Study of the Reactions between Vinylmagnesium Bromide and Imines Derived from (*R*)-Glyceraldehyde − The Key Step in the Stereodivergent Synthesis of Conveniently Protected, Enantiopure *syn*- and *anti*-2-Amino-1,3,4-butanetriol Derivatives

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A total stereodivergent method for the synthesis of enantiopure *syn*- and *anti*-2-amino-1,3,4-butanetriol (ABT) derivatives from inexpensive and readily available D-mannitol has been developed. Key steps include: (a) the diastereoselective addition of vinylmagnesium bromide to conveniently protected *N*-benzylimines derived from (*R*)-glyceraldehyde, and (b) the oxidative degradation of the C–C double bond of the resultant *syn*- and *anti*-vinylaminodiol derivatives. The addition of vinylmagnesium bromide in diethyl ether to the *N*-benzylimine derived from (*R*)-2,3-*O*-isopropylideneglyceraldehyde affords the *anti*-vinylaminodiol derivative, while the reaction with the *N*-benzylimine derived from (*R*)-2,3-di-*O*-benzylglyceraldehyde affords the *syn*-vinylaminodiol derivative, both with excellent diastereoselectivities (*de* > 98/2). Moreover, a reversal of the stereochemical course of the reaction is produced when (*R*)-2,3-*O*-isopropylideneglyceraldehyde *N*-benzylimine is precomplexed with ZnI_2, in this case yielding the *syn* addition adduct as the major compound. Different reaction conditions (reagent molar ratio, reaction temperature) have been tested in order to determine their influences on the observed yields and diastereoselectivities. From the results of this study and a subsequent crossover experiment, some interesting mechanistic considerations can be inferred. Enantiopure *anti*- and *syn*-vinylaminodiol adducts have been successfully converted into conveniently protected *anti*- and *syn*-2-amino-1,3,4-butanetriol (ABT) derivatives, key building blocks in the asymmetric synthesis of biologically active compounds.

Introduction

The construction of versatile building blocks provides us with powerful tools for the efficient synthesis of biologically active natural products. In this context, 2-amino-1,3,4-butanetriol (ABT) is a highly functionalized compound that, when conveniently protected, has been used as a key building block in the asymmetric synthesis of the sphingoid base scaffold,[1] several kinds of antibiotics,[2] unusual hydroxylated amino acids,[3] a variety of analogues of carbohydrates,[4] Nelfinavir (a potent HIV-protease inhibitor),[5] and other biologically active compounds.[6] Consequently, synthetic organic chemists have devoted significant efforts to the development of new strategies for the synthesis of enantiopure ABT equivalents. One of the most commonly used methods involves the functional group manipulation of naturally occurring chiral compounds such as L-ascorbic acid,[2a,2f,4b,6a] D-isoascorbic acid,[1c,7] and tartaric acid derivatives.[1e,2b,6b,8] In this approach, the stereogenic centers in the resultant ABT derivatives are all directly derived from the starting material.

Alternatively, several asymmetric syntheses of ABT equivalents involving the stereoselective formation of new stereogenic centers in the substrate through the influence of a chiral group have been explored in recent years. From the point of view of retrosynthetic analysis (Scheme 1), the synthetic routes developed to date can be divided into four classes: (i) stereoselective addition of two heteroatoms to a disubstituted alkene, either directly, by a Sharpless asymmetric aminohydroxylation,[8a,9] or stepwise, by ring-opening of an epoxide or aziridine intermediate with a heteronucleophile (nitrogen or oxygen, respectively)[2b,2d,2g,3c,4a,5a,5b,10] (disconnection a), (ii) asymmetric addition of one heteroatom by α-hydroxylation of a chiral thioester[11] (disconnection b) or by electrophilic amination of a chiral β-hydroxy ester[12] (disconnection c), (iii) addition of hydrogen by diastereoselective reduction of a chiral β-ketosulfoxide[1c] (disconnection d) or of carbonyl derivatives of L-erythrulose[13] (disconnection e), and (iv) enzymatic hydration of chlorofumaric acid[14] (disconnection f).

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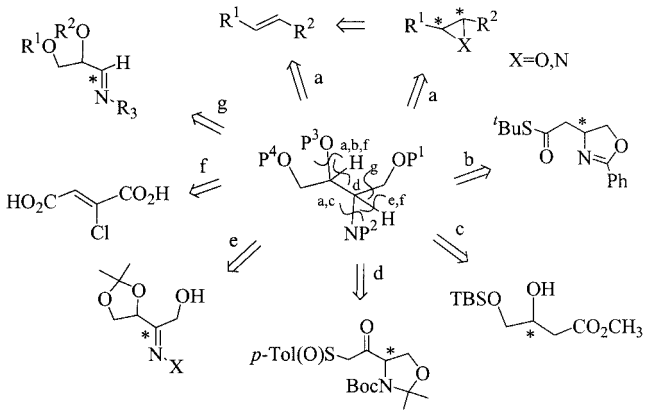
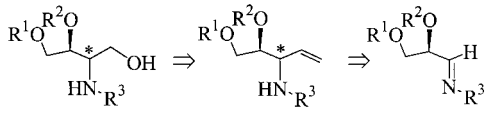


Scheme 1. General retrosynthetic analysis for the synthesis of ABT derivatives

The practical utilization of the ABT derivatives as versatile building blocks requires that the compounds be available on large scales and in conveniently protected forms for the selective treatment of their three hydroxyl groups and amino group. Unfortunately, many of the synthetic routes outlined above do not fulfil these requirements. We envisaged a new and efficient synthetic approach to the preparation of conveniently protected ABT derivatives from inexpensive D-glyceraldehyde, involving the creation of the bond between C^1 and C^2 [15] (disconnection g).

