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Diastereoselective syntheses of 2-amino propargyl alcohols. Chiral building blocks for enantiopure amino γ-lactones and 5-hydroxy-piperidinone derivatives

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Abstract—α-Dibenzylamino aldehydes, derived from the corresponding natural α-amino acids, react with metal acetylides to yield *anti*-amino propargyl alcohols in good yield and diastereomeric excess. *syn* Amino alcohols are prepared from the *anti* diastereoisomers and all of them are elaborated in few steps to enantiopure amino lactones and hydroxy-piperidin-2-ones.

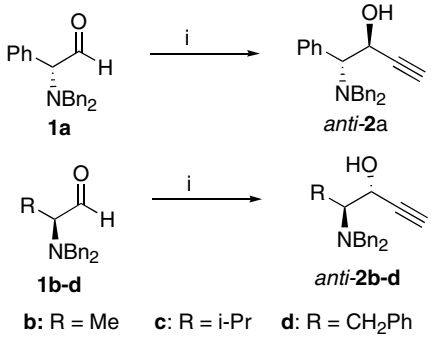
The asymmetric synthesis of propargyl 1,2-amino alcohols has attracted a great interest[1] because they have been used as building blocks for different types of enantiopure organic compounds.[2] Some interesting syntheses of these substrates have been described, including diastereoselective reductions,[3] condensations,[4] and additions to chiral imines,[5] but the most direct method consists of the reaction of chiral α-amino aldehydes with organometallics.[1]

The major problem for that reaction refers to the control of the stereoselection and generally, mixtures of *anti* and *syn* diastereoisomers are obtained, although the nature of either the organometallic or the substituents at the nitrogen atom allows for the formation of one diastereoisomer in moderate to good diastereomeric excess (de).[6] In this way, lithium acetylides react with dibenzylamino aldehydes leading to *anti* diastereoisomers in excellent de,[1,7] but with diethylzinc yielding the *syn* adduct as the major isomer.[8]

In this letter, we present a direct, highly diastereoselective synthesis of both diastereoisomers of 4-substituted 4-dibenzylamino but-1-yn-3-ols from α-dibenzylamino aldehydes[8,9] and their transformation into enantiopure γ-lactones and 5-hydroxy-piperidinone derivatives.

The reaction of D-dibenzylamino phenylglycinal **1a** with ethynylmagnesium bromide in a mixture of THF and diethyl ether at 0 °C yielded the *anti*-1,2-amino propargyl alcohol (*anti*-**2a**) in 78% yield and moderate diastereoselectivity (dr = 4:1). In the same way, the reaction of L-dibenzylamino aldehydes **1b–d** yielded the corresponding *anti* amino alcohols **2b–d** in good yield and de (Scheme 1 and Table 1).

The preparation of the minor diastereoisomer formed in the reaction from L-valinal (*syn*-**2c**) was envisaged from *anti*-**2c** by oxidation to the corresponding ketone and hydride reduction as previously described[8] for different amino alcohols, but attempts to oxidize *anti*-**2c** failed giving complex mixtures of reaction under all the



Scheme 1. Reagents and conditions: (i) 1. HCCMgBr, THF/Et_2O, 0 °C; 2. Aqueous NH_4Cl.

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Table 1. Stereoselective ethynylation of α-dibenzylamino aldehydes **1a–d**

Entry	1	2	Yield (%)[a]	*anti*:*syn*[b]
1	**1a**	**2a**	78	82:18
2	**1b**	**2b**	73	91:9
3	**1c**	**2c**	71	90:10
4	**1d**	**2d**	47	92:8

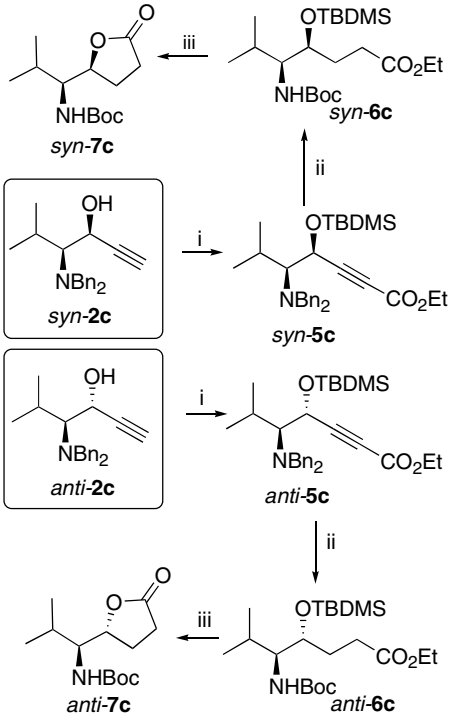
[a] Numbers correspond to combined yield of pure and isolated diastereoisomers.
[b] The diastereomeric ratio was determined by integration of the signals of ^{1}H NMR spectra of the reaction mixture.

