JOC Article

Diastereoselective Aldolization of α-Aminonitriles. Diastereoselective Synthesis of β-Amino Alcohols and β,γ-Diamino Alcohols

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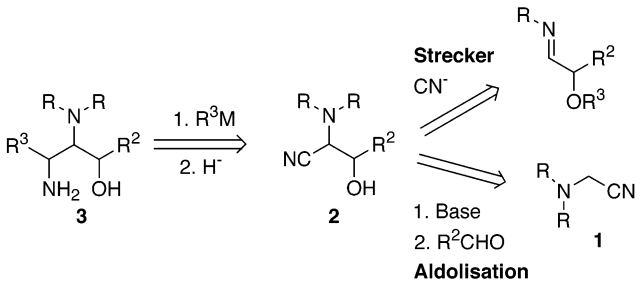
Aldolization performed by addition of lithiated *N*-benzyl-*N*-*tert*-butylaminoacetonitrile to aldehydes provides diastereomerically pure *anti*-β-hydroxy-α-aminonitriles. They are transformed into *syn*,*anti*-protected β,γ-diamino alcohols by a two-step procedure, involving addition of a Grignard reagent and reduction. The cleavage of the *N*-*tert*-butyl group is achieved by a simple acidic treatment. The application of this methodology to chiral, nonracemic aldehydes is studied. Starting from D-isopropylideneglyceraldehyde, an *anti*, *anti*, *syn*, *anti*-(2*R*,3*S*,4*S*,5*R*,6*R*)-diaminotriol is prepared in acceptable yield and with a good level of diastereoselectivity.

Introduction

α-Aminonitriles **1** are very popular bifunctional synthons that have found numerous synthetic applications.[1] It was shown in the late 1950s that such compounds, if they bear an α-hydrogen, are easily deprotonated in the α-position by strong bases, leading to metalated α-aminonitriles **1**, which may undergo various and efficient nucleophilic reactions.[2] Among these reactions, the addition to aldehydes is documented but has been mainly used for the preparation of compounds where the nitrile functionality is removed after reaction via either a reductive decyanation, leading to amines, or a retro-Strecker reaction, leading to carbonyl compounds.[1,3] The metalated α-aminonitriles act in this case either as masked acyl anions or as α-aminocarbanions. Because of this, little is known about the stereochemical course of the aldol-type reaction performed by the addition of these organometallic reagents to aldehydes. This lack of information contrasts strongly with the number of results described with metalated arylacetonitriles.[4] The synthetic utility of such a reaction may provide access to functionalized aldols **2** with the possible control of the relative and absolute configuration of two stereocenters. The preparation of these aldols, which are precursors of β-hydroxy-α-amino acids, an important class of amino acids, is generally performed by a diastereoselective Strecker-type reaction.[5] In this way, *syn*-aldols are obtained as the major products. We were interested in the development of a diastereo- and enantioselective access to β,γ-diamino alcohols **3**[6] that may provide access to all the possible diastereomers. These stereotriads might be obtained from the aldols **2** by a sequence of reactions involving the addition of an organometallic reagent to the nitrile group followed by an in situ reduction of the intermediate imine,[7] as shown in Scheme 1. We report herein the synthesis of compounds of type **3**, which resulted in the development of a diastereose-

SCHEME 1



* Corresponding author. Tel: (33) 1 44275567. Fax: (33) 1 44277567.

(1) Enders, D.; Shilvock, J. P. *Chem. Soc. Rev.* **2000**, *29*, 359−373.

(2) (a) Hauser, C. R.; Taylor, H. M.; Ledford, T. G. *J. Am. Chem. Soc.* **1959**, *82*, 1786−1789. (b) Taylor, H. M.; Hauser, C. R. *J. Am. Chem. Soc.* **1959**, *82*, 1790−1792. (c) Taylor, H. M.; Hauser, C. R. *J. Am. Chem. Soc.* **1959**, *82*, 1960−1965

(3) (a) Stork, G., Jacobson, R. M., Levitz, R *Tetrahedron Lett.* **1979**, *20*, 771−774. (b) Husson, H.-P, Royer, J. *Chem. Soc. Rev.* **1999**, *28*, 383. (c) Enders, D.; Lotter, H. *Tetrahedron Lett.* **1982**, *23*, 639−642.

(4) (a) Carlier, P. R.; Moon Lo, K. *J. Org. Chem.* **1994**, *59*, 4053−4055. (b) Carlier, P. R.; Moon Lo, K.; Lo, M. M.-C.; Williams, I. D. *J. Org. Chem.* **1995**, *60*, 7511−7517. (c) Carlier, P. R.; Moon Lo, K.; Lo, M. M.-C.; Lo, P. C.-K.; Lo, C. W.-S. *J. Org. Chem.* **1997**, *62*, 6316−6321. Mecozzi, T., Petrini, M., Profeta, R. *J. Org. Chem.* **2001**, *66*, 8264−8267. Carlier, P. R., Madura, J. D. *J. Org. Chem.* **2002**, *67*, 3832−3840.

(5) (a) Zandbergen, P., Brussee, J. Van Der Gen, A.*Tetrahedron: Asymmetry* **1992**, *3*, 769−774. (b) Cainelli, G., Giacomini, D., Treré, A, Galletti, P. *Tetrahedron: Asymmetry* **1995**, *6*, 1593−1600. (c) Chakraborty, T. K., Jayaprakash, S. *Tetrahedron Lett.* **1997**, *38*, 8899−8902. (d) Badorrey, R., Cativiela, C., Diaz-de-Villegas, M. D., Galvez, J. A. A. *Tetrahedron: Asymmetry* **2000**, *11*, 1015−1025. Davis, F. A., Srirajan, V., Fanelli, D. L., Portonovo, P. *J. Org. Chem.* **2000**, *65*, 7663−7666.

(6) (a) Cromwell, N.H., Tsou, K. C. *J. Org. Chem.* **1950**, *15*, 1219−1223. (b) Klein, J. L., Combret, J. C. *Bull. Soc. Chim. Fr.* **1983**, 28−32.

(7) Brussee, J.; Dofferhoff, F.; Kruse, C. G.; Van Der Gen, A. *Tetrahedron* **1990**, *46*, 1653−1658.

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SCHEME 2

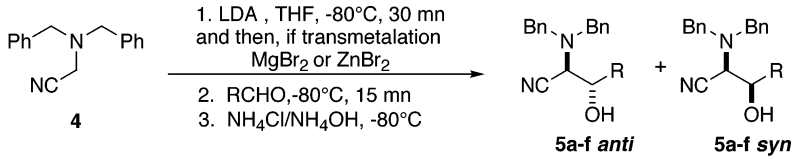


TABLE 1. Addition of Metalated Dibenzylaminoacetonitrile 4 to Aldehydes

entry	R	M	solvent	product	*anti*/*syn*[a]	yield (%)[b]
1	Ph	Li	THF	**5a**	50/50	75
2	Mes	Li	THF	**5b**	63/37	68
3	crotyl	Li	THF	**5c**	71/29	70
4	*n*-Bu	Li	THF	**5d**	70/30	70
5	*c*-Hex	Li	THF	**5e**	80/20	65
6	*t*-Bu	Li	THF	**5f**	91/09	65
7	*c*-Hex	Li	THF+ TMEDA	**5e**	80/20	70
8	*c*-Hex	Li	Et_2O	**5e**	80/20	50
9	*c*-Hex	$MgBr^c$	THF	**5e**	80/20	67
10	*c*-Hex	$ZnBr^c$	THF	**5e**	80/20	37

[a] Determined by ^1H NMR of the crude mixture. [b] Reported yields are weight recoveries of the combined *syn*- and *anti*-stereoisomers. The byproduct results from the addition of LDA to **4** to give the corresponding amide. [c] Two hours at −40 °C and then 0 °C.

lective aminoacetonitrile aldol reaction and the diastereoselective synthesis of some *syn*,*anti*-*β*,*γ*-diamino alcohols.

Results and Discussion

The first part of this study was an examination of the stereochemical course of the addition of metalated unsubstituted α-aminonitriles **1** to aldehydes. The first attempts were performed with *N*,*N*-dibenzylaminoacetonitrile **4**[8] via deprotonation with LDA at low temperature and quenching of the resulted anion with several aldehydes (Scheme 2, Table 1).

As can be seen in Table 1, the addition of lithiated *N*,*N*-dibenzyl aminonitrile to several aldehydes in THF was not diastereoselective (entries 1−5). High diastereoselectivity was only achieved with the bulky pivalaldehyde (entry 6). The use of TMEDA as a cosolvent or Et_2O rather than THF (entries 5, 7 and 8) did not change the diatereoselectivity. Additionally, a lower temperature (−100 °C) or transmetalation with $MgBr_2$ or $ZnBr_2$ (entries 9 and 10) had no effect. The *anti* relative configuration of the major diastereomer was assigned on the basis of an X-ray analysis of the crystalline aldol **5f**.[9,10] Last, we have shown that the aldolization was not under thermodynamic control, since deprotonation of the pure *syn* aldol **5f** with LDA in THF gave **5f** completely unchanged after several hours of stirring. Since the diastereoselectivity of the aldol reaction seems to be sensitive to steric factors, the influence of other nitrogen substituents on α-aminonitriles **6**−**9** was examined via addition of the lithiated derivatives to cyclohexylcarboxaldehyde (entries 1−4, Table 2).

