dimethyl-4-piperidinone (**8**) was either prepared[32] or purchased (Sumitomo or Howard Hall International). (+)-Di-*p*-toluoyl-D-tartaric acid monohydrate was purchased from Toray Industries, Inc. Solutions of lithium diisopropylamide (LDA) were purchased from either Aldrich or FMC Lithco. The term "3A ethanol" refers to denatured ethanol containing 5% methanol. Proton and carbon NMR spectra were obtained at 500 and 75.5 MHz, respectively. NMR chemical shifts are reported in δ units referenced either to TMS or to residual proton signals in the deuterated solvents. All yields are corrected for chemical purity of both the limiting reagent and the product (i.e. yield = (weight of product × purity/MW of product)/(weight of limiting reagent × purity/MW of limiting reagent) × 100). If the purity of a product is not specified, it is greater than 99%.

**1-Bromo-3-(1-methylethoxy)benzene.**[33] A mixture of ethanol (880 mL), potassium carbonate (448 g, 3.24 mol), *m*-bromophenol (387 g, 2.24 mol), 2-bromopropane (400 g, 3.25 mol), and water (88 mL) was heated at reflux (78 °C) for 16 h. Water (880 mL) was added to the reaction mixture, and 900 mL of solvent was removed by distillation at atmospheric pressure over 4 h. Heptane (880 mL) was added to the reaction mixture, and the layers were separated. The aqueous layer was extracted with heptane (80 mL), and the combined organic fractions were washed sequentially with 1 N HCl (300 mL), water (300 mL), 1 N NaOH (300 mL), and water (300 mL). Removal of the solvent by rotary evaporation afforded 453.6 g of crude product. Distillation through a short-path column (81−85 °C, 2 Torr) afforded 431.5 g of a colorless liquid (94% purity, 84% yield). Spectral data: $^1$H NMR ($CDCl_3$) δ 1.32 (d, *J* = 6.0 Hz, 6H), 4.51 (septet, *J* = 6.1 Hz, 1H), 6.80 (ddd, *J* = 8.2, 2.4, 0.9 Hz, 1H), 7.03 (d, *J* = 2.1 Hz, 1H), 7.05 (m, 1H), 7.11 (t, *J* = 8.2 Hz, 1H); $^{13}$C NMR ($CDCl_3$) δ 21.1 (2C), 69.5, 113.9, 118.3, 122.0, 122.7, 129.7, 158.0; IR ($CHCl_3$) 3030, 2982, 1588, 1572, 1474, 1115, 959, 872 cm$^{-1}$. Anal. Calcd for $C_9H_{11}BrO$: C, 50.26; H, 5.15; Br, 37.15. Found: C, 50.49; H, 5.26; Br, 37.38.

***cis*-(±)-1,3-Dimethyl-4-[3-(1-methylethoxy)phenyl]-4-piperidinol (23).** *n*-BuLi (565 mL, 1.47 M in heptane, 0.831 mol) was added dropwise to a solution of 1-bromo-3-(1-methylethoxy)benzene (200 g, 94% purity, 0.870 mol) in THF (540 mL) over 1 h at −75 °C, and the resulting solution was stirred for 1 h. 1,3-Dimethyl-4-piperidinone (106.7 g, 0.8389 mol) was then added over 1 h while maintaining the reaction

(29) Oppolzer, W.; Moretti, R.; Thome, S. *Tetrahedron Lett.* **1989**, *30*, 6009.

(30) The MeOH/$H_2O$ ratio is critical for a successful crystallization. At lower MeOH levels a gum is formed.

(31) The isobutyl ester was used because multigram quantities of ester **37** were also needed for preclinical evaluation.

(32) Howton, D. R. *J. Org. Chem.* **1945**, *10*, 277.

(33) Procedure developed by Dr. Mary Peters, Eli Lilly and Company, unpublished results, 1987.

temperature below −70 °C, and the resulting mixture was kept below −60 °C for 1.5 h. The reaction was quenched by adding the cold reaction mixture to 6 N HCl (280 mL) while keeping the temperature at 25 °C, and then the pH was adjusted to 1 with 12 N HCl (ca. 8 mL). After phase separation, heptane (320 mL) and 50% aqueous NaOH (48 mL) were added to the aqueous layer (pH = 13−14), and the resulting mixture was allowed to stand at room temperature overnight. The layers were separated at 45 °C, and the warm aqueous layer was extracted with heptane (320 mL). The combined organic fractions were washed with water (120 mL) at 45 °C. The resulting organic layer was concentrated to a volume of 235 mL by vacuum distillation (55 °C, 100 Torr). Heptane (380 mL) was added to the crude product (ca. 9:1 ratio of diastereomers), and the mixture was reheated to 55 °C. The reaction mixture was seeded at 45 °C and allowed to cool slowly overnight to room temperature. The slurry was then cooled to 0 °C for about 2 h and filtered, and the cake was washed with cold heptane (135 mL). The white solid was dried (in vacuo at 50 °C) to give 151.8 g of **23** (69% yield), mp 75.0−76.0 °C. Spectral data for **23**: $^1$H NMR ($CDCl_3$) $\delta$ 0.63 (d, $J$ = 6.9 Hz, 3H), 1.32 (d, $J$ = 6.2 Hz, 6H), 1.69 (dd, $J$ = 14.0, 1.4 Hz, 1H), 1.85 (s, 1H), 2.10−2.22 (m, 2H), 2.25−2.31 (m, 1H), 2.33 (s, 3H), 2.38 (t, $J$ = 12.1 Hz, 1H), 2.66 (br d, $J$ = 11.1 Hz, 1H), 2.74 (br d, $J$ = 9.35 Hz, 1H), 4.54 (septet, $J$ = 6.0 Hz, 1H), 6.75 (d, $J$ = 8.2 Hz, 1H), 7.00 (d, $J$ = 7.6 Hz, 1H), 7.03 (m, 1H), 7.22 (t, $J$ = 7.9 Hz, 1H); $^{13}$C NMR ($CDCl_3$) $\delta$ 12.9, 22.7 (2C), 39.9, 41.2, 46.8, 52.2, 59.5, 70.4, 74.0, 113.4, 114.5, 117.6, 129.8, 149.7, 158.5; IR ($CHCl_3$) 3610, 2978, 2941, 2805, 1606, 1582, 1483, 1468, 1116, 952 cm$^{-1}$. Anal. Calcd for $C_{16}H_{25}NO_2$: C, 72.96; H, 9.57; N, 5.32. Found: C, 72.82; 9.46, N, 5.11.

**Carbonic Acid, Ethyl (3*S*,4*R*)-1,3-Dimethyl-4-[3-(1-methylethoxy)-phenyl]-4-piperidinyl Ester Compound with (+)-D-2,3-Bis[(4-methylbenzoyl)oxy]butanedioic Acid (1:1) (25·(+)-DTTA).** Ethyl chloroformate (205 mL, 2.14 mol) was added over 60 min to a solution of **23** (463 g, 1.76 mol) in ethyl acetate (2.28 L) while maintaining the temperature below 15 °C. When the addition was complete, the reaction mixture was allowed to warm to 25 °C and was stirred for an additional 3 h. The reaction was quenched by pouring into a mixture of 5 N NaOH (750 mL) and ethyl acetate (100 mL). The organic fraction was washed with water (240 mL). Removal of the solvent by rotary evaporation afforded 591 g (93% purity,[34] 93% yield) of a viscous oil.

