Pergamon

Tetrahedron Letters 43 (2002) 291–293

TETRAHEDRON LETTERS

The first direct synthesis of α-mangostin, a potent inhibitor of the acidic sphingomyelinase

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Received 22 October 2001; revised 5 November 2001; accepted 9 November 2001

Abstract—A total synthesis of α-mangostin **1a** has been achieved. The key cyclization reaction to construct the xanthone framework was undertaken by employing the PPh_3–CCl_4 conditions. The inhibitory activities of **1a** and the benzophenone intermediate **16** against the acidic sphingomyelinase were discussed.

From among extensive investigations to acquire new active substances in cancer chemotherapy, inhibitory activity against the acidic sphingomyelinase closely related to apoptosis-induction was found in α-mangostin **1a**,[1] known as a component of mangosteen *Garcinia mangostana* L. (Guttiferae).[2] While such biological activities were confirmed as a competitive antagonist of the histamine H1 receptor,[3a] inhibition of topoisomerases I and II,[3b] antibacterial activity against *Helicobacter pylori*,[3c] anti-inflammatory activities[3d] and inhibition of oxidative damage of human LDL,[3e] no synthesis of **1a** carrying the intriguing highly-functionalized xanthone structure has been published, with the exception of the formal process by Lee:[4] β-mangostin **1b** and dimethylmangostin **1d** were synthesized from chroman derivatives. Since conversion of **1d** into three other mangostins **1a**–**c** was accomplished, the synthesis of **1d** constituted the total synthesis of **1a**.[5] Accordingly, an effective synthetic route to **1a** and related derivatives, would be required to understand the detailed mode of action of their inhibitory activities. This background prompted us to initiate a synthetic investigation of **1a**.

According to the retrosynthetic analysis (Fig. 1), it might be reasonable that α-mangostin **1a** would be cleaved at the diaryl ether moiety, and the resulted benzophenone would be divided into two aromatic derivatives (**A**, **B**). Upon employing this strategy, the following problems would be solved: (1) the specific phenol groups should be effectively activated and/or protected to construct the diaryl ether moiety in a regioselective manner. (2) Since the prenyl groups tend to cyclize leading to the corresponding chroman derivatives,[4] all of the reaction steps should be manipulated under mild reaction conditions.

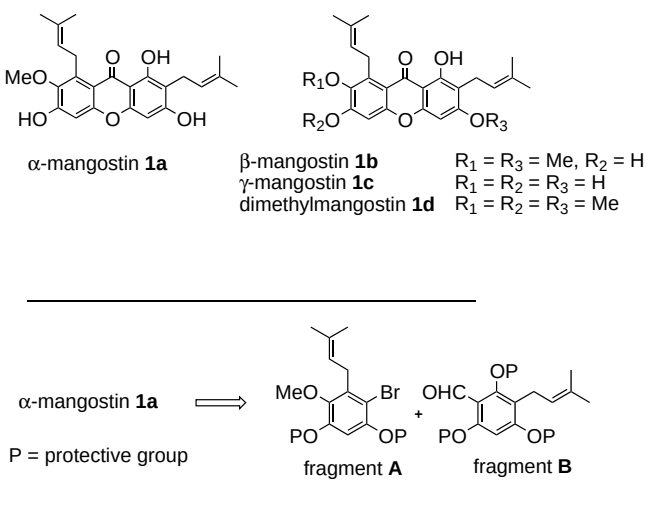

Figure 1. Mangostins **1a**–**d**, and the retrosynthetic analysis of **1a**.

Keywords: *Garcinia mangostana* L.; α-mangostin; acidic sphingomyelinase; apoptosis.

