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Highly Stereoselective Synthesis of Stereochemically Defined Polyhydroxylated Propargylamines by Alkynylation of *N*-Benzylimines Derived from (*R*)-Glyceraldehyde

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The addition of the lithium derivative of *tert*-butyldimethylsilyl propargyl ether to *N*-benzylimines derived from (*R*)-2,3-*O*-isopropylideneglyceraldehyde has been achieved with acceptable yields and high diastereoselectivities. The *syn*/*anti* diastereoselectivity of the addition reaction can be controlled and reversed by the appropriate use of Lewis acids as imine precomplexing agents. Double stereodifferentiation processes using imines derived from (*R*)-2,3-*O*-isopropylideneglyceraldehyde and (*R*)- or (*S*)-α-methylbenzylamine as starting materials occur with total stereocontrol to afford *syn* and *anti vic*-propargylamino alcohol derivatives with orthogonally protected hydroxymethyl groups on both sides of the central core.

Introduction

Optically active α-substituted propargylamine units are present in a variety of biologically active compounds[1] and are versatile building blocks and intermediates for a large number of synthetic applications.[2] In general, synthetic routes that provide reliable and convenient access to this scaffold in enantiomerically pure form are still scarce,[3] and of these, nucleophilic addition of alkynylides to chiral imines or related carbonyl derivatives is often the method of choice for the asymmetric synthesis of α-substituted propargylamines.[4] Recently, catalytic enantioselective procedures have emerged as a very appealing alternative to the asymmetric synthesis of these compounds.[5] Such addition reactions are intrinsically efficient because a new stereogenic centre and a new C–C bond are created in a single operation.

Enantiomerically pure vicinal amino alcohol derivatives represent another interesting family of nitrogenated compounds as they play an important role in synthetic and medicinal chemistry.[6] 1,2-Amino alcohols are widely used as chiral auxiliaries and metal ligands in catalytic asymmetric synthesis and they are crucial structural features in a large number of natural products and synthetic compounds of pharmacological interest. As a result of their synthetic significance, quite a number of stereoselective synthetic methodologies to produce vicinal amino alcohols and their derivatives have been developed in recent years.[6] Among them, the asymmetric addition of organometallic reagents to C=N bonds in chiral protected α-hydroxyimines is one of the most attractive and direct approaches affording these substructures.[7] Surprisingly, the extension of this methodology to the use of organometallic reagents derived from terminal alkynes for the synthesis of enantiomerically pure vicinal propargylamino alcohol derivatives, an interesting class of compounds thanks to their potential in synthesis,[8] has hardly been developed. Indeed, to the best of our knowledge, there are only four reports on stereoselective additions of alkynylmetallics to protected chiral α-hydroxy imines. Martin and co-workers[9] reported the addition of trimethylsilylethynylmagnesium bromide to an imine derived from L-sorbose to give the *syn* product with total diastereoselectivity, whilst Evans et al.[10] described the exclusive formation of the *anti* diastereoisomer in the nucleophilic addition of 3,3-diethoxy-1-lithiopropyne to a cyclic imine derived from D-ribitol. More recently, Trost et al.[11] reported the reaction between an *N*-allylimine derived from (*R*)-glyceraldehyde and an alkynyllithium trimethylaluminate, giving the corresponding amino alcohol derivative of *anti* configuration with high diastereoselectivity. This compound has been used as a key intermediate in the stereoselective synthesis of the lipophilic antibiotic (+)-streptazolin. Shimizu and co-workers[12] have described the reaction between an imine derived from *meso*-tartaric acid and lithium trimethylsilylacetylide to give either the *syn* product – albeit in a low yield (17%) – when the reaction was conducted in the presence of $BF_3{\cdot}Et_2O$, or the *anti* product in 55% yield. Finally, during the preparation of this manuscript Díez and

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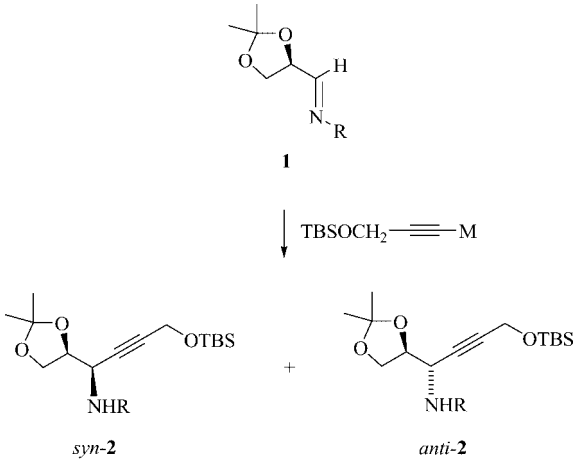
co-workers[13] reported that the addition of the lithium anion of tetrahydro-2-(2-propynyloxy)-2*H*-pyran to imine **1a** takes place with acceptable levels of diastereoselectivity in the presence of cerium trichloride.

