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A versatile approach to pyrrolidine azasugars and homoazasugars based on a highly diastereoselective reductive benzyloxymethylation of protected tartarimide

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Abstract—A highly diastereoselective synthesis of enantio-enriched all *trans*-3,4-dibenzyloxyl-5-benzyloxymethyl-2-pyrrolidinone **13a** was developed based on SmI_2-mediated benzyloxymethylation of *O*,*O*′-dibenzyltartarimide. The versatility of **13a** and its antipode as the key building blocks for the asymmetric synthesis of pyrrolidine azasugars and homoazasugars has been demonstrated by elaborating them into naturally occurring DAB 1 (**1**), LAB 1 (**2**), *N*-hydroxyethyl-DAB 1 (**4**), 6-deoxy-DMDP **7**, and 5-*epi*-radicamine B **36** as well as the reductive ring-opening product **35**.

1. Introduction

Many pyranoses and furanoses with the ring oxygen replaced by an amino group, known as imino sugars or azasugars,[1] are sugar mimics, which have been found to inhibit specific enzymes such as glycosidases.[1] Because glycosidases are involved in several important biological processes, these polyhydroxylated alkaloids have stimulated interest in the development of specific glycosidase inhibitors for studying and treating metabolic disorders such as diabetes, or as antiviral, antibacterial, and anticancer agents or as immunomodulators, and are providing biochemists with molecular tools for probing several important processes, such as the metastasis of some cancers, the immune response, and virus replication. In particular, α-glucosidase inhibitors have shown potential as therapeutic agents for type II diabetes[2a] and HIV-1 infection.[2b]

1,4-Dideoxy-1,4-imino-D-arabinitol (**1**, known as DAB 1) was isolated from two types of leguminose plants *Arachniodes standishii*[3a,4a] and *Angylocalyx boutiqueanus*.[3b] The antipode of DAB 1 is a synthetic product.[4] LAB 1 was shown to be a potent inhibitor of the α-L-arabinofuranosidase III of *Monilinia fructigena*,[5a] and a much more powerful inhibitor of sucrase and some mouse gut α-glucosidases than DAB 1.[5b] It is also a promising candidate for treatment of type II diabetes,[5c] and was one of the most powerful anti-HIV agents among 47 aminosugar derivatives screened.[5c–e] Structurally related nectrisine (FR 900483) (**3**) is a fungal metabolite isolated from *Nectria lucida*.[6] DAB 1 and nectrisine exhibit extremely potent yeast α-glucosidase inhibitory activities [$IC_{50}=1.8\times10^{-7}$ M[4b] and 4.8×10^{-8} M,[7] respectively]. The *N*-hydroxyethylated derivative of DAB 1, namely, *N*-hydroxyethyl-DAB 1[8] (**4**) was isolated from the seeds of African legume *Angylocalyx pynaertii*, while the oxidation product of DAB 1, L-2,3-*trans*-3,4-*trans*-dihydroxyproline (DHP) (**5**), was isolated from the acid hydrolyzates of the toxic mushroom *Amanita virosa*.[9]

Moreover, many C-5 carbon-substituted derivatives of DAB 1, known as homoazasugars or aza-C-glycosides are either natural products or sugar mimics showing enhanced bioactivities and at the same time exhibiting higher stability toward chemical and enzyme degradation.[10] For example, 2,5-dihydroxymethyl-3,4-dihydroxypyrrolidine (DMDP) **6** occurs in many disparate species of plants,[11a] and was also isolated from *Streptomyces*;[11b] the 6-deoxy analog of DMDP (6-deoxy-DMDP)[12,8] **7**, a unique molecule in inhibiting β-mannosidase,[11] was isolated from the seeds of African legume *A. pynaertii*; radicamine B (**8**) and broussonetine W (**9**) are two structurally related compounds recently isolated from *Lobelia chinensis* Lour (Campanulaceae), which also show α-glucosidase inhibitory activity.[13]

Consequently, the synthesis of polyhydroxylated pyrrolidine alkaloids/azasugars has attracted much attention, and a number of methods have been developed.[4,14–17] In view of the

Keywords: Azasugars; DAB 1; LAB 1; 6-Deoxy-DMDP; *epi*-Radicamine B; Alkaloids; Pyrrolidine; Hydroxymethylation; Diastereoselective synthesis.
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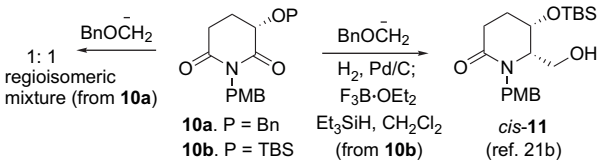
presence of α-hydroxymethyl-dihydroxypyrrolidine[1a] **1** as the common structural feature in many azasugars, an attractive approach to these compounds would be that allowing installation of the α-hydroxymethyl group in a straightforward manner. Although optically active tartaric acid has been used to synthesize this class of compounds,[15i,s,16d] such as DAB 1 (**1**), LAB 1[15i,s] (**2**), nectrisine (**3**),[16d] and broussonetine C,[18] methods for the introduction of the hydroxymethyl group into the α-position of a pyrrolidine or a piperidine ring have generally been accomplished by indirect and multistep procedures.[15s,18,19] In some of these approaches, low diastereoselectivities have been observed.[15i,16d] As a part of our ongoing project aimed at the development of malimide/3-hydroxyglutarimide-based synthetic methodologies,[20] and in continuation of our studies on the asymmetric synthesis of azasugars and related compounds,[21] we report herein a short and highly diastereoselective approach for the enantioselective synthesis of DAB 1 (**1**), LAB 1 (**2**), *N*-hydroxyethyl-DAB 1 (**4**), 6-deoxy-DMDP **7**, and 5-*epi*-radicamine B **36** as well as the reduced-ring-opening product **35** based on the direct introduction of a benzyloxymethyl group via the reductive benzyloxymethylation of tartarimide **14** or *ent*-**14**.

2. Results and discussion

In our recent efforts to develop a flexible method for the synthesis of 2-benzyloxymethyl-2-piperidinone by the stepwise reductive 2-benzyloxymethylation of the protected 3-hydroxyglutarimides (Scheme 1),[21b] several abnormal phenomena have been observed. For example, the 2-benzyloxymethylation of the *O*-benzyl protected 3-hydroxyglutarimide **10a** led, unexpectedly, to two regioisomeric carbinols in a 1:1 ratio; while although the 2-benzyloxymethylation of the *O*-*tert*-butyldimethylsilyl protected 3-hydroxyglutarimide **10b** proceeded with an 81:19 regioselectivity (C-2/C-6), the subsequent reductive dehydroxylation could only be achieved after O-debenzylation, and led, unexpectedly,[21b] to *cis*-diastereomer **11** as the major product.



Scheme 1.

Because the above-mentioned regioselection is no longer a problem for tartarimide,[22] a normal stepwise *trans*-diastereoselective reductive benzyloxymethylation could be expected. Thus, a general approach for the asymmetric synthesis of azasugars such as those shown in Figure 1, and homoazasugars[10] such as phosphonoazasugar **16**[16e] is depicted retrosynthetically in Scheme 2, in which (3*S*,4*R*,5*R*)-5-benzyloxymethyl-3,4-dibenzyloxyl-2-pyrrolidinones **13** have been selected as the common intermediates. To test the feasibility of our approach, we first focused on the synthesis and applications of 2-pyrrolidinone **13a**.

The requisite D-*O*,*O*′-dibenzyltartarimide **14** was prepared from D-tartaric acid by the modification of the known

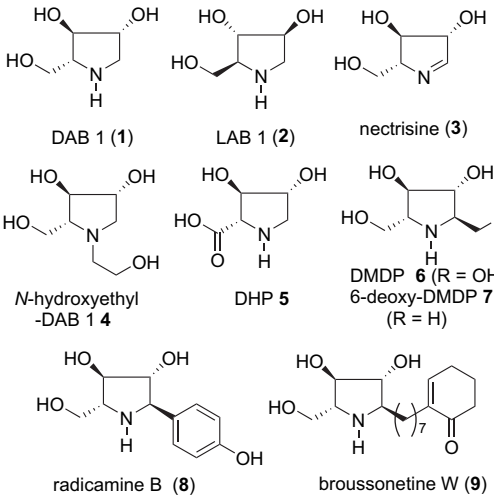
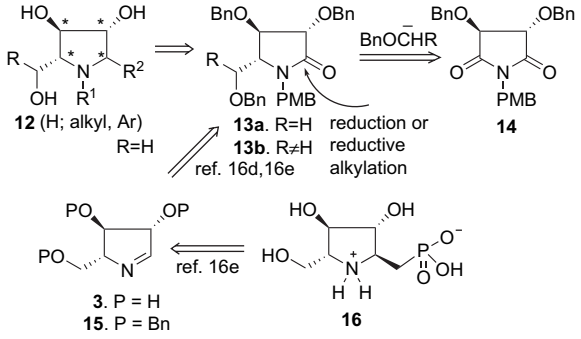
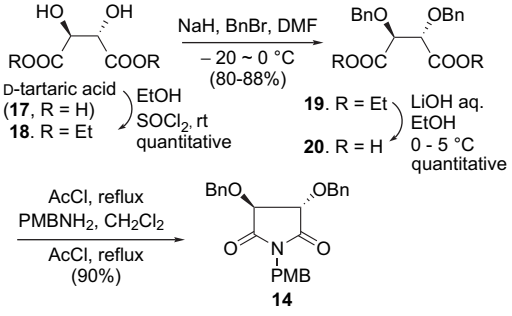


Figure 1. Some naturally occurring five-membered azasugars and related polyhydroxylated pyrrolidine alkaloids.



