Efficient Synthesis of Tetrahydroxylated Pyrrolizidines by Nitrone Cycloaddition Leading to Unnatural Stereoisomers of 7-Deoxycasuarine

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Dedicated to Professor Heinz Heimgartner on the occasion of his 70th birthday

Abstract: A convenient and efficient method has been used for the synthesis of ten new tetrahydroxylated pyrrolizidines **12a**,**b**, **13a**–**c**, **14a**,**b**, and **15a**–**c** starting from sugar-derived cyclic nitrones prepared from D-xylose, D-arabinose, D-ribose, and L-arabinose, through a five-step reaction sequence. Pyrrolizidine **12a** is an enantiomer of 7-deoxycasuarine and pyrrolizidine **12b** an enantiomer of the as yet unknown 7-deoxyuniflorine A. This method expands the scope of nitrone cycloadditions and is flexible enough for the synthesis of various stereoisomers of highly polyhydroxylated pyrrolizidines.

Key words: sugar-derived cyclic nitrones, cycloaddition, iminosugars, pyrrolizidines, stereoselective synthesis

Iminosugars are monosaccharide analogues with nitrogen instead of oxygen in the ring. Due to the structural resemblance of polyhydroxylated alkaloids to carbohydrates, they are considered as sugar mimics and many of them exhibit promising glycosidase[1] and glycosyltransferase[2] activity, making them potential drug candidates against viral infections, cancer, and diabetes.[3] Among naturally occuring iminosugars, the rapidly expanding class of polyhydroxylated pyrrolizidines[4] has attracted significant attention because of the selective inhibitory activity associated with several of these alkaloids.[1] For example, in the polyhydroxylated pyrrolizidine class alexine (**1**) has been shown to exhibit antiviral and anti-HIV activity,[5] hyacinthacine A_2 (**2**) was found to be a selective inhibitor of amyloglucosidase[6] (*Aspergilus niger*), and 7-deoxycasuarine (**3**, Figure 1) showed specific and competitive inhibition activity against amyloglucosidase (*Rhizopus* mould).[4b–e]

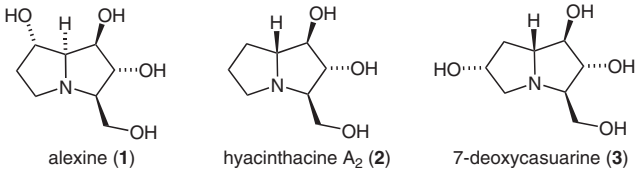

Figure 1 Selected polyhydroxylated pyrrolizidines

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Nitrones have become important building blocks in organic synthesis.[7] During recent years we have developed protocols for the preparation of optically active nitrone templates for asymmetric 1,3-dipolar cycloadditions.[8] Enantiomerically pure polyfunctional cyclic nitrones, which have been widely used in the synthesis of various natural and biologically active nitrogen-containing compounds, are especially valuable in the synthesis of pyrrolizidines.[4]

Since the biological activity varies with the position and stereochemistry of the hydroxy groups on the pyrrolizidine skeleton,[1a] and as only a few syntheses of 3-(hydroxymethyl)-pyrrolizidine-1,2,6-triol skeletons have been reported to date,[6,7] we have focused our attention upon developing a simple and efficient route for the synthesis of these biologically important polyhydroxylated alkaloids. In this communication we wish to describe a synthetic strategy based on 1,3-dipolar cycloaddition of chiral sugar-derived cyclic nitrones **4**–**7** (Figure 2), recently described by Yu and coworkers,[9] with methyl acrylate followed by subsequent N–O bond cleavage accompanied with spontaneous cyclization into the pyrrolizidine skeleton.

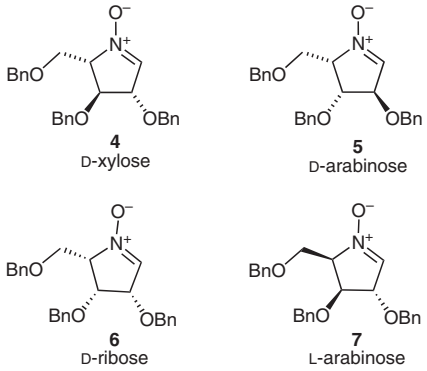
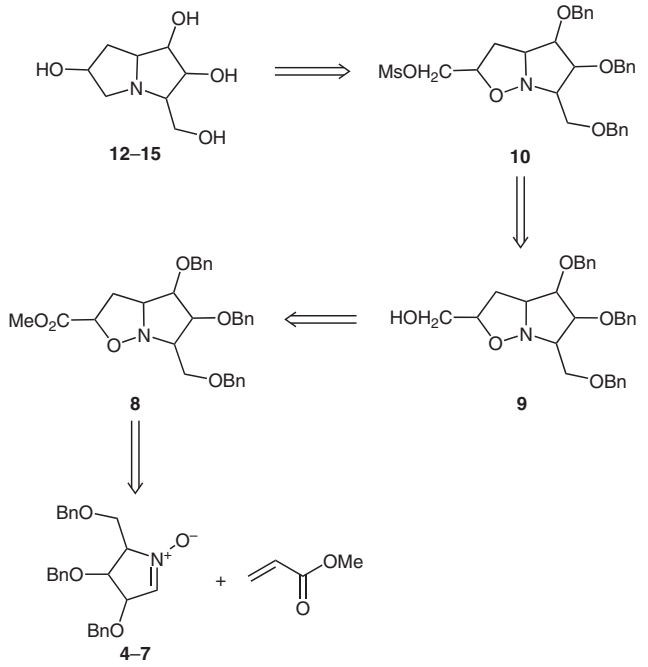


