Serendipitous Synthesis and Configurational Assignment of (–)-Gabosine J

Tony K. M. Shing,* Y. Chen, Ho T. Wu

Department of Chemistry and Center of Novel Functional Molecules, The Chinese University of Hong Kong, Shatin, Hong Kong, P. R. of China
Fax +85226035057; E-mail: tonyshing@cuhk.edu.hk

Received: 22.03.2012; Accepted after revision: 06.05.2012

Abstract: 2-*epi*-Gabosine I, unambiguously synthesized from benzyl D-mannopyranoside in nine steps with 34% overall yield, has been shown to be identical to gabosine J by NMR spectral analysis, thereby indicating that the relative stereochemistry of gabosine J was incorrectly determined formerly as a *syn*-triol. The relative and absolute configurations of (–)-gabosine J are now revised and confirmed as (2*S*,3*S*,4*R*)-trihydroxy-5-hydroxymethylcyclohex-5-en-1-one. Since the specific rotation of the natural product has not been recorded, the absolute configuration of natural gabosine J is either (–)-gabosine J or its enantiomer.

Key words: carbohydrates, Wittig reaction, stereoselective synthesis, natural products, enones

Gabosine C is the first member of a group of naturally occurring perhydroxylated cyclohexanones and cyclohexenones, fractionated from *Streptomyces* strains in 1974.[1] Subsequently, 14 more gabosines (Figure 1) have been discovered and reported.[2,3a] These metabolites were found to display interesting bioactivities, but the cytotoxic and cancerostatic properties of COTC,[3b] a crotonyl ester of gabosine C, have attracted much attention and stimulated chemists to prepare analogues for chemotherapy evaluation[4] as well as for study of the mechanism of cytotoxicity.[5]

Recently, COTC and its analogues have been shown by others and by us to suppress anticancer drug resistance in alkylating agents such as melphalan[6] and cisplatin,[7] respectively. Hence, we wanted to make 2-*epi*-gabosine I (**4**) which then would be elaborated into a gabosine D ether analogue in order to study the synergistic effect with cisplatin in antitumor activity.[7] Interestingly, by comparing the spectral data of synthetic **4** with those of 15 natural gabosines, we discovered by chance that both the ^{1}H NMR and ^{13}C NMR spectra of synthetic 2-*epi*-gabosine I (**4**) were in good agreement with those of gabosine J. The structure of natural gabosine J was therefore incorrectly assigned as *syn*-triol **3** (Figure 2) in the past and according to the best of our knowledge, neither the synthesis nor the specific rotation of natural gabosine J has been reported.

