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Synthesis of *ent*-gabosine E from D-mannose by intramolecular nitrone–olefin cycloaddition

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ABSTRACT

Intramolecular nitrone–olefin cycloaddition in a mannose template followed by N–O cleavage, quaternization of the resulting amine, and finally oxidative elimination of the amino group affords, after deprotection, *ent*-gabosine E in enantiomerically pure form.

The name 'gabosines' has been given to a group of 14 carba-sugars isolated from *Streptomyces* strains.[1] The majority are diastereoisomeric 4,5,6-trihydroxy-2-cyclohexenones with an additional methyl, hydroxymethyl, or acetoxymethyl group at the 2- or 3-positions (Fig. 1), and exhibit a variety of biological activities such as antiprotozoal activity, DNA binding properties, and enzyme inhibition. Related natural products include the glyoxylase I inhibitor COTC[2] (Fig. 1) isolated from *Streptomyces filipensis*, the plant growth factor streptol,[1c] its diastereoisomer MK7607[3] isolated from *Curvularia eragrostidis* which possesses herbicidal activity, the antibiotic rancinamycins,[4a] and numerous structurally related natural products.[4] Furthermore, gabosine-like compounds are constituents of complex entities such as acarbose and/or have been used as intermediates for the synthesis of biologically interesting compounds.

As a consequence, a number of synthetic approaches toward gabosines and related compounds have been reported in the literature,[5] usually starting from carbohydrates or quinic acid. Despite the existence of these synthetic methods for converting sugars into gabosines, a general route starting from a monosaccharide leading to a 4,5,6-trihydroxy-2-hydroxymethyl-2-cyclohexenone with transfer of chirality to the products and allowing the synthesis of any of its diastereoisomers, is needed. Such general methods exist only for gabosines with a 3-hydroxymethyl[5i] or 2-methyl[5k] substituent. Whilst investigating a general synthetic scheme to gabosines with a 3-hydroxymethyl substituent, we considered that our recent work[6] on the synthesis of chiral cyclopentenones might be useful and applicable in this case.

Starting from a hexose, a carbocyclic ring with a hydroxymethyl group could be prepared by an intramolecular nitrone–olefin cycloaddition and further manipulation of the cycloadduct (Scheme 1). The installation of an enone group in protected gabosine **1** could be accomplished by quaternization and subsequent oxidative elimination of hydroxyamine **2**, which could be obtained by N–O bond cleavage in bicyclic isoxazolidine **3**. The latter is the intramolecular cycloadduct of the nitrone derived from the sugar template **4**, which in turn is easily prepared from a hexose. Thus, following this route and assuming that no epimerization would occur during the reaction sequence, the absolute configurations of the C-2, C-3, and C-4 chiral centers of the starting sugar should be transferred to the C-4, C-5, and C-6 positions of the final gabosine. Importantly, this sequence gives us the opportunity to selectively protect the three secondary hydroxy groups, allowing oxidation of the fourth hydroxyl as necessary. It is also worth noting that the stereoselectivity of the cycloaddition reaction is of less

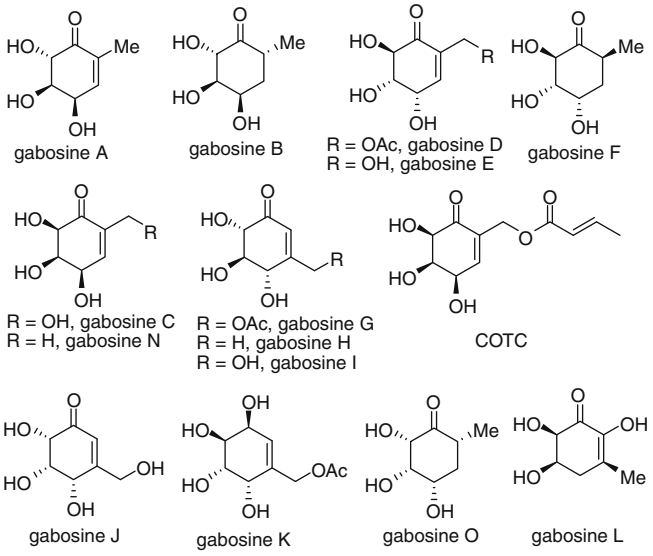

Figure 1. Structure of known isolated gabosines.

