Stereocontrol between Remote Atom Centers in Acyclic Substrates. Anti Addition of Hydride to 1,5-, 1,6-, and 1,7-Hydroxy Ketones†

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For conformationally unconstrained, acyclic organic compounds, the control of stereogenic centers at remote positions of a chain, that is, at a distance of four or more atom centers, remains a challenging problem in asymmetric synthesis. We report on our studies of 1,5, 1,6, and 1,7 diastereoselectivity in hydride reductions of acyclic hydroxy amino ketones and related compounds, which were sparked by our discovery of high 1,5 diastereocontrol (>10:1) with substrates such as **17** and **23**. We have been able to achieve both high 1,5- and 1,6-anti diastereocontrol in the reduction of 1,5- and 1,6-hydroxy ketone substrates, respectively. However, the level of 1,7-anti diastereocontrol with 1,7-hydroxy ketones was only moderate. More specifically, reduction of **23** to **24** with *R*-alpine-hydride or $Zn(BH_4)_2$ in CH_2Cl_2 (predominantly) at −78 °C gave high 1,5-anti stereoselectivity (anti/syn = 10:1 or 13:1, respectively), and reduction of **34** to **35** with *R*-alpine-hydride (CH_2Cl_2) gave high 1,6-anti selectivity (anti/syn = 12:1, respectively), whereas reduction of **46** to **44** with *R*-alpine-hydride (CH_2Cl_2) gave only moderate 1,7-anti stereoselectivity (anti/syn = 3:1). Results for reductions of 1,5- and 1,6-hydroxy ketone substrates having the *N*-benzyl structural subunit replaced (i.e., **27** → **28**, **29** → **30**, **31** → **32**, **52** → **53**, **54a** → **55a**, **54b** → **55b**, **54c** → **55c**, and **56** → **57**) clearly indicate that the stereoelectronic character of this subunit plays a critical role in the attainment of high anti asymmetric induction. Thus, while we obtained exceptionally high 1,6-anti stereoselectivity in the reduction of the *N*-mesitylmethyl substrate, **54c**, to 1,6-diols **55c** (anti/syn = 22:1) with *R*-alpine-hydride at −78 °C in CH_2Cl_2, the *N*-methyl substrate, **54b**, gave a relatively modest anti/syn ratio of 3:1. The diminished anti/syn ratio of 4:1 in the *R*-alpine-hydride reduction of methoxy amino ketone **50** to **51** also indicates the importance of the free hydroxyl group for attaining high 1,6-anti stereoselectivity. To rationalize the high remote anti stereocontrol in such acyclic systems, we discuss a chelation-controlled mechanism, involving external hydride addition to a bicyclic metal complex with a coordinated ketone carbonyl (e.g., **33**) vs internal hydride addition to a monocyclic metal complex with an uncoordinated ketone carbonyl (e.g., **58**).

In dealing with conformationally unconstrained, acyclic organic compounds, the control of stereogenic centers at remote positions of the chain, that is, at a distance of four or more atom centers, remains a challenging task.[1] Only during the past 10 years has this difficult problem in asymmetric synthesis succumbed to a stream of notable successes. The types of substrates used in successful transformations have varied greatly, but the most remarkable cases are those involving substrates devoid of any conformationally rigidifying structural features, such as a cyclic array or an alkene group, to serve as a facilitator for the transfer of asymmetry (the "stereocommunication" event[1]). Indeed, various examples of high 1,4,[1,2] 1,5,[2o,r,3] 1,6,[4] and 1,7 to 1,14[5] remote asymmetric induction in "strictly acyclic systems" have now appeared in the literature, including our own preliminary results concerning 1,5 and 1,6 diastereocon-

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† This paper is dedicated to Prof. Kurt Mislow on the occasion of his 75th birthday.

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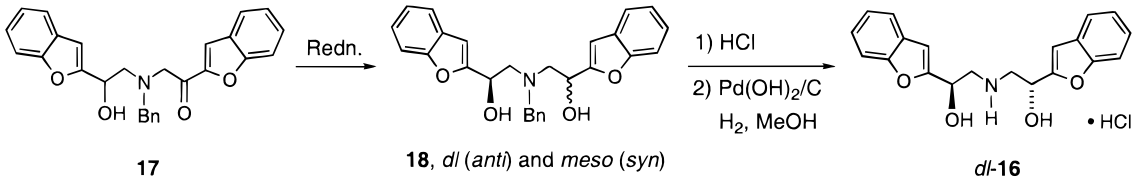
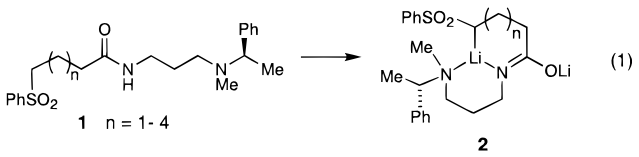
Scheme 1



17 **18**, *dl* (*anti*) and *meso* (*syn*) *dl*-**16**

trol in the addition of hydride to hydroxy amino ketones.[6] It is particularly encouraging for future progress in this field that these positive results have been associated with diverse synthetic transformations, such as aldol condensations,[3b] 1,4 conjugate additions,[2b] alkylations,[2a] direct additions to aldehydes and ketones,[2h,s,4a,6] molecular rearrangements,[2d] and free radical reactions.[3c] A striking recent development is the 1,13/1,14 stereocontrol in the aldol condensation of benzaldehyde with chiral acyclic sulfones to produce only two of four possible diastereomers.[5a,b] Other exciting examples include the highly selective 1,7 asymmetric induction in tin(IV) bromide promoted condensations of aldehydes with 6-hydroxyallylstannanes (syn/anti = 95:5),[5c] the 1,6 induction in tin(IV) bromide promoted reactions between aldehydes and 6-hydroxy-5-methyl-hex-2-enyl(tributyl)stannanes (anti/syn = 93:7),[4b] the 1,5 asymmetric induction in aldol condensations of methyl ketones (anti/syn = 95:5),[3b] and the 1,4 induction in the alkylation of *N*-acylated pseudoephedrines (99% de).[2a] In the context of remote asymmetric induction, there are several remarkable examples of stereocommunication over four or more atom centers in systems with a cyclic array (e.g., cyclic acetal, oxazoline, cyclic boronate), which could well supply a certain measure of conformational constraint. For these types of substrates, which are not "strictly acyclic", high 1,4,[7] 1,5,[8] 1,6,[9] and 1,7[10] asymmetric inductions have been realized.

A common feature present in many of the examples of high remote diastereocontrol seems to be interaction between a prostereogenic center and a remote stereogenic center by means of a highly organized intermediate species, especially one involving formation of a *transient cyclic metal complex that can bring the prostereogenic center and the remote stereocenter into reasonable proximity*. This is illustrated nicely by the work of Magnus and co-workers, where reacting chiral amino sulfone amides **1** are presumably disposed as bicyclic metal chelates **2**, bringing the stereogenic element into the vicinity of the reacting carbanion center to achieve 1,13 asymmetric induction in alkylation with benzaldehyde (eq 1, $n = 4$).[5a,b] Besides this type of chelation control, remote acyclic diastereocontrol has also been effected well with π-allyltricarbonyl iron complexes[8g] and arene tricarbonyl chromium complexes.[8l] Examples of effective 1,4 and 1,5 asymmetric induction in the absence of putative chelation control have also appeared in the literature, such as in alkylation of pseudoephedrines,[2a] in stereoselective addition to alkoxy acetals,[2f] and in C-alkylation of, or 1,4-addition to, Evans-type oxazolidinones[7i,8c] or Oppolzer-type camphorsultams.[7b,8m]



(1)

Several examples of high remote diastereocontrol in the addition of nucleophiles to ketones have been reported.[2h,s,4a,6,7a,8n,9d,10a–c] For example, Akhoon and Myles achieved high (>99:1) 1,4 asymmetric induction in the diastereoselective additions of Grignard reagents to chiral α-keto acetals **3** (eq 2),[7a] wherein a bicyclic magnesium chelate, **6**, is believed to be the reactive species that allows for asymmetric induction in alcohol formation. Meyers and co-workers[9d] developed an interesting case of 1,6 remote asymmetric induction in the preparation of chiral phthalides by using chiral oxazolines, in which treatment of **7** with Grignard reagents gave moderate to high (maximum of 90:10) diastereose-

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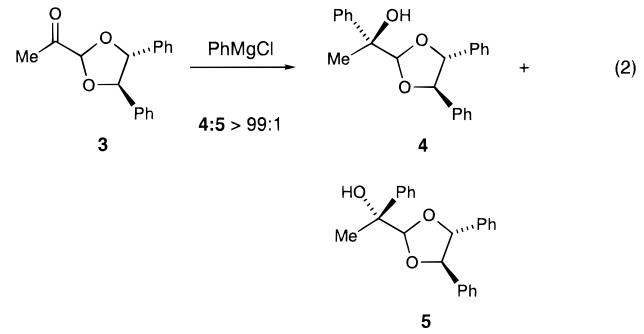
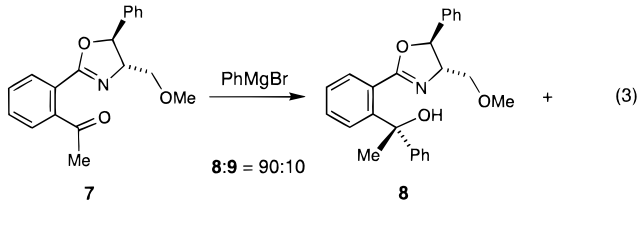
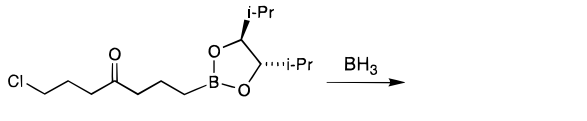
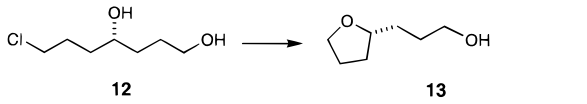
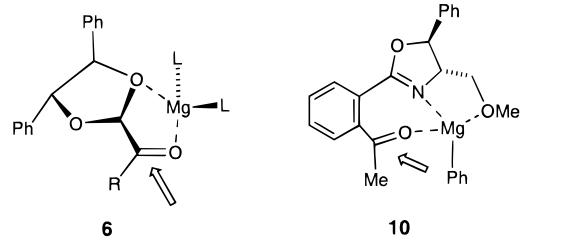
lective addition to the ketone (eq 3), and proposed a chelation-control model, **10**, that takes advantage of the conformational rigidity imparted by the oxazoline ring. Molander and Bobbitt[10a] achieved excellent 1,7 asymmetric induction in the reduction of chiral keto boronates in the preparation of enantiomerically enriched (93% ee) secondary alcohols bearing alkyl substituents that have little steric or electronic differentiation (eq 4) and suggested a six-membered-ring transition state, **14**, involving chelation of the ketone carbonyl to the boron center.

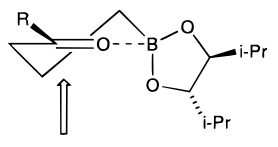








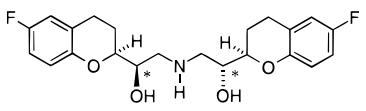




We have been interested in the addition of hydride to acyclic 1,n-hydroxy ketones since our discovery of high 1,5 and 1,6 asymmetric induction with anti selectivity (e.g., Scheme 1).[6] We suggested that these transformations might occur via a chelation-control mechanism entailing formation of a bicyclic metal chelate. The reacting substrate here contains no conformational constraint, such as imparted by a cyclic acetal, oxazoline, or cyclic boronate, to assist in the transfer of asymmetry; i.e., the substrate is *strictly acyclic*. Our exciting preliminary findings of high asymmetric induction by a single remote stereogenic center in these strictly acyclic substrates have sparked further studies to define the scope and limitations of the process, in terms of substrate structure, reducing agents, solvents, and reaction temperature. In this paper, we disclose the results of this research along with a mechanistic discussion of transition-state metal chelate models to help rationalize the observed stereochemical outcomes.

Results and Discussion

Our entry into the field of remote acyclic stereocontrol was instigated by a project on analogues of the cardiovascular drug nebivolol (**15**).[11] There are a total of 10 possible stereoisomers for this structure (4 dl and 2 meso forms), and the investigational drug substance is a racemic mixture of the (S,R,R,R) and (R,S,S,S) enantiomers, with the latter exhibiting potent, selective β_1-adrenergic blocking activity.[11] In the search for nebivolol analogues, we wanted to limit the number of possible stereoisomers by eradicating the stereogenic centers in the chromane units. Therefore, we set out to synthesize bis-benzofuran analogue **16** (Scheme 1), which is merely comprised of one dl pair and one meso form. As a straightforward synthetic approach, we hoped to identify suitable conditions for controlling the stereochemistry of the reduction of **17**[12] to obtain the desired dl form of **18**. In 1988, when our work commenced, there was little precedent in the literature to guide us in successfully effecting such an *acyclic* 1,5 reduction. In fact, examples of high asymmetric induction by a singular, remote stereogenic center bearing a hydroxyl group in nucleophilic addition to acyclic hydroxy ketones are uncommon,[2m−p,s] particularly with hydride as the nucleophile.[1,2s,13] In a report by Maier et al.,[14] the reduction of δ-hydroxy ketone **19** with $LiAlH_4$ in Et_2O provided the corresponding 1,5 diols with a anti/syn ratio of just 55:45. However, we thought at the outset that the diastereoselectivity for the reduction of **17** with $LiAlH_4$ might be better because of the amine nitrogen atom in the chain, which could conceivably cooperate with the hydroxyl to direct hydride delivery.



Racemic mixture of (*S,R,R,R*) and (*R,S,S,S*) enantiomers

(*S,R,R,R*) is a potent, selective β_1-adrenergic blocker

Nebivolol (**15**)

Reductions of 1,5-Hydroxy Ketones. Reduction of **17**[12] with $LiAlH_4$ in ether resulted in a negligible degree of asymmetric induction (dl/meso **18** = 1:1), and the bulkier $LiAlH(O\text{-}t\text{-}Bu)_3$ also showed no selectivity (Table 1, entries 7 and 8). The dl and meso products were isolated as a mixture, and the anti/syn ratios were determined by ^1H NMR in $CDCl_3$ (at 300 or 400 MHz) on account of the two diastereotopic benzyl protons of the

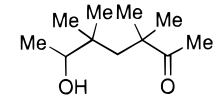
Table 1. Reduction of 17 to *dl*-(*anti*)- and *meso*-(*syn*)-18

entry	reagent	solvent	dl/meso
1[a]	$Pd(OH)_2$, H_2	MeOH	1:1[b]
2[c]	$NaBH_4$	MeOH	1:1[d]
3[c]	$NaBH_4/CeCl_3$	MeOH	1:1[d]
4	$NaBH(OAc)_3$	THF	1:1[d]
5	Red-Al[e]	CH_2Cl_2	1:1[f]
6	K-selectride[g]	THF	1:1[f]
7	$LiAlH_4$	Et_2O	1:1[d]
8	$LiAlH(O\text{-}t\text{-}Bu)_3$	THF	1:1[f]
9	$(i\text{-}Bu)_2AlH$[h]	CH_2Cl_2	1:1[d]
10	BH_3·THF	THF	1:1[f]
11	BH_3·pyridine	THF	1:1[f]
12	BH_3·Me_2S	THF	1:1[f]
13	**22**[i]	THF	1:1[f]
14	**21**[i]	THF	2:1[d]
15	$Zn(BH_4)_2$	Et_2O	2.5:1[d]
16[j]	**20**[i]	THF	7:1[d]

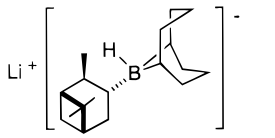
[a] At 23 °C for 2 h. [b] *N*-debenzylated products, *dl*- and *meso*-**16**, were obtained; the ratio was determined by ^{13}C NMR. [c] At 5 °C for 2 h. [d] The ratio was determined by ^1H NMR. [e] 65 wt % in toluene. [f] Ratio was estimated by TLC. [g] 1.0 M in THF. [h] 1.0 M in toluene. [i] 0.5 M in THF. [j] Started at −98 °C, then slowly warmed to 23 °C over 18 h (adapted from ref 6a.).

anti isomer, which fortuitously appeared as a pair of doublets (so-called "AB quartet") at δ 3.75 and 3.92 (J = 13.7 Hz), while the two enantiotopic benzyl protons in the syn isomer appeared as a sharp singlet at δ 3.79.

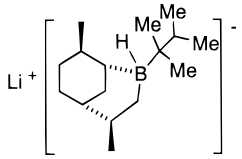
In an attempt to achieve an excess of anti over syn diols, we explored 14 additional reducing agents (Table 1). The reactions were conducted at −78 °C, then slowly warmed to 23 °C over 18 h (unless otherwise noted). Most of the reactions delivered virtually no diastereoselection (Table 1). However, with *R*-alpine-hydride[15] (**20**; entry 16) we obtained a useful level of anti diastereoselectivity (dl/meso = 7:1) and were able to isolate analytically pure *dl*-**18** in 34% yield. With the alpine-hydride reducing agent, there is an issue of enantioselectivity in the dl diol because of the chiral reagent's high enantiomeric enrichment. Interestingly, however, this dl product had virtually no enantiomeric enrichment, as assessed by 400-MHz ^1H NMR with (*S*)-(+)-2,2,2-trifluoromethyl-1-(9-anthryl)-ethanol (in $CDCl_3$).[16] With $Zn(BH_4)_2$ in ether (entry 15) and lithium thexyl-(*R*)-limonylborohydride (**21**) in THF (entry 14), modest 1,5 asymmetric induction was observed, but none of the reducing agents produced an excess of meso (syn) over dl (anti) diols. NB-Enantride (**22**), which is structurally related to *S*-alpine-hydride (the enantiomer of **20**) and reported to be more effective for the asymmetric reduction of ketones,[17] was surprisingly ineffective (entry 13).



19



(*R*)-20



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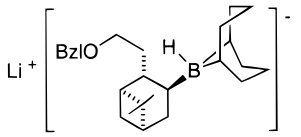


22

Our results with **17** suggested the intermediacy of a metal chelate with external hydride delivery, as discussed by Baker et al.[18] for the 1,3 asymmetric reduction of a γ-hydroxy ketone with $LiEt_3BH$. Thus, we reasoned that the stereoselectivity might be enhanced by changing conditions to favor a more rigid chelate species, for example, by using a less coordinating solvent and by lowering the reaction temperature. In follow-up studies we used **23**,[19] a simpler, more readily available δ-hydroxy ketone, as the substrate (Scheme 2; Table 2). The reduced products were isolated as a mixture, and the anti/syn ratios were determined by ^1H NMR in $CDCl_3$. The diastereotopic benzyl protons of the anti isomer again appeared as a pair of doublets (δ 3.70 and 3.99, J = 13.5 Hz), while the two protons in the syn isomer appeared as a singlet (δ 3.83).

The following observations from a series of experiments with **23** are noteworthy (Table 2). (1) When **23** was reduced with *R*-alpine-hydride under the conditions employed for **17**, similar diastereoselectivity was achieved (entry 1). (2) The 1,5 asymmetric induction is independent of reagent chirality, as the R and S forms of **20** furnished the same ratio of dl/meso **24** (cf. entries 1 and 2). (3) The anti/syn selectivity increased with decreasing temperature (entries 3−5). (4) The structure of the hydride anion plays an important role, with a bulkier hydride anion leading to a higher ratio of dl/meso **24** (entries 7−9; also see Table 1). (5) Replacement of THF as the solvent by noncoordinating CH_2Cl_2 (the solvent composition with the THF from the reducing agent was ca. 90% CH_2Cl_2) significantly enhances 1,5 selectivity (cf. entries 3 and 7, 11 and 12).

