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Reduction of an Enaminone: Synthesis of the Diamino Alcohol Core of Ritonavir

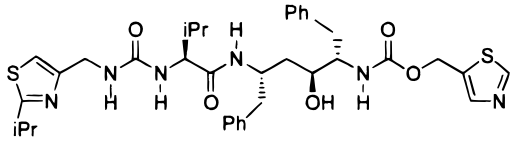
Anthony R. Haight,*,† Timothy L. Stuk,§ Michael S. Allen,† Lakshmi Bhagavatula,‡ Michael Fitzgerald,‡ Steven M. Hannick,‡ Francis A. J. Kerdesky,‡ Jerome A. Menzia,† Shyamal I. Parekh,† Timothy A. Robbins,† David Scarpetti,⊥ and Jien-Heh J. Tien†

Chemical Process Research, D54P, and Process Research, D45L, Abbott Laboratories, 1401 Sheridan Road, North Chicago, Illinois 60064

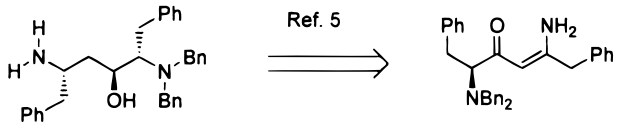
Abstract:

The reduction of (5*S*)-2-amino-5-dibenzylamino-4-oxo-1,6-diphenylhex-2-ene was optimized for diastereoselectivity and overall conversion to (2*S*,3*S*,5*S*)-5-amino-2-dibenzylamino-3-hydroxy-1,6-diphenylhexane (2a). A two-step reduction sequence is described wherein the enamine is reduced with a borane-sulfonate derivative followed by reduction of the resulting ketone with sodium borohydride. The desired 2a was obtained with 84% diastereoselectivity and an acyclic 1,4 stereoinduction ratio of 14:1. This methodology has been used to produce multikilogram quantities of the diamino alcohol core of Ritonavir and should be general to the synthesis of related diamino hydroxyethylene isosteres.

Reduction of enaminones is an important method for obtaining 1,3-amino alcohols.[1] This can be accomplished by using hydrogenation[1,2] or hydride reduction[1,3] methods. Typically the products are obtained with varying levels of cleavage products due to the forcing conditions required.[2] To develop a scalable synthesis of the HIV protease inhibitor, Ritonavir (Norvir, **1**),[4] a practical method of obtaining the diamino alcohol **2a** was required. Previously, we reported on the preparation of **2a** by a sequential reduction of the enaminone **3** using a borohydride complex with methanesulfonic acid (MSA) for reduction of the enamine, followed by treatment with trifluoroacetoxyborohydride to reduce the carbonyl.[5] In this paper, we report on the optimization of conditions to obtain improved diastereoselectivity for the reduction of the readily available enaminone **3**.[6]



1, Ritonavir



2a **3**

Results and Discussion

Reduction of **3** using metal hydrides in inert solvents was found to be ineffective. However, treatment of **3** with sodium cyanoborohydride using acetic acid as the solvent was shown to reduce **3** to yield a mixture of **2a**−**d** (Scheme 1) in a 1:(3) ratio [**2a**:(**2b** + **2c** + **2d**)] (Table 1, entry 1).[7] Manipulation of the acid or solvent in order to improve the selectivity offered little enhancement (entries 2−5). By preforming a trifluoroacetoxyborohydride complex with sodium borohydride and trifluoroacetic acid (TFA),[8] the selectivity could be improved to favor the desired isomer with 44% diastereoselectivity (entry 7). To obtain complete reduction, however, it was necessary to add excess TFA (entries 6 vs 7).

Mineral acids such as sulfuric acid yielded amino alcohols **2a**−**d** as a minor product, while the major products were the amino ketones **4a** and **4b** (Scheme 2).[9] Weaker acids such as acetic acid gave almost no amino alcohol, yielding instead the intermediate ketones **4a** and **4b**. The unreactive nature of the carbonyl when using sodium borohydride reducing agents is believed to be due to derivatization of the carbonyl as a boron enolate. This complex most likely is hydrolyzed by the addition of excess trifluoroacetic acid (entry 7, Table 1).

Addition of excess sodium borohydride to the *in-situ* prepared amino ketones had no effect on reducing the

* Corresponding author. E-mail: Anthony.Haight@ln.ssw.abbott.com. Fax: 847-937-3864.

† Chemical Process Research, D-54P.

‡ Process Research Department, D-45L.

§ Current address: Parke-Davis, 188 Howard Ave., Holland, MI 49424.

⊥ Current address: Guilford Pharmaceuticals, Inc., 6611 Tributary St., Baltimore, MD 21224.

(1) Greenhill, J. V. *Chem. Soc. Rev.* **1977**, *6*, 277.

(2) (a) Greenhill, J. V.; Ramli, M.; Tomassini, T. *J. Chem. Soc., Perkin Trans. 1* **1975**, 588. (b) Martin, J. C.; Barton, K. R.; Gott, P. G.; Meen, R. H. *J. Org. Chem.* **1966**, *31*, 943. (c) Occhiato, E. G.; Guarna, A.; Spinetti, L. M. *Tetrahedron* **1993**, *49*, 10629.

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(6) Haight, A. R.; Stuk, T. L.; Menzia, J. A.; Robbins, T. A. *Tetrahedron Lett.* **1997**, *38*, 4191.

(7) The product ratio was determined by comparison to independently synthesized isomers of **2**.

(8) Gribble, G. W.; Nutaitis, C. F. *Org. Prep. Proc. Int.* **1985**, *17*, 317.

(9) The amino ketones **4a**/**b** are prone to β-amino elimination and are, therefore, not routinely isolated.

