Synthesis of Trehazolin from D-Glucose

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Trehazolin (**2**) is a specific inhibitor of trehalase, an enzyme that cleaves the reserve carbohydrates of many insects. We describe a short and efficient synthesis of trehazolin (**2**) and trehazolamine (**5**) that mimics its hypothetical biosynthesis. Starting molecule for the synthesis of trehazolamine (**5**) is glucose from which three chiral centers are conserved during the reaction sequence. The remaining two chiral centers of trehazolamine (**5**) are formed stereoselectively in a reductive cyclization of ketooxime ether **16** and the reduction of oxime ether **18**. The overall yield of trehazolamine (**5**) is 22% over 8 steps from **15**. The synthesis of trehazolin (**2**) from trehazolamine (**5**) follows a known procedure and is achieved in 63% over 3 steps.

Introduction

The enzyme trehalase (α,α-trehalose glucosidase) plays an important role in the metabolism of insects and fungi because it cleaves trehalose (**1**), the characteristic blood sugar and reserve carbohydrate of many insects.[1] Thus, specific inhibitors of trehalase may find applications in the regulation of the metabolism of trehalose and function as insecticides. Trehazolin (**2**), first isolated in 1991 by Ando and co-workers[2] from the culture broth of *Micromonospora* strain SANK 62390, has been shown to be a potent and specific inhibitor of trehalase in vitro ($IC_{50} = 0.016\ \mu g/mL$ for silkworm trehalase). Therefore, it is not surprising that its total synthesis[3] and the elucidation of structure−activity relationships[4] have received much interest over the past 7 years. Trehazolin (**2**) closely resembles α,α-trehalose (**1**) (Figure 1) and possesses a pseudo-disaccharide structure composed of α-D-glucopyranosylamine and trehazolamine (**5**) linked by a cyclic isourea group. Thus, an obvious retrosynthesis (Scheme 1) of trehazolin (**2**) leads to two subunits: an α-D-glucopyranosyl isothiocyanate (**3**), which can be easily generated from 1,6-anhydro-β-D-glucose (**4**),[3c,5] and the aminocyclopentitol **5**, whose synthesis turned out to be a much more difficult task. Several syntheses of this highly functionalized molecule **5** have already been published,[3c−e,6] but all existing preparations involve multistep syntheses and modest overall yields. The known synthetic procedures have scarcely taken advantage of the given stereochemistry of starting materials.

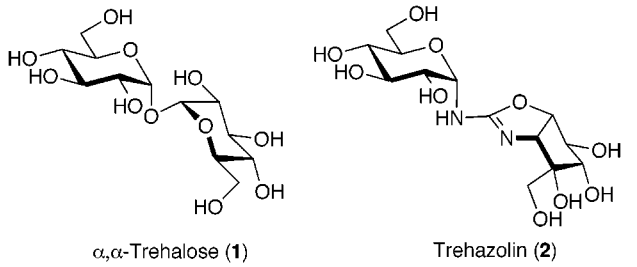
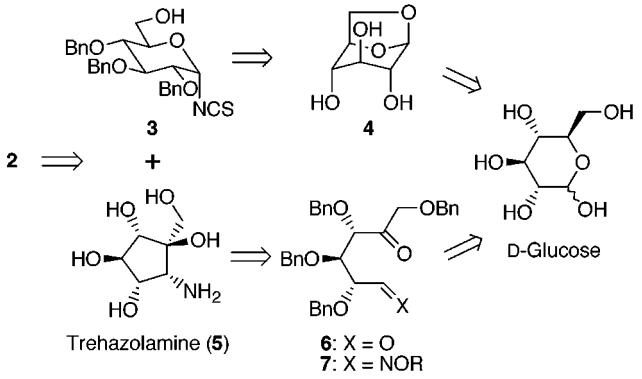


Figure 1. Structural similarities between α,α-trehalose (**1**) and trehazolin (**2**).

Scheme 1



To avoid the construction of each chiral center one after the other, we looked for a straightforward route making use of the already present chirality in D-glucose. The key step in such an approach would be a pinacol coupling of either a protected keto aldehyde **6** or ketooxime ether **7** (Scheme 1). Both compounds already incorporate three stereocenters of D-glucose and can easily be prepared from the latter. As a consequence, such a straightforward and efficient synthesis of trehazolamine (**5**) is strictly connected to the selectivity of the coupling reaction. The concept of this retrosynthesis follows a speculative biosynthesis[7] of trehazolin (**2**), which is outlined

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(1) Elbein, A. D. *Adv. Carbohydr. Chem. Biochem.* **1974**, *30*, 227.
(2) Ando, O.; Satake, H.; Itoi, K.; Sato, A.; Nakajima, M.; Takahashi, S.; Haruyama, H.; Ohkuma, Y.; Kinoshita, T.; Enokita, R. *J. Antibiot.* **1991**, *44*, 1165.
(3) (a) Ogawa, S.; Uchida, C. *Chem. Lett.* **1993**, 173. (b) Uchida, C.; Yamagishi, T.; Ogawa, S. *J. Chem. Soc., Perkin Trans. 1* **1994**, 589. (c) Ledford, B. E.; Carreira, E. M. *J. Am. Chem. Soc.* **1995**, *117*, 11811. (d) Kobayashi, Y.; Miyazaki, H.; Shiozaki, M. *J. Org. Chem.* **1994**, *59*, 813. (e) Ogawa, S.; Uchida, C. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1939.
(4) (a) Kobayashi, Y.; Shiozaki, M. *J. Org. Chem.* **1995**, *60*, 2570. (b) Uchida, C.; Ogawa, S. *Carbohydr. Lett.* **1994**, *1*, 77. (c) Uchida, C.; Yamagishi, T.; Kitahashi, H.; Iwaisaki, Y.; Ogawa, S. *Bioorg. Med. Chem.* **1995**, *3*, 1605. (d) Uchida, C.; Ogawa, S. *Bioorg. Med. Chem.* **1996**, *4*, 275. (e) Uchida, C.; Kitahashi, H.; Yamagishi, T.; Iwaisaki, Y.; Ogawa, S. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2775. (f) Uchida, C.; Kitahashi, H.; Watanabe, S.; Ogawa, S. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1707.
(5) Camarasa, M. J.; Fernández-Resa, P.; García-López, M. T.; De las Heras, F. G.; Méndez-Castrillón, P. P.; San Felix, A. *Synthesis* **1984**, 509.
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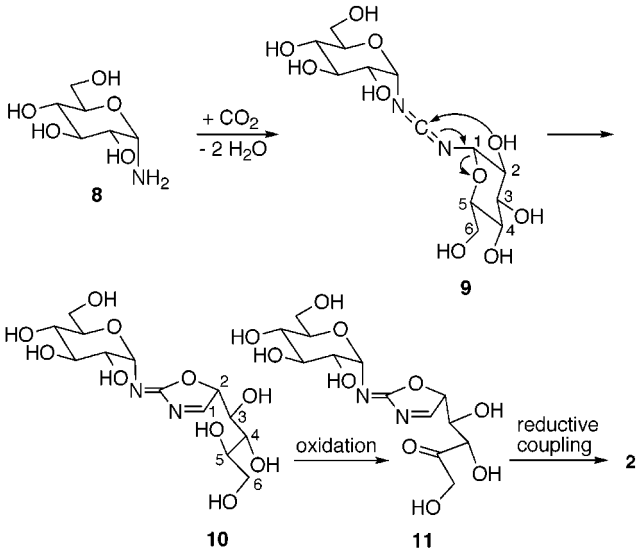
Scheme 2