The best selectivity of anti vs syn diols in the reduction of **23** was realized with $Zn(BH_4)_2$ in CH_2Cl_2 at −78 °C (anti/syn = 13:1, entry 12; the solvent composition with the Et_2O from the reducing agent was ca. 85% CH_2Cl_2). For most of the entries in Table 2, only modest yields were realized along with recovered starting material, and the use of excess reducing agent and/or an extended reaction time at −78 °C did not significantly increase the chemical conversion. This problem might be connected with the high proportion of cyclic hemiketal form, relative to the reducible acyclic keto form, in this substrate (**23**).

We investigated the issue of enantioselectivity in the dl diol from **23**. Reduction of **23** with *R*-alpine-hydride

(11) (a) Van Lommen, G.; De Bruyn, M.; Schroven, M. *J. Pharm. Belg.* **1990**, *45*, 355. (b) Van Neuten, L.; Dupont, A. G.; Vertommen, C.; Goyvaerts, H.; Robertson, J. *J. Hum. Hypertens.* **1997**, *11*, 139−144. (c) Van Bortel, L. M. A. B.; De Hoon, J. N. J. M.; Kool, M. J. F.; Wijnen, J. A. G.; Vertommen, C. I. M.; Van Nueten, L. G. M. *Eur. J. Clin. Pharmacol.* **1997**, *51*, 379−384. (d) Stoleru, L.; Wijns, W.; van Eyll, C.; Bouvy, T.; Van Nueten, L.; Pouleur, H. *J. Cardiovasc. Pharmacol.* **1993**, *22*, 183−190. (e) Also, see: Anon. *Drugs Future* **1991**, *16*, 964; **1995**, *20*, 1070; **1998**, *22*, 1169−1170. (f) Nebivolol hydrochloride is marketed in Germany by Menarini Company for the treatment of hypertension under the trade name Nebilet.

(12) We prepared **17** from 2-acetylbenzofuran in four steps using modified published procedures; see Experimental Section.

(13) Greeves, N. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 8, pp 1−24.

(14) Maier, G.; Roth, G.; Schmitt, R. K. *Chem. Ber.* **1985**, *118*, 704−721.

(15) Krishnamurthy, S.; Vogel, F.; Brown, H. C. *J. Org. Chem.* **1977**, *42*, 2534−2536.

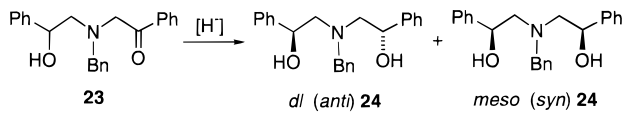
(16) Pirkle, W. H.; Hoover, D. J. *Top. Stereochem.* **1982**, *13*, 263−331.

(17) Midland, M. M.; Kazubski, A. *J. Org. Chem.* **1982**, *47*, 2495−2496.

(18) Baker, R.; Cottrell, I. F.; Ravenscroft, P. D.; Swain, C. J. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2463−2468.

(19) Prepared by a published procedure: Brown, C. L.; Lutz, R. E. *J. Org. Chem.* **1952**, *17*, 1187−1193.

Scheme 2

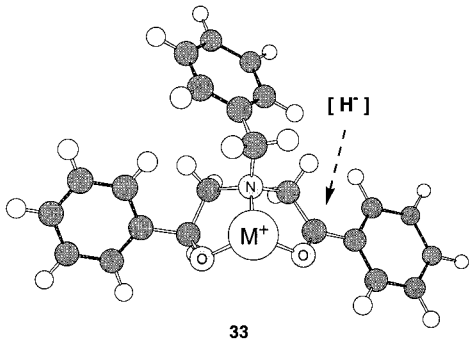


at −98 °C produced *dl*-**24** with no measurable optical rotation (589 nm). More importantly, there was no enantiomeric enrichment as determined by 400-MHz ^{1}H NMR with (*S*)-(+)-2,2,2-trifluoromethyl-1-(9-anthryl)-ethanol,[16] in agreement with the aforementioned result with **17**. As a control, we reduced $PhC(O)CH_2N(Bn)_2$ with *R*-alpine-hydride at −98 °C to the corresponding alcohol and found that it had a mere 10% enantiomeric excess (ee) by the chiral ^{1}H NMR assay.

To determine the impact of the phenyl groups in **23** on the diastereoselectivity, dimethyl 1,5-hydroxy ketone **25** was prepared from commercially available racemic α-(methylaminomethyl)benzyl alcohol and chloroacetone (Scheme 3). Reduction of **25** with *R*-alpine-hydride or with $LiBH_4$ at −78 °C in CH_2Cl_2 went very slowly. Increasing the reaction temperature to 0 °C gave diols **26** in 84% and 78% isolated yield with anti/syn ratios of 7.8:1 and 4:1, respectively, similar to the ratios obtained with the corresponding diphenyl system, **23** (Table 2).

The influence of the amine nitrogen (actually the N−Bn unit) in **23** was then investigated. We replaced the *N*-benzyl moiety with carbon or sulfur groups (Scheme 4). Thus, δ-hydroxy ketone **27**[20] was reduced in THF at −78 °C with *R*-alpine-hydride or $Zn(BH_4)_2$ to give an isomeric mixture of 1,5-diols **28** in a ratio of 1.2:1, as determined by 75-MHz ^{13}C NMR (from the intensities of three pairs of carbon signals: δ 22.04/22.11, 38.71/38.63, and 74.22/74.07) and 300-MHz ^{1}H NMR (from integrated areas for the OH peaks at δ 2.70 and 2.85). Sulfur-containing δ-hydroxy ketone **29** was prepared from partial reduction of the commercially available diketone with $NaBH_4$. Reduction of **29** to **30**[21] with *R*-alpine-hydride in THF at −78 °C also gave poor diastereoselectivity with an anti/syn ratio of 1.3:1 as estimated by ^{13}C NMR [from the peak intensities for δ 41.7 (anti CH_2), 42.2 (syn CH_2); 72.4 (anti CH), 73.2 (syn CH)]. This indicates that divalent sulfur is not effective as a stereodirecting entity in this situation. An oxygen-containing δ-hydroxy ketone was also prepared[22] and subjected to reduction, but no reaction was observed with *R*-alpine-hydride or $Zn(BH_4)_2$ from −78 to 23 °C, probably because of the high proportion of the cyclic hemiketal form in this substance (>95% by ^{13}C NMR). The nearly 1:1 anti/syn ratio for the reductions of **27** and **29** certainly underscores the importance of the amine nitrogen (N-substituted) in **17** and **23** for achieving the high 1,5 asymmetric induction. We then tested the stereochemical effect of the N substituent on 1,5 diastereoselectivity. *N*-methyl δ-hydroxy ketone **31**, prepared in 69% yield from 2-(methylamino)-1-phenylethanol and phenacyl bromide in the presence of *N*,*N*-diisopropylethylamine, was reduced with *R*-alpine-hydride in CH_2Cl_2 at −78 °C to afford **32** with an anti/syn ratio of 2.3:1 as estimated by ^{1}H NMR [from the peak intensities of N−Me at δ 2.41 (syn) and 2.45 (anti)], with the isomer assignment being based on ^{13}C NMR data in analogy with **24**. The loss of high diastereocontrol in the reduction of **31** to **32** clearly indicates that the steric properties of the N substituent can play an important role in achieving high 1,5 diastereoselectivity, with the bulkier benzyl group giving much better anti selectivity.

To rationalize our results for 1,5 diastereoselectivity, we initially proposed a *working model* involving a 5,5-bicyclic chelate structure, such as depicted in **33**, in which the lithium or zinc ion is complexed with the hydroxyl, amine, and ketone groups and endo attack on the bicyclic array by the hydride species leads to the anti 1,5-diols preferentially.[6a] This can account for the effects of solvent, Zn(II), nitrogen replacement, and NB-enantride (**22**). However, since this model does not fit well with our new results for the reduction of **31**, we are inclined to offer another viewpoint, which is presented later in some detail (vide infra).



33
5,5-Bicyclic Chelate Complex

An attempt was then made to achieve an excess of syn over anti diols possibly via internal hydride delivery. Thus, δ-hydroxy ketone **23** was reduced with tetramethylammonium triacetoxyborohydride, a well-known stereoselective reducing agent for β-hydroxy ketones by hydroxyl-directed intramolecular hydride delivery,[23] at 23 °C in MeCN−HOAc (1:1) to afford diols **24** in 75% yield with an anti/syn ratio of 1:1.5 (Table 2; entry 13). Although the syn vs anti selectivity is low, this is a rare example in which we obtained more syn than anti diol, possibly on account of hydroxyl-directed hydride delivery.

Reductions of 1,6- and 1,7-Hydroxy Ketones. The unusually high 1,5 asymmetric induction obtained with **17** and **23** encouraged us to prospect for high 1,6 and 1,7 acyclic diastereoselection in related reductions of hydroxy ketones, presumably via 5,6-, 6,6-, and 5,7-bicyclic chelation control. 1,6-Hydroxy ketone **34**, readily prepared from 2-(benzylamino)-1-phenylethanol and 3-chloropropiophenone in the presence of *N*,*N*-diisopropylethylamine, was reduced to 1,6-diols **35** by using various reducing reagents (Scheme 5; Table 3). In general, the reductions of **34** proceeded much more rapidly in CH_2Cl_2 at −78 °C and in higher yields than did the reductions of the corresponding 1,5-hydroxy ketone, **23**. The best selectivity for anti vs syn diols was obtained in the reduction of **34** with *R*-alpine-hydride (anti/syn = 12:1, entry 1). Reduction with $Zn(BH_4)_2$ or with lithium thexyl-

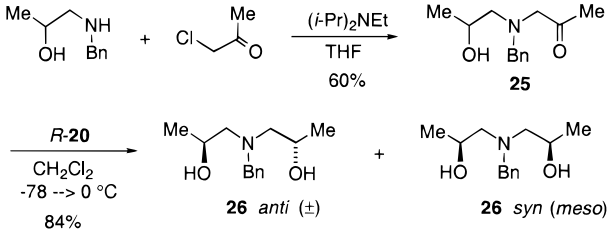
(20) Huang, R. L.; Williams, P. J. *J. Chem. Soc.* **1958**, 2637−2640.
(21) Valle, G.; Buso, M.; De Lucchi, O. *Z. Kristallogr.* **1987**, *181*, 95−98.
(22) Prepared from α-diazoacetophenone and 1-phenyl-1,2-ethanediol in the presence of boron trifluoride etherate (Mayfield, R. J.; Yates, P. *Org. Prep. Proced. Int.* **1971**, *3*, 201−204). The isolated product existed almost entirely in the cyclic hemiketal form (based on ^{13}C NMR data) with a ca. 1:1 ratio of diastereomers (based on ^{1}H NMR data).
(23) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560−3578.

Table 2. Reduction of 23 to *dl*-(*anti*)- and *meso*-(*syn*)-24[a]

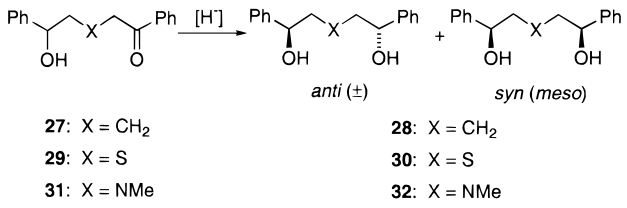
entry	reagent	temp (°C)	time (h)	solvent	dl/meso	yield (%)
1	*R*-alpine-hydride	−98 → 0	16	THF	6:1	57
2	*S*-alpine-hydride	−98 → 0	16	THF	6:1	62
3	*R*-alpine-hydride	−78	5.5	THF	6:1	17
4	*R*-alpine-hydride	−40	5	THF	4:1	37
5	*R*-alpine-hydride	0	2	THF	3:1	62
6	*R*-alpine-hydride	−40	5	CH_2Cl_2[b]	6:1	40
7	*R*-alpine-hydride	−78	26	CH_2Cl_2[b]	10:1	40
8	$LiEt_3BH$[c]	−78	26	CH_2Cl_2[b]	8:1	55
9	$LiBH_4$	−78	26	CH_2Cl_2	5:1	
10	$Zn(BH_4)_2$	0	2	THF[d]	2:1	
11	$Zn(BH_4)_2$	−40	5	THF[d]	4:1	
12	$Zn(BH_4)_2$	−78	26	CH_2Cl_2[d]	13:1	47
13	$Me_4NB(OAc)_3H$	25	2	MeCN−HOAc	1:1.5	75

[a] Ratios were determined by ^{1}H NMR; yields are for mixtures isolated from preparative TLC. [b] Reaction contains 10−15% THF from the reducing agent. [c] 1.0 M in THF. [d] Reaction contains 10−15% Et_2O from the reducing agent.

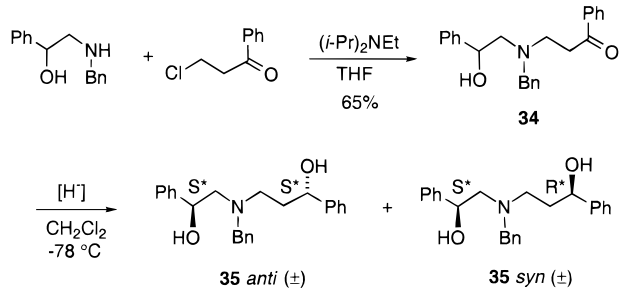
Scheme 3



Scheme 4



Scheme 5



(*R*)-limonylborohydride (**21**) also gave significant selectivity (anti/syn = 7.5:1 and 8:1, respectively, entries 2 and 4). It is noteworthy that no reduction was observed with NB-enantride (**22**) under the reaction conditions (entry 5). Reductions with $LiBH_4$ and bulky L-selectride gave the same modest selectivity (anti/syn = 2:1, entries 3 and 6), while K-selectride gave no selectivity at all (entry 7). Attempts to carry out the reaction with one mol equiv of *R*-alpine-hydride gave a complete reaction with significantly reduced selectivity (anti/syn = 3.2:1, entry 8), while reduction with one mol equiv of $Zn(BH_4)_2$ gave an incomplete reaction accompanied by diminished selectivity (anti/syn = 5.9:1, entry 9). In any event, such high diastereoselectivity for a 1,6 reduction in a strictly acyclic substrate, anti/syn = 12:1 (entry 1), is quite remarkable!

The diastereomeric ratios for **35** were nicely quantitated by HPLC and 400-MHz ^{1}H NMR. There were two different pairs of doublets for the aliphatic benzylic protons ("AB quartets") centered at δ 3.74 (anti) and δ 3.72 (syn), with no overlap of the signals because of a large chemical shift difference between the pair of doublets for the anti isomer [$\Delta\delta$(anti) = ca. 0.40 ppm] and a small difference between the pair of doublets for the syn isomer [$\Delta\delta$(syn) = ca. 0.11 ppm]. Since unambiguous assignment of the benzyl resonances required the synthesis of an authentic sample of *syn*- or *anti*-**35**, commercially available (*R*)-(+)-3-chloro-1-phenyl-1-propanol was reacted with benzylamine in the presence of KI and K_2CO_3 to give *N*-benzylamino alcohol **36** (Scheme 6). Attempts to alkylate **36** with (*R*)-2-chloro-1-phenylethanol resulted in very poor yields (<10%) of the desired 1,6-diols due to decomposition of the chlorohydrin under the reaction conditions (method A in Scheme 6). A neat reaction between **36** and (*R*)-styrene oxide at 120 °C afforded in 42% isolated yield of the anti diols **35** (R,R) (method B, Scheme 6), the ^{1}H NMR spectrum ($CDCl_3$) of which was identical to that of the major product obtained from the reduction of **34**, confirming the assignment. A better yield for the preparation of authentic **35** was obtained by using method C (Scheme 6). Thus, (*R*)-2-chloro-1-phenylethanol was reacted with benzylamine at 180 °C to give **37** in 80% yield, which was alkylated with (*S*)-3-chloro-1-phenyl-1-propanol to give the syn diols **35** (R,S) in 89% isolated yield. The ^{1}H NMR spectrum ($CDCl_3$) for **35** (R,S) was identical to that of the minor product obtained from the reduction of **34**.

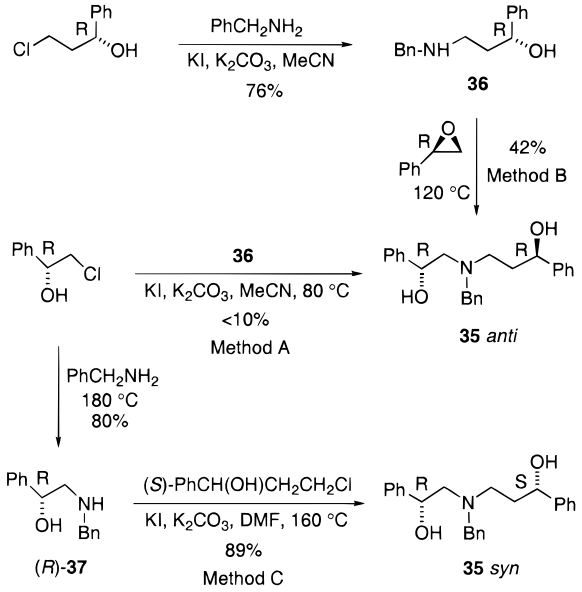
A "reversed" 1,6-hydroxy ketone **38** (R enantiomer only) was prepared from **36** and 2-bromoacetophenone and reduced with *R*-alpine-hydride or $Zn(BH_4)_2$ in CH_2Cl_2 at −78 °C to give 1,6-diols **35** in 75% and 72% yield, respectively (Scheme 7). The anti/syn ratios of 5:1 and 3:1, respectively, for this 1,6 acyclic system are signifi-

Table 3. Reduction of 34 to anti and syn diols 35[a]

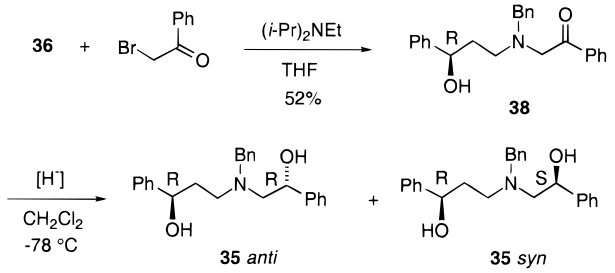
entry	reagent	equiv	time (h)	anti/syn[b]	yield (%)
1	*R*-alpine-hydride[c]	2.1	3	12:1[d]	83
2	$Zn(BH_4)_2$[e]	2.1	3	7.5:1[d]	83
3	$LiBH_4$	2.1	18	2:1[d]	77
4	**21**[c,f]	2.5	3	8:1	74
5	**22**[c,f]	2.5	3		no rxn
6	L-selectride[c,g]	2.1	1	2:1	77
7	K-selectride[c,g]	2.1	1	1:1	69
8	*R*-alpine-hydride[c]	1.0	3	3.2:1	79
9	$Zn(BH_4)_2$[e]	1.0	23	5.9:1	37[h]

[a] Reactions were conducted at −78 °C in CH_2Cl_2. [b] Ratio determined by HPLC except where noted. [c] Reaction contains 10−15% THF from the reducing agent. [d] Ratio determined by ^{1}H NMR. [e] Reaction contains 10−15% Et_2O from the reducing agent. [f] 0.5 M in THF. [g] 1.0 M in THF. [h] Reaction did not go to completion.

