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A Concise and Divergent Approach to Hydroxylated Piperidine Alkaloids and Azasugar Lactams

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The vinylogous Mannich reaction (VMR) between 2-(*tert*-butyldimethylsilyloxy)furan (TBSOF) and (R_S)-*t*-BS-imine **12a** and the application of the VMR adduct butenolide **13a** as a versatile chiral building block for the synthesis of hydroxylated piperidine alkaloids and azasugars were investigated. Firstly, both the *anti* diastereoselectivity and the chemical yield of the asymmetric VMR between TBSOF and (R_S)-*t*-BS-imine **12a** were improved by the use of $Sm(OTf)_3/H_2O$ (1.5 equiv.) as the promoter. Similar diastereoselectivities were also obtained with $Yb(OTf)_3/H_2O$, $Cu(OTf)_2/H_2O$, $Zn(OTf)_2/H_2O$, or the Brønsted acids TfOH or MsOH as the promotors. Secondly, an efficient four-step procedure for the elaboration of butenolide **13a** into piperidine alkaloid (–)-deoxoprosophylline (**2**) was established. Thirdly, by taking advantage of the olefin functionality in the butenolide **13a**, polyhydroxylated δ-lactams **23** and **21**, which are ready precursors of azasugars L-deoxyallonojirimycin (*ent*-**7**) and L-3-*epi*-fagomine (*ent*-**6**), were obtained in two and three steps, respectively, via dihydroxylated lactone **17**. The easily available synthetic intermediate **17** can also serve as a key intermediate for the synthesis of the glycosyl nucleoside amino acid cores of polyoxins and nikkomycins.

Introduction

6-Substituted 2-methyl- or 2-(hydroxymethyl)piperidin-3-ols are common structural features of many alkaloids[1] and azasugars.[2] Several alkaloids such as (–)-prosophylline (**1**, Figure 1), for example, were isolated from the leaves of the West African savanna tree *Prosopis africana* Taub[3] and from *Microcos philippinensis* (Perk.) Burret (*Tiliaceae*).[4] These alkaloids and their deoxygenated derivatives, such as (–)-deoxoprosophylline (**2**, also known as desoxoprosophylline), exhibited diverse biological properties including analgesic, antibiotic, anesthetic, and CNS stimulant activities.[5] The development of new selective acetylcholinesterase inhibitors from such an alkaloid has been reported recently.[6] Several hydroxylated piperidine alkaloids such as morusimic acids D (**3**) and E (**4**) have recently been isolated from the fruits of white mulberry *Morus alba* Linne (Moraceae), a tree native to China and Korea, growing in Turkey.[7] Interestingly, several polyhydroxylated piperidine alkaloids, known as azasugars or iminosugars, such as 1-deoxynojirimycin (DNJ, **5**) and 3-*epi*-fagomine (**6**) have been isolated from the roots, leaves, and fruits of white mulberry.[8] D-1-Deoxy-4-*epi*-nojirimycin (*allo*-DNJ, **7**) and α-4-*epi*-homonojirimycin (α-homoallonojirimycin, α-*allo*-HNJ, **8**) are iminosugars isolated from the Thai medicinal plants *Connarus ferrugineus*.[9] Prior to its isolation, *allo*-DNJ (**7**),[10] as well as its antipode,[11] had been synthesized several times.[10–12] Biological studies[13] showed that *allo*-DNJ showed a potent inhibitory activity against rat intestinal lactase and bovine liver cytosolic β-galactosidase,[10]

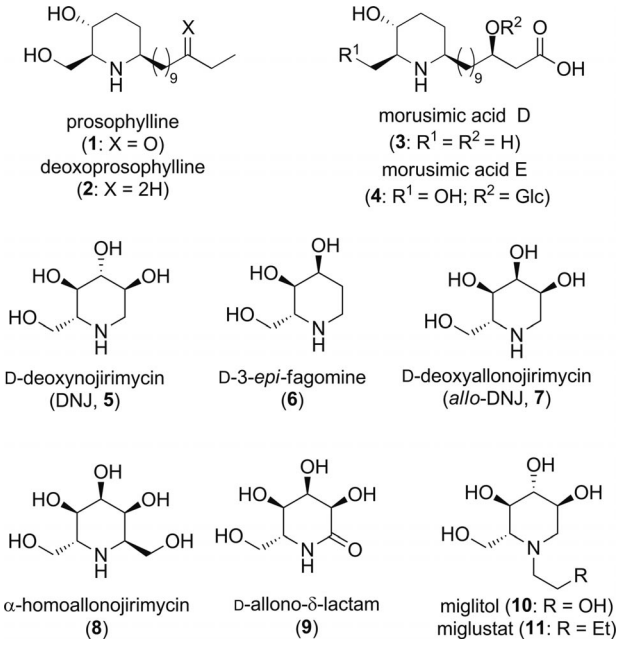

Figure 1. Structures of some hydroxylated piperidine alkaloids, azasugars, and azasugar lactams.