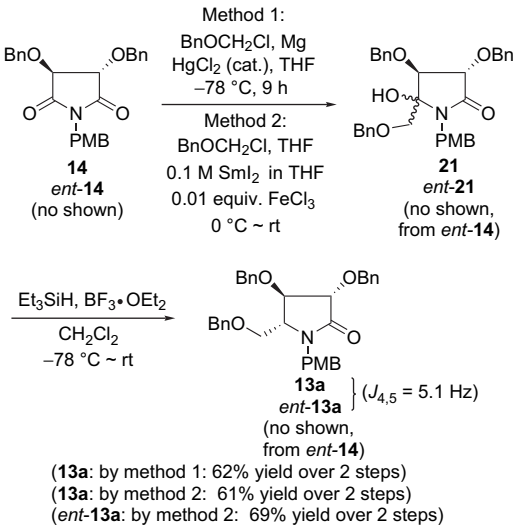
Scheme 2.

method (Scheme 3),[23] which allows using cheaper reagents and affords higher yields.



Scheme 3.

For the introduction of the benzyloxymethyl group,[24] we first attempted $HgCl_2$-mediated Grignard reaction[24e,h] under Barbier-type conditions (Scheme 4). Thus a THF solution of benzyloxymethyl chloride was added to a mixture of tartarimide **14**, Mg, and a catalytic amount of $HgCl_2$ at rt to give the desired *N*,*O*-acetal **21** as a diastereomeric mixture. The subsequent $BF_3\cdot OEt_2$-mediated reductive dehydroxylation of the diastereomeric mixture under standard conditions[20] led to the desired *trans*-benzyloxymethylated product **13a** as the only isolable diastereomer in 62% overall yield from **14**.



Scheme 4.

In addition to this approach, we also investigated a variant featuring the samarium diiodide-mediated benzyloxymethylation. Treatment of a mixture of tartarimide **14** and benzyloxymethyl chloride with a freshly prepared 0.1 M THF solution of SmI_2[25] containing 1% mol equiv of anhydrous $FeCl_3$[26] at rt for 1 h led to the desired *N*,*O*-acetal **21** in 84% yield. The subsequent $BF_3 \cdot OEt_2$-mediated reductive dehydroxylation[20,21b,22d–i,27] led to *trans*-diastereomer **13a** in 61% overall yield from **14**.

The stereochemistry of compound **13a** ($J_{4,5}$=5.1 Hz) deserves comment. While the vicinal coupling constants ($J_{4,5}$>6.0 Hz for *cis*-diastereomers **B**, **D** and $J_{4,5}$=0–4.4 Hz for *trans*-diastereomers **A**, **C**) (Fig. 2) are commonly used to determine the 4,5-relative stereochemistries of 4,5-disubstituted γ-lactams,[22d,28] substituted lactam **13a** seems to be a singular example which does not obey this empirical rule because it shows a larger vicinal coupling constant ($J_{4,5}$=5.1 Hz) and is in a marginal situation. The 4,5-*trans* stereochemistry of lactam **13a** was confirmed by converting **13a** to the known compounds **22**, **24** and to the target molecules described in this paper.

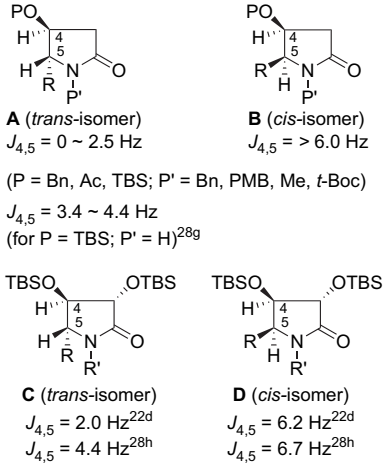
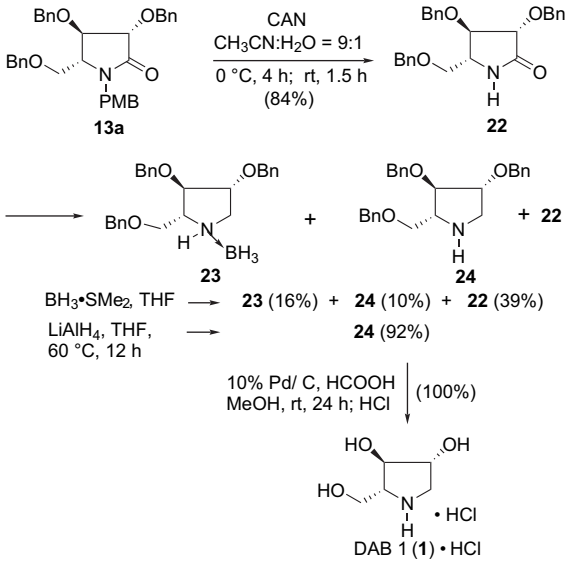


Figure 2. Vicinal coupling constants ($J_{4,5}$) of 4,5-disubstituted γ-lactams.

The different behaviors (reactivity and diastereoselectivity) of the *N*,*O*-acetal derived from TBS protected 3-hydroxyglutarimide **10b** (Scheme 1) and that derived from *O*,*O*′-dibenzyl protected tartarimide **14** (Scheme 4) toward the reductive dehydroxylation (**21**→**13a**) demonstrates once again the remarkable protecting group effect.[29]

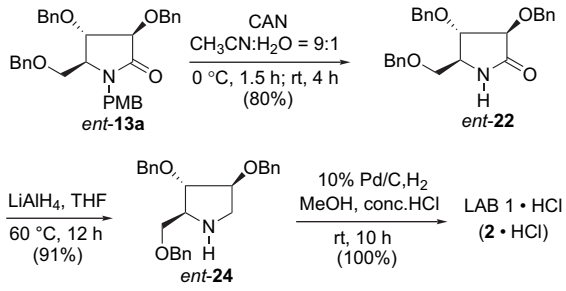
With the conditions for the desired reductive benzyloxymethylation of tartarimide **14** secured, we then investigated the synthetic applications of **13a**. Thus the PMB group in **13a** was cleaved under oxidative conditions[30] (CAN, MeCN–H_2O=9:1 v/v, 0 °C, 1.5 h, then rt, 4 h) to give the known lactam **22**[15g] in 84% yield (Scheme 5). Attempt to reduce amide **22** by borane complex ($BH_3 \cdot SMe_2$, THF, rt, 48 h) was far from satisfactory. After reaction for two days, the desired product **24** and its borane adduct **23** were obtained in only 10% and 16% yields, respectively, alongside with 39% of the recovered starting material **22**. However, when lithium aluminum hydride was used instead, the desired product **24**[15g] was obtained in 92% yield. Under the catalytic transfer hydrogenolytic conditions, triple debenzylation was achieved quantitatively to afford DAB 1 (**1**), which was characterized as its hydrochloride salt {$[\alpha]_D^{20}$ +36.1 (*c* 0.2, H_2O); lit.[15a] $[\alpha]_D^{20}$ +37.9 (*c* 0.53, H_2O); lit.[15g] $[\alpha]_D^{20}$ +32.5 (*c* 0.5, H_2O)}. Except for the minor differences in the optical rotation values, compounds **22**, **24**, and DAB 1 (**1**) hydrochloride salt show identical spectral data as those reported in the literature, confirming thus the 4,5-*trans* stereochemistry of lactam **13a**.



Scheme 5.

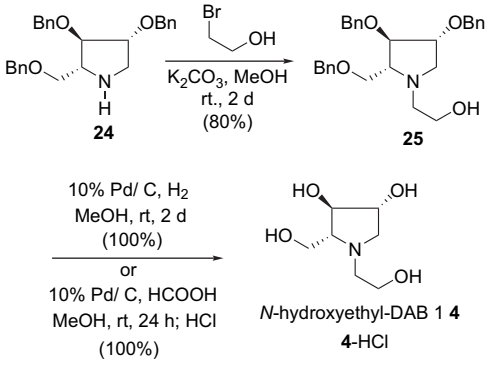
Starting from L-tartaric acid, and following the procedures described for the synthesis of DAB 1 (Schemes 3–5), the synthesis of LAB 1 (**2**) hydrochloride salt {$[\alpha]_D^{20}$ −41.1 (*c* 0.2, MeOH); lit.[15a] $[\alpha]_D^{20}$ −34.6 (*c* 0.37, H_2O); lit.[15g] $[\alpha]_D^{20}$ −36.5 (*c* 0.37, H_2O)} was achieved in high overall yield (Scheme 6). The ^1H and ^{13}C spectral data were identical to those of hydrochloride salt of DAB 1 (**1**).