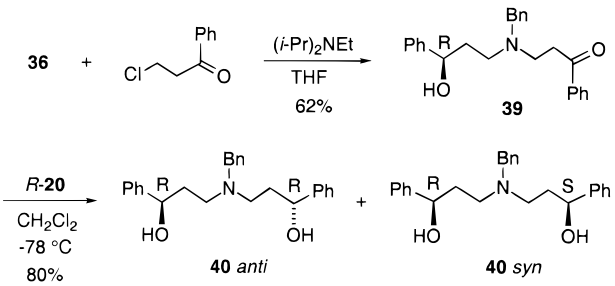
Scheme 6



Scheme 7



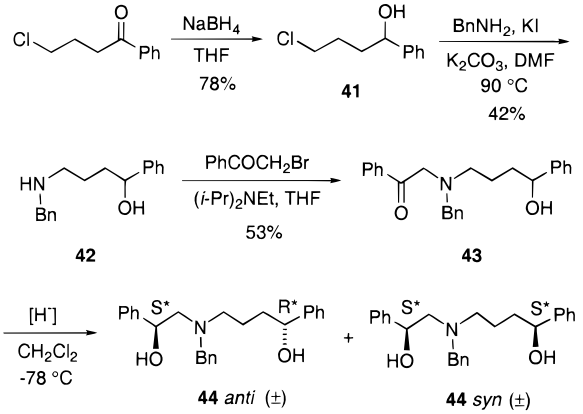
Scheme 8



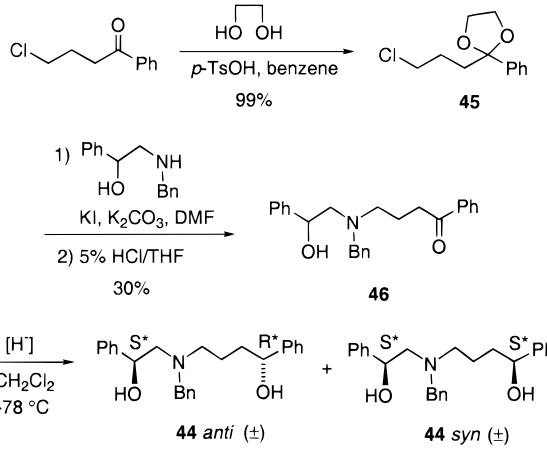
cant, albeit not remarkable. As far as 1,6 acyclic stereocontrol is concerned, a 5:1 ratio can be viewed as very meaningful. By comparison of this result with the reduction of **34**, it seems that the degree of 1,6 diastereoselectivity is dependent on the distance between the hydroxyl and amine groups, with *the β-hydroxy amine arrangement being preferred over the γ-hydroxy amine arrangement*.

Given the favorable results with the 1,6 system, we decided to pursue the related 1,7-hydroxy ketone cases. Hydroxy ketone **39** (R enantiomer) was prepared from **36** and reduced with *R*-alpine-hydride in CH_2Cl_2 at −78 °C to give 1,7-diols **40** in 80% yield (Scheme 8). In this instance, the anti/syn (dl/meso) ratio was a mere 1.2:1. The dl and meso products were assigned by ^{1}H NMR, as the two diastereotopic benzyl protons of the anti (dl) isomer appeared as a pair of doublets at δ 3.44 and 3.79 (J = 13.7 Hz) and the two enantiotopic benzyl protons in the syn (meso) isomer appeared as a singlet at δ 3.65. 1,7-Hydroxy ketone **43** containing a δ-hydroxy amine

Scheme 9



Scheme 10

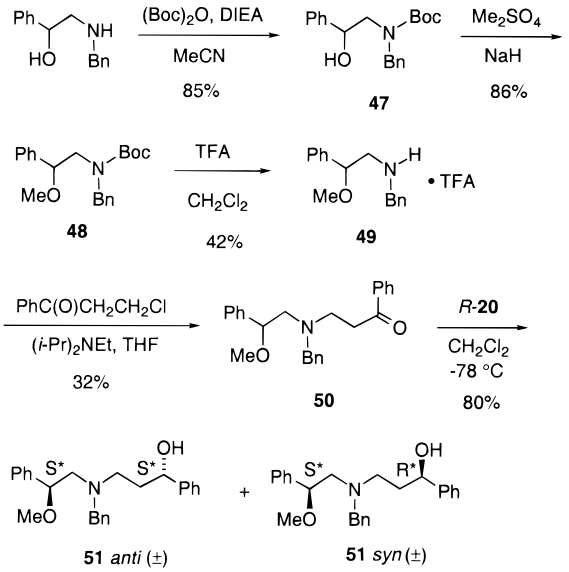


subunit was then prepared (Scheme 9) and reduced with *R*-alpine-hydride in CH_2Cl_2 at −78 °C to give 1,7-diols **44** in 88% yield. No asymmetric induction was observed here, with the anti/syn ratio being 1:1.

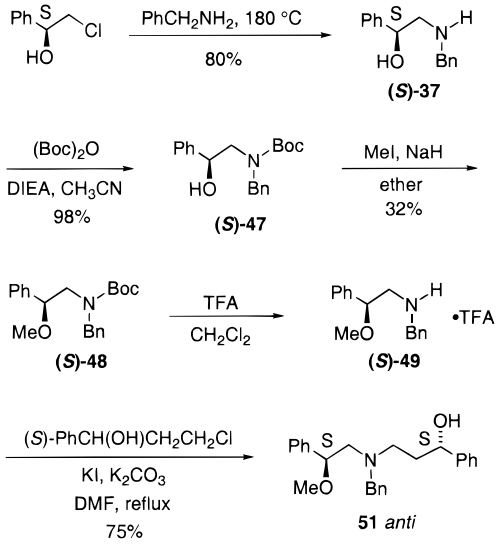
1,7-Hydroxy ketone **46** was thought to be a more promising substrate because of its β-hydroxy amino system. Since an attempt to prepare **46** via N-alkylation of 2-(benzylamino)-1-phenylethanol with 4-chlorobutyrophenone in the presence of *N*,*N*-diisopropylethylamine or KI/K_2CO_3 failed, the ketone was protected with ethylene glycol to afford **45** (Scheme 10). N-Alkylation of 2-(benzylamino)-1-phenyl-ethanol with **45** in the presence of KI/K_2CO_3 was followed by cleavage of the 1,3-dioxolane to give **46**. Reduction of **46** in CH_2Cl_2 at −78 °C with *R*-alpine-hydride or $Zn(BH_4)_2$ afforded 1,7-diols **44** in 84% and 63% yield, with anti/syn ratios of 3:1 and 1:2, respectively. The outcome with $Zn(BH_4)_2$ represents an unusual case favoring the syn isomer, but the degree of 1,7 stereocontrol in either direction is not particularly impressive. The isomer assignment for **44** is based on ^{1}H NMR data, in analogy with **35**. Thus, mixture **44** displayed two different pairs of doublets for the aliphatic benzylic protons ("AB quartets") centered at δ 3.72 (anti) and δ 3.70 (syn), with no overlap of the signals because of a large chemical shift difference between the pair of doublets for the anti isomer [$\Delta\delta$(anti) = ca. 0.45 ppm] and a small difference between the pair of doublets for the syn isomer [$\Delta\delta$(syn) = ca. 0.30 ppm].

Despite our modest results with the 1,7-hydroxy ketones, we can take solace from the impressive results with a 1,6-hydroxy ketone. Indeed, we have a very

Scheme 11



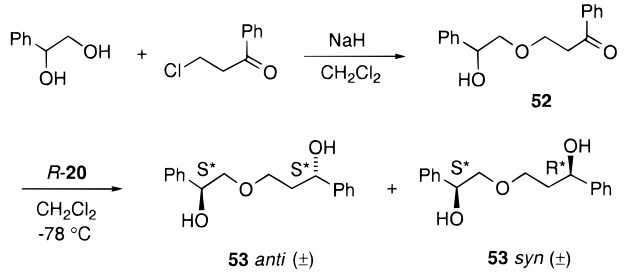
Scheme 12



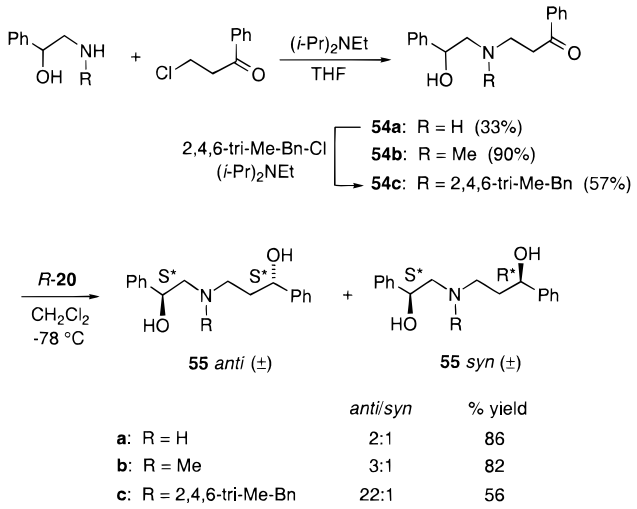
interesting example of high 1,6 asymmetric induction in an acyclic system, involving hydride reduction of a prochiral ketone (sp^2 center) six atoms removed from an existing stereocenter bearing a hydroxyl group (**34** → **35**, Scheme 5). The hydroxyl and intrachain nitrogen in **34** appear to participate in a metal chelate that serves to direct hydride addition. To test for the importance of a free hydroxyl, we prepared methoxy amino ketone **50**, via Boc derivative **47**, and subjected it to reduction with *R*-alpine-hydride at −78 °C in CH_2Cl_2 (Scheme 11). Methoxy amino alcohols **51** were isolated in 80% yield as a 4:1 mixture of the anti and syn forms, and the isomer assignment was established by the synthesis of an authentic sample of *anti*-**51** (Scheme 12). Clearly, methylation of the hydroxyl group in **34** caused a partial loss of stereoselectivity (anti/syn = 12:1 for the parent reaction, **34** → **35**). If one considers a 5,6 bicyclic chelate model as being crucial to the 1,6 diastereoselectivity, then the methoxy group must be reasonably effective as a ligand for lithium in this reaction, but not as effective as a hydroxyl.

We then proceeded to assess the influence of the intrachain nitrogen in **34** on the 1,6 diastereoselectivity.

Scheme 13



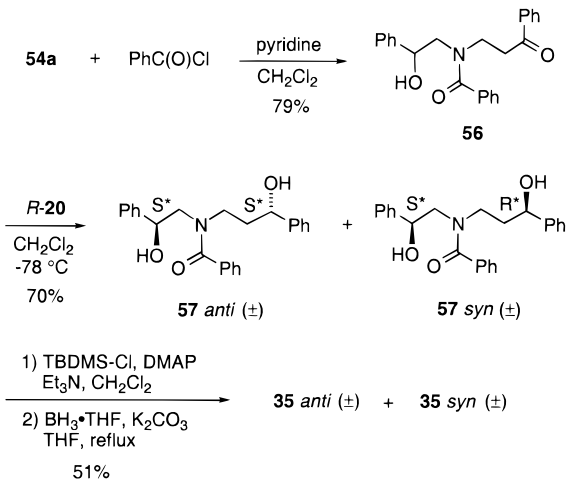
Scheme 14



	anti/*syn*	% yield
a: R = H	2:1	86
b: R = Me	3:1	82
c: R = 2,4,6-tri-Me-Bn	22:1	56

In the 1,5 system, replacement of the amine nitrogen (actually the N−Bn group) in 1,5-hydroxy ketone **23** with carbon or sulfur groups resulted in poor diastereoselectivity (Scheme 4). Unfortunately, the corresponding oxygen-containing 1,5-hydroxy ketone[22] did not reduce, probably because of the high proportion of the cyclic hemiketal form (six-membered ring) in the substrate (confirmed by ^{13}C NMR). Thus, the oxygen-containing 1,6-hydroxy ketone **52** was synthesized from 1-phenyl-1,2-ethanediol and 3-chloropropiophenone (Scheme 13), and ^{13}C NMR showed that it did not exist in the cyclic hemiketal form. Reduction of **52** with *R*-alpine-hydride proceeded to completion in 18 h at −78 °C to furnish a 1:1 mixture of syn and anti diols **53**, clearly demonstrating an abolition of anti stereoselectivity on replacement of N−Bn with O. We sought to evaluate the importance of the nitrogen substituent on the 1,6 diastereoselectivity. The benzyl group was removed from **34** to give N−H analogue **54a**, which was reduced with *R*-alpine-hydride in CH_2Cl_2 at −78 °C to yield 1,6-diols **55a** with just a 2:1 anti/syn ratio, as estimated by ^{13}C NMR (Scheme 14). The benzyl group in **34** was then replaced with a small methyl group, as in **54b**. Reduction of **54b** with *R*-alpine-hydride in CH_2Cl_2 at −78 °C yielded 1,6-diols **55b** with a relatively modest anti/syn ratio of 3:1 (estimated by ^{13}C NMR). The isomer assignments for **55a** and **55b** were based on ^{13}C NMR data in analogy with **35**. High 1,6 diastereoselectivity was also lost when the benzyl group in **34** was replaced by an electron-withdrawing acyl group (Scheme 15). Intermediate **54a** was *N*-acylated with benzoyl chloride in the presence of pyridine to give **56**, reduction of which with *R*-alpine-hydride at −78 °C led to a mixture of diols **57**. Since the ^1H NMR spectrum of **57** showed broad peaks, probably because of the presence of slowly interconverting rotamers from the amide

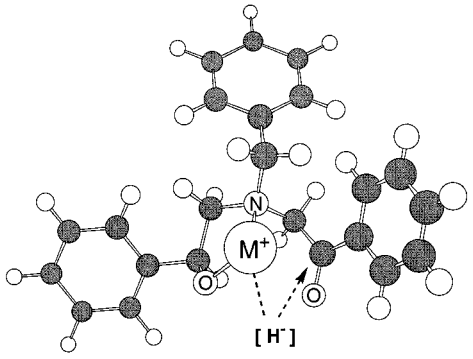
Scheme 15



group, the ratio of the two diastereomers was difficult to determine. Thus, the bis-silyl ether of **57** was prepared, the amide group was reduced to the corresponding amine with borane−THF, and the silyl groups were removed to give a mixture of diols **35**, which had an anti/syn ratio of only 1.5:1, as measured by ^{1}H NMR (Scheme 15). The results for replacement of the *N*-benzyl structural subunit in these 1,6-hydroxy ketones clearly indicate that the stereoelectronic character of this subunit plays a key role in the attainment of high 1,6 asymmetric induction. To improve the anti stereoselectivity, we reasoned that a bulkier benzyl group on the nitrogen might be advantageous. Consequently, **54a** was N-alkylated with 2,4,6-trimethylbenzyl chloride in the presence of *N*,*N*-diisopropylethylamine in THF−DMF at 60 °C to afford **54c**, which was reduced with *R*-alpine-hydride at −78 °C in CH_2Cl_2 to produce 1,6-diols **55c** in 56% yield with an exceptional anti/syn ratio of 22:1 (determined by 600-MHz ^{1}H NMR in analogy with **35**)!

Mechanistic Considerations. To rationalize our results for the 1,5-anti diastereoselectivity, we originally proposed a 5,5-bicyclic chelate structure, such as model **33**, in which the lithium or zinc ion is complexed with the hydroxyl, amine, and ketone groups in **17** or **23** to achieve high asymmetric induction.[6a] In the conformationally rigid array, endo attack by the hydride species would be sterically unfavorable, so that attack is preferred from the less hindered exo side, leading to the anti 1,5-diols preferentially. When the reaction is performed in THF, this good donor solvent presumably competes with the heteroatom groups in **17** or **23** for complexation of the metal center and thereby counteracts chelate formation. On the other hand, the relatively noncoordinating CH_2Cl_2 and low reaction temperature enhance chelate participation. With this external hydride delivery model, a bulkier hydride anion should give a higher ratio of anti 1,5-diols, as generally observed. The absence of good anti stereoselectivity with NB-enantride (**22**) may be associated with the presence of a coordinating ether group in the reagent itself, which could inhibit formation of the necessary chelate complex or contribute to a reorganization of the reactive complex. The results with nitrogen atom replacement are consistent with this scenario in that N−Bn → CH_2 (**27**) and N−Bn → S (**29**) gave very little selectivity.

However, given the additional data with the reduction of the *N*-methyl analogue **31**, we are compelled to offer another viewpoint. Although there was little change in anti stereoselectivity on replacing the phenyl groups in **23** with methyl groups (viz. **25**), replacing the benzyl group on the nitrogen in **23** with a methyl group (viz. **31**) resulted in a large loss in 1,5 diastereoselectivity. We suggest that a five-membered-ring complex forms with the ketone not involved in chelation and that reduction occurs via *internal hydride delivery*,[23] as shown in model **58**. Here, the steric interaction between the N−Bn and ketone carbonyl groups would force the ketone to adopt a suitable orientation to provide the anti diol. The difference between **23** and **31** could be attributed to the *N*-methyl group having much less influence on the orientation of the ketone than the larger N−Bn group. Lower temperatures may also enhance the control of the orientation of the ketone carbonyl, as noted by the effect of temperature on the stereoselectivity of the reaction of **23**. The results with amine replacement, N−Bn → CH_2 (viz. **27**) and N−Bn → S (viz. **29**), are consistent with this scenario. The good donor solvent THF may not favor the internal hydride delivery as much as the noncoordinating CH_2Cl_2 because of THF complexation to the metal center and disruption of the anti addition mechanism.



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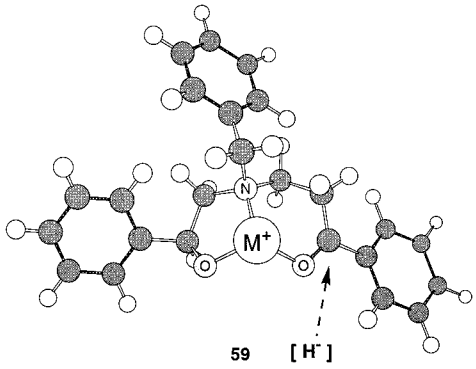
Intramolecular reduction

To account for the outstanding 1,6 acyclic diastereocontrol, we originally proposed a 5,6-bicyclic chelate structure, such as in model **59**.[6b] The lithium or zinc ion would be complexed with the hydroxyl, amine, and ketone groups in **34** to establish a conformationally rigid array, and the hydride species would attack the carbonyl in the six-membered ring from an axial direction to allow for an equatorial phenyl ring to develop in the transition state. This leads to the major anti 1,6-diol product. A model with a trans-like 5,6 ring fusion, where the nitrogen configuration is inverted, could also be entertained. However, this overly complicates something that is already rather speculative. In model **59**, anti selectivity would be favored by a bulkier nitrogen substituent, as we observed in the trend of stereoselectivity for the reduction of **34** and **54a**−**c**. Significantly, the anti/syn ratio improved as the substituent varied from hydrogen to methyl to benzyl to 2,4,6-trimethylbenzyl. Replacement of the *N*-benzyl group with an oxygen group (viz. **52**) abolished selectivity. When the N−Bn in **34** was replaced by NC(O)Ph (viz. **56**), a group with a similar steric size but with an electron-deficient nitrogen and an altered coordination site, little selectivity was obtained. Presumably, in the case of substrates **52** and **56**, there is an absence of coordination by the heteroatom center in the chain such that the putative bicyclic chelate cannot form. Although the methoxy group is also a reasonably

good ligand for lithium, it was not as effective for anti stereocontrol as the hydroxyl (cf. reductions of **34** and **50**).