The dimethylpyrrole derivative **6**, utilized by Uneyama,[11] and four other α-aminonitriles (**7**, **8**, **9a**, and **9b**) bearing bulky *N*-substituents were prepared as shown in Scheme 3. It is noteworthy that the *tert*-butyl derivatives **9a,b** were the most easily obtained of all these bulky substrates. The aldolization performed with the lithiated aminonitrile **6** in THF occurred in good yield but with poor selectivity (entry 1). This result points out the importance of the presence of a sp^3 nitrogen in the aminonitrile, probably due to steric factors. The use of Et_2O as a solvent slightly increased the diastereoselectivity, but led to the formation of a byproduct resulting from the addition of LDA to the nitrile, thus lowering the yield. Aminonitriles **7** and **8** gave the corresponding aldols in poor yields (entries 2 and 3), with a large amount of the starting material being recovered. The selectivity appeared to be high by ^1H NMR (see note *c*, Table 2), but with such low conversion, one must be cautious. This lack of efficiency could not be attributed to anion formation, as complete deprotonation was confirmed by deuteriolysis. Finally, the best result was obtained with **9a**, which provided the corresponding aldol in good yield and high selectivity (entry 4). Several aldehydes were then tested (Table 2, entries 5−8) with **9a**, and all of them were found to react cleanly with high selectivity (in all cases only one diastereomer was observed by ^1H NMR of the crude mixture).

All the aldols **10b**−**f** were crystalline compounds and could be purified by recrystallization. The anti relative configuration was determined by X-ray analysis of **10c**.[12] To rule out any π interaction in the transition state, we have checked that the addition of lithiated **9b** to cyclohexyl carboxaldehyde provided selectively the corresponding *anti*-aldol **10g** in good yield (Table 2, entry 9).

As was shown above, the selectivity appears to be kinetically controlled under our reaction conditions. Therefore, a flat six-membered transition state[4,13] involving a *N*-lithiated α-cyano anion[14] (Scheme 4) can be postulated in order to rationalize the anti-selectivity of the aldol reaction. Obviously, higher anti-selectivity is expected by increasing the size of the R^3 group of the aldehyde. Indeed, using the α-aminonitrile **4**, the best result was obtained with pivalaldehyde.

More difficult is the rationalization for the increase in

(8) Guillaume, D., Aitken, D. J., Husson, H. P. *Synlett*, **1991**, 747−749.

(9) Crystallographic data for the strustural analysis have been deposited with the Cambridge Crystallographic Data Center, CCDC No. 178177.

(10) The vicinal H_2-H_3 coupling constants in the ^1H NMR were found to be higher for all the minor (syn) diastereomers than the corresponding ones observed for the major (anti) diastereomers; see ref 4.

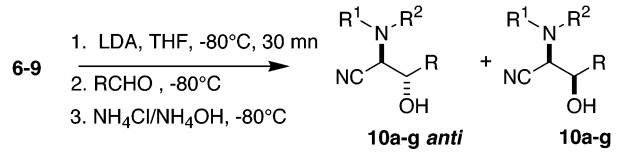
(11) Katagiri, T.; Irie, M.; Uneyama, K. *Org. Lett.* **2000**, *2*, 2423−2427

(12) Crystallographic data for the strustural analysis have been deposited with the Cambridge Crystallographic Data Center, CCDC No. 178048.

(13) Ishiguro, M.; Ikeda, N.; Yamamoto, H. *J. Org. Chem.* **1982**, *47*, 2225−2227.

(14) Enders, D.; Kirchhoff, J.; Gerdes, P.; Mannes, D.; Raabe, G.; Runsink, J.; Boche, G.; Marsch, M.; Ahlbrecht, H.; Sommer, H. *Eur. J. Org. Chem.* **1998**, *63*, 3−72. Fleming, F. F., Shook, B. C. *Tetrahedron* **2002**, *58*, 1−23.

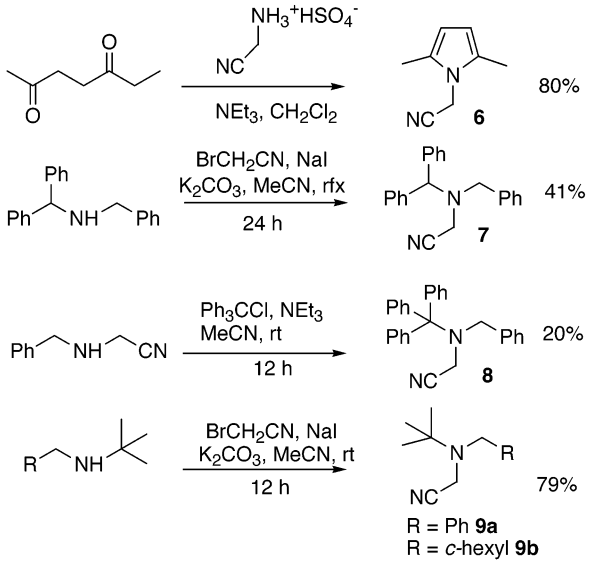
TABLE 2. Influence of the Nitrogen Substituents



entry	amino-nitrile	R	conditions	product	*anti*/*syn*[a]	yield (%)
1	**6**	*c*-Hex	−80 °C, 1 h	**10a-1**	67/33 in THF 75/25 in Et_2O	86[b] 63[b]
2	**7**	*c*-Hex	−80 to 0 °C, 1 h	**10a-2**	>95/5[c]	20[c]
3	**8**	*c*-Hex	−80 to 0 °C, 1 h	**10a-3**	>95/5[c]	50[c]
4	**9a**	*c*-Hex	−80 to −40 °C, 2 h	**10b**	>95/5	84
5	**9a**	*n*-Bu	−80 to −40 °C, 2 h	**10c**	>95/5	86
6	**9a**	*n*-Hex	−80 to −40 °C, 2 h	**10d**	>95/5	81
7	**9a**	*t*-Bu	−80 to −40 °C, 2 h	**10e**	>95/5	90
8	**9a**	Ph	−80 to −40 °C, 2 h	**10f**	>95/5	79
9	**9b**	*c*-Hex	−80 to −40 °C, 2 h	**10g**	>95/5	73

[a] Determined by ^{1}H NMR of the crude mixture. [b] Reported yields are weight recoveries of the combined *syn*- and *anti*-stereoisomers. [c] Aldol/starting material ratio in the crude mixture estimated by ^{1}H NMR. The anti/syn ratio was also estimated by ^{1}H NMR of this crude mixture.

SCHEME 3. Preparation of Aminonitriles 6−9



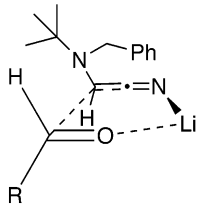
the selectivity observed with the aminoacetonitrile **9a,b**, where the nitrogen is a stereogenic center subject to fast equilibration. Indeed, it is very likely that the addition to the aldehyde occurs from the side of the less bulky nitrogen substituent, i.e. the benzyl group. Accordingly, the same selectivity should be obtained using **4** or **9a,b**. It is known that the presence of a bulky group on the nitrogen decreases the inversion barrier and leads to a flattened pyramid.[15] Therefore, the global steric influence of the nitrogen substituents is increased, leading to better selectivity.[16] Such a hypothesis would also account for a decrease of the aldolization rate (a few minutes at −80 °C with **4** and 2 h at −40 °C with **9a,b**).

Since complete control of the diastereoselectivity of the aminoacetonitrile aldol reaction was achieved with **9a**, we then examined the same reaction with chiral aldehydes. As reported in Table 3, three aldehydes (**11**−**13**) bearing a stereogenic center in the α-position were tested. Two diastereomers were obtained in a 1/1 ratio with the homochiral or racemic[17] *O*-TBDMS mandelic aldehyde **11** (entry 1). Poor selectivity was observed with both the racemic *O*-TBDMS lactic aldehyde **12** (62/38, entry 2) and the D-isopropyleneglyceraldehyde **13** (69/31, entry 3). We postulated that the *anti*-selectivity obtained with the achiral aldehydes was preserved. It meant, therefore, that the aldolization with these chiral aldehydes did not occur with good facial selectivity.[18] In all cases, the two diastereomers were inseparable by chromatography. But despite the low selectivity obtained with the protected glyceraldehyde, it was observed that the pure major diastereomer **14** could be isolated in reasonable yield (40%) by simple recrystallization of the crude mixture. The *anti*,*anti*-relationship (2*S*,3*R*,4*R*) of this compound was determined by X-ray analysis.[19]

The modest, but significant, selectivity in the formation of **14** might be rationalized by the addition of the lithiated ketene imine species to the aldehyde **13** according to a

(15) (a) Saunders, M.; Yamada, F. *J. Am. Chem. Soc.* **1963**, *85*, 1882. (b) Lehn, J.-M. Nitrogen Inversion. *Top. Curr. Chem.* **1970**, *15*, 311−377.

(16) As suggested by one of our reviewers, one may involve a transition state where the two *N*-substituents are roughly in the plane of the keteniminate, with the *t*-Bu group exo and the benzyl endo (see structure below). Such conformation would reduce steric congestion in the transition state energy, thereby negating the effect of any ground-state destabilization.



(17) These two experiments were run in order to perform a pseudo-Hoffmann test due to the possible but improbable configurational stability of lithiated α-aminonitriles. Hoffmann, R.; Lanz, J.; Metternich, R.; Tarara, G.; Hoppe, D. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1145−1146.

(18) (a) Similar results were obtained with configurationally stable allenyl zinc reagents: Poisson, J. F.; Normant, J. F. *J. Org. Chem.* **2000**, *65*, 6553−6560. (b) For a review on Cram's rule see: Mengel, A.; Reiser, O. *Chem. Rev.* **1999**, 1191−1223.

(19) Crystallographic data for the structural analysis have been deposited with the Cambridge Crystallographic Data Center, CCDC No. 178047.

SCHEME 4

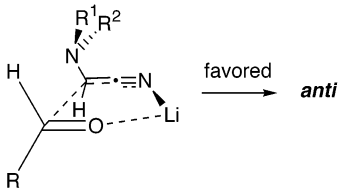
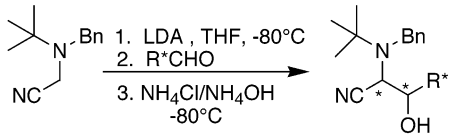
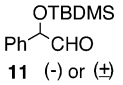
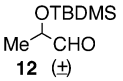
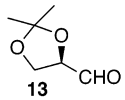


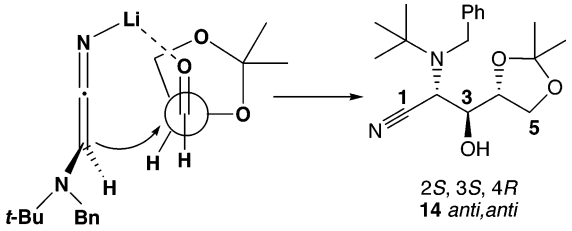
TABLE 3. Aldolization with Chiral Aldehydes



Entry	R*CHO	product	dr[a]	Yield (%)[b]
1	 **11** (-) or (±)	**11a**	50/50	69
2	 **12** (±)	**12a**	62/38	67
3	 **13**	**14**	69/31	60 (40)[c]

[a] Determined by ^{1}H NMR of the crude mixture. [b] Reported yields are weight recoveries of the combined stereoisomers. A small amount of an undetermined product was formed during the reaction. [c] Yield of pure major diastereomer recovered after recrystallization.