Figure 2 Sugar-derived nitrones

The retrosynthetic analysis is shown in Scheme 1, where 1,3-dipolar cycloaddition of chiral nitrones **4**–**7** derived from corresponding sugars with methyl acrylate provides fused isoxazolidine **8**, which can be converted into a corresponding hydroxymethyl derivative **9**. Following acti-

vation with mesyl chloride gives mesylate **10**, subsequent N–O bond cleavage allows the synthesis of pyrrolizidine skeleta **12–15** after cyclization.

The proposed synthetic plan, which in principle allows access to all stereoisomers of 3-hydroxymethyl-2,3,5,6,7,7a-hexyhydro-1*H*-pyrrolizine-1,2,6-triol (**12–15**), if realized, could be quite general and flexible since a variety of analogues of 7-deoxycasuarine (**3**) might be accessible by diversifying the starting carbohydrate-derived nitrones.



Scheme 1 Retrosynthetic analysis

Sugar-derived cyclic nitrones **4–7** were synthesized from the corresponding aldoses following an efficient and practical procedure described by Yu et al.[9] We have modified this procedure using *O*-*tert*-butyldiphenylsilylhydroxylamine[10] instead of NH_2OMe and TBAT[11] for the cyclization, and this provided nitrone **4** with an increased yield of 74%. This improved procedure was successfully extended to the synthesis of nitrones **5–7**.

The nitrone **4** was then treated with methyl acrylate in THF at room temperature for 24 hours to give a mixture of *anti*-stereoisomers **8a** and **8b** in a ratio of 80:20 and combined yield of 88%. The crude esters **8a** and **8b** (Scheme 2) were used directly in the reduction with DIBAL in THF at 0 °C to room temperature without further purification. After quenching with aqueous Rochelle salt and extraction (EtOAc), the hydroxymethylderivates **9a** and **9b** were separated by MPLC on silica gel (EtOAc–hexanes = 33:66) to give diastereomerically pure *anti-trans*-isoxazolidine **9a** as the major isomer and *anti-cis*-isomer **9b** as the minor isoxazolidine in a combined yield of 92%. The major isomer **9a** was subsequently treated with mesyl chloride and Et_3N in CH_2Cl_2 to furnish mesylate **10a** in 86% yield. Exposing **10a** to Zn in aqueous acetic acid for N–O bond cleavage led to the formation of pyrrolizidine **11a** in 93% yield after neutralization with a saturated solution of K_2CO_3, extraction (EtOAc) and purification on silica gel (EtOAc). Deprotection of the benzyl groups was achieved with H_2 on Pd/C (10 mol%) in MeOH and HCl at 50 °C overnight, to furnish the desired polyhydroxylated pyrrolizidine **12a** in 99% yield (Scheme 2). The synthesis of **12a** has thus been achieved in five steps with an overall yield of 51% from nitrone **4**.

Following the same four-step reaction sequence, the minor pyrroloisoxazolidine **8b** was analogously transformed into pyrrolizidine **12b**, an enantiomer of the as yet unknown 7-deoxyuniflorine A (Scheme 2). The latter two pyrrolizidines **12a** and **12b** are epimeric at C-6, and pyrrolizidine **12a** {$[\alpha]_D^{25}$ –14.2 (*c* 0.4, MeOH)} is the enantiomer of 7-deoxycasuarine, a more selective inhibitor[4c] than casuarine, alexine, or australine. 7-Deoxycasuarine (**3**) has been synthesized by Behr[12] {$[\alpha]_D^{20}$ +10.9 (*c* 0.11, H_2O)}, Goti[4b,e] {$[\alpha]_D^{20}$ +19.8 (*c* 0.26, H_2O)} and Carmona, Vogel, and co-workers[4c] {$[\alpha]_D^{25}$ +23 (*c* 0.3, MeOH)} by a strategy employing a nitrone prepared from commercially available tribenzyl D-arabinose.

