

# A Concise and Highly Efficient Synthesis of Trehazolin and Trehalamine Starting from D-Mannose

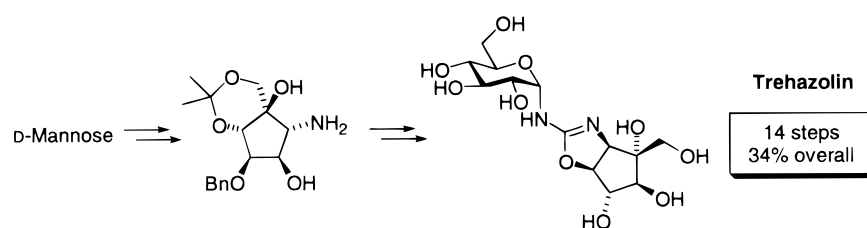
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## ABSTRACT



A concise synthesis of trehazolin, its aglycon, trehalamine, and a known analogue has been developed starting from D-mannose. This new approach features a very stereoselective and high-yielding ketone–oxime ether reductive carbocyclization promoted by samarium diiodide as a key step for the preparation of the aminocyclitol component and a mild and very efficient intramolecular triflate displacement reaction for the construction of the oxazoline ring.

Trehalose (**1**, Figure 1) is ubiquitously found in insects, being their principal blood sugar and used to support various energy-requiring functions, such as insect flight. Trehalose and trehalase have been reported to participate also in germination of ascospores in fungi. The development of specific and potent trehalase inhibitors is, consequently, of great interest for the plant protection industry. One such inhibitor, trehazolin (**2**), was isolated in 1991 from the culture broth of *Micromonospora* strain sp. SANK 62390 and from *Amycolatopsis trehalostatica*.<sup>1</sup> Previous syntheses of **2** involved rather long sequences (15–23 steps) with low overall yields (<5%).<sup>2</sup> The strategies adopted to this end comprised aldol-like reactions, 1,3-dipolar cycloaddition

(1) For a recent review on natural aminocyclopentitol glycosidase inhibitors, see: Berecibar, A.; Grandjean, C.; Siriwardena, A. *Chem. Rev.* **1999**, 99, 779–844. See also: Kobayashi, Y. *Carbohydr. Res.* **1999**, 315, 3.

(2) (a) Kobayashi, Y.; Miyazaki, H.; Shiozaki, M. *J. Org. Chem.* **1994**, 59, 813 and references therein. (b) Uchida, C.; Yamagishi, T.; Ogawa, S. *J. Chem. Soc., Perkin Trans. 1* **1994**, 589 and references therein. (c) Ledford, B. E.; Carreira, E. M. *J. Am. Chem. Soc.* **1995**, 117, 11811. (d) Li, J.; Lang, F.; Ganem, B. *J. Org. Chem.* **1998**, 63, 3403 and references therein. (e) Boiron, A.; Zillig, P.; Faber, D.; Giese, B. *J. Org. Chem.* **1998**, 63, 5877.