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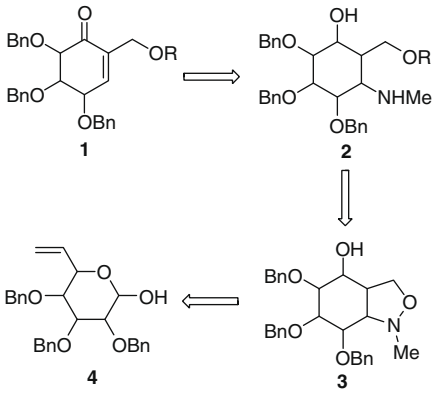
importance, since the newly formed stereocenters are subsequently destroyed.

D-Mannose was the starting material of choice, which would result in *ent*-gabosine E by transfer of its chirality to the final product, applying the above-mentioned methodology. Using the standard protection–deprotection manipulations, commercially available methyl α-D-mannopyranoside **5** was converted into the known compound **6** according to the literature[7] (Scheme 2). Next, the free primary hydroxy group was subjected to Swern oxidation and Wittig reaction to give the known template **7**.[8] Acetal hydrolysis was achieved by the treatment of **7** with H_2SO_4 and Ac_2O followed by hydrolysis of the intermediate acetate with EtONa in EtOH to give **8** in excellent yield. This intermediate was able to undergo the intramolecular nitrone cycloaddition upon condensation with MeNHOH.[9] After some experimentation, we found that the treatment of MeNHOH·HCl with EtONa/EtOH for 30 min, followed by addition to **8** gave the respective nitrone, which without isolation, afforded upon stirring for 24 h, the two cycloaddition products **9** and **10** in 80% combined yield and in a 2:1 ratio. It is interesting to note that when pyridine was used as the solvent and base in the reaction of **8** with MeNHOH·HCl, partial epimerization of the C-2 (sugar numbering) stereocenter took place. The two products **9** and **10** were separated by chromatography and their structures were elucidated by COSY and NOE experiments.[10,11]

The N–O bond of the major cycloadduct **9** was then cleaved using a standard procedure (Zn, AcOH) and the primary hydroxy group was selectively protected using TBSOTf to give compound **12** in 77% overall yield (two steps). Quaternization of the amino group of **12** followed by oxidative elimination led to protected *ent*-gabosine E **13**. This method has been used previously by us,[6] and others[12] for the regioselective formation of an enone functionality. Finally, the protecting groups were removed from **13** with BBr_3 and the expected *ent*-gabosine E **14** was obtained in 85% yield with spectroscopic data in good agreement with those reported for gabosine E.[1a,13]

Unfortunately, the minor cycloadduct **10** did not give **14** when we applied the same reaction sequence. Attempted oxidation of the free secondary hydroxy group after N–O bond scission to **15**, protection of the primary hydroxy group and quaternization of the amine did not give *ent*-gabosine, evidently because the H and Me_3N groups are not *anti*-disposed for elimination, a fact that confirmed the assigned structure of **10**.