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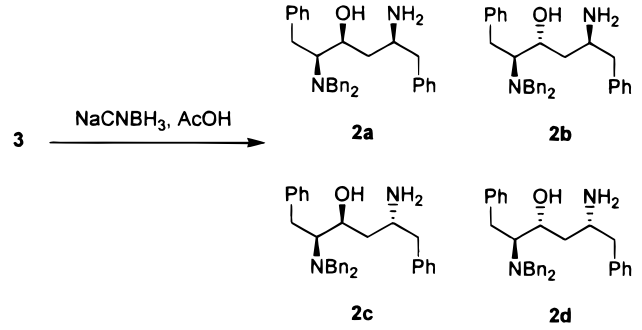
Scheme 1



Scheme 2

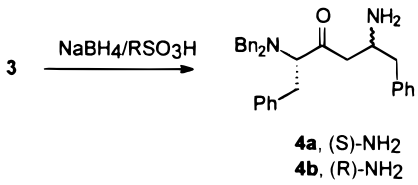


Table 1. **Reduction of 3 with borohydrides**

entry	hydride (equiv)	acid (equiv)	conditions[a]	conv (%)[b]	**2a**:(**2b** + **2c** + **2d**)[c]
1	$NaCNBH_3$ (3)	AcOH (2)	A	>90	1.0:(3)
2	$NaCNBH_3$ (4)	TFA (4)	A	>90	1.7:(1)
3	$NaCNBH_3$ (4)	TFA (4)	A[d]	>90	1.4:(1)
4	$NaCNBH_3$ (4)	TFA (4)	A[e]	>90	1.6:(1)
5	$NaCNBH_3$ (4)	TFA (4)	A[f]	>90	1.3:(1)
6	$NaBH_4$ (4)	TFA (8)	B	77	1.0:(1)
7	$NaBH_4$ (4)	TFA (14)	B	>98	2.6:(1)

[a] Unless otherwise indicated, all reactions were conducted under a nitrogen atmosphere using approximately 0.25−1.0 M THF solutions, between −10 and 10 °C. Method A: acid added to hydride/**3** in THF. Method B: **3** added to hydride complex. [b] Conversion calculated as HPLC peak area percent conversion. [c] Determined by HPLC analysis. [d] Hexane used as solvent. [e] Toluene used as solvent. [f] Methanol used as solvent.

Table 2. **Stepwise Reduction of 3 with borohydride reagents[a]**

entry	$NaBH_4$ (equiv)	acid (equiv)	additive (equiv)	second hydride (equiv)	conv (%)[b]	**2a**:(**2b** + **2c** + **2d**)[c]
1	4	TFA (8)	none	NaBH4 (2)	77	1:(1)
2	4	TFA (8)	TFA (4)	none	95	3:(1)
3	4	TFA (8)	TFA (4)	$NaBH_4$ (1)	>98	1.8:(1)
4	4	H_2SO_4(4)	none	none	33	− −
5	4	H_2SO_4(5)	TFA (4)	$NaBH(TFA)_3$ (4)	98	10.5:(1)

[a] Reactions were conducted under nitrogen by reacting **3** with borohydride complex prepared in 0.15−0.25 M THF with $NaBH_4$ and acid at −20 to 10 °C. Stirred 10−18 h at ambient temperature, cooled to 0−10 °C, and additive added followed by second borohydride. [b] Conversion calculated as HPLC peak area percent conversion. [c] Determined by HPLC analysis.

carbonyls in the reaction mixture (Table 2, entry 1), whereas addition of trifluoroacetic acid did allow for further reduction to take place (entry 2). A combination of both trifluoroacetic acid and sodium borohydride led to virtually complete conversions to the **2a**−**d** (entry 3).

Formation of the borane complex from 4 equiv of sodium borohydride with 4 equiv of sulfuric acid[10] led to complete consumption of **3** and formation of a mixture of **4a**/**b** and **2a**−**d** (entry 4). Treatment of the mixture with trifluoroacetic acid (4 equiv) and sodium tris(trifluoroacetoxy)borohydride (4 equiv) led to 98% conversion and a significant improvement in the diastereoselectivity (83% de) (entry 5).

With the trifluoroacetoxyborohydride method available to reduce *in-situ* prepared ketones **4a**/**b**, we reexamined what factors influenced the diastereoselectivity of the enamine reduction. First it was necessary to quantitate the amounts of the three undesired isomers being produced in the reaction to determine which isomers were reducing from 1,4 stereoinduction and which isomers were resulting from 1,2 stereoinduction. An HPLC method was developed which separated all four diastereomers; however, only the retention time of isomer **2a** had been conclusively assigned.[7]

Authentic samples of **2a**, **2b**, **2c**, and **2d** were obtained by reducing **3** with sodium borohydride/acetic acid to give **4a** and **4b** (Scheme 1). Flash chromatography yielded the separated unstable amino ketones **4a** and **4b**, which were immediately protected as the Boc-carbamates **5a** and **5b**. Reduction of **5a** to **6a**/**b** and deprotection led to formation of a mixture of isomers **2a** and **2b**. By comparison of the HPLC trace of independently prepared **2a** with the reduction/deprotection products of **5a**, the relative retention time of isomer **2b** could be assigned. For assignment of the retention times for isomers **2c** and **2d**, the characterization of at least one isomer was necessary. Ketone **5b** was reduced with sodium borohydride, and the resulting Boc-carbamates **6c**/**d** were separated by chromatography (Scheme 3).[11] Debenzylation of the **6c** isomer under catalytic transfer conditions gave the carbamate **7c**. Treatment of the 1,2-amino alcohol **7c** with 1,1′-carbonyldiimidazole resulted in formation of the oxazolidinone **8**. With the aid of COSY at 500 MHz, the H_4 and H_5 protons were assigned at 4.16 and 3.66 ppm, respectively (Scheme 3). The coupling constant between the ring protons of **8** (J_{4-5} = 4.7 Hz) was suggestive of a *trans* arrangement.[12] In the ROESY spectrum, an NOE was observed between the H_4 proton and the two methylene protons at 2.78 and 2.70 ppm confirming that these groups are *cis* to each other. Based on this, the stereochemistry of **6c**, and also **2c**, can be assigned as the 2*S*,3*S*,5*R* configuration. This leaves the **2d** isomer as the 2*S*,3*R*,5*R* isomer.