**Resolution.** (+)-Di-*p*-toluoyl-D-tartaric acid monohydrate (343 g, 0.850 mol) was added to a solution of **25** (285 g, 93% purity, 0.790 mol) in 3A ethanol (2.85 L) at 55 °C. The solution was heated to reflux and slowly cooled to room temperature with stirring (overnight). The mixture was cooled to 0 °C for 2 h and filtered, and the cake washed with cold ethanol (170 mL). The product (323.4 g, 81:19 ratio of diastereomers) was obtained as a white powder after drying (6 h at 50 °C). Recrystallization of the crude salt from 3A ethanol (10 mL/g of salt) afforded 232.8 g of **25·(+)-DTTA** (41% yield, 90% de,[35] 38% yield from **23**) as white powder: mp 153.5−155 °C; $[\alpha]^{25}_D$ +64.2° (*c* 1.01, MeOH). Spectral data for **25·(+)-DTTA**: $^1$H NMR ($CDCl_3$) $\delta$ 0.62 (d, $J$ = 6.8 Hz, 3H), 1.25−1.30 (m, 9H), 2.24−2.32 (m, 1H), 2.33 (s, 6H), 2.71 (s, 3H), 2.65−2.85 (m, 3H), 2.97 (d, $J$ = 15.2 Hz, 1H), 3.28 (d, $J$ = 9.8 Hz, 1H), 3.55 (d, $J$ = 11.0 Hz, 1H), 4.05−4.20 (m, 2H), 4.52 (septet, $J$ = 6.1 Hz, 1H), 5.82 (s, 2H), 6.69 (d, $J$ = 7.9 Hz, 1H), 6.73 (br s, 1H), 6.77 (dd, $J$ = 8.3, 2.0 Hz, 1H), 7.12 (d, $J$ = 8.2 Hz, 4H), 7.14−7.17 (m, 1H), 7.95 (d, $J$ = 8.1 Hz, 4H); $^{13}$C NMR ($CDCl_3$) $\delta$ 11.8, 14.2, 21.6 (2C), 21.98, 22.02, 30.1, 40.0, 43.5, 50.0, 55.9, 64.1, 70.0, 73.1 (2C), 82.3, 113.0, 115.1, 117.2, 127.0 (2C), 129.0 (4C), 129.6, 130.1 (4C), 140.7, 143.6 (2C), 152.8, 157.7, 165.8 (2C), 170.6 (2C); IR ($CHCl_3$) 2982, 1748, 1724, 1612, 1266, 1248, 1179, 1109 cm$^{-1}$. Anal. Calcd for $C_{39}H_{47}NO_{12}$: C, 64.90; H, 6.56; N, 1.94. Found: C, 65.20; H, 6.65; N, 1.91.

**Analysis of 25.** Optical purity: 90% ee by $^1$H NMR using chiral shift reagent;[35] $[\alpha]^{25}_D$ −10.2° (*c* 1.02, MeOH). Spectral data: $^1$H NMR ($CDCl_3$) $\delta$ 0.73 (d, $J$ = 6.8 Hz, 3H), 1.30−1.33 (m, 9H), 1.86−2.00 (m, 1H), 2.19 (td, $J$ = 12.1, 2.0 Hz, 1H), 2.25 (t, $J$ = 11.4 Hz, 1H), 2.33 (s, 3H), 2.33−2.40 (m, 1H), 2.65 (dd, $J$ = 11.5, 3.4 Hz, 1H), 2.79 (br d, $J$ = 11.6 Hz, 1H), 2.98 (dt, $J$ = 14.4, 2.5 Hz, 1H), 4.11−4.21 (m, 2H), 4.50 (septet, $J$ = 6.1 Hz, 1H), 6.75−6.79 (m, 3H), 7.21 (t, $J$ = 7.9 Hz, 1H); $^{13}$C NMR ($CDCl_3$) $\delta$ 12.6, 14.4, 22.0, 22.1, 32.8, 42.6, 45.9, 51.1, 58.9, 63.5, 69.9, 84.3, 113.2, 114.3, 117.3, 129.0, 143.4, 153.2, 157.7; IR ($CHCl_3$) 2980, 2942, 2805, 1743, 1604, 1584, 1278, 1260, 1235 cm$^{-1}$. Anal. Calcd for $C_{19}H_{29}NO_4$: C, 68.03; H, 8.71; N, 4.18. Found: C, 67.74; H, 8.66; N, 4.13.

**(*R*)-1,2,3,6-Tetrahydro-1,3-dimethyl-4-[3-(1-methylethoxy)phenyl]pyridine (26).** A 1-L three-neck round-bottom flask containing a magnetic stir bar and equipped with a thermometer, a 12-in. Vigreux column fitted with a short-path distillation condenser, and a glass stopper was charged with **25** (50.0 g, 0.149 mol) and Decalin (250 mL). After the system was evacuated and purged with nitrogen three times, the solution was heated at reflux (190−195 °C) for 24 h. The ethanol produced was removed by distillation. The yellow-orange solution was cooled to room temperature under nitrogen, and 1 N HCl (155 mL) was added with stirring. The aqueous layer was extracted with heptane (2 × 30 mL) to remove residual Decalin. NaOH (10 mL, 50% aq) was added (pH = 13), and the free base was extracted into heptane (130 mL). The organic fraction was dried over $Na_2SO_4$. Filtration, followed by removal of the solvent by rotary evaporation, afforded 36.5 g of **26** as a yellow-orange liquid (92% purity,[34] 92% yield). This material was used without further purification. An analytical sample was obtained by Kugelrohr distillation (160 °C/0.2 Torr). Optical purity: ca. 90% ee based on **25**; $[\alpha]^{25}_D$ −67.2° (*c* 1.01, MeOH). Spectral data: $^1$H NMR ($CDCl_3$) $\delta$ 1.00 (d, $J$ = 7.0 Hz, 3H), 1.33 (d, $J$ = 5.8 Hz, 6H), 2.37 (s, 3H), 2.40 (d, $J$ = 5.2 Hz, 1H), 2.68 (dd, $J$ = 11.2, 4.9 Hz, 1H), 2.85−2.94 (m, 1H), 2.97 (dt, $J$ = 16.7, 2.8 Hz, 1H), 3.09 (dt, $J$ = 16.7, 2.8 Hz, 1H), 4.53 (septet, $J$ = 6.1 Hz, 1H), 5.83 (t, $J$ = 3.1 Hz, 1H), 6.76 (dd, $J$ = 8.1, 2.3 Hz, 1H), 6.83 (t, $J$ = 1.9 Hz, 1H), 6.87 (d, $J$ = 7.8 Hz, 1H), 7.19 (t, $J$ = 7.9 Hz, 1H); $^{13}$C NMR ($CDCl_3$) $\delta$ 18.8, 22.11, 22.16, 32.2, 46.0, 55.5, 60.3, 69.8, 114.06, 114.13, 118.6, 122.6, 129.2, 141.1, 142.6, 157.9; IR ($CHCl_3$) 2979, 2940, 2789, 1603, 1576, 1194, 1117 cm$^{-1}$. Anal. Calcd for $C_{16}H_{23}NO$: C, 78.32; H, 9.45; N, 5.71. Found: C, 78.05; H, 9.42; N, 5.81.