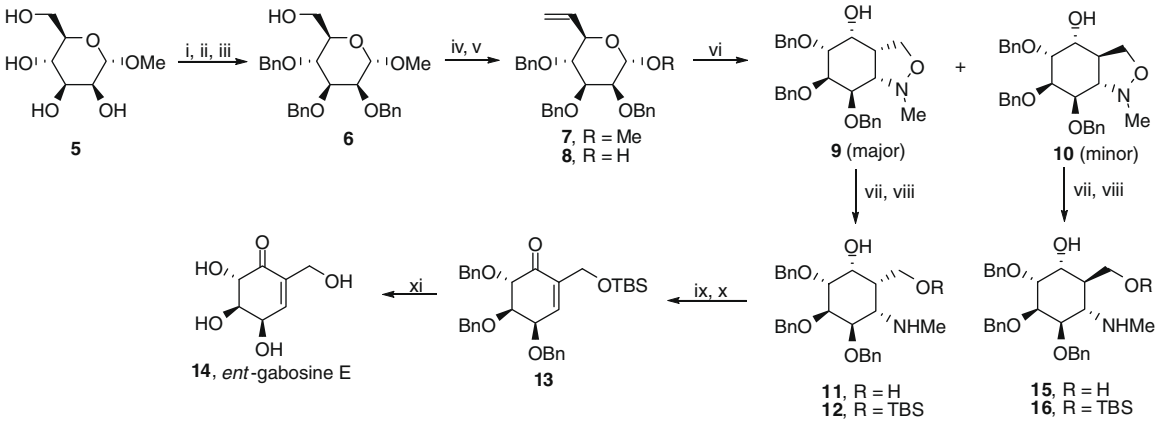
In summary, we have prepared enantiomerically pure *ent*-gabosine E in 11 steps and 12% overall yield starting from commercially available methyl α-D-mannopyranoside, using generally applicable reactions and procedures. In addition, interesting new aminocyclitols, such as **11** and **15**, are prepared as intermediates. Similarly, starting from other hexoses, diasteroisomers of **14** may be prepared and work in this direction is in progress.



Scheme 1. Retrosynthetic analysis of gabosine.

References and notes

1. (a) Bach, G.; Breiding-Mack, S.; Grabley, S.; Hammann, P.; Hütter, K.; Thiericke, R.; Uhr, H.; Wink, J.; Zeek, A. *Liebigs Ann. Chem.* **1993**, 241–250; (b) Tang, Y.-Q.; Maul, C.; Höfs, R.; Sattler, I.; Grabley, S.; Feng, X.-Z.; Zeek, A.; Thiericke, R. *Eur. J. Org. Chem.* **2000**, 149–153; (c) Höfs, R.; Scoppe, S.; Thiericke, R.; Zeek, A. *Eur. J. Org. Chem.* **2000**, 1883–1887.
2. Huntley, C. F. M.; Hamilton, D. S.; Creighton, D. J.; Ganem, B. *Org. Lett.* **2000**, *2*, 3143–3144. and references therein.
3. Song, C.; Jiang, S.; Singh, G. *Synlett* **2001**, 1983–1985. and references therein.
4. Selected publications: (a) Arjona, O.; Borallo, C.; Iradier, F.; Medel, R.; Plumet, J. *Tetrahedron Lett.* **1998**, *39*, 1977–1980. and references therein; (b) Arjona, O.; Iradier, F.; Mañas, R. M.; Plumet, J. *Tetrahedron Lett.* **1998**, *39*, 8335–8336; (c) Pan, X. P.; Chen, R. Y.; Yu, D.-Q. *Phytochemistry* **1998**, *47*, 1063–1066; (d) Hiroya, K.; Ogasawara, K. *Chem. Commun.* **1999**, 2197–2198.
5. (a) Mirza, S.; Molleyeres, L.-P.; Vasella, A. *Helv. Chim. Acta* **1985**, *68*, 988–996; (b) Tatsuda, K.; Yasuda, S.; Araki, N.; Takahashi, M.; Kamiya, Y. *Tetrahedron Lett.* **1998**, *39*, 401–402; (c) Lygo, B.; Swiatyj, M.; Trabsa, H.; Voyle, M. *Tetrahedron Lett.* **1994**, *35*, 4197–4200; (d) Lubineau, A.; Billault, I. *J. Org. Chem.* **1998**, *63*, 5668–5671; (e) Huntley, C. F. M.; Wood, H. B.; Ganem, B. *Tetrahedron Lett.* **2000**, *41*, 2031–2034; (f) Mehta, G.; Lakshminath, S. *Tetrahedron Lett.* **2000**, *41*, 3509–3512; (g) Shinada, T.; Fuji, T.; Ohtani, Y.; Yoshida, Y.; Ohfume, Y. *Synlett* **2002**, 1341–1343; (h) Ramana, G. V.; Rao, B. V. *Tetrahedron Lett.* **2005**, *46*, 3049–3051; (i) Shing, T. K. M.; Cheng, H. M. *J. Org. Chem.* **2007**, *72*, 6610–6613; (j) Monrad, R. N.; Fanefjord, M.; Hansen, F. G.; Jensen, N. M. E.; Madsen, R. *Eur. J. Org. Chem.*