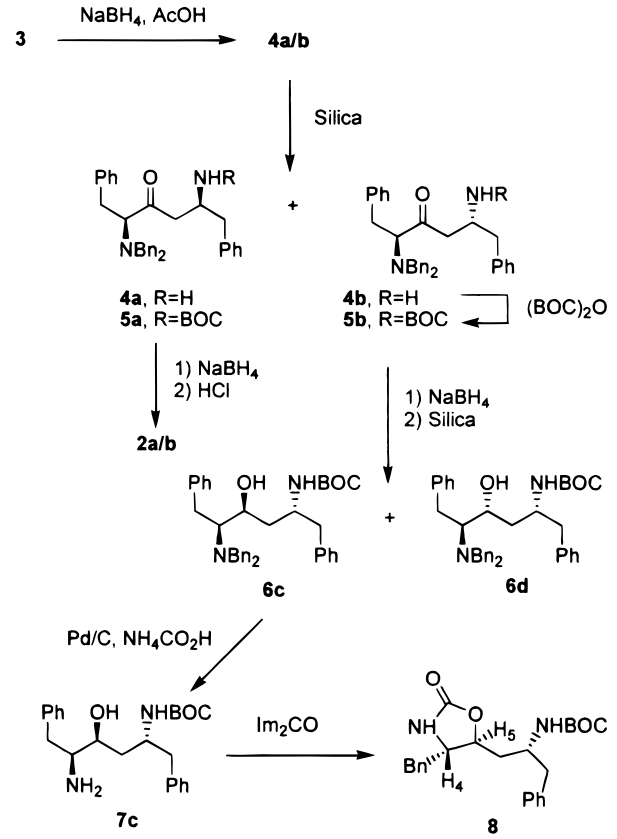
With the assignment of the isomers complete, a screening of borane derivatives suggested that a higher diastereoselectivity for the enamine reduction was possible using a borane generated from a sulfonic acid.[10] Treatment of a complex of sodium borohydride/sulfuric acid in THF followed by sodium bis(trifluoroacetoxy)borohydride yielded the desired **2a** with 73% overall diastereoselectivity (Table 3, entry 1). Unfortunately, stirring problems developed when preparing the borohydride/sulfuric acid mixture. The reaction became extremely thick as the sulfuric acid was slowly added to the sodium borohydride in THF. This is presumed to be

(10) Abiko, A.; Masamune, S. *Tetrahedron Lett.* **1992**, *33*, 5517.

(11) Due to the instability of **4a**/**b**, a more practical method of obtaining larger quantities of **6a**−**d** was to reduce **3** to **4a**/**b** and protect the crude reaction mixture with Boc_2O. Reduction of this mixture led to all four isomers **6a**−**d**, which could be separated by chromatography.

(12) Kempf, D. J.; Sowin, T. J.; Doherty, E. M.; Hannick, S. M.; Codavoci, L.; Henr;y, R. F.; Green, B. E.; Spanton, S. G.; Norbeck, D. W. *J. Org. Chem.* **1992**, *57*, 5692 and references therein.

Scheme 3



the result of ring opening of the solvent to give both ring-opened products and polymers. Addition of water (7 equiv) to the borohydride complex appeared to slow solvent decomposition while also thinning the reaction mixture. Unexpectedly, addition of water also increases the 1,4 stereoinduction and the overall diastereoselectivity of the reaction to 92% and 91%, respectively, with 95% conversion (entry 2). Replacement of sulfuric acid with MSA gave 78% de for the 1,4 induction and 74% de overall with >98% conversion (entry 3). On a laboratory scale, no problems were observed with the MSA in THF. However, when these reaction conditions (entry 3) were scaled up to 20 kg of **3**, problems with THF ring-opening byproducts were again observed. In order to avoid this, several other ether solvents were evaluated in the reaction. Dimethoxyethane (DME) proved superior as a solvent relative to THF. Under the acidic reaction conditions, DME did not appear to have a problem with polymerization. Adding water to the DME borohydride complex led to poor conversion to product; however, 2-propanol as a protic additive was found to improve the diastereoselectivity (entry 4). The exact role of the protic solvents in enhancing the diastereoselectivity is not known.

To obtain reproducible data regarding the diastereoselectivity of the reaction, the reductions needed to be carried out to completion. This was necessary because the stereoselectivity of the products decreases as the reaction progresses. This correlation between conversion and selectivity suggests that a kinetic preference is observed in the reduction of **4a**/**b**. Further evidence of this can be seen in the ratios of diastereomers produced (Tables 2 and 3). The **2a**:**2b** selectivity is generally quite high (15−20:1), while the 3*R*,5*R*,3*S*,5*R* isomers selectivity is typically low (1:1 to 4:1). the preference for reduction of **4a** presumably is due to a matched pairing, while isomer **4b** has a mismatched pairing. 1,2 Stereoinduction in both **4a** and **4b** favors the *S* configuration in the resulting amino alcohols, in agreement with a Felkin−Ahn type model.[13] However, carbonyl reduction of the assumed cyclic structures **9a** and **9b** (Figure 1) would come from the pseudoaxial direction favoring the *S* isomer from **4a** and the *R* isomer from **4b** (Figure 1).[14]

With the selectivity of the enamine reduction improved, other methods of decomplexing the boronate ester were studied. To compete with the bidentate chelation of **4a**/**b**, a bi- or tridentate chelating agent seemed necessary. Treatment with ethanolamine (4 equiv) followed by sodium borohydride in dimethylformamide gave >98% conversion to products with 75% de (entry 5).[15] Use of the tetradentate chelating agent triethanolamine (TEOA)[16] followed by sodium borohydride in dimethylformamide yielded the desired product with 80% diastereoselectivity (entry 6). While dimethylformamide worked well on a laboratory scale, the danger of using this as a solvent for sodium borohydride on a large scale[17] led us to replace this solvent with dimethylacetamide. Using these conditions on a multikilogram scale yielded the desired product in >98% conversion with 84% diastereoselectivity (entry 7).

Debenzylation of the dibenzyldiamino alcohols **2a**−**d** was then carried out using hydrogen-transfer conditions. Precipitation as the dihydrochloride salt yielded the desired hydroxyethylene isostere **10** in 60% overall yield from **3** in >95% de (Scheme 4).

Conclusion

This methodology demonstrates the ability to synthesize the diaminohydroxyethylene isostere **10** from *l*-phenylalanine in high overall yield, involving only two isolated solids, and using no chromatography. A method has been devised to reduce **3** to the amino alcohols **2a**−**d** with high diastereoselectivity. An acyclic 1,4 stereoinduction was optimized to an impressive 14:1 selectivity by tuning the solvent and acid.[18] This method should prove general for the reduction of enaminones in a syn-1,3 fashion to yield many types of 1,3-amino alcohols.

Experimental Section

General. (5*S*)-2-Amino-5-dibenzylamino-4-oxo-1,6-diphenylhex-2-ene (**3**) was prepared as previously reported.[6] Proton

(13) Reetz, M. T. *Angew. Chem.* **1991**, *30*, 1531.
(14) The attack of the hydride from the upper face leads to a chairlike transition state. See: Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon Press: Oxford, 1983; Chapter 6.
(15) $NaBH_4$ was added as a solution in DMF to avoid adding as a solid. Solubility data for $NaBH_4$: 18.0 g/100 g of dimethylformamide or 14.0 g/100 g of dimethylacetamide.
(16) Triethanolamine can sequester the boron completely as the triethanolamine borate even in water. See: Sonoda, A.; Takagi, N.; Ooi, K.; Hirotsu, T. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 161.
(17) Liu, Y.; Schwartz, J. *J. Org. Chem.* **1993**, *58*, 5005. Ganem, B.; Osby, J. O. *Chem. Rev.* **1986**, *86*, 763.
(18) An example of 1,4 induction in a similar system was recently reported. See: Captain, L. F.; Xia, X.; Liotta, D. C. *Tetrahedron Lett.* **1996**, *37*, 4293.

