Tetrahedron 67 (2011) 4774–4779

Contents lists available at ScienceDirect

Tetrahedron

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

Total synthesis of aldehyde-containing *Garcinia* natural products isomorellin and gaudichaudione A

Zong-Liang Liu [†], Xiao-Jian Wang [†,‡], Nian-Guang Li [§], Hao-Peng Sun, Jin-Xin Wang, Qi-Dong You [*]

Department of Medicinal Chemistry, China Pharmaceutical University, 24 Tongjiaxiang, Nanjing 210009, PR China

ARTICLE INFO

Article history:
Received 12 March 2011
Received in revised form 2 May 2011
Accepted 9 May 2011
Available online 13 May 2011

Keywords:
Total synthesis
Isomorellin
Gaudichaudione A
Bisalkylation
Claisen/Diels–Alder cascade reaction

ABSTRACT

The natural products, isomorellin and gaudichaudione A, with a 4-oxa-tricyclo[4.3.1.0^{3,7}] dec-8-en-2-one scaffold were synthesized for the first time using an efficient method. The key improvement of this method was the simultaneous bisalkylation of 5,6-dihydroxyxanthone with the bulky 2-methylbutyne group. This method obviously shortened the synthetic route and enhanced the total yield. Four analogues named forbesione, desoxymorellin, desoxygaudichaudione A, and gambogin containing the same caged structure were prepared using this method.

1. Introduction

Gamboge, the dried resin collected from tropical trees of the genus *Garcinia*, has been used as folk medicine for many years. A lot of caged xanthones isolated from gamboge, which contain a unique 4-oxa-tricyclo[4.3.1.0^{3,7}]dec-2-one scaffold, possess potent anti-tumor activity against a broad panel of cancer cell lines and draw much attention of medicinal chemists.[1] Gambogic acid is the most studied compound among cytotoxic caged xanthones, which shows promising anticancer effects both in vitro and in vivo against a variety of cancer cell lines, such as human breast cancer T47D cells,[2] human epatoma SMMC-7721 cells,[3,4] human leukemia L-60 and K562 cells etc.[5] Gaudichaudione A[6] activates caspase-3 and induced the apoptosis of Jurkat human leukemic cells. It has notable cytotoxicity against parental murine leukemic P388 and P388/DOX-resistant cells, but is less toxic toward normal human Chang liver cells.[7] Compared gaudichaudiones with gaudichaudiic acids, the aldehydes show in general stronger cytotoxicity than the acids.[6]

The unusual 4-oxa-tricyclo[4.3.1.0^{3,7}] dec-8-en-2-one scaffold has caught the attention of synthetic chemists. Over 30 years ago, an elegant proposal for the biosynthesis of isomorellin[8] was put forward by Quillinan and Scheinmann.[9] Unfortunately, they were hampered by the O-alkylation of 5,6-dihydroxy groups with bulky substituents. Till 2001 the first natural product with the caged structure, 1-*O*-methylforbesione, was synthesized by Nicolaou.[10] After that, Theodorakis et al. accomplished the total synthesis of several nature products, such as forbesione and desoxymorellin etc. in 2002 and 2003.[11–13] The total synthesis of gambogin was reported by Theodorakis in 2004 and Nicolaou in 2005.[14,15] Nicolaou et al. carried out the bisalkylation of the 5,6-dihydroxyl of xanthone by using isobutylaldehyde bromide through twice wittig reaction, however the four-step synthetic route was too long and the yield was unsatisfied. Meanwhile, Theodorakis substituted 3,5,6-trihydroxyl with 2-chloro-2-methylbutyne simultaneously, however, the resulted caged compound was not suitable for the further oxidative modification. To simplify the synthetic route as well as to improve the yield of the total synthesis, we developed an efficient alkylation route, which substituted the 5,6-dihydroxyl with the bulky 2-chloro-2-methylbutyne simultaneously. This method also enhanced the regioselectivity of the xanthone ring and led to the synthesis of structurally diverse caged xanthone compounds.

All the caged xanthones mentioned above contain an isopentene group on the caged ring. Till now there is no report about the synthesis of the natural products that contain an oxidized isopentene group on the caged ring. As natural caged xanthones coupled with an aldehyde group, such as gaudichaudione A always show potent anti-tumor activity, we think it is worthy to develop an efficient synthetic method for this series of compounds. Based on

* Corresponding author. Tel.: +8602583271351; e-mail address: youqidong@gmail.com (Q.-D. You).
† These authors contributed equally to this work.
‡ Present address: Institute of Materia Medica, Chinese Academy of Medical Sciences and Peking Union Medical College, 100050, China.
§ Present address: Nanjing University of Chinese Medicine, 210046, China.