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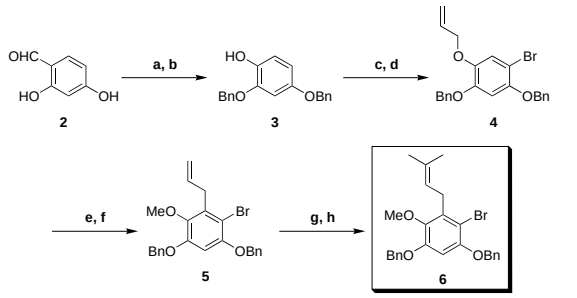
0040-4039/02/$ - see front matter
PII: S0040-4039(01)02137-2

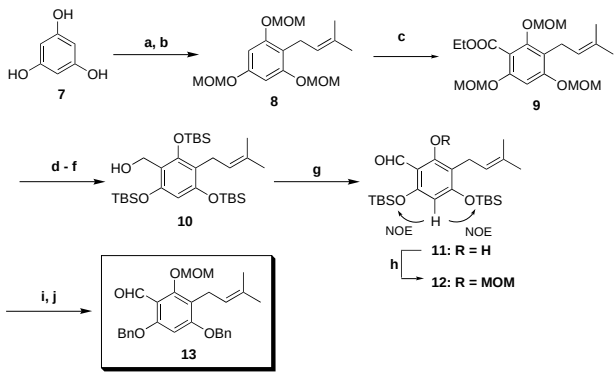
Synthesis of fragment 6. The synthesis was commenced by protection of 2,4-dihydroxybenzaldehyde **2** by benzyl groups, followed by Baeyer–Villiger oxidation and acid hydrolysis to provide the corresponding phenol **3** (Scheme 1). Compound **3** was subsequently submitted to bromination and allylation leading to **4** in high overall yield. Upon heating of **4** at 160°C, the expected Claisen rearrangement was effected to produce an allylbenzene, and the resulted phenol was protected as a methyl ether, leading to **5**. The Lemieux–Johnson oxidation of **5**, followed by the Wittig reaction provided the desired bromobenzene **6**.

Synthesis of fragment 13. Another fragment **13** was synthesized from 1,3,5-trihydroxybenzene (phloroglucinol) **7** (Scheme 2). Thus, **7** was exhaustively protected with MOM groups, and the following prenylation gave **8** in high overall yield. After introduction of ethoxycarbonyl groups to **8**, the resulting **9** was subsequently submitted to acid-catalyzed methanolysis, TBS-protection, then DIBAL-reduction to give benzyl alcohol **10**. Among such oxidation methods attempted as MnO_2, PCC, Swern and Dess–Martin oxidations, only IBX[6] effected the desired conversion of **10** into the aldehyde **11**, fortunately with concomitant removal of the TBS group adjacent to the prenyl group.[7] The position of the phenol generated was confirmed by the NOE experiments of **12**, as depicted in Scheme 2. For utilization in the following regioselective cyclization, this phenol was protected as an MOM ether to **12**, and the following manipulation involving the exchange of the TBS to benzyl groups, provided **13**. With the two benzaldehydes **12**, **13** in hand, both compounds were submitted to the coupling reaction with **6**.

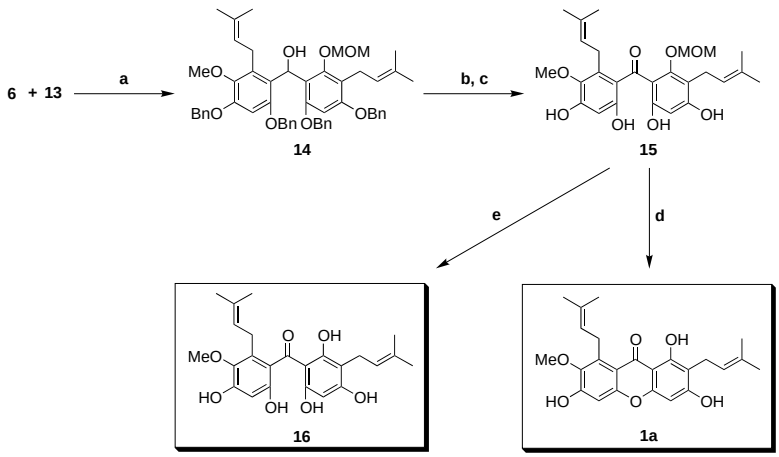
Coupling reaction to the target molecule. Coupling of **13** with an anion generated from **6** provided the corresponding alcohol **14** in moderate yield, although the case employing **12** was unsuccessful, probably owing to the steric hindrance of the TBS group (Scheme 3). Compound **14** was converted in two steps into the benzophenone **15**.[8] Although cyclization reactions under the usual acidic and basic conditions were unsuc-