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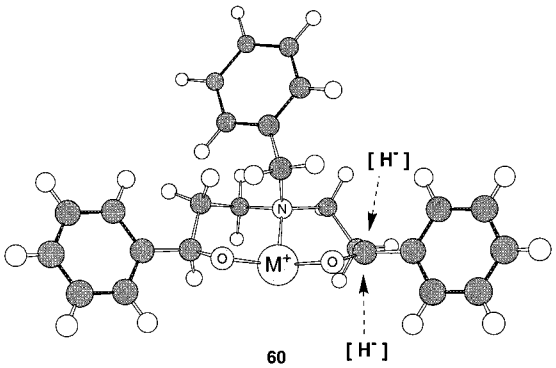
5,6-Bicyclic Chelate Complex

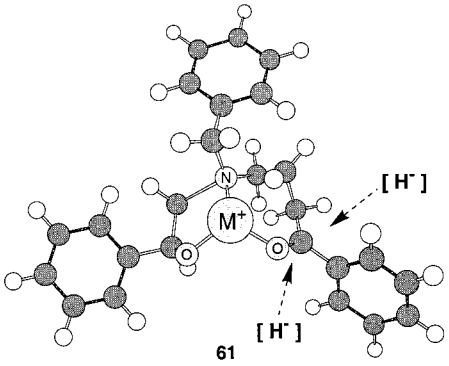
The reduction of 1,6-hydroxy ketones was complete within a couple of hours at −78 °C, while the reduction of 1,5-hydroxy ketones was not complete even after 24 h at −78 °C. This difference in reactivity could arise from the reduction occurring via different pathways. Thus, reduction of the 1,6-hydroxy ketones could proceed via a 5,6-bicyclic intermediate with the ketone carbonyl activated toward reduction because of metal complexation, whereas reduction of the 1,5-hydroxy ketones could proceed via an internal delivery of hydride with the ketone carbonyl not activated by complexation in a bicyclic intermediate.

The lack of stereocontrol for the 1,7-hydroxy ketones **39**, **43**, and **46** could be attributed to a modest facial preference for hydride attack in the corresponding 6,6- and 5,7-bicyclic chelates (see models **60** and **61**) or in the seven-membered-ring, monocyclic complex with the ketone uncoordinated to the metal.



60

6,6-Bicyclic Chelate Complex



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5,7-Bicyclic Chelate Complex

NMR Mechanistic Studies. We undertook NMR studies (400 MHz) in an attempt to identify the formation of well-defined metal chelates with representative hydroxy amino ketone substrates. Treatment of 1,5-hydroxy ketone **23** with up to 2 mol equiv of $LiBF_4$, in increments of 0.5 mol equiv, in THF-d_8 at 23 °C showed significant shifting of proton resonances and a change in the splitting patterns of the methylene protons α to nitrogen. However, ^{13}C NMR spectra suggested that the substrate remained in the cyclic ketal form (quaternary carbon at 95 ppm). Treatment of 1,6-hydroxy ketone **34** with up to 2.0 mol equiv of $LiBF_4$, in increments of 0.5 mol equiv, in THF-d_8 at 23 °C showed minor shifting of the proton resonances and the eventual appearance of olefinic signals, suggesting decomposition of the substrate. The 1,6-hydroxy ketone system, **34**, was treated with 1−2 mol equiv of $LiBF_4$ in THF-d_8 at 0, −53, and −83 °C. At −83 °C, a significant change in the splitting pattern was noted for the methylene protons between the amine and the hydroxyl carbon, from a single multiplet to two multiplets. While some of these NMR results suggest some type of chelation to Li and/or minor conformational changes, there was no strong evidence for the formation of bicyclic metal chelates or, for that matter, stable, highly organized metal complexes.

Some NMR experiments (400 MHz, 2D-COSY) were performed with **34** and Ti(*i*-OPr)$_4$, which we thought might generate a more stable, characterizable chelate. With 1 mol equiv of the titanium reagent at −80 °C in CH_2Cl_2, we observed two new species, possibly stereoisomers of a titanium complex, with the following changes in chemical shifts (**34** → **34** + Ti): δ 2.40/2.52 (pair of br m, CHOHCH_2N) → 2.60−2.65 (m) and 3.22/3.78 (dd/dd); 2.70/3.25 (pair of m, CH_2CH_2N) → 3.15−3.40 (br m); 3.1−3.4 (br m, CH_2C=O) → 3.15−3.40 (br m); 3.38/3.93 (pair of d, PhCH_2N) → 3.85/4.10 (pair of d); 4.30 (br s, OH); 4.73 (br s, C*H*OH) → 5.37/5.50 (pair of d); 7.90 (br s, *o*-benzoyl) → 7.68 (m). The greatest change in chemical shift occurred for the methine at the hydroxyl center ($\Delta\delta$ of 0.64 and 0.77), which is reasonable for titanium ester formation. Also, the methylenes next to nitrogen were shifted downfield to some degree, suggesting coordination of the nitrogen to titanium. However, the methylene next to the keto group did not experience a meaningful shift, suggesting that the carbonyl group is not strongly coordinated to the metal. The upfield shift of the *o*-benzoyl protons suggests that there is an interaction of the keto group with titanium. The NMR interpretation is complicated by the presence of two major species, clearly indicated by the multiple resonances for the methine; thus, we are not able to interpret these data in terms of precise structures for the titanium complexes.

Conclusion

High stereocontrol (ca. 10−20:1) between remote 1,5 and 1,6 stereocenters was achieved in the reduction of certain hydroxy amino ketones, namely **17**, **23**, **25**, **34**, and **54c**, with *R*-alpine-hydride or Zn(BH$_4$)$_2$. The anti diastereoselectivity was optimized in a noncoordinating solvent, such as CH_2Cl_2, and at diminished temperatures, such as −78 °C. The distance between the hydroxyl and amino groups had a greater effect on the diastereoselectivity than did the distance between the ketone and amino groups, with β-hydroxy amino compounds providing the best results. The stereoelectronic properties of

the intervening chain between the hydroxyl and ketone groups of the substrate played a key role in the 1,5 (cf. **23**, **27**, **29**, and **31**) and 1,6 (cf. **34**, **52**, **54a-c**, and **56**) asymmetric induction, with anti diastereoselectivity being strongly favored by a bulkier N−alkyl substituent. By way of a dramatic illustration, the reduction of **54c**, possessing an N−trimethylbenzyl group, with *R*-alpine-hydride at −78 °C in CH_2Cl_2 furnished **55c** with an impressive anti/syn ratio of 22:1. The reduction of **50** to **51** (anti/syn = 4:1) reflects on the importance of a free hydroxyl for achieving high 1,6-anti stereoselectivity. Interestingly, replacement of hydroxyl with a methoxyl significantly diminished, but did not destroy, anti stereocontrol.

One of the major challenges in synthetic organic chemistry is achieving good control of stereochemistry between remote sites in conformationally flexible systems. There are a limited number of examples of remote asymmetric induction in acyclic molecules with stereogenic and prostereogenic centers separated by distances of 1,5, 1,6, or greater, especially examples unperturbed by the presence of other, pre-existing stereogenic features. To be sure, no general reactions for the construction of remote chiral relationships in such acyclic systems are yet known. We have discovered a new reaction type that is capable of delivering high 1,5- and 1,6-anti asymmetric induction in a *strictly acyclic array*, presumably on the basis of a highly organized metal chelate. The hydroxyl and amino groups are involved in directing addition of the hydride reagent preferentially to one face of the ketone carbonyl. One can reasonably consider that a bicyclic chelation model may be responsible for the unusually high anti stereocontrol for the 1,6 acyclic system. However, this model appears to be a less likely participant in the 1,5 acyclic system. Despite the absence of a clear structural understanding of the mechanism for high 1,5- and 1,6-anti stereocontrol in these reductions, one can still draw consolation from the exciting stereochemical results.

Experimental Section

General Procedures. Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. ^1H and ^{13}C NMR spectra (300, 400, or 600 MHz for proton) were obtained in $CDCl_3$ (Me_4Si internal reference), unless noted otherwise. Chemical ionization mass spectra were obtained with methane as the reagent gas (1 torr). Analytical TLC was performed with Whatman 250-μm silica gel plates; preparative TLC was performed with Analtech 1000-μm silica gel GF plates. Flash column chromatography was conducted with flash column silica gel (40−63 μm), and column chromatography was conducted with standard silica gel. Preparative HPLC was performed on a Waters Prep 500A with silica gel columns. Analytical HPLC was carried out on a YMC basic column (25 cm × 4.6 mm), with detection at 254 nm by using a Waters 481 UV detector, unless noted otherwise. Microanalysis was performed by Robertson Microlit Laboratories, Inc.

1-(2-Benzofuranyl)-2-[[2-(2-benzofuranyl)-2-hydroxyethyl](phenylmethyl)amino]-ethanone (17). A solution of 2-acetylbenzofuran (219.7 g, 1.37 mol) in 2-pyrrolidinone (157 mL) was heated to reflux while being stirred mechanically under argon. 2-Pyrrolidinone hydrotribromide (701.6 g, 1.37 mol) was added as a solid portionwise over ca. 40 min. After 10 min, an exotherm occurred, which was controlled by a water bath. During the exotherm, the reaction turned from dark-orange-red to white; after the exotherm ceased (ca. 15 min), reflux was maintained by heating. After 1.5 h, another portion of the hydrotribromide (140 g, 0.028 mol) and 2-pyrrolidinone (26 mL) was added. The reaction was heated at reflux for 1.5 h, cooled to 10 °C, and filtered. The filtrate was concentrated in vacuo to a residue that was recrystallized twice from 95% ethanol (650 mL) to yield 2-(bromoacetyl)benzofuran (257.9 g, 79%) as beige crystals, mp 70−82 °C (lit.[24] mp 90−91 °C). A solution of 2-(bromoacetyl)benzofuran (100.0 g, 0.42 mol) in 2-pyrrolidinone was reacted with dibenzylamine (82.5 g, 0.42 mol) according to the procedure of Burger and Deinet,[25] and the crude product was partially dissolved in boiling 2-propanol and filtered. The filtrate was recrystallized from 2.5 L of 2-propanol to afford 71.3 g (48%) of free base as a tan solid, which was dissolved 2.5 L of ethyl acetate, acidified with HCl gas, and crystallized to furnish dibenzylaminoacetylbenzofuran hydrochloride (59.3 g, 36%) as a white solid, mp 196 °C, dec (lit.[25] mp 191 °C). A solution of this product (59.0 g, 0.151 mol) in methanol (100 mL) was combined with 20% $Pd(OH)_2/C$ and hydrogenated on a Parr apparatus at 60 psig for 45 min. The filtrate was concentrated in vacuo, and the residue was recrystallized from 2-propanol to afford 2-(1-hydroxy-2-benzylaminoethyl)benzofuran·HCl (33.5 g, 74%) as a white solid, mp 189−191 °C (lit.[25] mp 187.5 °C). A solution of this benzofuran (28.2 g, 0.93 mol) and *N*,*N*-diisopropylethylamine (24.0 g, 0.186 mol) in THF (370 mL) was cooled to 5 °C, treated with 2-(bromoacetyl)benzofuran (23.3 g, 0.098 mol), and slowly warmed to 23 °C over 16 h with stirring under nitrogen. The reddish-brown suspension was filtered, and the filtrate was concentrated in vacuo. The residue was partitioned between ethyl acetate (400 mL) and 3 N NaOH (100 mL), and the organic layer was rinsed twice with brine. The organic solution was dried (K_2CO_3) and concentrated in vacuo. The residue was recrystallized from methanol to afford **17** (26.3 g, 63%) as tan crystals, mp 116−119 °C. An analytical sample was purified by flash column chromatography ($CHCl_3$) and recrystallized from methanol to give **17** as beige crystals, mp 125−128 °C. ^1H NMR (mixture of two cyclic hemiketals, cis/trans = 5:1, and the ketone form) δ 2.60−2.80 (m, 2 H), 3.10−3.40 (m, 2.4 H), 3.65 (s, 2 H, cis ketal CH_2Ph), 3.89 (d, J = 13.5 Hz, 0.2 H, ketone CH_2Ph), 4.05−4.10 (m, 0.6 H, ketone CH_2Ph and CH_2C=O), 4.70 (br s, 0.2 H, OH), 4.77 (br s, 1H, OH), 4.90−5.07 (m, 0.2 H, trans ketal CH−O), 5.44 (dd, J = 11.4, 2.4 Hz, 1H, cis ketal CH−O), 6.71 (s, 0.2 H), 6.75 (s, 1 H), 6.91 (s, 1 H), 7.11−7.70 (m, 13 H). CI-MS m/z 426 (MH^+). IR (KBr; no carbonyl absorption because of a ring−chain equilibrium between the ketone form and two cyclic hemiketals) ν_{max} 3404 (s), 1471 (s), 1252 (s), 1163 (m), 1042 (s) cm^{-1}. Anal. Calcd for $C_{27}H_{23}NO_4$: C, 76.22; H, 5.45; N, 3.29. Found: C, 76.39; H, 5.43; N, 3.22.

(*R,*R**)-α,α′-[[(Phenylmethyl)imino]bis(methylene)]-bis-2-benzofuranmethanol (*anti*-18).** (*R*)-Alpine-hydride (148 mL, 0.074 mol; 0.5 M in THF) was added dropwise over 1.5 h to a stirred solution of **17** (15.0 g, 0.035 mol) in THF (300 mL) under argon at −95 to −98 °C. The reaction was slowly warmed to 0 °C over 18 h and concentrated in vacuo. The residue was dissolved in ethyl ether (400 mL) and extracted with aqueous 1 N HCl (200 mL; CAUTION, foaming). An oil separated from the ether layer and was collected with the acidic aqueous layer. The ether layer was extracted with 1 N HCl (3 × 100 mL), and the combined acidic potions (including the oil) were extracted with ethyl ether (2 × 200 mL), basified to ca. pH 11 with 50% aqueous NaOH, and extracted with ethyl ether (3 × 200 mL). The combined extracts were washed twice with brine, dried (K_2CO_3), and concentrated in vacuo to furnish crude **18** as a brown oil that was a 5:1 mixture of the anti and syn isomers (13.1 g, 87%). This oil was crystallized twice from methanol at −20 °C to give the anti isomer of **18** as a white solid (5.07 g, 34%), mp 103−104 °C. ^1H NMR δ 2.97−3.21 (m, 4 H), 3.68 (br s, 2 H, OH), 3.73 (d, J = 13.6 Hz, 1 H, CH_2Ph), 3.89 (d, J = 13.6 Hz, 1 H, CH_2Ph), 4.88 (dd, J = 8.9, 3.4 Hz, 2 H, CHOH), 6.59 (s,

(24) Shriner, R. L.; Anderson, J. *J. Am. Chem. Soc.* **1939**, *61*, 2705−2708.

(25) Burger, A.; Deinet, A. J. *J. Am. Chem. Soc.* **1945**, *67*, 566−569.

2 H), 7.12−7.34 (m, 9 H), 7.41 (d, J = 8.0 Hz, 2 H), 7.49 (d, J = 7.5 Hz, 2 H). FAB-MS m/z 428 (MH^+). The enantiomeric ratio of the anti isomer of **18** was determined by 400-MHz ^{1}H NMR by using 5 mg of sample and 60 mg of (*S*)-(+)-trifluoromethyl-1-(9-anthryl)ethanol in 1 mL of $CDCl_3$ at 21 °C. Useful spectral nonequivalence ($\Delta\delta$ = 0.02) was observed for the 3-position protons of the benzofuran groups at δ 6.552 and 6.572; ratio = 50:50 ± 5.

(*R*,S)-α,α′-[[(Phenylmethyl)imino]bis(methylene)]bis-2-benzofuranmethanol (*syn*-18).** A stirred suspension of **17** (5.00 g, 0.0118 mol) in methanol (300 mL) at 5 °C was treated with $NaBH_4$ (0.889 g, 0.0235 mol). After 1 h, the reaction was acidified with 3 N HCl (50 mL), basified to pH 11 with 3 N NaOH, and concentrated in vacuo. The residue was partitioned between CH_2Cl_2 and water and the organic layer was washed with brine, dried (K_2CO_3), and concentrated in vacuo to give crude **18** as a 1.3:1 mixture of the syn and anti isomers. These isomers were separated by preparative HPLC (CH_2Cl_2), after pre-equilibrating the column with CH_2Cl_2/MeOH/NH_4OH (90:9:1), to afford the syn isomer of **18** (1.76 g, 35%) as an amber oil. ^{1}H NMR δ 3.05−3.20 (m, 4 H), 3.32 (br s, 2 H, O*H*), 3.78 (s, 2 H, CH_2Ph), 4.89 (dd, J = 8.0, 4.9 Hz, 2 H, C*H*OH), 6.62 (s, 2 H), 7.12−7.30 (m, 9 H), 7.41 (d, J = 8.0 Hz, 2 H), 7.51 (d, J = 7.6 Hz, 2 H). FAB-MS m/z 428 (MH^+).

α,α′-[(Imino)bis(methylene)]bis-2-benzofuranmethanol (*anti*-16). A solution of *anti*-**18** (4.91 g, 0.115 mol) in methanol/concentrated NH_4OH (9:1; 80 mL) was combined with 20% $Pd(OH)_2$/C (0.323 g) and hydrogenated at 1 atm for 2 h. The mixture was filtered through Nylon 66 (0.45 μm) and concentrated in vacuo. The residue was recrystallized from methanol to give *anti*-**16** (2.75 g, 71%) as a white crystalline solid, mp 123−125 °C. ^{1}H NMR (DMSO-d_6) δ 1.94 (br s, 1 H, NH), 2.85−3.04 (m, 4 H, CH_2), 4.72−4.86 (m, 2 H, C*H*OH), 5.68 (d, J = 5.3 Hz, 2 H, CHO*H*), 6.72 (s, 2 H), 7.15−7.32 (m, 4 H), 7.52 (d, J = 8.0 Hz, 2 H), 7.57 (d, J = 7.6 Hz, 2 H). CI-MS m/z 338 (MH^+). Anal. Calcd for $C_{20}H_{19}NO_4$: C, 71.20; H, 5.68; N, 4.15. Found: C, 71.07; H, 5.63; N, 4.08.

α,α′-[Iminobis(methylene)bis-2-benzofuranmethanol (*syn*-16). A solution of the *syn*-**18** (3.62 g, 0.0085 mol) in methanol and concentrated NH_4OH (9:1; 59 mL) was combined with 20% $Pd(OH)_2$/C (0.238 g) and hydrogenated at 1 atm. After 3 h, another portion of 20% $Pd(OH)_2$/C (0.238 g) was added and stirring was continued for 1.5 h. The reaction was filtered through Nylon 66 (0.45 μm) and concentrated in vacuo. The residue was recrystallized twice from methanol to give *syn*-**16** (1.19 g, 41%) as a white crystalline solid, mp 125−127 °C. ^{1}H NMR (DMSO-d_6) δ 1.95 (br s, NH, 1 H), 2.83−3.06 (m, 4 H, CH_2), 4.70−4.85 (m, 2 H, C*H*OH), 5.70 (d, J = 4.9 Hz, 2 H, CHO*H*), 6.74 (s, 2 H), 7.13−7.33 (m, 4H), 7.52 (d, J = 7.9 Hz, 2 H), 7.57 (d, J = 7.5 Hz, 2 H). CI-MS m/z 338 (MH^+). Anal. Calcd for $C_{20}H_{19}NO_4$: C, 71.20; H, 5.68; N, 4.15. Found: C, 71.23; H, 5.68; N, 4.11.