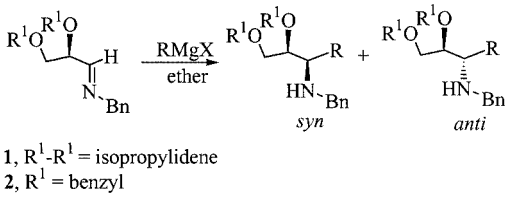
Results and Discussion

A simple retrosynthetic analysis shows that ABT derivatives can be derived from vinylaminodiol derivatives by oxidative cleavage of the C=C double bond. The key step in the synthesis involves the formation of vinylaminodiol intermediates by diastereoselective nucleophilic addition of a vinyl-metal reagent to imines derived from D-glyceraldehyde,[16] which are readily available on a multigram scale from D-mannitol (Scheme 2).



Scheme 2. Retrosynthetic analysis for the synthesis of ABT derivatives from D-glyceraldehyde imines.

We have previously reported[17−22] that nucleophilic attack of Grignard reagents on imines **1** and **2**, derived from (*R*)-2,3-*O*-isopropylideneglyceraldehyde and (*R*)-2,3-di-*O*-benzylglyceraldehyde, respectively, occurs with acceptable yields. In most cases, *syn*-aminodiol derivatives are obtained with excellent diastereoselectivity, although the stereochemical course of this reaction has proven to be strongly dependent on the nature of the Grignard reagent and on the type of hydroxy protecting group in the starting imine (Scheme 3, Table 1).



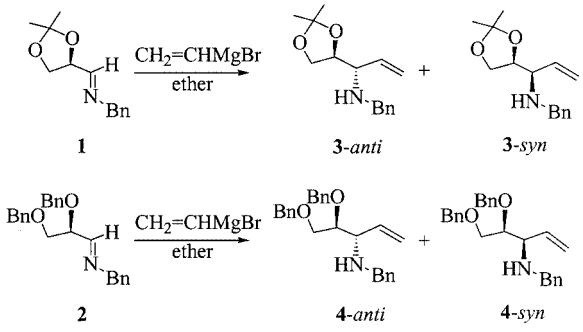
1, R^1-R^1 = isopropylidene
2, R^1 = benzyl

Scheme 3. Diastereoselective addition of organometallic reagents to chiral imines **1** and **2**

Table 1. Diastereoselective addition of Grignard reagents to chiral imines **1** and **2**

Entry	Imine	RMgX	Yield (%)	*T* (°C)	*syn*/*anti*	Ref.
1	**1**	CH_3MgBr	36	−30	55:45	[17]
2	**2**	CH_3MgBr	64	0	≥98:2	[18]
3	**1**	$PhCH_2MgCl$	75	−20	≥98:2	[19]
4	**2**	$PhCH_2MgCl$	68	−30	≥98:2	[19]
5	**1**	CH_2=$CHCH_2MgBr$	76	−30	70:30	[20a]
6	**2**	CH_2=$CHCH_2MgBr$	65	−30	75:25	[20b]
7	**1**	PhMgBr	69	0	≤2:98	[21]
8	**2**	PhMgBr	78	0	≥98:2	[21]
9	**1**	CH_2=CHMgBr	81	0	≤2:98	[22]

Given the precedent of reversal of diastereoselectivity in the addition of phenylmagnesium bromide, we decided to study the addition of vinylmagnesium bromide to *N*-benzylimines **1** and **2** in detail (Scheme 4).



Scheme 4. Diastereoselective addition of vinylmagnesium bromide to chiral imines **1** and **2**

As reported previously,[22] (*R*)-2,3-*O*-isopropylideneglyceraldehyde *N*-benzylimine (**1**) reacted with vinylmagnesium bromide in diethyl ether at 0 °C to give the corresponding *anti*-vinylaminodiol derivative **3**-*anti*. We subsequently investigated the effect of temperature, molar ratio, and protecting group on the yield and *syn*/*anti* selectivity, and the results are shown in Table 2.

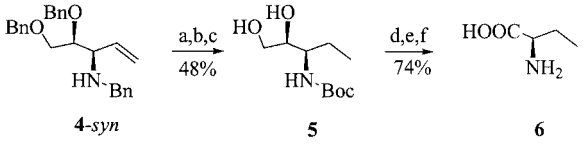
Under all experimental conditions tested with regard to changes in the reagent molar ratio and reaction temperature, the addition product with the *anti* relative configuration (**3**-*anti*) was obtained almost exclusively and in excellent yield when an excess of Grignard reagent was used in conjunction with imine **1**. This stereochemical outcome indicates that the nucleophilic attack of the organometallic

Table 2. Diastereoselective addition of vinylmagnesium bromide to chiral imines **1** and **2**; the reaction was carried out in dry diethyl ether by addition of the imine **1** or **2** to vinylmagnesium bromide under argon

Entry	Imine	CH_2=CHMgBr (equiv.)	T (°C)	Yield (%)[a]	*syn*/*anti*
1	**1**	1	−30	37	3.3:96.7[b]
2	**1**	2	−30	67	3.1:96.9[b]
3	**1**	3	−30	97	3.5:96.5[b]
4	**1**	3	20	86	3.2:96.8[b]
5	**1**	3	0	94	3.3:96.7[b]
6	**1**	3	−15	84	2.9:97.1[b]
7	**1**	3	−45	72	3.1:96.9[b]
8	**2**	1	−30	14	97.2:2.8[c]
9	**2**	2	−30	78	97.0:3.0[c]
10	**2**	3	−30	80	97.2:2.8[c]
11	**2**	2	20	80	97.3:2.7[c]
12	**2**	2	0	77	97.5:2.5[c]
13	**2**	2	−15	69	97.3:3.0[c]
14	**2**	2	−45	57	97.5:2.5[c]