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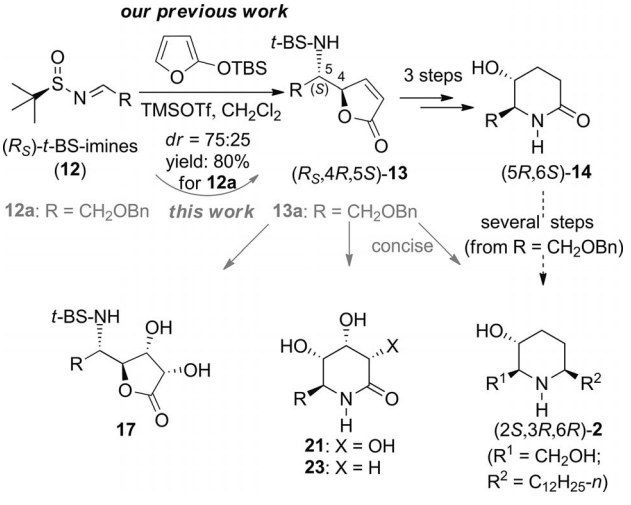
whereas L-*allo*-DNJ was a better inhibitor of α-mannosidase than D-*manno*-DNJ, and so might become a key compound for the drug design.[11] The compound D-*allono*-δ-lactam (**9**) has been synthesized for conformational analysis and evaluation as a glycosidase inhibitor.[14] These molecules have consequently become attractive synthetic targets for the development both of new synthetic methodologies and of new pharmaceuticals.[1,2,10–18]

The intensive studies on azasugars have led to the development of several pharmaceuticals.[2c] Miglitol (**10**), for example, is an oral antidiabetic drug currently used to treat type 2 diabetes, whereas Miglustat (**11**), marketed under the trade name Zavesca, is a drug developed by Actelion used to treat Type 1 Gaucher disease (GD1).

We recently developed a flexible approach to 5-aminoalkylbutenolides and 6-substituted 5-hydroxypiperidin-2-ones **14** (Scheme 1) based on the asymmetric vinylogous Mannich reactions (VMRs)[19,20] between 2-(*tert*-butyldimethylsilyloxy)furan (TBSOF)[20] and (R_S)- or (S_S)-*tert*-butanesulfinimines (*t*-BS-imines)[21] **12**.[22] The efficiency and versatility of the methodology prompted us to investigate its application to the asymmetric synthesis of alkaloids and azasugars. Here we report the results, including an improved *anti*-diastereoselective VMR between sulfinimine **12a** and TBSOF, together with concise and divergent elaboration of the adduct **13a** both to (–)-deoxoprosophylline (**2**) and to azasugar δ-lactams **23** and **21**, as well as to potential key intermediate **17** for the synthesis of the glycosyl nucleoside amino acid cores of polyoxins and nikkomycins.



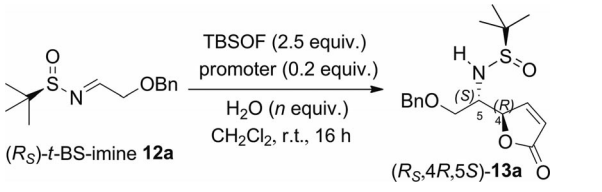
Scheme 1. Our synthetic plan for the development of vinylogous Mannich reaction adduct **13a** as a versatile building block for the synthesis of heterocycles.

Results and Discussion

In our previous TMSOTf-promoted VMRs between the Ellman sulfinimines **12** and TBSOF, good to excellent diastereoselectivities were obtained in most cases (Scheme 1). However, only a modest *anti* diastereoselectivity (*dr* = 75:25) was obtained with the benzyloxyethanal-derived sulfinimine **12a**.[22] In view of the potential use of the adduct **13a** in the asymmetric synthesis of piperidine alkaloids and azasugars,[16l,23] a further investigation into the VMR of (R_S)-*t*-BS-imine **12a** was undertaken with the goal of improving the diastereoselectivity. In the light of the beneficial effects of metal triflates (especially rare-earth metal triflates) in organic synthesis,[24,25] several $M(OTf)_n$ species were evaluated as promoters in the VMR between (R_S)-*t*-BS-imine **12a** and TBSOF.

As can be seen from Table 1, when (R_S)-*t*-BS-imine **12a** was treated with 2.5 equiv. of TBSOF in the presence of 0.2 equiv. of $Sm(OTf)_3$, in CH_2Cl_2 for 16 h, the desired butenolide **13a** was produced as a 51:49 mixture of diastereomers in 55% yield (Table 1, Entry 1). Favorable effects of water have been reported both in $M(OTf)_n$-mediated reactions[24a,26] and in VMRs,[27] so water was examined as an additive. When water (1.5 equiv.) was added to the above $Sm(OTf)_3$-promoted VMR, the reaction proceeded smoothly to give the adduct **13a** in excellent yield (93%) and with an improved 86:14 *anti*/*syn* diastereoselectivity (Entry 2). When the amount of water was increased to 10.0 equiv., only a slight decrease in diastereoselectivity (from 84:16 to 82:18) was observed and almost the same yield was maintained (Entry 3). A favorable effect of water

Table 1. The VMR between (R_S)-*t*-BS-imine **12a** and TBSOF.[a]