For the synthesis of azasugar **4**, simple treatment of **24** with 2-bromoethanol in DMF and in the presence of K_2CO_3 led to



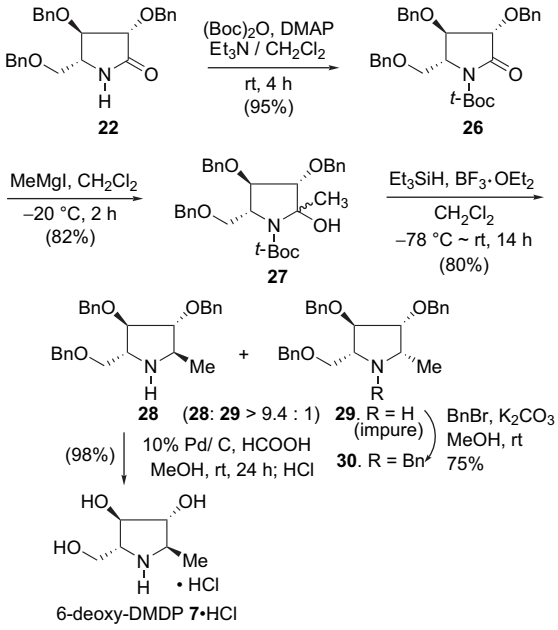
Scheme 6.

the desired product **25** in 54% yield alongside with 22% of the recovered starting material (Scheme 7). The yield was improved to 80% by using MeOH as the solvent. Compound **25** was subjected to catalytic transfer hydrogenolytic conditions to give *N*-hydroxyethyl-DAB 1 (**4**) in quantitative yield, whose spectroscopic data were identical with those reported for the natural product.[8] However, the sense of optical rotation was opposite to that reported {$[\alpha]_D^{20}$ −46.7 (*c* 0.3, H_2O); lit.[8] $[\alpha]_D^{20}$ +54.7 (*c* 0.38, H_2O); $[\alpha]_D^{20}$ −37.1 (*c* 0.2, H_2O) for its hydrochloride salt}. Because *N*-hydroxyethyl-DAB 1 (**4**) has also been obtained from DAB 1 (**1**),[8] the reason for these contrasting results is still unclear.



Scheme 7.

Next, we turned our attention to the synthesis of 2,5-disubstituted pyrrolidine alkaloid **7**. To this end, lactam **22** was first converted to Boc-activated derivative **26** (Scheme 8). For the subsequent introduction of the methyl group, a second stepwise reductive alkylation[31] (methylation) was investigated. Thus, treatment of methyl magnesium iodide with imide **26** led smoothly to *N*,*O*-acetal **27** as a diastereomeric mixture in 82% yield. This mixture, without further separation, was subjected to boron trifluoride etherate mediated triethylsilane reduction,[27] which afforded, in one-pot, the reductive dehydroxylation/*N*-deprotection products **28** and **29** (characterized as its *N*-benzyl derivative **30**) in 9.4:1 ratio with a combined yield of 80%. It was interesting to observe that by allowing the reaction to warm up and reacting at rt, deprotection of Boc could be achieved in one-pot. The stereochemistries of **28** and **29** were deduced from compounds **7** and **30**. The stereoconvergent formation of **29** from the diastereomeric mixture of *N*,*O*-acetal **27** implicates that the reductive dehydroxygenation proceeds through the intermediacy of the *N*-acyliminium intermediate **E** (Fig. 3).[32]



Scheme 8.

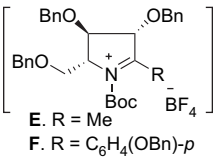
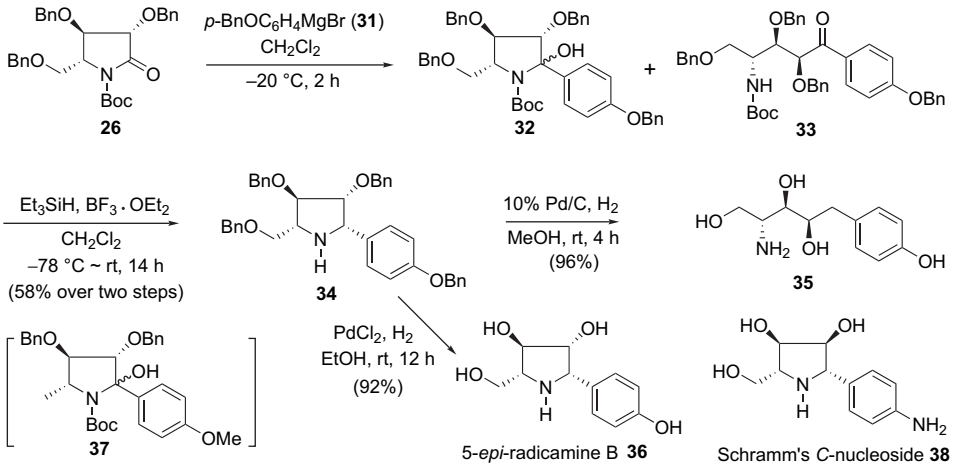


Figure 3. Plausible *N*-acyliminium intermediates **E** and **F** generated from **27** and **32/33**, respectively.

The cleavage of the three *O*-benzyl groups in **28** under transfer hydrogenolytic conditions furnished quantitatively 6-deoxy-DMDP **7**, which exhibits identical spectral data as those reported in the literature {$[\alpha]_D^{20}$ +41.2 (*c* 0.1, H_2O) for **7**·HCl; lit.[17d] $[\alpha]_D^{20}$ +45.0 (*c* 1.4, MeOH)}.

Finally, we tackled the synthesis of radicamine B.[33] Addition of Grignard reagent **31**[13c] with imide **26** (CH_2Cl_2, −20 °C) yielded **32** as a diastereomeric mixture alongside with the tautomer **33** (Scheme 9). In the light of the results obtained recently from these laboratories,[34] this isomeric mixture was used in the subsequent step without further separation. Thus the mixture **32/33** was treated with Et_3SiH–$BF_3\cdot OEt_2$ to give, via the *N*-acyliminium intermediate **F** (Fig. 3), the desired reductive dehydroxylation/*N*-deprotection product **34** in high diastereoselectivity (only one diastereomer was obtained) and in 58% overall yield from **26**. This result is surprising, since the attempt to perform the reductive dehydroxylation of similar carbinol **37** was reported to give pyrrole type product in high yield.[22g] Subjection of **34** to hydrogenolytic conditions (H_2, 1 atm, 10% Pd/C, MeOH, rt) for 4 h led directly to exhaustive debenzylation product **35** in 96% yield. Pyrrolidine **36** was obtained in 92% yield by using $PdCl_2$ as a pro-catalyst (H_2, 1 atm, $PdCl_2$, EtOH, rt, 12 h).[13c,33] The synthesis of **36** also provides a method for constructing the skeleton of Schramm's C-nucleoside **38**[35] with three stereocenters correctly established. Moreover, the possibility for a selective oxidative cleavage of *p*-alkoxyphenyl group into a carboxyl group[36] makes pyrrolidine **34** and compound **35** plausible intermediates for the



Scheme 9.

asymmetric synthesis of other homoazasugars[36b] and 3,4-dihydroxyglutamic acid,[28h] respectively.

The stereochemistries of **28** and **34** were determined, first by ^{1}H–^{1}H COSY experiments to confirm the proton assignment, and then by NOESY experiments. As shown in Figure 4, these experiments not only allow determining the C2/C5-*trans* relationship for **28** and the C2/C5-*cis* relationship for **34**, but also confirming the C2/C3-*trans* stereochemistries for both compounds.

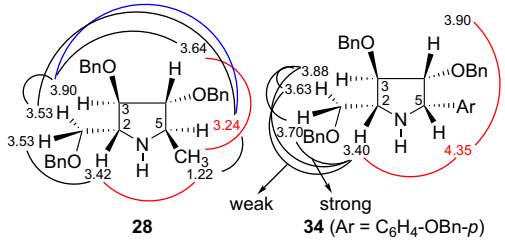


Figure 4. Observed NOE enhancements of compounds **28** and **34** in the NOESY experiments.

As regards the stereoselection of the reactions, Woerpel et al. have undertaken systematic studies to reveal the factors controlling the stereoselective reaction of five-membered ring oxocarbenium ions,[37] and concluded that the C-3 alkoxyl group principally governs the selectivity, leading to *cis*-selective addition. They also reclaimed[37] that the observations and analysis for the 3-alkoxyl oxocarbenium ion are relevant for the related nitrogen-containing compounds.[28a,38] In the present studies, the predominant formations of both 3,5-*cis*-**28** (via *N*-acyliminium intermediate **E**, Fig. 3) and 3,5-*trans*-**34** (via *N*-acyliminium intermediate **F**) might implicate that in our cases, the presence of the bulky *N*-protecting group (Boc) in both **E** and **F** makes them different from the five-membered ring oxocarbenium ions, and the factors controlling their stereoselective reduction require further mechanistic investigations.

