Tetrahedron Letters 50 (2009) 957–959

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Structural elucidation of daphniacetal A, a new oxa-cage compound isolated from *Daphniphyllum macropodum* Miq.

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ARTICLE INFO

Article history:
Received 13 October 2008
Revised 4 December 2008
Accepted 9 December 2008
Available online 13 December 2008

Keywords:
Asymmetric synthesis
Daphniacetal A
Daphniphyllaceae
Daphniphyllum macropodum Miq.
NMR

ABSTRACT

A new oxa-cage natural product daphniacetal A (1) was isolated from *Daphniphyllum macropodum* Miq. Its structure and relative configuration were established based on spectroscopic data and the single-crystal X-ray diffraction crystallography. Compound **1** was also synthesized for determination of its absolute configuration and evaluation of antioxidant effects.

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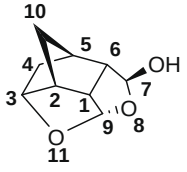
Oxa-cage compounds have attracted great interest as challenging projects for asymmetric synthesis.[1] However, there was rare report on natural oxa-cage compounds. In the course of our search for *Daphniphyllum* alkaloids with interesting ring system,[2,3] a new oxa-cage natural product, daphniacetal A (**1**), was isolated from the fruits of *Daphniphyllum macropodum* Miq. (Daphniphyllaceae). Herein, we describe the structural elucidation, asymmetric synthesis, and antioxidant effects of **1**.

The fresh fruits of *D. macropodum* (20 kg) were extracted with 95% EtOH. The extract was partitioned between EtOAc and tartaric acid. The aqueous layer was then basified to pH 10 followed by exhaustive extraction with $CHCl_3$. $CHCl_3$–soluble materials were subjected to an amino silica gel column ($CHCl_3$/MeOH 1:0 → 0:1), from which a fraction, eluted with $CHCl_3$/MeOH (10:1), was purified on normal H silica gel ($CHCl_3$/MeOH, 25:1 → 25:2) to afford compound **1** (0.0001%), which gave positive reactions with the Dragendorff reagent after being treated with 5% H_2SO_4 (CH_3CH_2OH) at 120 °C for 2 min.



Daphniacetal A (**1**)[4] was obtained as colorless needles (ether), mp 149–150 °C, with $[\alpha]_D$ +90.8 (CH_3OH, *c*, 0.2). Its molecular formula $C_9H_{12}O_3$ was established by HRESIMS, indicating four degrees of unsaturation. The IR absorption bands at 3441 cm^{-1} showed the presence of hydroxyl group in **1**. ^{13}C NMR spectra of **1** revealed 9 sp^3 signals as shown in Table 1, including two methylenes and seven methines. Among them, two sp^3-oxygenated carbons (δ_C 110.2

Table 1
^1H [δ_H (*J*, Hz)] and ^{13}C [δ_C] NMR data of daphniacetal A (**1**) in CD_3OD at 300 K

No.	^1H (δ_H)	^{13}C (δ_C)
1	3.18 (1H, 6.0, 12.0)	50.2
2	2.79 (1H, t, 5.5)	50.7
3	4.35 (1H, dt, 5.5, 3.0)	81.9
4a	1.70 (1H, br d, 12.0)	34.7
4b	1.50–1.56 (1H, m)	
5	2.32 (1H, br s)	38.5
6	2.49 (1H, dd, 6.0, 12.0)	55.3
7	5.24 (1H, s)	101.0
9	5.70 (1H, d, 6.0)	110.2
10a	1.62–1.66 (1H, m)	40.7
10b	1.52–1.56 (1H, m)	

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doi:10.1016/j.tetlet.2008.12.027

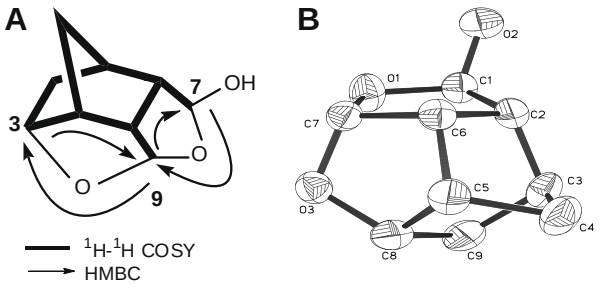
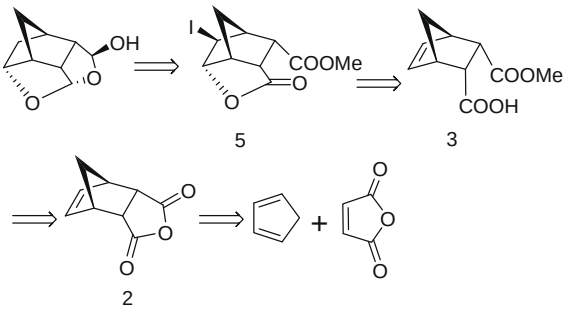


Figure 1. Selected 2D NMR correlations (A) and single-crystal X-ray structure (B) of **1**.