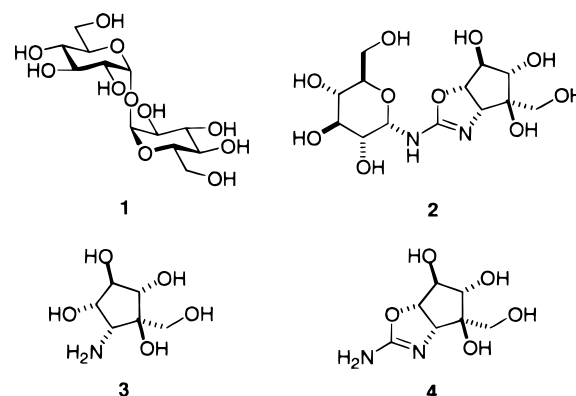


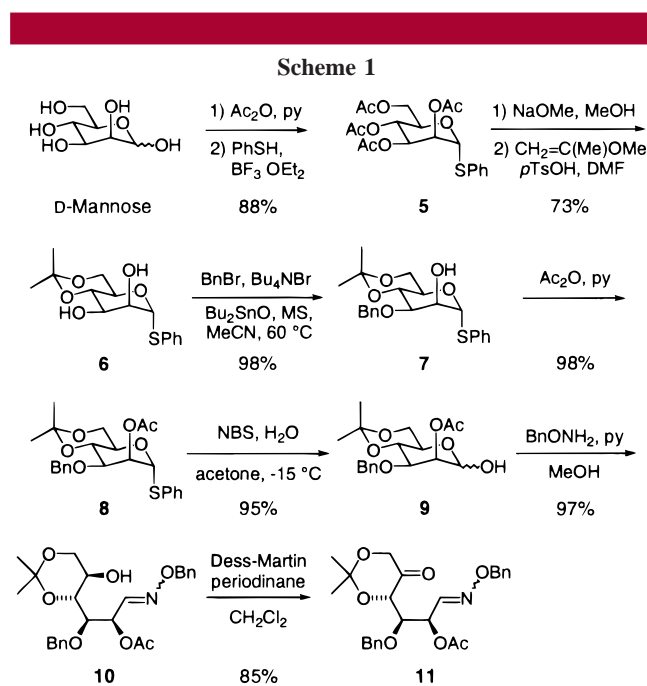
Figure 1.

reactions and radical carbocyclizations of carbohydrate derivatives, desymmetrization of substituted cyclopentene-4-meso-diols, and heterocycloadditions of cyclopentadienes.

Ketyl radical cyclizations promoted by samarium diiodide<sup>3</sup> are especially well suited for this endeavor since they afford directly a functionalized cycloalkanol and proceed under very mild conditions, usually in high yield and with a good level of stereocontrol. The use of chiral polyoxygenated precursors, conveniently prepared from carbohydrates, allows the facile preparation in this way of a diversity of enantiomerically pure complex cyclitols such as those present in the aminocyclitol class of glycosidase inhibitors.<sup>1</sup>

We have recently reported a short and very efficient synthesis of trehazolamine (**3**), the aminocyclitol moiety of **2**, using D-glucose as starting material and a high yielding C=O/C=O reductive carbocyclization as a key step.<sup>4</sup> Herein we disclose a new and more direct route to **2** and its aglycon, trehalamine (**4**), starting from D-mannose.<sup>5</sup> This new approach features a very stereoselective and high-yielding C=O/C=NOR reductive carbocyclization<sup>2e,6,7</sup> as key step for the preparation of the aminocyclitol component and a mild and very efficient intramolecular triflate displacement reaction for the construction of the oxazoline ring.

On the basis of previous observations on the general diastereoselectivity trends shown by C=O/C=NOR reductive carbocyclizations promoted by samarium diiodide<sup>7</sup> and the stereodirecting effect exerted by a cyclic ketone,<sup>2e,5,7d</sup> we designed compound **11** (Scheme 1) as the key carbocycliza-



tion precursor. This compound contains a cyclic acetal flanking the carbonyl group for the control of the stereo-