2-[(2-Hydroxy-2-phenylethyl)(phenylmethyl)amino]-1-phenylethanone (23). A solution of 2-bromoacetophenone (100.0 g, 0.50 mol) in THF (500 mL) was added at 5 °C over 45 min under argon to a stirred solution of dibenzylamine (99.1 g, 0.50 mol) and *N*,*N*-diisopropylethylamine (129.8 g, 1.01 mol). The reaction was slowly warmed to 23 °C over 18 h and filtered. The filtrate was concentrated in vacuo, and the residue was recrystallized from 2-propanol to afford the amino ketone as beige crystals (101.5 g, 67%), mp 81−82 °C (lit.[26] mp 81.5−82 °C). A solution of this material (99.4 g, 0.33 mol) in methanol (2 L) was treated with concentrated HCl (27 mL, 0.33 mol), combined with 20% $Pd(OH)_2$/C (9.20 g), hydrogenated on a Parr apparatus at 60 psig for 1 h, and filtered. The filtrate was concentrated in vacuo, and the residue was recrystallized from 2-propanol to afford 73.2 g (85%) of 2-benzylamino-1-phenylethanol·HCl as white crystals, mp 225−228 °C (lit.[19] mp 219.5−221.5 °C). A solution of the free base of this material (49.1 g, 0.22 mol) and *N*,*N*-diisopropylethylamine (54.8 g, 0.42 mol) in THF (370 mL) was cooled to 5 °C, treated with phenacyl bromide (44.4 g, 0.022 mol), and slowly warmed to 23 °C over 18 h with stirring. The resulting dark-brown suspension was filtered, and the filtrate was concentrated in vacuo. The residue was partitioned between CH_2Cl_2 and 3 N NaOH. The organic layer was rinsed twice with brine, dried (K_2CO_3), and concentrated in vacuo. The residue was dissolved in methanol (600 mL) and acidified with gaseous HCl. The deposited solid was collected and recrystallized from methanol to afford the HCl salt of **23** (57.5 g, 71%) as white crystals, mp 189−191 °C, dec. Analytical data were collected on the free base, **23**. ^{1}H NMR δ 2.22 (t, J = 11.3 Hz, 1 H), 2.36 (d, J = 11.2 Hz, 1 H), 2.94 (d, J = 11.1 Hz, 1 H), 3.03 (d, J = 11.2 Hz, 1 H), 3.61 (s, 2 H), 5.24 (dd, J = 2.7, 11.0 Hz, 1 H), 7.29−7.46 (m, 13 H), 7.70 (d, J = 6.8 Hz, 2 H). ^{13}C NMR δ 59.7, 62.2, 63.1, 71.8, 95.3, 125.7, 126.4, 127.4, 127.7, 128.0, 128.2, 128.4, 128.9, 129.1, 136.6, 139.8, 141.8. ES-MS m/z 346 (MH^+). FAB-HRMS calcd for $C_{23}H_{23}NO_2 + H^+$, 346.1807; found, 346.1818. The spectral data indicate that **23** is mainly in the cyclic tautomeric form.

2-[Benzyl-(2-hydroxy-2-phenylethyl)amino]-1-phenylethanol (24, anti/syn).[27] **A. Typical Alpine-Hydride Reduction.** To a solution of **23** (75 mg, 0.22 mmol) in CH_2Cl_2 (5 mL) at −78 °C was added dropwise *R*-alpine-hydride (0.46 mmol, 0.5 M in THF) via syringe over 35 min. The mixture was stirred at −78 °C for 26 h and quenched with water. The mixture was extracted with CH_2Cl_2, and the organic layer was washed (water, brine), dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by preparative TLC (hexanes/EtOAc, 2.5:1) to give 30 mg (40%) of **24** as a colorless viscous solid with an anti/syn ratio of 10:1. ^{1}H NMR δ 2.71−2.92 (m, 4 H), 3.70/3.99 (pair of d, J = 13.5 Hz, 1.82 H, anti PhCH_2), 3.83 (s, 0.18 H, syn PhCH_2), 4.70/4.76 (pair of dd, syn C*H*OH/anti C*H*OH, J = 10.3, 3.4 Hz for the anti isomer), 7.25−7.36 (m, 15 H). ^{13}C NMR δ 59.9, 62.7 (anti), 63.6 (syn), 70.9 (anti), 72.1 (syn), 125.9, 127.6, 127.7, 128.4, 128.6, 129.2, 138.0, 142.2. CI-MS m/z 348 (MH^+). FAB−HRMS calcd for $C_{23}H_{25}NO_2 + H^+$, 348.1964; found, 348.1976. A 1.5:1 anti/syn mixture of **24**, prepared by reducing **23** with $NaBH_4$ in methanol at 5 °C (as described for *syn*-**18**), gave the following spectral data. ^{1}H NMR (400 MHz) δ 2.58−2.91 (m, 4 H, 2 CH_2), 3.57 (br s, 2 H, OH), 3.64/3.92 (pair of d, J = 13.7 Hz, 0.6 H, anti PhCH_2), 3.83 (s, 0.8 H, syn PhCH_2), 4.63 (dd, J = 10.3, 4.6 Hz, 0.8 H, syn C*H*OH), 4.70 (dd, J = 10.3 Hz, 3.4 Hz, 1.2 H, anti C*H*OH), 6.95−7.55 (m, 15 H).

B. Typical $Zn(BH_4)_2$ Reduction.[28] To a solution of **23** (75 mg, 0.22 mmol) in CH_2Cl_2 (5 mL) at −78 °C was added dropwise $Zn(BH_4)_2$ (0.30 mmol, 0.5 M in Et_2O)[28] via syringe over 35 min. The mixture was stirred at −78 °C for 26 h and quenched with water. The mixture was extracted with CH_2Cl_2, and the organic layer was washed (water, brine), dried (Na_2SO_4), and concentrated in vacuo. The residue was separated by preparative TLC (hexanes/EtOAc, 2.5:1) to give 35 mg (47%) of **24** (anti and syn) as a colorless viscous solid with an anti/syn ratio of 13:1 (determined by ^{1}H NMR).

3-[(2-Hydroxypropyl)(phenylmethyl)amino]-2-propanone (25). To a solution of 1-benzylamino-2-propanol (660 mg, 4.0 mmol) and *N*,*N*-diisopropylethylamine (1.03 g, 8.0 mmol) in THF (25 mL) was added chloroacetone (555 mg, 6.0 mmol). The mixture was stirred at 60 °C for 20 h and concentrated in vacuo. The residue was separated by flash column chromatography (hexanes/EtOAc, 3:1) to afford 530 mg (60%) of **25** as a colorless viscous oil. ^{1}H NMR δ 1.10 (d, J = 6.3 Hz, 3 H), 1.35 (s, 3 H), 1.80 (t, J = 11.0 Hz, 1 H), 2.06 (d, J = 10.9 Hz, 1 H), 2.71 (t, J = 9.2 Hz, 2 H), 3.51 (s, 2 H), 3.99−4.10 (m, 1 H), 7.25−7.36 (m, 5 H). ^{13}C NMR δ 18.7, 25.1,

(26) Suzuki, T.; Takamoto, M.; Okamoto, T.; Takayama, H. *Chem. Pharm. Bull.* **1986**, *34*, 1888−1900.

(27) (a) For the R,R enantiomer of the anti isomer of **24**, see: Manickam, G.; Sundararjan, G. *Tetrahedron: Asymmetry* **1997**, *8*, 2271−2278. Dubois, L.; Fiaud, J.-C.; Kagan, H. B. *Tetrahedron: Asymmetry* **1995**, *6*, 1097−1104. Trost, B. M.; Van Vranken, D. L.; Bingel, C. *J. Am. Chem. Soc.* **1992**, *114*, 9327−9343. (b) An expansion/blowup of the *N*-benzyl methylene region of the ^{1}H NMR spectrum is presented in the Supporting Information (see the paragraph at the end of this paper regarding Supporting Information).

(28) Gensler, W. J.; Johnson, F.; Sloan, A. D. B. *J. Am. Chem. Soc.* **1960**, *82*, 6074−6081.

59.1, 61.3, 62.2, 65.0, 93.7, 127.0, 128.3, 129.9, 137.1. CI-MS *m*/*z* 222 (MH^+). Anal. Calcd for $C_{13}H_{19}NO_2 \cdot 0.1H_2O$: C, 69.99; H, 8.68; N, 6.28. Found: C, 69.76; H, 8.70; N, 6.19.

3-[(2-Hydroxypropyl)(phenylmethyl)amino]-2-propanol (26, anti/syn).[29] To a solution of **25** (35 mg, 0.16 mmol) in CH_2Cl_2 (7 mL) at −78 °C was added dropwise *R*-alpine-hydride (1.1 mL, 0.5 M in THF, 0.55 mmol) via syringe. The mixture was stirred at −78 °C, and no reaction was observed after 17 h. The cooling bath was removed, and the reaction mixture was allowed to warm to 0 °C within 2 h. After stirring at 0 °C for 1 h, the mixture was quenched with saturated aqueous NH_4Cl. The mixture was extracted with ethyl acetate, and the organic layer was washed (water, brine), dried (Na_2SO_4), and concentrated in vacuo. The residue was separated by preparative TLC (hexanes/EtOAc, 1:1) to give 30 mg (84%) of **26** as a colorless viscous oil with an anti/syn ratio of 7.8:1. ^{1}H NMR δ 1.02 (d, J = 6.3 Hz, 6 H), 2.37 (d, J = 6.4 Hz, 4 H), 3.44 (d, J = 13.7 Hz, 0.885 H, anti PhCH_2) 3.64 (s, 0.23 H, syn PhCH_2), 3.76−3.83 (m, 3 H, includes d for other anti PhCH_2), 7.18−7.29 (m, 5 H). ^{13}C NMR δ 20.2 (anti), 20.5 (syn), 59.7 (anti), 60.1 (syn), 62.0 (anti), 63.5 (syn), 63.9 (anti), 65.3 (syn), 127.3, 128.4, 128.9, 138.3. CI-MS *m*/*z* 224 (MH^+).

5-Hydroxyl-1,5-diphenyl-1-pentanone (27). A solution of 1,5-diphenyl-2,4-pentadiene-1-one[20] (119.2 g, 0.509 mol) in a 500 mL of benzene/ethanol (1:1) was treated with chlorotris-(triphenylphosphine)rhodium(I) (9.40 g, 0.0102 mol) and hydrogenated on a Parr apparatus at 50 psig and 50 °C for 1.5 h. (Note: The diol was the major product when the literature method[20] was used.) The reaction was cooled to 23 °C, concentrated in vacuo, diluted with ethyl ether (800 mL), and filtered. The filtrate was concentrated in vacuo and recrystallized from methanol (300 mL) at 5 °C to give 1,5-diphenyl-1-pentanone as a tan solid (91.7 g, 76%), mp 46−48 °C (lit.[20] mp 45−47 °C). *N*-Bromosuccimide (23.9 g, 0.134 mol) and benzoylperoxide (8.13 g, 0.034 mol) were added to a vigorously stirred, degassed, refluxing solution of this ketone (32.3 g, 0.134 mol) in CCl_4 (150 mL). The reaction was irradiated with a 150-W incandescent flood lamp for 15 min, cooled to 23 °C, and filtered. The filtrate was rinsed sequentially with saturated aqueous $NaHCO_3$, 1 N $Na_2S_2O_3$, and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was recrystallized from hexanes/EtOAc (9:1) to give 26.6 g (31%) of 5-bromo-1,5-diphenyl-1-pentanone as a white solid (lit.[20] mp 112−114 °C). This material was reacted with 5% aqueous KOH in 1,4-dioxane according to the literature method[20] to afford **27**, which was recrystallized from cyclohexane to afford white crystals, mp 78−80 °C (lit.[20] mp 79−80 °C). ^{1}H NMR (300 MHz) δ 1.71−2.00 (m, 4 H, 2 CH_2), 2.20 (br s,1 H, OH), 2.90−3.15 (m, 2 H, CH_2C═O), 4.60−4.85 (m, 1 H, C*H*OH), 5.15−5.25 (m, 0.03 H, ketal OC*H*OH), 7.15−7.70 (m, 8 H), 7.80−8.05 (m, 2 H). ^{13}C NMR (75 MHz) δ 20.3 (CH_2), 38.1 (CH_2), 38.4 (CH_2), 74.2 (CHOH), 125.7 (CH), 127.4 (CH), 127.9 (CH), 128.36 (CH), 128.43 (CH), 132.9 (CH), 136.8 (C), 144.4 (C), 200.0 (C═O). ES-MS *m*/*z* 255 (MH^+). The spectral data indicate that **27,** unlike **17** and **23**, exists almost exclusively (>95%) in the keto form.

1,5-Diphenyl-1,5-pentanediol (28, anti/syn).[4a,30] *R*-Alpine-hydride (1.65 mL, 0.5 M in THF, 0.83 mmol) was added dropwise under argon over 15 min to a stirred solution of **27** (100 mg, 0.39 mmol) in THF (2.5 mL) at −100 °C. The mixture was slowly warmed to 5 °C over 16 h and concentrated in vacuo. The residue was partitioned between 1 N HCl and ethyl ether; the organic layer was dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by preparative TLC (hexanes/EtOAc, 3:1) to give **28** (77 mg, 77%) as a syrupy 1.2:1 mixture of isomers. ^{1}H NMR (300 MHz, 77 mg/mL) δ 1.10−1.95 (m, 6 H, 3 CH_2), 2.70 (br s, 1.1 H, OH), 2.85 (br s, 0.9 H, OH), 4.57 (pair of dd that appears as a t, 2 H, C*H*OH), 7.10−7.45 (m, 10 H). ^{13}C NMR (75 MHz, 77 mg/mL) δ 22.04 (0.55 *C*H_2), 22.11 (0.45 *C*H_2), 38.63 (0.45 *C*H_2), 38.71 (0.55 *C*H_2), 74.07 (0.45 CH), 74.22 (0.55 CH), 125.76 (CH), 127.33 (CH), 128.31 (CH), 144.72 (0.55 C), 144.75 (0.45 C). ES-MS *m*/*z* 257 (MH^+). CI-HRMS calcd for $C_{17}H_{20}O_2 + NH_4^+$, 274.1807; found, 274.1793. Remarkably, the ^{1}H NMR spectrum revealed two OH signals, one for each isomer, allowing for their quantitation by integration. However, there was no evidence for a pair of triplets at δ 3.58 and 3.60, as reported by Neudeck and Schlögl for a 60-MHz ($CDCl_3$) spectrum of **28**.[30] Clearly, ^{13}C NMR is more sensitive for identifying the two isomers. We were unable to assign anti and syn isomers.

2-[(2-Hydroxy-2-phenylethyl)thio]-1-phenylethanone (29).[21] A solution of diphenacyl sulfide (307 mg, 1.13 mmol) and methanol (31 mL) was cooled to 0 °C and treated with $NaBH_4$ (11 mg, 0.29 mmol). The mixture was allowed to warm to 23 °C and was stirred for 24 h (reaction monitored by TLC: hexanes/EtOAc, 3:1; developed twice; visualized by UV and phosphomolybdic acid). After being stirred for 24 h, the mixture was recooled to 0 °C and more $NaBH_4$ (11 mg, 0.29 mmol) was added. The reaction was again warmed to 23 °C and stirred. After 24 h, the reaction was recooled to 0 °C and $NaBH_4$ (5.0 mg, 0.13 mmol) was added. The reaction was warmed to 23 °C and stirred for 6 h. TLC analysis showed only a trace of starting material and formation of a ca. 1:1 mixture of keto alcohol and diol. The mixture was poured into 30 mL of water at 0 °C, concentrated in vacuo to remove the methanol, and extracted with ethyl acetate (2 × 60 mL). The combined organic solution was washed with brine, dried ($MgSO_4$), and concentrated in vacuo to provide crude product (326 mg). The mixture was purified by column chromatography by using an ethyl acetate−hexanes gradient (10−35% EtOAc) to provide pure **29** (104 mg, 34%) as a light-yellow oil. ^{1}H NMR δ 2.80 (dd, J = 9.0, 14.0 Hz, 1 H), 2.94 (dd, J = 3.7, 14.0 Hz, 1 H), 3.26 (s, 1 H), 3.85 (d, J = 14.6 Hz, 1 H), 3.91 (d, J = 14.6 Hz, 1 H), 4.82 (m, 1 H), 7.20−7.40 (m, 5 H), 7.47 (dd, J = 7.1, 7.4 Hz, 2 H), 7.59 (t, J = 7.4 Hz, 1 H), 7.96 (d, J = 7.1 Hz, 2 H). ^{13}C NMR δ 37.3, 41.6, 72.1, 125.7, 127.7, 128.4, 128.5, 128.6, 133.5, 135.1, 142.4, 194.8. CI-MS *m*/*z* 273 (MH^+). Anal. Calcd for $C_{16}H_{16}O_2S$: C, 70.56; H, 5.92; S, 11.77. Found: C, 70.34; H, 5.92; S, 11.75.

α,α′-[(Thio)bis(methylene)]bis-benzenemethanol (30).[21] To a solution of the keto alcohol **29** (40 mg, 0.147 mmol) in CH_2Cl_2 (6.7 mL) stirring at −78 °C was added dropwise *R*-alpine-hydride (0.62 mL, 0.309 mmol) over 15 min. The reaction was stirred at −78 °C and assayed by TLC (25% hexanes/EtOAc, 3:1; developed twice; visualized with phosphomolybdic acid). After 1 h, a trace of **29** remained; after 3 h, the reaction was complete. The mixture was quenched with saturated aqueous NH_4Cl (2 mL) at −78 °C and allowed to warm to 23 °C. The aqueous layer was extracted with ethyl acetate (3 × 10 mL), and the combined extracts were dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by column chromatography by using an ethyl acetate−hexanes gradient (20−35% EtOAc) to provide the diols **30** (32.4 mg, 81%). The ratio was determined to be ca. 1.3:1 anti/syn by ^{13}C NMR peak intensities (δ 41.7 for anti CH_2, 42.2 for syn CH_2; 72.4 for anti CH, 73.2 for syn CH). The spectral data agreed with results already in the literature.[21] ^{1}H NMR δ 2.70−2.85 (m, 2 H), 2.85−3.00 (m, 2 H), 3.20 (s, 1 H, anti OH), 3.32 (s, 1 H, syn OH), 4.75−4.80 (m, 2 H), 7.20−7.40 (m, 10 H). ^{13}C NMR δ 41.7 and 42.2 (anti/syn isomers), 72.4 and 73.2 (anti/syn isomers), 125.7, 127.9, 128.4, 142.3, and 142.4 (anti/syn isomers). CI-MS *m*/*z* 239 ($MH^+ - 2H_2O$).

2-[(2-Hydroxy-2-phenylethyl)methylamino]-1-phenylethanone (31). To a solution of α-(methylaminomethyl)-benzyl alcohol (3.0 g, 22.0 mmol) and *N*,*N*-diisopropylethylamine (3.4 g, 26.3 mmol) in THF (145 mL) was added 3-chloropropiophenone (5.2 g, 26.1 mmol). The mixture was stirred at 23 °C for 24 h and then diluted with CH_2Cl_2. The solution was washed with aqueous NH_4Cl (100 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash column chromatography (hexanes/EtOAc, 2:1) to afford 3.05 g (69%) of **31** as a light-yellow viscous oil. ^{1}H NMR δ 2.04−2.24 (m, 2 H), 2.31 (s, 3 H), 2.89−2.99 (m, 2 H), 5.26

(29) For the S,S enantiomer of the anti isomer of **26**, see: Dubois, L.; Fiaud, J.-C.; Kagan, H. B. *Tetrahedron* **1995**, *51*, 3803−3812.

(30) Neudeck, H.; Schlögl, K. *Monatsh. Chem.* **1975**, *106*, 229−259.