In recent years we have been investigating reactions between conveniently protected *N*-benzylimines derived from (*R*)-glyceraldehyde and methyl, benzyl, allyl, vinyl and aryl organometallic reagents, mainly Grignard-type organometallics. With all these reagents we have obtained the corresponding chiral amino alcohol derivatives in good yields and with total diastereoselectivity.[14] In some cases we have even been able to develop efficient stereodivergent syntheses, either (i) by changing the 1,2-dihydroxy protecting groups in the starting imine,[14a,14d] or (ii) by choosing appropriate organometallic species with which to carry out the chemical process.[14b] The resulting *syn* or *anti* vicinal amino alcohol derivatives are versatile synthetic intermediates and we have used them in asymmetric syntheses of several classes of biologically active molecules.[14,15] In this paper we wish to disclose our results on the diasteeoselective alkynylation of *N*-benzylimines derived from (*R*)-2,3-*O*-isopropylideneglyceraldehyde with 3-(*tert*-butyldimethylsilyloxy)prop-1-ynyllithium in the presence or absence of a Lewis acid to afford *syn* and *anti* vicinal propargylamino alcohol derivatives, respectively, with orthogonally protected hydroxymethyl groups on both sides of the central core (Scheme 1). These compounds can be regarded as useful new building blocks as they have five possible points for further derivatisation: three hydroxy groups at C^1, C^2 and C^6, one amino group at C^3 and one C≡C triple bond.



Scheme 1. Diastereoselective addition of alkynylmetallics to chiral imines **1a**–**c**.

Results and Discussion

The *N*-benzylimine derived from (*R*)-2,3-*O*-isopropylideneglyceraldehyde (**1a**) was easily prepared on a multigram scale from inexpensive D-mannitol in a three-step process. Ketalisation of D-mannitol was performed by the procedure reported by Priestley,[16] which employed catalytic $SnCl_2$ and 2,2-dimethoxypropane, whilst the oxidative cleavage of 1,2:5,6-di-*O*-isopropylidene-D-mannitol was carried out with $NaIO_4$ as reported by Schmid.[17]

Reactivity between the chiral imine **1a** and 3-(*tert*-butyldimethylsilyloxy)prop-1-ynylmagnesium bromide, generated in situ from *tert*-butyldimethylsilyl propargyl ether and ethylmagnesium bromide, was investigated first. This reaction was not effective, however, with a complex reaction mixture being obtained after the starting imine had been consumed. On the other hand, the reaction between chiral imine **1a** and 3-(*tert*-butyldimethylsilyloxy)prop-1-ynyllithium (1 equiv.), generated in situ by deprotonation of the terminal alkyne with butyllithium[18] at –30 °C, afforded the desired vicinal propargylamino alcohol derivative **2a** as an 80:20 *syn*/*anti* mixture of diastereoisomers, though in very low yield. The effects of the amount of reagent, temperature, solvent and Lewis acid were subsequently explored and the results are summarised in Table 1.

In general, long reaction times were required to provide complete conversion of the starting imine and, after considerable experimentation, we observed that in the absence of Lewis acids the optimal yield (50%) and diastereoselectivity (*syn*/*anti* 91:9) were obtained when the imine was added at –30 °C to an excess of 3-(*tert*-butyldimethylsilyloxy)prop-1-ynyllithium (2 equiv.) in dry ether. Other reaction conditions such as the use of 1 or 3 equiv. of the organometallic reagent, a decrease or an increase in the reaction temperature, or the use of toluene or THF as the solvent usually decreased the reaction yield and did not increase (or even reduced) the stereoselection.

The stereochemical outcome of the addition reaction was shown to be dependent on the presence or absence of Lewis acids as precomplexing agents and the ability of these systems to form chelates.[19] Consequently, amino alcohol *syn*-**2a** was obtained preferentially in the absence of Lewis acid (Table 1, Entries 1–9) or with use of diethylaluminium chloride as a precomplexing agent (Table 1, Entry 11). In contrast, the addition reaction in the presence of boron trifluoride–diethyl ether resulted in the formation of *anti*-**2a** as the major compound (Table 1, Entry 13). Moreover, the reaction was found to depend on the order of addition of reagents, such that when the imine was added to a mixture of the organollithium reagent and boron trifluoride diethyl etherate the addition was not diastereoselective and the yield was very poor (Table 1, Entry 14). Separation of the *syn* and *anti* isomers was easily effected by flash chromatography.

The stereochemistry of the compound obtained in the absence of Lewis acid or with use of diethylaluminium chloride as a precomplexing agent presumably arises as a result of chelation control and can be explained by considering α-chelate A (see Figure 1).