assayed experimental conditions. This problem was circumvented by the oxidation of *anti*-**3c** under Swern's conditions to α-dibenzylamino ketone **4c** in 64% yield. Propargyl amino alcohol *anti*-**3c** was prepared, as a single diastereoisomer in 54% yield, by reaction of **1c** with lithium trimethylsilylacetylide in THF at −78 °C. The reduction of **4c** with lithium aluminum hydride in Et_2O at −78 °C, followed by desilylation with TBAF in THF at rt, gave *syn*-**2c** in 64% yield and excellent de (Scheme 2). After purification by flash chromatography, the stereochemistry of *syn*- and *anti*-**2** was established on the basis of their ^{1}H NMR spectral data.[10]

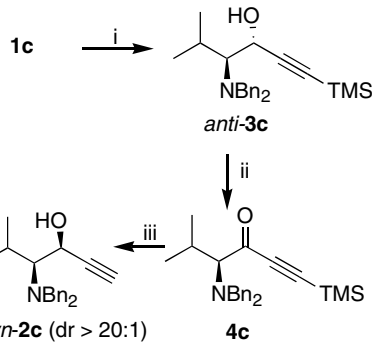
The interest of these 1,2-amino propargylalcohols as chiral synthons was firstly tested for *anti*- and *syn*-**2c**, by their conversion into dibenzylamino γ-lactones *syn*-**7c** and *anti*-**7c** (Scheme 3). The former has been previously prepared, because it is an important part of a compound (AG7088), which acts as rhinovirus protease inhibitor.[11] The unprotected aminoalcohols derived from *syn*- and *anti*-**5c** have also been used in the direct stereoselective syntheses of dipeptide isosteres.[12]

In our case, after protection of the hydroxyl group with TBDMSCl and imidazole, *syn*-**2c** was deprotonated with *n*-BuLi in THF at −78 °C and then reacted with ethyl chloroformate in THF at −40 °C to yield *syn*-**5c** in 78% yield. Hydrogenation of this compound over Perlman's catalyst in methanol and Boc anhydride led to *syn*-**6c**, which was transformed into the final amino lactone derivative *syn*-**7c** by deprotection with TBAF in THF at rt with subsequent lactonization. The same treatment on *anti*-**2c** gave *anti*-**7c** in 35% overall yield (Scheme 3).

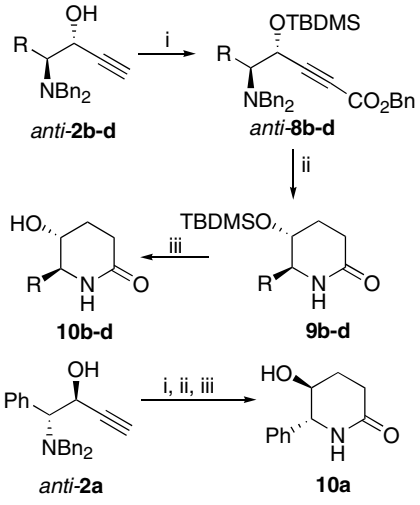
Finally, *anti*-**2a–d** were quickly transformed into enantiopure (5*R*,6*S*) or (5*S*,6*R*)-5-hydroxy-6-substituted piperidin-2-ones **10a–d** as shown in Scheme 4 and Table 2, depending on the configuration of the starting amino aldehyde derivatives. Protection of *anti*-**2a–d** as TBDMS



Scheme 3. Reagents and conditions: (i) 1. TBDMSCl, imidazole, DMF, rt. 2. *n*-BuLi (1.2 equiv), THF, −78 °C. 3. $ClCO_2Et$ (1.5 equiv), THF, −78 to −40 °C. 4. Aqueous NH_4Cl; (ii) H_2/Pd(OH)$_2$(C), Boc_2O, MeOH; (iii) TBAF, THF, rt.



Scheme 2. Reagents and conditions: (i) 1. TMSCCLi, THF/hexanes, −78 °C. 2. Aqueous NH_4Cl; (ii) Swern oxidation; (iii) 1. $LiAlH_4$, Et_2O, −78 °C. 2. TBAF, THF, rt.