SCHEME 5

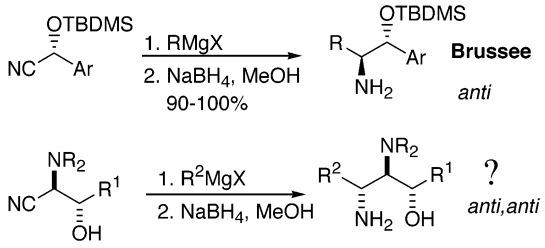


model involving a combination of a cyclic transition state (C_2−H, C_3−H relationship) and a Felkin type addition (C_3−H, C_4−H relationship, Scheme 5).[20]

Having examined the scope and the limitations of the aldol reaction, we next explored the possibility of using the sequence of alkylmetalation−reduction of the nitrile group, reported by Brussee (Scheme 6)[7] for the diastereoselective access to β,γ-diamino alcohols.

(20) The modest selectivity obtained with chiral aldehydes **12** and **13** is in accordance with the results generally obtained with these aldehydes. Moreover, it is possible that, due to the cyclic nature of the transition state, the attack of the lithiated ketene imine to the aldehyde does not occur in the Bürgi−Dunitz angle, which is important for the selectivity (see ref 18b).

SCHEME 6



The application of this three-step sequence to our substrates, which involves the addition of a Grignard reagent to the nitrile, methanolysis of the resulting *N*-metalloimine, and then reduction, was not obvious. Since addition of RMgX to α-aminonitriles usually results in the displacement of the nitrile group (Bruylants reaction),[21] our first attempt was to add *n*-BuLi, instead of *n*-BuMgBr, to the amino alcohol **10b** (Scheme 7). The addition was found to occur in THF, but not in Et_2O. The diastereomerically pure (^{1}H NMR) β,γ-diamino alcohol **15a** was then obtained, after methanolysis, by reduction with $NaBH_4$ in the presence of $MgBr_2$. We have observed that phenyl and allyl Grignard reagents added cleanly to the nitrile in THF.[22] In this case, $MgBr_2$ is not required to perform the reduction after methanolysis, and the diamino alcohols **15b,c** were obtained in good yield and as single diastereomers (Scheme 7).

Application of the latter sequence to the chiral nonracemic aldol **14**, using aryl, allyl, or alkyl Grignard reagents, led to the diamino alcohols **16 a**−**c** in good isolated yields and with excellent diastereocontrol (Scheme 8).

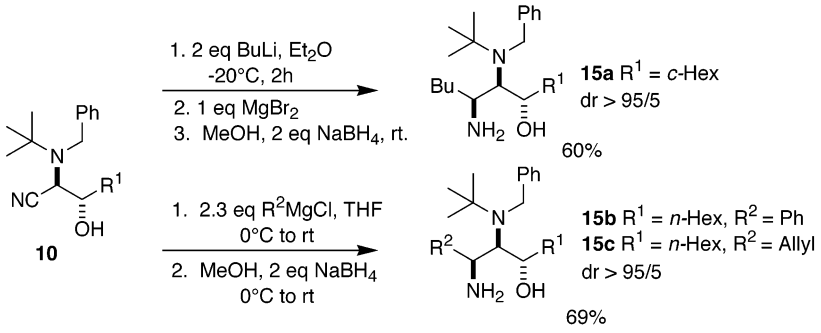
The use of crotylmagnesium bromide led to the adduct **16d**, arising from γ-addition, in good yield (79%) and with high selectivity (dr = 9/1, Scheme 8). The compounds **16c** and **16d** were purified by recrystallization, and the relative configuration of each major diastereomer was established by X-ray analysis.[23] Syn C_4−H,C_5−H and anti C_5−H,C_6−H relationships were observed. Therefore, the same syn C_4−H,C_5−H relative configuration was postulated for compounds **15a**−**c** and **16a**−**b** obtained by the same alkylation−reduction sequence. The stereodetermining step of Brussee's procedure is obviously the

(21) (a) Bruylants, P. *Bull. Soc. Chim. Belg.* **1924**, *33*, 467. (b) Ahlbrecht, H.; Dollinger, H. *Synthesis* **1985**, 743−748.

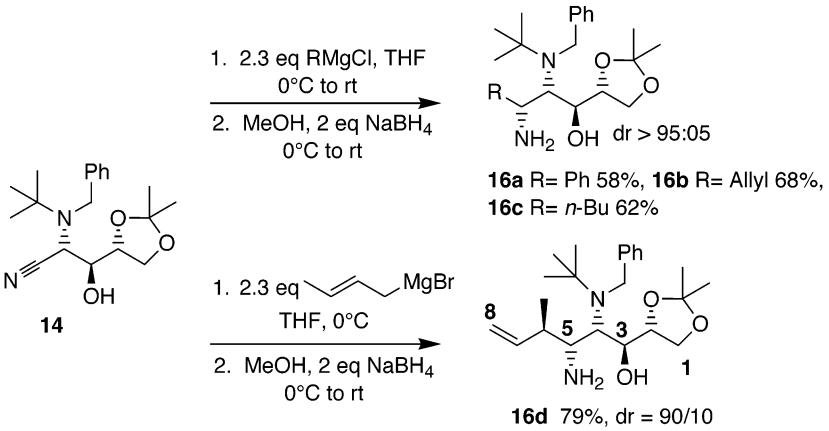
(22) The addition of Grignard reagents to the nitrile is surprising in the light of the Bruylants reaction. Such chemioselectivity is probably due to the steric effect of the *t*-Bu group, which prevents the formation of the immoniun intermediate. Indeed, we have observed that addition of BuMgBr to an aldol derived from **4** yielded exclusively to the Bruylants's product. Moreover, we also found that it was possible to perform the Bruylants reaction by addition of Grignard reagents to the immoniums derived from aldols **10d,e** as described by Couty and Agami: Agami, C, Couty, F., Ewano, G *Org. Lett.* **2000**, *2*, 2085−2088.

(23) Crystallographic data for the structural analysis have been deposited with the Cambridge Crystallographic Data Center, CCDC No. 178176 for **16c** and CCDC No. 178175 for **16d**.

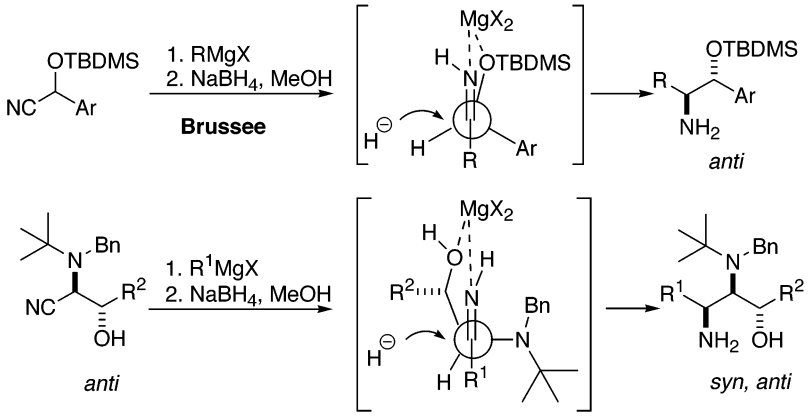
SCHEME 7



SCHEME 8



SCHEME 9



reduction of the imine by $NaBH_4$. The relative configuration observed by us and by Brussee were opposite. The anti-selectivity observed by Brussee was attributed to a chelated transition state involving the silyl ether moiety (Scheme 9). In our case, such a transition state involving chelation with a very bulky amino group is unlikely, and it leads to the opposite relative configuration that is observed. The transition state involving a Felkin type transition state, commonly proposed for the dibenzyl amino group,[24] and the chelated free hydroxyl group leads to the observed stereochemistry (Scheme 9).