Table 3. **Stepwise Reduction of 3 with Borane Sulfonate Complexes**[a]

entry	$NaBH_4$ (equiv)	acid (equiv)	additive (equiv)	second reduction (equiv)	conv (%)[b]	1,4 dr[c]	**2a−d** dr[c]
1[d]	4	H_2SO_4 (4)	TFA (6)	$NaBH_2(TFA)_2$ (4)	>98	nd	7:1
2[e]	5	H_2SO_4 (5)	none	$NaBH_3(TFA)$ (4), TFA (2)	95	25:1	21:1
3[e]	4	MSA (10)	none	$NaBH_3(TFA)$ (4), TFA(1)	>98	7:1	7:1[f]
4	4	MSA (10)	none	$NaBH_3(TFA)$ (4), TFA (1)	>98	16:1	14:1
5	4	MSA (10)	$HO(CH_2)_2NH_2$ (4)	$NaBH_4$ (1), DMF	>98	12:1	7:1
6	4	MSA (10)	TEOA (4)	$NaBH_4$ (4), DMF	>98	11:1	8:1
7	2.3	MSA (5)	TEOA (2.2)	$NaBH_4$ (1.5), DMAC	>98	14:1	12:1

[a] Reactions were conducted under nitrogen by reacting **3** with $NaBH_4$ precomplexed with RSO_3H in DME between −10 and 0 °C. Solution of **3** added at <10 °C in iPrOH/DME. Warmed to ambient temperature for 3−24 h. Additive added followed by borohydride at <10 °C. [b] Conversion calculated as HPLC peak area percent ratio of **2a−d**/**2a−d** + **3** + **4a**/**b**. [c] Determined by HPLC analysis of crude reaction mixture. [d] Reaction performed in THF. [e] Reaction performed in THF with 7.7 equiv of H_2O added to borohydride complex prior to addition of **3**. [f] Measured after debenzylation.

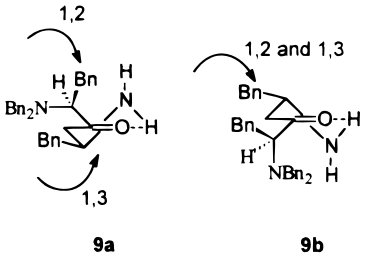
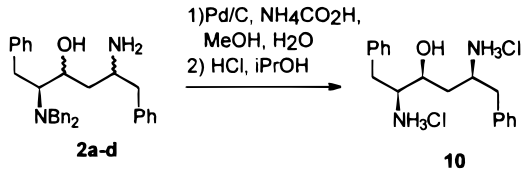


Figure 1.

Scheme 4



spectra were obtained at 300 and 500 MHz, and ^{13}C NMR spectra were obtained at 75 MHz.

(5*S*)-2-Amino-5-dibenzylamino-4-oxo-1,6-diphenylhex-2-ene (3). Enaminone **3** was prepared as previously described.[6] To a vessel were added 14.0 kg (84.7 mol) of *l*-phenylalanine, 27.0 kg (195 mol) of K_2CO_3, 4.8 kg (85.5 mol) of KOH, and 62.4 kg of tap water. This was stirred until the solution became homogeneous before adding 35.8 kg (284 mol) of benzyl chloride. The solution was heated to reflux for 5 h and cooled to 50 °C, and 55 kg of heptane was added. The aqueous layer was drained, and the organics were washed twice with 47 kg of H_2O/MeOH (1:2 w/w). The organics were concentrated *in vacuo* to give an oil.

The crude *l*-*N*,*N*-dibenzylphenylalanine benzyl ester was dissolved into 23 kg of methyl *tert*-butyl ether (MTBE) and 3.8 kg (92.6 mol) of CH_3CN. This was then slowly added to a slurry of 90% $NaNH_2$ (8.2 kg, 189 mol) in 58 kg of MTBE while keeping the temperature between −5 and 5 °C. The reaction was stirred for 2 h at 0−5 °C, and then vacuum was applied for 30 min to remove the ammonia. The solution was reconstituted with 17 kg of MTBE and warmed to 25 °C, and a 2 M solution of benzylmagnesium chloride in THF (72.4 kg, 140 mol) was slowly added. This was stirred for 2 h. The reaction was cooled to 5 °C and quenched by slow addition of 136 kg of 23% (w/w) aqueous citric acid. The layers were separated and the organics washed with 106 kg of 10% aqueous NaCl. The organics were concentrated *in vacuo*. The residue was diluted with 75 kg of EtOH and concentrated *in vacuo* again to remove other solvents. This residue was then crystallized from 150 kg of EtOH to give 33.85 kg (79%) of **3** (as a 1:1 EtOH solvate): mp 101−102 °C; IR ($CDCl_3$) 3630, 3500, 3110, 3060, 3030, 1620, 1595, 1520, 1495, 1450, 1300, 1250 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.8 (br s, 1H), 7.2 (m, 20H), 5.1 (s, 1H), 4.9 (br s, 1H), 3.8 (d, 2H, J = 14.7 Hz), 3.6 (d, 2H, J = 14.7 Hz), 3.5 (m, 3H), 3.2 (dd, 1H, J = 14.4, 7.5 Hz), 3.0 (dd, 1H, J = 14.4, 6.6 Hz); ^{13}C NMR (DEPT) ($CDCl_3$) δ 198.0, 162.8, 140.2, 140.1, 136.0(+), 129.5(+), 129.3(+), 128.9(+), 128.7(+), 128.1(+), 128.0(+), 127.3(+), 126.7(+), 125.6(+), 96.9(+), 66.5(+), 54.3(−), 42.3(−), 32.4(−); MS (CI) *m*/*z* (relative intensity) 461 ($[M + 1]^+$, 100).

Determination of the Enantiomeric Purity of 3. The compound was analyzed by HPLC (Chiracel OD column (Diacel Chemical), 20% 2-propanol/heptane, 210 nm). The retention times at 1 mL/min are 10 and 13.5 min for the *R* and *S* enantiomers, respectively. The ee of **3** is >99%.