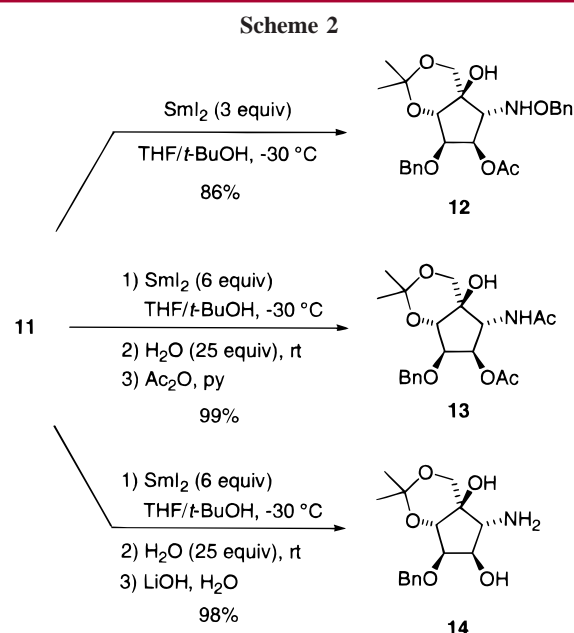
(3) For recent reviews on applications of samarium diiodide in organic synthesis, see: (a) Molander, G. A.; Harris, G. R. *Tetrahedron* **1998**, *54*, 3321. (b) Molander, G. A.; Harris, G. R. *Chem. Rev.* **1996**, *96*, 307. (c) Molander, G. A. *Org. React.* **1994**, *46*, 211. (d) Imamoto, T. *Lanthanides in Organic Synthesis*; Academic Press: London, 1994. (e) Molander, G. A. *Org. React.* **1994**, *46*, 211. (f) Molander, G. A. *Chem. Rev.* **1992**, *92*, 29.

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chemistry at the quaternary center generated in the cyclization, and the hydroxyl group vicinal to the oxime ether is conveniently differentiated to allow further necessary manipulations at this position in the resultant cyclitol.

Compound **11** was readily prepared from D-mannose as shown in Scheme 1. Zemplén deacetylation of known phenyl 1-thio- $\alpha$ -D-mannopyranoside **5**,<sup>8</sup> followed by monoacetonation under kinetic conditions,<sup>9</sup> gave diol **6**. Regioselective benzylation of the equatorial hydroxyl of **6** using tin activation<sup>10</sup> and acetylation of the remaining hydroxyl produced the fully protected thiomannoside **8**. Mild hydrolysis of the thiophenyl glycoside under oxidative conditions<sup>11</sup> provided hemiacetal **9** that was subsequently condensed with *O*-benzylhydroxylamine to give **10** as a mixture of isomeric oxime ethers (*E/Z* = 8:1). Oxidation of **10** using the Dess–Martin periodinane<sup>12</sup> afforded keto–oxime **11**.<sup>13</sup>

When compound **11** (mixture of oximes) was treated with SmI<sub>2</sub> (3 equiv) under our previously optimized conditions,<sup>4,7</sup> a smooth cyclization took place to give *O*-benzylhydroxylamine **12** as a single diastereoisomer in good yield (Scheme 2). Using a larger excess of reducing agent (6 equiv) in the



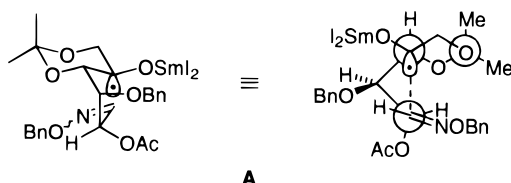
presence of water effected also the subsequent reduction of the hydroxylamino group to give the corresponding free amine.<sup>4,7</sup> In situ treatment with excess Ac<sub>2</sub>O and pyridine provided acetamide **13** in quantitative overall yield. Alter-

(5) This work was presented in part at the 19th International Carbohydrate Symposium, San Diego, 1998; Abstract BP050.