In this chelate the metal (Li or Al) coordinates with the nitrogen of the imine group and the adjacent oxygen to form a five-membered ring intermediate. The nucleophile then preferentially approaches *anti* to the large dioxolane

Table 1. Diastereoselective addition of $TBSOCH_2C{\equiv}CLi$ to chiral imines **1a**–**c**.

Entry	Imine	OM (equiv.)	Lewis acid (equiv.)	T (°C)	Solvent	Product	Yield (%)[a]	*syn*/*anti*[b]
1	**1a**	1	–[c]	–30	Et_2O	**2a**	20	80:20
2	**1a**	2	–[c]	–30	Et_2O	**2a**	50	91:9
3	**1a**	4	–[c]	–30	Et_2O	**2a**	40	88:12
4	**1a**	2	–[c]	20	Et_2O	**2a**	44	75:25
5	**1a**	2	–[c]	0	Et_2O	**2a**	40	81:19
6	**1a**	2	–[c]	–20	Et_2O	**2a**	42	79:21
7	**1a**	2	–[c]	–40	Et_2O	**2a**	38	90:10
8	**1a**	2	–[c]	–30	toluene	**2a**	36	68:32
9	**1a**	2	–[c]	–30	THF	**2a**	40	74:26
10	**1a**	2	Et_2AlCl (1)[d]	–30	Et_2O	–[f]	–	–
11	**1a**	2	Et_2AlCl (2)[d]	–30	Et_2O	**2a**	40	91:9
12	**1a**	2	$BF_3{\cdot}OEt_2$ (1)[d]	–30	Et_2O	–[f]	–	–
13	**1a**	2	$BF_3{\cdot}OEt_2$ (2)[d]	–30	Et_2O	**2a**	55	12:88
14	**1a**	2	$BF_3{\cdot}OEt_2$ (2)[e]	–30	Et_2O	**2a**	18	50:50
15	**1b**	2	–[c]	–30	Et_2O	–[g]	–	–
16	**1c**	2	–[c]	–30	Et_2O	–[g]	–	–
17	**1b**	2	Et_2AlCl (2)[d]	–30	Et_2O	–[g]	–	–
18	**1c**	2	Et_2AlCl (2)[d]	–30	Et_2O	–[g]	–	–
19	**1b**	2	$BF_3{\cdot}OEt_2$ (2)[d]	–30	Et_2O	**2b**	80	>2:98
20	**1c**	2	$BF_3{\cdot}OEt_2$ (2)[d]	–30	Et_2O	**2c**	65	15:85

[a] Diastereomeric mixture, isolated yield after column chromatography. [b] The crude reaction mixture was directly analysed by ^1H NMR spectroscopy and the diastereomeric ratio was determined from the relative intensities of characteristic protons. [c] The reaction was carried out by addition of the imine to $TBSOCH_2C{\equiv}CLi$. [d] The reaction was carried out by addition of $TBSOCH_2C{\equiv}CLi$ to the precomplexed imine. [e] Imine was added to a mixture of $TBSOCH_2C{\equiv}CLi$ and $BF_3{\cdot}OEt_2$. [f] Complex reaction mixture. [g] No reaction, even at room temperature.

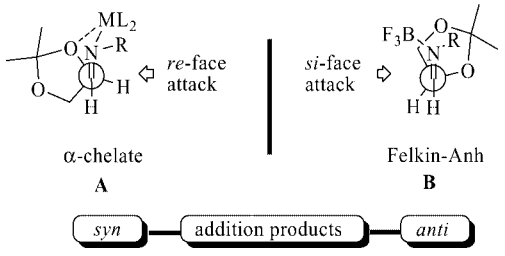


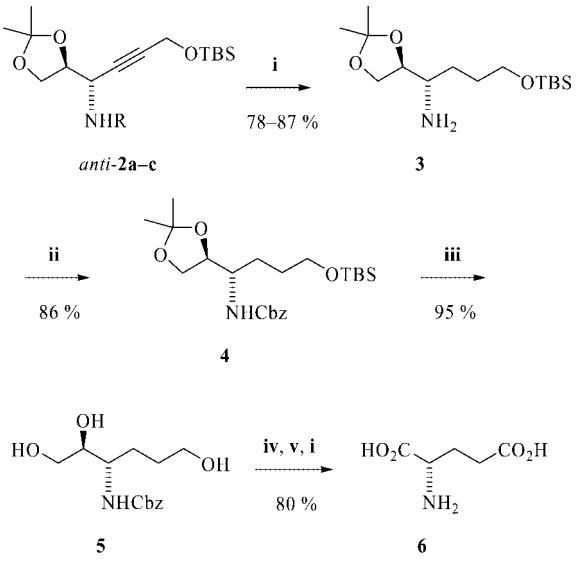
Figure 1. Stereocorrelation models for the addition of alkynylmetallics to imines **1a**–**c**.

substituent, giving rise to the observed *syn* major product. In the presence of boron trifluoride, Felkin–Anh-type intermediate B could account for the observed stereochemistry.