General Procedure for Enaminone Reduction. A suspension of $NaBH_4$ (30 kg, 790 mol) in ethylene glycol dimethyl ether (1176 kg) was cooled to less than −5 °C. Methanesulfonic acid (192 kg, 2 kmol) in ethylene glycol dimethyl ether (10 kg) was slowly added, keeping the temperature below 5 °C. *Caution: Borane is formed during this addition. Proper ventilation of the vessel is pertinent!* Once the addition was complete, a solution of i-PrOH (140 L), **3**[6] (122.5 kg, 266 mol), and ethylene glycol dimethyl ether (270 kg) was slowly added. The mixture was stirred for 12 h at 5 ± 5 °C. Triethanolamine (118 kg) was then slowly added to the reaction while maintaining the temperature below 5 °C. The solution was stirred at less than 5 °C for 30 min. A solution of $NaBH_4$ (25 kg, 660 mol) in dimethylacetamide (184 kg) was slowly added. The resulting suspension was stirred for 2 h at 15 ± 5 °C and then slowly quenched with water (1355 L). The temperature was warmed to ambient, and methyl *tert*-butyl ether 815 kg) was added. The layers were separated and the organics washed successively with 1 N NaOH (1520 L), 18% (w/w) NH_4Cl (1476 kg), and 7% (w/w) NaCl (1569 kg). The resulting organic solution could then be stored or carried on in further transformations. HPLC ratios of diastereomers **2a−d** were determined by analytical HPLC (475:525 [0.03]KH_2PO_4/CH_3-

CN, pH = 3.0, C-8 5-μm Hypersil column, λ = 205 nm, 1 mL/min and compared to standards; the mixture analyzed as follows: 2*S*,3*S*,5*R* isomer (9.2 min, 4%), 2*S*,3*R*,5*S* (10.5 min, 6%), 2*S*,3*S*,5*S* (11.3 min, 83%), and 2*S*,3*R*,5*R* (14.3 min, 2%). An analytical sample of the 2*S*,3*S*,5*S* isomer **2a** was prepared by flash chromatography [silica; 9:1:0.1 hexanes/i-PrOH/NH_4OH(aqueous)] to afford **2a** as a clear oil: IR ($CDCl_3$) 3400−2800 (br), 3090, 3060, 3030, 1600, 1580, 1490, 1450, 1370, 1300, 1100, 1070, 1030 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.2 (m, 20H), 4.15 (d, 2H, J = 14 Hz), 3.65 (ddd, 1H, J = 10, 5, 2 Hz), 3.5 (d, 2H, J = 14 Hz), 3.50-2.49 (m, 8H) 2.48 (dd, 1H, J = 14, 7 Hz), 1.60 (dt, 1H, J = 14, 10 Hz), 1.25 (dt, 1H, J = 14, 2 Hz); ^{13}C NMR (DEPT) ($CDCl_3$) δ 140.9, 140.2, 138.5, 129.4(+), 129.4-(+), 128.9(+), 128.4(+), 128.3(+), 128.2(+), 126.8(+), 126.3(+), 125.7(+), 72.1(+), 63.7(+), 55.0(−), 53.3(+), 46.4(−), 40.3(−), 30.3(−); MS (CI) *m*/*z* (relative intensity) 465 ($[M + 1]^+$, 100).

Flash chromatography also yielded samples of the other isomers, **2b**−**d**.

(2*S*,3*R*,5*S*)-5-Amino-2-dibenzylamino-3-hydroxy-1,6-diphenylhexane (2b): ^1H NMR ($CDCl_3$) δ 7.4−7.0 (m, 20H), 4.25−4.18 (m, 1H), 3.8−3.5 (m, 6H), 3.28−3.15 (m, 1H), 3.11−2.95 (m, 1H), 2.95−2.82 (m, 1H), 2.75 (dd, 1H, J = 13.0, 6.5 Hz), 2.70−2.40 (m, 3H), 1.75−1.55 (m, 2H); ^{13}C NMR (DEPT) ($CDCl_3$) δ 142.0, 140.1, 138.7, 129.6-(+), 129.3(+), 128.9(+), 128.6(+), 128.1(+), 126.8(+), 126.5(+), 125.6(+), 69.5(+), 67.1, 63.9(+), 54.7(−), 50.5-(+), 43.6(−), 38.7(−), 32.4(−); MS (CI) *m*/*z* (relative intensity) 465 ($[M + 1]^+$, 100).

(2*S*,3*S*,5*R*)-5-Amino-2-dibenzylamino-3-hydroxy-1,6-diphenylhexane (2c): ^1H NMR ($CDCl_3$) δ 7.4−6.9 (m, 20H), 3.97 (d, 2H, J = 13.5 Hz), 3.85 (ddd, 1H, J = 8.3, 8.3, 3 Hz), 3.40 (d, 2H, J = 13.5 Hz), 3.25−3.15 (m, 1H), 3.08 (dd, 1H, J = 13.5, 6.0 Hz), 2.88−2.75 (m, 1H), 2.70−2.45 (m, 6H), 1.45−1.25 (m, 2H); ^{13}C NMR (DEPT) ($CDCl_3$) δ 140.5, 139.1, 129.3(+), 129.0(+), 128.5(+), 128.4(+), 127.2(+), 126.2(+), 68.1(+), 64.2(+), 54.2(−), 49.6(+), 44.3(+), 40.5(−), 32.1(−); MS (CI) *m*/*z* (relative intensity) 465 ($[M + 1]^+$, 100).

(2*S*,3*R*,5*R*)-5-Amino-2-dibenzylamino-3-hydroxy-1,6-diphenylhexane (2d): ^1H NMR ($CDCl_3$) δ 7.4−6.9 (m, 20H), 4.05 (ddd, 1H, J = 12.0, 6.0, 1.2 Hz), 3.8−3.5 (m, 5H), 3.15−3.05 (m, 1H), 3.00 (d, 2H, J = 7.5 Hz), 3.0−2.6 (m, 4H), 2.58 (dd, 1H, J = 14.4, 8.1 Hz), 1.90 (d, 1H, J = 14.7 Hz), 1.1−0.9 (m, 1H); ^{13}C NMR (DEPT) ($CDCl_3$) δ 141.9, 140.2, 138.2, 129.7(+), 129.3 (+), 128.8(+), 128.6-(+), 128.1(+),128.0(+), 126.6(+), 125.5(+), 72.7(+), 64.3-(+), 54.7(−), 54.5(+), 47.3(−), 39.9(−), 32.2(−); MS (CI) *m*/*z* (relative intensity) 465 ($[M + 1]^+$, 100).