[a] The crude reaction mixture was directly analyzed by ^{1}H NMR spectroscopy and the yield was determined from the relative intensities of characteristic protons versus the aromatic protons of 1,3,5-trimethoxybenzene added after extractive workup and used as an internal standard. [b] Ratio determined by GC analysis of the crude reaction mixture. [c] Ratio determined by HPLC analysis of the crude reaction mixture. Chemical correlation (see text and Scheme 5) was used to identify the **4**-*syn* diastereomer.

species occurs at the diastereotopic *si*-face of the imine. Treatment of (*R*)-2,3-di-*O*-benzylglyceraldehyde *N*-benzylimine (**2**) with vinylmagnesium bromide in diethyl ether afforded the corresponding vinylaminodiol derivative in high yield when an excess of organometallic reagent was used and, under all experimental conditions tested, the addition product with a *syn* relative configuration (**4**-*syn*) was obtained with nearly total diastereoselectivity. This stereochemical outcome parallels that reported by Jäger et al.[23] for the addition of vinylmagnesium bromide to an *N*-benzylimine derived from (*S*)-2-*O*-benzylglyceraldehyde (*syn*/*anti* = 87:13) and indicates that nucleophilic attack occurs in these cases at the diastereotopic *re*-face of the imine. The stereochemical course of the addition reaction is therefore reversed by changing the type of hydroxy protecting group in the starting imine, as previously observed in the addition of phenylmagnesium bromide to imines **1** and **2**. In order to determine the absolute configuration at the newly formed stereogenic center, compound **4**-*syn* was further elaborated to give the known compound (*R*)-2-aminobutyric acid. Transformation of amine **4**-*syn* into the *N*-Boc-aminodiol **5** was conveniently performed by a three-step procedure, as attempts to perform a one-step synthesis of compound **5** by hydrogenolysis of **4**-*syn* in the presence of di-*tert*-butyl dicarbonate were unsuccessful, as also described previously for a related compound.[19] Nevertheless, selective benzylamine hydrogenolysis with concomitant reduction of the double bond in the presence of $Pd(OH)_2$ on carbon as a catalyst, followed by treatment of the resulting product with $(Boc)_2O$ and diisopropylethylamine and extensive hydrogenolysis of the resulting compound in the presence of $Pd(OH)_2$ on carbon as a catalyst, cleanly afforded the desired *N*-Boc-aminodiol in 48% overall yield. Subsequent treatment of compound **5** with an excess of sodium periodate in the presence of ruthenium trichloride, followed by acidic hydrolysis, gave 2-aminobutyric acid **6** (Scheme 5). Comparison of the specific rotation of compound **6** $[\alpha]_D^{20}$ = −7.76 (c = 4 in H_2O)} with the known value for (*R*)-2-aminobutyric acid {ref.[24] $[\alpha]_D^{20}$ = −7.8 (c = 4 in H_2O) } allowed us to determine the configurational assignment of compound **4**-*syn* unambiguously.

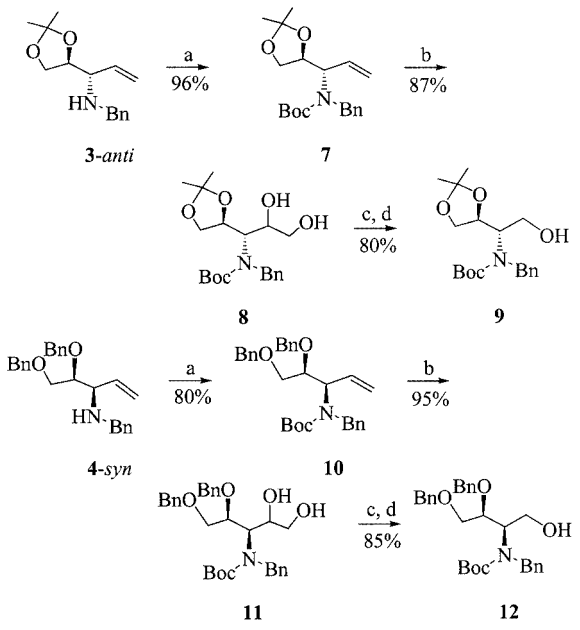


Scheme 5. Reagents and conditions: (a) H_2, $Pd(OH)_2$; (b) $(Boc)_2O$, iPr$_2$EtN; (c) H_2, $Pd(OH)_2$; (d) $RuCl_3$, $NaIO_4$; (e) dil. HCl; (f) ion exchange

Having obtained enantiopure vinylaminodiol derivatives **3**-*anti* and **4**-*syn*, we proceeded to study their conversion into conveniently protected ABT derivatives **9** and **12**. Initial protection of the amino functions in compounds **3**-*anti* and **4**-*syn* with the *N*-*tert*-butoxycarbonyl group was necessary to ensure that the subsequent reaction took place successfully. This reaction was carried out smoothly by a standard procedure with di-*tert*-butyl dicarbonate to afford compounds **7** and **10**, respectively. Subsequent dihydroxylation of the double bond was readily performed with osmium tetroxide and 4-methylmorpholine *N*-oxide (NMO) at room temperature to yield vicinal diols **8** and **11** as mixtures of diastereoisomers. Oxidation of these compounds by treatment with sodium periodate afforded the corresponding aldehydes, which were not purified but were directly reduced with $NaBH_4$ in ethanol to give the required enantiopure ABT derivatives **9** and **12**. The overall yields for enantiopure *anti* and *syn* ABT derivatives **9** and **12** from the starting glyceraldimines **1** and **2** were high; 61 and 48%, respectively (Scheme 6).