In order to achieve complete diastereoselectivity in the nucleophilic addition, a double stereodifferentiation strategy[20] was considered. In this approach, imines **1b** and **1c** were prepared from (*R*)-isopropylideneglyceraldehyde and (*S*)- or (*R*)-1-phenylethylamine, respectively (Scheme 1), and their reactivities with 3-(*tert*-butyldimethylsilyloxy)-prop-1-ynyllithium were assessed. Imines **1b** and **1c** did not react with the lithium acetylide in the absence of Lewis acid or in the presence of diethylaluminium chloride either at low temperature or at room temperature. Precomplexation of imines **1b** and **1c** with boron trifluoride proved to be effective, however,[21] and compounds **2b** and **2c** were isolated after addition of the lithium acetylide in acceptable yields. The stereochemical course of these reactions was mainly controlled by the α-stereogenic centre in the carbonyl moiety (1,2-asymmetric induction) and the Lewis acid, while the stereogenic centre in the amine moiety (1,3-asymmetric induction) modulated the diastereoselectivity of the process either upwards (matched pair) or downwards (mismatched pair). Thus, treatment of boron trifluoride-precomplexed imines **1b** and **1c** with the alkynyllithium produced compounds of *anti* relative configuration with complete stereocontrol when imine **1b** was the starting material. On the other hand, an 85:15 mixture of compounds *anti*-**2c**/*syn*-**2c** was obtained from imine **1c**. The α-(*S*,*S*) combination was therefore the matched pair for this process, while the α-(*S*,*R*) combination was the mismatched pair.

The assignment of the absolute configuration of the newly formed stereogenic carbon in the addition reactions was achieved by conversion of compounds *anti*-**2a**, *anti*-**2b** and *anti*-**2c** into known (*S*)-glutamic acid, as shown in Scheme 2.

Removal of the *N*-benzyl protecting groups with concomitant reduction of the C≡C triple bond was easily performed by hydrogenation of the corresponding compound *anti*-**2a**–**c** at atmospheric pressure in a methanolic solution and in the presence of Pd/C as the catalyst, to afford compound **3** in 87, 85 and 78% yields, respectively. Subsequent conversion of compound **3** into the corresponding *N*-benzyloxycarbonyl derivative was smoothly achieved by treatment with benzyl chloroformate in the presence of diisopropylethylamine to give compound **4** in 86% yield. Treatment of **4** with trifluoroacetic acid resulted in hydrolysis of both the ketal and the trialkylsilyloxy groups, and triol **5** was obtained in 95% yield. Finally, oxidative cleavage of the 1,2-diol moiety by treatment with excess sodium periodate and subsequent oxidation of the crude α-amino-δ-hydroxyaldehyde intermediate with sodium dichromate in aqueous sulfuric acid (Jones' reagent) gave Cbz-glutamic acid, which was hydrogenated without purification in the presence of Pd/C as a catalyst to afford enantiomerically pure (*S*)-glutamic acid **6** in an overall yield of 80% from **5**. Compound



Reagents: **i**. H_2, Pd/C; **ii**. $BnCO_2Cl$, DIPEA; **iii**. TFA, MeOH; **iv**. $NaIO_4$; **v**. $Na_2Cr_2O_7$, H_2SO_4

Scheme 2. Conversion of compounds *anti*-**2a**–**c** into (*S*)-glutamic acid.

6 was found to be identical with an authentic sample of (*S*)-glutamic acid upon comparison of their spectroscopic data and specific rotations,[22] which enabled the unambiguous assignment of the configurations of compounds **2a**–**c**. The enantiomeric purity of compound **6** was determined by chiral HPLC (>99:1), with use of *rac*-glutamic acid as the reference.[23] Amino acid **6** was detected as a single peak, showing that racemisation had not occurred to any appreciable extent during the reaction sequence.

Conclusions

In summary, we have shown that the *syn* and *anti* isomers of propargylamine **2a** can be obtained with high diastereoselectivity from the same starting material – *N*-benzylimine **1a**, derived from (*R*)-2,3-*O*-isopropylideneglyceraldehyde – by nucleophilic addition of $LiC{\equiv}CCH_2OTBS$ in the presence or absence of the appropriate Lewis acid. A double stereodifferentiation process using boron-precomplexed *N*-(*R*)-α-methylbenzylimine **1b** provided enantiomerically pure *anti* propargylamino alcohol derivative **2b** with total diastereoselectivity. These compounds can be regarded as multifunctional key intermediates for further derivatisation since they possess an amino group, an ethynyl group and several selectively protected hydroxy groups as substituents. These groups can be easily transformed into a variety of different functional groups. In particular, these compounds could be useful as building blocks for the preparation of a wide variety of biologically active compounds; research in this area is underway and will be reported in due course.