The relative configurations of the new compounds were assigned on the basis of NOESY experiments of **9a**, **10a**, **11b**, and **12b** (Figure 3). The observed interactions H-4b/H-5 and H-4a/H-3 of hydroxymethyl derivate **9a** indicate a *trans* relation between H-3 and H-5. The *anti* configuration between H-3 and H-6 was established by means of a negative mutual interaction between these protons. The H-3/H-6 *anti* configuration was also assigned through H-3/H-4a and H-6/H4b interactions of mesylate **10a**. The *anti-cis* configuration of the minor cycloadduct **8b** was assigned by correlation with pyrrolizidine **11b**, whose relative C6/C8 *trans* configuration was determined on the basis of H-7β/H-6, H-7α/H-7a interactions. The C1/C7a *anti* configuration could be seen from H-7β/H-1, H-7α/H-7a, and H-1/H-3 interactions in addition to negative H-1/H-7a interaction. NOE studies of the final pyrrolizidine **12b** proved the *trans* configuration by H-6/H-7β, H-7a/H-7α, and C1/C7a interactions and the *anti* configuration

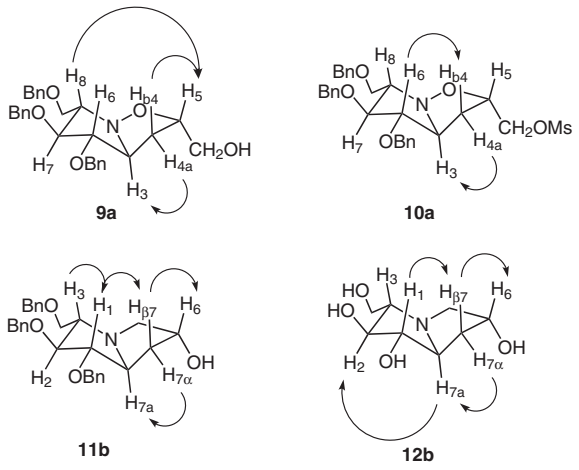
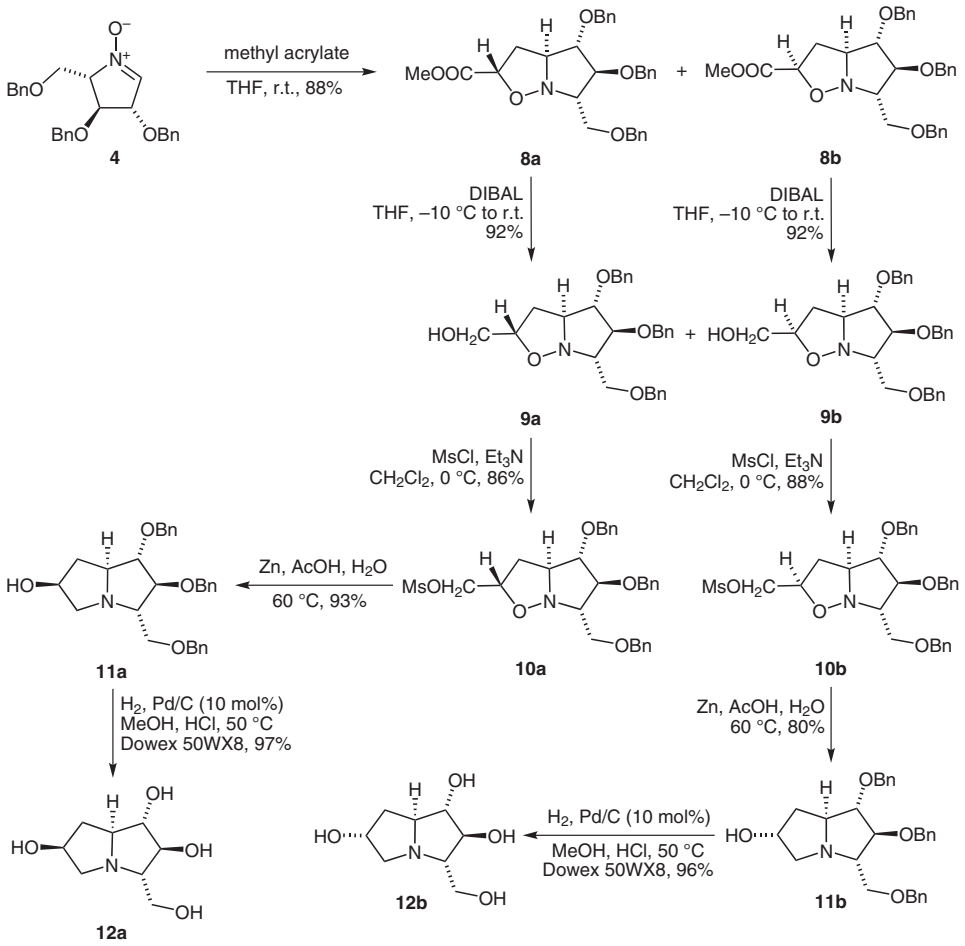