(2*S*,5*S*/*R*)-5-Amino-2-dibenzylamino-3-oxo-1,6-diphenylhexane (4a/b). To a THF (62.5 mL) solution of $NaBH_4$ (3.55 g, 94 mmol) at −10 °C was added a precooled solution of acetic acid (62.5 mL, 1.09 mol) over 10 min. This was stirred at rt for 30 min. After addition of **3** (10 g, 21.7 mmol) in two portions over 1 h, the reaction mixture was stirred for 14 h. The reaction was quenched with concentrated HCl (11.5 mL) and allowed to stir at rt for 30 min. The reaction was then diluted with CH_2Cl_2 (50 mL), water (150 mL), and 50% NaOH (100 mL). The separated aqueous layer was extracted twice with CH_2Cl_2 (50 mL). The organics were combined, dried over Na_2SO_4, and concentrated *in vacuo* to yield 10.63 g of a yellow syrup. The residue was subjected to column chromatography (silica; 1% MeOH/CH_2Cl_2) to give **4a** (420 mg, 4% yield) and **4b** (220 mg, 2% yield) as unstable oils (ca. 95% diastereomeric purity). These were carried on immediately. Extensive decomposition due to elimination prevented complete characterization of these intermediates.

4a: ^1H NMR ($CDCl_3$) δ 7.40−7.00 (m, 20H), 3.82 (d, 2H, J = 13.6 Hz), 3.59 (d, 2H, J = 13.6 Hz), 3.55−3.35 (m, 1H), 3.25−3.15 (m, 1H), 3.15 (dd, 1H, J = 13.5, 9.6 Hz), 2.92 (dd, 1H, J = 13.5, 4.5 Hz), 2.65−2.30 (m, 4H), 1.55 (br s, 2H); MS (DCI/NH_3) *m*/*z* (relative intensity) 463 ($[M + H]^+$, 20), 446 ($[M - NH_3]^+$, 15), 198 ($[Bn_2NH_2]^+$, 100).

4b: MS (DCI/NH_3) *m*/*z* (relative intensity) 446 ($[M - NH_3]^+$, 85), 198 ($[Bn_2NH_2]^+$, 100).

(2*S*,5*S*)-5-(*tert*-Butyloxycarbamoyl)amino-2-dibenzylamino-3-oxo-1,6-diphenylhexane (5a). A solution of amine **4a** (420 mg, 0.90 mmol) in THF (20 mL) was treated with di-*tert*-butyl dicarbonate (239 mg, 1.1 mmol) at rt for 1 h. The reaction mixture was diluted with ethyl acetate (ca. 50 mL), washed with 1 N NaOH (ca. 50 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The residue was subjected to column chromatography (silica; 15:1 hexanes/EtOAc) to give 270 mg (0.48 mmol, 53%) of **5a**: ^1H NMR ($CDCl_3$) δ 7.35−6.95 (m, 20H), 4.72−4.65 (m, 1H), 4.08−3.95 (m, 1H), 3.77 (d, 2H, J = 13.6 Hz), 3.58 (d, 2H, J = 13.6 Hz), 3.51 (m, 1H), 3.12 (dd, 1H, J = 13.4, 9.0 Hz), 2.91 (dd, 1H, J = 13.6, 4.6 Hz), 2.82 (dd, 1H, J = 18.0, 6.0 Hz), 2.75−2.70 (m, 2H), 2.33 (dd, 1H, J = 18.0, 5.4 Hz), 1.34 (s, 9H); MS (DCI/NH_3) *m*/*z* (relative intensity) 563 ($[M + 1]^+$, 100).

(2S,5R)-5-(*tert*-Butyloxycarbamoyl)amino-2-dibenzylamino-3-oxo-1,6-diphenylhexane (5b). A solution of amine **4b** (220 mg, 0.47 mmol) in THF (20 mL) was treated with di-*tert*-butyl dicarbonate (125 mg, 0.57 mmol) at rt for 3 h. The reaction mixture was diluted with EtOAc (ca. 50 mL), washed with 1 N NaOH (ca. 50 mL), dried over $MgSO_4$, and concentrated *in vacuo* to give 190 mg (0.34 mmol, 72%) of **5b**: ^1H NMR ($CDCl_3$) δ 7.35−7.05 (m, 18H), 6.82−6.72 (m, 2H), 5.20−5.10 (m, 1H), 4.05−3.90 (m, 1H), 3.77 (d, 2H, J = 13.6 Hz), 3.54 (d, 2H, J = 13.6 Hz), 3.41 (dd, 1H, J = 9.6, 3.7 Hz), 3.14 (dd, 1H, J = 13.2, 9.9 Hz), 2.89 (dd, 1H, J = 12.9, 3.3 Hz), 2.79 (dd, 1H, J = 17.6, 4.8 Hz), 2.75−2.70 (m, 1H), 2.50 (dd, 1H, J = 13.2, 8.5 Hz), 2.25 (dd, 1H, J = 17.6, 5.1 Hz), 1.38 (s, 9H); MS (DCI/NH_3) *m*/*z* (relative intensity) 563 ($[M + 1]^+$, 100).

(2*S*,3*S*/*R*,5*R*)-5-(*tert*-Butyloxycarbamoyl)amino-2-dibenzylamino-3-hydroxy-1,6-diphenylhexane (6c/d). To a THF (5 mL) and MeOH (1 mL) solution of **5b** (190 mg, 0.34 mmol) was added $NaBH_4$ (20 mg, 0.53 mmol) at 20−25 °C. The reaction mixture was stirred at rt for 3 h. Additional $NaBH_4$ (8 mg, 0.21 mmol) was added and the reaction mixture stirred at rt for 30 min. The reaction was diluted

with CH_2Cl_2 (ca. 20 mL), washed with water and then brine, and dried over $MgSO_4$. The solvent was concentrated *in vacuo* to yield an oil (160 mg).