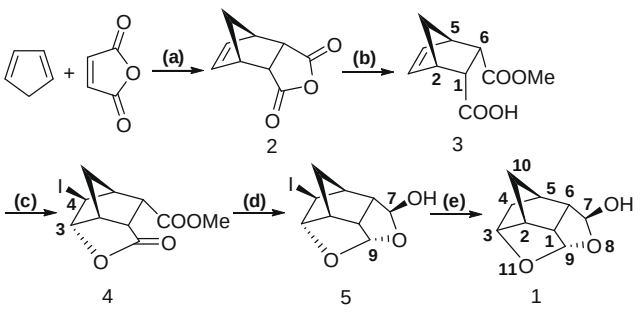
and 101.0) were attributable to acetal or hemi-acetal groups. With consideration of four degrees of unsaturation, it was assumed for the presence of quaternary cyclic system in **1**.

Comprehensive analysis of two-dimensional NMR data, including the results of ^{1}H–^{1}H COSY, HMQC, and HMBC experiments, shown in Figure 1, enabled to establish planar structure of **1** as an 8,11-dioxatetracyclo [4.3.1.^{2,5}1.^{4,7}0^{1,6}]undecane with hydroxyl group at C-7. The relative configuration of **1** was determined by NOESY experiments, and was confirmed by X-ray crystallographic analysis (Fig. 1).[5]

To further determine the absolute configuration of **1**, asymmetric total synthesis of **1** was applied. A retrosynthetic analysis (Scheme 1) of the target molecule **1**, involving the intermediate **3**, led to the identification of maleic anhydride and cyclopentadiene as the starting point for our synthesis. Additionally, cinchona alkaloid-mediated opening of prochiral cyclic anhydride **2** in the presence of methanol served as an effective stereo- and regioselective operation.[6]



Scheme 1. Retrosynthetic analysis of daphniacetal A (**1**).



Scheme 2. Asymmetric synthesis of (+)-daphniacetal A (**1**). Reagents and conditions: (a) in petrolum ether–EtOAc, rt, 4h, 55%; (b) quinidine–MeOH, in toluene/CCl4, −55 °C, 60 h, 92%, 97% ee; (c) I2, in pyridine, 70 °C, 12 h, 88%; (d) DIBAH, in *n*-C_6H_{14}, −78 °C, 1 h, 76%; (e) Bu_3SnH/AIBN, in toluene, 50 °C, 1.5 h, 68%.

As described in Scheme 2, Diels–Alder reaction between maleic anhydride and cyclopentadiene in solution of petroleum ether/EtOAc at room temperature gave *endo*-bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic anhydride (**2**) with the yield of 55%. Quinidine-mediated desymmetrization of *meso*-anhydride (**2**) with MeOH in toluene/CCl_4 at −55 °C for 60 h resulted in (+)-(1*R*,2*S*,5*R*,6*S*)-monoester (**3**) with 92% yield and 97% ee.[6–8] Treatment of **3** with iodine in pyridine at 70 °C for 12 h gave (+)-(3*S*,4*S*)-iodo-lactone (**4**) in 88% yield.[9,10] **4** was then reduced by DIBAH in THF at −78 °C for 1 h to produce corresponding (+)-(7*S*,9*S*)-iodo-cage (**5**) in 76% yield.[9,11] Finally, hydrogenolysis of **5** with Bu_3SnH and AIBN in toluene at 50 °C for 1.5 h afforded (+)-daphniacetal A (**1**) as colorless crystal with 68% yield. The physical, spectroscopic, and spectrometric data (^{1}H NMR, ^{13}C NMR, $[\alpha]^D$, and HRMS) of the synthetic material were well in consistence with those of the natural product.[12] Therefore, absolute configuration of the isolated **1** was determined as 1*R*,2*S*,3*S*,5*R*,6*S*,7*S*,9*S*.

Compound **1** showed no antioxidant effects against H_2O_2-induced impairment in PC12 cells.