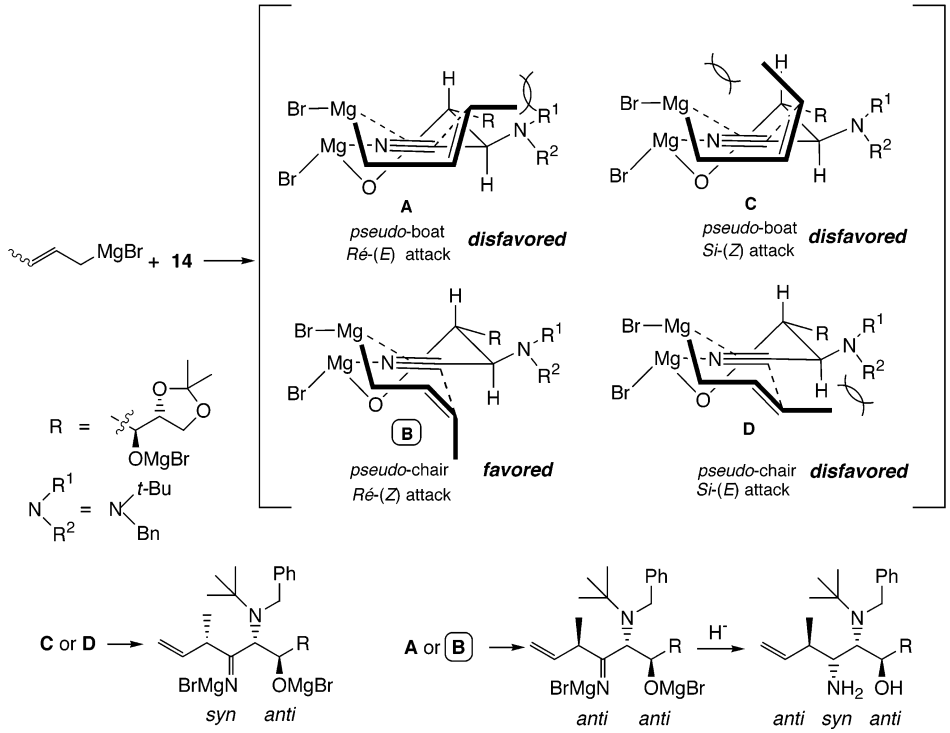
Concerning the formation of **16d**, the configuration of the C_6−H allylic center was controlled during the addition of the prochiral organometallic reagent (1,3-asymmetric induction). We presume that the observed C_4−H,C_6−H anti-relationship arises from an attack of the *Z*- or *E*-crotyl reagent (in rapid equilibrium)[25] on a rigid cyclic substrate formed by π-chelation between the nitrile and the magnesium alkoxide, as shown in Scheme 10. [26] Therefore, of the four possible transition states, two are the result of *re* face attack via a pseudo-boat (**A**) or a pseudo-chair (**B**) transition state. The others are the result of a *si* face attack again via a pseudo-boat (**C**) or a pseudo-chair (**D**) transition state. **A**, **C**, and **D** are destabilized by steric interactions. The most favorable situation is obtained in transition state **B**, which leads to the *anti* C_4−H,C_6−H relationship. The *anti*,*anti*,*syn*,-

(24) (a) Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1531−1546. Reetz, M. T. *Chem. Rev.* **1999**, *99*, 1121−1162.

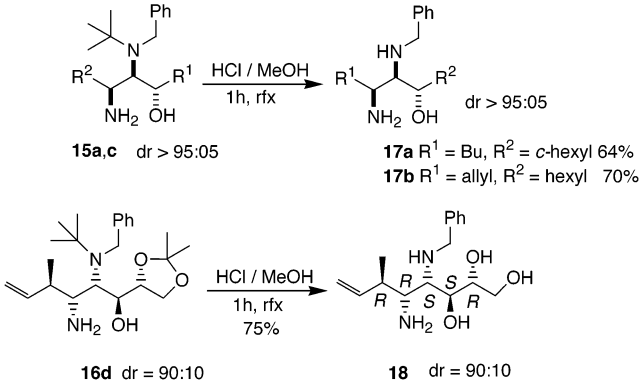
(25) Yamamoto, T.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207−2293.

(26) A free hydroxyl group seems to be required for the addition of the Grignard reagent. Indeed, we have observed that such addition on a OSi*t*-BuMe_2 protected derivative did not occur.

SCHEME 10



SCHEME 11



anti-isomer **16d** was then obtained by diastereoselective reduction as shown in Scheme 9.

The final cleavage of the N−*t*-Bu bond, although easily achieved in the amide series,[27] is rarely described for a tertiary amine.[28] We were very pleased to observe that simple treatment with a saturated methanolic solution of HCl under reflux afforded, after neutralization, the free amines **17a,b** and **18** in good yields and without isomerization (Scheme 11).

In conclusion, the lithiated *N*-benzyl-*N*-*tert*-butylaminoacetonitrile undergoes clean 1,2-addition to aldehydes, providing the corresponding diastereomerically pure *anti*-*β*-hydroxy-α-aminonitriles. These compounds are easily transformed into the *syn*,*anti*-protected *β*,*γ*-diamino alcohols by a two-step procedure involving an addition of a Grignard reagent to the nitrile followed by reduction of the resulting imine. The *N*-*tert*-butyl group is then cleaved by a simple treatment with acid. The application of the aldol reaction to chiral aldehydes occurs with poor facial selectivity. Nevertheless, starting from D-isopropylideneglyceraldehyde and using crotylmagnesium bromide, the *anti*,*anti*,*syn*,*anti*-(2*R*,3*S*,4*S*,5*R*,6*R*)-diaminotriol **18** is prepared in acceptable yield and with a good level of diastereoselectivity. Development of an asymmetric aldol reaction and preparation of the other stereotriads of *β*,*γ*-diamino alcohols are under investigation.

Experimental Section

General Considerations. Experiments involving organometallics were carried out under dry nitrogen atmosphere. All glassware was dried at 120 °C and assembled while hot under a stream of nitrogen. All moisture-sensitive reactants were handled under a nitrogen atmosphere. Low-temperature experiments were carried out by cooling a three-necked round botton flask with an acetone (−80 °C), acetonitrile (−40 °C) bath, frozen with liquid nitrogen. The flask was equipped with an internal thermometer, a nitrogen inlet, and a septum cap. Diethyl ether and tetrahydrofuran were distilled from sodium−benzophenone ketyl. Organomagnesium and organolithium reagents were titrated with 2-butanol (1 M solution in toluene) using, respectively, 2,2′-biquinolyl and 1,10-phenanthroline as indicators. Column chromatographies were performed over silica gel Si 60 (0.015−0.040 or 0.040−0.063 mesh). Thin layer chromatography (TLC) was performed over silica gel (0.25 mm; F-254) and visualized under a UV lamp (254 and 366 nm) and by using a 10% phosphomolybdic acid solution in ethanol (heating) or vanillin reagent (heating) or Dragendorf reagent. Optical rotations were measured at 20 °C. ^{1}H NMR spectra were recorded at 200 or 400 MHz and ^{13}C NMR spectra at 50 or 100 MHz, in $CDCl_3$ as a solvent. Chemical shifts are

(27) Earle, M. J.; Fairhurst, R. A.; Heaney, H.; Papageorgiou, G. *Synlett* **1990**, 621−623.

(28) For the cleavage of an *N*-*tert*-butyl group on a secondary amine, see: De Kimpe, N.; Sulmon, P.; Brunet, P. *J. Org. Chem.* **1990**, *55*, 5777−5784. Bundy, G. l.; Banitt, L. S.; Dobrowolski, P. J.; Palmer, J. R.; Schwartz, T. M.; Zimmermann, D. C.; Lipton, M. F.; Mauragis, M. A.; Veley, M. F.; Appell, R. B.; Clouse, R. C.; Daug, E. D. *Org. Process Dev.* **2001**, *5*, 144−151. Sachs, M. WO Patent 9636602, 1996. Kuznetsov, A. I.; Romanova, K. I.; Basargin, E. B.; Moskovkin, A. S.; Unkovski, B. V. *Khim. Geterotsikl. Soedin.* **1990**, *4*, 538−542.

reported in ppm (reference = TMS for ^{1}H spectra and $CDCl_3$ for ^{13}C spectra).

Preparation of Aminoacetonitriles. *N*-Benzhydryl-*N*-benzylaminoacetonitrile (7). Benzaldehyde (2.22 g, 0.021 mol) is added to a stirred solution of aminodiphenylmethane (3.66 g, 0.020 mol) in dichloromethane (25 mL) in the presence of molecular sieves (4 Å, 10 g). The mixture is stirred for 1 h at room temperature. Molecular sieves are filtered off. The filtrate is dried over sodium carbonate and the solvant is removed in vacuo to give the crude *N*-benzylidenebenzhydrylamine. The residue is then dissolved in methanol (15 mL). Sodium cyanoborohydride (4.88 g, 0.030 mol) is added, and then trifluoroacetic acid (3.10 mL, 0.040 mol) is added dropwise until dissolution of the suspension. The mixture is stirred at room temperature for 20 h and then neutralized by a 7:3 ammonium chloride/ammonium hydroxyde aqueous solution. The aqueous layer is extracted with diethyl ether (2 × 25 mL). The organic layer is dried over sodium sulfate and filtered, and the solvents are removed under reduced pressure. The oily residue is dissolved in diethyl ether and filtered over silica gel. Evaporation of diethyl ether affords *N*-benzylbenzhydrylamine (5.30 g, 97%) as a white solid which is then used without further purification. To an acetonitrile (50 mL) of *N*-benzylbenzhydrylamine (5.30 g, 0.020 mol) are added bromoacetonitrile (1.46 mL, 0.021 mol), potassium carbonate (4.15 g, 0.030 mol), and sodium iodide (3.70 g, 0.022 mol). The mixture is refluxed during 24 h, and then 100 mL of a saturated aqueous sodium carbonate solution is added. The solution is extracted with diethyl ether (4 × 25 mL), and the combined organic layers are washed with water (6 × 50 mL), dried over magnesium sulfate, filtered, and evaporated. The crude product is recrystallized in pentane/diethyl ether (8:2), yielding 2.58 g (41%) of **7** as white crystals. ^{1}H NMR (400 MHz): δ 7.62−7.22 (m, 15H, m), 4.76 (s, 1H), 3.72 (s, 2H), 3.39 (s, 2H). ^{13}C NMR (50 MHz): δ 141.5, 137.5, 129.1, 128.8, 127.8, 127.7, 114.8, 72.9, 55.8, 39.6. Anal. Calcd for $C_{22}H_{20}N_2$: C, 84.58; H, 6.45; N, 8.97. Found: C, 84.59; H, 6.47; N, 8.95.

***N*-Benzyl-*N*-tritylaminoacetonitrile (8).** To an acetonitrile solution (50 mL) of benzylamine (5.30 g, 0.020 mol) are added bromoacetonitrile (1.46 mL, 0.021 mol), potassium carbonate (4.15 g, 0.030 mol), and sodium iodide (3.70 g, 0.022 mol). The mixture is stirred at room temperature for 20 h and filtered. Trityl chloride (8.36 g, 0.030 mol) and triethylamine (6.40 mL, 0.040 mol) are then added, and the mixture is stirred overnight. A 250-mL portion of a saturated aqueous sodium carbonate solution is added. The solution is extracted with diethyl ether (4 × 75 mL), and the combined organic layers are washed with water (6 × 50 mL), dried over magnesium sulfate, filtered, and evaporated. The crude product is recrystallized in cyclohexane/ethyl acetate (9:1), yielding 3.18 g (41%) of **8** as a white solid. ^{1}H NMR (400 MHz): δ 7.65−7.25 (m, 20H, m), 3.90 (s, 2H), 3.69 (s, 2H). ^{13}C NMR (100 MHz): δ 147.0, 142.0, 137.4, 129.3, 128.9, 128.4, 128.0, 127.0, 115.0, 110.7, 77.6, 52.7, 38.5.