Experimental Section

General Remarks: All manipulations with air-sensitive reagents were carried out under dry argon 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 with a Waters HPLC system consisting of a Waters 600-E pump with a Waters 991 photodiode array detector; analytical resolutions were carried out on a 250 × 4.6 mm Chirobiotic T™ 5 μm column. NMR spectra were recorded with Bruker ARX 300 or Bruker AV 400 instruments operating at 300 or 400 MHz for ^{1}H NMR and 75 or 100 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. Optical rotations were measured with 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 CHNS elemental analyser.

Starting Materials: Chemicals for reactions were used as purchased from commercial sources. 1,2:5,6-Di-*O*-isopropylidene-D-mannitol,[16] (*R*)-2,3-*O*-isopropylideneglyceraldehyde[17] and 3-(*tert*-butyldimethylsilyloxy)-1-propyne[24] were prepared by literature procedures. Chiral imines **1a**–**c** were obtained by a previously described procedure for the synthesis of **1a**[25] and used immediately.

Compound 1a: ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C): δ = 1.43 (s, 3 H), 1.50 (s, 3 H), 3.99 (dd, J = 8.5, 6.2 Hz, 1 H), 4.23 (dd, J = 8.5, 6.8 Hz, 1 H), 4.64 (br s, 2 H), 4.64–4.68 (m, 1 H), 7.27–7.30 (m, 3 H), 7.34–7.40 (m, 2 H), 7.79 (dt, J = 5.0, 1.4 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C): δ = 25.4, 25.5, 64.6, 67.4, 77.0, 110.2, 127.1, 127.9, 128.5, 138.3, 164.1 ppm.

Compound 1b: ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C): δ = 1.41 (s, 3 H), 1.47 (s, 3 H), 1.51 (d, J = 6.7 Hz, 3 H), 4.00 (dd, J = 8.4, 6.2 Hz, 1 H), 4.24 (dd, J = 8.4, 6.8 Hz, 1 H), 4.39 (q, J = 6.7 Hz, 1 H), 4.64 (ddd, J = 6.8, 6.2, 5.0 Hz, 1 H), 7.32–7.38 (m, 5 H), 7.75 (dd, J = 5.0, 0.6 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C): δ = 24.3, 25.4, 26.5, 67.4, 69.3, 76.9, 110.2, 126.5, 127.0, 128.4, 144.0, 161.7 ppm.

Compound 1c: ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C): δ = 1.42 (s, 3 H), 1.46 (s, 3 H), 1.53 (d, J = 6.6 Hz, 3 H), 3.90 (dd, J = 8.5, 6.3 Hz, 1 H), 4.20 (dd, J = 8.5, 6.8 Hz, 1 H), 4.39 (q, J = 6.6 Hz, 1 H), 4.65 (ddd, J = 6.8, 6.3, 5.2 Hz, 1 H), 7.30–7.38 (m, 5 H), 7.74 (dd, J = 5.2, 0.6 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C): δ = 24.4, 25.4, 26.5, 67.4, 69.4, 77.1, 110.2, 126.5, 127.0, 128.5, 144.2, 161.7 ppm.

General Procedures for the Addition of Alkynylmetallics to Chiral Imines 1a–c

Procedure A: A solution of butyllithium in hexanes (1 M, 2 mL, 2 mmol) was slowly added at –78 °C under argon to a solution of 3-(*tert*-butyldimethylsilyloxy)prop-1-yne (342 mg, 2 mmol) in the corresponding dry solvent (2 mL). After having been stirred for 1 h at –78 °C the solution was warmed to the desired temperature, a solution of the corresponding chiral imine **1** (1 mmol) in the same dry solvent (3 mL) was added dropwise, and stirring was continued for 72 h at the same temperature. The reaction mixture was then

treated with saturated aqueous NH_4Cl (10 mL), the organic phase was separated, and the aqueous layer was extracted with diethyl ether (3 × 10 mL). The combined organic layers were dried with anhydrous $MgSO_4$, filtered and concentrated to give an oily residue, which was purified by silica gel column chromatography.

Procedure B: A solution of butyllithium in hexanes (1 M, 2 mL, 2 mmol) was slowly added at –78 °C under argon to a solution of 3-(*tert*-butyldimethylsilyloxy)-1-propyne (342 mg, 2 mmol) in the corresponding dry solvent (2 mL) and stirring was continued for 1 h at the same temperature. A solution of chiral imine **1** (1 mmol) in dry diethyl ether (2 mL) was added under argon to a solution of the corresponding Lewis acid (2 mmol) in dry diethyl ether. After having been stirred for 5 min at room temperature, the solution was cooled to –30 °C. An ethereal solution of 3-(*tert*-butyldimethylsilyloxy)prop-1-ynyllithium (2 mmol), obtained as described above, was slowly added and the reaction mixture was stirred for 24 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 (3 × 10 mL). The combined organic layers were dried with anhydrous $MgSO_4$, filtered and concentrated to give an oily residue, which was purified by silica gel column chromatography.