Acknowledgments

This research work was financially supported by the Natural Science Foundation of PR China (project No. 20672120). Authors were grateful to Professor Xun Gong, Kunming Institute of Botany, Chinese Academy of Sciences (CAS), for the collection and identification of the plant material.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.12.027.

References and notes

1. (a) Suri, S. C. *J. Org. Chem.* **1993**, *58*, 4153–4154; (b) Coxon, J. M.; Fong, S. T.; McDonald, D. Q. *Tetrahedron Lett.* **1991**, *32*, 7115–7118; (c) Marchand, A. P.; Reddy, G. M.; Watson, W. H.; Kashyap, R. *Tetrahedron* **1990**, *46*, 3409–3418; (d) Mehta, G.; Reddy, A. V. *J. Org. Chem.* **1987**, *52*, 460–462; (e) Mehta, G.; Rao, H. S. P.; Reddy, K. R. *J. Chem. Soc., Chem. Commun.* **1987**, 78–80; (f) Marchand, A. P.; LaRoe, W. D.; Sharma, G. V. M.; Suri, S. C.; Reddy, D. S. *J. Org. Chem.* **1986**, *51*, 1622–1625; (g) Mehta, G.; Rao, H. S. P. *J. Chem. Soc., Chem. Commun.* **1986**, 472–473; (h) Fessner, W. D.; Prinzbach, H. *Tetrahedron* **1986**, *42*, 1797–1802; (i) Mehta, G.; Nair, M. S. *J. Am. Chem. Soc.* **1985**, *107*, 7519–7524; (j) Singh, P. *J. Org. Chem.* **1979**, *44*, 843–846; (k) Barborak, J. C.; Smith, E. C. *J. Org. Chem.* **1976**, *41*, 1433–1437; (l) Marchand, A. P.; Chou, T. C. *Tetrahedron* **1975**, *31*, 2655–2658; (m) Sasaki, T.; Eguchi, S.; Kiriyama, T.; Hiroaki, O. *Tetrahedron* **1974**, *30*, 2707–2712; (n) Prinzbach, H.; Klaus, M. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 276–278.
2. (a) Li, C. S.; Di, Y. T.; Mu, S. Z.; He, H. P.; Zhang, Q.; Fang, X.; Zhang, Y.; Li, S. L.; Lu, Y.; Gong, Y. Q.; Hao, X. J. *J. Nat. Prod.* **2008**, *71*, 1202–1206; (b) Mu, S. Z.; Wang, J. S.; Yang, X. S.; He, H. P.; Li, C. S.; Di, Y. T.; Wang, Y.; Zhang, Y.; Fang, X.; Huang, L. J.; Hao, X. J. *J. Nat. Prod.* **2008**, *71*, 564–569; (c) Di, Y. T.; Liu, L. L.; Li, C. S.; Zhang, Y.; Zhang, Q.; Mu, S. Z.; Sun, Q. Y.; Yang, F. M.; Liu, H. Y.; Hao, X. J. *Helv. Chim. Acta* **2008**, *91*, 838–843;; (d) Tan, C. J.; Di, Y. T.; Wang, Y. H.; Wang, Y.; Mu, S. Z.; Gao, S.; Zhang, Y.; Kong, N. C.; He, H. P.; Zhang, J. X.; Fang, X.; Li, C. S.; Lu, Y.; Hao, X. J. *Tetrahedron Lett.* **2008**, *49*, 3376–3379; (e) Zhang, Y.; He, H. P.; Di, Y. T.; Mu, S. Z.; Wang, Y. H.; Wang, J. S.; Li, C. S.; Kong, N.; Gao, S.; Hao, X. J. *Tetrahedron Lett.* **2007**, *48*, 9104–9107; (f) Li, C. S.; Di, Y. T.; He, H. P.; Gao, S.; Wang, Y. H.; Lu, Y.; Zhong, J. L.; Hao, X. J. *Org. Lett.* **2007**, *9*, 2509–2512; (g) Di, Y. T.; He, H. P.; Wang, Y. S.; Li, L. B.; Lu, Y.; Gong, J. B.; Fang, X.; Kong, N. C.; Li, S. L.; Zhu, H. J.; Hao, X. J. *Org. Lett.* **2007**, *9*, 1355–1358; (h) Mu, S. Z. ; Wang, Y.; He, H. P.; Yang, X. W.; Wang, Y. H.; Di, Y. T.; Lu, Y.; Chang, Y.; Hao, X. J. *J. Nat. Prod.* **2006**, *69*, 1065–1069; (i) Di, Y. T.; He, H. P.; Liu, H. Y.; Du, Z. Z.; Tian, J. M.; Yang, X. W.; Wang, Y. H.; Hao, X. J. *Tetrahedron Lett.* **2006**, *47*, 5329–5331; (j) Di, Y. T.; He, H. P.; Lu, Y.; Yi, P.; Li, L.; Wu, L.; Hao, X. J. *J. Nat. Prod.* **2006**, *69*, 1074–1076; (k) Li, L.; He, H. P.; Di, Y. T.; Tian, J. M.; Hao, X. J. *Helv. Chim. Acta* **2006**, *89*, 1457–1462; (l) Li, L.; He, H. P.; Di, Y. T.; Gao, S.; Hao, X. J. *Tetrahedron Lett.* **2006**, *47*, 6259–6262; (m) Di, Y. T.; He, H. P.; Li, C. S.; Tian, J. M.; Mu, S. Z.; Li, S. L.; Gao, S.; Hao, X. J. *J. Nat. Prod.* **2006**, *69*, 1745–1748.
3. (a) Kong, N. C.; He, H. P.; Wang, Y. H.; Mu, S. Z.; Di, Y. T.; Hao, X. *J. Nat. Prod.* **2007**, *70*, 1348–1351; (b) Kong, N. C.; He, H. P.; Wang, Y. H.; Gao, S.; Di, Y. T.; Hao, X. J. *Helv. Chim. Acta* **2007**, *90*, 972–976.
4. Daphniacetal A (**1**): Colorless needles (ether), $[\alpha]_D^{20}$ +90.8 (*c*, 0.20, MeOH), mp 149–151 °C; IR λ_{max}^{KBr}: 3441(br, OH) cm^{-1}; ^{1}H (500 MHz) and ^{13}C NMR (125 MHz) data see Table 1; **E**I-MS (70 ev) *m/z*: 168 (M$^+$, 3), 151(18),