Figure 3 NOE experiments



Scheme 2

was confirmed by H-7α/H-7a, H-7β/H-1, H-7a/H-2 interactions as well as by a negative H-1/H-7a interaction. Subsequent X-ray analysis[13–16] of the benzylated pyrrolizidine **11b** confirmed the configuration of the new stereogenic centers at C1, C2, C3, C6, and C7a (Figure 4).

Subsequently, following the same five-step reaction sequence, the pyrroloisoxazolidines **8** prepared from chiral cyclic nitrones **5**–**7** derived from corresponding sugars (D-arabinose, D-ribose, and L-arabinose; Figure 2) with methyl acrylate were analogously transformed into the novel tetrahydroxylated pyrrolizidines **13a**–**c**, **14a**,**b**, and **15a**–**c** (Figure 5).[17]

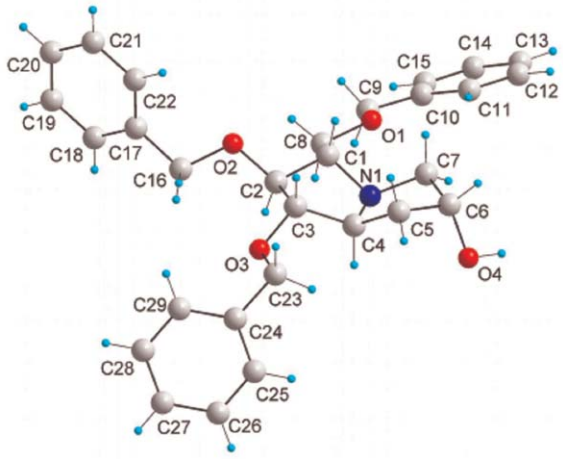


Figure 4 The molecular structure of **11b**, with the numbering scheme[16] of the asymmetric unit. Displacement ellipsoids are drawn at the 50% probability level.

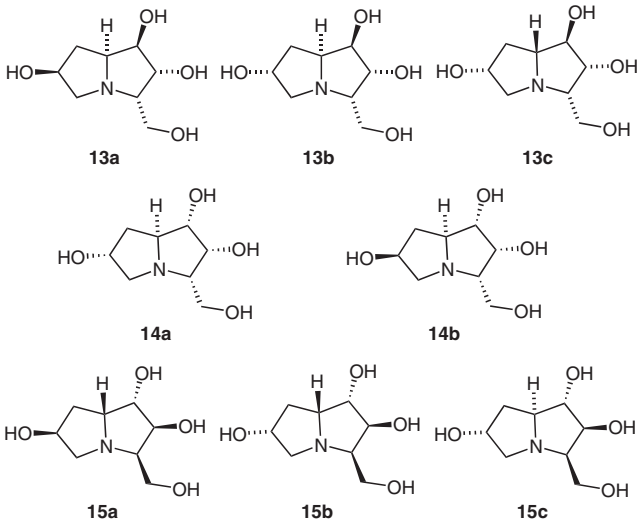


Figure 5 Novel non-natural tetratetrahydroxylated pyrrolizidines

In conclusion, a convenient and efficient method has been developed for the synthesis of a series of new tetrahydroxylated pyrrolizidines **12a**,**b**, **13a–c**, **14a**,**b**, and **15a–c** starting from sugar-derived cyclic nitrones prepared from D-xylose, D-arabinose, D-ribose, and L-arabinose, through a five-step reaction sequence. Pyrrolizidine **12a** is an enantiomer of 7-deoxycasuarine and pyrrolizidine **12b**, an enantiomer of the as yet unknown 7-deoxyuniflorine A. This method expands the scope of nitrone cycloadditions and is flexible for the synthesis of various stereoisomers of highly polyhydroxylated pyrrolizidines.

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References and Notes

(1) (a) Tyler, P. C.; Winchester, B. G. In *Iminosugars as Glycosidase Inhibitors. Nojirimycin and Beyond.*; Stütz, A. E., Ed.; Wiley-VCH: Weinheim, **1999**. (b) Asano, N.; Nash, R. J.; Molyneux, R. J.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2000**, *11*, 1645.

(2) Compain, P.; Martin, O. R. *Curr. Top. Med. Chem.* **2003**, *3*, 541.