Scheme 1. (a) BnBr, K_2CO_3, DMF, rt, 96%; (b) *m*CPBA, CH_2Cl_2, rt; 6 M HCl, MeOH, rt 95% in two steps; (c) Br_2, $CHCl_3$, rt, 84%; (d) allyl bromide, K_2CO_3, DMF, rt, 80%; (e) 160°C, 73%; (f) MeI, K_2CO_3, DMF, rt, 87%; (g) OsO_4, $NaIO_4$, Et_2O/H_2O (1/1), rt, 95%; (h) *i*$PrPh_3P^+I^-$, *n*BuLi, THF, 0°C, 72%.



Scheme 2. (a) NaH, MOMCl, DMF, rt, 96%; (b) *n*BuLi; prenyl bromide, THF, 0°C, 89%; (c) *n*BuLi; $(EtO)_2CO$, THF, 0°C, 95%; (d) CSA, MeOH, 60°C, 100%; (e) TBSCl, DMAP, Et_3N, DMF, rt, 100%; (f) DIBAL-H, toluene, −78°C, 78%; (g) IBX, toluene/DMSO (1/1), rt, 76%; (h) NaH, MOMCl, CH_2Cl_2, rt, 65%; (i) TBAF, THF, 0°C, 100%; (j) BnBr, K_2CO_3, DMF, rt, 98%.



Scheme 3. (a) *s*BuLi, THF, −78°C, 49%; (b) IBX, toluene/DMSO (1/1), rt, 76%; (c) 10% Pd/C, HCO_2NH_4, acetone, rt, 63%; (d) PPh_3, CCl_4, THF, rt, then silica gel, 43%; (e) CSA, MeOH, rt, 76%.

cessful, the PPh_3–CCl_4 protocol[9] with the following silica gel treatment, enabled the desired cyclization, as well as removal of the MOM group directly to give α-mangostin **1a**. This method was developed in this laboratory for conversion of β-triketide into the corresponding γ-pyrones under mild acidic conditions. Transformation of **15** into **1a** might be initiated by phosphorylation of the phenols, and the following abstraction of triphenylphosphine oxide effected the cyclization. Deprotection of the MOM group was simultaneously conducted with the plausible active species ($Ph_3P^+Cl{\cdot}CCl_3^-$). The spectroscopic data of the synthetic sample was identical with those of the natural product.[1]

Biological activity. The biological assessment of the benzophenone derivative (e.g. **16**) possessing similar functions to **1a**, has not been reported, in contrast to tetrahydro- and diacetyl-xanthones **17** and **18** derived from **1a**: the hydrophylic phenols were essential to exhibit the activity (**18**), whereas the olefinic moiety gave no critical effect (**17**) (Fig. 2). Accordingly, compound **15** was converted by acid hydrolysis into **16** to confirm its activity as part of our biochemical investigation of **1a**. In the biological assay in the presence of acidic sphingomyelinase and NBD–sphingomyelin,[1] the benzophenone **16**[10] exhibited the comparable inhibitory activity to that of **1a** (**1a**: IC_{50} 4.21 μg/ml; **16**: IC_{50} 16.56 μg/ml). Since lower cytotoxicity than that of **1a** was observed, **16** will provide new information towards understanding the mechanism of the acidic sphingomyelinase-regulated apoptosis. Extensive investigation of the structure–activity relationship is in progress.

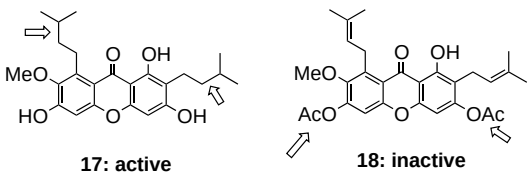


Figure 2. α-Mangostin derivatives **17**, **18** and their inhibitory activities against the acidic sphingomyelinase (Ref. 1).