Compound *syn*-2a: Treatment of imine **1a** (1.5 g, 6.85 mmol) with 3-(*tert*-butyldimethylsilyloxy)prop-1-ynyllithium (13.70 mmol) as described in Procedure A yielded compound **2a** as a 91:9 mixture of *syn*/*anti* diastereoisomers, from which the major compound *syn*-**2a** (oil, 1.17 g, 44%) was isolated by silica gel column chromatography (eluent: diethyl ether/hexane, 1:2). $[\alpha]_D^{20}$ = –51.20 (*c* = 1.0 in $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz, 25 °C): δ = 0.01 (s, 6 H), 0.80 (s, 9 H), 1.19 (s, 3 H), 1.20 (s, 3 H), 1.79 (br s, 1 H), 3.30 (dt, *J* = 7.4, 1.5 Hz, 1 H), 3.69 (d, *J* = 13.5 Hz, 1 H), 3.79 (dd, *J* = 8.4, 5.7 Hz, 1 H), 3.92 (dd, *J* = 8.4, 6.1 Hz, 1 H), 3.92 (d, *J* = 13.5 Hz, 1 H), 4.04 (ddd, *J* = 7.4, 6.1, 5.7 Hz, 1 H), 4.22 (d, *J* = 1.5 Hz, 2 H), 7.09–7.24 (m, 5 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C): δ = –5.3, 18.0, 25.2, 25.6, 26.5, 50.9, 51.5, 53.2, 66.8, 77.7, 82.2, 83.4, 109.7, 126.8, 128.1, 128.1, 139.4 ppm. IR (neat): $\tilde{\nu}$ = 3331 cm^{-1}. HRMS (FAB) for $C_{22}H_{36}NO_3Si$ $[M + H]^+$: calcd. 390.2464; found: 390.2475.

Compound *anti*-2a: Treatment of imine **1a** (500 mg, 2.28 mmol) precomplexed with $BF_3{\cdot}OEt_2$ (4.56 mmol) with 3-(*tert*-butyldimethylsilyloxy)prop-1-ynyllithium (4.56 mmol) as described in Procedure B yielded compound **2a** as a 12:88 mixture of *syn*/*anti* diastereoisomers, from which the major compound *anti*-**2a** (oil, 399 mg, 45%) was isolated by silica gel column chromatography (eluent: diethyl ether/hexane, 1:2). $[\alpha]_D^{20}$ = +64.45 (*c* = 1.0 in $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz, 25 °C): δ = 0.12 (s, 6 H), 0.91 (s, 9 H), 1.33 (s, 3 H), 1.42 (s, 3 H), 1.86 (br s, 1 H), 3.47 (dt, *J* = 4.7, 1.7 Hz, 1 H), 3.80 (d, *J* = 13.1 Hz, 1 H), 3.96 (dd, *J* = 8.2, 6.7 Hz, 1 H), 4.03 (dd, *J* = 8.2, 6.5 Hz, 1 H), 4.04 (d, *J* = 13.1 Hz, 1 H), 4.18 (ddd, *J* = 6.7, 6.5, 4.7 Hz, 1 H), 4.37 (d, *J* = 1.7 Hz, 2 H), 7.19–7.39 (m, 5 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C): δ = –5.2, 18.1, 25.3, 25.7, 26.4, 51.2, 51.6, 51.7, 66.7, 77.6, 82.5, 83.6, 109.5, 126.9, 128.2, 128.2, 139.6 ppm. IR (neat): $\tilde{\nu}$ = 3352 cm^{-1}. HRMS (FAB) for $C_{22}H_{36}NO_3Si$ $[M + H]^+$: calcd. 390.2464; found: 390.2473.

Compound *anti*-2b: Treatment of imine **1b** (1 g, 4.30 mmol) precomplexed with $BF_3{\cdot}OEt_2$ (8.60 mmol) with 3-(*tert*-butyldimethylsilyloxy)prop-1-ynyllithium (8.60 mmol) as described in Procedure B yielded compound **2b** as a single diastereoisomer. Purification of the crude product by silica gel column chromatography (eluent: diethyl ether/hexane, 1:3) yielded compound *anti*-**2b** (oil, 1.38 g, 80%). $[\alpha]_D^{20}$ = –15.93 (*c* = 1.0 in $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 0.10 (s, 6 H), 0.89 (s, 9 H), 1.29 (d, *J* = 6.5 Hz, 3 H), 1.32 (s, 3 H), 1.43 (s, 3 H), 1.64 (br s, 1 H), 3.56 (dt, *J* = 5.0, 1.7 Hz, 1 H), 3.97 (dd, *J* = 8.3, 6.5 Hz, 1 H), 4.03 (dd, *J* = 8.3, 6.3 Hz, 1 H), 4.07–4.17 (m, 2 H), 4.31 (d, *J* = 1.7 Hz, 2 H), 7.18–7.38 (m, 5 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = –5.1, 18.3, 22.2, 25.4, 25.8, 26.5, 50.5, 51.8, 55.1, 67.1, 77.6, 82.7, 83.4, 109.7, 126.8, 127.1, 128.4, 145.8 ppm. IR (neat): $\tilde{\nu}$ = 3405 cm^{-1}. HRMS (FAB) for $C_{23}H_{38}NO_3Si$ $[M + H]^+$: calcd. 404.2620; found: 404.2612.