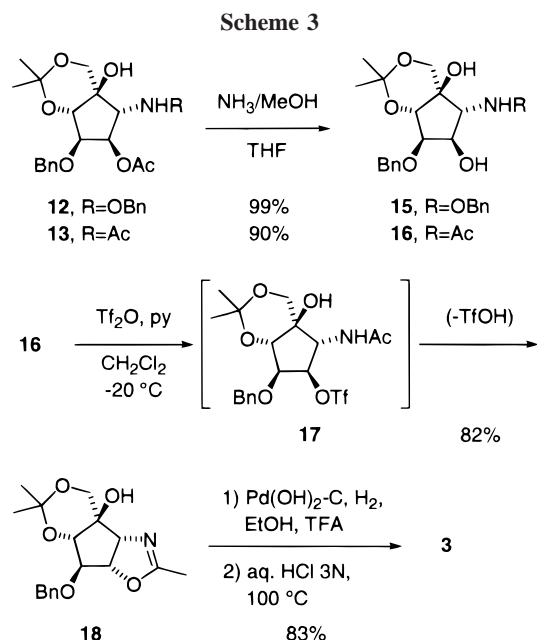
(6) (a) Corey, E. J.; Pyne, S. G. *Tetrahedron Lett.* **1983**, 2821. (b) Hanamoto, T.; Inanaga, J. *Tetrahedron Lett.* **1991**, *32*, 3555. (c) Shono, T.; Kise, N.; Fujimoto, T. *Tetrahedron Lett.* **1991**, *32*, 525. (d) Shono, T.; Kise, N.; Fujimoto, T.; Yamanami, A.; Nomura, R. *J. Org. Chem.* **1994**, *59*, 1730. (e) Naito, T.; Tajiri, K.; Harimoto, T.; Ninomiya, I.; Kiguchi, T. *Tetrahedron Lett.* **1994**, *35*, 2205. (f) Kiguchi, T.; Tajiri, K.; Ninomiya, I.; Naito, T. *Tetrahedron Lett.* **1995**, *36*, 253. (g) Tormo, J.; Hays, D. S.; Fu, G. C. *J. Org. Chem.* **1998**, *63*, 201. (h) Naito, T.; Nakagawa, K.; Nakamura, T.; Kasei, A.; Ninomiya, I.; Kiguchi, T. *J. Org. Chem.* **1999**, *64*, 2003, and references cited therein.

natively, addition of an aqueous solution of LiOH to the crude reaction mixture produced the hydrolysis of the ester to afford aminodiol **14**, also in quantitative overall yield.

The stereochemistry of the carbocyclic products was unambiguously established through  $^1\text{H}$  NMR and 2D NOE-SY studies.<sup>14</sup> Compounds **12**–**14** have the correct stereochemistry of trehalosamine (**3**) at all except the stereocenter corresponding to C-2 in the starting sugar, as initially envisioned. This stereochemical outcome can be rationalized in terms of transition state **A**,<sup>2e,7d</sup> where the more stable axial ketyl radical anion<sup>15</sup> attacks the oxime group in its conformation with the least 1,3-allylic strain.



However, all attempts to selectively invert the stereochemistry of this center in the de-*O*-acylated derivatives **15** and **16** (Scheme 3) using either Mitsunobu conditions or a



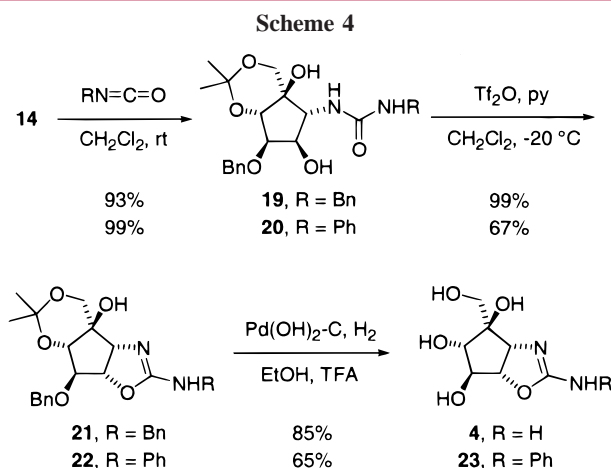
two-step oxidation–reduction sequence failed. After some experimentation, we found that when **16** was treated with