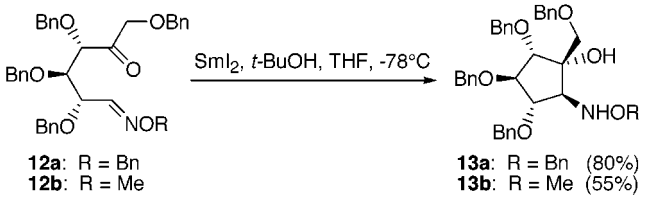


in Scheme 2. Two molecules of glucosamine (**8**) would react with a CO_2 donor to give the carbodiimide **9**, which leads to the oxazolinone derivative **10**. Subsequent regioselective oxidation and stereoselective pinacol type coupling would then afford trehazolin (**2**). In this paper, we report a straightforward synthesis of trehazolamine (**5**) which includes stereoselective pinacol type coupling reactions and a stereoselective oxidation−reduction sequence.

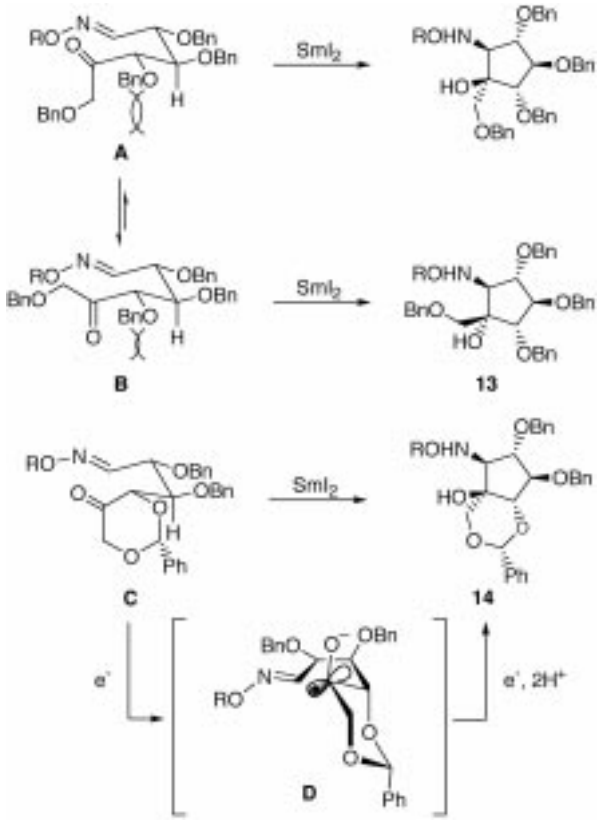
Results and Discussion

Ring formation via radical cyclization is known to be stereoselective in many cases.[8] Recently, several reports on intramolecular radical pinacol couplings of dicarbonyl compounds[9] and intramolecular radical cyclizations between carbonyl groups and oxime ethers[10] have been published. These reactions performed by samarium diiodide (SmI_2) or tributyltin hydride (Bu_3SnH) offer straightforward and selective access to cyclitols and aminocyclitols starting from protected sugars. Marco-Contelles and Chiara et al.[10d] reported the intramolecular radical cyclization of a ketooxime ether **12a** derived from D-glucose (Scheme 3). This reaction using SmI_2 gave

Scheme 3



Scheme 4



aminocyclitol **13a** in good yield as the only diastereoisomer,[11] but both newly created stereocenters are opposite to those of trehazolamine (**5**). The formation of aminocyclitol **13** as the major isomer in the SmI_2-induced pinacol type coupling reaction can be rationalized by a preferred conformation **B** of ketooxime **12** in which 1,3-diaxial repulsion is minimized (Scheme 4).[12] Electron transfer from SmI_2 to the carbonyl group leads to an intermediate ketyl radical anion that undergoes a 5-exo-trig cyclization reaction with a chairlike transition state. This yields product **13** with the undesired configurations at the newly formed stereogenic carbon atoms. To invert the stereochemistry of the coupling reaction, we connected the oxygen atoms at C-4 and C-6 by forming a six-membered cyclic acetal. This changes the orientation of the keto group, as shown in conformation **C** (Scheme 4), and the intermediate ketyl radical anion **D** is axially attacked by the oxime ether.[13] After another one-electron

(7) To our knowledge the biosynthesis of trehazolin (**2**) is not known.

(8) (a) Giese, B.; Kopping, B.; Goebel, T.; Dickhaut, J.; Thoma, G.; Kulicke, K.; Trach, F. *Org. React. (N.Y.)* **1996**, *48*, 301. (b) Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions*; VCH: New York 1996; Chapter 2.