Entry	Promoter	Equiv. of H_2O	**13a**/*syn* diastereomer[b] (% yield)[c]
1	$Sm(OTf)_3$	–	51:49 (55)
2	$Sm(OTf)_3$	1.5	86:14 (93)
3	$Sm(OTf)_3$	10	82:18 (92)
4	$Yb(OTf)_3$	–	59:41 (64)
5	$Yb(OTf)_3$	1.5	85:15 (90)
6	$Eu(OTf)_3$	1.5	75:25 (36)
7	$Cu(OTf)_2$	1.5	85:15 (85)
8	$Zn(OTf)_2$	1.5	84:16 (88)
9	TfOH[d]	–	82:18 (79)
10	MsOH[d]	–	84:16 (87)
11	–	1.5	NR[e]
12	TfOH[f]	1.5[f]	trace[f]
13	TfOH[g]	1.5[g]	84:16 (75)
14	$Sm(OTf)_3$	–[h]	84:16 (83)

[a] General experimental conditions: $M(OTf)_x$ (0.1 mmol) in CH_2Cl_2 (4 mL), H_2O (0.75 mmol), compound **12a** (0.5 mmol), and TBSOF (1.25 mmol) under N_2, at room temp. for 16 h. [b] Ratios determined by analysis of the ^1H NMR spectra of the crude mixtures. [c] Combined and isolated yields. [d] 0.8 equiv. of TfOH or MsOH were used, and the reactions were conducted at –78 °C for 2 h. [e] No reaction. [f] 0.01 M TfOH-containing water was used, and the reaction was conducted at room temp. for 16 h; a trace of product was observed, but the ratio was not determined. [g] 0.2 equiv. of TfOH was used, and the reaction was conducted at room temp. for 0.5 h. [h] 1.5 equiv. of MeOH was used instead of H_2O.

was also observed with the $Yb(OTf)_3$-catalyzed VMR (Entries 4, 5). Screening of other metal triflates in the presence of 1.5 equiv. of water was then performed. When $Eu(OTf)_3$ was used, a lower diastereoselectivity and a poor yield (Entry 6) were obtained. With $Cu(OTf)_2$ or $Zn(OTf)_2$ as the catalyst, diastereoselectivities similar to those achieved with $Sm(OTf)_3$ and $Yb(OTf)_3$ were observed, but lower yields were obtained (Entries 7, 8). The results are surprising because both $Cu(OTf)_2$ and $Zn(OTf)_2$ are sensitive to water, whereas $Sm(OTf)_3$ and $Yb(OTf)_3$ are water-tolerant Lewis acids. It seemed that the roles in these reactions were played by other forms of Cu^{2+} and Zn^{2+} catalysts generated in situ (vide infra). However, triflic acid[28] had already been shown to be an effective promoter for the VMR. Indeed, when the VMR between **12a** and TBSOF was carried out in the presence of TfOH or MsOH as the catalyst, similar diastereoselectivities and yields were obtained (Entries 9, 10).

To provide insight into the possible role of water in the $M(OTf)_n/H_2O$-mediated VMR, a control experiment in the presence solely of 1.5 equiv. of water was undertaken. No formation of the desired product was observed (Table 1, Entry 11). This result implies that water is not a direct promoter for the reaction. To investigate the effect of trace amounts of TfOH that might be formed in situ from the reaction between $Sm(OTf)_3$ and water,[24a] the reaction was run in the presence of 1.5 equiv. of a 0.01 M aqueous solution of TfOH, and only a trace of product was detected by TLC monitoring (Entry 12). This result demonstrated that traces of TfOH also did not play a role in the reaction. These results allowed us to assume that an active Sm^{III} species was formed due to the presence of water. A six-membered reactive transition state containing both a Sm–O chelation and an H–N hydrogen bond (**A** or **B**) is suggested (Figure 2); this on one hand activates the sulfinimine and on the other hand improves the diastereoselectivity of the reaction. It could also explain why use of more water has little effect either on yields or on diastereoselectivities. This model can also be used to explain the results of the $Cu(OTf)_2/H_2O$- or $Zn(OTf)_2/H_2O$-mediated VMR (Entries 7 and 8). Conversely, the results of the $Cu(OTf)_2/H_2O$- or $Zn(OTf)_2/H_2O$-mediated reaction also support the proposed mechanism. To judge on the more plausible transition state out of **A** and **B**, the $Sm(OTf)_3$/MeOH-mediated reaction was conducted, and gave the desired adduct **13a** in a yield of 83% and in a *dr* of 84:16 (Entry 14). This result (via transition state **C**) supports the transition state **B**. Finally, when the reaction was conducted in the presence of 0.2 equiv. of TfOH and 1.5 equiv. of water (Entry 13), the result obtained was almost the same as that in the absence of water (Entry 9).

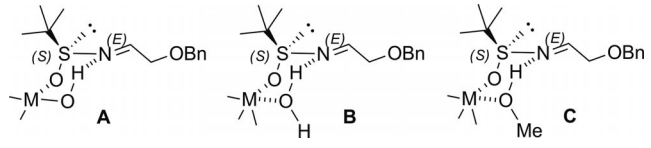
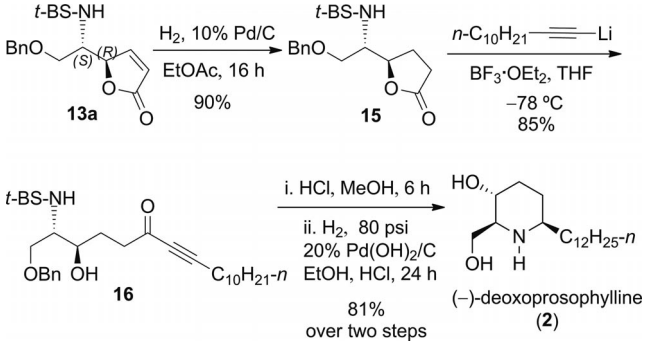


Figure 2. Plausible reactive species in the $M(OTf)_n/H_2O$-mediated VMR.