Compound *anti*-2c: Treatment of imine **1c** (500 mg, 2.15 mmol), precomplexed with $BF_3{\cdot}OEt_2$ (4.30 mmol), with 3-(*tert*-butyldimethylsilyloxy)prop-1-ynyllithium (4.30 mmol) as described in Procedure B yielded compound **2c** as a 15:85 mixture of *syn*/*anti* diastereoisomers, from which the major compound *anti*-**2c** (oil, 449 mg, 52 %) was isolated by silica gel column chromatography (eluent: diethyl ether/hexane, 1:3). $[\alpha]_D^{20}$ = –25.20 (*c* = 1.0 in $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 0.12 (s, 6 H), 0.91 (s, 9 H), 1.33 (d, *J* = 6.4 Hz, 3 H), 1.33 (s, 3 H), 1.39 (s, 3 H), 1.85 (br s, 1 H), 3.07 (dt, *J* = 4.5, 1.5 Hz, 1 H), 3.78 (dd, *J* = 8.2, 7.0 Hz, 1 H), 3.97 (dd, *J* = 8.2, 6.5 Hz, 1 H), 4.07–4.17 (m, 2 H), 4.36 (d, *J* = 1.5 Hz, 2 H), 7.18–7.38 (m, 5 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = –5.1, 18.2, 24.9, 25.4, 25.7, 26.3, 50.4, 51.6, 55.4, 67.1, 77.9, 82.9, 83.4, 109.4, 126.4, 127.0, 128.3, 144.5 ppm. IR (neat): $\tilde{\nu}$ = 3340 cm^{-1}. HRMS (FAB) for $C_{23}H_{38}NO_3Si$ $[M + H]^+$: calcd. 404.2620; found: 404.2628.

Representative Procedure for the Synthesis of Compound 3: Pd/C (10%, 150 mg) was added to a solution of compound *anti*-**2a** (1 g, 2.57 mmol) in absolute ethanol (15 mL) and the mixture was hydrogenated at atmospheric pressure with stirring at room temperature for 12 h. After completion of the reaction the catalyst was removed by filtration and the filtrate was concentrated to dryness. The resulting crude material was purified by silica gel column chromatography (eluent: ethyl acetate/hexane, 6:1) to afford compound **3** (oil, 677 mg, 87% yield). $[\alpha]_D^{20}$ = –4.10 (*c* = 1.0 in $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 0.00 (s, 6 H), 0.85 (s, 9 H), 1.12–1.22 (m, 1 H), 1.31 (s, 3 H), 1.38 (s, 3 H), 1.40 (br s, 2 H), 1.42–1.70 (m, 3 H), 2.86–2.95 (m, 1 H), 3.59 (t, *J* = 6.0 Hz, 2 H), 3.75–3.85 (m, 1 H), 3.91–4.01 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = –5.3, 18.3, 25.2, 25.9, 26.5, 29.4, 30.1, 52.3, 63.0, 65.2, 79.4, 108.8 ppm. IR (neat): $\tilde{\nu}$ = 3356 cm^{-1}. HRMS (FAB) for $C_{15}H_{33}NO_3Si$ $[M + H]^+$: calcd. 304.2307; found: 304.2299.