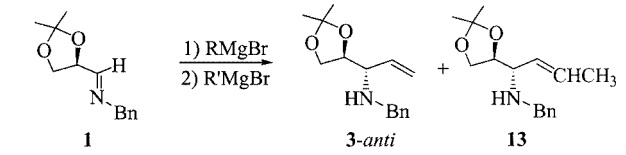
Mechanistic Considerations

Despite synthetic progress in the addition of C-nucleophiles such as Grignard reagents to chiral α-alkoxy carbonyl derivatives,[16] fundamental questions concerning the molecular reaction mechanism still remain unanswered. The first step involves the formation of a coordination complex between the organometallic species and the carbonyl derivative, and the second, and rate-limiting, step is associated with the formation of the C−C bond. In the last step, the question of how the nucleophile reaches the carbonyl C-atom cannot always be answered unequivocally. In order to investigate this subject, a crossover experiment involving competitive addition of vinylmagnesium bromide and 1-propenylmagnesium bromide to imine **1** was carried out. Thus, three equivalents of vinylmagnesium bromide were added to imine **1** in diethyl ether at −78 °C (a temperature at which it had previously been observed that significant C−C bond formation did not occur), followed 10 minutes



Scheme 6. Reagents and conditions: (a) $(Boc)_2O$, iPr_2EtN; (b) OsO_4, NMO; (c) $NaIO_4$; (d) $NaBH_4$

later by the addition of three equivalents of 1-propenylmagnesium bromide. The reaction mixture was then allowed to warm up to −30 °C. The resulting product from the addition of the vinyl group was obtained predominately (**3**-*anti*/**13**, 7:3). A reverse in the order of addition of the reagents produced a reversal in the product selectivity, with an even greater disparity in the ratio of products (**3**-*anti*/**13**, 1:9) (Scheme 7).



Scheme 7. Competitive addition of vinylmagnesium bromide and 1-propenylmagnesium bromide to imine **1**

This result suggests that complex aggregates are formed through coordination of the Grignard reagent to the basic centers on the starting α-alkoxy imine **1** (the nitrogen atom of the imine moiety and possibly some of the oxygen atoms in the α- and β-positions). In the second step it appears that the vinyl groups undergo an intramolecular shift from magnesium to the imine C-atom, giving rise to the C−C bond formation.

The theory of nucleophilic additions to α-chiral carbonyl derivatives is currently a matter of debate, particularly with respect to the origin of the stereoselectivity,[25] and several models to predict the stereochemical outcome of this reaction have been widely employed.[16,26] For non-chelation-

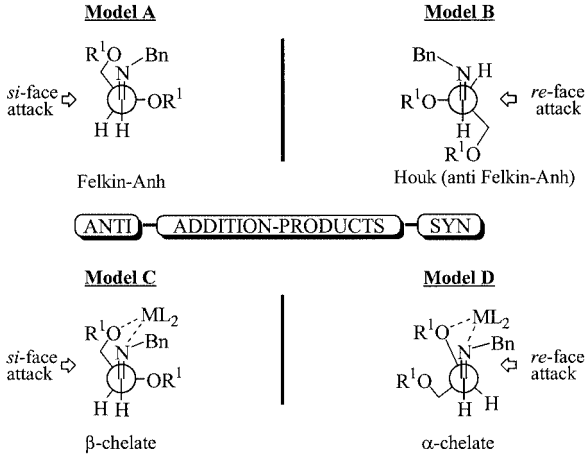


Figure 1. Competitive stereocorrelation models for the addition of a nucleophile to imines bearing an α-stereogenic atom

controlled reactions, the Felkin−Anh model (Figure 1, model A) has been widely utilized to explain the diastereofacial selectivity. In some cases, however, an anti-Felkin−Anh model (Figure 1, model B), similar to those developed by Houk[27] for alkenes, is more consistent with the observed diastereoselectivities.[28] In models A and B, the largest group on the α-stereocenter[29] [the α-alkoxy group for imines derived from (*R*)-glyceraldehyde] is situated orthogonally with respect to the C=N group. The main difference between these models is that the medium-sized substituent [the α-alkoxymethyl group for imines derived from (*R*)-glyceraldehyde] occupies the *anti* position in model B rather than the *syn* position (model A), in order to avoid steric interaction with the *N*-substituents. In contrast, model B predicts considerable steric interaction between the incoming nucleophile and the medium-sized substituent.[30]

Moreover, in the reactions between organometallic reagents and imines derived from α,β-dialkoxyaldehydes, such as (*R*)-glyceraldehyde, two different chelate models involving either five-membered or six-membered chelates can be considered. The β-chelate model (Figure 1, model C) involves simultaneous coordination of the metal both to the imine nitrogen and to the β-alkoxy group, while the α-chelate model (Figure 1, model D) entails simultaneous coordination of the metal atom both to the imine nitrogen and to the α-alkoxy group. As depicted in Figure 1, the attack of the organometallic species at the less hindered *si*-face of the imine group both in the non-chelated Felkin−Anh model (A) and in the β-chelate model (C) would explain the predominant formation of *anti* addition products. Diastereoisomers with a *syn* relative configuration, derived from attack at the *re*-face of the imine, would be expected to be the major products when the non-chelate model B or α-chelate model D were operative.