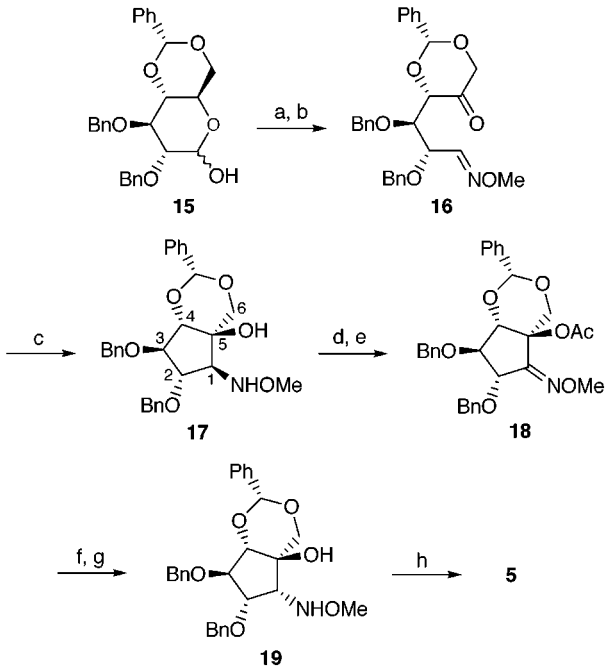
(9) (a) Hays, D. S.; Fu, G. C. *J. Am. Chem. Soc.* **1995**, *117*, 7283. (b) Molander, G. A.; Kenny, C. *J. Am. Chem. Soc.* **1989**, *111*, 8236. (c) Uenishi, J.; Masuda, S.; Wakabayashi, S. *Tetrahedron Lett.* **1991**, *32*, 5097. (d) Chiara, J. L.; Valle, N. *Tetrahedron: Asymmetry* **1995**, *6*, 1895. (e) Chiara, J. L.; Martín-Lomas, M. *Tetrahedron Lett.* **1994**, *35*, 2969. (f) Chiara, J. L.; Cabri, W.; Hanessian, S. *Tetrahedron Lett.* **1991**, *32*, 1125. (g) Guidot, J. P.; Le Gall, T.; Mioskowski, C. *Tetrahedron Lett.* **1994**, *36*, 6671. (h) Carpintero, M.; Fernández-Mayoralas, A.; Jaramillo, C. *J. Org. Chem.* **1997**, *62*, 1916. (i) Wirth, T. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 61. (j) Adinolfi, M.; Barone, G.; Iadonisi, A.; Mangoni, L. *Tetrahedron Lett.* **1998**, *39*, 2021. (k) Chiara, J. L. In *Carbohydrate Mimics: Concepts and Methods*; Chapleur, Y., Ed.; Wiley-VCH: Weinheim, 1998; Chapter 7.

(10) (a) Kiguchi, T.; Tajiri, K.; Ninomiya, I.; Naito, T.; Hiramatsu, H. *Tetrahedron Lett.* **1995**, *36*, 253. (b) Chiara, J. L.; Marco-Contelles, J.; Khiar, N.; Gallego, P.; Destabel, C.; Bernabé, M. *J. Org. Chem.* **1995**, *60*, 6010. (c) Naito, T.; Tajiri, K.; Harimoto, T.; Ninomiya, I.; Kiguchi, T. *Tetrahedron Lett.* **1994**, *35*, 2205. (d) Marco-Contelles, J.; Gallego, P.; Rodríguez-Fernández, M.; Khiar, N.; Destabel, C.; Bernarbé, M.; Martínez-Grau, A.; Chiara, J. L. *J. Org. Chem.* **1997**, *62*, 7397, and references therein. (e) Tormo, J.; Hays, D. S.; Fu, G. *J. Org. Chem.* **1998**, *63*, 201. (f) Fallis, A. G.; Brinza, I. M. *Tetrahedron* **1997**, *53*, 17543.

(11) Upon cyclization with Bu_3SnH of the methylated analogue **12b**, Naito and co-workers[10a] received a mixture of **13b** and its epimer at the quaternary center with almost no selectivity. Reaction of the methyloxime ether **12b** with SmI_2 confirmed the results obtained by Marco−Contelles:[10d] almost only **13b** was obtained. Thus, the nature of the metal and not that of the oxime ether seems to determine the selectivity of the coupling.

(12) (a) Sturino, C. F.; Fallis, A. G. *J. Am. Chem. Soc.* **1994**, *116*, 7447. (b) Sturino, C. F.; Fallis, A. G. *J. Org. Chem.* **1994**, *59*, 6514.

Scheme 5[a]

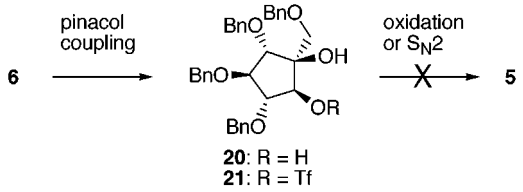


[a] Reagents and conditions: (a) $MeONH_2$·HCl, py, 40 °C (quant); (b) Dess−Martin periodinane, CH_2Cl_2 (quant); (c) SmI_2 (5 equiv), *t*-BuOH (2.5 equiv), THF, −78 °C to rt (84%); (d) Ac_2O, py, DMAP; (e) $Pb(OAc)_4$, PhH, 40 °C (44%, two steps); (f) K_2CO_3, MeOH; (g) $LiAlH_4$, MeONa, THF, −20 °C (67%, two steps); (h) Na, NH_3 (liq), −78 °C (>90%).

transfer, the aminocyclitol **14** with the desired configuration at the quaternary carbon atom should be formed.

Compound **15**, in which the O-atoms at C-4 and C-6 are fixed by a ring, can be easily prepared from D-glucose.[14] Carbohydrate derivative **15** was converted quantitatively to the open chain *O*-methyloxime ether. Dess−Martin oxidation[15] afforded ketone **16**, which was used without further purification for the subsequent intramolecular coupling step (Scheme 5). Treatment of **16** with SmI_2 in THF at −78 °C gave exclusively diastereoisomer **17** in 84% yield.[16] The configuration at the newly created chiral centers in **17** was established by ^1H NMR analysis and NOE measurements.[17] The stereochemistry of aminocyclitols **17** and **5** differs only in the configuration at C-1,[18] which carries the *O*-methylhydroxyamino group. We decided to invert the configuration at this stereocenter in an oxidation−reduction sequence in order to preserve the stereochemistry of the quaternary carbon C-5. However, several attempts to oxidize the methoxyamine **17** to the desired *O*-methyloxime failed, and protection of the tertiary alcohol of **17** turned out to be necessary.[19] The oxidation of the acetylated *O*-methoxyamine to the oxime ether **18** was also not an easy task. Lead tetraacetate[20] was the only

Scheme 6



oxidizing agent that gave product **18**, but with a modest yield (44%).[21] After deprotection of the tertiary hydroxy group, the resulting *O*-methyloxime was reduced to **20** by $LiAlH_4$ in the presence of MeONa[22] in THF at −20 °C.[23] A possible explanation for the complete stereoselectivity of this reaction may be the complexation of $LiAlH_4$ by the adjacent tertiary hydroxy group, which is activated by MeONa. In addition, access to the sp^2 carbon of the oxime ether is easier from the less shielded upper side[24] of the cyclopentane ring than from below (two versus three shielding groups). Full deprotection of **19** with sodium in liquid ammonia afforded trehazolamine (**5**).[25] Starting from **15**, the overall yield is 22% for eight steps.