Alternative Preparation of 6a−d. To a THF (100 mL) solution of $NaBH_4$ (7.10 g, 188 mmol) at −10 °C was added a precooled solution of acetic acid (125 mL, 2.2 mol) over 10 min. This was stirred at rt for 15 min. After addition of **3** (20 g, 43.5 mmol), the reaction mixture was stirred for 3 h at rt. The reaction was quenched with concentrated HCl (23 mL) and allowed to stir at rt for 15 min. The reaction was then diluted with water (100 mL) and 50% NaOH (110 mL). The layers were separated, and the aqueous layer was extracted twice with EtOAc (100 mL). The organics were combined, dried over Na_2SO_4, and concentrated *in vacuo* to yield a yellow syrup. The residue was subjected to column chromatography (silica; 1% CH_3OH/CH_2Cl_2) to give a mixture of **4a** and **4b** as well as traces of the alcohols **2a−d** (15.71 g). The residue was taken up in THF (250 mL) and treated with di-*tert*-butyl dicarbonate (8.91 g, 41 mmol) at rt for 4 h. The reaction mixture was diluted with EtOAc (100 mL) and concentrated *in vacuo*. The residue was subjected to column chromatography (silica; 16:1 hexanes/EtOAc) to give 14.0 g (24.9 mmol, 57%) of **5a**/**b**. The mixture was diluted with THF (250 mL) and MeOH (50 mL) and treated with $NaBH_4$ (1.14 g, 30 mmol). The reaction was stirred for 30 min at rt, concentrated *in vacuo*, and diluted with EtOAc (ca. 100 mL). This was washed successively with water and brine and dried over $MgSO_4$. Concentration *in vacuo* gave 13.9 g (25 mmol) of **6a−d**. The isomers were separated by eluting through a silica column with nitrogen pressure using a gradient of MTBE/hexane (5:95 to 50:50). The isomers eluted in the order **6c** (4.59 g), **6b** (0.96 g), **6a** (6.80 g), **6d** (0.77 g). Mixed fractions were discarded.

(6a): ^{1}H NMR ($CDCl_3$) δ 7.35−7.00 (m, 20H), 4.82 (br s, 1H), 4.32 (s, 1H), 3.90 (d, 2H, J = 13.5 Hz), 3.79 (apparent dq, 1H, J = 6.8, 6.8 Hz), 3.65−3.55 (m, 1H), 3.38 (d, 2H, J = 13.5 Hz), 3.05 (dd, 1H, J = 15.0, 6.0 Hz), 2.85−2.72 (m, 2H), 2.71−2.55 (m, 2H), 1.55−1.45 (m, 1H), 1.39 (s, 9H), 1.30−1.15 (m, 1H); ^{13}C NMR (DEPT) ($CDCl_3$) δ 155.6, 140.2, 138.9, 138.3, 129.6(+), 129.1(+), 129.0(+), 128.6(+), 128.5(+), 128.2(+), 127.2(+), 126.2(+), 126.1(+), 78.9, 69.4(+), 64.3(+), 54.0(−), 51.3(+), 41.2(−), 38.3(−), 32.0(−), 28.4(+); MS (CI) *m*/*z* (relative intensity) 565 ([M + 1]+, 100).

(6b): ^{1}H NMR ($CDCl_3$) δ 7.35−7.05 (m, 20H), 4.39 (d, 1H, J = 9.6 Hz), 4.15−4.00 (m, 1H), 3.85−3.75 (m, 2H), 3.68−3.58 (m, 4H), 3.08−2.95 (m, 1H), 2.95−2.85 (m, 2H), 2.75 (d, 2H, J = 6.3 Hz), 1.55−1.30 (m, 2H), 1.42 (s, 9H); ^{13}C NMR (DEPT) ($CDCl_3$) δ 157.0, 141.5, 140.1, 137.7, 129.6(+), 129.3(+), 128.8(+), 128.5(+), 128.1(+), 128.1(+), 126.7(+), 126.5(+), 125.7(+), 79.8, 67.8(+), 63.7(+), 54.9(−), 48.1(+), 41.5(−), 41.2(−), 32.5(−), 28.4(+); MS (CI) *m*/*z* (relative intensity) 565 ([M + 1]$^+$, 100).

(6c): ^{1}H NMR ($CDCl_3$) δ 7.35−7.05 (m, 20H), 4.70 (d, 1H, J = 9.0 Hz), 4.25 (s, 1H), 4.10−3.95 (m, 3H), 3.57 (br s, 1H), 3.40 (d, 2H, J = 15 Hz), 3.05−2.75 (m, 3H), 2.55 (dd, 2H, J = 15, 9 Hz), 1.85−1.70 (m, 1H), 1.35 (s, 9H), 0.95−0.85 (m, 1H); ^{13}C NMR (DEPT) ($CDCl_3$) δ 156.2, 140.8, 139.9, 138.2, 129.4(+), 129.3(+), 129.0(+), 129.0(+), 128.4(+), 128.3(+), 126.9(+), 126.4(+), 125.8(+), 79.3, 67.4(+), 63.9(+), 54.9(−), 49.0(+), 41.2(−), 38.8(−), 30.6(−), 28.4(+); MS (CI *m*/*z* (relative intensity) 565 ([M + 1]$^+$, 100).

(6d): ^{1}H NMR ($CDCl_3$) δ 7.35−7.10 (m, 18H), 7.05−6.90 (m, 2H), 4.95−4.85 (m, 1H), 3.75−3.65 (m, 4H), 3.55 (d, 2H, J = 15.0 Hz), 3.10−2.85 (m, 3H), 2.75−2.55 (m, 3H), 1.95 (ddd, 1H, J = 13.5, 2.2, 2.2 Hz), 1.40 (s, 9H), 1.40−1.25 (m, 1H); ^{13}C NMR (DEPT) ($CDCl_3$) δ 155.8, 140.3, 139.5, 138.3, 129.5(+), 129.2(+), 128.9(+), 128.9(+), 128.4(+), 128.3(+), 127.0(+), 126.4(+), 126.0(+), 79.4, 70.7(+), 63.7(+), 55.0(−), 52.2(+), 41.7(−), 38.1(−), 31.8(−), 28.4(+); MS (CI) *m*/*z* (relative intensity) 565 ([M + 1]$^+$, 100).