With access to butenolide **13a** secured, we next investigated its application to the synthesis of hydroxylated piperidine alkaloids.[1,15] (–)-Deoxoprosophylline (**2**)[16] was selected as our target molecule. Although we had already demonstrated that butenolide **13** could be converted into 2-piperidinone derivative **14** by a three-step procedure,[22] and had also developed a versatile method for direct transformation of lactams to piperidines by reductive alkylation,[29] additional protection/deprotection steps were still required to complete the total synthesis of piperidine alkaloids as shown in Scheme 1.

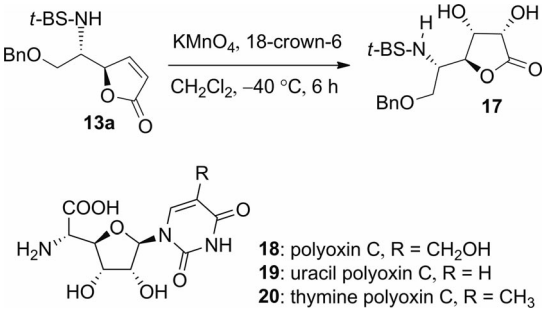
We envisaged that the synthetic route could be greatly simplified if we firstly undertake the ring-opening alkylation of lactone **13a**, instead of ring-expansion to 2-piperidinone **14** (cf. Scheme 2). The *anti*-butenolide **13a** was thus subjected to catalytic hydrogenation (H_2, 1 atm, 10% Pd/C, EtOAc, room temp., 16 h) to give lactone **15** (90% yield). This was treated with 2.0 equiv. of the alkynyltrifluoroborate[30] generated in situ from dodec-1-ynyllithium and $BF_3{\cdot}OEt_2$, to give the desired ynone **16** in 85% yield. Cleavage of the chiral auxiliary in compound **16** with 4 M HCl in MeOH (r.t., 6 h), followed by catalytic hydrogenation under acidic conditions [H_2, 80 psi, 20% $Pd(OH)_2/C$, EtOH, HCl, room temp., 24 h], produced (–)-deoxoprosophilline (**2**) in 81% yield over two steps. The physical and spectroscopic data for our synthetic product are in agreement with those reported [m.p. 88–89 °C; lit.[16a] 90–91 °C. $[\alpha]_D^{23}$ = –16.4 (c = 1.0, $CHCl_3$); lit.[16r] $[\alpha]_D^{25}$ = –15.9 (c = 0.62, $CHCl_3$)]. The previously documented[16i] 2,6-*cis* diastereoselectivity in the last catalytic hydrogenation was thus confirmed.



Scheme 2. Concise synthesis of (–)-deoxoprosophylline (**2**).

To demonstrate the applicability of the butenolide **13a** in the synthesis of azasugars, the syntheses of azasugar lactams **21** and **23** (Scheme 1) were carried out. The most straightforward approach could only be achieved by taking advantage of the olefin functionality in butenolide **13a**. Epoxidation of **13a** was first attempted. Unfortunately, under a variety of conditions, the starting butenolide were recovered. Dihydroxylation of butenolide **13a** was then investigated. The use of the $K_2Os_2O_2(OH)_4$/NMO oxidation system failed to produce the desired product,[31] but the utilization of $KMnO_4$ in combination with crown ether[32] turned out to be fruitful. Treatment of **13a** with $KMnO_4$ and 18-crown-6 at –40 °C for 6 h produced the desired dihydroxylated product **17** as the sole observable diastereomer[33] in

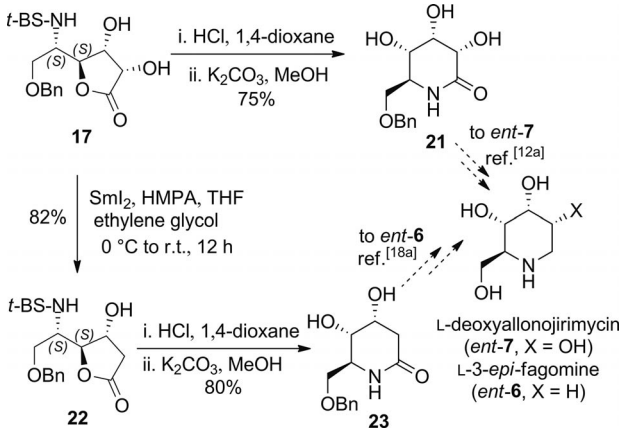
68% yield (Scheme 3). Lower yields were obtained when the reaction was run at a higher or lower temperature. No over-oxidation of sulfinamide was observed. The stereochemistry of the hydroxylated lactone **17** was assigned according to the literature precedents.[31–33]



Scheme 3. Synthesis of compound **17**, a potential intermediate of the glycosyl nucleoside amino acid cores of the polyoxins and nikkomycins.