Another possibility to obtain **5** would start from keto aldehyde **6**. Well-known pinacol coupling of **6** afforded *cis*-diol **20** as major product (Scheme 6).[9j,k] However, we succeeded in neither S_N2 displacement of the triflate in **21** by a nitrogen nucleophile nor oxidizing the secondary hydroxy group of **20**.[26] It is not surprising that the oxidation of the secondary hydroxy group in compound **20** is much more difficult than the oxidation of the methoxyamino group in compound **18**, because the α-effect makes hydroxylamines easier to oxidize than alcohols.[20b]

Analogous to a known procedure[3a] we synthesized trehazolin (**2**): The isothiocyanate **3**[3c] was coupled with crude trehazolamine (**5**) in DMF to give the thiourea derivative **22**. Ring closure to an oxazolin with yellow HgO and subsequent deprotection with sodium in liquid ammonia afforded trehazolin (**2**) that was identical with the natural product ($[\alpha]^{20}_D$, NMR, TLC).[27,28] This three-step conversion from trehazolamine (**5**) to trehazolin (**2**) occurred in 63% yield (Scheme 7).

Conclusion

A straightforward "stereoeffective" short synthesis of trehazolamine (**5**) including two highly stereoselective

(13) (a) Wu, Y.; Houk, K. N. *J. Am. Chem. Soc.* **1992**, *114*, 1656. (b) Inanaga, J.; Katsuki, J.; Ujikawa, O.; Yamaguchi, M. *Tetrahedron Lett.* **1991**, *32*, 4921.

(14) Qiao, L.; Veredas, J. C. *J. Org. Chem.* **1993**, *58*, 3480.

(15) Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899, and references therein.

(16) Almost the same results (yield and diastereoselectivity) were obtained at 0 °C. When the reaction was performed with Bu_3SnH/AIBN in refluxing benzene a mixture of products **17** and its epimer at the quaternary center *epi*-**17** were obtained (see Experimental Section).

(17) See Supporting Information.

(18) Using carbohydrate numbering.

(19) The use of most oxidizing agents resulted in formation of compound **16**.

(20) (a) Norman, R. O. C.; Purchase, R.; Thomas, C. B. *J. Chem. Soc., Perkin Trans. 1* **1972**, 1701. (b) Weiss, R. H.; Furfine, E.; Hausleden, E.; Dixon, D. W. *J. Org. Chem.* **1984**, *49*, 4969.

(21) Swern oxidation, Dess−Martin periodinane, Br_2/Et_3N, Br_2/Na_2CO_3, TEMPO or NaOCl failed.

(22) In the absence of MeONa, the reaction was messy.

(23) Narasaka, K.; Ukaji, Y.; Yamazaki, S. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 525.

(24) Reference plane: paper sheet; molecule as depicted in Scheme 5.

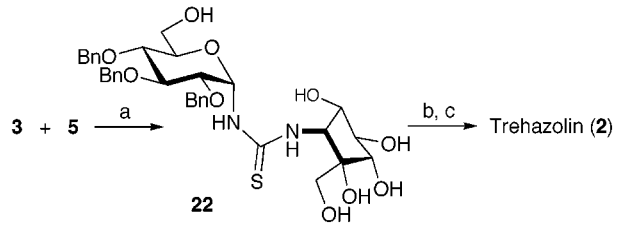
(25) ^1H and ^{13}C NMR as well as TLC of product **5** were identical to that already described in the literature.[3d,6a] The $[\alpha]^{20}_D$ measured was not significant because the literature value[6a] ($[\alpha]^{20}_D = +1.7$ (*c* 0.41, MeOH)) is very low.

(26) For more details see Supporting Information.

(27) Found for **2**: $[\alpha]^{20}_D = +122$ (*c* 0.49, H_2O); literature: $[\alpha]^{20}_D = +99.5$ (*c* 0.41, H_2O),[2] $[\alpha]^{20}_D = +105$ (*c* 0.36, H_2O),[3a] $[\alpha]^{20}D = +112.7$ (*c* 0.59, H_2O).[3b]

(28) With regard to the literature,[3c] intermediates in the transformation of **5** to **2** showed different physical data (^1H NMR, ^{13}C NMR, $[\alpha]^{20}_D$, IR, TLC).

Scheme 7[a]



[a] Reagents and conditions: (a) DMF (69%); (b) HgO, MeCN; (c) Na, NH_3 (liq), −78 °C (91%, two steps).

steps has been achieved. Our synthesis takes advantage of the chirality of D-glucose and provides a tool for the inversion of a stereocenter carrying an amino group adjacent to a hydroxy group.

Experimental Section

General. Unless otherwise stated, reactions were conducted under an atmosphere of Ar. All reagents were commercially available and used without further purification. Solvents for workup and flash chromatography are distilled prior to use. Dry CH_2Cl_2, dry benzene, and dry DMSO were obtained commercially, and THF was freshly distilled from sodium/benzophenone. Flash column chromatography was performed on silica gel 60 (230−400 mesh). Melting points are uncorrected. NMR spectra were recorded at 300 MHz (^{1}H) and 75 MHz (^{13}C) at room temperature unless otherwise mentioned. Chemical shifts are reported in ppm downfield from TMS or with reference to solvent. Mass spectroscopy was performed with an FAB ionization method (matrix: nitrobenzyl alcohol) and addition of potassium chloride.