**(3*R*,4*S*)-1,2,3,4-Tetrahydro-1,3,4-trimethyl-4-[3-(1-methylethoxy)phenyl]pyridine (27).** *n*-BuLi (70.0 mL, 1.6 M in hexane, 112 mmol) was added with stirring over 30 min to a solution of **26** (19.6 g, 92% purity, 73.5 mmol) in THF (175 mL) while maintaining the temperature at −10 to −20 °C. When the addition was complete, the deep red reaction mixture was stirred for an additional 30 min at −15 °C. The solution was then cooled to −50 °C, and dimethyl sulfate (7.7 mL, 81 mmol) was added dropwise over 30 min at −50 °C. The reaction is very exothermic! When the addition was complete, the yellow-brown mixture was stirred for an additional 30 min at −50 °C and then slowly transferred via cannula into a dilute solution of aqueous $NH_4OH$ (15.5 mL of aqueous $NH_4OH$/55 mL of water) and heptane (70 mL) at 0 °C. The mixture was warmed to 25 °C and stirred an additional 2 h. The phases were separated, and the organic layer was washed with water (40 mL). Removal of the solvent by rotary evaporation afforded 21.4 g of **27** (86% purity,[34] 96% yield) as an orange liquid, which was used immediately in the next step without purification. An analytical sample was obtained by Kugelrohr distillation (165 °C/0.25 Torr). Optical purity: $[\alpha]^{25}_D$ −57.8° (*c* 1.01, MeOH, ca. 90% ee based on **25**). Spectral data: $^1$H NMR ($CDCl_3$) $\delta$ 0.59 (d, $J$ = 7.0 Hz, 3H), 1.33 (d, $J$ = 6.1 Hz, 6H), 1.43 (s, 3H), 1.87−1.95 (m, 1H), 2.47 (t, $J$ = 10.9 Hz, 1H), 2.67 (s, 3H), 2.66−2.69 (m, 1H), 4.34 (d, $J$ = 7.9 Hz, 1H), 4.52 (septet, $J$ = 6.1 Hz, 1H), 5.97 (d, $J$ = 7.8 Hz, 1H), 6.71 (dd, $J$ = 7.9, 2.4 Hz, 1H), 6.95−6.96 (m, 2H), 7.17 (t, $J$ = 8.2 Hz, 1H); $^{13}$C NMR ($CDCl_3$) $\delta$ 15.0, 22.14, 22.16, 28.0, 38.8, 40.1, 42.5, 52.8, 69.7, 106.2, 112.7, 117.3, 121.2, 127.8,

(34) HPLC conditions for analysis of **25**, **26**, **27**, **28**: Zorbax RX-C8 (25 cm), 75% 0.1% trifluroracetic acid/25% acetonitrile, 2 mL/min, 273 nm.

(35) Analysis of the free base by $^1$H NMR using *S*-(+)-2,2,2-trifluoro-1-(9-anthryl)-ethanol as a chiral shift reagent showed the product to be a 95:5 ratio of enantiomers (by integration of the methyl doublets at 0.40 and 0.53 ppm).

135.2, 148.0, 157.0; IR ($CHCl_3$) 3009, 2977, 1643, 1604, 1577, 1483, 1119, 975 $cm^{-1}$. Anal. Calcd for $C_{17}H_{25}NO$: C, 78.72; H, 9.71; N, 5.40. Found: C, 78.71; H, 9.77; N, 5.52.

**(3*R*,4*R*)-1,3,4-Trimethyl-4-[3-(1-methylethoxy)phenyl]-piperidine Compound with (+)-D-2,3-Bis[(4-methylbenzoyl)oxy]butanedioic Acid (1:1) (28).** To a solution of **27** (21.2 g, 86% purity, 70.3 mmol) in methanol (195 mL) at 0 °C was added sodium borohydride (4.20 g, 111 mmol) while keeping the temperature below 15 °C. When the addition was complete, the reaction mixture was stirred for 3 h at 25 °C. The reaction was quenched by the addition of acetone (21 mL) and a saturated solution of $NaHCO_3$ (25 mL). The solvent was removed by rotary evaporation, and the residue was dissolved in EtOAc (95 mL) and water (95 mL). The phases were separated, the aqueous phase was extracted with EtOAc (20 mL), and the combined organic fractions were washed with water (95 mL). Removal of the solvent by rotary evaporation afforded 20.5 g (82% purity,[34] 92% yield) of a yellow liquid. The crude product was purified by crystallization of the (+)-di-*p*-toluoyl-D-tartaric acid salt from 3A ethanol (ca. 5 mL/g of salt). The salt was further purified by heating a heterogeneous mixture of the crude solid at reflux in 3A ethanol (5 mL/g of salt) for 2 h, cooling to 0 °C, and filtering. This "hot reslurry" procedure gave equivalent purity (greater than 99%)[34] and superior yields (33.4 g, 80% yield) to those of a typical recrystallization process: mp 150.0−151.5 °C; $[\alpha]^{25}_D$ +113.6° (*c* 1.02, MeOH). Spectral data: $^1$H NMR (DMSO-$d_6$) $\delta$ 0.65 (d, $J$ = 7.1 Hz, 3H), 1.26 (d, $J$ = 5.9 Hz, 6H), 1.31 (s, 3H), 1.72 (d, $J$ = 14.1 Hz, 1H), 2.15−2.28 (m, 2H), 2.37 (s, 6H), 2.65 (s, 3H), 2.95−3.14 (m, 2H), 3.15−3.25 (m, 2H), 4.60 (septet, $J$ = 6.1 Hz, 1H), 5.66 (s, 2H), 6.75 (br s, 1H), 6.76 (d, $J$ = 7.1 Hz, 1H), 6.78 (d, $J$ = 7.7 Hz, 1H), 7.21 (t, $J$ = 8.1 Hz, 1H), 7.30 (d, $J$ = 8.1 Hz, 4H), 7.83 (d, $J$ = 8.1 Hz, 4H); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 14.6, 21.2 (2C), 21.9 (2C), 26.8, 36.5, 37.0, one aliphatic carbon under residual DMSO signal, 43.0, 49.6, 55.0, 68.9, 72.5 (2C), 112.5, 113.5, 117.4, 128.0 (2C), 129.2−129.4 (10C), 143.7 (2C), 157.5, 165.0 (2C), 168.4 (2C); IR ($CHCl_3$) 2979, 1725, 1612, 1579, 1268, 1179, 1109 $cm^{-1}$. Anal. Calcd for $C_{37}H_{45}NO_9$: C, 68.61; H, 7.00; N, 2.16. Found: C, 68.76; H, 7.03; N, 2.30.

**Analysis for Free Base of 28.** Optical purity: 99.9% ee by chiral HPLC;[36] $[\alpha]^{25}_D$ +76.2° (*c* 1.01, MeOH). Spectral data: $^1$H NMR ($CDCl_3$) $\delta$ 0.80 (d, $J$ = 7.0 Hz, 3H), 1.30 (s, 3H), 1.32 (d, $J$ = 6.1 Hz, 3H), 1.33 (d, $J$ = 6.0 Hz, 3H), 1.55−1.62 (m, 1H), 1.95−2.02 (m, 1H), 2.27 (s, 3H), 2.29−2.33 (m, 2H), 2.48−2.54 (m, 2H), 2.76−2.80 (m, 1H), 4.53 (septet, $J$ = 6.1 Hz, 1H), 6.70 (dd, $J$ = 8.1, 2.3 Hz, 1H), 6.82 (t, $J$ = 2.0 Hz, 1H), 6.85 (d, $J$ = 7.8 Hz, 1H), 7.20 (t, $J$ = 8.0 Hz, 1H); $^{13}$C NMR ($CDCl_3$) $\delta$ 16.5, 22.09, 22.13, 27.6, 30.7, 38.0, 38.8, 46.8, 52.3, 58.6, 69.7, 112.0, 114.4, 118.1, 128.9, 151.9, 157.8; IR ($CHCl_3$) 3009, 2979, 2939, 2805, 1606, 1580, 1486, 1385, 1257, 1118, 986 $cm^{-1}$. Anal. Calcd for $C_{17}H_{27}NO$: C, 78.11; H, 10.41; N, 5.36. Found: C, 78.05; H, 10.41; N, 5.38.

