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Biological Activities of α-Mangostin Derivatives against Acidic Sphingomyelinase

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Abstract—Deprenyl and benzofenone-type congeners of α-mangostin **1** have been synthesized to understand their role for the inhibitory activity against sphingomyelinase (SMase). While removal of the prenyl group of the right side (**11** and **12**) caused loss of the selectivity between ASMase (acidic sphingomyelinase) and NSMase (neutral sphingomyelinase), the prenyl group of the left side appeared to increase the inhibitory activities (**16** and **17**).

α-Mangostin **1**, isolated from *Garcinia mangostana* L. (Guttiferae)[1] as a representative xanthone-class natural products of plant origin, revealed highly selective inhibitory activity against acidic sphingomyelinase,[2] in addition to diverse biological activities of this molecule.[3] Despite such intriguing biological activities, to our knowledge, there was only one formal synthesis of **1** by Lee: the chroman precursor was converted into β-mangostin,[4] demethylation of which was reported to provide **1**.[5] In this context, we reported a new efficient total synthesis of **1** by using the diaryl ether construction under mild dehydration conditions, [6] developed by our group.[7] Fortunately, the benzophenone derivative **2** obtained as a synthetic intermediate, was observed to possess inhibitory activity against ASMase comparable to that of **1**, while its cytotoxicity was 1/10-fold less than that of **1**. In addition, Umezawa reported that the tetrahydro derivative **3** exhibited reduction of the selective inhibition against ASMase and NSMase: the NSMase activity was two times stronger than that of **1**.[2] These findings prompted us to acquire further information on the structure- activity relationship (SAR) of SMase. We describe herein our investigation-process, in particular related to the effect of the diaryl ether moieties, as well as the prenyl side chains (Fig. 1).

At the outset, the deprenyl derivatives of the corresponding aromatic moieties **5** and **7**, were synthesized. Thus, 2,4-dihydrobenzaldehyde **4** was benzylated, followed by the Baeyer–Villiger oxidation and acidic hydrolysis to give the corresponding phenol, which on regioselective bromination and methylation provided **5** in good overall yield (Scheme 1). Compound **7** was synthesized by the known procedure[8] using the Vilsmeier–Haack–Viehe reaction of 1,3,5-trihydroxybenzene **6**, followed by exhaustive methoxymethylation.

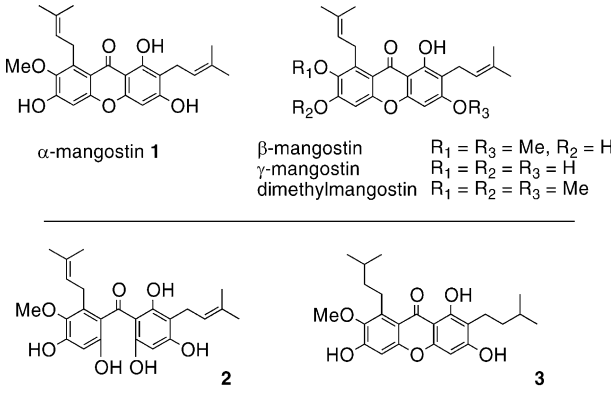

Figure 1. Structures of mangostins and its derivatives.

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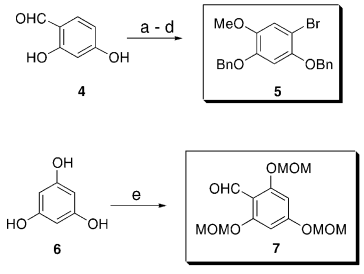
Synthesis of 11 and 12

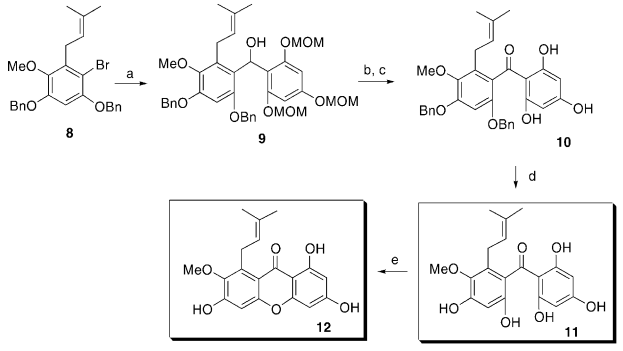
Exposure of bromide **8**[6] to *s*-BuLi gave the corresponding lithio derivative, which on coupling with **7** provided **9** (Scheme 2). Oxidation of the benzyl alcohol by IBX[9] and transacetalization afforded benzofenone **10**, which was hydrogenolized to give **11**. Treatment of **10** with silica gel[9] effected the desired cyclization to give xanthone **12**.