Synthesis of 4,6-*O*-Benzylidene-2,3-*O*-bis(phenylmethyl)-1-(*O*-methyloxime)-D-*xylo*-hexos-5-ulose (16). A solution of **15**[14] (3.32 g, 7.39 mmol) and $MeONH_2$·HCl (2.46 g, 29.4 mmol, 4 equiv) in dry pyridine (60 mL) was stirred at 40−45 °C for 24 h. Concentration in vacuo and coevaporation with PhMe afforded a yellow residue which was extracted with CH_2Cl_2 and H_2O, dried (Na_2SO_4), and concentrated in vacuo. The yellowish oil (*E*/*Z* 5:1, 3.52 g, quant.) obtained was used without further purification for the next step: R_f = 0.43 (*E*-isomer); R_f = 0.29 (*Z*-isomer) (pentane/CH_2Cl_2/Et_2O 1:1:1); IR (film) (*E*/*Z* 5:1) ν 3473, 1393, 1076, 1049 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ *E*-isomer, 7.47−7.26 (m, 15H), 7.42 (d, J = 7.9 Hz, 1H), 5.37 (s, 1H), 4.81, 4.69 (2 AB, J_{AB} = 11.8 Hz, 2H), 4.68, 4.52 (2 AB, J_{AB} = 11.6 Hz, 2H), 4.45 (dd, J = 6.3, 7.9 Hz, 1H), 4.21 (dd, J = 5.2, 10.7 Hz, 1H), 3.90 (m, 1H), 3.88 (dd, J = 3.4, 6.3 Hz, 1H), 3.87 (s, 3H), 3.68 (dd, J = 3.4, 9.3 Hz, 1H), 3.48 (dd, J = 10.2, 10.7 Hz, 1H), 2.02 (d, J = 4.1 Hz, OH); *Z*-isomer, 7.47−7.26 (m, 15H), 6.85 (d, J = 7.1 Hz, 1H), 5.40 (s, 1H), 5.18 (dd, J = 5.5, 7.1 Hz, 1H), 4.79, 4.67 (2 AB, J_{AB} = 11.8 Hz, 2H), 4.63, 4.54 (2 AB, J_{AB} = 11.6 Hz, 2H), 4.21 (dd, J = 5.2, 10.7 Hz, 1H), 3.90 (m, 1H), 3.88 (m, 1H), 3.83 (s, 3H), 3.68 (dd, J = 5.3, 10.7 Hz, 1H), 3.49 (dd, J = 10.2, 10.7 Hz, 1H), 1.93 (d, J = 4.1 Hz, OH); ^{13}C NMR ($CDCl_3$) δ *E*-isomer, 147.5, 137.6, 137.4, 128.5, 128.4, 128.3, 128.2, 128.1, 127.9, 127.8, 101.1, 80.4, 77.4, 77.0, 74.0, 71.6, 70.7, 61.9, 61.8; *Z*-isomer, 149.6, 137.7, 137.5, 128.5, 128.4, 128.3, 128.2, 128.1, 127.9, 127.8, 101.2, 80.5, 77.0, 71.6, 74.1, 72.4, 70.8, 62.2, 62.0; MS (FAB + KCl) m/z 516 (MK^+), 478 (MH^+). Anal. Calcd for $C_{28}H_{31}NO_6$ (477.56): C, 70.41; H, 6.55; N, 2.93; Found: C, 70.25; H, 6.53; N, 2.87.

To a solution of Dess−Martin periodinane[15] (1.31 g, 3.09 mmol) in dry CH_2Cl_2 (40 mL) was added after 10 min a solution of crude oxime ether of **15** (1.06 g, 2.21 mmol) in dry CH_2Cl_2 (12 mL). The mixture was stirred at room temperature until no starting material could be detected by TLC (2−3 h). After dilution with Et_2O (15 mL) and stirring for 10 min, the foggy solution was extracted with Et_2O, a solution of 10 g of $Na_2S_2O_3$ in saturated $NaHCO_3$ (80 mL), and saturated $NaHCO_3$, dried (Na_2SO_4), and concentrated in vacuo to afford **16** (mainly *E*, 1.14 g, quant.) as a yellowish oil. The crude ketone **16** was used without further purification for the following step: R_f = 0.44 (*E* and *Z*) (pentane/CH_2Cl_2/Et_2O 10:10:1); IR (film) (*E*-isomer) ν 1738, 1606, 1100 (br) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ *E*-isomer, 7.68 (d, J = 7.9 Hz, 1H), 7.59 (d, J = 8.4 Hz, 2H), 7.28 (d, J = 6.8 Hz, 2H), 7.23−7.00 (m, 11H), 5.38 (s, 1H), 4.72, 4.57 (2 AB, J_{AB} = 11.5 Hz, 2H), 4.52, 4.31 (2 AB, J_{AB} = 11.6 Hz, 2H), 4.62−4.52 (m, 2H), 4.22 (d, J = 17.6 Hz, 1H), 4.39 (dd, J = 2.5, 6.9 Hz, 1H), 3.73 (s, 3H), 3.86 (d, J = 17.6 Hz, 1H); ^{13}C NMR (C_6D_6) δ *E*-isomer, 204.2, 148.2, 138.5, 138.2, 137.9, 129.1, 128.5, 128.4, 128.4, 128.1, 127.9, 127.7, 126.6, 99.0, 82.2, 78.9, 76.7, 74.6, 72.5, 71.7, 61.6; *Z*-isomer, 204.2, 149.6, 138.7, 138.2, 138.0, 129.1, 128.5, 128.4, 128.4, 128.1, 127.9, 127.7, 126.6, 99.1, 82.0, 78.7, 76.7, 74.8, 72.4, 71.7, 61.8; MS (FAB + KCl) m/z 514 (MK^+), 476 (MH^+). Anal. Calcd for $C_{28}H_{29}NO_6$ (475.54): C, 70.72; H, 6.15; N, 2.94. Purification was not possible.

[1*R*-(1α,2α,3*β*,4α,5*β*)]-5,6-*O*-Benzylidene-3,4-bis(phenylmethoxy)-2-(methoxyamino)cyclopentanol (17) and [1*S*-(1α,2*β*,3α,4*β*,5α)]-5,6-*O*-Benzylidene-3,4-bis(phenylmethoxy)-2-(methoxyamino)cyclopentanol (*epi*-17). Cyclization with SmI_2. To a stirred and carefully deoxygenated (evaporation at the vacuum pump, Ar; 3×) solution of dried crude keto methyloxime **16** (*E*/*Z* 5:1; 1.91 g, 4.02 mmol) and *t*-BuOH (1.10 mL, 11.7 mmol, 2.9 equiv) in dry THF (220 mL) was added at −78 °C a ca. 0.1 M solution of SmI_2 (commercial, 186 mL, 18.6 mmol, 4.6 equiv) in THF. After 2 h of stirring at −78 °C, the temperature was slowly raised to room temperature overnight. Extraction of the yellow solution with Et_2O, $NaHCO_3$, 10% $Na_2S_2O_3$, and brine, drying (Na_2SO_4), and evaporation in vacuo afforded **17** with minor impurities. Filtration over a bed of silica gel (pentane/CH_2Cl_2/Et_2O 2:1:1) gave **17** (1.63 g, 84%).