**(3*R*,4*R*)-3,4-Dimethyl-4-[3-(1-methylethoxy)phenyl]-1-piperidinecarboxylic Acid Phenyl Ester (28b).** Compound **28** (61.9 g, 95.6 mmol) was neutralized with 2 N NaOH (114.7 mL, 229.4 mmol, 2.4 equiv) in toluene (265 mL). The free base was isolated, redissolved in dry toluene (160 mL), and heated to 85 °C. Phenyl chloroformate (17.2 g, 110 mmol) was added slowly, and the solution was heated at reflux for 2 h. After the solution was cooled to 45 °C, aqueous NaOH (5 mL of 50% aqueous NaOH in 40 mL of water) was added, and the mixture was allowed to cool to room temperature with stirring. The organic fraction was washed with 1:1 MeOH/1 N HCl (3 × 50 mL), 1:1 MeOH/1 N NaOH (50 mL), and water (50 mL). Removal of the solvent by rotary evaporation afforded 33.9 g of **28b** (97% yield) as an oil which solidified upon standing: mp 63 °C; $[\alpha]^{25}_D$ +61.0° (*c* 1.00, MeOH). Spectral data: $^1$H NMR ($CDCl_3$) $\delta$ 0.70−0.80 (m, 3H), 1.34 (d, $J$ = 6.0 Hz, 6H), 1.41 (s, 3H), 1.63 (d, $J$ = 13.1 Hz, 1H), 2.00−2.10 (m, 1H), 2.29−2.32 (m, 1H), 3.10−3.56 (m, 2H), 3.97−4.05 (m, 1H), 4.25−4.38 (m, 1H), 4.54 (septet, $J$ = 6.1 Hz, 1H), 6.73 (dd, $J$ = 8.1, 2.3 Hz, 1H), 6.81 (br s, 1H), 6.84 (d, $J$ = 7.9 Hz, 1H), 7.05−7.15 (m, 1H), 7.17 (t, $J$ = 7.5 Hz, 1H), 7.23 (t, $J$ = 8.0 Hz, 1H), 7.27 (d, $J$ = 8.4 Hz, 1H), 7.34 (br t, $J$ = 7.4 Hz, 1H), 7.41 (t, $J$ = 4.3 Hz, 1H); $^{13}$C NMR ($CDCl_3$, additional signals due to amide rotamers) $\delta$ 14.3, 22.0 (2C), 26.4, 29.1, 29.6, 38.3, 38.4, 38.7, 40.3, 40.7, 45.9, 46.5, 69.6, 112.1, 112.2, 113.9, 117.5, 120.8, 121.6, 125.0, 126.2, 129.1, 129.4, 150.9, 157.8; IR ($CHCl_3$) 3012, 2979, 1780, 1706, 1606, 1595, 1581, 1432, 1245, 983 $cm^{-1}$. Anal. Calcd for $C_{23}H_{29}NO_3$: C, 75.17; H, 7.95; N, 3.81. Found: C, 74.95; H, 7.72; N, 3.54.

**(3*R*,4*R*)-3-(3,4-Dimethyl-4-piperidinyl)phenol (7).** Compound **28b** (14.0 g, 38.0 mmol), 48% HBr (17.1 mL, 151 mmol), and glacial acetic acid (17.1 mL) were combined and heated at reflux for 18 h. When the reaction was complete, the solution was allowed to cool to room temperature, and 50 mL of water was added. The solution was extracted with methyl *tert*-butyl ether (3 × 30 mL) to remove the phenol byproduct. The aqueous phase was titrated with a solution of 15% NaOH to a pH of 8.5−8.8. Methanol (15 mL) was added to solubilize any gummy solids, and the pH was adjusted to 10.3−10.5 with 15% NaOH to precipitate the product. The mixture was stirred for 1.5 h at 25 °C, cooled to 0 °C, filtered, and washed with cold water (10 mL). Drying (70 °C/5 Torr) afforded 6.86 g of **7** (88% yield) as a tan crystalline solid: mp 179.4 °C; $[\alpha]^{25}_D$ +114.2° (*c* 1.01, MeOH); $[\alpha]^{25}_{365}$ +383° (*c* 1.01, MeOH). Spectral data: $^1$H NMR (DMSO-$d_6$) $\delta$ 0.67 (d, $J$ = 7.0 Hz, 3H), 1.29 (s, 3H), 1.40 (d, $J$ = 12.9 Hz, 1H), 1.79−1.89 (m, 1H), 2.00 (td, $J$ = 12.4, 5.0 Hz, 1H), 2.56 (d, $J$ = 11.9 Hz, 1H), 2.82 (td, $J$ = 12.3, 2.6 Hz, 1H), 2.89 (br d, $J$ = 11.5 Hz, 1H), 3.09 (dd, $J$ = 12.6, 3.1 Hz, 1H), 6.57 (dd, $J$ = 7.9, 1.9 Hz, 1H), 6.69 (br s, 1H), 6.72 (d, $J$ = 7.9 Hz, 1H), 7.11 (t, $J$ = 7.9 Hz, 1H); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 14.9, 27.2, 30.4, 37.7, 38.4, 42.0, 47.8, 112.1, 112.3, 115.8, 128.8, 152.3, 157.2; IR (KBr) 3291, 2939, 2665 (br), 2566 (br), 1583, 705 $cm^{-1}$. Anal. Calcd for $C_{13}H_{19}NO$: C, 76.06; H, 9.33; N, 6.82. Found: C, 76.27; H, 9.19; N, 6.88.

**(*S*)-1-Cyclohexyl-1,3-propanediol (31).** The (*S*)-phenylpropane-1,3-diol (**30**) (4.0 g, 26.3 mmol) was dissolved in 12 mL of 2-propanol. The 5% $Rh/Al_2O_3$ (1.0 g) was slurried in 8 mL of 2-propanol and added to the diol solution in a Parr bottle. The catalyst was then rinsed with 4 mL of 2-propanol. The mixture was shaken at 50 psi of hydrogen for 9 h at 25 °C. The catalyst was removed by filtration through Celite. Removal of the solvent by rotary evaporation afforded 3.93 g of **31** (97% pure by capillary GC,[24] 92% yield) as a colorless oil: $[\alpha]^{25}_D$ −23.4° (*c* 1.03, MeOH). Spectral data: $^1$H NMR ($CDCl_3$) $\delta$ 0.95−1.30 (m, 5H), 1.31−1.38 (m, 1H), 1.60−2.00 (m, 7H), 2.66 (br s, 1H), 2.88 (br s, 1H), 3.59 (br s, 1H), 3.75−3.90 (m, 2H); $^{13}$C NMR ($CDCl_3$) $\delta$ 26.2, 26.3, 26.5, 28.2, 28.9, 35.2, 44.0, 61.8, 76.2; IR ($CHCl_3$) 3622, 3600−3020, 3015, 2931, 2856, 1059, 1044 $cm^{-1}$. Anal. Calcd for $C_9H_{18}O_2$: C, 68.31; H, 11.47. Found: C, 68.24; H, 11.37.

