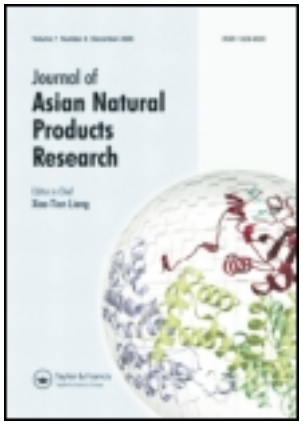

Journal of Asian Natural Products Research

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/ganp20

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Published online: 25 Jun 2013.

To cite this article: Jing-Xu Gong, He-Yao Wang, Wen-Fei He, Zhen-Zhong Wang, Wei Xiao & Yue-Wei Guo (2013) A concise synthesis of xestospongic acid methyl ester with pancreatic lipase inhibitory activity, Journal of Asian Natural Products Research, 15:8, 916-919, DOI: 10.1080/10286020.2013.804815

To link to this article: http://dx.doi.org/10.1080/10286020.2013.804815

Journal of Asian Natural Products Research, 2013
Vol. 15, No. 8, 916–919, http://dx.doi.org/10.1080/10286020.2013.804815

A concise synthesis of xestospongic acid methyl ester with pancreatic lipase inhibitory activity

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(*Received 28 November 2012; final version received 9 May 2013*)

Xestospongic acid methyl ester, a naturally brominated fatty acid with potent pancreatic lipase inhibitory activity *in vitro*, was synthesized from 5-hexynol in 30% total yield.

Keywords: brominated fatty acid; xestospongic acid methyl ester; pancreatic lipase inhibitor; synthesis

1. Introduction

Brominated fatty acids have received considerable attention in the last few decades because of their unique chemical structures such as increased chain length, unusual unsaturation patterns, and potential biological activities ranging from anti-HIV, antifungal to Na + /K + ATPase [1]. Brominated fatty acids belong to unusual natural products, and most of them were found in marine sponges, whereas some in terrestrial lichen [2–7]. During our investigation of components of the ether extract of the marine sponge, *Xestospongia testudinaria*, collected from Beihai China, we found that the crude extract showed interesting pancreatic lipase inhibitory effects. In order to elucidate the responsible pancreatic lipase inhibitory compounds, we systematically investigated the chemical composition of the sponge, and it lead to the isolation of xestospongic acid methyl ester (**1**), a brominated fatty acid previously isolated from Mayotte *X. testudinaria* by Bourguet-Kondracki et al. [8]. *In vitro* pharmacological evaluation of compound **1** revealed that it exhibited strong pancreatic lipase inhibitory activity with an IC_{50} value of 3.1 μM (L.-F. Liang et al., unpublished data). Although this compound demonstrated a remarkable biological potential, the scarcity of available sample from natural sources is a major problem for additional study of structure–activity relationship (SAR) and structural derivatization/modification. Therefore, an efficient synthetic route is required to explore sufficient amount of the title compound for the more in-depth pharmacological studies. Herein, we describe a practical synthesis of xestospongic acid methyl ester.

2. Results and discussion

According to retrosynthesis analysis (Scheme 1), the target compound could be obtained from the Sonogashira coupling reaction [9] of 1,2-dibromoethylene with intermediate **6**. Compound **6**, in turn, could be generated from the Cu (I) catalyzed cross coupling reaction [10] of 1,9-decadiyne with methyl 6-bromo-5-hexynate, which was synthesized from 5-hexynol.

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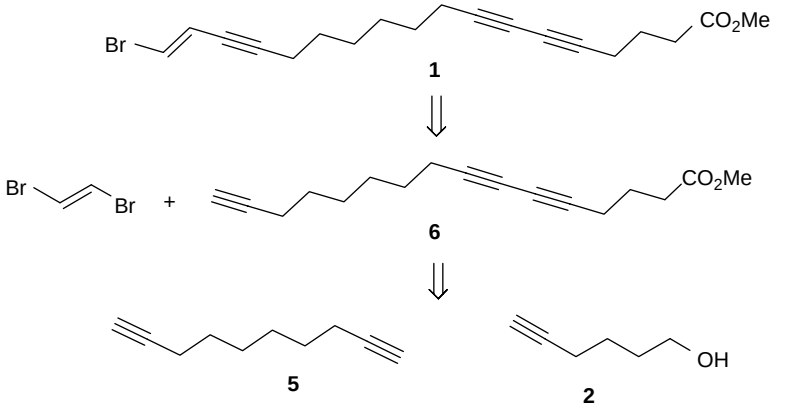
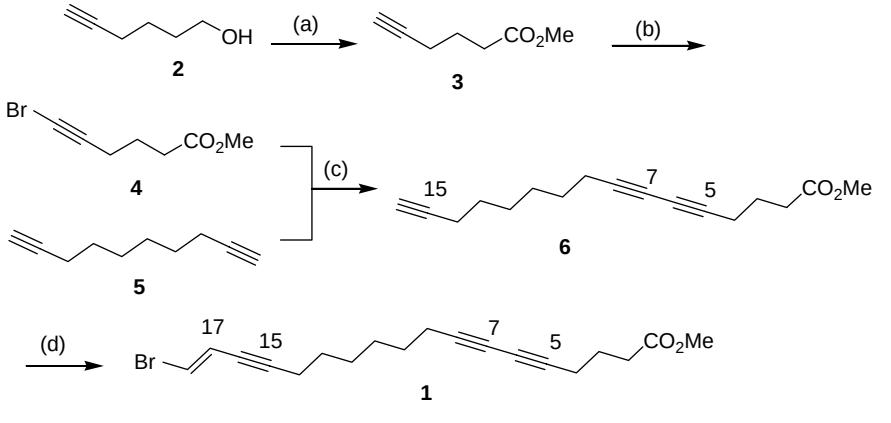