***N*-Benzyl-*N*-*tert*-butylaminoacetonitrile (9a) and *N*-Cyclohexylmethyl-*N*-*tert*-butylaminoacetonitrile (9b).** To an acetonitrile solution (30 mL) of *N*-benzyl-*tert*-butylamine or *N*-cyclohexylmethyl-*tert*-butylamine (0.020 mol) are added bromoacetonitrile (1.46 mL, 0.021 mol), potassium carbonate (5.53 g, 0.040 mol), and sodium iodide (3.00 g, 0.020 mol). The mixture is stirred overnight at room temperature, and then 100 mL of a saturated aqueous sodium carbonate solution is added. The solution is extracted with diethyl ether (4 × 25 mL), and the combined organic layers are washed with water (6 × 50 mL), dried over magnesium sulfate, filtered, and evaporated. The crude product is chromatographied over silica gel (eluant: pentane/diethyl ether 9:1), yielding 3.20 g (79%) of **9a** or 3.3 g (79%) of **9b** as colorless oils. **(9a)** ^{1}H NMR (400 MHz): δ 7.38−7.26 (m, 5H), 3.84 (s, 2H), 3.45 (s, 2H), 1.30 (s, 9H).^{13}C NMR (100 MHz): δ 138.9, 128.7, 127.5, 118.2, 55.3, 51.5, 35.8, 27.5. IR (film, cm^{-1}): 3080, 3060, 3030, 2930, 2920, 2880. Anal. Calcd for $C_{13}H_{18}N_2$: C, 77.18; H, 8.97; N, 13.85. Found: C, 77.09; H, 9.04; N, 13.78. **(9b)** ^{1}H NMR (400 MHz): δ 3.6 (s, 2H), 2.44 (d, J = 4.5 Hz, 2H), 1.75 (m, 5H), 1.18 (m + s, 13H), 0.83 (m, 2H). ^{13}C NMR (100 MHz): δ 118.6, 54.9, 54.11, 36.7, 36.1, 31.5, 27.2, 29.9, 26.2.

General Procedure for the Aldolization. To a THF solution (15 mL) of aminonitrile (1.0 mmol) at −80 °C under nitrogen atmosphere is added dropwise LDA (2 M in heptane, 1.1 mmol, 0.550 mL). After 15−30 mn at this temperature, a THF solution (2 mL) of aldehyde (1.1 mmol) is added dropwise. The solution is stirred (for the conditions, see the text) and then quenched with a 7:3 ammonium chloride/ammonium hydroxyde aqueous solution. The mixture is extracted with diethyl ether (3 × 15 mL), and the combined organic layers are dried over magnesium sulfate and evaporated. The crude adduct is purified by column chromatography over silica gel.

***anti*- And *syn*-*N*,*N*-Dibenzyl-2-amino-3-hydroxy-3-phenylpropionitrile (5a).** Purification by column chromatography over silica gel (eluant: pentane/diethyl ether 80:20) affords pure *anti*- and *syn*-**5a** (0.255 g, 75%) as colorless crystals. ^{1}H NMR (400 MHz): δ 7.45−7.23 (m, 15H), 4.76 (d, J = 9.7 Hz, 1H), 4.13 (d, J = 13.3 Hz, 2H), 3.85 (s, 1H), 3.59 (d, J = 9.7 Hz, 1H), 3.56 (d, J = 13.3 Hz, 2H). (m, 15H), 3.85 (d, J = 8.6 Hz, 1H), 3.78 (s, 1H), 3.43 (d, J = 13.7 Hz, 2H). ^{13}C NMR (100 MHz): δ 140.1, 138.4, 137.6, 136.9, 133.8, 129.5, 129.4, 129.1, 128.9, 127.3, 116.9, 115.17, 73.6, 71.2, 61.0, 60.5, 56.4, 56.3. IR (film, cm^{-1}): 3440, 3060, 2220. Anal. Calcd for $C_{23}H_{22}N_2O$: C, 80.67; H, 6.48; N, 8.18. Found: C, 80.70; H, 6.51; N, 8.15.

***anti*- And *syn*-*N*,*N*-Dibenzyl-2-amino-3-hydroxy-3-mesitylpropionitrile (5b).** Purification by column chromatography over silica gel (eluant: pentane/diethyl ether 70:30) affords pure *anti*-**5b** (0.140 g, 36%) as colorless crystals. ^{1}H NMR (400 MHz): δ 7.30−7.07 (m, 10H), 6.79 (s, 2H), 5.44 (d, J = 9.2 Hz, 1H), 4.28 (d, J = 9.2 Hz, 1H), 4.00 (d, J = 13.9 Hz, 2H), 3.45 (d, J = 13.9 Hz, 2H), 2.35 (s, 3H), 2.02 (s, 6H). ^{13}C NMR (100 MHz): δ 138.1, 137.6, 137.4, 132.3, 130.7, 128.9, 128.8, 127.9, 117.2, 69.5, 58.4, 56.7, 21.2, 20.5. Purification by column chromatography over silica gel (eluant: pentane/diethyl ether 90:10) affords pure *syn*-**5b** (0.100 g, 26%). Recrystallization from pentane, ether (9/1) gives colorless crystals (mp 137 °C). ^{1}H NMR (400 MHz): δ 7.46−7.36 (m, 10H), 6.82 (s, 1H,), 6.72 (s, 1H, s), 5.30 (d, J = 10.5 Hz, 1H), 4.16 (d, J = 13.1 Hz, 2H), 4.09 (d, J = 9.2 Hz, 1H), 3.57 (d, J = 13.1 Hz, 2H,), 3.47 (s, 1H), 2.41 (s, 3H), 2.24 (s, 3H,), 1.73 (s, 3H). ^{13}C NMR (100 MHz): δ 138.1, 137.6, 137.3, 136.6, 131.7, 129.8, 129.5, 129.4, 129.1, 128.3, 115.3, 66.6, 56.1, 56.0, 21.1, 20.9, 19.6.

***anti*- And *syn*-*N*,*N*-Dibenzyl-2-amino-3-hydroxyl-4-enenitrile (5c).** Purification by column chromatography over silica gel (eluant: pentane/diethyl ether 75:25) affords pure *anti*-**5c** (0.176 g, 57%) as a yellow oil. ^{1}H NMR (400 MHz) δ 7.38−7.25 (m, 10H), 5.78 (m, J = 15.3 Hz, 1H), 5.39 (ddd, J = 15.3 Hz, J = 7.2 Hz, J = 1.6 Hz, 1H), 4.38 (m, 1H), 3.97 (d, J = 13.6 Hz, 2H), 3.56 (d, J = 8.0 Hz, 1H), 3.43 (d, J = 13.6 Hz, 2H), 2.02 (d, J = 4.4 Hz, 1H), 1.78 (dd, J = 7.2 Hz, J = 1.6 Hz, 3H). ^{13}C NMR (100 MHz): δ 137.6, 130.4, 130.0, 128.9, 128.7, 127.7, 116.5, 71.7, 58.8, 56.1, 17.8. IR (film, cm^{-1}): 3440, 2210. Anal. Calcd for $C_{20}H_{22}N_2O$: C, 78.40; H, 7.24; N, 9.14. Found: C, 78.24; H, 7.20; N, 8.99. Purification by column chromatography over silica gel (eluant: pentane/diethyl ether 90:10) affords pure *syn*-**5c** (0.075 g, 23%) as a yellow oil. ^{1}H NMR (400 MHz): δ 7.42−7.32 (m, 10H), 5.93 (m, 1H), 5.39 (ddd, J = 15.2 Hz, J = 7.1 Hz, J = 1.1 Hz, 1H), 4.21 (dd, J = 9.6 Hz, J = 9.6 Hz, 1H), 4.04 (d, J = 13.4 Hz, 2H), 3.51 (d, J = 13.4 Hz, 2H), 3.45 (d, J = 9.6 Hz, 1 H), 3.32 (s, 1H), 1.74 (d, J = 6.6 Hz, 3H). ^{13}C NMR (100 MHz): δ 136.7, 132.7, 129.1, 129.0, 128.1, 127.6, 115.1, 69.8, 59.0, 55.9, 17.9.

***anti*- And *syn*-*N*,*N*-Dibenzyl-2-amino-3-hydroxyheptanenitrile (5d).** Purification by column chromatography over silica gel (eluant: pentane/diethyl ether 75:25) affords pure *anti*-**5d** (0.170 g, 53%) as a colorless oil. ^{1}H NMR (400 MHz): δ 7.42−7.27 (m, 10H), 3.98 (d, J = 13.5 Hz, 2H), 3.92 (m, 1H, m), 3.51 (d, J = 8.2 Hz, 1 H), 3.45 (d, J = 13.5 Hz, 2H), 2.00 (s, 1 H), 1.85−1.80 (m, 1H), 1.33−1.14 (m, 5H), 0.88 (m, J =

7.3 Hz, 3H). ^{13}C NMR (100 MHz): δ 137.9, 129.3, 129.0, 128.1, 117.0, 70.9, 59.9, 56.9, 33.7, 27.0, 22.9, 14.4. IR (film, cm^{-1}): 3060, 2230. Purification by column chromatography over silica gel (eluant: pentane/diethyl ether 85:15) affords pure *syn*-**5d** (0.050 g, 17%). ^{1}H NMR (400 MHz): δ 7.40−7.28 (m, 10H), 4.03 (d, J = 13.4 Hz, 2H), 3.85−3.78 (m, 1H), 3.48 (d, J = 13.4 Hz, 2H), 3.41 (d, J = 9.5 Hz, 1H), 3.23 (s, 1H), 1.72−1.25 (m, 6H), 0.90 (m, J = 6.7 Hz, 3H).