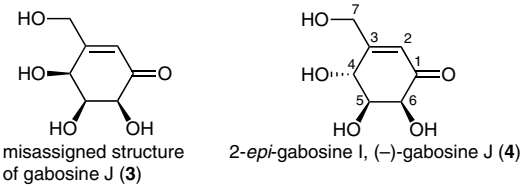


Figure 2 Structures of gabosine J

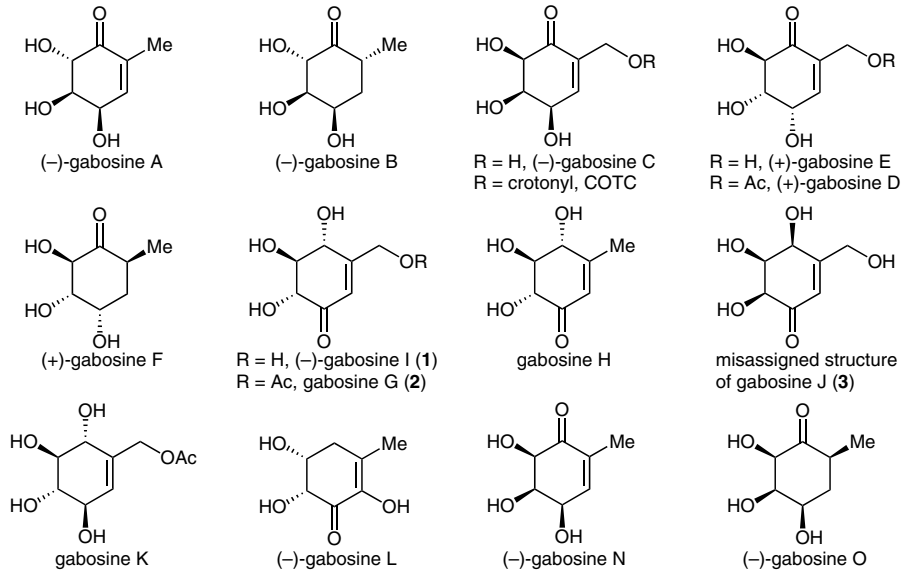
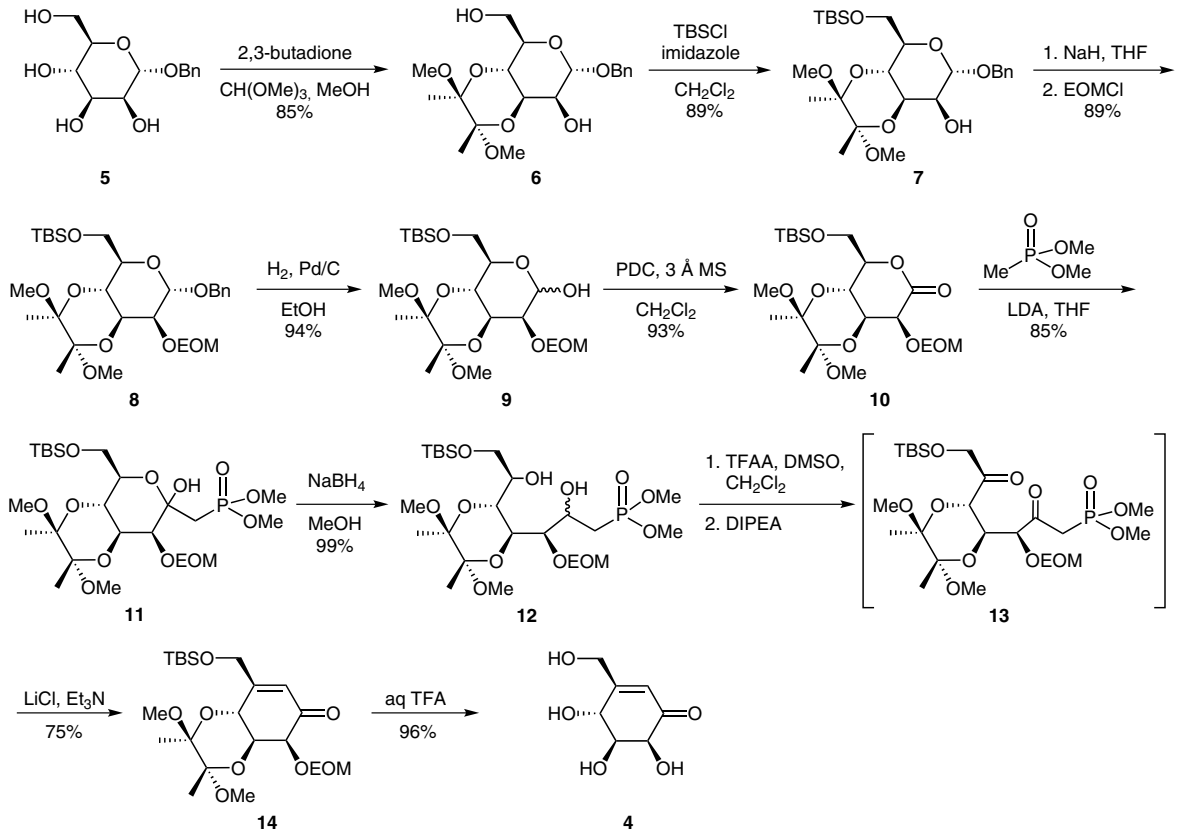


Figure 1 Structures of gabosines

SYNLETT 2012, 23, 1793–1796
Advanced online publication: 29.06.2012
DOI: 10.1055/s-0031-1290402; Art ID: ST-2012-W0269-L



Scheme 1 Synthesis of (–)-gabosine J from D-mannose

Our previous efforts on gabosine synthesis have produced COTC,[8] gabosines A, D, E, G, I, K, F, and O.[9] Our latest work was on gabosine I synthesis via carbocyclization of D-glucose using a Wittig–Horner (Wadsworth–Emmons–Horner) alkenation as the pivotal reaction.[10] Differential protection of the hydroxy functions would allow facile elaboration of the harvested enone into other cyclohexenoid target molecules. Now, the synthesis of 2-*epi*-gabosine I (**4**), shown in Scheme 1, is also based on this tactic because the blocking groups are stable and amenable to selective deprotection.