Compound 4: Benzyl chloroformate (410 mg, 2.40 mmol) was added to a solution of compound **3** (500 mg, 1.65 mmol) and diisopropylethylamine (632 mg, 4.90 mmol) in dry dichloromethane (10 mL) and the reaction mixture was stirred at room temperature for 15 h. The reaction mixture was treated with water and extracted with dichloromethane, and the organic layer was dried with anhydrous $MgSO_4$, filtered and concentrated in vacuo to afford a crude product, which was purified by silica gel column chromatography (eluent: diethyl ether/hexane, 1:4) to afford compound **4** (620 mg, 86% yield). M.p. 58.5 °C. $[\alpha]_D^{20}$ = –6.56 (*c* = 1.0 in $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz, 60 °C): δ = 0.03 (s, 6 H), 0.88 (s, 9 H), 1.32 (s, 3 H), 1.39 (s, 3 H), 1.48–1.69 (m, 3 H), 1.69–1.80 (m, 1 H), 3.57–3.65 (m, 2 H), 3.66–3.76 (m, 1 H), 3.75 (dd, *J* = 8.3, 6.0 Hz, 1 H), 3.98 (dd, *J* = 8.3, 6.8 Hz, 1 H), 4.04–4.10 (m, 1 H), 4.73 (br s, 1 H), 5.04 (d, *J* = 16.0 Hz, 1 H), 5.07 (d, *J* = 16.0 Hz, 1 H), 7.25–7.36 (m, 5 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz, 60 °C): δ = –5.3, 18.3, 25.2, 26.0, 26.4, 27.3, 28.9, 53.5, 62.7, 66.8, 78.3, 109.5, 128.1, 128.1, 128.5, 136.8, 156.3 ppm. IR (nujol): $\tilde{\nu}$ = 1655 cm^{-1}. $C_{23}H_{39}NO_5Si$ (437.6): calcd. C 63.12, H 8.98, N 3.20; found: C 63.06, H 9.07, N 3.12.

Compound 5: Trifluoroacetic acid (0.1 mL) was added to a solution of compound **4** (300 mg, 0.68 mmol) in methanol/water (10 mL, 3:1) and the reaction mixture was stirred at room temperature for 15 h. On completion of the reaction the methanol was removed under reduced pressure and the resulting solution was diluted with water (15 mL) and washed with dichloromethane. Lyophilisation of the aqueous layer gave compound **5** (184 mg, 95%) as a white solid. M.p. 136–138 °C. ^{1}H NMR ([D$_6$]DMSO, 400 MHz, 25 °C): δ = 1.23–1.38 (m, 2 H), 1.39–1.56 (m, 1 H), 1.57–1.66 (m, 1 H), 3.22–3.46 (m, 6 H), 4.30 (dd, J = 6.1, 4.8 Hz, 1 H), 4.39 (dd, J = 6.0, 4.8 Hz, 1 H), 4.57 (d, J = 4.5 Hz, 1 H), 4.98 (d, J = 13.0 Hz, 1 H), 5.03 (d, J = 13.0 Hz, 1 H), 6.90 (d, J = 8.7 Hz, 1 H), 7.27–7.39 (m, 5 H) ppm. ^{13}C NMR ([D$_6$]DMSO, 100 MHz, 25 °C): δ = 26.0, 29.2, 52.6, 60.8, 63.3, 65.0, 73.7, 127.6, 127.7, 128.3, 137.4, 156.1 ppm. IR (neat): $\tilde{\nu}$ = 3360, 1680 cm^{-1}. $C_{14}H_{21}NO_5$ (283.3): calcd. C 59.35, H 7.47, N 4.94; found: C 59.19, H 7.36, N 5.03.

Compound 6: Small portions of $NaIO_4$ (302 mg, 1.41 mmol) were added to a stirred solution of compound **5** (100 mg, 0.35 mmol) in methanol (10 mL) and the mixture was stirred for 3 h at room temperature. On completion of the reaction the mixture was filtered and concentrated under reduced pressure. The resulting residue was dissolved in diethyl ether (15 mL), filtered and concentrated under reduced pressure. Jones' reagent (10 mL) was added at 0 °C to a solution of the residue in acetone (10 mL) and the reaction mixture was stirred at 0 °C for 4 h. The solution was concentrated under reduced pressure and the residue was dissolved in dichloromethane, diluted with water and extracted with dichloromethane. The combined organic extracts were dried with anhydrous $MgSO_4$, filtered and concentrated in vacuo to afford a crude product, which was dissolved in dichloromethane and hydrogenated at atmospheric pressure by stirring at room temperature for 24 h in the presence of Pd/C (10%, 10 mg). After completion of the reaction the catalyst was removed by filtration and the filtrate was concentrated to dryness to afford (*S*)-glutamic acid (41 mg, 80%) as a white solid. M.p. 204.5 °C (dec) [ref.[22] m.p. 205 °C. (dec)]. $[\alpha]_D^{20}$ = +31.0 (c = 2.0 in 5 N HCl) [ref.[22] $[\alpha]_D^{20}$ = +31.5 (c = 2.0 in 5 N HCl)]. ^{1}H NMR (D$_2$O, 400 MHz, 25 °C): δ = 1.97–2.11 (m, 2 H), 2.31–2.50 (m, 2 H), 3.70 (t, J = 6.4 Hz, 1 H) ppm. ^{13}C NMR (D$_2$O, 100 MHz, 25 °C): 28.0, 32.5, 56.3, 176.3, 179.6 ppm. IR (nujol): $\tilde{\nu}$ = 3400, 1675 cm^{-1}.

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