Cyclization with Bu_3SnH. A stirred solution of dried crude keto methyloxime **16** (567 mg, 1.09 mmol) in dry benzene (40 mL) was heated to reflux. A solution of Bu_3SnH (1.33 mL, 5.00 mmol, 4.6 equiv) and AIBN (82 mg, 0.50 mmol, 0.46 equiv) in benzene (12 mL) was then added over a period of 4 h. After another 2 h, the reaction mixture was cooled to room temperature and concentrated in vacuo to a cloudy, colorless oil. Purification by flash chromatography (pentane/CH_2Cl_2/Et_2O 2:1:1) resulted in a mixture of compounds **17** and *epi*-**17** (**17**/*epi*-**17** 1.7:1). Further purification by flash chromatography on alumina (pentane/CH_2Cl_2/acetone 10:10:1) afforded *epi*-**17** with some tin impurities (80 mg, 15%) and a mixture of **17**, *epi*-**17**, and tin impurities (190 mg, 35%). **17:** R_f = 0.41 (SiO_2, pentane/CH_2Cl_2/Et_2O 1:1:1), R_f = 0.23 (alumina neutral, pentane/CH_2Cl_2/acetone 5:5:1); $[\alpha]^{20}_D$ = −8.2 (*c* 1.16, $CHCl_3$); IR (film) ν 3460 (br), 1610, 1460, 1100 (br) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.50−7.20 (m, 15H), 5.88 (d, J = 2.8 Hz, NH), 5.49 (s, 1H), 4.70, 4.50 (2 AB, J_{AB} = 11.8 Hz, 2H), 4.63, 4.51 (2 AB, J_{AB} = 11.7 Hz, 2H), 4.32 (d, J = 11.3 Hz, 1H), 4.08 (s, 1H), 4.06 (dd, J = 4.0, 9.2 Hz, 1H), 3.99 (d, J = 4.0 Hz, 1H), 3.92 (dd, J = 2.8, 9.2 Hz, 1H), 3.81 (d, J = 11.3 Hz, 1H), 3.64 (s, br, OH), 3.51 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 138.0, 137.6, 137.5, 129.0, 128.4, 128.2, 128.1, 127.9, 127.9, 127.7, 126.3, 100.3, 87.6, 83.7, 83.2, 72.2, 71.9, 70.9, 70.5, 65.1, 62.0; MS (FAB + KCl) m/z 516 (MK^+), 478 (MH^+). Anal. Calcd for $C_{28}H_{31}NO_6$ (477.56): C, 70.42; H, 6.54; N, 2.93. Found: C, 70.30; H, 6.73; N, 2.94. *epi*-**17:** R_f = 0.41 (SiO_2, pentane/CH_2Cl_2/Et_2O 1:1:1); R_f = 0.35 (alumina neutral, pentane/CH_2Cl_2/acetone 5:5:1); ^{1}H NMR ($CDCl_3$) δ 7.55−7.24 (m, 15H), 5.56 (s, 1H), 5.15 (d, J = 4.8 Hz, NH), 4.77, 4.65 (2 AB, J_{AB} = 11.8 Hz, 2H), 4.63 (s, 2H), 4.38 (dd, J = 5.1, 9.1 Hz, 1H), 4.16 (d, J = 11.0 Hz, 1H), 4.09 (d, J = 9.1 Hz, 1H), 4.03 (d, J_{AB} = 11.0 Hz, 1H), 3.68 (dd, J = 2.5, 5.1 Hz, 1H), 3.47 (dd, J = 2.5, 4.8 Hz, 1H), 3.46 (s, 3H), 3.27 (s, br, OH); ^{13}C NMR ($CDCl_3$) δ 138.2, 137.9, 137.1, 129.1, 128.3, 128.2, 128.1, 128.0, 127.9, 127.7, 127.5, 126.0, 101.5, 84.4, 84.0, 83.5, 73.9, 72.4, 71.8, 71.7, 68.3, 61.5; ^{13}C NMR (C_6D_6) δ 139.1, 138.8, 138.0, 129.1, 128.3, 128.2, 128.1, 128.0, 127.9, 127.7, 127.5, 126.0, 101.7, 84.8, 84.5, 84.2, 74.2, 72.6, 72.1, 71.7, 68.7, 61.2. Further characterization was not possible.

Synthesis of [2*R*-(2α,3*β*,4α,5*β*)]-2-(Acetyloxy)-1-(*O*-methyloxime)-3,6-*O*-benzylidene-4,5-bis(phenylmethoxy)cyclopentanone (18). To a stirred solution of alcohol **17** (1.63 g, 3.41 mmol) in dry pyridine (15 mL) were added at room temperature Ac_2O (8.0 mL, 85 mmol, 25 equiv) and DMAP (30 mg). After one night of stirring at room temperature, the reaction mixture was slowly quenched by addition of MeOH (50 mL) and stirred for another 2 h. After evaporation to dryness, the residue was extracted with Et_2O, saturated NH_4Cl, and brine and dried ($MgSO_4$), and the solvent was evaporated in vacuo to give the acetate of **17** (1.78 g, quant.) as yellowish oil: $R_f = 0.30$ (pentane/CH_2Cl_2/Et_2O 2:2:1); $[\alpha]^{20}_D = -18.1$ (*c* 1.1, $CHCl_3$); IR (film) ν 3240 (br), 1644, 1090 (br) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.50−7.23 (m, 15H), 6.48 (s, NH), 5.51 (s, 1H), 4.87 (dd, $J = 3.9$, 10.4 Hz, 1H), 4.72, 4.53 (2 AB, $J_{AB} = 11.8$ Hz, 2H), 4.60, 4.53 (2 AB, $J_{AB} = 12.0$ Hz, 2H), 4.53 (d, $J = 10.4$ Hz, 1H), 4.09 (d, $J = 12.1$ Hz, 1H), 4.07 (s, 1H), 3.92 (d, $J = 3.9$ Hz, 1H), 3.84 (d, $J = 12.1$ Hz, 1H), 3.72 (s, 3H), 2.18 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 175.5, 138.0, 137.6, 137.4, 129.1, 128.3, 128.3, 128.1, 127.8, 127.7, 126.2, 100.4, 86.6, 82.7, 80.6, 72.3, 71.6, 70.7, 69.8, 68.4, 62.1, 21.0; MS (FAB + KCl) *m*/*z* 558 (MK^+), 520 (MH^+), 414. Anal. Calcd for $C_{30}H_{33}NO_7$ (519.60): C, 69.35; H, 6.40; N, 2.70. Found: C, 69.16; H, 6.58; N, 2.79.