125(49), 122(100), 93(61); HRESIMS *m/z*: 169.0860 (calcd for $C_9H_{10}O_3$, $[M+H]^+$ 169.0859).

5. Crystallographic data for daphniacetal A (**1**) have been deposited at the Cambridge Crystallographic Data Center (Deposition no. CCDC 692676). Copies of the data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.htm.
6. Bolm, C.; Schiffers, I.; Atodiresei, I.; Hackenberger, C. P. R. *Tetrahedron: Asymmetry* **2003**, *14*, 3455–3467.
7. Bolm, C.; Schiffers, I.; Dinter, C. L.; Gerlach, A. *J. Org. Chem.* **2000**, *65*, 6984–6991.
8. Compound **3**: Colorless needles (petroleum ether), mp 76–78 °C; $[\alpha]_D^{20}$ +8.0 (*c*, 2.0, CCl_4). ^{13}C NMR ($CDCl_3$, 125 MHz) δ_C 178.5, 172.9, 135.6, 134.2, 51.5, 48.8, 48.2, 48.0, 46.6, 46.0.
9. (a) Zefirov, N. S.; Sereda, G. A.; Sosonuk, S. E.; Zyk, N. V.; Likhomanova, T. I. *Synthesis* **1995**, *11*, 1359–1361; (b) Tsai, S. H.; Wu, H. J.; Chung, W. S. *J. Chin. Chem. Soc.* **1996**, *43*, 445–449.
10. Compound **4**: White solid, mp 117–120 °C; $[\alpha]_D^{20}$ +48.1 (*c*, 2.2, acetone). ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 176.3 (C-9), 170.6 (C-7), 88.7 (C-3), 52.4 (MeO), 49.3 (C-2), 48.6 (C-6), 48.4 (C-5), 40.3 (C-1), 37.6 (C-10), 24.9 (C-4).
11. Compound **5**: White solid, mp 72–74 °C; $[\alpha]_D^{20}$ +120.3 (*c*, 1.5, acetone). ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 109.0 (C-9), 98.9 (C-7), 90.5 (C-3), 53.7 (C-6), 49.6 (C-2), 47.5 (C-1), 47.1 (C-5), 39.8 (C-8), 29.3 (C-4).
12. S0ynthetic compound **1**: Colorless needles (petroleum ether–acetone), mp 150–152 °C; $[\alpha]_D^{20}$ +91.0 (*c*, 0.2, MeOH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 109.9 (C-9), 101.1 (C-7), 90.5 (C-3), 55.4 (C-6), 50.9 (C-2), 50.1 (C-1), 40.7 (C-10), 38.6 (C-5), 34.7 (C-4).