3. Conclusion

In summary, we have demonstrated that all *trans*-5-benzyloxymethyl-3,4-dibenzyloxyl-2-pyrrolidinone **13a** can be synthesized by direct reductive benzyloxymethylation of *O*,*O*′-dibenzyltartarimide in highly diastereoselective manner, and **13a** is a versatile building block for the asymmetric synthesis of pyrrolidine type azasugars and homoazasugars. In addition, the possibility to perform a selective oxidation of a primary alcohol, in the presence of secondary alcohol,[39,40] to a carboxylic acid makes **24** a potential precursor for the synthesis of all *trans*-L-dihydroxyproline (DHP) (**5**).[15d,36b] Further studies on the synthesis of **13a** and use of **13a/13b** for the enantiospecific syntheses of other homoazasugars and other alkaloids are in progress in these laboratories.

4. Experimental

4.1. General

Melting points were determined on an X-4 digital micro melting point apparatus and were uncorrected. Infrared spectra were measured with a Nicolet Avatar 330 FT-IR spectrometer using film KBr pellet technique. ^{1}H NMR spectra were recorded in $CDCl_3$ on a Bruker AV400 or a Varian unity +500 spectrometer with tetramethylsilane as an internal standard. Chemical shifts are expressed in δ (ppm) units downfield from TMS. Mass spectra were recorded by Bruker Dalton Esquire 3000 plus LC–MS apparatus.[41] Optical rotations were measured with a Perkin–Elmer 341 automatic polarimeter. Flash column chromatography was carried out on silica gel (300–400 mesh). THF was distilled over sodium. Dichloromethane was distilled over P_2O_5. Petroleum ether (60–90 °C) is abbreviated as P.E.

4.1.1. (3*S*,4*S*)-1-(4-Methoxybenzyl)-3,4-dibenzyloxyl-2,5-pyrrolidinedione (14). To a solution of D-tartaric acid (10.00 g, 66.67 mmol) in EtOH (100 mL) was added dropwise $SOCl_2$ (10.7 mL, 146.7 mmol). The mixture was stirred at rt overnight. The solvent was evaporated in vacuum and CH_2Cl_2 (20 mL) was added to the mixture. The resulting mixture was washed with saturated aqueous $NaHCO_3$ and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuum. The

residue was purified by flash column chromatography on silica gel eluting with ethyl acetate–P.E. (1:1) to give the known diethyl tartarate **18**[23] (13.7 g, yield, 100%) as a colorless oil. $[\alpha]_D^{20}$ −25.0 (*c* 0.2, H_2O). IR (film): 3328, 2985, 2939, 1742, 1642, 1235, 1090 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.33 (t, *J*=7.2 Hz, 6H, 2×CH_3), 3.38 (d, *J*=6.9 Hz, 2H, 2×OH), 4.32 (q, *J*=7.2 Hz, 4H, 2×$MeCH_2$), 4.55 (d, *J*=6.9 Hz, 2H, 2×OCH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0 (2C), 62.4 (2C), 72.0 (2C), 171.5 (2C) ppm. Anal. Calcd for $C_8H_{14}O_6$: C, 46.60; H, 6.84. Found: C, 46.42; H, 7.28.

To a suspension of NaH (60% in mineral oil, 1.36 g, 34.07 mmol) in dry DMF (40 mL) was added dropwise a solution of **18** (3.51 g, 17.04 mmol) in DMF (10 mL) at −20 °C. The reaction was stirred for 30 min at the same temperature, then to the mixture was added BnBr (6.1 mL, 51.12 mmol) and the stirring was continued for 40 min. The mixture was stirred at 0 °C for 1 h. The reaction was quenched by cautionary addition of water (250 mL) and extracted with Et_2O (5×40 mL). The combined extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuum. The residue was purified by flash column chromatography on silica gel eluting with ethyl acetate–P.E. (1:6) to give **19**[23] (5.59 g, 85%) as a colorless oil. $[\alpha]_D^{20}$ −133.8 (*c* 0.8, $CHCl_3$). IR (film): 2982, 2904, 1755, 1731, 1454, 1269, 1106 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.18 (t, *J*=7.1 Hz, 6H, 2×CH_3), 4.07 (dq, *J*=10.7, 7.1 Hz, 2H, 2×$MeCH_2$), 4.20 (dq, *J*=10.7, 7.1 Hz, 2H, 2×$MeCH_2$), 4.39 (s, 2H, 2×BnOCH), 4.45 (d, *J*=12.0 Hz, 2H, 2×$PhCH_2O$), 4.87 (d, *J*=12.0 Hz, 2H, 2×$PhCH_2O$), 7.20–7.35 (m, 10H, Ar) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0 (2C), 61.2 (2C), 73.1 (2C), 78.3 (2C), 127.8, 128.2, 128.3, 136.9, 169.1 (2C) ppm; MS (ESI, *m*/*z*): 387 ($M+H^+$, 100).

A mixture of **19** (12.77 g, 33.08 mmol) and $LiOH·H_2O$ (5.56 g, 132.38 mol) in a mixture of EtOH–H_2O (v/v 3:1, 136 mL) was stirred at 0–5 °C overnight. After removal of ethanol under reduced pressure, the residue was acidified with concd HCl to reach pH 2 and the resultant mixture was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and filtered. The solvent was removed under reduced pressure to give **20**[23] (10.9 g, yield, 100%) as a colorless oil, which was used in the next step without further purification.

A mixture of **20** (10.9 g, 33.03 mmol) and acetyl chloride (20 mL) was refluxed for 4 h. After concentrating under reduced pressure, the residue was dissolved in CH_2Cl_2 (15 mL), to which was added a solution of *p*-methoxybenzylamine (5.2 mL, 39.64 mmol) in CH_2Cl_2 (15 mL) at 0 °C. The resultant mixture was refluxed for 5 h, and then concentrated in vacuum. The residue was dissolved in acetyl chloride (20 mL) and refluxed for 6 h. After concentration of the reaction mixture in vacuum, the residue was purified by column chromatography on silica gel eluting with ethyl acetate–P.E. (1:4) to give **14** (12.81 g, yield, 90%) as white crystals. Mp 137–138 °C (ethyl acetate–P.E.). $[\alpha]_D^{20}$ −148.8 (*c* 0.8, $CHCl_3$). IR (KBr pellet): 2936, 1715, 1514, 1343, 1249, 1106 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 3.77 (s, 3H, CH_3O), 4.36 (s, 2H, 2CH), 4.57 (d, *J*=14.3 Hz, 1H, $PhCH_2N$), 4.61 (d, *J*=14.3 Hz, 1H, $PhCH_2N$), 4.74 (d, *J*=11.6 Hz, 2H, $2PhCH_2O$), 4.97 (d, *J*=11.6 Hz, 2H, $2PhCH_2O$), 6.83 (d, *J*=8.3 Hz, 2H, Ar), 7.24–7.37 (m, 12H, Ar) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 41.7, 55.3, 73.5 (2C), 78.8 (2C), 114.1, 127.2, 128.3, 128.5, 130.5, 136.5, 159.4, 172.4 (2C) ppm; MS (ESI, *m*/*z*): 432 ($M+H^+$, 100). Anal. Calcd for [$C_{26}H_{25}NO_5$+2/3H_2O]: C, 70.41; H, 5.98; N, 3.16. Found: C, 70.33; H, 6.02; N, 3.34.

4.1.2. (3*S*,4*R*,5*R*)-5-Benzyloxymethyl-3,4-dibenzyloxyl-1-(4-methoxybenzyl)-pyrrolidin-2-one (13a).

4.1.2.1. Method 1: by Mg/$HgCl_2$-mediated benzyloxymethylation. To a two-necked, 100-mL round-bottomed bottle containing tartarimide **14** (770 mg, 1.79 mmol), magnesium turnings (357 mg, 14.88 mmol), mercury(II) chloride (55 mg), and anhydrous THF (12 mL) was added, at rt and under an N_2 atmosphere, a solution of benzyloxymethyl chloride (60% purity, 2.49 mL, 10.74 mmol) in THF (18 mL) over 1 h. The mixture was stirred at rt for 7 h. The resulting mixture was diluted with water (30 mL), and a 2 N solution of HCl was added until a clear solution formed. The mixture was extracted with dichloromethane (3×35 mL). The combined extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuum. The residue was purified by a short column of silica gel eluting with ethyl acetate–P.E. (1:3) to give **21** (800 mg, yield, 81%) as a diastereomeric mixture, which was used in the next step without further purification.

To a cooled (−78 °C) solution of diastereomeric mixture of **21** (800 mg, 1.45 mmol) in dry dichloromethane (20 mL) was added under argon atmosphere triethylsilane (3.3 mL, 20.93 mmol) and boron trifluoride etherate (0.54 mL, 4.34 mmol). After stirring at −78 °C for 8 h, the stirring was continued overnight while the temperature was allowed to rise. The reaction was quenched with saturated aqueous sodium bicarbonate (15 mL) and extracted with dichloromethane (3×25 mL). The combined extracts were dried (Na_2SO_4), filtered, and concentrated in vacuum. The residue was chromatographed on a column of silica gel eluting with ethyl acetate–P.E. (3:2) to give **13a** (777 mg, yield, 62% over two steps) as a white solid. Mp 90 °C (P.E–ethyl acetate=6:1). $[\alpha]_D^{20}$ +4.0 (*c* 1.2, $CHCl_3$).