(3) (a) Pearson, M. S. M.; Mathé-Allainmat, M.; Fargeas, J.; Lebreton, J. *Eur. J. Org. Chem.* **2005**, 2159. (b) Watson, A. A.; Fleet, G. W. J.; Asano, N.; Molyneux, R. J.; Nash, R. J. *Phytochemistry* **2001**, *56*, 265. (c) Asano, N.; Kato, A.; Watson, A. A. *Mini-Rev. Med. Chem.* **2001**, *1*, 145.

(4) (a) Yoda, H. *Curr. Org. Chem.* **2002**, *6*, 223. (b) Cardona, F.; Faggi, E.; Cignori, F.; Cacciarini, M.; Goti, A. *Tetrahedron Lett.* **2003**, *44*, 2318. (c) Carmona, A. T.; Whigtman, R. H.; Robina, I.; Vogel, P. *Helv. Chim. Acta* **2003**, *86*, 3066. (d) Brandi, A.; Cardona, F.; Cicchi, S.; Cordero, F. M.; Goti, A. *Chem. Eur. J.* **2009**, *15*, 7808. (e) Bonaccini, C.; Chioccioli, M.; Parmeggiani, C.; Lo Re, D.; Soldaini, G.; Vogel, P.; Bello, C.; Goti, A.; Gratteri, P. *Eur. J. Org. Chem.* **2010**, 5574. (f) Hu, X.-G.; Jia, Y.-M.; Xiang, J.; Yu, C.-Y. *Synlett* **2010**, 982. (g) Kubán, J.; Kolarovič, A.; Fišera, L.; Jäger, V.; Humpa, O.; Prónayová, N. *Synlett* **2001**, 1866. (h) Reddy, P. V.; Kooš, P.; Veyron, A.; Greene, A. E.; Delair, P. *Synlett* **2009**, 1141. (i) Tamayo, J. A.; Lo Re, D.; Sánchez-Cantalejo, F. *J. Org. Chem.* **2009**, *74*, 5679. (j) Desvergnes, S.; Py, S.; Vallée, Y. *J. Org. Chem.* **2005**, *70*, 1459. (k) Argyropoulos, N. G.; Gkizis, P.; Coutoli-Argyropoulos, E. *Tetrahedron* **2008**, *64*, 8752. (l) Delso, I.; Tejero, T.; Goti, A.; Merino, P. *Tetrahedron* **2010**, *66*, 1220. (m) Koch, D.; Maechling, S.; Blechert, S. *Tetrahedron* **2007**, *63*, 7112.

(5) Taylor, D. L.; Nash, R. J.; Fellows, L. E.; Kang, M. S.; Tyms, A. S. *Antiviral Chem. Chemother.* **1992**, *3*, 273.

(6) Asano, N.; Kuroi, H.; Ikeda, K.; Kizu, H.; Kameda, Y.; Kato, A.; Adachi, I.; Watson, A. A.; Nash, R. J.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2000**, *11*, 1.

(7) (a) Frederickson, M. *Tetrahedron* **1997**, *53*, 403. (b) Gothelf, K. V.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 863. (c) Merino, P.; Franco, S.; Merchan, F. L.; Romero, P.; Tejero, T.; Uriel, T. S. *Tetrahedron: Asymmetry* **2003**, *14*, 3731. (d) Osborn, H. M. I.; Gemmel, N.; Harwood, L. M. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2419. (e) Koumbis, A. E.; Gallos, J. K. *Curr. Org. Chem.* **2003**, *7*, 585. (f) Pellissier, H. *Tetrahedron* **2007**, *63*, 3235. (g) Fišera, L. In *Topics in Heterocyclic Chemistry. Heterocycles from Carbohydrate Precursors*; El Ashry, E. S. H., Ed.; Springer: Berlin, **2007**, 287.

(8) (a) Kubán, J.; Blanáriková, I.; Fišera, L.; Jarošková, L.; Fengler-Veith, M.; Jäger, V.; Kožíšek, J.; Humpa, O.; Prónayová, N.; Langer, V. *Tetrahedron* **1999**, *55*, 9501. (b) Fischer, R.; Drucková, A.; Fišera, L.; Rybár, A.; Hametner, C.; Cyrański, M. K. *Synlett* **2002**, 1113. (c) Kubán, J.; Kolarovič, A.; Fišera, L.; Jäger, V.; Humpa, O.; Prónayová, N.; Ertl, P. *Synlett* **2001**, 1862. (d) Blanáriková-Hlobilová, I.; Kopaničáková, Z.; Fišera, L.; Cyrański, M. K.; Salanski, P.; Jurczak, J.; Prónayová, N. *Tetrahedron* **2003**, *59*, 3333. (e) Fischer, R.; Drucková, A.; Fišera, L.; Hametner, C. *ARKIVOC* **2002**, *(viii)*, 80. (f) Dugovič, B.; Fišera, L.; Cyranski, M. K.; Hametner, C.; Prónayová, N.; Obranec, M. *Helv. Chim. Acta* **2005**, *88*, 1432. (g) Rehák, J.; Fišera, L.; Kožíšek, J.; Perašínová, L.; Steiner, B.; Kooš, M. *ARKIVOC* **2008**, *(viii)*, 18. (h) Rehák, J.; Fišera, L.; Podolan, G.; Kožíšek, J.; Perašínová, L. *Synlett* **2008**, 1260. (i) Rehák, J.; Fišera, L.; Prónayová, N. *ARKIVOC* **2009**, *(vi)*, 146.