***anti*- And *syn*-*N*,*N*-Dibenzyl-2-amino-3-cyclohexyl-3-hydroxypropionitrile (5e).** Purification by column chromatography over silica gel (eluant: pentane/diethyl ether 75:25) affords pure *anti*-**5e** (0.176 g, 50%) as a colorless oil. ^{1}H NMR (400 MHz): δ 7.40−7.27 (m, 10H), 3.97 (d, J = 13.4 Hz, 2H), 3.74 (m, 1H), 3.67 (d, J = 8.6 Hz, 1H), 3.45 (d, J = 13.4 Hz, 2H), 2.04 (s, 1H), 1.78−0.81 (m, 11H). ^{13}C NMR (100 MHz): δ 138.0, 129.4, 129.0, 128.1, 117.4, 74.7, 57.2, 56.9, 39.3, 30.6, 26.9, 26.6, 26.3, 24.3. IR (film, cm^{-1}) 3460, 2230. Anal. Calcd for $C_{23}H_{28}N_2O$: C, 79.27; H, 8.10; N, 8.04. Found: C, 79.06; H, 8.34; N, 7.61. Purification by column chromatography over silica gel (eluant: pentane/diethyl ether 85:15) affords pure *syn*-**5e** (0.050 g, 15%). ^{1}H NMR ($CDCl_3$): δ 7.40−7.27 (m, 10H), 4.03 (d, J = 13.3 Hz, 2H), 3.70 (m, 1H), 3.61 (d, J = 9.7 Hz, 1 H), 3.48 (d, J = 13.3 Hz, 2 H), 1.77−0.85 (m, 11 H).

***anti*-*N*,*N*-Dibenzyl-2-amino-4,4-dimethyl-3-hydroxyvaleronitrile (5f).** Recrystallization (cyclohexane or pentane/diethyl ether 2:1) affords pure *anti*-**5f** (0.209 g, 65%) as colorless crystals (mp 110 °C). ^{1}H NMR (400 MHz): δ 7.47−7.27 (m, 10H, m), 4.17 (d, J = 13.8 Hz, 2H), 3.86 (d, J = 1.8 Hz, 1H), 3.56 (d, J = 1.8 Hz, 1H), 3.43 (d, J = 13.8 Hz, 2H), 2.00 (s 1H), 0.78 (s, 9H). ^{13}C NMR (100 MHz): δ 137.0, 132.7, 127.9, 127.6, 126.6, 120.4, 114.5, 79.9, 55.0, 54.3, 34.7, 24.3. Anal. Calcd for $C_{21}H_{26}N_2O$: C, 78.22; H, 8.13; N, 8.69. Found: C, 78.17; H, 8.26; N, 8.51.

3-Cyclohexyl-2-(2′,5′-dimethylpyrrolyl)-3-hydroxypropionitrile (10a-1). Major diastereomer ^{1}H NMR (400 MHz): δ 5.83 (s, 2H), 5.03 (d, J = 7.1 Hz, 1H) 3.98 (m, 1H), 2.73 (s, 1H), 2.33 (s, 6H), 1.81−1.10 (m, 11H). ^{13}C NMR (100 MHz): δ 128.5, 116.7, 108.1, 76.1, 49.6, 39.0, 30.1, 26.4, 26.1, 25.9, 25.6, 13.6. Minor diastereomer ^{1}H NMR (400 MHz): δ 5.80 (s, 2H), 4.94 (d, J = 9.7 Hz, 1H), 3.92 (d, J = 9.7 Hz, 1H), 2.58−1.14 (m, 17H). ^{13}C NMR (100 MHz): δ 129.0, 115.9, 107.8, 75.6, 48.7, 39.6, 30.6, 26.4, 26.3, 26.0, 24.5, 13.8. Anal. Calcd for $C_{15}H_{22}N_2O$: C, 73.13; H, 9.00; N, 11.37. Found: C, 72.93; H, 9.14; N, 11.17.

***N*-Benzyl-*N*-*tert*-butyl-2-amino-3-cyclohexyl-3-hydroxypropionitrile (10b).** Purification by column chromatography over silica gel (eluant: pentane/diethyl ether 85:15) affords pure **10b** (0.264 g, 84%) as white solid. ^{1}H NMR (400 MHz): δ 7.36−7.18 (m, 5H), 4.22 (d, J = 17.1 Hz, 1H), 4.13 (d, J = 7.8 Hz, 1H), 3.93 (d, J = 17.1 Hz, 1H), 3.26−3.21 (m, 1H), 1.85 (d, J = 5.4 Hz, 1H), 1.78−1.04 (m, 11H), 1.21 (s, 9H). ^{13}C NMR (100 MHz): δ 143.2, 128.6, 127.2, 126.9, 120.0, 75.9, 57.3, 55.4, 51.5, 38.4, 30.6, 27.9, 26.6, 26.4, 26.2, 25.4. IR (film, cm^{-1}): 3420, 2220. Anal. Calcd for $C_{20}H_{30}N_2O$: C, 76.39; H, 9.62; N, 8.91. Found: C, 76.42; H, 9.58; N, 8.86.

***N*-Benzyl-*N*-*tert*-butyl-2-amino-3-hydroxyheptanenitrile (10c).** Recrystallization of the crude adduct (pentane) affords pure **10c** (0.248 g, 86%) as colorless crystals (mp 67 °C). ^{1}H NMR (400 MHz): δ 7.36−7.19 (m, 5H), 4.22 (d, J = 16.7 Hz, 1H), 3.91−3.86 (m, 2H), 3.28 (m, 1H), 2.01 (s, 1H), 1.86 (m, 1H), 1.44−0.88 (m, 5H), 1.20 (s, 9H), 0.86 (t, J = 7.3 Hz, 3H). ^{13}C NMR (100 MHz): δ 141.8, 128.5, 127.4, 126.8, 119.6, 72.0, 58.5, 57.0, 51.5, 33.5, 28.0, 27.8, 22.6, 14.1. IR (film, cm^{-1}): 3420, 2220. Anal. Calcd for $C_{18}H_{28}N_2O$: C, 74.96; H, 9.78; N, 9.71. Found: C, 74.81; H, 9.94; N, 9.71.

***N*-Benzyl-*N*-*tert*-butyl-2-amino-3-hydroxynonanenitrile (10d).** Purification by column chromatography over silica gel (eluant: pentane/diethyl ether 9:1) affords pure **10d** (0.252 g, 80%) as white solid. ^{1}H NMR (400 MHz): δ 7.36−7.14 (m, 5H), 4.21 (d, J = 16.7 Hz, 1H), 3.92−3.21 (m, 2H), 3.24 (m, 1H), 2.06 (s, 1H), 1.85 (m, 1H), 1.45−0.92 (m, 9H), 1.19 (s, 9H), 0.87 (t, J = 6.9 Hz, 3H). ^{13}C NMR (100 MHz): δ 141.8, 128.4, 127.4, 126.9, 119.5, 72.0, 58.4, 56.9, 51.4, 33.8, 31.8, 29.1, 27.8, 25.7, 22.6, 14.1. IR (film, cm^{-1}): 3400, 2220.

***N*-Benzyl-*N*-*tert*-butyl-2-amino-4,4-dimethyl-3-hydroxyvaleronitrile (10e).** Recrystallization of the crude adduct (pentane/diethyl ether 9:1) affords pure **10e** (0.255 g, 88%) as colorless crystals (mp 118 °C). ^{1}H NMR (400 MHz): δ 7.44−7.19 (m, 5H), 4.32 (s, 1H), 4.22 (d, J = 17.6 Hz, 1H), 4.17 (d, J = 17.6 Hz, 1H), 3.44 (dd, J = 6.6 Hz, J = 0.8 Hz, 1H), 1.71 (d, J = 6.6 Hz, 1H), 1.20 (s, 9H), 0.98 (s, 9H). ^{13}C NMR (100 MHz): δ 143.0, 128.6, 126.6, 119.2, 82.5, 57.7, 52.3, 50.8, 35.9, 27.8, 26.1. IR (film, cm^{-1}): 3430, 2230. Anal. Calcd for $C_{18}H_{28}N_2O$: C, 74.96; H, 9.78; N, 9.71. Found: C, 75.01; H, 9.87; N, 9.66.

***N*-Benzyl-*N*-*tert*-butyl-2-amino-3-hydroxy-3-phenylpropionitrile (10f).** Recrystallization of the crude adduct (pentane/diethyl ether 9:1) affords pure **10f** (0.244 g, 79%) as colorless crystals (mp 132 °C). ^{1}H NMR (400 MHz): δ 7.38−7.22 (m, 10H), 4.61 (d, J = 6.0 Hz, 1H), 4.31 (d, J = 6.0 Hz, 1H), 4.23 (d, J = 17.0 Hz, 1H), 4.11 (d, J = 17.0 Hz, 1H), 2.18 (s, 1H); 1.08 (s, 9H). ^{13}C NMR (100 MHz): δ 142.0, 140.0, 128.7, 128.5, 127.5, 127.1, 126.9, 118.7, 75.3, 59.2, 57.3, 51.4, 27.6. IR (film, cm^{-1}): 3500, 2220. Anal. Calcd for $C_{20}H_{24}N_2O$: C, 77.89; H, 7.84; N, 9.08. Found: C, 77.83; H, 7.98; N, 9.26.

***N*-Cychohexylmethyl-*N*-*tert*-butyl-2-amino-3-cyclohexyl-3-hydroxypropionitrile (10g).** Recrystallization of the crude adduct (pentane/diethyl ether 9:1) affords pure **10g** (0.233 g, 73%) as colorless crystals (mp 142 °C). ^{1}H NMR (400 MHz): δ 3.95 (d, J = 5.5 Hz, 1H), 3.51 (bd, J = 5.5 Hz, 1H), 2.73 (dd, J = 7.5 Hz, J = 5.5 Hz, 1H), 2.35 (dd, J = 7.5 Hz, J = 5.5 Hz, 1H), 2−0.9 and 1.36 (m + s, 31 H). ^{13}C NMR (100 MHz): δ 120.8, 75.8, 57.15, 56.4, 55.2, 40.0, 38.1, 32.3, 31.9, 31.1, 28.2, 27.1, 26.8. Anal. Calcd for $C_{20}H_{36}N_2O$: C, 74.95; H, 11.32; N, 8.74. Found: C, 74.99; H, 11.35; N, 8.69.