**(*S*)-3-Cyclohexyl-3-hydroxypropyl (4-Bromobenzene)-sulfonate (32).** Diol **31** (7.70 g, 97% purity, 47.2 mmol), triethylamine (10.2 mL, 73.0 mmol), and 4-(dimethylamino)-pyridine (0.59 g, 4.9 mmol) were dissolved in $CH_2Cl_2$ (100 mL), and the solution was cooled to 0 °C. A solution of 4-bromobenzenesulfonyl chloride (13.1 g, 51.2 mmol) in $CH_2Cl_2$ (50 mL) was added over 30 min, and the mixture was stirred for 1 h at 0 °C. The reaction mixture was washed successively with 0.5 N HCl (120 mL), water (100 mL), and a saturated solution of $NaHCO_3$ (100 mL) and was dried over anhydrous $MgSO_4$. Removal of the solvent by rotary evaporation at 60 °C followed by recrystallization of crude product from toluene (20 mL) and cyclohexane (160 mL) afforded 15.9 g of **32** (96% purity,[37] 86% yield) as a white crystalline solid: mp 57.0−58.5 °C. Optical purity: 94.2% ee;[24] $[\alpha]^{25}_D$ −18.8° (*c* 1.0, MeOH). Spectral data: $^1$H NMR ($CDCl_3$) $\delta$ 0.90−1.05 (m, 2H), 1.05−1.30 (m, 4H), 1.54 (s, 1H), 1.59−1.71 (m, 3H), 1.72−1.79 (m, 3H), 1.86−1.92 (m, 1H), 3.44−3.48 (m, 1H), 4.18−4.22 (m, 1H), 4.27−4.32 (m, 1H), 7.70 (d, $J$ = 8.6 Hz, 2H), 7.77 (d, $J$ = 8.6 Hz, 2H); $^{13}$C NMR ($CDCl_3$) $\delta$ 26.0, 26.2, 26.4, 27.8, 28.9, 33.3, 43.8,

(36) HPLC conditions: column, Chiralcel OD (25 cm, Daicel Ind.); mobile phase, 1% *i*-PrOH and 0.2% $Et_2NH$ in hexane (1.0 mL/min); detector, 273 nm. $t_R$ = 5.5 min (free base of **28**), 6.5 min (*ent*-**28**).

(37) HPLC conditions for analysis of **28**, **28b**, **7**, **32**, **1**: Zorbax RX (25 cm); 40 °C; gradient with acetonitrile and 0.1 M $NaH_2PO_4$ (pH = 3), 15% acetonitrile for 2 min then program to 70% acetonitrile in 18 min and hold for 10 min; 1.5 mL/min, 262 nm. $t_R$ = 4.5 min (**7**), 13.6 min (free base of **28**), 14.3 min (**1**), 22.3 min (**32**), 25.7 min (**28b**).

69.0, 71.9, 129.0, 129.4 (2C), 132.6 (2C), 135.3; IR ($CHCl_3$) 3650, 3050, 3010, 2931, 2856, 1579, 1365, 1187, 1178, 923, 825 $cm^{-1}$. Anal. Calcd for $C_{15}H_{21}BrO_4S$: C, 47.75; H, 5.61; Br, 21.18; S, 8.50. Found: C, 48.04; H, 5.65; Br, 20.94; S, 8.60.

**(α*S*,3*R*,4*R*)-α-Cyclohexyl-4-(3-hydroxyphenyl)-3,4-dimethyl-piperidinepropanol (1).**[38] A mixture of **7** (36.0 g, 0.175 mol), **32** (69.3 g, 0.183 mol), $NaHCO_3$ (20.2 g, 0.240 mol), and 1,2-dimethoxyethane (DME, 400 mL) was heated at reflux (85 °C) for 8 h. After the reaction was complete, the reaction mixture was cooled to 25 °C and diluted with THF (512 mL), and Celite (27.0 g) was added. After being stirred for 30 min, the mixture was cooled to 0 °C and stirred for 1 h. The mixture was filtered to remove the sodium brosylate/celite, and the cake was washed with THF (2 × 164 mL). The filtrate and washes were combined and concentrated to 140 g by rotary evaporation at 85 °C. The concentrate was then diluted with EtOAc (600 mL) and concentrated to 250 g. The resulting solution was filtered, and the filter was washed with hot EtOAc (2 × 75 mL). The filtrate was reconcentrated to 250 g. The slurry was cooled to 0 °C and stirred for 2 h. The solid was then collected and washed with cold EtOAc (2 × 120 mL). After the solid was dried at 40 °C in vacuo, 50.5 g of **1** (98% purity,[37] 82% yield) was obtained: mp 156.0−159.6 °C; $[\alpha]^{25}_D$ +73.1° (*c* 1.0, MeOH). Spectral data: $^1$H NMR ($CDCl_3$) $\delta$ 0.54 (d, $J$ = 7.1 Hz, 3H), 0.95−1.26 (m, 5H), 1.28 (s, 3H), 1.33−1.40 (m, 1H), 1.50−1.55 (m, 2H), 1.61−1.73 (m, 5H), 1.91−1.96 (m, 2H), 2.27 (td, $J$ = 12.9, 4.3 Hz, 1H), 2.37 (dd, $J$ = 11.5, 2.9 Hz, 1H), 2.45 (td, $J$ = 12.0, 1.9 Hz, 1H), 2.59 (dt, $J$ = 12.8, 3.5 Hz, 1H), 2.67 (td, $J$ = 12.2, 2.7 Hz, 1H), 2.83 (d, $J$ = 11.4 Hz, 1H), 2.88 (d, $J$ = 11.4 Hz, 1H), 3.58 (br t, $J$ = 8.2 Hz, 1H), 6.60 (dd, $J$ = 8.0, 2.1 Hz, 1H), 6.67 (br s, 1H), 6.70 (d, $J$ = 8.0 Hz, 1H), 7.08 (t, $J$ = 7.9 Hz, 1H), 7.30−7.50 (br s, 2H, $D_2O$ exchange); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 16.0, 25.8, 26.0, 26.3, 27.2, 27.7, 28.7, 30.0, 30.2, 37.95, 38.03, 43.5, 50.2, 55.2, 56.4, 74.3, 112.2, 112.5, 116.0, 128.8, 151.6, 157.1; IR (KBr) 3112, 2925, 1604, 1443, 1236, 705 $cm^{-1}$; UV (EtOH) $\lambda_{max}$ 201, $\epsilon$ 18 851; 274, $\epsilon$ 2068. Anal. Calcd for $C_{22}H_{35}NO_2$: C, 76.47; H, 10.21; N, 4.05. Found: C, 76.45; H, 10.21; N, 4.08.