(dd, $J = 2.8$, 8.2 Hz, 1 H), 7.30−7.47 (m, 8 H), 7.72 (d, $J = 6.7$ Hz, 2 H). ^{13}C NMR δ 45.7, 61.9, 65.0, 71.6, 95.5, 125.7, 126.4, 127.4, 127.8, 127.9, 140.0, 142.3. ES-MS *m/z* 270 (MH^+). Anal. Calcd for $C_{17}H_{19}NO_2 \cdot 0.1H_2O$: C, 75.31; H, 7.14; N, 5.17. Found: C, 74.98; H, 7.19; N, 4.84.

2-[(2-Hydroxy-2-phenylethyl)methylamino]-1-phenylethanol (32, anti/syn). Reduction of **31** (85 mg, 0.32 mmol) with 2.2 mol equiv of *R*-Alpine-Hydride (CH_2Cl_2, −78 °C, 24 h) and isolation by preparative TLC (CH_2Cl_2/MeOH, 95:5) gave 51 mg (35%) of **32** (60% of **31** was recovered) as a colorless viscous oil with an anti/syn ratio of 2.3:1 (determined by ^{1}H and ^{13}C NMR). ^{1}H NMR δ 2.41 (s, 0.9 H, syn NMe) and 2.45 (s, 2.1 H, anti NMe), 2.52−2.77 (m, 4 H), 4.68−4.73 (m, 2 H), 7.21−7.39 (m, 10 H). ^{13}C NMR δ 42.0 (syn), 43.2 (anti), 65.6 (anti), 66.6 (syn), 70.4 (anti), 70.9 (syn), 125.8, 127.5, 128.3, 142.0. ES-MS *m/z* 272 (MH^+). Anal. Calcd for $C_{17}H_{21}NO_2 \cdot 0.7H_2O$: C, 71.86; H, 7.96; N, 4.93. Found: C, 71.99; H, 7.57; N, 4.48.

3-[(2-Hydroxy-2-phenylethyl)(phenylmethyl)amino]-1-phenyl-1-propanone (34). To a solution of 2-benzylamino-1-phenylethanol (5.00 g, 22.0 mmol) and *N*,*N*-diisopropylethylamine (4.23 g, 32.7 mmol) in THF (150 mL) was added 3-chloropropiophenone (3.70 g, 22.0 mmol). The mixture was stirred at 23 °C for 16 h and then diluted with ethyl acetate (200 mL). The organic solution was washed with water (50 mL) and brine (50 mL), dried (Na_2SO_4), and concentrated in vacuo. The crude product was purified by flash column chromatography (hexanes/EtOAc, 2:1) to afford 6.30 g (80%) of **34** as a colorless viscous oil. ^{1}H NMR (400 MHz, 2D-COSY) δ 2.57−2.65 (dd, $J = 13.5$, 10.1 Hz, 1 H, CHOHC*H*$_2$N), 2.70−2.75 (dd, $J = 3.5$, 13.5 Hz, 1 H, CHOHC*H*$_2$N), 2.92−3.00 (m, 1 H, CH$_2$C*H*$_2$N), 3.15−3.23 (m, 3 H, CH$_2$C*H*$_2$N and CH$_2$C=O), 3.58 (d, $J = 13.7$ Hz, 1 H, PhCH$_2$N), 3.93 (d, $J = 13.7$ Hz, 1 H, PhCH$_2$N), 4.71 (dd, $J = 3.5$, 10.1 Hz, 1 H, C*H*OH), 7.22−7.37 (m, 10 H), 7.49 (dd, $J = 7.7$ Hz, 2 H, *m*-benzoyl), 7.60 (dd, $J = 7.3$ Hz, 1 H, *p*-benzoyl), 7.92 (d, $J = 7.5$ Hz, 2 H, *o*-benzoyl). ^{13}C NMR δ 36.3, 49.3, 59.0, 63.0, 69.8, 125.8, 127.1, 127.2, 127.3, 128.0, 128.2, 128.3, 128.4, 128.5, 128.8, 133.1, 136.7, 138.2, 142.0, 199.2. ES-MS *m/z* 360 (MH^+). Anal. Calcd for $C_{24}H_{25}NO_2$: C, 80.20; H, 7.01; N, 3.90. Found: C, 79.80; H, 7.04; N, 3.86.

α-[2-[(2-Hydroxy-2-phenylethyl)(phenylmethyl)amino]-ethyl]benzenemethanol (35, anti/syn). To a solution of **34** (24 mg, 0.067 mmol) in dry CH_2Cl_2 (3 mL) at −78 °C was added dropwise *R*-alpine-hydride (0.5 M in THF, 0.28 mL, 0.14 mmol) via syringe. The mixture was stirred at −78 °C for 3 h, quenched with water, allowed to warm to 23 °C, and extracted with ethyl acetate. The organic layer was washed (water, brine), dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by preparative TLC (hexanes/EtOAc, 4:1) to give diol **35** as a mixture of anti and syn isomers. The diastereomeric ratio for **35**, anti/syn = 12:1 in this case, was nicely quantitated by HPLC [YMC Basic column, 25 cm × 4.6 mm; 0.1% TFA−water (A)/0.1% TFA−acetonitrile (B); 1 mL/min; gradient, 0−5 min 80%A/20%B, 5−30 min 50% A/50%B, 30−35 min 80%A/20%B; $t_R = 25.1$ min for the syn isomer, $t_R = 25.8$ min for the anti isomer, $t_R = 27.3$ min for hydroxy ketone **34**; $\lambda = 210$ nm] and by 400-MHz ^{1}H NMR. ^{1}H NMR δ 1.81−2.07 (m, 2 H), 2.57−3.00 (m, 4 H), 3.54/3.94 (pair of d, $J = 13.2$ Hz, 1.85 H, anti PhC*H*$_2$), 3.66/3.77 (pair of d, $J = 13.2$ Hz, 0.15 H, syn PhC*H*$_2$), 4.73−4.87 (m, 2 H), 7.23−7.39 (m, 15 H).[27b] ^{13}C NMR δ 35.6, 51.7 (syn), 52.7 (anti), 59.2 (syn), 59.5 (anti), 62.7(syn), 62.9 (anti), 70.9, 73.5 (syn), 74.5 (anti), 125.5, 125.6, 127.1, 127.2, 128.3, 128.5, 128.8, 129.3, 131.2, 137.8, 142.2, 144.4. CI-MS *m/z* 362 (MH^+). Anal. Calcd for $C_{24}H_{27}NO_2 \cdot 0.5H_2O$: C, 77.81; H, 7.62; N, 3.78. Found: C, 77.80; H, 7.42; N, 3.59.

(*R*)-α-[2-[(Phenylmethyl)amino]ethyl]benzenemethanol (36).[31] A solution of (*R*)-(+)-3-chloro-1-phenylpropanol (2.00 g, 11.7 mmol, Aldrich), benzylamine (3.76 g, 35.1 mmol), potassium iodide (3.49 g, 21.0 mmol), and potassium carbonate (2.90 g, 21.0 mmol) in acetonitrile (180 mL) was heated at 75 °C with stirring for 48 h. The reaction mixture was cooled to 23 °C and filtered; the filtrate was concentrated in vacuo, and the residue was dissolved in ethyl acetate. The solution was washed (water, brine), dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography (CH_2Cl_2/MeOH, 9:1) to afford 2.15 g (76%) of **36** as a colorless tacky solid. $[\alpha]^{24}_D$ +29.2 (*c* 1.0, MeOH). ^{1}H NMR δ 1.82−2.00 (m, 2 H), 2.88−3.01 (m, 2 H), 3.85 (s, 2 H), 4.94 (dd, $J = 3.2$, 8.5 Hz, 1 H), 7.25−7.38 (m, 10 H). ^{13}C NMR δ 36.6, 47.0, 53.2, 74.8, 125.4, 126.9, 127.6, 128.1, 128.5, 128.6, 128.9, 137.4, 144.5. CI-MS *m/z* 242 (MH^+). Anal. Calcd for $C_{16}H_{19}NO \cdot 0.03CH_2Cl_2$: C, 78.95; H, 7.88; N, 5.75. Found: C, 79.19; H, 7.48; N, 6.11.

Synthesis of Authentic anti Diols 35 (R,R). A neat mixture of **36** (36 mg, 0.15 mmol) and (*R*)-styrene oxide (108 mg, 0.90 mmol) was stirred at 120 °C for 2 h. The crude mixture was cooled and purified by preparative TLC (CH_2Cl_2/MeOH, 20:1) to afford 23 mg (42%) of **35** (anti, R,R) as a colorless viscous oil. ^{1}H NMR δ 1.81−2.05 (m, 2 H), 2.57−2.80 (m, 3 H), 2.90−2.99 (m, 1 H), 3.53 (d, $J = 13.2$ Hz, 1 H), 3.93 (d, $J = 13.2$ Hz, 1 H), 4.73−4.81 (m, 2 H), 7.23−7.39 (m, 15 H). CI-MS *m/z* 362 (MH^+). The ^{1}H NMR spectrum was identical with that of the major product obtained from the reduction of ketone **34**

(*R*)-α-[2-[(Phenylmethyl)amino]methyl]benzenemethanol ((*R*)-37).[32] (*R*)-2-Chloro-1-phenylethanol (5.33 g, 34.0 mmol, Aldrich) and benzylamine (8.53 g, 79.6 mmol) were heated to 180 °C for 2 h. The crude mixture was cooled and purified by flash column chromatography (CH_2Cl_2/MeOH/concentrated NH_4OH, 92:7:1) to afford 6.20 g (80%) of (*R*)-**37** as a colorless viscous oil. ^{1}H NMR δ 2.74 (dd, $J = 3.3$, 8.8 Hz, 1 H), 2.91 (dd, $J = 8.6$, 3.6 Hz, 1 H), 3.81 (d, $J = 3.6$ Hz, 2 H), 4.72 (dd, $J = 5.3$, 3.5 Hz, 1 H), 7.24−7.39 (m, 10 H). ^{13}C NMR δ 53.4, 56.4, 71.7, 125.7, 127.0, 127.4, 128.1, 128.3, 139.8, 142.4. CI-MS *m/z* 228 (MH^+). Anal. Calcd for $C_{15}H_{17}NO$: C, 79.27; H, 7.54; N, 6.17. Found: C, 79.19; H, 7.48; N, 6.11.

Synthesis of Authentic syn Diols 35 (R,S). A mixture of (*R*)-**37** (1.0 g, 4.4 mmol), (*S*)-3-chloro-1-phenylpropanol (1.5 g, 8.8 mmol, Aldrich), potassium iodide (1.5 g, 9.0 mmol), and potassium carbonate (1.2 g, 8.7 mmol) in DMF (29 mL) was heated at 160 °C for 14 h. The reaction was cooled and concentrated in vacuo. The residue was dissolved in ethyl acetate and washed sequentially with saturated aqueous ammonium chloride (2 × 10 mL), water (2 × 10 mL), and brine (2 × 10 mL). The organic layer was dried ($MgSO_4$) and concentrated. The residue was purified by flash column chromatography (hexanes/EtOAc, 4:1) to afford 1.42 g (89%) of **35** (syn, R,S) as a colorless viscous oil. ^{1}H NMR δ 1.91−1.98 (m, 2 H), 2.69 (d, $J = 6.5$ Hz, 2 H), 2.75−2.92 (m, 2 H), 3.66 (d, $J = 13.3$ Hz, 1 H), 3.78 (d, $J = 13.3$ Hz, 1 H), 4.77 (t, $J = 6.5$ Hz, 1 H), 4.86 (t, $J = 6.5$ Hz, 1 H), 7.28−7.37 (m, 15 H). ES-MS *m/z* 362 (MH^+). The ^{1}H NMR spectrum was identical with that of the minor product obtained from the reduction of ketone **34**.

(*R*)-2-[(3-Hydroxy-3-phenylpropyl)(phenylmethyl)amino]-1-phenylethanone (38). To a solution of **36** (405 mg, 1.7 mmol) and *N*,*N*-diisopropylethylamine (260 mg, 2.0 mmol) in THF (11 mL) was added 2-bromoacetophenone (340 mg, 1.7 mmol). The reaction mixture was stirred at 23 °C for 24 h and diluted with ethyl acetate. The solution was washed with water (20 mL) and brine (20 mL), dried (Na_2SO_4), and concentrated in vacuo. The crude product was purified by flash column chromatography (hexanes/EtOAc, 2.3:1) to afford 580 mg (96%) of **38** as a colorless viscous oil. $[\alpha]^{24}_D$ +27.1 (*c* 0.39, $CHCl_3$). ^{1}H NMR δ 1.88−1.94 (m, 2 H), 2.92−2.97 (m, 2 H), 3.74 (d, $J = 13.1$ Hz, 1 H), 3.94 (d, $J = 13.1$ Hz, 1 H), 3.98 (d, $J = 8.3$ Hz, 2 H), 4.95−4.99 (m, 1H), 7.19−7.45 (m, 12 H), 7.55 (dd, $J = 7.2$ Hz, 1 H), 7.86 (d, $J = 7.6$ Hz, 2 H). ^{13}C NMR δ 35.6, 53.0, 58.3, 59.0, 74.2, 125.6, 126.9, 127.6, 127.9, 128.2, 128.6, 129.4, 133.4, 135.8, 137.7, 144.8, 197.4. ES-MS *m/z* 360

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(MH^+). Anal. Calcd for $C_{24}H_{25}NO_2$: C, 80.19; H, 7.01; N, 3.90. Found: C, 79.66; H, 7.01; N, 3.91.

(*R*)-3-[(3-Hydroxy-3-phenylpropyl)(phenylmethyl)amino]-1-phenylpropanone (39). To a solution of **36** (425 mg, 1.76 mmol) and *N*,*N*-diisopropylethylamine (252 mg, 1.95 mmol) in THF (12 mL) was added 3-chloropropiophenone (300 mg, 1.78 mmol). The reaction mixture was stirred at 23 °C for 24 h and diluted with ethyl acetate. The solution was washed (water, brine), dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography (hexanes/EtOAc, 2:1) to afford 400 mg (61%) of **39** as a colorless viscous oil. ^{1}H NMR δ 1.83−1.95 (m, 2 H), 2.70−3.09 (m, 4 H), 3.19 (t, J = 7.2 Hz, 2 H), 3.54 (d, J = 13.2 Hz, 1 H), 3.84 (d, J = 13.2 Hz, 1 H), 4.86 (dd, J = 3.6, 8.0 Hz, 1 H), 7.28−7.40 (m, 10 H), 7.44 (t, J = 7.4 Hz, 2 H), 7.55 (t, J = 7.2 Hz, 1 H), 7.90 (d, J = 7.2 Hz, 2 H). ^{13}C NMR δ 34.7, 36.1, 48.9, 53.0, 59.1, 75.1, 125.4, 126.8, 127.4, 128.0, 128.1, 128.5, 129.2, 133.1, 136.5, 137.6, 144.7, 199.8. ES-MS *m*/*z* 374 (MH^+). Anal. Calcd for $C_{25}H_{27}NO_2 \cdot 0.2H_2O$: C, 79.63; H, 7.33; N, 3.72. Found: C, 79.83; H, 7.44; N, 3.38.

3-[((*R*)-3-Hydroxy-3-phenylpropyl)(phenylmethyl)amino]-1-phenylpropanol (40, anti/syn). Reduction of **39** (25 mg, 0.067 mmol) with *R*-alpine-hydride (2.1 mol equiv, CH_2Cl_2, −78 °C, 2 h) and isolation by preparative TLC (CH_2Cl_2/MeOH, 9:1) gave 20 mg (80%) of **40** as a viscous oil, anti/syn = 1.2:1 (determined by ^{1}H NMR). ^{1}H NMR δ 1.75−1.98 (m, 4 H), 2.52−2.83 (m, 4 H), 3.44/3.79 (pair of d, J = 13.1 Hz, 1.10 H, anti CH_2Ph), 3.65 (s, 0.90 H, syn CH_2Ph), 4.75−4.81 (m, 2 H), 7.17−7.40 (m, 15 H). ^{13}C NMR δ 35.2, 51.7, 58.7, 73.7, 125.4, 126.6, 127.1, 127.4, 127.9, 128.2, 128.5, 128.7, 128.8, 131.8, 137.6, 144.6. ES-MS *m*/*z* 376 (MH^+). Anal. Calcd for $C_{25}H_{27}NO_2 \cdot 0.3H_2O$: C, 78.72; H, 7.83; N, 3.68. Found: C, 78.33; H, 7.43; N, 3.45.

4-(Phenylmethyl)amino-1-phenylbutanol (42). Sodium borohydride (1.2 g, 32.1 mmol) was added to a solution of 3-chloropropiophenone (5.69 g, 31.2 mmol) in THF (310 mL) at 0 °C. The reaction was stirred for 1 h at 0 °C and quenched with saturated aqueous NH_4Cl (10 mL) and water (100 mL). The solution was concentrated in vacuo and extracted with CH_2Cl_2. The organic solution was dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by flash column chromatography (hexanes/EtOAc, 4:1) to afford 4.5 g (78%) of **41** as a pale-yellow viscous oil.[33] ^{1}H NMR δ 1.73−2.10 (m, 4 H), 3.50−3.3.58 (m, 2 H), 4.69 (t, J = 5.6 Hz, 1 H), 7.25−7.38 (m, 5 H). ^{13}C NMR δ 28.8, 36.0, 44.9, 73.8, 125.7, 127.6, 128.5, 144.2. Anal. Calcd for $C_{10}H_{13}ClO \cdot 0.5H_2O$: C, 65.05; H, 7.10; N, 19.20. Found: C, 65.28; H, 7.20; N, 18.88. A solution of **41** (5.5 g, 29.8 mmol), benzylamine (4.8 g, 44.8 mmol), potassium iodide (9.9 g, 59.6 mmol), and potassium carbonate (8.2 g, 59.3 mmol) in DMF (300 mL) was stirred at 90 °C for 72 h. The reaction mixture was cooled to 23 °C and diluted with CH_2Cl_2 (100 mL). The solution was washed with water (30 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography (hexanes/EtOAc, 4:1) to afford 3.2 g (42%) of **42** as a colorless viscous oil. ^{1}H NMR δ 1.58−1.96 (m, 4 H), 2.60−2.67 (m, 1 H), 2.68−2.83 (m, 1 H), 3.78 (s, 2 H), 4.66 (dd, J = 3.2, 5.0 Hz, 1 H), 7.18−7.37 (m, 10 H). ^{13}C NMR δ 26.8, 39.2, 49.1, 53.6, 73.5, 125.5, 126.6, 127.1, 127.4, 127.5, 128.0, 128.3, 128.5, 145.93. ES-MS *m*/*z* 256 (MH^+). FAB−HRMS calcd for $C_{17}H_{21}NO + H^+$, 256.1701; found, 256.1706.

2-[(4-Hydroxy-4-phenylbutyl)(phenylmethyl)amino]-1-phenylethanone (43). To a solution of **42** (1.3 g, 5.1 mmol) and *N*,*N*-diisopropylethylamine (0.8 g, 6.2 mmol) in THF (34 mL) was added 2-bromoacetophenone (1.2 g, 6.0 mmol). The mixture was stirred at 23 °C for 24 h and diluted with CH_2Cl_2. The solution was washed with aqueous NH_4Cl (100 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash column chromatography (hexanes/EtOAc, 2:1) to afford 1.0 g (53%) of **43** as a light-yellow viscous oil. ^{1}H NMR δ 1.58−1.80 (m, 4 H), 2.68−2.81 (m, 2 H), 3.86 (s, 2 H), 4.63 (t, J = 5.3 Hz, 1 H), 7.22−7.42 (m, 7 H), 7.53 (t, J = 7.3 Hz, 1 H), 7.85 (d, J = 7.5 Hz, 2 H). ^{13}C NMR δ 23.7, 37.6, 54.3, 58.4, 58.8, 73.7, 125.7, 127.0, 127.2, 128.0, 128.3, 128.4, 131.1, 145.2, 198.2. ES-MS *m*/*z* 374 (MH^+). Anal. Calcd for $C_{25}H_{27}NO_2 \cdot 0.3H_2O$: C, 79.25; H, 7.35; N, 3.70. Found: C, 79.63; H, 7.33; N, 3.58.