Scheme 4. Reagents and conditions: (i) 1. TBDMSCl, imidazole, DMF, rt. 2. *n*-BuLi (1.2 equiv), THF, −78 °C. 3. $ClCO_2Bn$ (1.5 equiv), THF, −78 to −40 °C. 4. Aqueous NH_4Cl; (ii) 1. H_2/Pd(OH)$_2$(C), MeOH. 2. DCC, 4-PPY, CH_2Cl_2; (iii) TBAF, THF, rt.

Table 2. Yields (%) for the transformations summarized in Scheme 4

Substrate	i (%)	ii (%)	iii (%)
anti-**2a**	56	70	90
anti-**2b**	57	79	76
anti-**2c**	60	68	74
anti-**2d**	58	72	81

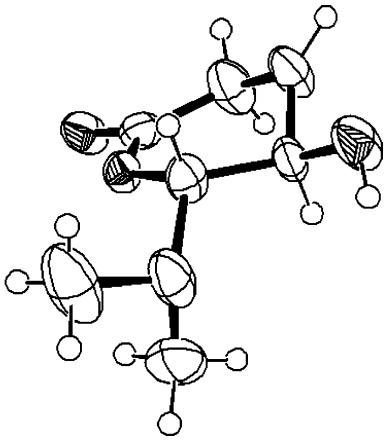


Figure 1. ORTEP representation of X-ray structure for compound **10c**.

ether, followed by deprotonation with *n*-BuLi and reaction with benzyl chloroformate, yielded *anti*-**8a–d** in good yields. Hydrogenation over Perlman's catalyst of *anti*-**8a–d** gave the TBDMS derivative of the corresponding saturated δ-amino γ-hydroxy acid, which was cyclized,[13] without isolation, to 2-piperidinones **9a–d** by treatment with dicyclohexylcarbodiimide and 4-pyrrolidinopyridine in methylene chloride at rt. Deprotection of **9a–d** with TBAF in THF yielded **10a–d** that was isolated by flash chromatography and crystallization.[14] The stereochemistry for compound **10c** was established by X-ray diffraction analysis[15] (Fig. 1), and extended for all the piperidinones.

Compounds **10a–d** and related piperidin-2-ones have been used as starting materials in the asymmetric synthesis of different alkaloids[16] and our method complements other diastereoselective syntheses previously described.[17]

In summary, the described methodology allows for the preparation of diastereoisomeric enantioenriched amino propargyl alcohols and their transformation into useful chiral building blocks for the synthesis of complex molecules. Different enantiopure 6-substituted 5-hydroxy-piperidin-2-ones can be easily prepared from commercially available α-amino acids.