4.1.2.2. Method 2: by SmI_2/$FeCl_3$-mediated benzyloxymethylation. A freshly prepared solution of SmI_2 (0.1 M in THF) containing anhydrous $FeCl_3$ (1.6 mg, 0.01 mmol) in anhydrous THF (10 mL) was quickly added to a mixture of **14** (226 mg, 0.53 mmol) and benzyloxymethyl chloride (60% purity, 0.35 mL, 1.57 mmol) in anhydrous THF (4 mL) under argon atmosphere at 0 °C. The mixture was allowed to react at rt for 1 h. The reaction was quenched with saturated aqueous sodium bicarbonate (5 mL) and extracted with ether (3×20 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuum. The residue was purified by flash column chromatography on silica gel eluting with ethyl acetate–P.E. (1:3) to give *N*,*O*-acetal **21** (246 mg, yield, 84%) as a mixture of two diastereomers, which was used in the next step without further purification.

Following the procedure described above, the diastereomeric mixture of **21** (246 mg, 0.44 mmol) was converted to

13a (172 mg, yield, 61% from **14**) as white crystals. Mp 86–87 °C (ethyl acetate–P.E.). $[\alpha]_D^{20}$ +3.4 (*c* 1.7, $CHCl_3$). IR (KBr pellet): 3031, 2902, 2868, 1699, 1451, 1247, 1106 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 3.38–3.45 (m, 2H, H-5, H-6), 3.52 (dd, *J*=5.2, 11.6 Hz, 1H, H-6), 3.77 (s, 3H, CH_3O), 3.94 (d, *J*=14.8 Hz, 1H, $PhCH_2N$), 4.05 (dd, *J*=5.1, 5.2 Hz, 1H, H-4), 4.21 (d, *J*=5.2 Hz, 1H, H-3), 4.35 (d, *J*=12.0 Hz, 1H, $PhCH_2O$), 4.42 (d, *J*=12.0 Hz, 1H, $PhCH_2O$), 4.45 (d, *J*=11.7 Hz, 1H, $PhCH_2O$), 4.56 (d, *J*=11.7 Hz, 1H, $PhCH_2O$), 4.83 (d, *J*=11.7 Hz, 1H, $PhCH_2O$), 4.94 (d, *J*=14.8 Hz, 1H, $PhCH_2N$), 5.13 (d, *J*=11.7 Hz, 1H, $PhCH_2O$), 6.78 (d, *J*=8.7 Hz, 2H, Ar), 7.05 (d, *J*=8.7 Hz, 2H, Ar), 7.20–7.48 (m, 15H, Ar) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 43.7, 55.3, 59.4, 67.4, 72.1, 72.4, 73.2, 78.8, 81.1, 114.0, 127.6, 127.7, 127.8, 127.9, 128.0, 128.2, 128.3, 128.4, 128.5, 128.6, 129.4, 129.7, 137.5, 137.6, 137.8, 159.0, 171.3 ppm; MS (ESI, *m/z*): 560 ($M+Na^+$, 21), 538 ($M+H^+$, 100). Anal. Calcd for $C_{34}H_{35}NO_5$: C, 75.95; H, 6.56; N, 2.61. Found: C, 75.56; H, 6.54; N, 2.56.

4.1.2.3. (3*R*,4*S*,5*S*)-5-Benzyloxymethyl-3,4-dibenzyloxyl-1-(4-methoxybenzyl)-pyrrolidin-2-one (*ent*-13a). Starting from L-tartaric acid, and using the method described in Sections 4.1.1 and 4.1.2.2, *ent*-**13a** was synthesized as white crystals. Mp 86–87 °C. $[\alpha]_D^{20}$ −3.1 (*c* 1.73, $CHCl_3$).

4.1.3. (3*S*,4*R*,5*R*)-5-Benzyloxymethyl-3,4-dibenzyloxypyrrolidin-2-one (22). To a solution of **13a** (279 mg, 0.52 mmol) in a mixed solvent system (MeCN–H_2O 9:1, v/v, 10 mL) was added ceric ammonium nitrate (1.423 g, 2.60 mmol) at 0 °C. After stirring at the same temperature for 4 h, the mixture was allowed to react at rt for 1.5 h. The reaction was quenched with H_2O (10 mL) and extracted with ethyl acetate (3×10 mL). The combined extracts were washed with saturated aqueous sodium bicarbonate and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuum. The residue was purified by flash column chromatography on silica gel eluting with ethyl acetate–P.E. (1:2) to give **22** (182 mg, yield, 85%) as white crystals. Mp 58–59 °C (ethyl acetate–P.E.) (lit.[15g] mp 54.5–56 °C). $[\alpha]_D^{20}$ −2.1 (*c* 1.1, $CHCl_3$) {lit.[15g] $[\alpha]_D$ −3.9 (*c* 0.77, $CHCl_3$)}. IR (KBr pellet): 3223, 3031, 2866, 1714, 1453, 1358, 1106, 1027 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 3.32 (dd, *J*=8.5, 9.2 Hz, 1H, H-6), 3.61 (dd, *J*=3.5, 9.2 Hz, 1H, H-6), 3.67 (ddd, *J*=3.5, 5.9, 8.5 Hz, 1H, H-5), 3.89 (dd, *J*=5.9, 6.1 Hz, 1H, H-4), 4.22 (d, *J*=6.1 Hz, 1H, H-3), 4.48 (s, 2H, $PhCH_2O$), 4.51 (d, *J*=11.7 Hz, 1H, $PhCH_2O$), 4.60 (d, *J*=11.7 Hz, 1H, $PhCH_2O$), 4.80 (d, *J*=11.6 Hz, 1H, $PhCH_2O$), 5.12 (d, *J*=11.6 Hz, 1H, $PhCH_2O$), 6.03 (br s, 1H, NH), 7.20–7.45 (m, 15H, Ar) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 56.1, 71.4, 72.3, 72.6, 73.5, 80.8, 81.1, 127.7, 127.8, 127.9, 128.0, 128.3, 128.4, 128.5, 128.6, 137.4, 137.5, 137.6, 173.1 ppm; MS (ESI, *m/z*): 418 ($M+H^+$, 96), 440 ($M+Na^+$, 100). Anal. Calcd for $C_{26}H_{27}NO_4$: C, 74.80; H, 6.52; N, 3.35. Found: C, 74.39; H, 6.54; N, 3.31.

4.1.4. (3*R*,4*S*,5*S*)-5-Benzyloxymethyl-3,4-dibenzyloxypyrrolidin-2-one (*ent*-22). Starting from *ent*-**13a**, and using the method described in Section 4.1.3, *ent*-**22** was synthesized as white crystals. Mp 58–59 °C. $[\alpha]_D^{20}$ +1.9 (*c* 2.56, $CHCl_3$).

4.1.5. (2*R*,3*R*,4*R*)-2-Benzyloxymethyl-3,4-dibenzyloxypyrrolidine (24).

4.1.5.1. Method 1: amide reduction using $BH_3 \cdot SMe_2$. To a solution of **22** (332 mg, 0.80 mmol) in anhydrous THF (8 mL) was added $BH_3 \cdot SMe_2$ (0.4 mL, 4.00 mmol) at 0 °C. After stirring at rt for two days, the reaction was quenched with MeOH (2 mL) and H_2O (3 mL). The resulting mixture was further stirred at 60 °C for 3 h, and then extracted with Et_2O (3×10 mL). The combined extracts were successively washed with saturated aqueous sodium bicarbonate and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuum. The residue was purified by flash column chromatography on silica gel eluting with ethyl acetate–P.E. (1:10, then 5:1) to give **23** (53 mg, yield, 16%) and **24** (32 mg, yield, 10%) and recovered starting material **22** (129 mg, yield, 39%). Compound **23**: white crystals; mp 55–56 °C (ethyl acetate–P.E.). $[\alpha]_D^{20}$ +34.8 (*c* 0.4, $CHCl_3$). IR (KBr pellet): 3244, 3030, 2918, 2366, 2320, 2273, 1453, 1362, 1168, 1096 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.60 (br s, 3H, BH_3), 2.99–3.05 (m, 1H, H-2), 3.09 (dd, *J*=4.3, 12.4 Hz, 1H, H-5), 3.37 (dd, *J*=4.3, 12.4 Hz, 1H, H-5), 3.57 (dd, *J*=1.2, 10.1 Hz, 1H, H-6), 3.94 (ddd, *J*=1.2, 4.3, 4.3 Hz, 1H, H-4), 4.01 (dd, *J*=3.2, 10.1 Hz, 1H, H-6), 4.13 (dd, *J*=1.2, 5.3 Hz, 1H, H-3), 4.42–4.60 (m, 6H, $3PhCH_2O$), 4.63 (br s, 1H, NH), 7.20–7.40 (m, 15H, Ar) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 59.0, 64.5, 70.6 (2C), 71.9, 73.2, 79.9, 83.4, 127.3, 127.4, 127.5, 127.6, 127.7, 127.8, 128.2, 128.3, 136.9, 137.0, 137.1 ppm; MS (ESI, *m/z*): 418 ($M+H^+$, 100). Anal. Calcd for [$C_{26}H_{32}NO_3B+2H_2O$]: C, 68.88; H, 8.00; N, 3.09. Found: C, 68.60; H, 7.89; N, 3.33.