The main limitation of the models discussed above is that they simply consider facial selectivity on the basis of purely enthalpic grounds. Recently, Cainelli et al. pointed out the importance of evaluating entropic contributions with a careful control of the dependence of stereoselectivity on

temperature.[31] The stereoselectivity (S) of an addition reaction onto an imine can be expressed in terms of differential free activation energy by the modified Eyring equation [Equation (1)].[32]

$$\text{Ln } S = \ln(k/k') = \ln([anti]/[syn]) = -\Delta\Delta G^{\ddagger}/RT = -\Delta\Delta H^{\ddagger}/RT + \Delta\Delta S^{\ddagger}/R \quad (1)$$

where k and k' are the observed overall rate constants and $\Delta\Delta G^{\ddagger}$ is the difference in face activation energies for *si*- and *re*-face attack. In diastereoselective reactions, k/k' can be expressed in terms of the final concentration ratio of the *anti* and *syn* diastereoisomers. Therefore, on the basis of Equation (1), temperature-dependence measurements should allow the evaluation of diastereoselectivity in terms of activation enthalpy and entropy.

The data collected in Table 2 (entries 3 to 7 for imine **1** and entries 9 and 11 to 14 for imine **2**) were analyzed by use of Equation (1). When this relationship is plotted, the slope corresponds to the difference in the activation enthalpies ($\Delta\Delta H^{\ddagger} = \Delta H^{\ddagger}_{anti} - \Delta H^{\ddagger}_{syn}$) and the intercept represents the difference in the activation entropies ($\Delta\Delta S^{\ddagger} = \Delta S^{\ddagger}_{anti} - \Delta S^{\ddagger}_{syn}$). The resulting Eyring plot (lnS vs. reciprocal absolute temperature) for the addition of vinylmagnesium bromide to imines **1** and **2** in diethyl ether is presented in Figure 2. No significant variation in the stereoselectivity was observed in the temperature range examined, meaning that stereoselectivity depends exclusively on entropic factors in this case.

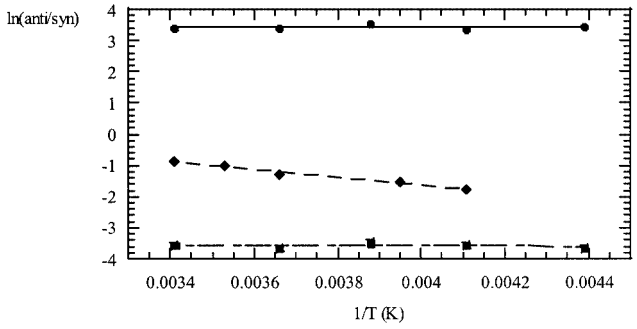


Figure 2. Eyring plots for the addition of vinylmagnesium bromide to imine **2** (solid squares) and to imine **1** (circles) in the absence of ZnI_2 and for the addition of vinylmagnesium bromide to imine **1** (diamonds) in the presence of ZnI_2

Other research groups have also recognized the importance of entropy in controlling stereoselective processes.[33] The entropy control over the diastereoselectivity suggests that steric and stereoelectronic interactions between imine substituents and the approaching Grignard reagent across the two diastereotopic faces do not play any significant role in determining the stereochemical outcome of the reaction, a situation that limits the utility of current models for the interpretation of the 1,2-asymmetric induction in this kind of process.

In order to favor the formation of chelated intermediates, we studied the stereochemical course of the addition of vinylmagnesium bromide to imines **1** and **2** in the presence of a chelating Lewis acid, in this case ZnI_2. Addition products were obtained in acceptable yields only when imine **1** was used as the starting material. The results obtained under different reaction conditions are shown in Table 3. As far as diastereoselectivity is concerned, addition reactions to both imines **1** and **2** resulted in high degrees of *syn* stereoselectivity. Therefore, by comparison of the addition of vinylmagnesium bromide in the absence or in the presence of ZnI_2, a reversal of diastereoselectivity was achieved with imine **1** but similar behavior was not observed with imine **2**.

Table 3. Diastereoselective addition of vinylmagnesium bromide to chiral imines **1** and **2** in the presence of ZnI_2; the reaction was carried out in dry diethyl ether by addition of vinylmagnesium bromide (3 equiv.) to the corresponding imine previously complexed with ZnI_2 (1 equiv.) under argon

Entry	Imine	*T* (°C)	Yield (%)[a]	*syn*/*anti*[b]
1	**1**	20	63	70.4:29.6
2	**1**	10	67	73.7:26.3
3	**1**	0	70	78.2:21.8
4	**1**	−10	78	80.5:19.5
5	**1**	−20	75	82.4:17.6
6	**1**	−30	54	85.5:14.5
7	**1**	−40	0	−

[a] The crude reaction mixture was directly analyzed by ^{1}H NMR spectroscopy and the yield was determined from the relative intensities of characteristic protons versus aromatic protons of 1,3,5-trimethoxybenzene added after extractive workup and used as an internal standard. [b] Ratio determined by GC analysis of the crude reaction mixture.