Acknowledgments

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14. Selected data for compounds **10a–d**. (5*S*,6*R*)-5-Hydroxy-6-phenylpiperidin-2-one (**10a**). Colorless solid, mp 182–183 °C (from EtOAc). $[\alpha]_D^{23}$ +31.6 (*c* 0.75, MeOH). IR (KBr): 3293, 1633, 1359, 1085, 752, 703 cm^{-1}. ^1H NMR (CD_3OD): 1.84 (m, 2H, C*HH*CHOH); 2.41 (m, 1H, C*H*HCO); 2.57 (m, 1H, CH*H*CO); 3.90 (m, 1H, C*H*OH); 4.46 (d, 1H, $J = 4.7$ Hz, C*H*N); 4.91 (br s, 2H, O*H* and N*H*); 7.25–7.45 (m, 5H, Har). ^{13}C NMR (CD_3OD): 25.9 (*C*H_2CO); 28.4 (*C*H_2CHOH); 64.6 (*C*HN); 70.5 (*C*HOH); 128.1, 129.0, 129.8 (*C*Har); 142.1 (*C*ar); 174.9 (*C*O). $C_{11}H_{13}NO_2$ (191.2): calcd C 69.09, H 6.85, N 7.32; found C 68.84, H 6.71, N 7.38. (5*R*,6*S*)-5-Hydroxy-6-methylpiperidin-2-one (**10b**). Colorless solid, mp 141–142 °C (from EtOAc/hexane). $[\alpha]_D^{23}$ −20.0 (*c* 0.5, MeOH). IR (KBr): 3360, 3172, 1647, 1346, 1073, 944, 827 cm^{-1}. ^1H NMR (CD_3OD): 1.22 (d, 3H, $J = 6.5$ Hz, CH_3); 1.80 (m, 1H, C*H*HCHOH); 2.00 (m, 1H, CH*H*CHOH); 2.30 (m, 1H, C*H*HCO); 2.45 (m, 1H, CH*H*CO); 3.31 (dq, 1H, $J = 6.5$ Hz, $J = 5.9$ Hz, C*H*N); 3.56 (ddd, 1H, $J = 8.8$ Hz, $J = 5.9$ Hz, $J = 3.2$ Hz, C*H*OH); 4.89 (br s, 2H, O*H* and N*H*). ^{13}C NMR (CD_3OD): 20.4 (*C*H_3); 27.7 (*C*H_2CO); 29.0 (*C*H_2CHOH); 55.7 (*C*HN); 70.1 (*C*HOH); 174.2 (*C*O). $C_6H_{11}NO_2$ (129.2): calcd C 55.80, H 8.58, N 10.84; found C 55.66, H 8.48, N 10.90. (5*R*,6*S*)-5-Hydroxy-6-isopropylpiperidin-2-one (**10c**). Colorless solid, mp 84–85 °C (from EtOAc/hexane). $[\alpha]_D^{23}$ −7.7 (*c* 0.4, $CHCl_3$). IR (KBr): 3370, 1634, 1260, 1084, 830, 705 cm^{-1}. ^1H NMR ($CDCl_3$): 0.92 (d, 3H, $J = 6.7$ Hz, CH_3); 0.96 (d, 3H, $J = 7.0$ Hz, CH_3); 1.90 (m, 3H, C*HH*CHOH and C*H*(CH_3)$_2$); 2.29 (ddd, 1H, $J = 18.0$ Hz, $J = 8.1$ Hz, $J = 6.5$ Hz, C*H*HCO); 2.48 (dt, 1H, $J = 18.0$ Hz, $J = 6.4$ Hz, CH*H*CO); 3.07 (m, 1H, C*H*N); 3.59 (br s, 1H, OH); 3.85 (m, 1H, C*H*OH); 6.24 (br s, 1H, N*H*). ^{13}C NMR ($CDCl_3$): 16.7 (*C*H_3); 19.6 (*C*H_3); 27.3 (*C*H_2CO); 27.8 (*C*H_2CHOH); 29.8

((CH$_3$)$_2$*C*H); 64.1 (*C*HN); 65.1 (*C*HOH); 172.6 (*C*O). $C_8H_{15}NO_2$ (157.2): calcd C 61.12, H9.62, N 8.91; found C 60.88, H 9.49, N 9.00.(5*R*,6*S*)-6-Benzyl-5-hydroxypiperidin-2-one (**10d**). Colorless solid, mp 101–102 °C (from EtOAc). $[\alpha]_D^{23}$ −37.9 (*c* 1.2, MeOH). IR (film): 3305, 3208, 1643, 1360, 1069, 763, 724, 700 cm^{-1}. ^{1}H NMR (CD$_3$OD): 1.82 (m, 1H, C*H*HCHOH); 1.98 (m, 1H, CH*H*CHOH); 2.21 (dt, 1H, $J = 18.0$ Hz, $J = 6.3$ Hz, C*H*HCO); 2.44 (m, 1H, CH*H*CO); 2.81 (dd, 1H, $J =$ 13.8 Hz, $J = 6.7$ Hz, C*H*HPh); 2.90 (dd, 1H, $J = 13.8$ Hz, $J = 6.3$ Hz, CH*H*Ph); 3.54 (m, 1H, C*H*N); 3.71 (m, 1H, C*H*OH); 4.90 (br s, 2H, OH and N*H*); 7.20–7.35 (m, 5H, *H*ar). ^{13}C NMR (CD$_3$OD): 26.7 (*C*H$_2$CO); 28.3 (*C*H$_2$CHOH); 41.3 (*C*H$_2$Ph); 61.2 (*C*HN); 66.5 (*C*HOH); 128.0, 129.8, 130.7 (*C*Har); 138.6 (*C*ar); 174.5 (*C*O). $C_{12}H_{15}NO_2$ (205.2): calcd C 70.22, H 7.37, N 6.82; found C 69.90, H 7.24, N 6.91.

15. Crystallographic data can be obtained from the Cambridge Crystallographic Data Center, 12, union Road, Cambridge CB2 1EZ, UK, E-mail: deposit@ccdc.cam.ac.uk.
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