4-[(2-Hydroxy-2-phenylethyl)(phenylmethyl)amino]-1-phenylbutanol (44, anti/syn). Reduction of **43** (68 mg, 0.18 mmol) with *R*-alpine-hydride (2.5 mol equiv, CH_2Cl_2, −78 °C, 2.5 h) and isolation by flash column chromatography (CH_2Cl_2/MeOH, 99:1) gave 60 mg (88%) of **44** as a colorless viscous oil; anti/syn = 1:1 (quantitated by ^{1}H NMR). ^{1}H NMR δ 1.52−1.83 (m, 4 H), 2.45−2.73 (m, 4 H), 3.50/3.94 (pair of d, J = 13.4 Hz, 1.00 H, anti CH_2Ph), 3.55/3.84 (pair of d, J = 13.4 Hz, 1.00 H, syn CH_2Ph), 4.5628−4.75 (m, 2 H), 7.24−7.35 (m, 15 H). ^{13}C NMR δ 23.3 (syn), 23.5 (anti), 37.1 (syn), 37.5 (anti), 54.0 (anti), 54.1 (syn), 58.7 (syn), 58.9 (anti), 62.6 (syn), 62.8 (anti), 69.8 (anti), 69.9 (syn), 74.0, 125.8, 127.2, 127.3, 127.8, 128.2, 128.3, 128.4, 129.2, 137.8, 142.2, 144.8. ES-MS *m*/*z* 376 (MH^+). Anal. Calcd for $C_{25}H_{29}NO_2 \cdot 1.0H_2O$: C, 76.31; H, 7.95; N, 3.56. Found: C, 76.30; H, 7.60; N, 3.26.

4-[(2-Hydroxy-2-phenylethyl)(phenylmethyl)amino]-1-phenylbutanone (46). In a flask equipped with a Dean−Stark trap, a solution of 4-chlorobutyrophenone (3.00 g, 16.4 mmol), ethylene glycol (1.56 g, 25.1 mmol), and *p*-toluenesulfonic acid monohydrate (312 mg, 1.64 mmol) in benzene (55 mL) was stirred at 90 °C for 18 h. The reaction mixture was cooled to 23 °C and diluted with ethyl acetate (100 mL). The solution was washed with 10% Na_2CO_3 (30 mL), water (30 mL), and brine (30 mL), then dried (Na_2SO_4), and concentrated in vacuo to give 3.70 g (99%) of ketal **45** as a yellow solid.[34] ^{1}H NMR δ 1.81−1.91 (m, 2 H), 2.04 (t, J = 6.4 Hz, 2 H), 3.53 (t, J = 6.8 Hz, 2 H), 3.77 (t, J = 6.8 Hz, 2 H), 4.02 (t, J = 6.8 Hz, 2 H), 7.29−7.37 (m, 3 H), 7.44 (d, J = 7.6 Hz, 2 H). ^{13}C NMR δ 27.1, 37.8, 45.1, 64.5, 110.0, 125.6, 128.0, 128.2, 142.3. Anal. Calcd for $C_{12}H_{15}ClO_2$: C, 63.58; H, 6.67. Found: C, 63.34; H, 6.65. A solution of 2-benzylamino-1-phenylethanol (1.02 g, 4.5 mmol), **45** (2.07 g, 9.1 mmol), potassium iodide (1.50 g, 9.0 mmol), and potassium carbonate (1.24 g, 9.0 mmol) in DMF (90 mL) was stirred at 90 °C for 24 h. The mixture was cooled to 23 °C and diluted with ethyl acetate (100 mL). The solution was washed (water, brine), dried (Na_2SO_4), and concentrated in vacuo. The residue was treated with 5% aqueous HCl in THF at 23 °C for 24 h. The mixture was neutralized with 1 N NaOH, extracted with CH_2Cl_2 (100 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash column chromatography (hexanes/EtOAc, 4:1) to afford 500 mg (30%) of **46** as a colorless viscous oil. ^{1}H NMR δ 1.88−2.10 (m, 2 H), 2.55−2.75 (m, 4 H), 2.89−3.00 (m, 2 H), 3.51 (d, J = 13.4 Hz, 1 H), 3.91 (d, J = 13.4 Hz, 1 H), 4.69 (dd, J = 4.2, 9.6 Hz, 1 H), 7.21−7.32 (m, 10 H), 7.44 (dd, J = 7.6 Hz, 2 H), 7.55 (dd, J = 7.4 Hz, 1 H), 7.91 (d, J = 7.2 Hz, 2 H). ^{13}C NMR δ 21.2, 35.9, 53.1, 58.4, 62.4, 69.6, 125.8, 127.2, 127.3, 127.9, 128.2, 128.4, 128.5, 128.8, 129.0, 132.9, 136.8, 138.3, 142.1, 199.6. ES-MS *m*/*z* 374 (MH^+). Anal. Calcd for $C_{25}H_{27}NO_2 \cdot 0.5H_2O$: C, 78.50; H, 7.38; N, 3.66. Found: C, 78.64; H, 7.09; N, 3.45.

Reduction of 1,7-Hydroxy Ketone 46 to 44. Reduction of **46** (25 mg, 0.067 mmol) with *R*-alpine-hydride (2.5 mol equiv, CH_2Cl_2, −78 °C, 2.5 h) and isolation by preparative TLC (hexanes/EtOAc, 3:1) gave 21 mg (84%) of **44**; anti/syn = 3:1 (determined by ^{1}H NMR). Reduction of **46** with $Zn(BH_4)_2$ (4.0 mol equiv, CH_2Cl_2, −78 °C, 22 h) gave a 63% TLC isolated yield of **44**; anti/syn = 1:2 (^{1}H NMR).

(2-Hydroxy-2-phenylethyl)phenylmethyl Carbamic Acid 1,1-Dimethylethyl Ester (47). 2-Benzylamino-1-phenylethanol (3.0 g, 13.2 mmol) was dissolved in acetonitrile (150 mL), and the solution was treated with *N*,*N*-diisopropylethylamine (4.6 mL, 26.4 mmol). The solution was cooled with stirring to 0 °C, when the starting material separated. The suspension was treated with di-*tert*-butyl carbonate (3.17 g, 14.52 mmol), and the resulting mixture was warmed to 23 °C.

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After the mixture was stirred for 18 h, TLC analysis (5% MeOH/CH_2Cl_2, ninhydrin) showed completion of the reaction. The reaction was diluted with ether (200 mL), and the mixture was washed sequentially with 0.1 N HCl (2 × 50 mL), water (2 × 30 mL), and brine (1 × 30 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo to give **47** (4.54 g, 100% crude yield). The product solidified on standing; it was recrystallized from hot hexanes and dried in vacuo at 45 °C for 12 h to give **47** (3.66 g, 85%) as white crystals, mp 77−78 °C. ^{1}H NMR (DMSO-d_6) δ 1.33/1.36 (s, 9H, Boc rotamers), 3.05−3.35 (m, 2H), 4.30−4.53 (m, 2H), 4.81 (m, 1H), 5.51 (m, 1H), 7.15−7.40 (m, 10 H). ^{13}C NMR (DMSO-d_6) δ 29.7, 51.8/53.0 (Boc rotamers), 55.5/56.0 (Boc rotamers), 72.9/73.2 (Boc rotamers), 80.5, 127.7, 128.6, 128.8, 128.9, 129.8, 130.1, 140.2/140.5 (Boc rotamers), 145.4, 156.7. CI-MS *m*/*z* 328 (MH^+). Anal. Calcd for $C_{20}H_{25}NO_3$: C, 73.37; H, 7.70; N, 4.28. Found: C, 73.23; H, 7.60; N, 4.42.

(2-Methoxy-2-phenylethyl)phenylmethyl Carbamic Acid 1,1-Dimethylethyl Ester (48). An oven-dried 50-mL pointed flask was charged with a NaH oil dispersion (34 mg, 60% dispersion, 0.84 mmol), and the dispersion was washed with pentane (2 × 2 mL). The resulting solid was suspended in anhydrous ether (2 mL), and the suspension was cooled with stirring to 0 °C. The stirred suspension was treated dropwise with a solution of **47** (250 mg, 0.763 mmol) and dimethyl sulfate (0.08 mL, 0.84 mmol) in ether (2 mL). The reaction was allowed to warm to 23 °C. After the mixture was stirred for 4 h, TLC analysis (EtOAc/hexanes, 1:3; phosphomolybdic acid) showed incomplete reaction. The mixture was cooled to 0 °C and treated sequentially with dimethyl sulfate (0.08 mL, 0.84 mmol) and the 60% NaH oil dispersion (34 mg, 0.84 mmol). After the mixture was stirred for an additional 18 h, TLC analysis showed completion of the reaction. The reaction was cooled to 0 °C and diluted with anhydrous ether (20 mL). The reaction was quenched with saturated aqueous NH_4Cl (10 mL). The organic phase was washed (water, brine), dried ($MgSO_4$), and concentrated to give a quantitative yield of crude product, which was purified by column chromatography (hexanes/EtOAc, 9:1) to yield **48** (222.5 mg, 86%) as a colorless oil. ^{1}H NMR δ 1.43/1.48 (s, 9 H, Boc rotamers), 3.23 (s, 3 H), 3.25−3.50 (m, 2 H), 4.30−4.60 (m, 3 H), 7.10−7.40 (m, 10 H). ^{13}C NMR δ 28.3, 50.9/52.1 (Boc rotamers), 52.7/53.5 (Boc rotamers), 56.9, 79.7, 82.4/83.1 (Boc rotamers), 126.5, 126.8, 126.9, 127.6, 127.7, 128.3, 138.3/138.7 (Boc rotamers), 139.9, 155.8. CI-MS *m*/*z* 342 (MH^+). Anal. Calcd for $C_{21}H_{27}NO_3$: C, 73.87; H, 7.97; N, 4.10. Found: C, 73.97; H, 8.00; N, 4.12.

***β*-Methoxy-*N*-(phenylmethyl)benzeneethanamine (49)·TFA.** A stirred solution of Boc-amine **48** (898 mg, 2.63 mmol) in CH_2Cl_2 (3.7 mL) at 0 °C was treated dropwise with trifluoroacetic acid (3.7 mL, 48.0 mmol). The reaction was warmed to 23 °C and stirred for 1 h, at which time TLC analysis (EtOAc/hexanes, 35:65; ninhydrin stain) showed complete reaction. The mixture was concentrated to dryness and azeotropically treated with CH_2Cl_2 (3 × 5 mL). The oily residue was further dried on a vacuum pump and then crystallized from ether/hexanes. The solid was dried in vacuo for 18 h at 45 °C to provide the TFA salt of **49** (605 mg, 65%) as a white crystalline solid, mp 85−87 °C. ^{1}H NMR δ 2.95 (dd, J = 12.8, 10.1 Hz, 1 H), 3.03 (dd, J = 12.8, 3.2 Hz, 1 H), 3.19 (s, 3 H), 4.12 (s, 2 H), 4.52 (dd, J = 10.1, 3.2 Hz, 1 H), 7.20−7.50 (m, 10 H). ^{13}C NMR δ 51.1, 51.9, 56.5, 78.9, 126.5, 128.7, 128.8, 129.1, 129.4, 129.9, 130.5, 136.9. CI-MS *m*/*z* 242 (MH^+). FAB−HRMS calcd for $C_{16}H_{19}NO + H^+$, 242.1544; found, 242.1538. Anal. Calcd for $C_{16}H_{19}NO{\cdot}CF_3CO_2H$: C, 60.80; H, 5.67; N, 3.94. Found: C, 60.80; H, 5.75; N, 3.89.

3-[(2-Methoxy-2-phenylethyl)(phenylmethyl)amino]-1-phenylpropanone (50). To a solution of unrecrystallized **49**·TFA (1.94 g, 4.4 mmol) in THF (28 mL) being stirred at 0 °C was added *N*,*N*-diisopropylethylamine (3.4 mL, 19.5 mmol) and 3-chloropropiophenone (783 mg, 4.6 mmol). The mixture was allowed to warm to 23 °C. After the mixture was stirred for 48 h, TLC analysis (MeOH/CH_2Cl_2,1:9; ninhydrin stain) showed a trace of starting material and product formation. The mixture was concentrated, and the residue was diluted with ethyl acetate. The solution was washed with 0.01 N HCl (3 × 10 mL) and brine (2 × 10 mL). The organic layer was dried (Na_2SO_4) and concentrated to dryness. Although chromatographic purification of the crude product proved difficult, it was eventually purified by column chromatography with an ethyl acetate−hexanes gradient (5−20% EtOAc) to give **50** (521 mg, 32%) as an orange oil. ^{1}H NMR δ 2.68 (dd, J = 13.9, 5.0 Hz, 1 H) 2.90 (dd, J = 13.9, 7.2 Hz, 1 H), 2.95−3.15 (m, 4 H), 3.19 (s, 3 H), 3.69 (d, J = 13.8 Hz, 1 H), 3.83 (d, J = 13.8 Hz, 1 H), 4.25 (dd, J = 7.2, 5.0 Hz, 1 H), 7.20−7.35 (m, 10 H), 7.42 (dd, J = 7.6, 7.3 Hz, 2 H), 7.53 (t, J = 7.3 Hz, 1 H), 7.85 (d, J = 7.6 Hz, 2 H). ^{13}C NMR δ 36.8, 50.1, 56.7, 59.7, 61.1, 82.8, 126.9, 127.5, 128.0, 128.1, 128.2, 128.5, 128.6, 128.8, 132.9, 136.9, 139.4, 141.1,199.7. CI-MS *m*/*z* 374 (MH^+). FAB−HRMS calcd for $C_{25}H_{27}NO_2 + H^+$, 374.2120; found, 374.2114.

3-[(2-Methoxy-2-phenylethyl)(phenylmethyl)amino]-1-phenylpropanol (51, anti/syn). A solution of methoxy ketone **50** (32.5 mg, 0.087 mmol) in CH_2Cl_2 (4 mL) at −78 °C was treated dropwise with *R*-alpine hydride (0.37 mL, 0.185 mmol) over 15 min. After being stirred for 3 h, the reaction was quenched with saturated aqueous NH_4Cl. The mixture was warmed to 23 °C, and the layers were separated. The organic layer was dried (Na_2SO_4) and concentrated to dryness. The residue was purified by preparative TLC (hexanes/EtOAc, 1:3) to provide diols **51** (26.4 mg, 80%). ^{1}H NMR δ 1.77−1.95 (m, 2 H), 2.50−2.55 (m, 1 H), 2.72−2.80 (m, 1 H), 2.87−3.00 (m, 2 H), 3.24 (s, 3 H), 3.47 (d, J = 13.2 Hz, syn, 0.2 H), 3.61 (d, J = 13.3 Hz, anti, 0.8H), 3.88 (d, J = 13.3 Hz, anti, 0.8 H), 4.03 (d, J = 13.2 Hz, syn, 0.2 H), 4.30 (dd, J = 3.4, 9.1 Hz, 1 H), 4.80 (dd, J = 2.6, 9.1 Hz, 1 H), 7.22−7.37 (m, 15 H). The anti/syn ratio was determined to be 4.0:1 by HPLC (YMC basic 25 cm × 4.6 mm; mobile phase 0.1% TFA−water (A) and 0.1% TFA−acetonitrile (B) with a linear ratio of 65% A/35% B; 1 mL/min; λ = 210 nm; injection volume, 5 μL; t_R = 25.7 min (syn isomer), 27.0 min (anti isomer)). The data were in line with those for the authentic anti isomer.

(*S*)-(2-Hydroxy-2-phenylethyl)phenylmethyl Carbamic Acid 1,1-Dimethylethyl Ester ((*S*)-47). (*S*)-2-Chloro-1-phenylethanol (5.33 g, 34.0 mmol, Aldrich) and benzylamine (3.64 g, 34.0 mmol) were stirred at 180 °C for 2 h and then cooled to 23 °C. The crude product, obtained as for (*R*)-**37**, was purified by flash column chromatography (CH_2Cl_2/MeOH/NH_4OH, 93:6:1) to afford 6.20 g (80%) of (*S*)-**37** as a colorless viscous oil. The ^{1}H NMR spectrum was identical with that for (*R*)-**37**. To a solution of (*S*)-**37** (1.23 g, 5.4 mmol) and *N*,*N*-diisopropylethylamine (1.40 g, 10.8 mmol) in acetonitrile (60 mL) was added di-*tert*-butyl carbonate (1.3 g, 6.0 mmol). The mixture was stirred at 23 °C for 21 h and diluted with CH_2Cl_2 (100 mL). The solution was washed with saturated aqueous NH_4Cl (20 mL), water (20 mL), and brine (20 mL) and then dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash column chromatography (CH_2Cl_2/MeOH/NH_4-OH, 97:2:1) to afford 1.60 g (98%) of (*S*)-**47** as a colorless viscous oil. ^{1}H NMR δ 1.48 (s, 9 H), 3.30−3.54 (m, 2 H), 4.15−4.46 (m, 2 H), 4.85−4.90 (m, 1 H), 7.18−7.30 (m, 10 H). ^{13}C NMR δ 28.3, 52.4, 55.5, 74.0, 125.7, 127.2, 128.5, 142.3, 157.9. Anal. Calcd for $C_{20}H_{25}NO_3{\cdot}0.8H_2O$: C, 70.28; H, 7.85; N, 4.10. Found: C, 69.98; H, 7.47; N, 4.22.

(*S*)-(2-Methoxy-2-phenylethyl)phenylmethyl Carbamic Acid 1,1-Dimethylethyl Ester ((*S*)-48). To a cooled solution (0 °C) of (*S*)-**47** (600 mg, 1.8 mmol) in ethyl ether (20 mL) was added sodium hydride (50 mg, 2.0 mmol), followed by methyl iodide (320 mg, 2.3 mmol). The reaction mixture was stirred at 23 °C for 1 h and then quenched with water (5 mL). The solution was extracted with ethyl acetate (50 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography (hexanes/EtOAc,1.5:1) to afford 200 mg (32%) of (*S*)-**48** as a colorless viscous oil. ^{1}H NMR δ 1.48 (s, 9 H), 3.23 (s, 3 H), 3.28−3.48 (m, 2 H), 4.37−4.49 (m, 3 H), 7.19−7.34 (m, 10 H). ^{13}C NMR δ 28.4, 52.3, 53.6, 57.0, 79.8, 126.7, 127.7, 128.4, 142.3, 157.9. FAB−HRMS calcd for $C_{21}H_{28}NO_3 + H^+$, 342.2069; found, 342.2040.

***β*-Methoxy-*N*-(phenylmethyl)benzeneethanamine·TFA ((*S*)-49).** To a cooled solution (0 °C) of (*S*)-**48** (160 mg, 0.5 mmol) in CH_2Cl_2(2 mL) was added trifluoroacetic acid (3.0 g, 26.3 mmol). The reaction mixture was stirred at 0 °C for 1

h and concentrated in vacuo to afford 165 mg (98%) of (*S*)-**49** as a white solid. ^{1}H NMR δ 2.95−3.12 (m, 2 H), 3.18 (s, 3 H), 4.17 (s, 2 H), 4.47 (dd, J = 2.8, 10.2 Hz, 1 H), 7.23−7.39 (m, 10 H). ^{13}C NMR δ 51.4, 52.1, 56.5, 78.6, 126.4, 128.9, 129.8. FAB-HRMS calcd for $C_{16}H_{19}NO + H^+$, 242.1547; found, 242.1545.