References

1. Okudaira, C.; Ikeda, Y.; Komdo, S.; Furuya, S.; Hirabayashi, Y.; Koyano, T.; Saito, Y.; Umezawa, K. *J. Enzym. Inhib.* **2000**, *15*, 129–138.
2. Isolation: Schmid, W. *Liebigs Ann. Chem.* **1855**, *93*, 83–88; Dragendorff, O. *Liebigs Ann. Chem.* **1930**, *482*, 280–301. Structural determination: Yates, P.; Stout, G. H. *J. Am. Chem. Soc.* **1958**, *80*, 1691–1700; Scheinmann, F. *Chem. Commun.* **1967**, 1015–1017; Stout, G. H.; Krahn, M. M.; Yates, P.; Bhat, H. B. *Chem. Commun.* **1968**, 211–212.
3. (a) Chairungsrilerd, N.; Furukawa, K.; Ohta, T.; Nozoe, S.; Ohizumi, Y. *Eur. J. Pharmacol.* **1996**, *314*, 351–356; (b) Tosa, H.; Iinuma, M.; Tanaka, T.; Nozaki, H.; Ikeda, S.; Tsutsui, K.; Tsutsui, K.; Yamada, M.; Fujimori, S. *Chem. Pharm. Bull.* **1997**, *45*, 418–420; (c) Hasegawa, H.; Sasaki, S.; Aimi, N.; Takayama, H.; Koyana, T. *Jpn. Patent* 1996, 08231396; (d) Shankarayan, D.; Gopalakrishnan, C.; Kameswaran, L. *Arch. Int. Pharmacodyn. Ther.* **1979**, *239*, 257–269; (e) Williams, P.; Ongsakul, M.; Proudfoot, J.; Croft, K.; Beilin, L. *Free Rad. Res.* **1995**, *23*, 175–184.
4. Lee, H.-H. *J. Chem. Soc., Perkin 1* **1981**, 3205–3213.
5. Jefferson, A.; Quillinan, A. J.; Scheinmann, F.; Sim, K. Y. *Aust. J. Chem.* **1970**, *23*, 2539–2543.
6. (a) Frigerio, M.; Santagostino, M.; Sputore, S. *J. Org. Chem.* **1999**, *64*, 4537–4538; (b) Nicolaou, K. C.; Zhong, Y.-L.; Baran, P. S. *J. Am. Chem. Soc.* **2000**, *122*, 7596–7597; (c) Wirth, T. *Angew. Chem., Int. Ed.* **2001**, *40*, 2812–2814.
7. Steric hindrance of the TBS group interfered with the prenylation of the tri-TBS derivative of **7**. Accordingly, a stepwise process was required as described in Scheme 2.
8. When using the tri-MOM derivative of **13**, efforts to remove the protective groups from the corresponding benzophenone product were unsuccessful. Upon reacting even under CSA in MeOH (30°C) conditions, by-products possessing a chroman-framework with MOM groups were observed, cf. Mahabusarakam, W.; Pakawatchai, C.; Wiriyachitra, P.; Taylor, W. C.; Skelton, B. W.; White, A. H. *Aust. J. Chem.* **1998**, *51*, 249–254.
9. (a) Arimoto, H.; Nishiyama, S.; Yamamura, S. *Tetrahedron Lett.* **1990**, *31*, 5619–5620; (b) Yamamura, S.; Nishiyama, S. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 2025–2037.
10. **16**: δ_H ($CDCl_3$) 1.39 (3H, s), 1.50 (3H, s), 1.75 (3H, s), 1.80 (3H, s), 3.32–3.34 (4H, complex), 3.76 (3H, s), 4.97 (1H, m), 5.23 (1H, m), 5.91 (1H, s) and 6.50 (1H, s); δ_C ($CDCl_3$) 17.5, 17.9, 21.5, 25.4, 25.8, 25.9, 29.1, 61.9, 95.8, 102.8, 106.4, 106.8, 118.4, 121.1, 121.8, 134.1, 134.2, 139.7, 150.8, 152.1, 160.0, 161.4, 163.2 and 196.1.