On the other hand, no variation in the diastereoselectivity was observed on using imine **2** as the substrate and modifying the reaction temperature whereas the diastereofacial selectivity observed when starting from the ZnI_2-precomplexed imine **1** was very sensitive to temperature changes, the *syn*/*anti* ratio increasing with decreasing reaction temperature (Table 3, entries 1 to 6). These data were treated by the least-squares method in order to obtain a linear relationship in the Eyring plot (Figure 2), and the calculated differential activation parameters were $\Delta\Delta H^{\ddagger} = 2.48 \pm 0.16$ kcal·mol^{-1} and $\Delta\Delta S^{\ddagger} = 6.67 \pm 0.57$ cal·mol^{-1}·K^{-1}. It is interesting to note that both $\Delta\Delta H^{\ddagger}$ and $\Delta\Delta S^{\ddagger}$ have the same sign in this case. This means that while entropy favors the formation of the *anti* isomer, enthalpy favors the formation of the *syn* isomer. At low temperatures, the *syn* isomer is more favored and it is $\Delta\Delta H^{\ddagger}$ that mainly controls the stereoselectivity. As a consequence, an analysis based on the enthalpy contributions due to steric and stereoelectronic interactions in the transition state, as in the case of classical chelated or non-chelated models, appears quite appropriate to explain our results, and the predominant formation of *syn* isomers is generally attributed to an α-chelate transition state (Figure 1, model D).

The postulated formation of an α-chelate by complexation of imine **1** with zinc to explain the observed *syn* selectivity is supported by NMR spectroscopy. Addition of

$ZnCl_2$ to a solution of imine **1** in diethyl ether[34] induces significant low- or high-field shifts in the ^1H NMR signals of H^1, H^2, and H^4 and the ^{13}C NMR signals of C^1 and C^2 (Figure 3). Deshielding of H^1, H^4, and − mainly − C^1 indicates coordination of a zinc atom to the imine nitrogen, while the substantial deshielding of H^2 and shielding of C^2 indicates additional coordination of Zn to the α-oxygen atom of the dioxolane ring.

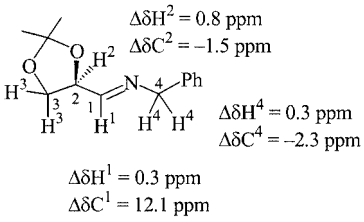


Figure 3. Chemical shift differences induced by $ZnCl_2$ in the ^1H and ^{13}C NMR spectra of imine **1** in dry diethyl ether

Conclusion

In summary, this strategy provides an efficient stereodivergent synthesis of enantiopure *anti* and *syn*-2-amino-1,3,4-butanetriol (ABT) derivatives from D-mannitol. The key step is the addition of vinylmagnesium bromide to conveniently protected imines derived from glyceraldehyde, which can be easily obtained on multigram scales from inexpensive D-mannitol. The stereochemical course of this reaction can be controlled by changing the hydroxy protecting groups in the starting imine or, in the case of isopropylidene-protected imine **1**, by carrying out the reaction in the presence or in the absence of a chelating Lewis acid, such as ZnI_2. We have paid particular attention to establishing how the C−C bond formation takes place and interpreting the stereochemical outcomes of the addition reactions. Although more expensive than D-mannitol, L-mannitol is readily available from L-mannonic γ-lactone,[35] and so this methodology can be used for the synthesis of all four conveniently protected ABT stereoisomers.

Experimental Section

General Remarks: All manipulations with air-sensitive reagents were carried out under dry argon atmospheres by use of standard Schlenk techniques. Whenever possible the reactions were monitored by TLC. TLC was performed on precoated silica gel polyester plates and products were viewed by use of UV light (254 nm) and anisaldehyde/sulfuric acid/ethanol (2:1:100). Column chromatography was performed on silica gel (Kieselgel 60). Melting points were determined in open capillaries with a Büchi capillary melting point apparatus and are not corrected. HPLC was performed on a Waters HPLC system consisting of a Waters 600-E pump equipped with a Waters 991 photo-diode array detector, analytical resolutions were carried out on a 250 × 4.6 mm ID Waters Spherisorb® 5 μm silica column. GC was performed on a HP-5890 apparatus, analytical resolutions were carried out on a 30 m × 0.25 mm × 0.35 μm cross-linked methyl silicone capillary column. NMR spectra were recorded on Varian Unity 300 or Bruker ARX 300 instruments operating at 300 MHz for ^1H NMR and 75 MHz for ^{13}C NMR with a 5 mm probe. All chemical shifts are relative to deuterated solvent signals, δ in ppm, *J* in Hz. The following abbreviations are used: s, singlet; d, doublet; t, triplet; m, multiplet; br. s, broad singlet; br. d, broad doublet; dd, doublet of doublets. The ^1H NMR and ^{13}C NMR spectra of *N*-Boc-protected compounds were not conclusive at room temperature, due to the presence of a dynamic equilibrium between rotamers caused by the restricted rotation of the nitrogen-carbon bond of the urethane group. In order to overcome this problem, NMR spectra of these compounds were acquired at 60 °C. The temperature was controlled by a VT unit with a flow of temperature-regulated nitrogen gas. Optical rotations were measured on a Jasco 1020 polarimeter at 20 °C, with concentrations given in g/100 mL. High-resolution mass spectra (HRMS) were recorded on a VG-autospec instrument. Elemental analyses were performed with a Perkin−Elmer 200 C,H,N,S elemental analyzer.

Starting Materials: Diethyl ether was distilled from sodium benzophenone ketyl. Chemicals for reactions were used as purchased from Aldrich Chemical Co. Imines **1** and **2** were prepared from the corresponding aldehydes according to previously described procedures.[36]

General Procedure for the Addition of Vinylmagnesium Bromide to Chiral Imines 1 and 2: A solution of the corresponding chiral imine (1 mmol) in dry diethyl ether (1.5 mL) was added dropwise at −30 °C under argon to a stirred solution of vinylmagnesium bromide in THF (1 M, 3 mL, 3 mmol) diluted with dry diethyl ether (15 mL). After stirring for 12 h at −30 °C, the reaction mixture was treated with saturated aqueous NH_4Cl (10 mL), the organic phase was separated, and the aqueous layer was extracted with diethyl ether. The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated to give an oily residue, which was purified by silica gel column chromatography.