Scheme 2. Reagents and conditions: (i) TrCl, pyridine, 20 °C, 24 h, 84%; (ii) BnCl, NaH, DMF, 20 °C, 12 h, 90%; (iii) H_2SO_4, MeOH (abs), 20 °C, 1 h, 84%; (iv) $(COCl)_2$, DMSO, Et_3N, DCM, −60 °C then $Ph_3P^+CH_3Br^-$, *n*-BuLi 1.6 M in hexanes, THF, −70 °C, 1 h, 72%; (v) H_2SO_4, Ac_2O, 0 °C, 10 min, then EtONa, EtOH, 0 °C, 10 min, 91%; (vi) MeNHOH·HCl, EtONa, EtOH, then 20 °C, 24 h, 80%; (vii) Zn, AcOH, reflux, 1 h; (viii) TBSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C, 45 min, 77% for **12**, 80% for **16**; (ix) excess MeI, K_2CO_3, THF, 24 h; (x) Dess–Martin periodinane, CH_2Cl_2, 20 °C, 30 min, 80% from **12**; and (xi) BBr_3, CH_2Cl_2, −78 °C, 45 min, 85%.

2009, 396–402; (k) Mac, D. H.; Samineni, R.; Petrignet, J.; Srihari, P.; Chandrasekhar, S.; Yadav, J. S.; Grée, R. *Chem. Commun.* **2009**, 4117–4119.