4.1.5.2. Method 2: amide reduction using $LiAlH_4$. A solution of **22** (201 mg, 0.48 mmol) in anhydrous THF (5 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (96 mg, 2.53 mmol) in anhydrous THF (5 mL) at 0 °C. After stirring at 60 °C for 12 h, the reaction was cooled and quenched cautiously with water (2 mL). The resulting mixture was filtered and the solid was washed with EtOAc. The filtrate was dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuum. The residue was purified by flash column chromatography on silica gel eluting with ethyl acetate–P.E. (5:1) to give **24** (178 mg, yield, 92%) as a colorless oil. $[\alpha]_D^{20}$ +7.1 (*c* 1.2, $CHCl_3$) {lit.[15g] $[\alpha]_D$ +3.5 (*c* 0.79, $CHCl_3$)}. IR (film): 3058, 3030, 2862, 1453, 1365, 1206, 1097, 1029 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 2.11 (br s, 1H, NH), 3.07 (d, *J*=3.8 Hz, 2H, H-5), 3.22 (ddd, *J*=4.7, 5.2, 5.4 Hz, 1H, H-2), 3.53 (dd, *J*=5.4, 9.4 Hz, 1H, H-6), 3.59 (dd, *J*=5.2, 9.4 Hz, 1H, H-6), 3.85 (dd, *J*=1.8, 4.7 Hz, 1H, H-3), 3.99 (ddd, *J*=1.8, 3.8, 3.8 Hz, 1H, H-4), 4.41–4.55 (m, 6H, $3PhCH_2O$), 7.21–7.40 (m, 15H, Ar) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 51.1, 64.1, 70.4, 71.0, 71.8, 73.1, 84.5, 85.7, 127.4, 127.5, 127.6, 127.7, 127.8, 128.2, 128.3, 138.0, 138.1, 138.2 ppm; MS (ESI, *m/z*): 404 ($M+H^+$, 100). Anal. Calcd for $C_{26}H_{29}NO_3$: C, 77.39; H, 7.24; N, 3.47. Found: C, 77.55; H, 7.22; N, 3.70.

4.1.6. (2*S*,3*S*,4*S*)-2-Benzyloxymethyl-3,4-dibenzyloxypyrrolidine (*ent*-24). Starting from *ent*-**22**, and using the method described in Section 4.1.5.2, *ent*-**24** was synthesized as a colorless oil. $[\alpha]_D^{20}$ −4.7 (*c* 1.2, $CHCl_3$).

4.1.7. (2*R*,3*R*,4*R*)-3,4-Dihydroxy-2-hydroxymethylpyrrolidine hydrochloride (1·HCl). A methanolic solution

(5 mL) of **24** (46 mg, 0.11 mmol) was stirred at rt in the presence of 10% Pd/C (130 mg) and a catalytic amount of HCOOH for 24 h. The catalyst was removed by filtration and the reaction mixture was concentrated. To the crude was slowly added at 0 °C a mixture of MeOH (5 mL) and acetyl chloride (0.01 mL). After stirring for 30 min at 0 °C, the resulting mixture was evaporated in vacuum, further evaporation under high vacuum gave DAB 1 hydrochloride salt (**1**·HCl) (19 mg, yield, 100%), which is pure enough to give satisfactory physical and spectral data. Pale yellow syrup. $[\alpha]_D^{20}$ +36.1 (*c* 0.2, H_2O); $[\alpha]_D^{20}$ +38.0 (*c* 0.2, MeOH) {lit.[15a] $[\alpha]_D^{20}$ +37.9 (*c* 0.53, H_2O); lit.[15g] $[\alpha]_D^{20}$ +32.5 (*c* 0.5, H_2O)}. IR (film): 3346, 2929, 1593, 1450, 1384, 1071 cm^{-1}. ^1H NMR (400 MHz, D_2O) δ 3.28 (dd, *J*=2.5, 12.5 Hz, 1H, H-5), 3.46–3.54 (m, 2H, H-2, H-5), 3.76 (dd, *J*=8.1, 12.2 Hz, 1H, H-6), 3.88 (dd, *J*=4.7, 12.2 Hz, 1H, H-6), 3.99–4.03 (m, 1H), 4.22–4.28 (m, 1H) ppm; ^{13}C NMR (100 MHz, D_2O) δ 50.0, 59.0, 66.6, 74.3, 75.7 ppm; HRESIMS calcd for $[C_5H_{11}NO_3+H]^+$: 134.0812; found: 134.0814.

4.1.8. (2*S*,3*S*,4*S*)-3,4-Dihydroxy-2-hydroxymethylpyrrolidine hydrochloride (2·HCl). Starting from *ent*-**24**, and using the method described in Section 4.1.7, LAB 1 hydrochloride salt (**2**·HCl) was synthesized as pale yellow syrup {$[\alpha]_D^{20}$ −41.1 (*c* 0.2, MeOH); lit.[15a] $[\alpha]_D^{20}$ −34.6 (*c* 0.37, H_2O); lit.[15g] $[\alpha]_D^{20}$ −36.5 (*c* 0.37, H_2O)}.

4.1.9. (2*R*,3*R*,4*R*)-2-Benzyloxymethyl-3,4-dibenzyloxyl-1-hydroxyethylpyrrolidine (25). To a suspension of **24** (186 mg, 0.46 mmol) and K_2CO_3 (310 mg, 2.25 mmol) in MeOH (6 mL) was added 2-bromoethanol (0.2 mL, 2.77 mmol). After stirring for 48 h at rt, the reaction mixture was filtered and the solid was washed with CH_2Cl_2. The filtrate was concentrated in vacuum. The residue was purified by flash column chromatography on silica gel eluting with ethyl acetate–P.E. (1:1) to give **25** (165 mg, yield, 80%) as a colorless oil. $[\alpha]_D^{20}$ −25.2 (*c* 0.4, $CHCl_3$). IR (film): 3440, 3062, 3030, 2914, 2863, 1459, 1454, 1366, 1209, 1098 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 2.55 (dt, *J*=12.6, 3.8 Hz, 1H, H-6), 2.65 (dd, *J*=5.3, 10.5 Hz, 1H, H-5), 2.80–2.92 (m, 2H, H-2, OH, D_2O exchangeable), 3.04 (ddd, *J*=4.8, 8.9, 12.6 Hz, 1H, H-6), 3.24 (dd, *J*=1.4, 10.5 Hz, 1H, H-5), 3.49–3.64 (m, 4H, H-7, H-8), 3.88 (dd, *J*=1.2, 3.8 Hz, 1H, H-3), 3.97 (ddd, *J*=1.2, 1.4, 5.3 Hz, 1H, H-4), 4.40–4.54 (m, 6H, $3PhCH_2O$), 7.24–7.35 (m, 15H, Ar) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 56.9, 57.1, 59.7, 68.9, 70.8, 71.1, 71.3, 73.2, 81.7, 84.9, 127.4, 127.5, 127.6, 127.7, 128.3, 128.4, 137.9, 138.0, 138.1 ppm; MS (ESI, *m*/*z*): 448 ($M+H^+$, 100); HRESIMS calcd for $[C_{28}H_{33}NO_4+H]^+$: 448.2482; found: 448.2488.

4.1.10. (2*R*,3*R*,4*R*)-3,4-Dihydroxy-1-hydroxyethyl-2-hydroxymethylpyrrolidine (4). A methanolic solution (5 mL) of **25** (36 mg, 0.08 mmol) was stirred at rt in the presence of 10% Pd/C (108 mg) under 1 atm hydrogen pressure for 48 h. The catalyst was removed by filtration and the reaction mixture was concentrated. Further evaporation under high vacuum gave **4** (14 mg, yield, 100%), which is pure enough to give satisfactory physical and spectral data. Pale yellow syrup. $[\alpha]_D^{20}$ −49.6 (*c* 0.3, MeOH); $[\alpha]_D^{20}$ −46.7 (*c* 0.3, H_2O) {lit.[8] $[\alpha]_D^{20}$ +54.7 (*c* 0.38, H_2O)}. IR (film): 3359, 2926, 1407, 1048 cm^{-1}. ^1H NMR (400 MHz, D_2O) δ 2.45–2.54 (m, 2H), 2.72 (dd, *J*=5.6, 11.2 Hz, 1H, H-5), 2.90–2.96 (m, 1H), 2.98 (dd, *J*=2.4, 11.2 Hz, 1H, H-5), 3.57–3.63 (m, 4H), 3.85 (dd, *J*=2.7, 4.8 Hz, 1H, H-3), 4.03 (ddd, *J*=2.4, 2.7, 5.6 Hz, 1H, H-4) ppm; ^{13}C NMR (100 MHz, D_2O) δ 56.3, 58.7, 59.2, 60.8, 72.1, 75.4, 78.7 ppm; HRESIMS calcd for $[C_7H_{15}NO_4+H]^+$: 178.1074; found: 178.1075.