(9) Wang, W. B.; Huang, M. H.; Li, Y. X.; Rui, P. X.; Hu, X. G.; Zhang, W.; Su, J. K.; Zhang, Z. L.; Zhu, J. S.; Xu, W. H.; Xie, X. Q.; Jia, Y. M.; Yu, Ch. I. *Synlett* **2010**, 488.

(10) Denmark, S. E.; Dappen, M. S.; Sear, N. L.; Jacobs, R. T. *J. Org. Chem.* **1990**, *112*, 3466.

(11) Tamura, O.; Toyao, A.; Ishibashi, H. *Synlett* **2002**, 1344.

(12) Behr, B. J.; Erard, A.; Guillerm, G. *Eur. J. Org. Chem.* **2002**, 1256.

(13) **Crystal Data of Compound 11b**
$C_{29}H_{33}NO_4$, M = 459.56, monoclinic, $P2_1$, a = 13.197 (2) Å, b = 6.0914 (4) Å, c = 16.757 (3) Å, V = 1257.0(2) Å^3, Z = 2, D_x = 1.214 Mg m^{-3}, μ (Cu Kα) = 0.639 mm^{-1}, F(000) = 492, colorless block, 0.152 × 0.228 × 0.860 mm^{-3}, 15292 diffractions measured (R_{int} = 0.026), 4082 unique, $wR2$ = 0.0759, conventional R = 0.0284 on I values of 4032 diffractions with $I > 2.0\,\sigma(I)$, $(\Delta/\sigma)_{max}$ = 0.001, S = 1.039 for all data and 311 parameters. Unit cell determination and intensity data collection (θ_{max} = 74.87°) were performed on a Gemini R diffractometer[14] at 100 (1) K. Structure solution was done using direct methods[15] and refinements were achieved by full-matrix least-squares method[15] on F**2. Further details of the crystal structure investigation can be obtained from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK (CCDC deposition no. 818367).

(14) Oxford Diffraction(2010). CrysAlis PRO. Oxford Diffraction Ltd, Abingdon, England.

(15) Sheldrick, G. M. *Acta Crystallogr., Sect. A: Found. Crystallogr.* **2008**, *46*, 112.

(16) Brandenburg, K. *DIAMOND*; Crystal Impact GbR: Bonn, **2006**.

(17) **Typical Experimental Procedure for Cycloaddition**
The nitrone (5.39 mmol) was dissolved in THF (50 mL) and methyl acrylate was added (21.56 mmol). The mixture was stirred for 48 h at r.t. The mixture was then concentrated under reduced pressure, and the residue was purified by MPLC (EtOAc–hexanes = 33:66).
Representative Data for Products
Compound **9a**: $[\alpha]_D^{25}$ +41.6 ($CHCl_3$, c 3.04). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.35–7.23 (m, 15 H, OCH_2Ph), 4.60–4.48 (m, 6 H, OCH_2Ph), 4.29 (m, 1 H, H-5), 4.04 (dd, 1 H, H-7, J = 3.9, 5.6 Hz), 3.96 (dd, 1 H, H-6, J = 3.9 Hz), 3.75 (m, 2 H, H-3, H-10b), 3.66 (dd, 1 H, H-9b, J = 4.7, 10.0 Hz), 3.60 (dd, 1 H, H-9a, J = 5.6, 10.0 Hz), 3.55 (dd, 1 H, H-10a,

J = 4.5, 12.3 Hz), 3.33 (dd, 1 H, H-8, *J* = 5.6, 10.8 Hz), 2.32 (ddd, 1 H, H-4b, *J* = 7.3, 8.8, 15.8 Hz), 2.16 (ddd, 1 H, H-4a, *J* = 5.6, 7.3, 12.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.2–127.5 (OCH_2*Ph*), 87.1 (C-6), 83.8 (C-7), 77.2 (C-5), 73.3, 72.3, 71.7 (O*C*H_2Ph), 69.7 (C-9), 69.6 (C-8), 68.5 (C-3), 63.1 (C-10), 35.4 (C-4). IR: 3238, 3032, 2921, 2852, 1496, 1454, 1357, 1143, 1093, 1078, 1025, 738, 695 cm^{-1}. TOF MS (ESI): *m/z* calcd for $C_{29}H_{34}NO_5$ [MH$^+$]: 476.2437; found: 476.2433.