Scheme 1. Retrosynthetic analysis for xestospongic acid methyl ester.

As outlined in Scheme 2, the synthesis of methyl spongoate was started from the commercially available compound, 5-hexynol **2**, and it was oxidized by CrO_3 in the presence of H_2SO_4 in acetone, then methylated with CH_2N_2 to give methyl 5-hexynoate **3**. Compound **3** was brominated with N-bromosuccinimide (NBS) in the presence of $AgNO_3$ to yield bromo-alkyne **4**, 87%. The palladium-catalyzed cross-coupling reaction of **4** with 1,9-decadiyne **5** afforded in 55% of the desired triyne **6**. Exactly 1 equiv. of bromoalkyne **4** was added dropwise to a mixture of 1,9-decadiyne **5** and the reagents in MeOH to minimize the coupling of **4** to both the terminals of **5** [10]. The final step is the coupling reaction between **6** and a mixture of *cis-/trans*-1,2-dibromoethylene in the presence of $Pd(PPh_3)_4$ and CuI in Et_3N with 75% yield; alkyne **6** reacts preferentially with the *trans*-isomer of 1,2-dibromoethylene, which is consistent with a previous report that *trans*-1,2-dibromoethylene is more reactive than the corresponding *cis*-isomer in the Pd-catalyzed cross-coupling reactions [11]. The spectroscopic data of the synthetic product **1** were identical to those of the naturally occurring product [8].



Scheme 2. Reagents and conditions. (a) 1. CrO_3, H_2SO_4, acetone, 0–5°C, 2 h, 2. CH_2N_2, ether, r.t., 85% two steps; (b) NBS, $AgNO_3$, acetone, r.t., 87%; (c) CuCl, Et_2NH, $NH_2OH{\cdot}HCl$, MeOH, r.t., overnight, 55%; and (d) 1,2-dibromoethylene (*cis–trans* mixture), $Pd(PPh_3)_4$, CuI, Et_3N, r.t., overnight, 75%.

In summary, the first total synthesis of xestospongic acid methyl ester (**1**) has been achieved in five steps with 30% overall yield. The synthesis is amenable to large scale and a similar strategy will allow the synthesis of related brominated fatty acids and analogs of **1** for further SAR study.

3. Experimental

3.1. General experimental procedures

All the reagents were obtained from commercial sources and used without further purification. The NMR spectra were measured on Bruker-DRX-400 spectrometer (Bruker Biospin AG, Fällanden, Germany) at 400 MHz for ^{1}H and 100 MHz for ^{13}C. Chemical shifts *(δ)* are expressed in ppm and coupling constants (*J*) in Hz. Electron ionization mass spectrocopy and high-resolution electrospray ionization mass spectroscopy were recorded on Finnigan MAT-95 (Thermo Finnigan, Bremen, Germany). Commercial silica gel (Qingdao Haiyang Chemical Group Co., Qingdao, China; 200–300 mesh) was used for column chromatography and precoated silica gel plates (SHGF-254, Yantai Jiangyou Silica Gel Developmemt Co. Ltd, Yantai, China) were used for analytical thin layer chromatography (TLC).

3.2. General procedures for the synthetic compounds

3.2.1. Compound 3

To a solution of 5-hexyn-1-ol (1.5 g, 15.3 mmol) in acetone (25 ml) at 0°C was added dropwise a solution of Jones reagents (30 ml), and the mixture was allowed to warm to room temperature. Water was added, and the resulting mixture was extracted with ether, washed successively with water and brine, dried ($MgSO_4$), and the solvent was concentrated to half. A freshly prepared solution of CH_2N_2 in Et_2O was added dropwise to the acid until the solution remained pale yellow and no more N_2 was evolved. The mixture was washed with NaOH solution and H_2O, dried ($MgSO_4$), and evaporated. The residue was subjected to flash chromatography to give the title compound **3** (1.6 g, 85% yield) as colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 1.85 (m, 2H, H-3), 1.95 (t, 1H, $J = 2.1$ Hz, H-6), 2.24 (dt, 2H, $J = 7.2$, 2.1 Hz, H-4), 2.47 (t, 2H, $J = 7.2$ Hz, H-2), 3.67 (s, 3H, OCH_3).