4.1.11. (2*R*,3*R*,4*R*)-3,4-Dihydroxy-1-hydroxyethyl-2-hydroxymethylpyrrolidine hydrochloride (4·HCl). A methanolic solution (5 mL) of **25** (40 mg, 0.09 mmol) was stirred at rt in the presence of 10% Pd/C (120 mg) and a catalytic amount of HCOOH for 24 h. The catalyst was removed by filtration and the reaction mixture was concentrated. To the crude was slowly added at 0 °C a mixture of MeOH (5 mL) and acetyl chloride (0.01 mL). After stirring for 30 min at 0 °C, the resulting mixture was evaporated in vacuum, further evaporation under high vacuum gave *N*-hydroxyethyl-DAB 1 hydrochloride salt (**4**·HCl) (18 mg, yield, 98%), which is pure enough to give satisfactory physical and spectral data. Pale yellow syrup. $[\alpha]_D^{20}$ −35.7 (*c* 0.2, MeOH); $[\alpha]_D^{20}$ −37.1 (*c* 0.2, H_2O). IR (film): 3357, 2935, 2844, 1591, 1442, 1386, 1074 cm^{-1}. ^1H NMR (400 MHz, D_2O) δ 3.19–3.27 (m, 1H), 3.42–3.52 (m, 3H), 3.60 (dd, *J*=1.2, 12.4 Hz, 1H, H-5), 3.79–3.92 (m, 4H, H-7, H-8), 4.01 (dd, *J*=2.7, 3.1 Hz, 1H, H-3), 4.22–4.27 (m, 1H, H-4) ppm; ^{13}C NMR (100 MHz, D_2O) δ 56.5, 58.0, 58.4, 59.2, 73.9, 75.0, 76.0 ppm; HRESIMS calcd for $[C_7H_{15}NO_4+H]^+$: 178.1074; found: 178.1075.

4.1.12. (3*S*,4*R*,5*R*)-5-Benzyloxymethyl-1-(*tert*-butoxycarbonyl)-3,4-dibenzyloxy-pyrrolidin-2-one (26). To a solution of **22** (725 mg, 1.74 mmol) and DMAP (29 mg, 0.09 mmol) in CH_2Cl_2 (15 mL) was successively added NEt_3 (0.53 mL, 3.82 mmol) and a solution of $(Boc)_2O$ (0.8 mL, 3.47 mmol) in CH_2Cl_2 (5 mL). After stirring at rt for 4 h, the reaction was quenched with saturated aqueous sodium bicarbonate (5 mL) and extracted with CH_2Cl_2 (3×20 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuum. The residue was purified by flash column chromatography on silica gel eluting with ethyl acetate–P.E. (1:6) to give **26** (852 mg, yield, 95%) as a colorless oil. $[\alpha]_D^{20}$ −73.7 (*c* 0.6, $CHCl_3$). IR (film): 3031, 2979, 1790, 1755, 1720, 1455, 1306, 1027 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.49 (s, 9H, $3CH_3$), 3.65–3.72 (m, 2H, H-5, H-6), 4.05–4.14 (m, 3H, H-3, H-4, H-6), 4.45–4.55 (m, 4H, $2PhCH_2O$), 4.72 (d, *J*=11.8 Hz, 1H, $PhCH_2O$), 4.94 (d, *J*=11.8 Hz, 1H, $PhCH_2O$), 7.20–7.50 (m, 15H, Ar) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.9 (3C), 61.2, 67.9, 71.6, 72.4, 73.2, 76.6, 80.5, 83.6, 127.6, 127.7, 127.9, 128.0, 128.2, 128.3, 128.4, 128.5, 137.1, 137.2, 137.7, 149.6, 170.7 ppm; MS (ESI, *m*/*z*): 540 ($M+Na^+$, 100). Anal. Calcd for $C_{31}H_{35}NO_6$: C, 71.93; H, 6.82; N, 2.71. Found: C, 72.32; H, 6.85; N, 2.75.

4.1.13. (2*R*,3*R*,4*R*,5*R*/*S*)-2-Benzyloxymethyl-3,4-dibenzyloxyl-5-methylpyrrolidine (28 and 29). To a cooled (−20 °C) solution of **26** (391 mg, 0.76 mmol) in anhydrous CH_2Cl_2 (10 mL) was added dropwise a solution of MeMgI (2 M, 0.75 mL, 1.50 mmol) in diethyl ether under nitrogen atmosphere. After stirring at the same temperature for 2 h, the reaction was quenched with saturated aqueous solution

of ammonium chloride (5 mL) and extracted with CH_2Cl_2 (3×20 mL). The combined extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuum. The residue was purified by flash column chromatography on silica gel eluting with ethyl acetate–P.E. (1:1) to give *N*,*O*-acetal **27** (332 mg, yield, 82%) as an inseparable mixture of two diastereomers, which was used in the next step without further separation.

To a cooled (−78 °C) solution of diastereomer mixture **27** (332 mg, 0.62 mmol) in anhydrous CH_2Cl_2 (10 mL) was added dropwise triethylsilane (0.98 mL, 7.6 mmol) and boron trifluoride etherate (0.23 mL, 2.2 mmol) under nitrogen atmosphere. After stirring at −78 °C for 6 h, the mixture was allowed to react at rt and stir overnight. The reaction was quenched with saturated aqueous sodium bicarbonate and extracted with CH_2Cl_2 (3×20 mL). The combined extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuum. The residue was purified by flash column chromatography on silica gel eluting with ethyl acetate to give two diastereomers **28** and **29** (in 9.4:1 ratio, 208 mg, combined yield, 80%). Major diastereomer **28**: colorless oil. $[\alpha]_D^{20}$ +16.4 (*c* 0.3, $CHCl_3$). IR (film): 3030, 2864, 1453, 1364, 1099 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.22 (d, *J*=6.6 Hz, 3H, CH_3), 2.10 (br s, 1H, NH), 3.22 (dq, *J*=5.4, 6.6 Hz, 1H, H-5), 3.39–3.44 (m, 1H, H-2), 3.52 (d, *J*=6.1 Hz, 2H, H-6), 3.64 (dd, *J*=3.5, 5.4 Hz, 1H, H-4), 3.88 (dd, *J*=3.5, 3.7 Hz, 1H, H-3), 4.48–4.56 (m, 6H, 3$PhCH_2O$), 7.20–7.40 (m, 15H, Ar) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.5, 57.3, 61.7, 70.8, 71.8, 71.9, 73.2, 86.7, 91.1, 127.6, 127.7, 127.8, 127.9, 128.4, 138.1, 138.2, 138.3 ppm; MS (ESI, *m*/*z*): 418 ($M+H^+$, 100); HRESIMS calcd for $[C_{27}H_{31}NO_3+H]^+$: 418.2377; found: 418.2369.

4.1.14. (2*R*,3*R*,4*R*,5*S*)-1-Benzyl-2-benzyloxymethyl-3,4-dibenzyloxyl-5-methylpyrrolidine (30). To a suspension of **29** (20 mg, 0.05 mmol) and K_2CO_3 (30 mg, 0.22 mmol) in MeOH (2 mL) was added benzyl bromide (0.04 mL, 0.30 mmol). After stirring for 24 h at rt, the reaction mixture was filtered and the solid was washed with CH_2Cl_2. The filtrate was concentrated in vacuum. The residue was purified by flash column chromatography on silica gel eluting with ethyl acetate–P.E. (1:25) to give **30** (18 mg, yield, 75%) as a colorless oil. $[\alpha]_D^{20}$ +43.1 (*c* 0.2, $CHCl_3$). IR (film): 3029, 2923, 2859, 1494, 1452, 1367, 1092 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.23 (d, *J*=6.4 Hz, 3H, CH_3), 3.01–3.09 (m, 2H, H-2, H-5), 3.19 (dd, *J*=4.8, 9.5 Hz, 1H, H-6), 3.35 (dd, *J*=9.2, 9.5 Hz, 1H, H-6), 3.65 (d, *J*=1.2, 4.6 Hz, 1H, H-4), 3.70 (d, *J*=14.0 Hz, 1H, $PhCH_2N$), 3.84 (dd, *J*=1.2, 2.0 Hz, 1H, H-3), 3.93 (d, *J*=14.0 Hz, 1H, $PhCH_2N$), 4.30 (d, *J*=12.0 Hz, 1H, $PhCH_2O$), 4.33 (d, *J*=12.2 Hz, 1H, $PhCH_2O$), 4.40 (d, *J*=12.0 Hz, 1H, $PhCH_2O$), 4.45 (d, *J*=12.1 Hz, 1H, $PhCH_2O$), 4.50 (d, *J*=12.2 Hz, 1H, $PhCH_2O$), 4.52 (d, *J*=12.1 Hz, 1H, $PhCH_2O$), 7.20–7.35 (m, 20H, Ar) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 57.4, 61.2, 68.6, 70.8, 71.4, 71.9, 72.9, 83.0, 83.9, 126.9, 127.3, 127.4, 127.5, 127.6, 127.7, 127.8, 128.1, 128.2, 128.3, 129.4, 138.4, 138.5, 139.0 ppm; MS (ESI, *m*/*z*): 508 ($M+H^+$, 100); HRESIMS calcd for $[C_{34}H_{37}NO_3+H]^+$: 508.2846; found: 508.2842.