6. (a) Gallos, J. K.; Goga, E. G.; Koumbis, A. E. *J. Chem. Soc., Perkin Trans. 1* **1994**, 613–614; (b) Gallos, J. K.; Damianou, K. C.; Dellios, C. C. *Tetrahedron Lett.* **2001**, *42*, 5769–5771; (c) Gallos, J. K.; Stathakis, C. I.; Kotoulas, S. S.; Koumbis, A. E. *J. Org. Chem.* **2005**, *70*, 6884–6890; (d) Stathakis, C. I.; Gallos, J. K. *Tetrahedron Lett.* **2008**, *49*, 6804–6806.
7. (a) Borén, H. B.; Eklind, K.; Garegg, P. J.; Lindberg, B.; Pilotti, Å. *Acta Chem. Scand.* **1972**, 4143–4146; (b) Jaramillo, C.; Chiara, J.-L.; Martin-Lomas, M. *J. Org. Chem.* **1994**, *59*, 3135–3141.
8. (a) Aurrecoechea, J. M.; López, B.; Arrate, M. *J. Org. Chem.* **2000**, *65*, 6493–6501; (b) Aurrecoechea, J. M.; Arrate, M.; Gil, J. H.; López, B. *Tetrahedron* **2003**, *59*, 5515–5522.
9. (a) Shing, T. K. M.; Elsley, D. A.; Gillhouley, J. G. *J. Chem. Soc., Chem. Commun.* **1989**, 1280–1282; (b) Peet, N. P.; Huber, E. W.; Farr, R. A. *Tetrahedron* **1991**, *47*, 7537–7550; (c) Koumbis, A. E.; Gallos, J. K. *Curr. Org. Chem.* **2003**, *7*, 585–628; (d) Bashiardes, G.; Cano, C.; Mausé, B. *Synlett* **2005**, 1425–1428; (e) Shing, T. K. M.; Cheng, H. M.; Wong, W. F.; Kwong, C. S. K.; Li, J.; Lau, C. B. S.; Leung, P. S.; Cheng, C. H. K. *Org. Lett.* **2008**, *10*, 3145–3148; (f) Shing, T. K. M.; Wong, W. F.; Ikeno, T.; Yamada, T. *Chem. Eur. J.* **2009**, *15*, 2693–2707.
10. The proton signal assignment of diastereoisomers **9** and **10** was made by H,H-COSY experiments. Significant NOE enhancements were observed between the two bridged protons (3a-H and 7a-H) as well as between 3a-H and 4-H in compound **9**, whereas no considerable enhancement was shown between 7-H and 7a-H. On the other hand, in compound **10**, an NOE enhancement was observed between 7-H and 3a-H, but no significant enhancements between the two bridged protons (3a-H and 7a-H) as well as between the couples 3a-H, 4-H and 7-H, 7a-H were evident.
11. Selected data. *Compound* **9**: oil, $[\alpha]_D$ −54.2 (*c* 1.0, $CHCl_3$); IR (neat film) 3500 (br) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.66 (s, 3H, Me), 2.70 (m, 1H, 6-H), 3.15 (m, 2H, 1-H), 3.79 (dd, *J* = 5.2, 4.0 Hz, 1H), 3.85 (dd, *J* = 6.4, 2.8 Hz, 1H), 3.89 (dd, *J* = 5.2, 2.8 Hz, 1H), 4.06 (t, *J* = 8.0 Hz, 1H), 4.11 (dd, *J* = 7.2, 6.4 Hz, 1H), 4,20 (br s, 1H), 4.48 (d, *J* = 12.0 Hz, 1H), 4.52 (d, *J* = 12.0 Hz, 1H), 4.62 (d, *J* = 12.0 Hz, 1H), 4.64 (d, *J* = 12.0 Hz, 1H), 4.68 (d, *J* = 12.0 Hz, 1H), 4.72 (d, *J* = 12.0 Hz, 1H), 7.25-7.40 (m, 15H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 44.6, 44.8, 66.8, 67.2, 68.3, 72.6, 73.2 (two peaks), 75.4, 76.1, 79.5, 127.6, 127.7 (two peaks), 127.8, 127.9, 128.3, 128.4, 128.5, 137.8, 138.5, 138.7; HRMS *m*/*z* 476.2440 $[C_{29}H_{34}NO_5$ $(M+H)^+$ requires 476.2431]. *Compound* **10**: oil, $[\alpha]_D$ −48.7 (*c* 0.9, $CHCl_3$); IR (neat film) 3500 (br) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.10 (br s, 1H), 2.69 (m, 1H), 2.83 (t, *J* = 10.8 Hz, 1H), 2.85 (s, 3H), 3.69 (t, *J* = 3.2 Hz, 1H), 3.83 (m, 3H, 2-H), 3.94 (dd, *J* = 10.8, 3.2 Hz, 1H), 4.07 (t, *J* = 6.8 Hz, 1H), 4.33 (d, *J* = 12.0 Hz, 1H), 4.36 (d, *J* = 12.0 Hz, 1H), 4.42 (d, *J* = 12.0 Hz, 1H), 4.44 (d, *J* = 