Compound **10a**: $[\alpha]_D^{25}$ +40.0 ($CHCl_3$, *c* 0.71); mp 93–95 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.37–7.23 (m, 15 H, OCH_2*Ph*), 4.56–4.50 (m, 6 H, O*C*H_2Ph), 4.43 (m, 1 H, H-5), 4.24 (m, 2 H, H-10a, H-10b), 4.03 (dd, 1 H, H-7, *J* = 3.8, 5.8 Hz), 3.96 (dd, 1 H, H-6, *J* = 3.8 Hz), 3.75 (ddd, 1 H, H-3, *J* = 3.8, 5.4, 8.9 Hz), 3.65 (dd, 1 H, H-9b, *J* = 5.0, 9.8 Hz), 3.57 (dd, 1 H, H-9a, *J* = 5.8, 9.8 Hz), 3.35 (dd, 1 H, H-8, *J* = 5.8, 10.9 Hz), 3.00 (s, 3 H, OMs), 2.25 (m, 2 H, H-4a, H-4b). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 138.1–127.5 (OCH_2*Ph*), 86.9 (C-6), 83.9 (C-7), 74.3 (C-5), 73.2, 72.1, 71.8 (O*C*H_2Ph), 70.0 (C-8), 69.7 (C-9), 69.3 (C-10), 68.2 (C-3), 37.5 (OMs), 35.6 (C-4). IR: 3027, 2880, 1497, 1454, 1336, 1178, 1101, 1074, 990, 964, 908, 819, 734, 694, 526 cm^{-1}. TOF MS (ESI): *m/z* calcd for $C_{30}H_{36}NO_7S$ [MH$^+$]: 554.2212; found: 554.2040.

Compound **11a**: $[\alpha]_D^{25}$ –10.3 ($CHCl_3$, *c* 2.10). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.40–7.24 (m, 15 H, OCH_2*Ph*), 4.75–4.55 (m, 6 H, O*C*H_2Ph), 4.36 (m, 1 H, H-6), 4.19 (dd, 1 H, H-1, *J* = 6.3 Hz), 3.98 (dd, 1 H, H-2, *J* = 6.3, 7.6 Hz), 3.63 (dd, 1 H, H-4b, *J* = 4.3, 9.4 Hz), 3.55 (dd, 1 H, H-4a, *J* = 6.6, 9.4 Hz), 3.50 (m, 2 H, H-3, H-8), 3.10 (dd, 1 H, H-5b, *J* = 3.9, 11.1 Hz), 2.95 (dd, 1 H, H-5a, *J* = 4.0, 11.1 Hz), 2.17 (ddd, 1 H, H-7β, *J* = 5.5, 8.3, 13.5 Hz), 1.90 (m, 1 H, H-7α). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 140.8–129.0 (OCH_2*Ph*), 90.9 (C-1), 87.1 (C-2), 74.9 (C-6), 74.7 (C-4), 74.5, 73.8, 73.4 (O*C*H_2Ph), 70.4 (C-3), 68.4 (C-7a), 64.1 (C-5), 41.9 (C-7). IR: 3383, 3030, 2858, 1496, 1453, 1363, 1100, 1067, 1027, 908, 733, 695, 607 cm^{-1}. TOF MS (ESI): *m/z* calcd. for $C_{29}H_{34}NO_4$ [MH$^+$]: 460.2488; found: 460.2181.

Compound **12a**: $[\alpha]_D^{25}$ –14.2 (MeOH, *c* 0.26). ^{1}H NMR (300 MHz, CD_3OD): δ = 4.55 (m, 1 H, H-6), 4.22 (dd, 1 H, H-1, *J* = 7.9 Hz), 3.87 (m, 3 H, H-2, H-4a, H-4b), 3.71 (m, 1 H, H-7a), 3.48 (m, 1 H, H-3), 3.35 (m, 2 H, H-5a, H-5b), 2.21 (m, 2 H, H-7α, H-7β). ^{13}C NMR (75 MHz, CD_3OD): δ = 81.4 (C-1), 76.6 (C-2), 73.5 (C-6), 73.1 (C-3), 69.5 (C-7a), 62.6 (C-5), 60.6 (C-4), 38.4 (C-7). IR: 3269, 2931, 1634, 1435, 1377, 1335, 1097, 1041, 988, 927, 860, 607, 511 cm^{-1}. TOF MS (ESI): *m/z* calcd for $C_{29}H_{34}NO_4$ [MH$^+$]: 190.1079; found: 190.1042.