It is worth noting that differently protected analogues of dihydroxylated lactone **17** (antipode) have served as the key intermediates for the synthesis of the glycosyl nucleoside amino acid cores of polyoxins and nikkomycins.[31,33] The polyoxins and nikkomycins constitute a small group of complex peptidyl nucleoside antibiotics, which are very promising leads for the development of non-toxic antifungal therapeutics.[31,33] Our easy access to lactone **17** thus paved the way for the concise and diastereoselective synthesis of those natural products (Scheme 3).

With the hydroxylated lactone **17** in hand, the syntheses of azasugar lactams **21** and **23** were undertaken (Scheme 4). Compound **17** was subjected to acidic hydrolysis (HCl, 12 M, 1,4-dioxane, room temp., 6 h) to remove the chiral auxiliary. The resulting aminolactone was then treated with K_2CO_3 in MeOH at room temp. for 23 h to give the ring-expanded δ-lactam **21**[34] in 75% yield over two steps.



Scheme 4. Asymmetric synthesis of azasugar lactams **21** and **23**. HMPA = hexamethylphosphoric triamide (hexamethylphosphoramide).

For the synthesis of lactam **23**, the α-hydroxy group in lactone **17** had to be reductively eliminated. SmI_2-based chemistry appeared to be suitable.[35] Indeed, in the presence of HMPA and ethylene glycol, treatment of lactone **17** with a 0.1 M solution of SmI_2 (4 equiv.) in THF at room temp. for 12 h produced the α-dehydroxylated product **22** smoothly in 82% yield. Lactone **22** was converted into lactam **23** in 80% yield by the same procedure as described for the transformation of **17** to **21** (Scheme 4).

Lactam **21** could be converted into L-1-deoxyallonojirimycin (*ent*-**7**),[12a] an inhibitor of α-mannosidase.[11] Similarly, lactam **23** is a ready precursor of L-3-*epi*-fagomine (*ent*-**6**),[18b,36] a moderate inhibitor both of α-glucosidase and of β-galactosidase.[18e]

Conclusions

In summary, an improved diastereoselective synthesis of butenolide **13a** through the VMR between TBSOF and (R_S)-*t*-BS-imine **12a** is reported. Thanks to the multiple functionalities of butenolide **13a**, an efficient and divergent approach for the total synthesis of piperidine alkaloids and azasugar lactams has been developed. (–)-Deoxoprosophilline (**2**) was synthesized in five steps starting from (R_S)-*t*-BS-imine **12a** in an overall yield of 49%. This represents the most efficient total synthesis of (–)-deoxoprosophilline (**2**) from commercially available starting materials (six steps). From butenolide **13a**, polyhydroxylated δ-lactams **23** and **21**, key intermediates for the synthesis of azasugars, were synthesized in two and three steps, respectively, via dihydroxylated lactone intermediate **17**. In addition, the easy access to lactone **17** paved the way for the concise and diastereoselective synthesis of the glycosyl nucleoside amino acid cores of the polyoxins and nikkomycins.

Experimental Section

Typical Procedure for the Synthesis of (R_S,4*R*,5*S*)-5-[(Benzyloxymethyl)(*tert*-butylsulfinylamino)methyl]furan-2(5*H*)-one (13a): H_2O (0.014 mL, 0.75 mmol, 1.5 equiv.), (*R*,*E*)-*N*-benzyloxyethylidene-*tert*-butanesulfinamide[21f] (**12a**, 127 mg, 0.50 mmol, 1.0 equiv.), and 2-(*tert*-butyldimethylsilyloxy)furan (TBSOF, 247 mg, 1.25 mmol, 2.5 equiv.) were sequentially added under N_2 to a suspension of $Sm(OTf)_3$ (60 mg, 0.10 mmol, 0.20 equiv.) in CH_2Cl_2 (4.0 mL). After the mixture had been stirred for 16 h at room temperature, H_2O (5.0 mL) was added. The mixture was extracted with CH_2Cl_2 (10 mL × 3). The combined organic layers were dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: EtOAc/hexane 1:1, *v*/*v*) to give butenolide **13a** (134 mg, 80%) and butenolide **13b** (22 mg, 13%). The physical and spectroscopic data for butenolide **13a** and **13b** are identical with those we reported previously.[22]

(R_S,4*R*,5*S*)-5-[(Benzyloxymethyl)(*tert*-butylsulfinylamino)methyl]-furan-2(4*H*)-one (15): The hydrogenation of **13a** was performed by the protocol we described previously,[22] to give lactone **15** in 90% yield. Its physical and spectroscopic data are identical to those we reported previously.[22]

(R_S)-*N*-[(2*S*,3*R*)-1-Benzyloxy-3-hydroxy-6-oxooctadec-7-yn-2-yl-2-methylpropan-2-yl]sulfinamide (16): *n*BuLi (0.38 mL, 2.4 M,