(7) For previous work from our group on  $\text{C}=\text{O}/\text{C}=\text{NOR}$  reductive carbocyclizations promoted by samarium diiodide, see ref 4 and the following: (a) Chiara, J. L.; Marco-Contelles, J.; Khiar, N.; Gallego, P.; Destabel, C.; Bernabé, M. *J. Org. Chem.* **1995**, *60*, 6010. (b) Marco-Contelles, J. L.; Gallego, P.; Rodríguez-Fernández, M.; Khiar, N.; Destabel, C.; Bernabé, M.; Martínez-Grau, A.; Chiara, J. L. *J. Org. Chem.* **1997**, *62*, 7397. (c) Chiara, J. L. in *Carbohydrate Mimics: Concepts and Methods*; Chapleur, Y., Ed.; Wiley-VCH: New York, 1998; Chapter 7. (d) Bobo, S.; Storch de Gracia, I.; Chiara, J. L. *Synlett*, in press.

(8) Kametani, T.; Kawamura, K.; Honda, T. *J. Am. Chem. Soc.* **1987**, *109*, 3010.

triflic anhydride in the presence of pyridine at low temperature, a smooth cyclization took place by intramolecular  $\text{S}_{\text{N}}2$  displacement of the triflate ester in transient intermediate **17** by the carbonyl oxygen to give oxazoline **18** in good yield (Scheme 3).<sup>16</sup> Compound **18** was fully deprotected by catalytic hydrogenolysis of the *O*-benzyl group followed by acidic hydrolysis of the oxazoline and the isopropylidene groups to yield trehalosamine (**3**). The physical and spectroscopic data of synthetic **3** were identical to those described for the natural compound.<sup>17</sup> This route afforded **3** in 14 steps and 29% overall yield from D-mannose.

With the final objective of applying this procedure in the final steps of our synthesis of trehalosin (**2**), we set out to test it for the construction of a 2-aminoxazoline ring. Thus, model *N*-alkyl and *N*-aryl ureas **19** and **20** (Scheme 4),



respectively, were prepared in high yield by treatment of **14** with the corresponding isocyanates. Gratifyingly, the reaction of **19** and **20** with triflic anhydride in the presence of pyridine at low temperature produced the 2-aminoxazolines **21** and **22**, respectively, in high yield with concomitant inversion of stereochemistry at the required position. Complete deprotection of **21** by hydrogenolysis under acidic conditions afforded trehalamine (**4**). The physical and spectroscopic data of synthetic **4** were identical to those described for the natural compound.<sup>17</sup> This route to **4** involved 13 steps and proceeded in 37% overall yield from D-mannose. Deprotection of **22**

(9) Gelas, J.; Horton, D. *Carbohydr. Res.* **1978**, *67*, 371.

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(11) (a) Groneberg, R. D.; Miyazaki, T.; Stylianides, N. A.; Schulze, T. J.; Stahl, W.; Schreiner, E. P.; Suzuki, T.; Iwabuchi, Y.; Smith, A. L.; Nicolaou, K. C. *J. Am. Chem. Soc.* **1993**, *115*, 7593. (b) Motawia, M. S.; Marcussen, J.; Moeller, B. L. *J. Carbohydr. Chem.* **1995**, *14*, 1279.

(12) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.

(13) PCC or Swern oxidation proceeded with partial epimerization at C-4 (sugar numbering).

(14) See Supporting Information for  $^1\text{H}$  NMR and NOESY data.

(15) (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.