Transacetalization[11] of the commercially available benzyl α-D-mannopyranoside (**5**)[12] with butadione occurred at OH-3,4 (cf. glucopyranoside)[10] as the only *trans*-diol and gave the known acetal **6**[13] in 85% yield. Regioselective silylation of the primary hydroxy group in **6** afforded ether **7** in 89% yield. The last free alcohol in **7** was blocked as an ethoxymethyl ether to give compound **8** under basic conditions in a good yield. The anomeric benzyl ether was hydrogenolyzed to give lactol **9** which then was oxidized to lactone **10** in a good overall yield. Addition of the lithium salt of methylphosphonate to lactone **10** furnished lactol phosphonate **11** in 85% yield. Difficulties were encountered during the attempted oxidation of the ring-opened form of lactol **11** to the corresponding diketone, hence **11** was hydride reduced to produce heptitol **12** in almost quantitative yield. Swern oxidation[14] was proved to be the best method to convert diol **12** into diketone **13**, which was carbocyclized in the same pot to yield enone **14**. The Wittig–Horner alkenation was induced smoothly with triethylamine, and the addition of LiCl[15,16] shortened the reaction time. Global deprotection of **14** with aqueous acid gave 2-*epi*-gabosine I (**4**) in 96% yield.[17] Hence, 2-*epi*-gabosine I (**4**) was constructed from benzyl mannoside **5** in nine steps with 34% overall yield. The ^{1}H NMR spectral data of **4** in methanol-d_4 (Table 1) are in accord with the literature values,[2a] and the ^{13}C NMR data of **4** have perfect matched with those of natural gabosine J (Table 2). Therefore, the absolute configuration of (–)-gabosine J (**4**) {$[\alpha]_D^{20}$ –75.0 (*c* 0.70, MeOH)} is now established as 2*S*,3*S*,4*R* and is identical to 2-*epi*-gabosine I.

Table 1 Comparison of ^{1}H NMR Data (δ) in MeOH-d_4 of **4** and Natural Gabosine J

	2-H	4-H	5-H	6-H	7-H_2
ref. 2a	6.09, t, *J* = 2.0 Hz	4.17, m	4.17, m	4.54, d, *J* = 2.5 Hz	4.21/4.40, 2 dd, *J* = 17.5, 2.0 Hz
synthetic **4**	6.10, t. *J* = 1.8 Hz	4.16–4.25, m	4.16–4.25, m	4.55, d, *J* = 2.5 Hz	4.16–4.25, m, 4.34, dd, *J* = 17.8, 1.6 Hz

Table 2 Comparison of ^{13}C NMR Data (δ) in MeOH-d_4 of **4** and Natural Gabosine J

	C1	C2	C3	C4	C5	C6	C7
ref. 2a	199.9	63.3	162.3	76.6[a]	73.9[a]	69.9[a]	122.2
synthetic **4**	199.9	63.2	162.2	76.5[a]	73.8[a]	69.9[a]	122.1

[a] Tentative assignment.

To conclude, 2-*epi*-gabosine I (**4**) was successfully synthesized in nine steps from commercially available benzyl mannopyranoside with an overall yield of 34% and found to be identical to (–)-gabosine J (**4**). The relative and absolute configurations of (–)-gabosine J are now revised as (2*S*,3*S*,4*R*)-trihydroxy-5-hydroxymethylcyclohex-5-en-1-one (**4**). However, since the specific rotation of natural gabosine J has not been recorded, the absolute configuration of the natural product is either (–)-gabosine J (**4**) or its enantiomer. It is noteworthy that the present synthesis offers a short, efficient, and enantiospecific route towards enone **14** with differential protection and makes it an attractive intermediate for the synthesis of other heavily oxygenated cyclohexenoid natural products.