0.92 mmol, 2.0 equiv.) was added slowly at –78 °C under argon to a solution of dodec-1-yne (160 mg, 0.96 mmol, 2.1 equiv.) in dry THF (4.0 mL). The reaction mixture was stirred for 45 min at the same temperature, after which $BF_3{\cdot}Et_2O$ (0.11 mL, 0.92 mmol, 2.0 equiv.) was added dropwise. Stirring was continued for 10 min, and then lactone **15** (156 mg, 0.46 mmol, 1.0 equiv.) in THF (2.5 mL) was added. The resulting mixture was stirred for 2 h at the same temperature, after which a solution of saturated NH_4Cl/NH_4OH (2:1, *v*/*v*, 2.0 mL) was added. The mixture was allowed to warm to room temperature, poured into water (8 mL), and extracted with Et_2O (10 mL × 4). The combined organic layers were dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: EtOAc/hexane 1:2) to give compound **16** (198 mg, 85%) as a pale yellow oil. $[\alpha]_D^{20}$ = –19.8 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 0.88 (t, $^3J_{H,H}$ = 6.9 Hz, 3 H, 18-CH_3), 1.23–1.38 [m, 23 H, *t*Bu, (11–17)-H], 1.52–1.59 (m, 2 H, 10-H), 1.64–1.74 (m, 1 H, 4-H), 1.92–2.00 (m, 1 H, 4-H), 2.33 (t, $^3J_{H,H}$ = 7.1 Hz, 2 H, 9-H), 2.64–2.80 (m, 2 H, 5-H), 3.12 (d, $^3J_{H,H}$ = 6.5 Hz, 1 H, OH), 3.27–3.32 (m, 1 H, 2-H), 3.64–3.70 (m, 1 H, 3-H), 3.75 (dd, $^3J_{H,H}$ = 9.8, 3.8 Hz, 1 H, 1-H), 3.91 (dd, $^3J_{H,H}$ = 9.8, 4.1 Hz, 1 H, 1-H), 3.98 (d, $^3J_{H,H}$ = 8.5 Hz, 1 H, NH), 4.48 (d, $^3J_{H,H}$ = 11.8 Hz, 1 H, CH_2Ph), 4.57 (d, $^3J_{H,H}$ = 11.8 Hz, 1 H, CH_2Ph), 7.25–7.35 (m, 5 H, Ar-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 13.9, 18.7, 22.4, 22.5 (3 C), 27.5, 27.6, 28.7, 28.8, 29.1, 29.2, 29.3, 31.7, 41.7, 55.9, 59.7, 70.1, 71.7, 73.3, 80.7, 94.5, 127.7 (3 C), 128.3 (2 C), 137.4, 187.7 ppm. IR (film): $\tilde{\nu}$ = 3376, 2925, 2855, 2210, 1672, 1453, 1364, 1193, 1051, 784 cm^{-1}. HRMS (ESI): calcd. for $C_{29}H_{47}NNaO_4S$ $[M + Na]^+$ 528.3118; found 528.3123.

(–)-Deoxoprosophylline (2): A HCl/MeOH solution (4 M, 3.0 mL) was added at room temperature under N_2 to a solution of compound **16** (90 mg, 0.18 mmol) in MeOH (3.0 mL). After having been stirred for 4 h, the reaction mixture was concentrated and the residue was dissolved in CH_2Cl_2 (20 mL). The resulting solution was washed successively with a saturated aqueous solution of Na_2CO_3 and brine, dried with Na_2SO_4, filtered, and concentrated. The residue was dissolved in EtOH (2.0 mL). Concd. HCl (0.10 mL) and 20% $Pd(OH)_2$/C (50 mg) were added to the solution. The mixture was stirred under hydrogen (80 psi) for 24 h. The catalyst was filtered off through a Celite pad, and the pad was washed with EtOH. The filtrates were concentrated, and the residue was dissolved in water (5 mL) and extracted with diethyl ether (10 mL). The aqueous layer was basified by addition of an aqueous solution of NaOH (1 M) and extracted thoroughly with $CHCl_3$ (10 mL × 5). The combined organic layers were dried with Na_2SO_4, filtered, and concentrated. The residue was purified by chromatography on silica gel ($CHCl_3$/MeOH/NH_4OH 100:5:1) to afford (–)-deoxoprosophylline (**2**) as a pale yellow solid (43 mg, 81%), which was recrystallized from acetone to give a white solid, m.p. 88–89 °C (acetone) (lit.[16a] 90–91 °C). $[\alpha]_D^{20}$ = –16.4 (*c* = 1.0, $CHCl_3$) [lit.[16r] $[\alpha]_D^{25}$ = –15.9 (*c* = 0.62, $CHCl_3$)]. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C, TMS): δ = 0.87 (t, $^3J_{H,H}$ = 6.9 Hz, 3 H, 12′-CH_3), 1.11–1.34 [m, 24 H, 3-H, 4-H, (1′-11′)-H], 1.72–1.75 (m, 1 H, 4-H), 1.99–2.04 (m, 1 H, 3-H), 2.48–2.55 (m, 2 H, 1-H, 5-H), 3.13 (br. s, 3 H, all are exchangeable with D_2O, OH, NH), 3.43 (ddd, $^3J_{H,H}$ = 10.8, 9.4, 4.6 Hz, 1 H, 2-H), 3.68 (dd, $^3J_{H,H}$ = 10.9, 5.6 Hz, 1 H, CH_2O), 3.81 (dd, $^3J_{H,H}$ = 10.9, 4.5 Hz, 1 H, CH_2O) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C, TMS): δ = 14.1, 22.6, 26.2, 29.3, 29.6 (3 C), 29.7 (2 C), 29.8, 30.8, 31.9, 33.6, 36.4, 55.9, 63.2, 63.6, 69.5 ppm. IR (film): $\tilde{\nu}$ = 3266, 3176, 2920, 2850, 1467, 1454, 1193, 1056, 784 cm^{-1}. HRMS (ESI): calcd. for $C_{18}H_{38}NO_2$ $[M + H]^+$ 300.2897; found 300.2899.