4.1.15. (2*R*,3*R*,4*R*,5*R*)-3,4-Dihydroxyl-2-hydroxymethyl-5-methylpyrrolidine hydrochloride (7·HCl). A methanolic solution (5 mL) of **28** (62 mg, 0.15 mmol) was stirred at rt in the presence of 10% Pd/C (200 mg) and a catalytic amount of HCOOH for 24 h. The catalyst was removed by filtration and the reaction mixture was concentrated. To the crude was slowly added at 0 °C a mixture of MeOH (5 mL) and acetyl chloride (0.01 mL). After stirring for 30 min at 0 °C, the resulting mixture was evaporated in vacuum, further evaporation under high vacuum gave hydrochloride salt of 6-deoxy-DMDP (**7**·HCl) (22 mg, yield, 98%), which is pure enough to give satisfactory physical and spectral data. Compound **7**: pale yellow syrup. $[\alpha]_D^{20}$ +40.5 (*c* 0.3, MeOH); $[\alpha]_D^{20}$ +41.2 (*c* 0.1, H_2O) {lit.[17d] $[\alpha]_D^{20}$ +45.0 (*c* 1.4, MeOH)}. IR (film): 3373, 2938, 1636, 1392, 1105, 1051 cm^{-1}. ^1H NMR (400 MHz, D_2O) δ 1.35 (d, *J*=6.8 Hz, 3H, CH_3), 3.43 (dq, *J*=7.0, 6.8 Hz, 1H, H-5), 3.48 (ddd, *J*=3.9, 6.8, 6.8 Hz, 1H, H-2), 3.75 (dd, *J*=6.8, 12.2 Hz, 1H, H-6), 3.80 (dd, *J*=7.0, 7.2 Hz, 1H, H-4), 3.84 (dd, *J*=3.9, 12.2 Hz, 1H, H-6), 3.95 (dd, *J*=6.8, 7.2 Hz, 1H, H-3) ppm; ^{13}C NMR (100 MHz, D_2O) δ 14.4, 57.4, 58.2, 62.1, 74.4, 79.0 ppm; HRESIMS calcd for $[C_6H_{13}NO_3+H]^+$: 148.0968; found: 148.0969.

4.1.16. (2*R*,3*R*,4*R*,5*S*)-2-(Benzyloxymethyl)-5-(4-benzyloxyphenyl)-3,4-dibenzyloxy-pyrrolidine (34). To a cooled (−20 °C) solution of **26** (434 mg, 0.84 mmol) in anhydrous CH_2Cl_2 (10 mL) was added dropwise a solution of 4-benzyloxy-phenyl magnesium bromide[13c] (1 M, 2.5 mL, 2.50 mmol) in diethyl ether under nitrogen atmosphere. After stirring at the same temperature for 2 h, the reaction was quenched with saturated aqueous solution of ammonium chloride (6 mL) and extracted with dichloromethane (3×10 mL). The combined extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuum. The residue was purified by flash column chromatography on silica gel eluting with ethyl acetate–P.E. (1:6) to give a mixture of **32** (a diastereomeric mixture) and its ring-opening tautomer **33** (415 mg, combined yield, 81%).

To a cooled (−78 °C) solution of a mixture of **32** and **33** (415 mg, 0.59 mmol) in dry dichloromethane (10 mL) was added dropwise triethylsilane (0.94 mL, 5.9 mmol) and boron trifluoride etherate (0.22 mL, 1.77 mmol) under nitrogen atmosphere. After stirring at −78 °C for 6 h, the mixture was allowed to react at rt and stir overnight. The reaction was quenched with saturated aqueous sodium bicarbonate and extracted with dichloromethane (3×10 mL). The combined extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuum. The residue was purified by flash column chromatography on silica gel eluting with ethyl acetate–P.E. (1:4) to give **34** (287 mg, yield, 58% from **26**) as a white solid. Mp 79–80 °C (ethyl acetate–P.E.). $[\alpha]_D^{20}$ +34.0 (*c* 1.25, $CHCl_3$). IR (KBr pellet): 3061, 2861, 1510, 1454, 1238 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 3.37–3.42 (m, 1H, H-2), 3.63 (dd, *J*=6.3, 9.3 Hz, 1H, H-6), 3.70 (dd, *J*=5.4, 9.3 Hz, 1H, H-6), 3.86 (dd, *J*=1.3, 4.5 Hz, 1H, H-3), 3.90 (dd, *J*=1.3, 4.6 Hz, 1H, H-4), 4.04 (d, *J*=12.0 Hz, 1H, $PhCH_2O$), 4.12 (d, *J*=12.0 Hz, 1H, $PhCH_2O$), 4.35 (d, *J*=4.5 Hz, 1H, H-5), 4.50 (s, 2H, $PhCH_2O$), 4.53 (d, *J*=12.0 Hz, 1H, $PhCH_2O$), 4.57 (d, *J*=12.0 Hz, 1H, $PhCH_2O$), 5.08 (s, 2H, $PhCH_2O$), 6.91–6.98 (m, 4H, Ar), 7.19–7.46 (m, 20H, Ar) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 63.2, 64.6, 70.1, 71.6, 71.7, 71.9, 73.2, 85.0, 85.9, 114.4, 127.5, 127.6, 127.7, 127.8,

127.9, 128.0, 128.1, 128.2, 128.3, 128.4, 128.5, 129.4, 131.0, 137.2, 138.1, 138.2, 138.4, 158.0 ppm; MS (ESI, *m/z*): 608 ($M+Na^+$, 8), 586 ($M+H^+$, 100). Anal. Calcd for [$C_{39}H_{39}NO_4$+2H_2O]: C, 75.34; H, 6.97; N, 2.25. Found: C, 75.89; H, 6.97; N, 2.36.

4.1.17. 4-[(2*R*,3*R*,4*R*)-4-Amino-2,3,5-trihydroxypentyl]-phenol (35). A methanolic solution (4 mL) of **34** (40 mg, 0.07 mmol) was stirred at rt in the presence of 10% Pd/C (200 mg) under 1 atm hydrogen pressure for 4 h. The catalyst was removed by filtration and the reaction mixture was concentrated. Further evaporation under high vacuum gave **35** (14 mg, yield, 96%), which is pure enough to give satisfactory physical and spectral data. Pale yellow syrup. $[\alpha]_D^{20}$ +21.0 (*c* 0.3, MeOH). IR (film): 3372, 2925, 1611, 1385, 1036 cm^{-1}. ^1H NMR (400 MHz, D_2O) δ 2.69 (dd, *J*=8.5, 13.8 Hz, 1H, H-1), 2.77 (dd, *J*=5.6, 13.8 Hz, 1H, H-1), 3.42–3.47 (m, 1H, H-4), 3.67–3.73 (m, 2H, H-5), 3.80–3.86 (m, 2H, H-2, H-3), 6.79 (d, *J*=8.6 Hz, 2H, Ar), 7.10 (d, *J*=8.6 Hz, 2H, Ar) ppm; ^{13}C NMR (100 MHz, D_2O) δ 38.2, 55.5, 58.1, 69.0, 72.1, 115.4, 129.7, 130.7, 154.0 ppm; MS (ESI, *m/z*): 228 ($M+H^+$, 100); HRESIMS calcd for [$C_{11}H_{17}NO_4$+H]$^+$: 228.1230; found: 228.1236.

4.1.18. (2*R*,3*R*,4*R*,5*S*)-2-(Hydroxymethyl)-5-(4-hydroxyphenyl)pyrrolidine-3,4-diol (36). An ethanolic solution (4 mL) of **34** (34 mg, 0.06 mmol) was stirred at rt in the presence of $PdCl_2$ (183 mg) under 1 atm hydrogen pressure for 12 h. The catalyst was removed by filtration and the reaction mixture was concentrated. Further evaporation under high vacuum gave **36** (12 mg, yield, 92%), which is pure enough to give satisfactory physical and spectral data. Pale yellow syrup. $[\alpha]_D^{20}$ +47.7 (*c* 0.3, MeOH). IR (film): 3388, 2925, 1619, 1408, 1072 cm^{-1}. ^1H NMR (400 MHz, D_2O) δ 3.51–3.58 (m, 1H, H-2), 3.61–3.66 (m, 1H), 3.85 (dd, *J*=8.6, 12.2 Hz, 1H, H-6), 3.95 (dd, *J*=4.8, 12.2 Hz, 1H, H-6), 4.12 (dd, *J*=1.2, 2.2 Hz, 1H), 4.31 (d, *J*=2.3 Hz, 1H, H-5), 6.88 (d, *J*=8.5 Hz, 2H, Ar), 7.32 (d, *J*=8.5 Hz, 2H, Ar) ppm; ^{13}C NMR (100 MHz, D_2O) δ 59.4, 64.5, 67.2, 75.9, 76.4, 115.7, 121.8, 129.7, 156.2 ppm; MS (ESI, *m/z*): 226 ($M+H^+$, 100); HRESIMS calcd for [$C_{11}H_{15}NO_4$+H]$^+$: 226.1074; found: 226.1077.

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