Acknowledgment

This work was supported by a Strategic Investment Scheme administered by the Center of Novel Functional Molecules of The Chinese University of Hong Kong and by a Direct Grant from The Chinese University of Hong Kong.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

References

(1) Tatsuta, K.; Tsuchiya, T.; Mikami, N.; Umezawa, S.; Umezawa, H.; Naganawa, H. *J. Antibiot.* **1974**, *27*, 579.
(2) (a) Bach, G.; Breiding, M. S.; Grabley, S.; Hammann, P.; Hütter, K.; Thiericke, R.; Uhr, H.; Wink, J.; Zeeck, A. *Liebigs Ann. Chem.* **1993**, *3*, 241. (b) Tang, Y. Q.; Maul, C.; Höfs, R.; Sattler, I.; Gabley, S.; Feng, X.-Z.; Zeeck, A.; Thiericke, R. *Eur. J. Org. Chem.* **2000**, 149.
(3) (a) Takeuchi, T.; Chimura, H.; Hamada, M.; Umezawa, H.; Yoshka, H.; Oguchi, N.; Takahashi, Y.; Matsuda, A. *J. Antibiot.* **1975**, *28*, 737. (b) Chimura, H.; Nakamura, H.; Takita, T.; Takeuchi, T.; Umezawa, M.; Kato, K.; Saito, S.; Tomisawa, T.; Iitaka, Y. *J. Antibiot.* **1975**, *28*, 743.
(4) (a) Aghil, O.; Bibby, M. C.; Carrington, S. J.; Double, J.; Douglas, K. T.; Phillips, R. M.; Shing, T. K. M. *Anti-Cancer Drug Des.* **1992**, *7*, 67. (b) Oaksmith, J. M.; Ganem, B. *Tetrahedron Lett.* **2009**, *50*, 3497.
(5) (a) Hamilton, D. S.; Ding, Z.; Ganem, B.; Creighton, D. J. *Org. Lett.* **2002**, *4*, 1209. (b) Hamilton, D. S.; Zhang, X.; Ding, Z.; Hubatsch, I.; Mannervik, B.; Houk, K. N.; Ganem, B.; Creighton, D. J. *J. Am. Chem. Soc.* **2003**, *125*, 15049. (c) Joseph, E.; Eiseman, J. L.; Hamilton, D. S.; Wang, H.; Tak, H.; Ding, Z.; Ganem, B.; Creighton, D. J. *J. Med. Chem.* **2003**, *46*, 194.
(6) Kamiya, D.; Uchihata, Y.; Ichikawa, E.; Kato, K.; Umezawa, K. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1111.
(7) Wang, C.-H.; Wu, H. T.; Cheng, H. M.; Yen, T.-J.; Lu, I.-H.; Chang, H. C.; Jao, S.-C.; Shing, T. K. M.; Li, W.-S. *J. Med. Chem.* **2011**, *54*, 8574.
(8) (a) Shing, T. K. M.; Tang, Y. *J. Chem. Soc., Chem. Commun.* **1990**, 312. (b) Shing, T. K. M.; Tang, Y. *Tetrahedron* **1990**, *46*, 6575.
(9) (a) Gabosines G and I: Shing, T. K. M.; Cheng, H. M. *J. Org. Chem.* **2007**, *72*, 6610. (b) Gabosines A, D, and E: Shing, T. K. M.; Cheng, H. M. *Org. Biomol. Chem.* **2009**, *7*, 5098. (c) Gabosine K: Shing, T. K. M.; Cheng, H. M. *Synlett* **2010**, 142. (d) Gabosines I and K: Shing, T. K. M.; Chen, Y.; Ng, W. L. *Synlett* **2011**, 1318. (e) Gabosines F and O: Shing, T. K. M.; So, K. H.; Kwok, W. S. *Org. Lett.* **2009**, *11*, 5070.
(10) Shing, T. K. M.; Chen, Y.; Ng, W. L. *Tetrahedron* **2011**, *67*, 6001.
(11) Ley, S. V.; Baeschlin, D. K.; Dixon, D. J.; Foster, A. C.; Ince, S. J.; Priepke, H. W. M.; Reynolds, D. J. *Chem. Rev.* **2001**, *101*, 53.
(12) Zunk, M.; Kiefel, M. J. *Tetrahedron Lett.* **2011**, *52*, 1296.