**Methyl (3*R*,4*R*)-4-(3-Hydroxyphenyl)-3,4-dimethyl-1-piperidinepropanoate (33).** Methyl acrylate (46.4 mL, 0.515 mol) was added over 3 min to a suspension of **7** (70.5 g, 0.343 mol) in THF (1 L) at 45 °C. After 4 h the reaction mixture was cooled to room temperature and filtered through Celite to give a clear amber solution. The solvent and excess methyl acrylate were removed by concentration of the solution via rotary evaporation at 40 °C to a net weight of 120 g. The crude product was redissolved in THF (180 g) to give a 33.3% solution (by weight)[39] of **33** for use in the benzylation step (96% yield by HPLC);[40] $[\alpha]^{25}_D$ +75.3° (*c* 1.01, MeOH). Spectral data: $^1$H NMR ($CDCl_3$) $\delta$ 0.73 (d, $J$ = 7.0 Hz, 3H), 1.29 (s, 3H), 1.57 (br d, $J$ = 12.1 Hz, 1H), 1.92−2.00 (m, 1H), 2.29 (td, $J$ = 12.4, 4.3 Hz, 1H), 2.40 (td, $J$ = 11.6, 2.7 Hz, 1H), 2.52 (t, $J$ = 7.3 Hz, 2H), 2.56−2.60 (m, 2H), 2.64−2.76 (m, 2H), 2.81−2.85 (m, 1H), 3.66 (s, 3H), 5.50−6.20 (br s, 1H, $D_2O$ exch), 6.62 (dd, $J$ = 8.1, 2.3 Hz, 1H), 6.74 (br s, 1H), 6.82 (d, $J$ = 8.1 Hz, 1H), 7.15 (t, $J$ = 7.9 Hz, 1H); $^{13}$C NMR ($CDCl_3$) $\delta$ 16.1, 27.5, 30.8, 32.0, 38.4, 38.9, 49.9, 51.7, 53.9, 55.8, 112.6, 113.2, 117.7, 129.2, 151.6, 156.1, 173.4; IR ($CHCl_3$) 3600, 3600−3100, 1732, 1440 $cm^{-1}$. Anal. Calcd for $C_{17}H_{25}NO_3$: C, 70.07; H, 8.65; N, 4.81. Found: C, 67.80; H, 8.26; N, 4.73 (viscous oil which contains 2.5 wt % THF).

**Methyl (α*S*,3*R*,4*R*)-4-(3-Hydroxyphenyl)-3,4-dimethyl-α-(phenylmethyl)-1-piperidinepropanoate Hydrochloride (34).** A dry 250-mL three-neck round-bottom flask equipped with a mechanical stirrer, a thermometer, and a rubber septum was purged with nitrogen and charged with THF (100 mL) and a 2.0 M solution of LDA (17.6 mL, 35.2 mmol). The yellow solution was cooled to −30 °C, and the solution of **33** (15.2 g, 32.8% by weight in THF, 17.2 mmol) was added over 20 min at −28 °C. The dianion precipitated during the addition. After 15 min benzyl bromide (5.81 g, 34.3 mmol) was added over 5 min while maintaining the temperature between −15 and −20 °C. Most of the solid dissolved during the addition. The reaction mixture was stirred for 3 h at this temperature.

The reaction mixture was quenched by adding 1 N HCl (22 mL, 22 mmol) and adjusting the pH to 10.6−9.5 with 12 N HCl (ca. 2.3 mL) while keeping the temperature below −10 °C. Heptane (50 mL) was added, and the layers were separated. Methanol (25 mL) was added to the organic layer, and the solution was cooled to −5 °C. The hydrochloride salt was formed by sparging anhydrous HCl (ca. 1.3 g) into the solution while maintaining the temperature below 5 °C until the mixture was acidic (pH = 1, moist litmus paper). The mixture was concentrated via rotary evaporation to a net weight of 32.6 g (20% of initial weight) prior to the addition of methanol (36 mL), which resulted in the precipitation of a white solid after a few minutes. The mixture was stirred overnight at room temperature. After cooling to 0 °C for 1.25 h the precipitate was filtered, the cake was washed with cold methanol (10 mL), and the product was dried (50 °C/5 Torr) to give 2.93 g (35% yield, 72% de[41]) of a white powder. The crude product (2.75 g, 72% de, 5.66 mmol) was added to methanol (14 mL), and the slurry was heated at reflux for 2 h. The mixture was cooled to room temperature with stirring and then cooled to 0 °C for 1 h. The precipitate was filtered, washed with cold methanol (1.5 mL), and dried (50 °C/5 Torr) to afford 2.32 g of **34** (95% yield, 94% de[41]) as a white solid. Overall yield was 34% from **33**. Recycling the undesired diastereomer (free base, dianion formation with LDA (3 equiv), protonation, and HCl salt formation) increased the overall yield from 34% to 55%.

Analytical data for both the salt and the free base are recorded. The solubility of the HCl salt is very low in most solvents. In DMSO **34** exists as an 85:15 mixture of diastereomeric salts due to the axial and equatorial protonation of the piperidine nitrogen, giving rise to a complicated $^1$H NMR spectrum.

**Analytical Data (34).** Mp 230.0−232.0 °C dec. Spectral data: $^1$H NMR (DMSO-$d_6$) $\delta$ (0.78 (d, $J$ = 7.2 Hz, 0.85 × 3H) and 1.02 (d, $J$ = 7.2 Hz, 0.15 × 3H), diastereomeric salts), (1.28 (s, 0.15 × 3H), 1.34 (s, 0.85 × 3H), diastereomeric salts), 1.76 (br d, 1H), 2.10−2.48 (m, 2H), 2.75−3.65 (m, 12H), 6.60−6.90 (m, 3H), 7.11 (t, $J$ = 7.8 Hz, 1H), 7.15−7.35 (m, 5H), 9.43 (br s, 1H), 9.75 (br s, 1H); IR (KBr) 3174, 1732, 1620, 1586, 1276, 785, 749, 706 $cm^{-1}$. Anal. Calcd for $C_{24}H_{32}ClNO_3$: C, 68.97; H, 7.72; N, 3.35; Cl, 8.48. Found: C, 69.27; H, 7.84; N, 3.42; Cl, 8.38.

**Analytical Data for Free Base of 34.** Mp 81.0−84.0 °C; $[\alpha]^{25}_D$ +67.1° (*c* 1.02, MeOH). Spectral data: $^1$H NMR ($CDCl_3$) $\delta$ 0.73 (d, $J$ = 7.0 Hz, 3H), 1.27 (s, 3H), 1.51 (br d, $J$ = 12.8 Hz, 1H), 1.89−1.96 (m, 1H), 2.25 (td, $J$ = 12.5, 4.5 Hz, 1H), 2.36−2.42 (m, 2H), 2.49 (dd, $J$ = 11.2, 2.9 Hz, 1H), 2.62 (br d, $J$ = 10.9 Hz, 1H), 2.70 (dd, $J$ = 12.1, 9.2 Hz, 1H), 2.75 (d, $J$ = 11.3 Hz, 1H), 2.80 (dd, $J$ = 13.2, 5.4 Hz, 1H), 2.88−2.98 (m, 2H), 3.55 (s, 3H), 5.04 (br s, 1H), 6.62 (dd, $J$ = 8.0, 2.3 Hz, 1H), 6.74 (br s, 1H), 6.81 (d, $J$ = 8.1 Hz, 1H), 7.13−7.20 (m, 4H), 7.24−7.27 (m, 2H); $^{13}$C NMR ($CDCl_3$) $\delta$ 16.0, 27.4, 30.6, 36.7, 38.5, 38.9, 46.1, 50.9, 51.5, 55.3, 60.4, 112.4, 112.9, 117.9, 126.4, 128.5 (2C), 128.8 (2C), 129.2, 139.2, 152.5, 155.8, 176.0; IR ($CHCl_3$) 3597, 3382 (br), 2953, 2812, 1729, 919 $cm^{-1}$. Anal. Calcd for $C_{24}H_{31}NO_3$: C, 75.56; H, 8.19; N, 3.67. Found: C, 75.63; H, 8.29; N, 3.66.