To a stirred solution of the acetate of **17** (202 mg, 0.389 mmol) in dry benzene (20 mL) was added at room temperature in three portions (every 12 h) $Pb(OAc)_4$ (300 mg, 0.67 mmol, 1.74 equiv). The mixture was stirred at 40 °C for a total of 40 h and then quenched with saturated $NaHCO_3$, extracted with Et_2O, saturated $NaHCO_3$ and brine. Drying of the combined organic extracts ($MgSO_4$) and evaporation in vacuo gave a oily residue. Flash chromatography (pentane/CH_2Cl_2/Et_2O 8:3:1) afforded product **18** (88 mg, 44%) as a yellowish oil. $R_f = 0.38$ (pentane/CH_2Cl_2/Et_2O 4:1:1); $[\alpha]^{20}_D = -1.5$ (*c* 1.1, $CHCl_3$); IR (film) ν 1732 (br), 1651 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.47−7.25 (m, 15H), 5.74 (s, 1H), 5.09 (dd, $J = 1.1$, 2.4 Hz, 1H), 4.81 (dd, $J = 1.1$, 2.7 Hz, 1H), 4.76, 4.62 (2 AB, $J_{AB} = 11.4$ Hz, 2H), 4.52, 4.47 (2 AB, $J_{AB} = 11.8$ Hz, 2H), 4.47, 4.39 (2 AB, $J_{AB} = 11.1$ Hz, 2H), 4.07 (dd, $J = 2.4$, 2.7 Hz, 1H), 4.00 (s, 3H), 1.98 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 170.2, 157.1, 138.2, 137.7, 137.5, 129.1, 128.3, 128.3, 128.2, 128.1, 127.8, 127.7, 127.7, 126.4, 98.5, 85.8, 80.1, 80.0, 80.2, 72.9, 71.9, 65.0, 62.9, 21.8; MS (FAB + KCl) *m*/*z* 556 (MK^+), 518 (MH^+), 412. Anal. Calcd for $C_{30}H_{31}NO_7$ (517.58): C, 69.62; H, 6.04; N, 2.71. Found: C, 69.34; H, 6.18; N, 2.70.

Synthesis of [1*R*-(1α,2*β*,3*β*,4α,5*β*)]-5,6-*O*-Benzylidene-3,4-bis(phenylmethoxy)-2-(methoxyamino)cyclopentanol (19). Methyloxime **18** (92.0 mg, 0.178 mmol) and K_2CO_3 (10 mg) in MeOH (5 mL) were stirred at room temperature for 30 min. Extraction with Et_2O, saturated $NaHCO_3$, and brine, drying ($MgSO_4$), and evaporation of solvents at reduced pressure gave the alcohol of **18** (88 mg, quant.) as a yellowish oil: $R_f = 0.30$ (pentane/CH_2Cl_2/Et_2O 3:1:1); $[\alpha]^{20}_D = +23$ (*c* 1.0, $CHCl_3$); IR (film) ν 3510 (br), 1078 (br) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.45−7.24 (m, 15H); 5.52 (s, 1H); 4.77, 4.64 (2 AB, $J_{AB} = 11.6$ Hz, 2H); 4.73 (d, $J = 1.5$ Hz, 1H); 4.51, 4.45 (2 AB, $J_{AB} = 11.8$ Hz, 2H), 4.59 (d, $J = 11.1$ Hz, 1H), 4.27 (dd, $J = 1.3$, 1.5 Hz, 1H), 4.02 (d, $J = 1.3$ Hz, 1H), 3.97 (d, $J = 11.1$ Hz, 1H), 4.02 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 160.9, 138.3, 137.4, 136.7, 129.1, 128.6, 128.2, 128.1, 127.8, 127.6, 126.6, 100.3, 72.5, 83.9, 83.0, 78.2, 72.9, 72.0, 69.5, 62.6; MS (FAB + KCl) *m*/*z* 514 (MK^+), 476 (MH^+), 370. Anal. Calcd for $C_{28}H_{29}NO_6$ (475.55): C, 70.72; H, 6.15; N, 2.94. Found: C, 70.66; H, 6.27; N, 2.86.

To a stirred solution of $LiAlH_4$ (202 mg, 5.3 mmol, 35 equiv) and MeONa (164 mg, 3.04 mmol, 20 equiv) in dry THF (5 mL) at −78 °C was added after 15 min a solution of the alcohol of **18** (72.3 mg, 0.152 mmol) in dry THF (3 mL). The temperature was raised to −20 °C and maintained until TLC analysis showed no more starting material. Careful quenching with water (10 mL) at −78 °C and extraction at room temperature with Et_2O, saturated $NaHCO_3$, and brine followed by drying ($MgSO_4$) and evaporation of solvents at reduced pressure gave a pale yellow residue. Flash chromatography (pentane/CH_2Cl_2/Et_2O 2:1:1) afforded product **19** (48.2 mg, 67%) as a yellowish oil: $R_f = 0.15$ (pentane/CH_2Cl_2/Et_2O 3:1:1); $[\alpha]^{20}_D = -19$ (*c* 0.76, $CHCl_3$); IR (film) ν 3420 (br), 1497, 1454, 1097 (br) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.47−7.28 (m, 15H), 6.22 (d, $J = 7.8$ Hz, NH), 5.65 (s, 1H), 4.64, 4.59 (2 AB, $J_{AB} = 11.8$ Hz, 2H), 4.62 (s, 2H), 4.44 (d, $J = 11.5$ Hz, 1H), 4.26 (dd, $J = 4.0$, 6.1 Hz, 1H), 4.12 (dd, $J = 2.1$, 4.0 Hz, 1H), 4.03 (d, $J = 2.1$ Hz, 1H), 3.75 (dd, $J = 6.1$, 7.8 Hz, 1H), 3.73 (d, $J = 11.5$ Hz, 1H), 3.51 (s, 3H), 2.70 (s, OH); ^{13}C NMR ($CDCl_3$) δ 138.4, 137.9, 137.5, 128.9, 128.4, 128.3, 128.2, 127.8, 127.8, 127.7, 126.2, 98.4, 86.3, 85.6, 81.4, 76.7, 72.5, 72.1, 69.2, 67.5, 61.2; MS (FAB + KCl) *m*/*z* 516 (MK^+), 478 (MH^+), 325. Anal. Calcd for $C_{28}H_{31}NO_6$ (477.56): C, 70.42; H, 6.54; N, 2.93. Found: C, 70.47; H, 6.78; N, 3.01.