Compound 3-*anti*: Eluent ethyl acetate/hexane, 1:3. Yield 81%. All physical and spectroscopic data were identical to those previously reported.[22]

Compound 4-*syn*: Eluent diethyl ether/hexane, 1:1. Yield 62%, oil. $[\alpha]_D^{20} = -11.2$ (*c* = 1.15 in $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 2.07 (br. s, 1 H), 3.21−3.31 (m, 1 H), 3.55−3.65 (m, 2 H), 3.58 (d, *J* = 13.5 Hz, 1 H), 3.70−3.75 (m, 1 H), 3.82 (d, *J* = 13.5 Hz, 1 H), 4.49 (d, *J* = 12.3 Hz, 1 H), 4.53 (d, *J* = 12.3 Hz, 1 H), 4.56 (d, *J* = 11.7 Hz, 1 H), 4.78 (d, *J* = 11.7 Hz, 1 H), 5.20 (dd, *J* = 16.8, *J* = 1.8 Hz, 1 H), 5.22 (dd, *J* = 8.4, *J* = 1.8 Hz, 1 H), 6.70 (ddd, *J* = 16.8, *J* = 8.4, *J* = 10.5 Hz, 1 H), 7.10−7.42 (m, 15 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 50.9, 62.3, 70.6, 73.0, 73.3, 81.0, 118.3, 126.7, 127.5, 127.6, 127.6, 127.8, 128.1, 128.2, 128.3, 128.3, 137.7, 138.3, 138.5, 140.6 ppm. HRMS (FAB) for $C_{26}H_{30}NO_2$ [M + H^+]: calcd. 388.2276; found 388.2285.

Compound 5: $Pd(OH)_2/C$ (20%, 100 mg) was added to a solution of compound **4-*syn*** (859 mg, 2.22 mmol) in absolute ethanol (6 mL) and the mixture was hydrogenated at atmospheric pressure by shaking at room temperature for 12 h. After completion of the reaction, the mixture was filtered and concentrated in vacuo. The resulting *N*-debenzylated product, together with diisopropyl ethylamine (30 mg, 0.23 mmol), was dissolved in dry THF (15 mL), and di-*tert*-butyl dicarbonate (970 mg, 4.45 mmol) was added. The mixture was stirred at 60 °C for 2 h and concentrated in vacuo to afford a crude product, which was purified by silica gel column chromatography by elution with (i) diethyl ether/hexane (1:7) and (ii) di-

ethyl ether/hexane (1:4) to afford 445 mg (50% yield) of a crude product. This product was dissolved in ethanol (15 mL) and hydrogenated with $Pd(OH)_2/C$ (20%, 100 mg) as a catalyst at room temperature and atmospheric pressure for 2 h. When the reaction was complete the catalyst was removed by filtration and the filtrate was evaporated to dryness. The resulting crude material was purified by silica gel column chromatography, with elution with ethyl acetate, to afford **5** (232 mg, 95% yield) as a white solid. M.p. 71−73 °C. $[\alpha]_D^{20} = +37.9$ ($c = 1$ in $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz, 60 °C): δ = 0.96 (t, $J = 7.5$ Hz, 3 H), 1.43 (s, 9 H), 1.53−1.62 (m, 2 H), 2.30 (br. d, $J = 4.8$ Hz, 1 H), 2.80 (br. s, 1 H), 3.44−3.62 (m, 3 H), 3.63−3.74 (m, 1 H), 4.60 (br. d, $J = 9$ Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz, 60 °C): δ = 10.8, 25.0, 28.3, 52.8, 63.7, 72.9, 80.0, 157.3 ppm. $C_{10}H_{21}NO_4$ (219.3): calcd. C 54.77, H 9.65, N 6.39; found C 54.85, H 9.71, N 6.43.

Compound 6: Small portions of $NaIO_4$ (665 mg, 3.11 mmol) were added to a stirred solution of compound **5** (170 mg, 0.78 mmol) in a mixture of acetonitrile/carbon tetrachloride/water (2:2:3) (10 mL). On completion of the addition, the mixture was vigorously stirred for 5 min and treated with $RuCl_3.H_2O$ (9.2 mg, 0.04 mmol). The mixture was stirred for a further 2 h at room temperature. Dichloromethane (25 mL) was added, and the mixture was extracted with aqueous $NaHCO_3$ (1 M). The aqueous solution was washed with diethyl ether, carefully acidified to pH 3 at 0 °C with aqueous $KHSO_4$ (1 M), and then extracted with diethyl ether. The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The resulting residue was dissolved in THF (5 mL) and hydrolyzed by stirring with hydrochloric acid (3 N, 10 mL) for 2 h at room temperature. The reaction mixture was washed with diethyl ether and the solvents were evaporated in vacuo to give the crude amino acid hydrochloride, which was purified by ion-exchange chromatography (Dowex 50 × 8) to afford compound **6** (59 mg, 74%) as a white solid. All physical and spectroscopic data for the obtained compound were identical to the data reported in the literature for (*R*)-2-aminobutyric acid.[24]

General Procedure for *N*-Boc Protection of Compounds 3-*anti* and 4-*syn*: Di-*tert*-butyl dicarbonate (545 mg, 2.5 mmol) was added to a solution of the corresponding vinylmagnesium bromide addition adduct (1 mmol) and diisopropyl ethylamine (13 mg, 0.1 mmol) in dry dioxane (5 mL) and the reaction mixture was stirred at 50 °C for 15 h. The reaction mixture was treated with diethyl ether and carefully acidified at 0 °C with aqueous $KHSO_4$ (1 M). The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo to afford a crude product, which was purified by silica gel column chromatography.