Synthesis of 16 and 17

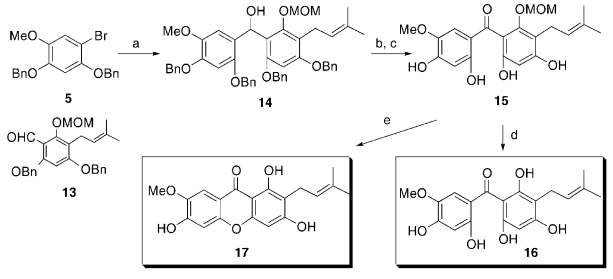
Compound **5** was lithiated and coupled with **13**[6] to give the corresponding benzyl alcohol **14**, which on oxidation with IBX[9] and hydrogenolysis gave benzophenone **15** (Scheme 3). While deprotection under acidic conditions provided **16**, treatment of **15** with the PPh_3–CCl_4 protocol,[7,10] afforded xanthone **17** in moderate yield.



Scheme 1. (a) BnBr, K_2CO_3/DMF, 96%; (b) mCPBA/CH_2Cl_2, then 6 M HCl/MeOH, 95%; (c) Br_2/$CHCl_3$, 84%; (d) MeI, K_2CO_3/DMF, 97%; (e) $POCl_3$/DMF, then MOMCl, NaH/DMF, 54%.



Scheme 2. (a) *s*-BuLi/THF, then **7**, 49%; (b) IBX/PhMe–DMSO (1:1), 82%; (c) CSA/MeOH, 81%; (d) 10% Pd/C, cyclohexene/EtOH, 97%; (e) silica gel, 74%.



Scheme 3. (a) *s*-BuLi/THF, then **13**, 41%; (b) IBX/PhMe–DMSO (1:1), 100%; (c) 10% Pd/C, HCO_2NH_4/acetone, 88%; (d) TsOH/MeOH, 94%; (e) Ph_3P, CCl_4/THF, then silica gel, 61%.

Table 1. Inhibitory activities of α-mangostin **1** and its derivatives against sphingomyelinase (SMase)

Compd	IC_{50} (μg/mL)	
	ASMase	NSMase
11	5.3	10.2
12	5.25	8.9
16	24.0	72.5
17	34.5	>100
2	16.5	48.5
α-Mangostin **1**	5.15	46.5

Biological Activity

Procedure

A mixture of NBD-sphingomyelin, sphingomyelinase and a sample was incubated at 37 °C for 30 min. Enzymatic activity in the mixture was determined by measuring the fluorescence intensity of ceramide produced.

Compounds **11** and **12**, carrying no prenyl group at the right residue, maintained comparable activity to that of **1**, although selectivity between ASMase and NSMase was diminished by increase of their activities against NSMase (Table 1). This property was similar to the case of saturation of the olefinic bonds of the prenyl groups.[2] When compared with **1** and **2**, the right prenyl group might be responsible for the selectivity against ASMase and NSMase. In contrast, benzophenone **16** and xanthone **17** without the left-prenyl group, kept the selectivity, while the ASMase activities reduced to ca. 1/10 of that of **1**. These observations indicated each prenyl group might be required to express the highly selective inhibitory activity against ASMase.

Acknowledgements

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10. The substutution pattern of the aromatic moiety might affect the difficulty of the diaryl ether production. Treatment with PPh_3–CCl_4, followed by silica gel, was required in the cases of **1** and **17**, whereas **12** was produced only by exposure to silica gel. The detailed reactivity profile is still unclear.