(13) Pmoch, C.; Pakulski, Z. *Tetrahedron: Asymmetry* **2008**, *19*, 1494.
(14) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165.
(15) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183.
(16) **Synthesis of Enone 14**
To a mixture of 3 Å MS (200 mg), CH_2Cl_2 (3 mL), and DMSO (0.36 ml, 5.00 mmol) was added dropwise TFAA (0.42 mL, 3.00 mmol) at –78 °C under N_2. After 30 min, a solution of the diols **12** (0.265 mg, 0.45 mmol) in CH_2Cl_2 (2 mL) was added dropwise. The reaction mixture was stirred for an additional 5 h at –78 °C, and DIEPA (1.75 mL, 10.00 mmol) was added dropwise. The reaction mixture was stirred at –78 °C for 15 min and then warmed to 25 °C over a period of 2 h. LiCl (38 mg, 0.90 mmol) and Et_3N (0.25 mL, 1.80 mmol) was added to the reaction mixture, and stirring was continued for an additional 1.5 h at the same temperature. The reaction mixture was then filtered, and the filtrate was concentrated under vacuum. Flash chromatography (hexane–EtOAc = 8:1) of the crude residue yielded enone **14** (0.144 mg, 70%) as a yellow oil. $[\alpha]_D^{20}$ 137.4 (*c* 1.23, $CHCl_3$). R_f = 0.6 (*n*-hexane–EtOAc, 3:1). IR (thin film): 2953, 2886, 2857, 1685, 1630, 1472, 1378, 1257, 1164, 1114, 1034 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.05 (3 H, s), 0.06 (3 H, s), 0.88 (9 H, s), 1.17 (3 H, t, *J* = 7.2 Hz), 1.31 (3 H, s), 1.30 (3 H, s), 3.23 (3 H, s), 3.27 (3 H, s), 3.52–3.63 (2 H, m), 3.94 (1 H, dd, *J* = 2.7, 13.2 Hz), 4.12 (1 H, dd, *J* = 1.5, 3.0 Hz), 4.33 (1 H, dt, *J* = 1.8, 18.3 Hz), 4.58 (1 H, d, *J* = 18.3 Hz), 4.80 (2 H, s), 4.93 (1 H, dt, *J* = 1.2, 8.7 Hz), 6.12 (1 H, dd, *J* = 1.2, 2.1 Hz). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = –4.9, –4.8, 15.5, 18.2, 18.3, 18.8, 26.4, 26.5, 48.7, 48.7, 61.4, 64.1, 66.0, 71.6, 77.3, 95.1, 100.5, 100.9, 122.2, 162.6, 194.7. ESI-MS: *m/z* (%) = 483 (100) $[M + Na]^+$. ESI-HRMS: *m/z* calcd for $C_{22}H_{40}O_8Si$ $[M + Na]^+$: 483.2385; found: 483.2392.
(17) **Synthesis of (–)-Gabosine J (4)**
To enone **14** (35 mg, 0.08 mmol) was added TFA (2 mL) and

H_2O (0.1 mL) at r.t. The resulting solution was stirred for 5 min at r.t. Concentration of the solution followed by flash chromatography ($CHCl_3$–MeOH = 8:1) yielded (–)-gabosine J (**4**; 12 mg, 96%) as colorless oil. $[\alpha]_D^{20}$ –75.0 (*c* 0.70, MeOH). R_f = 0.3 ($CHCl_3$–MeOH = 4:1). IR (thin film): 3311, 2912, 1682, 1438, 1384, 1119, 1087, 1040 cm^{-1}. ^1H NMR (300 MHz, MeOD): δ = 4.16–4.25 (3 H, m), 4.41 (1 H, dd, *J* = 17.8, 1.7 Hz), 4.55 (1 H, d, *J* = 2.5 Hz), 6.10 (1 H, t, *J* = 1.7 Hz). ^{13}C NMR (75.47 MHz, MeOD): δ = 63.2, 69.9, 73.8, 76.5, 122.1, 162.2, 199.9. ESI-MS: *m/z* (%) = 197 (100) $[M + Na]^+$. ESI-HRMS: *m/z* calcd for $C_7H_{10}O_5$ $[M + Na]^+$: 197.0420; found: 197.0423.