(*R*$_S$,2*S*,3*R*,4*S*,5*S*)-5-[(Benzyloxymethyl)(*tert*-butylsulfinylamino)-methyl]-3,4-dihydroxyfuran-2(4*H*)-one (17): $KMnO_4$ (350 mg, 2.21 mmol) was added in small portions at –40 °C to a vigorously stirred solution of compound **13a** (610 mg, 1.81 mmol) and 18-crown-6 (100 mg, 0.36 mmol) in CH_2Cl_2 (10.0 mL). The reaction mixture was then stirred for 6 h at the same temperature. The reaction was quenched with $Na_2S_2O_3{\cdot}5H_2O$ (820 mg, 3.30 mmol), and the mixture was carefully acidified with a solution of HCl (2 M). It was then extracted with CH_2Cl_2 (10 mL × 3), dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: EtOAc) to afford the starting material **13a** (61 mg, 10%) and the desired compound **17** (434 mg, 68%) as a white solid, m.p. 65–66 °C. $[\alpha]_D^{20}$ = –25.1 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.21 (s, 9 H, *t*Bu), 1.87 (s, 2 H, OH), 3.47–3.55 (m, 1 H, 5-H), 3.60–3.65 (m, 1 H, 4-H), 3.75 (dd, $^3J_{H,H}$ = 9.8, 4.1 Hz, 1 H, 6-H), 3.81 (dd, $^3J_{H,H}$ = 9.8, 3.0 Hz, 1 H, 6-H), 4.42–4.48 (m, 2 H, 2-H, 3-H), 4.50 (d, $^3J_{H,H}$ = 8.1 Hz, 1 H, NH), 4.52 (d, $^3J_{H,H}$ = 11.1 Hz, 1 H, CH_2Ph), 4.57 (d, $^3J_{H,H}$ = 11.1 Hz, 1 H, CH_2Ph), 7.29–7.37 (m, 5 H, Ar-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 22.5 (3 C), 56.3, 56.6, 68.4, 68.5, 69.4, 73.4, 84.4, 127.7 (2 C), 127.8, 128.4 (2 C), 137.3, 175.8 ppm. IR (film): $\tilde{\nu}$ = 3303, 2963, 2925, 2868, 1781, 1449, 1379, 1130, 1047 cm^{-1}. HRMS (ESI): calcd. for $C_{17}H_{25}NO_6S$ $[M + Na]^+$ 394.1300; found 394.1294.

(3*S*,4*S*,5*S*,6*S*)-6-Benzyloxymethyl-3,4,5-trihydroxypiperidin-2-one (21): A solution of HCl (12 M, 0.67 mL, 8.0 mmol) was added to a stirred solution of compound **17** (297 mg, 0.80 mmol) in 1,4-dioxane (4.0 mL). The reaction mixture was stirred at room temperature for 5 h and then concentrated under reduced pressure. The residue was dissolved in dry MeOH (4.0 mL), and anhydrous K_2CO_3 (552 mg, 4.0 mmol) was added at room temperature. After having been stirred overnight, the mixture was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: CH_2Cl_2/MeOH 5:1) to give compound **21** (160 mg, 75%) as a colorless oil. $[\alpha]_D^{20}$ = –56.5 (*c* = 1.0, MeOH). ^{1}H NMR (400 MHz, CD_3OD, 25 °C, TMS): δ = 3.62 (dd, $^3J_{H,H}$ = 9.2, 5.9 Hz, 1 H, 7-H), 3.67 (ddd, $^3J_{H,H}$ = 8.3, 5.9, 2.2 Hz, 1 H, 6-H), 3.73 (dd, $^3J_{H,H}$ = 9.2, 2.2 Hz, 1 H, 7-H), 3.87 (dd, $^3J_{H,H}$ = 8.3, 2.0 Hz, 1 H, 5-H), 4.05 (d, $^3J_{H,H}$ = 2.6 Hz, 1 H, 3-H), 4.15 (dd, $^3J_{H,H}$ = 2.6, 2.0 Hz, 1 H, 4-H), 4.59 (br. s, 2 H, CH_2Ph), 5.50 (s, 1 H, NH), 7.27–7.39 (m, 5 H, Ar-H) ppm. ^{13}C NMR (100 MHz, CD_3OD, 25 °C, TMS): δ = 54.0, 65.8, 68.0, 69.1, 71.1, 72.3, 126.6 (2 C), 126.8, 127.3 (2 C), 137.3, 172.4 ppm. IR (film): $\tilde{\nu}$ = 3332, 2913, 2859, 1661, 1453, 1300, 1105 cm^{-1}. HRMS (ESI): calcd. for $C_{13}H_{17}NO_5$ $[M + Na]^+$ 290.1004; found 290.1003.