(38) The coupling procedure with a nonaqueous workup allows for the potential recovery and recycling of sodium brosylate. John Quatroche, Eli Lilly and Company, unpublished results, 1987.

(39) The concentration was determined by the amount of THF added to the crude product (assuming 100% yield). The concentration can be determined by HPLC using the amino acid of **33** as the external standard (preferred method) or by integration of the signals from THF and **33** in the $^1$H NMR spectrum.

(40) HPLC conditions for **33**−**35**: column, Zorbax SB-Phenyl (4.6 mm × 250 mm); mobile phase; solvent A ($CH_3CN$), solvent B (0.1% TFA), gradient, 30% A:70% B (5 min), increase over 10 min to 70% A:30% B; detector, 273 nm. $t_R$ = 5.5 min (**33**), 14.6 min (**35**), and 16.7 min (**34**).

(41) HPLC conditions for analysis of the diastereomers: column, Chiralcel OD (4.6 mm x 250 mm, Regis); Mobile phase, 8% *n*-PrOH and 0.5% $Et_2NH$ in hexane (1.0 mL/min); column temperature, 40 °C; detector, 273 nm. $t_R$ = 11.5 min ((3*R*,4*R*,α*S*)-isomer) and 13.3 min ((3*R*,4*R*,α*R*)-isomer)).

**(α*S*,3*R*,4*R*)-4-(3-Hydroxyphenyl)-3,4-dimethyl-α-(phenylmethyl)-1-piperidinepropanoic Acid Monohydrate (35).** Compound **34** (25.0 g, 94% de, 58.0 mmol) was added to a solution of 50% aqueous NaOH (20.0 g, 250 mmol) in water (230 mL), and the mixture was stirred at room temperature for 4 h. The mixture was then filtered through No. 1 Whatman paper. Methanol (240 mL) was charged to the filtrate,[30] and the pH was adjusted to 6.0 with concentrated hydrochloric acid (32.1 g). *After the product had precipitated*, most of the methanol was removed by rotary evaporation (50 °C, 100 Torr). The slurry was stirred for 4 h, the pH was readjusted to 6.0, and the slurry was stirred at 0 °C for 1.5 h. The desired product was filtered and washed with water (3 × 50 mL). After drying in an air dryer at 25 °C overnight, the desired monohydrate product **35** was isolated as a white granular solid (21.3 g, 94% yield on an anhydrous basis, 96% de, 4.07% $H_2O$ by Karl Fischer analysis (calcd for monohydrate: 4.70%)): mp 178.0−180.0 °C dec; $[\alpha]^{25}_D$ +95.7° (*c* 1.01, MeOH). Spectral data: $^1$H NMR (DMSO-$d_6$) $\delta$ 0.65 (d, $J$ = 7.0 Hz, 3H), 1.21 (s, 3H), 1.51 (d, $J$ = 13.2 Hz, 1H), 1.90−2.00 (m, 1H), 2.12 (td, $J$ = 12.8, 4.3 Hz, 1H), 2.37 (dd, $J$ = 10.9, 5.6 Hz, 1H), 2.43−2.53 (m, 2H), 2.60 (t, $J$ = 11.2 Hz, 1H), 2.65−2.75 (m, 2H), 2.75−2.85 (m, 2H), 2.91 (dd, $J$ = 13.4, 7.3 Hz, 1H), 6.54 (dd, $J$ = 7.9, 2.0 Hz, 1H), 6.65 (br s, 1H), 6.68 (d, $J$ = 7.9 Hz, 1H), 7.07 (t, $J$ = 7.9 Hz, 1H), 7.16−7.21 (m, 3H), 7.24−7.27 (m, 2H), 9.14 (br s, 1H); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 15.5, 26.9, 29.6, 35.2, 37.5, 37.7, 42.7, 49.7, 53.7, 58.8, 112.2, 112.3, 115.9, 126.0, 128.2 (2C), 128.7 (2C), 128.9, 139.4, 151.2, 157.1, 175.1; IR (KBr) 3600, 3360, 3272, 2967, 1622, 1585, 1363, 844 cm$^{-1}$. Anal. Calcd for $C_{23}H_{31}NO_4$: C, 71.66; H, 8.10; N, 3.63. Found: C, 72.29; H, 8.10; N, 3.71. Analysis is off due to incomplete hydration (vide supra).

**2-Methylpropyl Glycine, *p*-Toluenesulfonic Acid Salt (36).** A mixture of toluene (600 mL), glycine (22.5 g, 300 mmol), *p*-toluenesulfonic acid monohydrate (62.8 g, 330 mmol), and isobutyl alcohol (60 mL, 650 mmol) was heated at reflux, and the water was removed as it was formed via a Dean-Stark trap. After 2 h the reaction mixture was homogeneous (109 °C), and no additional water was being formed. After an additional 1.5 h, the reaction mixture was cooled to 50 °C and concentrated via rotary evaporation at 60 °C to a net weight of 135 g. The residue was added to hot EtOAc (450 mL) and hexane (450 mL), and the solution was heated to reflux and then allowed to cool slowly (seeded at 38 °C to initiate crystallization). After cooling at 5 °C for 1 h, the product was filtered and dried overnight (40 °C, 5 Torr). A total of 89.1 g of **36** (98% yield) was obtained as a white crystalline solid: mp 77.2−79.6 °C; p$K_a$ (67% aqueous DMF) = 7.68. Spectral data: $^1$H NMR ($CDCl_3$) $\delta$ 0.82 (d, $J$ = 6.9 Hz, 6H), 1.79 (septet, $J$ = 6.8 Hz, 1H), 2.33 (s, 3H), 3.66 (br s, 2H), 3.78 (d, $J$ = 6.6 Hz, 2H), 7.10 (d, $J$ = 8.1 Hz, 2H), 7.72 (d, $J$ = 8.2 Hz, 2H), 8.03 (br s, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 18.9 (2C), 21.3, 27.4, 40.3, 72.0, 126.1 (2C), 128.9 (2C), 140.3, 141.4, 167.5; IR ($CHCl_3$) 3300−2600, 3018, 2970, 1752, 1125, 1034, 1011 cm$^{-1}$. Anal. Calcd for $C_{13}H_{21}NO_5S$: C, 51.47; H, 6.98; N, 4.62; S, 10.57. Found: C, 51.74; H, 6.77; N, 4.76; S, 10.73.