Compound **13a**: $[\alpha]_D^{25}$ +20.4 (MeOH, *c* 0.83). ^{1}H NMR (300 MHz, CD_3OD): δ = 4.36 (m, 1 H, H-6), 4.20 (d, 1 H, H-2, *J* = 2.6 Hz), 4.08 (m, 1 H, H-7a), 3.95 (d, 1 H, H-1, *J* = 3.8 Hz), 3.85 (dd, 1 H, H-4b, *J* = 6.4, 11.1 Hz), 3.75 (dd, 1 H, H-4a, *J* = 6.7, 11.1 Hz), 3.30 (m, 1 H, H-3), 3.20 (dd, 1 H, H-5b, *J* = 4.1, 11.7 Hz), 2.87 (dd, 1 H, H-5a, *J* = 3.5, 11.7 Hz), 2.07 (m, 2 H, H-7α, H-7β). ^{13}C NMR (75 MHz, CD_3OD): δ = 79.6 (C-2), 77.0 (C-1), 73.9 (C-6), 72.0 (C-3), 68.9 (C-7a), 62.4 (C-5), 61.4 (C-4), 32.9 (C-7). IR: 3238, 2925, 2871, 1645, 1435, 1034, 1251, 1029, 908, 674, 608, 512 cm^{-1}. TOF MS (ESI): *m/z* calcd for $C_{29}H_{34}NO_4$ [MH$^+$]: 190.1079; found: 190.1005.

Compound **14a**: $[\alpha]_D^{25}$ +5.7 (MeOH, *c* 1.16). ^{1}H NMR (300 MHz, CD_3OD): δ = 4.51 (m, 1 H, H-6), 4.21 (dd, 1 H, *J* = 3.6 Hz, H-2), 3.91 (m, 2 H, H-4a, H-1), 3.75 (m, 2 H, H-4b, H-7a), 3.05 (m, 2 H, H-3, H-5a), 2.95 (dd, 1 H, *J* = 4.4, 11.4 Hz, H-5b), 2.07 (ddd, 1 H, *J* = 4.4, 7.3, 12.4 Hz, H-7β), 1.98 (ddd, 1 H, *J* = 4.4, 7.3, 12.4 Hz, H-7α). ^{13}C NMR (75 MHz, CD_3OD): δ = 79.2 (C-1), 75.4 (C-2), 73.3 (C-6), 72.5 (C-3), 68.8 (C-7a), 63.2 (C-5), 61.5 (C-4), 39.1 (C-7). IR: 3329, 3209, 2974, 2910, 2876, 2738, 2475, 2399, 1460, 1323, 1226, 1140, 1098, 1057, 1031, 965, 716, 407 cm^{-1}. TOF MS (ESI): *m/z* calcd for $C_{29}H_{34}NO_4$ [MH$^+$]: 190.1079; found: 190.1070.

Compound **15a**: $[\alpha]_D^{25}$ –15.8 (MeOH, *c* 1.00). ^{1}H NMR (600 MHz, CD_3OD): δ = 4.55 (m, 1 H, H-6), 4.29 (dt, 1 H, *J* = 3.9, 8.4 Hz, H-7a), 4.22 (m, 1 H, H-2), 3.96 (d, 1 H, *J* = 3.9 Hz, H-1), 3.85 (dd, 1 H, *J* = 5.8, 11.2 Hz, H-4a), 3.80 (dd, 1 H, *J* = 8.1, 11.2 Hz, H-4b), 3.27 (dd, 1 H, *J* = 2.7, 11.5 Hz, H-5a), 3.23 (ddd, 1 H, *J* = 3.4, 5.8, 8.1 Hz, H-3), 2.91 (dd, 1 H, *J* = 4.2, 11.5 Hz, H-5b), 2.33 (ddd, 1 H, *J* = 5.1, 7.3, 12.3 Hz, H-7α), 1.77 (ddd, 1 H, *J* = 3.4, 8.4, 12.3 Hz, H-7β). ^{13}C NMR (150 MHz, CD_3OD): δ = 80.2 (C-2), 75.7 (C-1), 74.7 (C-6), 72.5 (C-3), 69.9 (C-8), 63.6 (C-5), 60.5 (C-4), 32.6 (C-7). IR: 3261, 2927, 2866, 2709, 1417, 1309, 1282, 1231, 1036, 972, 916, 901, 773, 719, 592, 538 cm^{-1}. TOF MS (ESI): *m/z* calcd for $C_{29}H_{34}NO_4$ [MH$^+$]: 190.1079; found: 190.1132.