***N*-Benzyl-*N*-*tert*-butyl-2-amino-4-(*tert*-butyldimethyl)-silyloxy-3-hydroxy-4-phenylbutyronitrile (11a).** Purification by column chromatography over silica gel (eluant: pentane/diethyl ether 95:05) affords pure aldol **11a** (0.366 g, 81%) as a mixture of two diastereomers (dr = 50/50). Anal. Calcd for $C_{27}H_{41}N_2O_2Si$: C, 71.63; H, 8.91; N, 6.19. Found: C, 71.72; H, 9.08; N, 6.17. HRMS (CI$^+$, CH_4): calcd for $C_{27}H_{41}N_2O_2Si$ ($M + H^+$) 453.2937, found 453.2930.

***N*-Benzyl-*N*-*tert*-butyl-2-amino-4-(*tert*-butyldimethyl)-silyloxy-3-hydroxyvaleronitrile (12a).** Purification by column chromatography over silica gel (eluant: pentane/diethyl ether 9:1) affords pure aldol (0.230 g, 59%) as a mixture of two diastereomers (dr = 62:38). Major diastereomer . ^{1}H NMR (200 MHz): δ 7.42−7.15 (m, 5H), 4.47 (d, J = 4.4 Hz, 1H), 4.22 (d, J = 17.7 Hz, 1H), 4.07 (d, J = 17.7 Hz, 1H), 3.79 (m, 1H), 3.52 (m, 1H), 1.90 (d, J = 4.4 Hz, 1H), 1.18 (s, 9H), 1.16 (d, J = 7.4 Hz, 3H), 0.87 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H). ^{13}C NMR (50 MHz): δ 142.7, 128.8, 126.9, 126.6, 118.8, 78.7, 77.4, 69.0, 57.7, 53.4, 51.4, 27.7, 25.9, 19.4, −4.1, −4.7. Minor diastereomer. ^{1}H NMR (200 MHz): δ 7.42−7.15 (m, 5H), 4.24 (d, J = 17.2 Hz, 1H), 4.14 (m, 1H), 4.06 (d, J = 8.8 Hz, 1H), 3.91 (d, J = 17.2 Hz, 1H), 3.13 (dd, J = 8.8 Hz, J = 9.3 Hz, 1H), 1.24 (s, 9H), 0.91 (s, 9H), 0.87 (d, J = 6.4 Hz, 3H), 0.15 (s, 3H), 0.14 (s, 3H). Anal. Calcd for $C_{22}H_{38}N_2O_2Si$: C, 67.64; H, 9.80; N, 7.17. Found: C, 67.80; H, 9.97; N, 6.97.

***N*-Benzyl-*N*-*tert*-butyl-4,5-*O*-isopropylidene-2-amino-3,4,5-trihydroxyvaleronitrile (14).** Recrystallization of the crude adduct (pentane/diethyl ether 9:1) affords the pure major diastereomer **14** (0.146 g, 44%) as colorless crystals (mp 140 °C). $[\alpha]^{20}_D = -9.0$ (*c* 1.2, $CHCl_3$). ^{1}H NMR (400 MHz): δ 7.43−7.22 (m, 5H), 4.49 (d, J = 3.1 Hz, 1H), 4.26 (d, J = 17.4 Hz, 1H), 4.06 (m, 1H), 4.05 (m, J = 17.4 Hz, 1H), 3.99 (dd, J = 8.6 Hz, J = 6.4 Hz, 1H), 3.88 (dd, J = 8.6 Hz, J = 4.1 Hz, 1H), 3.62 (m, 1H), 1.76 (d, J = 4.8 Hz, 1H), 1.42 (s, 3H), 1.33 (s, 3H), 1.21 (s, 9H). ^{13}C NMR (100 MHz): δ 142.1, 129.0, 127.1, 126.7, 117.9, 109.8, 75.9, 75.2, 66.2, 57.6, 53.7, 51.2, 27.6, 27.1, 25.0. IR (film, cm^{-1}): 3460, 2220. Anal. Calcd for $C_{19}H_{28}N_2O_3$: C, 68.65; H, 8.49; N, 8.43. Found: C, 68.42; H, 8.70; N, 8.38.

General Procedure for the Alkylmagnesiation−Reduction Sequence. To a THF solution (5 mL) of β-hydroxy-α-αminonitrile (1.0 mmol) at 0 °C under nitrogen atmosphere is added dropwise the Grignard reagent (2.3 mmol). The solution is stirred until complete consumption of the starting material (TLC, eluant: cyclohexane/ethyl acetate 8:2), which usually requires 2 h at 0 °C and 1 h at room temperature. The reaction mixture is quenched with methanol (15 mL), and sodium borohydride (0.080 g, 2.0 mmol) is added at 0 °C. The solution is allowed to warm slowly to room temperature and stirred overnight. A 7:3 ammonium chloride/ammonium hydroxyde aqueous solution is added and the mixture is extracted with ethyl acetate (3 × 15 mL). The combined organic layers are dried over magnesium sulfate, filtered, and evaporated under reduced pressure. The crude β,γ-diamino alcohol is purified by column chromatography over silica gel.

2-*N*-Benzyl-2-*N*-*tert*-butyl-2,3-diamino-1-cyclohexylheptan-1-ol (15a). 2-*N*-Benzyl-2-*N*-*tert*-butyl-1,2-diamino-1-phenylnonan-3-ol (15b). Purification by column chromatography over silica gel (eluant: cyclohexane/ethyl acetate 7:3 to 0:1) affords pure **15b** (0.275 g, 69%) as a yellow solid. ^{1}H NMR (200 MHz): δ 7.52−7.15 (m, 10H), 4.66 (d, J = 18.2 Hz, 1H), 4.24 (d, J = 3.0 Hz, 1H), 4.10 (d, J = 18.2 Hz, 1H), 3.98 (m, 1H), 3.10 (d, J = 3.0 Hz, 1H), 1.68−1.18 (m, 10H), 0.91−0.84 (m, 3H), 0.71 (s, 9H). ^{13}C NMR (50 MHz): δ 145.3, 128.3, 127, 126.9, 126.0, 75.3, 65.7, 56.8, 56.5, 49.6, 38.6, 32.1, 29.6, 28.2, 26.7, 22.9, 14.3. IR (film, cm^{-1}): 3360, 3090, 3050, 3020. Anal. Calcd for $C_{26}H_{40}N_2O$: C, 78.74; H, 10.17; N, 7.06. Found: C, 78.72; H, 10.17; N, 6.81.

2-*N*-Benzyl-2-*N*-*tert*-butyl-1,2-diamino-1-phenylnonan-3-ol (15b). Purification by column chromatography over silica gel (eluant: cyclohexane/ethyl acetate 7:3 to 0:1) affords pure **46a** (0.275 g, 69%) as a yellow solid. ^{1}H NMR (200 MHz) δ 7.52−7.15 (m, 10H), 4.66 (d, J = 18.2 Hz, 1H), 4.24 (d, J = 3.0 Hz, 1H), 4.10 (d, J = 18.2 Hz, 1 H), 3.98 (m, 1 H), 3.10 (d, J = 3.0 Hz, 1 H), 1.68−1.18 (m, 10 H), 0.91−0.84 (m, 3 H), 0.71 (s, 9 H). ^{13}C NMR (50 MHz) δ 145.3, 128.3, 127.2, 126.9, 126.0, 75.3, 65.7, 56.8, 56.5, 49.6, 38.6, 32.1, 29.6, 28.2, 26.7, 22.9, 14.3. IR (film, cm^{-1}): 3090, 3050, 3020 Anal. Calcd for $C_{26}H_{40}N_2O$: C, 78.74; H, 10.17; N, 7.06. Found: C, 78.72; H, 10.17; N, 6.81.

5-*N*-Benzyl-5-*N*-*tert*-butyl-4,5-diaminododec-1-en-6-ol (15c). Purification by column chromatography over silica gel (eluant: cyclohexane/ethyl acetate 7:3 to 0:1) affords pure **15c** (0.245 g, 68%) as a white solid. ^{1}H NMR (200 MHz): δ 7.46−7.08 (m, 5H), 5.73 (m, 1H), 5.16−5.02 (m, 2H), 4.64 (d, J = 18.7 Hz, 1H), 4.12 (d, J = 18.7 Hz, 1H), 4.00 (m, 1H), 2.99 (m, 1H), 2.84 (s, 1H), 2.58−2.32 (m, 2H), 1.74−1.12 (m, 10H), 1.04 (s, 9H), 0.94−0.82 (m, 3H). ^{13}C NMR (50 MHz): δ 144.9, 135.6, 128.3, 126.6, 125.8, 118.1, 75.4, 61.6, 57.1, 52.4, 49.8, 41.9, 38.6, 32.0, 29.5, 28.6, 26.5, 22.8, 14.2. Anal. Calcd for $C_{23}H_{40}N_2O$: C, 76.61; H, 11.18; N, 7.77. Found: C, 77.03; H, 11.34; N, 7.40.