3.2.2. Compound 4

$AgNO_3$ (20 mg, 0.12 mmol) was added to a solution of compound **2** (1.51 g, 12 mmol) and NBS (2.14 g, 12 mmol) in 10 ml acetone; the mixture was stirred at room temperature for 2 h. Progress of the reaction was monitored by TLC, and when the starting material was consumed, the mixture was diluted with 15 ml petroleum ether. The reaction mixture was then washed twice with 10 ml cold distilled water. The aqueous layers were combined and extracted three times with 15 ml petroleum ether:Et_2O (1:1). The organic layers were combined, washed with 40 ml brine solution, and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was subjected to flash chromatography to give the title compound **4** (2.14 g, 87%) as colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.83 (m, 2H, H-3), 2.29 (t, 2H, $J = 7.1$ Hz, H-4), 2.43 (t, 2H, $J = 7.4$ Hz, H-2), 3.67 (s, 3H, OCH_3); electrospray ionization mass spectroscopy (ESI-MS) *m/z*: 205.0, 207.0 $[M + 1]^+$.

3.2.3. Compound 6

To a round-bottomed flask equipped with a stirring bar under nitrogen were added 10 ml of MeOH, $NH_2OH{\cdot}HCl$ (31 mg, 0.45 mmol), 10 ml 70% aqueous solution of $EtNH_2$, CuCl (45 mg, 0.45 mmol), and diyne **5** (1.2 g, 9 mmol) in that order. Bromoalkyne **4** (1.85 g, 9 mmol) in 5 ml

methanol was added over a period of one and a half hours to the reaction mixture via a syringe pump, keeping the temperature between 30 and 35°C, and the mixture was stirred for an additional 1 h. The product was isolated by extraction with Et_2O and the combined organic layers were washed with saturated NH_4Cl solution and dried over $MgSO_4$. The solvents were removed under reduced pressure and the residue was purified over silica gel (5% Ether/Hex) to give the title compound **6** (1.28 g, 55%) as colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.41 (m, 4H, H-11, 12), 1.51 (m, 4H, H-10, 13), 1.84 (m, 2H, H-3), 1.94 (t, 1H, $J = 2.5$ Hz, H-16), 2.19 (dt, 2H, $J = 2.7$, 6.9 Hz, H-14), 2.25 (t, 2H, $J = 6.9$ Hz, H-9), 2.33 (t, 2H, $J = 6.9$ Hz, H-4), 2.45 (t, 2H, $J = 7.3$ Hz, H-2), 3.67 (s, 3H, OCH_3); ^{13}C NMR (125 MHz, $CDCl_3$): 18.5, 18.8, 19.3, 23.6, 28.3, 28.4, 32.8, 51.7, 65.3, 66.3, 68.3, 76.1, 77.9, 84.7, 173.5. ESI-MS *m/z*: 259.2 $[M + 1]^+$.

3.2.4. Compound *1*

To a round-bottomed flask equipped with a stirring bar under nitrogen were added triethylamine (50 ml), $Pd(PPh_3)_4$ (0.21 g, 0.18 mmol), CuI (70 mg, 0.36 mmol), a mixture of *cis*- and *trans*-dibromoethylene (0.98 ml, 12 mmol), and compound **6** (0.78 g, 3 mmol). The resulting solution was stirred at room temperature for 16 h. The mixture was then diluted with $CHCl_3$ (20 ml) and filtered through a pad of Florisil using $CHCl_3$. The solvents were removed under reduced pressure and the crude mixture was purified over a silica gel column to afford the product as pale yellow oil (0.81 g, 75%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.39 (m, 4H, H-11, 12), 1.52 (m, 4H, H-10, 13), 1.85 (m, 2H, H-3), 2.20 (dt, $J = 6.9$, 1.8 Hz, 2H, H-14), 2.25 (t, $J = 6.9$ Hz, 2H, H-9), 2.33 (t, $J = 6.9$ Hz, 2H, H-4), 2.44 (t, $J = 7.2$ Hz, 2H, H-2), 3.68 (s, 3H, OCH_3), 6.16 (dt, $J = 1.8$, 14.1 Hz, 1H, H-17), 6.56 (d, $J = 14.1$ Hz, 1H, H-18); ^{13}C NMR (125 MHz, $CDCl_3$): 18.6, 19.1, 19.3, 23.5, 28.1, 28.2, 28.2, 28.3, 32.7, 51.6, 65.2, 66.2, 76.0, 77.3, 77.7, 93.0, 117.0, 118.0. ESI-MS *m/z*: 363.1, 365.3 $[M + 1]^+$.

Acknowledgments

The research work was financially supported by the Natural Science Foundation of China (Nos 81072572, 81273430, and 21021063), National Marine '863' Project (Nos 2011AA09070102 and 2013AA092902), the SKLDR/SIMM Projects (Nos SIMM1203ZZ-03, SIMM1105KF-04, and SIMM1203KF-12), W.-F.H. thanks China Postdoctoral Science Foundation Grant (No. 2012M520956).

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