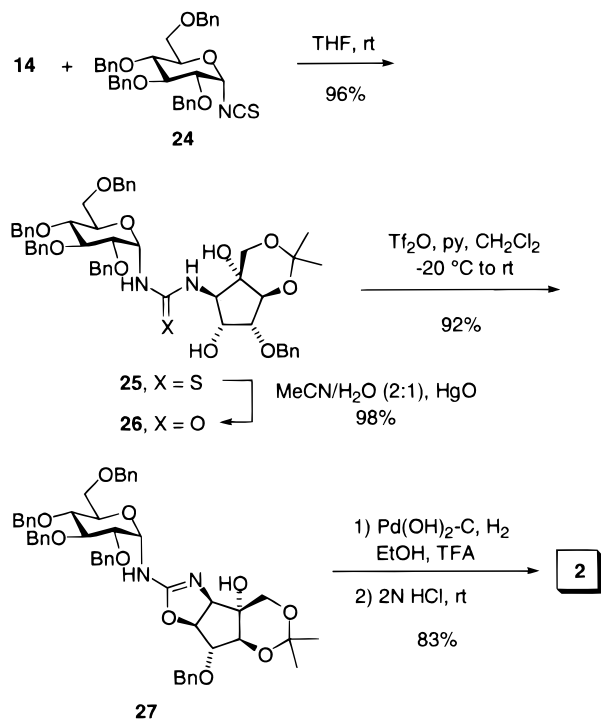
(16) For a former report on oxazoline ring formation under similar conditions, see: Kuo, C. H.; Wendler, N. L. *Tetrahedron Lett.* **1978**, 211.

(17) Ando, O.; Nakajima, M.; Hamano, K.; Itoi, K.; Takahashi, S.; Takamatsu, Y.; Sato, A.; Enokita, R.; Okazaki, T.; Haruyama, H.; Kinoshita, T. *J. Antibiot.* **1993**, *46*, 1116.

under similar conditions gave **23** that was recently prepared by Ogawa and co-workers<sup>18</sup> and shown to be a moderate  $\alpha$ -glucosidase inhibitor.

With this success in hand, we were now ready to complete our synthesis of **2**. As in previously described routes,<sup>2</sup> we condensed our aminocyclitol **14** with  $\alpha$ -glucosyl isothiocyanate **24**<sup>19</sup> to give thiourea **25** (Scheme 5). Treatment of **25**

Scheme 5



with aqueous acetonitrile in the presence of yellow HgO gave urea **26** in quantitative yield.<sup>20</sup> In the event, the reaction of

**26** with triflic anhydride and pyridine under our previously optimized conditions produced the smooth cyclization to the 2-aminooxazoline **27** in very good yield with concomitant inversion of stereochemistry, as required. Hydrogenolysis of the *O*-benzyl groups and acid cleavage of the isopropylidene acetal afforded finally trehazolin (**2**), whose physical and spectroscopic data were identical to those described for the natural compound.<sup>21</sup> This new route to **2** involved only 14 chemical operations from commercially available D-mannose and proceeded in 34% overall yield, a considerable improvement over previous strategies.

In summary, we have developed a concise and efficient synthesis of trehazolin (**2**), trehalamine (**4**), and known<sup>18</sup> trehazolin analogue **23** using D-mannose as starting material. The approach underscores the utility of C=O/C=NOR reductive carbocyclizations promoted by samarium diiodide for the efficient preparation of complex aminocyclitols under very mild conditions. The hydroxyl group at C-2 in the starting sugar played a key dual role along the route. First, it served as an element of stereocontrol in the carbocyclization reaction. Second, it allowed the subsequent construction of the oxazoline ring under very mild conditions by an intramolecular S<sub>N</sub>2 reaction that adjusted the final stereochemistry of the carbocycle. This strategy opens a facile entry to the stereocontrolled preparation of a diversity of analogues of **2**,<sup>1</sup> work that is currently in progress in our laboratory.<sup>22</sup>

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**Supporting Information Available:** Complete experimental procedures and characterization data for the new compounds in Schemes 1–5 and <sup>1</sup>H NOE data for compound **12**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(20) For a recent review on thiocarbonyl to carbonyl group conversion, see: Corsaro, A.; Pistarà, V. *Tetrahedron* **1998**, *54*, 15027.

(21) 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.

(22) 2-Aminothiazoline analogues of **2** can be readily obtained by reaction of **14** with an isothiocyanate followed by treatment of the corresponding thiourea with triflic anhydride and pyridine at low temperature (I. Storch de Gracia and J. L. Chiara, unpublished results).