[1*R*-(1α,2*β*,3α,4*β*,5*β*)]-5-Amino-1-(hydroxymethyl)-1,2,3,4-cyclopentanetetrol (5). To a stirred mixture of sodium (240 mg, 10 mmol, 110 equiv) in liquid ammonia (15 mL) at −78 °C was added a solution of compound **19** (43.1 mg, 0.093 mmol) in dry THF (3 mL). After 30 min at −78 °C, NH_4Cl (700 mg, 13 mmol, 145 equiv) was added and ammonia allowed to evaporate at room temperature. Salts were removed using cation exchange chromatography (34 cm^3 wet Dowex 50 WX4, elution with 0.5 M NH_4OH) to afford **5** (14.3 mg, >90% according to ^1H NMR) with some minor impurities. The obtained crude product was used without further purification (yield calculated after following step): $R_f = 0.26$ (MeCN/H_2O/AcOH 3:5:2); ^1H NMR (CD_3OD) δ 3.94 (dd, $J = 5.0$, 6.9 Hz, 1H), 3.85 (dd, $J = 5.0$, 6.2 Hz, 1H), 3.78 (d, $J = 11.8$ Hz, 1H), 3.68 (d, $J = 11.8$ Hz, 1H), 3.68 (d, $J = 6.2$ Hz, 1H), 3.15 (d, $J = 6.9$ Hz, 1H); ^{13}C NMR (CD_3OD) δ 83.9, 83.1, 79.5, 73.8, 63.5, 59.9.

[1*R*-(1α,2*β*,3α,4*β*,5α)]-*N*-[2,3,4,5-Tetrahydroxy-2-(hydroxymethyl)cyclopentyl]-*N*′-[2,3,4-tris-*O*-(phenylmethyl)-α-D-glucopyranosyl]thiourea (22). To a solution of crude **5** (product from the previous step; 0.105 mmol) in DMF (1 mL) was added a solution of **3**[3c] (62.0 mg, 0.126 mmol, 1.2 equiv) in DMF (1 mL). After 24 h, the solvent was evaporated and the residue purified by flash chromatography (CH_2Cl_2/MeOH 20:1 to 10:1) to afford the thiourea derivative **22** (48.5 mg, 69%, 2 steps) as a colorless oil. Data different from the literature:[3c] $R_f = 0.22$ (CH_2Cl_2/MeOH 10:1); $[\alpha]^{20}_D = +153$ (*c* 2.42, $CHCl_3$); IR (KBr) ν 3405 (br), 1541, 1490, 1363, 1070 (br) cm^{-1}; ^1H NMR (CD_3CN) δ 7.80 (br, NH), 7.33−7.25 (m, 15H), 7.13 (br, NH), 5.61 (br, 1H), 4.89−4.56 (m, 8H), 4.30−4.06 (m, 4H), 3.89−3.29 (m, 12H); ^{13}C NMR (CD_3CN) δ 185.4, 140.0, 139.5, 138.8, 129.4, 129.3, 129.2, 129.1, 129.0, 128.9, 128.8, 128.6, 128.5, 83.6, 83.5, 82.5, 82.3, 80.1, 78.9, 78.4, 76.0, 75.5, 75.4, 73.5, 73.2, 63.3, 62.9, 62.2; MS (FAB + KCl) *m*/*z* 709 (MK^+), 671 (MH^+).

Synthesis of Trehazolin (2). To a solution of the thiourea **22** (48.4 mg, 0.0722 mmol) in dry MeCN (4 mL) was added in three portions yellow HgO (155 mg, 0.72 mmol, 10 equiv). After 24 h of vigorous stirring, the mixture was filtered through a bed of Celite and the latter rinsed with CH_2Cl_2/MeOH 5:1. A second filtration over silica gel (CH_2Cl_2/MeOH 5:1) afforded protected trehazolin (45.5 mg, quant.) as a colorless oil which was used without further purification. Data different from the literature:[3c] $R_f = 0.15$ (CH_2Cl_2/MeOH 10:1); $[\alpha]^{20}_D = +69$ (*c* 0.79, $CHCl_3$); IR (KBr) ν 3408 (br), 1664 (br), 1453, 1384, 1069 (br) cm^{-1}; ^1H NMR (CD_3CN) δ 7.29−7.21 (m, 15H), 5.50 (d, $J = 4.9$ Hz, NH), 4.86−4.68 (m, 6H), 4.59−4.37 (m, 6H), 4.00 (s, br, 1H), 3.89−3.53 (m, 10H), 3.35 (t, $J = 6.8$ Hz, 1H); ^{13}C NMR (CD_3CN) δ 161.4, 140.1, 139.6, 139.1, 129.4, 129.3, 129.2, 129.1, 128.9, 128.9, 128.8, 128.6, 128.4, 88.8, 84.1, 82.2, 81.9, 81.7, 79.6, 79.2, 78.7, 76.1, 75.9, 75.5, 72.8, 72.5, 63.9, 62.3; MS (FAB + KCl) *m*/*z* 675 (MK^+), 637 (MH^+), 205.

To a stirred mixture of sodium (92 mg, 4.0 mmol, 60 equiv) in liquid ammonia (10 mL) at −78 °C was added a solution of the protected trehazolin (42.6 mg, 0.0670 mmol) in dry THF (4 mL). After 30 min at −78 °C, NH_4Cl (270 mg, 5.0 mmol, 75 equiv) was added and ammonia allowed to evaporate at room temperature. Chromatography (12.5 cm^3 wet Dowex 50 WX4, elution with 0.5 M NH_4OH) followed by lyophilization provided trehazolin (**2**) (22.4 mg, 91%): $R_f = 0.40$ (MeCN/H_2O/AcOH 6:3:1); $[\alpha]^{20}_D = +122$ (*c* 0.49, H_2O); ^1H NMR (D_2O) 5.15 (d, $J = 5.2$, 1H); 4.76 (dd, $J = 2.4$, 8.5, 1H), 4.17 (d, $J = 8.5$ Hz, 1H)), 4.02 (dd, $J = 2.3$, 4.7 Hz, 1H), 3.77 (d, $J = 4.7$ Hz,

1H), 3.63 (d, J = 12.1 Hz, 1H), 3.62 (dd, J = 2.2, 12.1 Hz, 1H), 3.57 (dd, J = 5.2, 9.8 Hz, 1H), 3.55 (dd, J = 4.9, 12.1 Hz, 1H), 3.52 (d, J = 12.1 Hz, 1H), 3.46 (dd, J = 8.7, 9.8 Hz, 1H), 3.37 (ddd, J = 2.2, 4.9, 10.2 Hz, 1H), 3.22 (dd, J = 8.7, 10.2 Hz, 1H); ^{13}C NMR (D_2O) δ 161.0, 87.3, 82.8, 80.6, 80.3, 80.1, 73.0, 72.9, 72.0, 69.9, 69.5, 61.9, 60.6.

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Supporting Information Available: HETCOR data of **17**, tables of ^{1}H NOE differences of **17** and *epi*-**17**, experimental procedures and physical data of the products **6**, **20** and **21**, and attempts of transformation of **20** and **21** to **5** (11 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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