12.0 Hz, 1H), 4.48 (d, *J* = 12.0 Hz, 1H), 4.73 (d, *J* = 12.0 Hz, 1H), 7.25–7.40 (m, 15H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 47.5, 49.4, 67.7, 68.2, 69.5, 71.9, 73.2, 73.7, 74.8, 79.6, 80.4, 127.7, 127.9, 128.1, 128.4, 128.6, 137.7, 138.0, 138.1; HRMS *m*/*z* 476.2438 $[C_{29}H_{34}NO_5$ $(M+H)^+$ requires 476.2431]. *Compound* **12**: oil, $[\alpha]_D$ −12.7 (*c* 1.5, $CHCl_3$); IR (neat film) 3325 cm^{-1}; ^1H NMR (C_6D_6, 400 MHz, some peaks are broad due to conformer interconversion) δ 0.11 (s, 3H), 0.12 (s, 3H), 1.01 (s, 9H), 2.17 (s, 3H), 2.34 (br m, 1H, 6-H), 3.07 (br m, 1H), 3.95 (dd, *J* = 10.4, 3.2 Hz, 1H), 4.04 (m, 4H), 4.23 (br, 1H), 4.49 (d, *J* = 12.0 Hz, 1H), 4.60 (d, *J* = 12.0 Hz, 1H), 4.62 (d, *J* = 12.0 Hz, 1H), 4.64 (d, *J* = 12.0 Hz, 1H), 4.75 (d, *J* = 12.0 Hz, 1H), 4.81 (d, *J* = 12.0 Hz, 1H), 7.05–7.40 (m, 15H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −5.4, 18.2, 25.9, 34.7, 39.9, 58.7, 61.3, 69.6, 72.5, 72.9, 73.3, 75.9, 76.4, 80.2, 127.4, 127.5, 127.8, 128.3, 138.7, 138.8, 139.1; HRMS *m*/*z* 592.3469 $[C_{35}H_{50}NO_5Si$ $(M+H)^+$ requires 592.3453]. *Compound* **13**: oil, $[\alpha]_D$ −91.1 (*c* 1.2, $CHCl_3$); IR (neat film) 1680 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.08 (s, 3H), 0.09 (s, 3H), 0.93 (s, 9H), 3.96 (dd, *J* = 8.0, 3.2 Hz, 1H), 4.36 (m, 3H), 4.44 (br s, 1H), 4.69 (d, *J* = 11.2 Hz, 1H), 4.72 (d, *J* = 12.0 Hz, 2H), 4.79 (d, *J* = 12.0 Hz, 1H), 4.81 (d, *J* = 12.0 Hz, 1H), 4.91 (d, *J* = 11.2 Hz, 1H), 6.88 (d, *J* = 4.8 Hz, 1H), 7.25–7.40 (m, 15H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −5.5, −5.45, 18.3, 25.9, 59.5, 72.2, 72.5, 73.2, 74.0, 78.8, 80.3, 127.7 (two peaks), 127.8, 128.0, 128.3 (two peaks), 128.4, 137.8, 138.1, 138.2, 138.6, 138.9, 196.4; HRMS *m*/*z* 559.2882 $[C_{34}H_{43}O_5Si$ $(M+H)^+$ requires 559.2874]. *Compound* **16**: oil; IR (neat film) 3325 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.11 (s, 3H), 0.12 (s, 3H), 0.90 (s, 9H), 2.05 (m, 1H), 2.60 (s, 3H), 3.13 (t, *J* = 10.8 Hz, 1H), 3.76 (m, 3H), 3.87 (dd, *J* = 10.5, 7.5 Hz, 1H), 4.03 (d, *J* = 8.7 Hz, 1H), 4.12 (dd, *J* = 10.8, 4.5 Hz, 1H), 4.27 (d, *J* = 11.1 Hz, 1H), 4.43 (d, *J* = 11.1 Hz, 1H), 4.44 (d, *J* = 12.0 Hz, 2H), 4.58 (d, *J* = 12.0 Hz, 1H), 4.64 (d, *J* = 12.0 Hz, 1H), 7.20–7.40 (m, 15H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −5.8, −5.7, 18.1, 25.8, 33.9, 42.0, 60.1, 64.5, 67.6, 71.5, 71.9, 73.2, 73.9, 76.5, 77.8, 127.8, 128.0 (two peaks), 128.1, 128.2, 128.4 (two peaks), 128.5, 128.8, 137.4, 137.7, 137.8; HRMS *m*/*z* 592.3460 $[C_{35}H_{50}NO_5Si$ $(M+H)^+$ requires 592.3453].
12. (a) Jiang, S.; Singh, G.; Wightman, R. H. *Tetrahedron Lett.* **1994**, *35*, 5505–5508; (b) van Boggelen, M. P.; van Dommelen, B. F. G. H.; Singh, G. *Tetrahedron Lett.* **1995**, *36*, 1899–1902; (c) Jiang, S.; McCullough, K. J.; Mekki, B.; Singh, G.; Wightman, R. H. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1805–1814; (d) van Boggelen, M. P.; van Dommelen, B. F. G. A.; Jiang, S.; Singh, G. *Tetrahedron* **1997**, *53*, 16897–16910.
13. For *ent*-gabosine E **14**, $[\alpha]_D^{20}$ −145.7 (*c* 0.35, MeOH) [for gabosine E lit.[1a] $[\alpha]_D$ +148 (*c* 0.85, MeOH) and +152 (*c* 1.0, H_2O)].