Compound 7: Eluent ethyl acetate/hexane, 1:9. Yield 96%. All physical and spectroscopic data were identical to those previously reported.[22]

Compound 10: Eluent diethyl ether/hexane, 1:8. Yield 80%, oil. $[\alpha]_D^{20} = +9.3$ ($c = 1$ in $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz, 60 °C): δ = 1.38 (s, 9 H), 3.49 (dd, $J = 10.8$, $J = 1$ Hz, 1 H), 3.64 (dd, $J = 10.8$, $J = 3.2$ Hz, 1 H), 4.10−4.19 (m, 1 H), 4.22−4.38 (m, 2 H), 4.45 (d, $J = 12$ Hz, 1 H), 4.51 (d, $J = 12$ Hz, 1 H), 4.53 (d, $J = 11.7$ Hz, 1 H), 4.59−4.72 (m, 1 H), 4.73 (d, $J = 11.7$ Hz, 1 H), 4.91−5.11 (m, 2 H), 5.90−6.10 (m, 1 H), 7.10−7.39 (m, 15 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz, 60 °C): δ = 28.5, 51.8, 62.6, 71.0, 73.0, 73.5, 79.4, 79.4, 118.5, 126.6, 127.4, 127.5, 127.6, 127.8, 128.0, 128.2, 128.3, 134.9, 138.5, 139.0, 139.6, 157.3 ppm. HRMS (FAB) for $C_{31}H_{37}NO_4$ [M^+]: calcd. 487.2722; found 487.2732.

General Procedure for Dihydroxylation of Compounds 7 and 10: A solution of OsO_4 in 2-methyl-2-propanol (2.5 wt%, 2.5 mL, 0.0245 mmol) was added at room temperature to a stirred solution of *N*-methylmorpholine *N*-oxide (175 mg, 1.5 mmol) and the corresponding alkene (1 mmol) in a mixture of acetone/water (10:1, 10 mL). When TLC analysis indicated consumption of the alkene, excess $NaHSO_3/Na_2S_2O_5$ was added, and the darkened reaction mixture was stirred for 30 min at room temperature. The acetone was evaporated in vacuo and the aqueous solution was treated with diethyl ether. The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by silica gel column chromatography, with elution with (i) ethyl acetate/hexane, 1:1 and (ii) ethyl acetate, to afford the dihydroxylated compound as a mixture of diastereoisomers, which was used as such in the next step.

General Procedure for the Synthesis of ABT Derivatives 9 and 12: $NaIO_4$ (257 mg, 1.2 mmol) was added to a stirred solution of the corresponding diol (1 mmol) in methanol (10 mL) and the mixture was vigorously stirred for 12 h at room temperature. On completion, the reaction mixture was filtered and concentrated in vacuo. The resulting residue was dissolved in diethyl ether and filtered, and the solvents were evaporated in vacuo. Sodium borohydride (380 mg, 10 mmol) was added to a solution of the crude aldehyde in ethanol (10 mL), and the reaction mixture was stirred for 16 h at room temperature. The reaction mixture was carefully acidified with aqueous HCl (1 N), the ethanol was evaporated in vacuo, and the aqueous solution was extracted with dichloromethane. The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo to afford a crude product, which was purified by silica gel column chromatography, with elution with diethyl ether/hexane, 2:1.

Compound 9: Yield 80%, oil. $[\alpha]_D^{20} = +5.6$ ($c = 1$ in $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz, 60 °C): δ = 1.26 (s, 3 H), 1.35 (s, 3 H), 1.44 (s, 9 H), 3.60 (dd, $J = 6.6$, $J = 8.4$ Hz, 1 H), 3.73−3.95 (m, 5 H), 4.30−4.38 (m, 1 H), 4.43 (d, $J = 15.6$ Hz, 1 H), 4.53 (d, $J = 15.6$ Hz, 1 H), 7.20−7.33 (m, 5 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz, 60 °C): δ = 25.4, 26.7, 28.4, 50.8, 61.6, 62.8, 67.5, 75.8, 80.9, 109.6, 127.4, 127.6, 128.6, 139.1, 156.4 ppm. HRMS (FAB) for $C_{19}H_{30}NO_5$ [M + H^+]: calcd. 352.2124; found 352.2129.

Compound 12: Yield 85%, oil. $[\alpha]_D^{20} = -12.7$ ($c = 1$ in $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz, 60 °C): δ = 1.51 (s, 9 H), 3.70−3.90 (m, 6 H), 4.22−4.40 (m, 2 H), 4.59 (d, $J = 12$ Hz, 1 H), 4.59 (d, $J = 11.4$ Hz, 1 H), 4.65 (d, $J = 12$ Hz, 1 H), 4.78 (d, $J = 11.4$ Hz, 1 H), 4.88 (d, $J = 15.6$ Hz, 1 H), 7.20−7.33 (m, 15 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz, 60 °C): δ = 28.4, 53.4, 62.4, 63.3, 70.2, 73.1, 73.6, 77.4, 80.6, 127.0, 127.5, 127.6, 127.6, 127.7, 127.8, 128.3, 128.4, 128.4, 138.4, 138.8, 139.4, 157.2 ppm. HRMS (FAB) for $C_{30}H_{38}NO_5$ [M + H^+]: calcd. 492.2750; found 492.2746.

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