(2*S*,3*S*,5*R*)-2-Amino-5-(*tert*-butyloxycarbamoyl)amino-3-hydroxy-1,6-diphenylhexane (7c). An ethanol (2.3 mL) solution of **6c** (140.2 mg, 0.248 mmol) was slurried with 10% palladium on carbon (24 mg). To this mixture was added NH_4CO_2H (80.1 mg) in water (280 μL). This was then heated to reflux for 3 h, cooled to rt for 12 h, and filtered through a pad of Celite. The filtrate was concentrated *in vacuo*, diluted with EtOAc (20 mL), and washed successively with water and brine. The organics were dried over $MgSO_4$ and concentrated to dryness to give **7c** as a white solid (87.2 mg, 0.227 mmol, 92%): ^{1}H NMR (DMSO-d_6) δ 7.30−7.10 (m, 10H), 6.62 (d, 1H, J = 9 Hz), 4.39 (m, 1H), 3.75 (m, 1H), 3.40−3.30 (m, 2H), 2.75−2.25 (m, 5H), 1.50 (m, 3H), 1.30 (s, 9H); ^{13}C NMR (DMSO-d_6) δ 155.3, 140.3, 139.2, 129.1, 129.1, 128.0, 127.9, 125.7, 125.5, 77.3, 69.2, 57.2, 49.1, 41.3, 40.6, 38.2, 28.2; MS (DCI/NH_3) *m*/*z* (relative intensity) 385 ([M + 1]$^+$, 100).

(4*S*,5*S*,2′*R*)-4-Benzyl-5-[(2*R*)-2-(amino-*tert*-butyloxycarbamyl)-3-phenylpropyl]oxazolidinone (8). A THF (10 mL) solution of **7c** (100.3 mg, 0.26 mmol) was treated at rt with CDI (55.0 mg, 0.34 mmol) and DMAP (6.6 mg, 0.05 mmol). The reaction mixture was stirred at rt for 3 h. The reaction was diluted with EtOAc (30 mL) and washed successively with 1 M HCl and brine. The organics were dried over $MgSO_4$ and concentrated *in vacuo* to a white powder (100.1 mg). Purification by preparative TLC (10% CH_3OH/CH_2Cl_2) gave 72.2 mg (67%) **8**: ^{1}H NMR (DMSO-d_6) δ 7.66 (s, 1H), 7.30−7.11 (m, 10H), 6.71 (d, 1H, J = 7.5 Hz), 4.16 (ddd, 1H, J = 9.5, 4.7, 4.7 Hz), 3.75 (m, 1H), 3.66 (m, 1H), 2.78 (dd, 1H, J = 12.5, 5.0 Hz), 2.70 (dd, 1H, J = 12.5, 5.0 Hz), 2.70−2.60 (m, 2H), 1.70−1.55 (m, 2H), 1.33 (s, 9H); ^{13}C NMR (DEPT) (DMSO-d_6) δ 157.6, 155.0, 138.5, 136.4, 129.5(+), 129.1(+), 128.2(+), 128.0 (+), 126.4(+), 125.9(+), 77.4, 77.0(+), 57.7(+), 48.6(+), 40.9(−), 39.5(−), 38.7(−), 28.2(+); HRMS *m*/*z* [M + K]$^+$ calcd for $C_{24}H_{30}N_2O_4K_1$, 449.1843, found 449.1840.

(2*S*,3*S*,5*S*)-2,5-Diamino-3-hydroxy-1,6-diphenylhexane Dihydrochloride (10). A solution of crude 5-amino-2-(dibenzylamino)-3-hydroxy-1,6-diphenylhexanes, **2a−d** (20 kg, 43 mol), MeOH (320 L), aqueous ammonium formate (13.6 kg in 23 L of water), and 5% palladium on carbon (4.0 kg, 50−60% water by weight) was heated to reflux for 6 h. The cooled suspension was filtered through a bed of

diatomaceous earth, and the cake was washed with MeOH (2 × 30 kg). The filtrtae was concentrated *in vacuo* to an oil. The residue was dissolved in EtOAc (175 L) and washed successively with 1 N NaOH (200 L), 20% brine (195 L), and water (97 L). The organics were concentrated *in vacuo*. To the oil was added i-PrOH (205 L) and concentrated HCl (aqueous, 17 L). The suspension was heated to reflux for 1 h, cooled over 6 h to 25 °C, and held at that temperature for 12 h. The slurry was filtered, and the cake was washed with EtOAc (30 L). The product could be recrystallized if greater purity was desired. The solids were resuspended in i-PrOH (120 L) and water (6.3 L). This slurry was heated at reflux for 1 h, cooled to 25 °C, and stirred for 12 h. The slurry was filtered, and the cake was washed with i-PrOH (15 kg). This afforded 8.9 kg (60% from **3**) (>99% HPLC purity) of a white powder: R_f 0.25 (34:30:25:8:4 $CHCl_3$/EtOAc/CH_3OH/H_2O/AcOH); mp > 300 °C; $[\alpha]^{20}_D$ +80° (*c* 0.2, CH_3OH); IR (Nujol) 3090, 3060, 3000−2800 (br), 2825, 2050, 1735, 1650, 1600, 1590, 1495, 1445, 1045 cm^{-1}; ^1H NMR (CD_3OD) δ 7.3 (m, 10H), 3.83 (ddd, 1H, J = 11.0, 3.3, 3.3 Hz), 3.63 (m, 1H), 3.38 (ddd, 1H, J = 7.2, 7.2, 3.5 Hz), 2.95 (m, 4H), 1.90 (ddd, 1H, J = 14.5, 11.0, 7.3 Hz), 1.76 (ddd, 1H, J = 14.5, 3.0, 3.0 Hz); ^{13}C NMR (DEPT) (CD_3OD) δ 136.8, 136.6, 130.5(+), 134.4(+), 130.2(+), 128.6(+), 128.5(+), 68.9(+), 58.5(+), 53.2(+), 39.9(−), 36.9(−), 36.7(−).

The data for the free base are as follows: ^1H NMR ($CDCl_3$) δ 7.3 (m, 10H), 3.7 (ddd, 1H, J = 10.5, 3.0, 3.0 Hz), 3.1 (m, 1H), 2.8 (m, 3H), 2.55 (dd, 1H, J = 9.0, 13.5 Hz), 2.5 (d, 1H, J = 8.4, 13.5 Hz), 1.7 (ddd, 1H, J = 15, 4.5, 4.5 Hz), 1.55 (ddd, 1H, J = 15.0, 12.0, 12.0 Hz); ^{13}C NMR (DEPT) ($CDCl_3$) δ 139.7, 138.3, 129.3(+), 129.2(+), 128.5(+), 128.4(+), 126.4(+), 74.5(+), 57.5(+), 54.0(+), 47.3(−), 41.3(−), 39.1(−); MS (CI) m/z (relative intensity) 285 ($[M + 1]^+$, 100). Anal. Calcd for $C_{18}H_{24}N_2O$: C, 76.02; H, 8.51; N, 9.85. Found: C, 76.07; H, 8.12; N, 9.82.

Supporting Information Available

Copies of NMR spectra (27 pages). See any current masthead page for Web access instructions.

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