(*R*$_S$,3*R*,4*S*,5*S*)-5-[(Benzyloxymethyl)(*tert*-butylsulfinylamino)-methyl]-4-hydroxyfuran-2(4*H*)-one (22): A solution of freshly prepared SmI_2 in THF (0.1 M, 30.0 mL, 3.0 mmol) was added slowly to a degassed THF solution (10.0 mL) of compound **17** (278 mg, 0.75 mmol), ethylene glycol (0.57 mL, 9.0 mmol), and hexamethylphosphoric triamide (HMPA, 1.2 mL, 6.9 mmol) in THF. The mixture was stirred at room temperature for 10 h. The reaction was quenched with a saturated aqueous solution of $NaHCO_3$ (2 mL), and the mixture was diluted with diethyl ether (10 mL). The organic phase was separated, washed with a saturated aqueous solution of $Na_2S_2O_3$, dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: EtOAc/hexane 6:1) to give compound **22** (218 mg, 82%) as a colorless oil. $[\alpha]_D^{20}$ = –6.0 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.22 (s, 9 H, *t*Bu), 2.59 (dd, $^3J_{H,H}$ = 17.9, 6.3 Hz, 1 H, 2-H), 2.81 (dd, $^3J_{H,H}$ = 17.9, 7.8 Hz, 1 H, 2-H), 3.56 (br. s, 1 H, OH), 3.59–3.66

(m, 1 H, 5-H), 3.82 (dd, $^3J_{H,H}$ = 9.8, 3.8 Hz, 1 H, 6-H), 3.88 (dd, $^3J_{H,H}$ = 9.8, 2.9 Hz, 1 H, 6-H), 3.97 (d, $^3J_{H,H}$ = 8.3 Hz, 1 H, NH), 4.36 (dd, $^3J_{H,H}$ = 5.3, 5.1 Hz, 1 H, 4-H), 4.46–4.52 (m, 1 H, 3-H), 4.54 (d, $^3J_{H,H}$ = 11.5 Hz, 1 H, CH_2Ph), 4.62 (d, $^3J_{H,H}$ = 11.5 Hz, 1 H, CH_2Ph), 7.32–7.41 (m, 5 H, Ar-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 22.6 (3 C), 36.9, 56.5, 56.9, 67.9, 70.4, 74.0, 86.8, 128.0 (2 C), 128.3, 128.7 (2 C), 136.8, 173.9 ppm. IR (film): $\tilde{\nu}$ = 3303, 2917, 2868, 1781, 1453, 1362, 1175, 1047 cm^{-1}. HRMS (ESI): calcd. for $C_{17}H_{25}NO_5S$ [M + Na]$^+$ 378.1351; found 378.1358.

(4*R*,5*S*,6*S*)-6-(Benzyloxymethyl)-4,5-dihydroxypiperidin-2-one (23): A solution of HCl (12 M, 0.50 mL, 6.0 mmol) was added to a stirred solution of compound **22** (213 mg, 0.60 mmol) in 1,4-dioxane (4 mL). The reaction mixture was stirred at room temperature for 5 h and then concentrated under reduced pressure. The residue was dissolved in dry MeOH (4 mL), and anhydrous K_2CO_3 (414 mg, 3.0 mmol) was added at room temperature. After having been stirred overnight, the mixture was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: CH_2Cl_2/MeOH 6:1) to give compound **23** (121 mg, 80%) as a colorless oil. $[\alpha]_D^{20}$ = –33.5 (*c* = 1.0, $CHCl_3$). ^1H NMR (400 MHz, D_2O, 25 °C, TMS): δ = 2.40 (dd, $^3J_{H,H}$ = 18.1, 5.0 Hz, 1 H, 3-H), 2.58 (dd, $^3J_{H,H}$ = 18.1, 4.4 Hz, 1 H, 3-H), 3.55–3.64 (m, 2 H, 7-H), 3.65–3.70 (m, 1 H, 6-H), 3.87 (dd, $^3J_{H,H}$ = 7.1, 2.5 Hz, 1 H, 5-H), 4.10 (ddd, $^3J_{H,H}$ = 5.0, 4.4, 2.5 Hz, 1 H, 4-H), 4.56 (br. s, 2 H, CH_2Ph), 7.32–7.40 (m, 5 H, Ar-H) ppm. ^{13}C NMR (100 MHz, D_2O, 25 °C, TMS): δ = 37.0, 53.5, 66.8, 68.3, 71.3, 73.4, 127.7 (2 C), 127.9, 128.5 (2 C), 137.4, 171.0 ppm. IR (film): $\tilde{\nu}$ = 3299, 2917, 2868, 1640, 1449, 1399, 1317, 1068 cm^{-1}. HRMS (ESI): calcd. for $C_{13}H_{17}NO_4$ [M + Na]$^+$ 274.1055; found 274.1057.

Supporting Information (see footnote on the first page of this article): ^1H and ^{13}C NMR spectra of compounds **2**, **16**, **17**, **21**, **22**, **23**.

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