3-[(2-Methoxy-2-phenylethyl)(phenylmethyl)amino]-1-phenylpropanol (*anti*-51). A solution of (*S*)-**49** (202 mg, 0.9 mmol), potassium iodide (300 mg, 1.8 mmol), potassium carbonate (250 mg, 1.8 mmol), and (*S*)-3-chloro-1-phenylpropanol in DMF was refluxed for 18 h. The mixture was concentrated in vacuo and diluted with ethyl acetate (50 mL). The solution was washed with saturated aqueous ammonium chloride (10 mL), water (10 mL), and brine (10 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by flash column chromatography (hexanes/EtOAc, 9:1) to afford 248 mg (75%) of *anti*-**51** as a colorless viscous oil. $[\alpha]^{24}_D$ +28.5 (*c* 1.0, $CHCl_3$). ^{1}H NMR δ 1.73−1.95 (m, 2 H), 2.49−2.55 (m, 1 H), 2.71−2.78 (m, 1 H), 2.89−2.98 (m, 2 H), 3.23 (s, 3 H), 3.60 (d, J = 13.4 Hz, 1H), 3.87 (d, J = 13.3 Hz, 1 H), 4.30 (dd, J = 3.2, 9.0 Hz, 1 H), 4.80 (dd, J = 2.5, 9.2 Hz, 1 H), 7.21−7.39 (m, 15 H). ^{13}C NMR δ 35.5, 53.9, 56.7, 59.7, 61.3, 75.1, 82.1, 125.7, 126.7, 127.8, 128.5, 130.9, 138.3, 140.4, 145.2. Anal. Calcd for $C_{25}H_{29}NO_2$: C, 79.97; H, 7.79; N, 3.74. Found: C, 79.79; H, 7.70; N, 3.56. This material was used to assign the anti isomer in the anti/syn mixture of **51** from the reduction of **50**.

3-(2-Hydroxy-2-phenylethoxy)-1-phenylpropanone (52). A solution of 1-phenyl-1,2-ethanediol (1.3 g, 9.4 mmol) in CH_2Cl_2 (50 mL) was cooled to 0 °C, and sodium hydride (230 mg, 9.4 mmol) was added in portions. After the mixture was stirred at 0 °C for 30 min, 3-chloropropiophenone (1.6 g, 9.5 mmol) was added and the reaction was stirred at 23 °C for 1 h. The reaction was quenched with saturated aqueous ammonium chloride (10 mL) and diluted with CH_2Cl_2 (100 mL). The solution was washed (water, brine), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash column chromatography (hexanes/EtOAc, 2:1) to afford 400 mg (16%) of **52** as a white solid. ^{1}H NMR δ 3.28 (t, J = 6.0 Hz, 2 H), 3.49 (t, J = 9.4 Hz, 1 H), 3.67 (dd, J = 3.2, 6.9 Hz, 1 H), 3.90−4.06 (m, 2 H), 4.90 (d, J = 9.0 Hz, 1 H), 7.25−7.40 (m, 5 H), 7.47 (dd, J = 7.9 Hz, 2 H), 7.58 (dd, J = 7.4 Hz, 1 H), 7.97 (d, J = 7.2 Hz, 2 H). ^{13}C NMR δ 38.5, 66.1, 72.5, 76.6, 126.2, 127.7, 128.1, 128.4, 128.7, 133.3, 136.8, 140.2, 198.4. Anal. Calcd for $C_{17}H_{18}O_3$: C, 75.54; H, 6.72. Found: C, 75.34; H, 6.71.

3-(2-Hydroxy-2-phenylethoxy)-1-phenylpropanol (53, anti/syn). Reduction of **52** (49 mg, 0.18 mmol) with *R*-alpine-hydride (2.2 mol equiv, −78 °C, 18 h) and isolation by flash column chromatography (hexanes/EtOAc, 7:3) provided 40 mg (82%) of **53** as a colorless oil; anti/syn = 1:1 (quantitated by ^{1}H NMR). ^{1}H NMR (DMSO-d_6) δ 1.57−1.85 (m, 2 H, CH_2Ph), 3.30−3.56 (m, 4 H), 4.56−4.62/4.63−4.69 (2 m, 0.50 H each), 5.14/5.32 (2 d, J = 4.5 Hz, 0.50 H each), 7.20−7.37 (m, 10 H). ^{13}C NMR (DMSO-d_6) δ 29.8, 69.2, 71.2, 73.1, 78.0, 127.4, 128.0, 128.4, 128.7, 129.6, 129.7, 145.0, 147.8. Anal. Calcd for $C_{17}H_{20}O_3 \cdot 0.1H_2O$: C, 74.39; H, 7.44. Found: C, 74.06; H, 7.69.

3-(2-Hydroxy-2-phenylethylamino)-1-phenylpropanone (54a). To a solution of 2-amino-1-phenylethanol (0.96 g, 7.0 mmol) and *N*,*N*-diisopropylethylamine (1.81 g, 14.0 mmol) in THF (30 mL) cooled with an ice bath was added dropwise a solution of 3-chloropropiophenone (1.20 g, 7.14 mmol) in THF (16 mL). The reaction mixture was stirred at 23 °C for 5 h, at which time TLC indicated that reaction was complete. A copious white precipitate formed. The mixture was stored at 5 °C overnight, and the solids were collected and washed with ether (4 × 30 mL). The solids were partitioned between 1 N NaOH (30 mL) and CH_2Cl_2 (80 mL). The organic solution was washed (water, brine), dried (Na_2SO_4), and concentrated in vacuo to afford 0.63 g (33%) of **54a** as a colorless solid. ^{1}H NMR δ 2.72 (dd, J = 9.2, 12.2 Hz, 1 H), 2.96 (dd, J = 3.6, 12.3 Hz, 1 H), 3.01−3.22 (m, 4 H), 4.72 (dd, J = 3.3, 9.1 Hz, 1 H), 7.26−7.39 (m, 10 H), 7.48 (dd, J = 7.7 Hz, 2 H), 7.58 (dd, J = 7.2 Hz, 1 H), 7.96 (d, J = 7.5 Hz, 2 H). ^{13}C NMR δ 38.7, 44.1, 57.2, 71.6, 125.8, 127.5, 128.0, 128.4, 128.7, 133.3, 142.4, 199.5. ES-MS m/z 270 (MH^+). An analytically pure sample was obtained by flash column chromatography (hexanes/EtOAc, gradient of 90:10 to 50:50). Anal. Calcd for $C_{17}H_{19}NO_2 \cdot 0.1H_2O$: C, 75.31; H, 7.14; N, 5.17. Found: C, 75.23; H, 7.00; N, 5.25.

3-[(2-Hydroxy-2-phenylethyl)methylamino]-1-phenylpropanone (54b). To a solution of α-(methylaminomethyl)-benzyl alcohol (1.06 g, 7.0 mmol) and *N*,*N*-diisopropylethylamine (1.81 g, 14.0 mmol) in THF (46 mL) was added 3-chloropropiophenone (1.42 g, 8.4 mmol). The mixture was stirred at 23 °C for 5 h and filtered. The filtrate was concentrated in vacuo, the residue was dissolved in ethyl acetate, and the solution was washed (0.01 N HCl, brine). The organic solution was treated with 14 mL of 1 N HCl in ether and 40 mL of ether. The mixture was cooled to 0 °C, and the solvent was decanted. The sticky residue was triturated with ether and dissolved in 0.01 N HCl (15 mL). The aqueous solution was washed with ether (2 × 10 mL), basified with 1 N NaOH (14 mL), and extracted with ethyl acetate (2 × 30 mL). The organic solution was washed with brine (2 × 15 mL), dried (Na_2SO_4), and concentrated in vacuo to afford 1.78 g (90%) of **54b** as a colorless solid. ^{1}H NMR δ 2.39 (s, 3 H), 2.53−2.56 (m, 2 H), 2.83−2.92 (m, 1 H), 3.05−3.21 (m, 3 H), 4.72 (dd, J = 5.0, 8.8 Hz, 1 H), 7.24−7.60 (m, 8 H), 7.97 (d, J = 7.3 Hz, 2 H). ^{13}C NMR δ 36.4, 42.1, 52.5, 66.1, 69.5, 125.9, 127.4, 128.1, 128.3, 128.7, 133.2, 136.9, 142.1, 199.2. CI-MS m/z 284 (MH^+). An analytically pure sample was obtained by flash column chromatography (hexanes/EtOAc, 70:30). Anal. Calcd for $C_{18}H_{21}NO_2$: C, 76.30; H, 7.47; N, 4.95. Found: C, 75.98; H, 7.36; N, 4.75.

3-[(2-Hydroxy-2-phenylethyl)(2,4,6-trimethylbenzyl)-amino]-1-phenylpropanone (54c). A mixture of **54a** (455 mg, 1.69 mmol), 2,4,6-trimethylbenzyl chloride (514 mg, 3.05 mmol), and *N*,*N*-diisopropylethylamine (873 mg, 6.77 mmol) in THF−DMF (4:1, 18 mL) was stirred at 50 °C for 30 h. The mixture was concentrated in vacuo, and the residue was separated by flash column chromatography (hexanes/EtOAc/Et_3N, 6:1:0.2; quickly to avoid the decomposition of the product on the column) to give 387 mg (57%) of **54c** as a colorless viscous solid. ^{1}H NMR δ 2.22 (s, 3 H), 2.31 (s, 6 H), 2.53−2.69 (m, 2 H), 2.89−2.99 (m, 1 H), 3.05−3.24 (m, 3 H), 3.59 (d, J = 12.5 Hz, 1 H), 3.85 (d, J = 12.5 Hz, 1 H), 4.63 (dd, J = 3.2, 10.0 Hz, 1 H), 6.77 (s, 2 H), 7.21−7.36 (m, 5 H), 7.42 (t, J = 7.4 Hz, 2 H), 7.55 (t, J = 7.3 Hz, 1 H), 7.86 (d, J = 7.4 Hz, 2 H). ^{13}C NMR δ 20.2, 20.8, 36.6, 47.1, 49.8, 53.2, 57.3, 62.9, 70.2, 125.8, 127.2, 128.0, 128.1, 128.5, 128.8, 129.0, 129.2, 131.1, 133.0, 136.5, 136.7, 137.5, 142.1, 199.4. ES-MS m/z 402 (MH^+). Free base **54c** was converted to an HCl salt in ether by adding 1 N HCl in ether (colorless solid). The resulting colorless solid was collected and triturated with ether. Anal. Calcd for $C_{27}H_{31}NO_2 \cdot 1.0HCl \cdot 0.4H_2O$: C, 72.84; H, 7.43; N, 3.15; Cl, 7.96. Found: C, 72.98; H, 7.41; N, 3.12; Cl, 8.15.

3-(2-Hydroxy-2-phenylethylamino)-1-phenylpropanol (55a, anti/syn). Reduction of **54a** (81 mg, 0.30 mmol) with *R*-alpine-hydride (3.1 mol equiv, CH_2Cl_2, −78 °C, 4.5 h) and isolation by preparative TLC (CH_2Cl_2/MeOH/NH_4OH, 90:9:1) gave 70 mg (86%) of **55a** as a colorless viscous oil; anti/syn = 2:1 (quantitated by ^{1}H NMR; quantitated and assigned by ^{13}C NMR). ^{1}H NMR δ 1.76−1.98 (m, 2 H), 2.72−3.01 (m, 4 H), 4.78−4.92 (m, 2 H), 7.16−7.42 (m, 10 H). ^{13}C NMR δ 36.9 (syn), 37.2 (anti), 47.5 (syn), 47.6 (anti), 56.5 (syn), 56.7 (anti), 72.0 (syn), 72.1 (anti), 74.7 (syn), 74.8 (anti), 125.5, 125.7, 127.1, 127.7, 128.2, 128.4, 142.1, 144.4. CI-MS m/z 272 (MH^+). Anal. Calcd for $C_{17}H_{21}NO_2 \cdot 0.7H_2O$: C, 71.91; H, 7.96; N, 4.94. Found: C, 71.99; H, 7.83; N, 4.98.

3-[(2-Hydroxy-2-phenylethyl)methylamino]-1-phenylpropanol (55b, anti/syn). Reduction of **54b** (85 mg, 0.30 mmol) with *R*-alpine-hydride (2.1 mol equiv, −78 °C, 4.5 h) and isolation by preparative TLC (CH_2Cl_2/MeOH, 92:8) gave 70 mg (82%) of **55b** as a colorless viscous oil; anti/syn = 3:1 (quantitated by ^{1}H NMR; quantitated and assigned by ^{13}C NMR). ^{1}H NMR δ 1.82−1.95 (m, 2 H), 2.39 (syn), 2.40 (anti) (2 s, 3 H), 2.44−2.88 (m, 4 H), 4.78−4.91 (m, 2 H), 7.26−7.38 (m, 10 H). ^{13}C NMR δ 35.1 (syn), 35.2 (anti), 42.0 (syn), 42.4 (anti), 55.7 (syn), 55.9 (anti), 66.0 (anti), 66.2 (syn), 70.3, 73.8

(syn), 74.4 (anti), 125.5, 125.8, 127.2, 127.5, 128.2, 128.3, 142.1, 144.5. CI-MS *m*/*z* 286 (MH^+). Free base **55b** was converted to an HCl salt in ether by adding 1 N HCl in ether (colorless solid). Anal. Calcd for $C_{18}H_{23}NO_2 \cdot 1.0HCl \cdot 0.4H_2O$: C, 65.70; H, 7.60; N, 4.26, Cl, 10.77. Found: C, 65.95; H, 7.47; N, 4.14; Cl, 10.92.

3-[(2-Hydroxy-2-phenylethyl)(2,4,6-trimethylbenzyl)-amino]-1-phenylpropanol (55c, anti and syn). Reduction of **54c** (80 mg, 0.20 mmol) with *R*-alpine-hydride (2.1 mol equiv, CH_2Cl_2, −78 °C, 4.5 h) and isolation by preparative TLC (hexanes/EtOAc, 4:1) gave 45 mg (56%) of **55c** as a colorless viscous oil; anti/syn = 22:1 (determined by 600-MHz ^{1}H NMR). ^{1}H NMR δ 1.83−1.88 (m, 1 H), 1.99−2.05 (m, 1 H), 2.33 (s, 3 H), 2.40 (syn), 2.42 (anti) (2s, 6 H), 2.64−2.67 (m, 2 H), 2.79 (dd, J = 10.3, 13.3 Hz, 1 H), 2.93 (m, 1 H), 3.62 and 3.64 (d, J = 12.6 Hz, anti; d, J = 12.7 Hz, syn; 1 H), 3.89 and 3.95 (d, J = 12.7 Hz, syn; d, J = 12.6 Hz, anti; 1 H), 4.69 (dd, J = 3.8 and 8.6 Hz, 1 H), 4.79 (d, J = 8.8 Hz, 1 H), 6.93 (s, 2 H), 7.26−7.37 (m, 10 H). CI-MS *m*/*z* 404 (MH^+). Free base **55c** was converted to an HCl salt in ether by adding 1 N HCl in ether (colorless solid). Anal. Calcd for $C_{27}H_{33}NO_2 \cdot 1.0HCl \cdot 0.4H_2O$: C, 72.51; H, 7.84; N, 3.13; Cl, 7.93. Found: C, 72.76; H, 7.54; N, 2.93; Cl, 8.06.

***N*-(2-Hydroxy-2-phenylethyl)-*N*-(3-oxo-3-phenylpropyl)benzamide (56).** To a cooled (0 °C) solution of **54a** (500 mg, 1.9 mmol) in CH_2Cl_2 (37 mL) was added benzoyl chloride (300 mg, 1.9 mmol) dropwise. The reaction mixture was stirred at 0 °C for 1 h and then treated with pyridine (150 mg, 1.9 mmol). After being stirred at 0 °C for 4 h, the mixture was washed with water (50 mL) and brine (50 mL), dried ($MgSO_4$), and concentrated in vacuo. The crude product was purified by flash column chromatography (hexanes/EtOAc, 2:1) to afford 550 mg (79%) of **56** as a colorless viscous oil. ^{1}H NMR δ 2.51 (br s, 2 H), 3.16−3.60 (m, 3 H), 3.78−3.98 (m, 1 H), 4.70 and 4.90 (br s, 1 H), 7.28−7.62 (m, 12 H), 7.82 (d, J = 7.3 Hz, 1 H), 8.10 (d, J = 7.5 Hz, 2 H). ^{13}C NMR δ 36.2, 43.3, 56.6, 58.4, 72.1, 72.5, 127.4, 127.9, 128.5, 128.9, 130.0, 130.6, 131.0, 135.0, 138.8, 144.8, 172.9, 199.9, 200.9. ES-MS *m*/*z* 374 (MH^+). Anal. Calcd for $C_{24}H_{23}NO_3 \cdot 0.4H_2O$: C, 75.73; H, 6.30; N, 3.68. Found: C, 75.98; H, 6.18; N, 3.53.

***N*-(2-Hydroxy-2-phenylethyl)-*N*-(3-hydroxy-3-phenylpropyl)benzamide (57, anti/syn).** Reduction of **56** (86 mg, 0.23 mmol) with 2.2 mol equiv of *R*-alpine-hydride (−78 °C, CH_2Cl_2, 20 h) and isolation by flash column chromatography (hexanes/EtOAc, 1:1) gave 61 mg (70%) of **57** as a colorless viscous oil. ^{1}H NMR (T = 353 K) δ 1.89 (br s, 2 H), 3.50 (br s, 4 H), 4.51 and 4.80 (br s, 1 H), 4.97 (br s, 1 H), 7.17−7.63 (m, 15 H). ES-MS *m*/*z* 376 (MH^+). Since the complex ^{1}H NMR would not permit the assay of stereoisomers, benzamide **57** was reduced to the corresponding amine **35**. Thus, *tert*-butyldimethylsilyl chloride (55 mg, 0.36 mmol) was added to a solution of **57** (61 mg, 0.16 mmol), 4-(dimethylamino)pyridine (15 mg, 0.12 mmol), and triethylamine (0.07 mL, 0.50 mmol) in CH_2Cl_2 (1.2 mL). The reaction mixture was stirred at 23 °C for 18 h and then diluted with CH_2Cl_2 (50 mL). The solution was washed with water (10 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was dissolved in THF (0.25 mL), borane−THF (0.4 mL, 0.4 mmol) was added, and the mixture was refluxed for 6 h. Aqueous K_2CO_3 (0.6 mL, 0.24 mmol) was added, and the mixture was refluxed for 1 h. The mixture was cooled and diluted with ethyl acetate (50 mL). The solution was washed (water, brine), dried (Na_2SO_4), and concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (1 mL) and treated with tetrabutylammonium fluoride (0.65 mL, 0.65 mmol). After 1 h, the mixture was diluted with CH_2Cl_2 and washed with water. After being dried ($MgSO_4$) and concentrated in vacuo, the residue was purified by preparative TLC (CH_2Cl_2/MeOH/NH_4OH, 90:9:1) to afford 30 mg (51%) of **35** as a colorless viscous oil with an anti/syn ratio of 1.5:1 (by ^{1}H NMR). ^{1}H NMR was consistent with the structural assignment and compared favorably with earlier data for anti/syn mixtures of **35** (*vide supra*).

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Supporting Information Available: Proton NMR spectra for **24**, **35**, and **44** with a focus on the *N*-benzyl proton signals used to quantitate anti and syn isomers (5 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.

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