**[[2(*S*)-[[4(*R*)-(3-Hydroxyphenyl)-3(*R*),4-dimethyl-1-piperdinyl]methyl]-1-oxo-3-phenylpropyl]amino]acetic Acid 2-Methylpropyl Ester (37).** Amino acid **35** (20.1 g, 96% de, 4.1% $H_2O$, 51.4 mmol), amino ester **36** (17.6 g, 58.0 mmol), and 1-hydroxybenzotriazole monohydrate (7.83 g, 58.0 mmol) were added to THF (144 mL). To this solution was added $Et_3N$ (8.08 mL, 58.0 mmol), followed by dicyclohexylcarbodiimide (12.0 g, 58.0 mmol) dissolved in THF (60 mL). The mixture was stirred at 25 °C under nitrogen[42] for 2 days. The slurry was cooled at 0 °C for 2 h and then filtered to remove around 98% of the 1,3-dicyclohexylurea (DCU). The filtrate was then evaporated to near dryness (40 °C/10 Torr). The oil was taken up in EtOAc (250 mL), and the organic layer was washed with a pH 10 buffer solution (250 mL of a 0.5 M $Na_2CO_3$−$NaHCO_3$ solution), followed by brine (250 mL). The organic layer was dried over $Na_2SO_4$, cooled with stirring to −20 °C, and allowed to set unstirred at −20 °C overnight (16 h). The precipitated DCU and drying agent were removed by filtration. Removal of the solvent by rotary evaporation afforded to 25.0 g of **37** (91% purity, 96% de, 92% yield) as an amorphous, tacky solid which was used without purification: $[\alpha]^{25}_D$ +55.0° (*c* 1.01, MeOH). Spectral data: $^1$H NMR ($CDCl_3$) $\delta$ 0.71 (d, $J$ = 7.0 Hz, 3H), 0.91 (d, $J$ = 6.6 Hz, 6H), 1.25 (s, 3H), 1.57 (d, $J$ = 12.7 Hz, 1H), 1.91 (septet, $J$ = 6.6 Hz, 1H), 1.92−2.00 (m, 1H), 2.25−2.35 (m, 2H), 2.37 (dd, $J$ = 12.7, 4.0 Hz, 1H), 2.45 (t, $J$ = 11.6 Hz, 1H), 2.57−2.71 (m, 4H), 2.83 (d, $J$ = 10.9 Hz, 1H), 3.34 (dd, $J$ = 13.9, 4.5 Hz, 1H), 3.83 (dd, $J$ = 18.3, 3.3 Hz, 1H), 3.90 (d, $J$ = 6.7 Hz, 2H), 4.19 (dd, $J$ = 18.3, 5.9 Hz, 1H), 5.75 (br s, 1H), 6.65 (dd, $J$ = 8.0, 2.3 Hz, 1H), 6.75 (t, $J$ = 1.7 Hz, 1H), 6.79 (d, $J$ = 6.1 Hz, 1H), 7.14 (t, $J$ = 7.9 Hz, 1H), 7.18−7.21 (m, 3H), 7.26−7.29 (m, 2H), 9.0 (br s, 1H); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 15.8, 18.7 (2C), 27.1, 27.2, 29.9, 35.6, 37.8, 38.0, 40.6, 44.3, 49.9, 55.0, 59.7, 70.0, 112.1, 112.4, 115.9, 125.8, 128.1 (2C), 128.7 (2C), 128.8, 140.1, 151.7, 157.1, 169.8, 174.1; IR ($CHCl_3$) 3600, 3010, 2967, 2936, 1741, 1711, 1658 cm$^{-1}$. Anal. Calcd for $C_{29}H_{40}N_2O_4$: C, 72.47; H, 8.39; N, 5.83. Found: C, 72.21; H, 8.53; N, 6.12.

**[[2(*S*)-[[4(*R*)-(3-Hydroxyphenyl)-3(*R*),4-dimethyl-1-piperdinyl]methyl]-1-oxo-3-phenylpropyl]amino]acetic Acid Dihydrate (2).** One molar NaOH (77 mL, 77 mmol, 3.0 equiv) was added slowly to a solution of **37** (12.5 g, 91% purity, 96% de, 23.7 mmol) in 3A ethanol (315 mL) and water (74 mL) over 15 min at 25 °C (pH = 12−13). After 45 min the solution was neutralized (pH = 6.0) by addition of concentrated hydrochloric acid and seeded. The mixture was stirred at 25 °C for 2 h and filtered, and the cake was washed with water (30 mL). The crystals were dried overnight (25 °C, 33% relative humidity) by pulling air through the product in the filter funnel under slight suction to give 10.2 g of the dihydrate **2** (99% de,[43] 7.95% $H_2O$ by Karl Fischer analysis (theoretical: 7.4% $H_2O$), 93% yield on an anhydrous basis): mp 210−213 °C; $[\alpha]^{25}_D$ +51.8° (*c* 1.00, DMSO). Spectral data: $^1$H NMR (DMSO-$d_6$) $\delta$ 0.73 (d, $J$ = 6.9 Hz, 3H), 1.26 (s, 3H), 1.53 (d, $J$ = 12.9 Hz, 1H), 1.98 (br s, 1H), 2.22 (td, $J$ = 12.5, 4.0 Hz, 1H), 2.33 (dd, $J$ = 12.3, 5.5 Hz, 1H), 2.40 (t, $J$ = 10.7 Hz, 1H), 2.49 (d, $J$ = 11.0 Hz, 1H), 2.62 (dd, $J$ = 12.3, 8.9 Hz, 1H), 2.68−2.71 (m, 2H), 2.81 (d, $J$ = 11.3 Hz, 1H), 2.85−2.98 (m, 2H), 3.73 (dd, $J$ = 17.7, 5.3 Hz, 1H), 3.76 (dd, $J$ = 17.7, 5.6 Hz, 1H), 6.60 (dd, $J$ = 8.0, 2.0 Hz, 1H), 6.71 (br s, 1H), 6.75 (d, $J$ = 7.9 Hz, 1H), 7.13 (t, $J$ = 7.9 Hz, 1H), 7.22 (t, $J$ = 7.2 Hz, 1H), 7.23−7.32 (m, 4H), 8.38 (t, $J$ = 5.6 Hz, 1H), 9.18 (br s, 1H); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 15.7, 27.0, 29.8, 35.6, 37.9, 38.0, 41.2, 43.9, 50.1, 54.8, 59.8, 112.3, 112.5, 116.1, 126.0, 128.2 (2C), 128.9 (2C), 129.0, 140.0, 151.5, 157.2, 171.4, 173.7; IR (KBr) 3419, 3204, 3028, 1684, 1591 cm$^{-1}$. Anal. Calcd for the anhydrate of **2**, which was obtained by block drying at 120 °C prior to analysis, $C_{25}H_{32}N_2O_4$: C, 70.73; H, 7.60; N, 6.60. Found: C, 70.97; H, 7.64; N, 6.36.

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**Supporting Information Available:** A summary of the results of our pilot plant scale synthesis of **7** from *N*-ethyl-4-

(42) An orange impurity is formed if any oxygen is present.

(43) HPLC chiral assay conditions for analysis of diastereomer: column, ES-OVM; mobile phase, 10% acetonitrile in 0.02 M phosphate buffer (0.5 mL/min); column temperature, 30 °C; detector, 273 nm. $t_R$ = 8.3 min (**2**) and 11.3 min (α*R*,3*R*,4*R* isomer).

piperidinone along with a brief description of the modifications made to the literature procedures; experimental procedures for carbonates **13**, **19**, **22a**, and **22c**−**g** and the propionate ester of alcohol **23**; and the $^1$H NMR spectra for compounds **1**, **2**, **7**, **13**, **19**, **22a**, **22c**−**g**, **23**−**28b**, **30**−**37**, and the (3*R*,4*R*,α*R*)-isomers of **34**, **35**, **37**, and **2** (42 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information. The authors have deposited atomic coordinates for compounds **34** and **35** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.

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