4-*N*-Benzyl-4-*N*-*tert*-butyl-1,2-*O*-isopropylidene-4,5-diamino-2,3-dihydroxy-5-phenylpentan-1-ol (16a). Purification by column chromatography over silica gel (eluant: cyclohexane/ethyl acetate 7:3 to 0:1) affords pure **16a** (0.235 g, 57%) as a white solid. $[\alpha]^{20}_D$ = −88 (*c* 1.0, $CHCl_3$).^{1}H NMR (200 MHz): δ 7.55−7.19 (m, 10H), 4.68 (d, J = 18.2 Hz, 1H), 4.30−4.24 (m, 2H), 4.16 (d, J = 18.2 Hz, 1H), 4.13 (m, 1H), 4.05−3.95 (m, 2H), 3.71 (d, J = 2.1 Hz, 1H), 1.42 (s, 6H), 0.71 (s, 9H). ^{13}C NMR (50 MHz): δ 144.8, 128.3, 128.2, 126.9, 126.8, 126.0, 109.5, 78.4, 77.5, 68.7, 60.7, 57.2, 56.1, 49.8, 27.8, 26.5, 25.4. IR (film, cm^{-1}): 3360, 3300, 3085, 3040, 3010. HRMS (CI$^+$, CH_4): calcd for $C_{25}H_{37}N_2O_3$ (M + H$^+$) 413.2804, found 413.2803.

4-*N*-Benzyl-4-*N*-*tert*-butyl-1,2-*O*-isopropylidene-4,5-diamino-2,3-dihydroxypent-7-en-1-ol (16b). Purification by column chromatography over silica gel (eluant: cyclohexane/ethyl acetate 7:3 to 0:1) affords pure **16b** (0.255 g, 68%) as a white solid. $[\alpha]^{20}_D$ = −12 (*c* 1.0, $CHCl_3$). ^{1}H NMR (200 MHz): δ 7.46−7.12 (m, 5H), 5.88−5.66 (m, 1H), 5.18−5.05 (m, 2H), 4.69 (d, J = 18.2 Hz, 1H), 4.23 (m, 1H), 4.17 (d, J = 18.2 Hz, 1H), 4.09−3.93 (m, 3H), 3.41 (d, J = 2.5 Hz, 1H), 3.01 (m, 1H), 2.67−2.35 (m, 2H), 1.41 (s, 3H), 1.37 (s, 3H), 1.12 (s, 9H). ^{13}C NMR (50 MHz): δ 144.9, 135.5, 128.4, 126.7, 125.9, 118.4, 109.5, 79.0, 77.6, 68.8, 57.6, 57.3, 51.9, 50.1, 42.1, 28.5, 26.5, 25.5. IR (film, cm^{-1}): 3350, 3300, 3050, 2960, 1630. Anal. Calcd for $C_{22}H_{36}N_2O_3$: C, 70.18; H, 9.64; N, 7.44. Found: C, 70.01; H, 9.76; N, 7.29.

4-*N*-Benzyl-4-*N*-*tert*-butyl-1,2-*O*-isopropylidene-4,5-diamino-2,3-dihydroxynonan-1-ol (16c). Recrystallization of the crude adduct (cyclohexane/ethyl acetate 9:1) affords **16c** (0.240 g, 61%) as colorless crystals (mp 115 °C). $[\alpha]^{20}_D$ = −13.2 (*c* 1.0, $CHCl_3$). ^{1}H NMR (200 MHz): δ 7.33−7.09 (m, 5H,), 4.69 (d, J = 18.7 Hz, 1H); 4.19 (m, 1H), 4.18 (d, J = 18.7 Hz, 1H), 4.05−3.92 (m, 3H), 3.35 (d, J = 2.0 Hz, 1H), 2.94 (m, 1H), 1.85−1.58 (m, 2H), 1.49−1.01 (m, 4H), 1.42 (s, 3H), 1.38 (s, 3H), 1.11 (m, 9H), 0.96 (t, J = 6.9 Hz, 3H). ^{13}C NMR (50 MHz): δ 145.2, 128.4, 126.6, 125.8, 109.4, 79.0, 77.6, 68.7, 57.6, 57.1, 53.0, 50.3, 37.1, 28.5, 28.4, 26.5, 25.5, 22.9, 14.3. IR (film, cm^{-1}): 3350, 3300, 3050 Anal. Calcd for $C_{23}H_{40}N_2O_3$: C, 70.37; H, 10.27; N, 7.14. Found: C, 70.29; H, 9.81; N, 7.19.

4-*N*-Benzyl-4-*N*-*tert*-butyl-1,2-*O*-isopropylidene-4,5-diamino-2,3-dihydroxy-6-methylpent-7-en-1-ol (16d). Purification by column chromatography over silica gel (eluant: cyclohexane/ethyl acetate 7:3 to 0:1) affords pure **16d** (0.310 g, 79%) as colorless crystals (mp 142 °C). $[\alpha]^{20}_D$ = +23 (*c* 0.8, $CHCl_3$). ^{1}H NMR (200 MHz): δ 7.48−7.15 (m, 5H), 5.60−5.52 (m, 1H), 5.20−5.09 (m, 2H), 4.68 (d, J = 18.6 Hz, 1H), 4.23 (m, 1H), 4.20 (d, J = 18.6 Hz, 1H), 4.06−3.93 (m, 3H, m), 3.60 (d, J = 1.5 Hz, 1H), 2.86 (m,1H), 2.60 (dd, J = 9.8 Hz, J = 1.5 Hz, 1H), 1.43 (s, 3H, s), 1.37 (s, 3H, s), 1.15 (s, 9H), 1.10 (d, J = 6.0 Hz, 3H). ^{13}C NMR (50 MHz): δ 144.9, 141.5, 128.4, 126.6, 125.9, 116.9, 109.4, 78.4, 77.4, 68.9, 57.8, 57.0, 54.2, 50.4, 41.7, 28.6, 26.5, 25.5, 18.8. IR (film, cm^{-1}): 3360, 3050, 2970, 2900, 1630. Anal. Calcd for $C_{23}H_{38}N_2O_3$: C, 70.73; H, 9.81; N, 7.17. Found: C, 70.53; H, 9.87; N, 7.05.

Deprotection of the *N*-*tert*-Butyl-β,γ-Diamino Alcohols. General Procedure. The β,γ-diamino alcohol (1.0 mmol) is dissolved in a saturated methanolic solution of hydrogen chloride (5 mL). The mixture is refluxed for 1 h and neutralized by a saturated aqueous solution of sodium carbonate (10 mL). Extraction with ethyl acetate (3 × 15 mL) and drying of the combined organic layers with magnesium sulfate, filtration, and evaporation under reduced pressure afford the crude free diamino alcohols.

2-*N*-Benzyl-2,3-diamino-1-cyclohexylheptan-1-ol (17a). Purification by column chromatography over neutral aluminum oxyde (eluant: methanol) affords pure **17a** (0.203 g, 64%) as a colorless oil. ^{1}H NMR (200 MHz): δ 7.32−7.17 (m, 5H), 3.94 (d, J = 13.3 Hz, 1H), 3.68 (d, J = 13.3 Hz, 1H), 3.43 (dd, J = 8.9 Hz, J = 3.0 Hz, 1H), 2.96 (m, 1H), 2.51 (s, 1H), 2.23 (m, 1H), 1.85−0.75 (m, 19H). ^{13}C NMR (50 MHz): δ 140.8, 128.7, 128.3, 127.0, 77.8, 56.4, 52.9, 51.5, 41.8, 36.1, 30.4, 28.9, 28.3, 26.6, 26.0, 22.8, 19.6, 14.1. IR (film, cm^{-1}): 3300, 3060, 3040, 2920, 2850, 1950. HRMS (CI$^+$, CH_4): calcd for $C_{20}H_{35}N_2O$ (M + H$^+$) 319.2749, found 319.2743.

5-*N*-Benzyl-4,5-diamino-6-hydroxydodec-1-ene (17b). Purification by column chromatography over neutral aluminum oxide (eluant: methanol) affords pure **17b** (0.212 g, 70%) as a colorless oil. ^{1}H NMR (200 MHz): δ 7.38−7.21 (m, 5H), 5.63 (m, 1H), 5.08−4.91 (m, 2H), 3.94 (d, J = 12.8 Hz, 1H), 3.77 (m, 1H), 3.72 (d, J = 12.8 Hz, 1H), 3.08 (m, 1H), 2.34 (m, 1H), 2.28−2.20 (m, 2H), 1.61−0.78 (m, 13H). ^{13}C NMR (50 MHz): δ 140.6, 135.2, 128.7, 128.5, 127.2, 118.1, 73.2, 59.9, 53.1, 51.0, 40.5, 35.8, 32.0, 29.9, 26.4, 22.7, 14.3. IR (film, cm^{-1}): 3300, 3060, 3020, 2930, 2860, 1940, 1870, 1810. HRMS (CI$^+$, CH_4): calcd for $C_{19}H_{33}N_2O$ (M + H$^+$) 305.2593, found 305.2591.

4-*N*-Benzyl-1,2-*O*-isopropylidene-4,5-diamino-2,3-dihydroxy-6-methylpent-7-en-1-ol (18). Purification by column chromatography over neutral aluminum oxyde (eluant: methanol) affords pure **18** (0.220 g, 75%) as a colorless oil. $[\alpha]^{20}_D$ = +21 (*c* 1.0, $CHCl_3$). ^{1}H NMR (200 MHz): δ 7.38−7.22 (m, 5H), 5.56 (m, 1H), 5.11−5.00 (m, 2H), 3.94 (d, J = 12.3 Hz, 1H),

3.90−3.62 (m, 5H), 3.00 (d, $J = 2.5$ Hz, 1H), 2.72 (m, 1H); 2.29 (m, 1H), 0.88 (d, $J = 6.9$ Hz, 3H). ^{13}C NMR (50 MHz): δ 141.8, 140.3, 128.6, 128.5, 127.3, 116.5, 73.4, 73.0, 64.7, 56.3, 55.5, 53.2, 43.3, 17.7. IR (film, cm^{-1}): 3340, 3060, 2960, 2920, 2860, 1930, 1880. HRMS (CI^+, CH_4): calcd for $C_{16}H_{27}N_2O_3$ ($M + H^+$) 295.2022, found 295.2017.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of **5a**−**f** (anti and syn), **6**, **7**, **8**, **9a**−**b**, **10a**−**g**, **11a**, **12a**, **14**, **15a**−**c**, **16a**−**d**, **17a**−**b**, **18** and ORTEP drawings for *anti*-**5f**, **10c**, **14**, **16c**, and **16d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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