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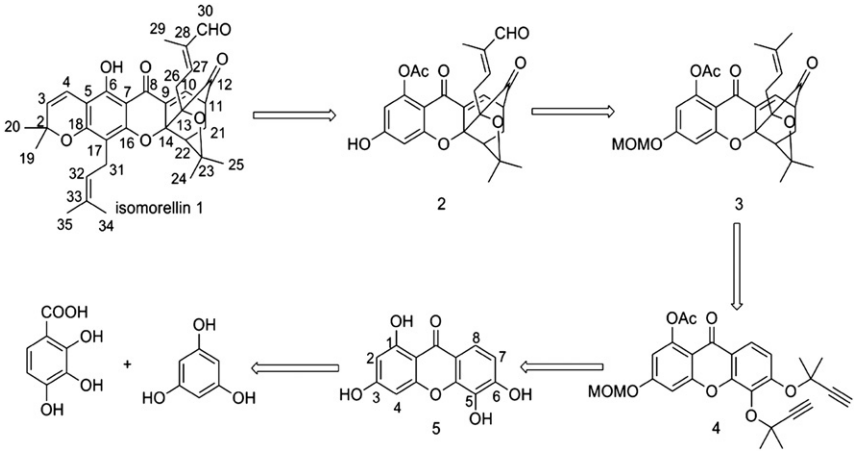
doi:10.1016/j.tet.2011.05.029

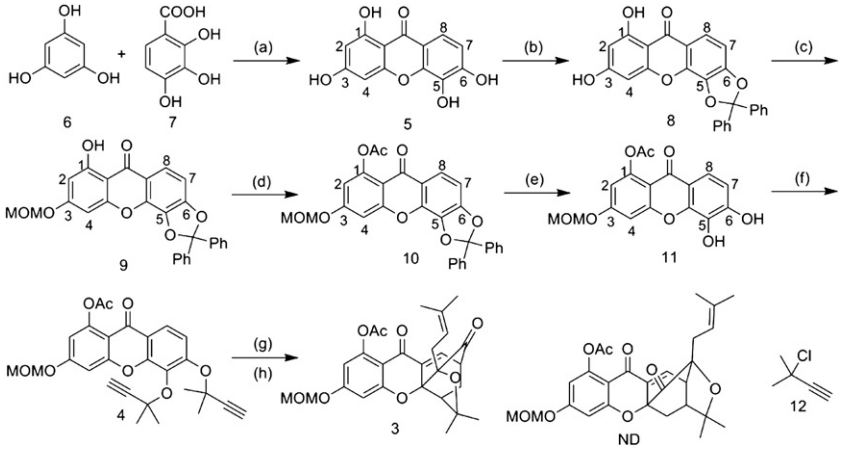
the 5,6-bisalkylation method mentioned above, we successfully carried out the total synthesis of two aldehyde coupled caged xanthones named isomorellin and gaudichaudione A. Another four caged compounds including forbesione, desoxymorellin, desoxygaudichaudione A, and gambogin were also prepared in an obviously enhanced yield.

2. Results and discussion

We have previously reported a selective protection of xanthone.[16] Based on the method, we focused our attention on the synthesis of natural products containing an oxidized isopentene group on the caged ring, such as isomorellin and gaudichaudione A. The retrosynthetic analysis was outlined in Scheme 1. In this route, there is one main problem that needs to be solved: efficient preparation of the key intermediate **3**.



Scheme 1. Retrosynthetic analysis of isomorellin **1**.



Scheme 2. Synthetic route of compound **3**. Reagents and conditions: (a) $ZnCl_2$, $POCl_3$, 65 °C, 3 h, 45%; (b) Ph_2CCl_2, DIPEA, Ph_2O, 170 °C, 0.5 h, 85%; (c) MOMCl, K_2CO_3, acetone, 25 °C, 5 h, 95%; (d) Ac_2O, DMAP, CH_2Cl_2, 25 °C, 4 h, 94%; (e) H_2, Pd/C, THF/MeOH, 50 °C, 12 h, 95%; (f) $(CH_3)_2CClC{\equiv}CH$, KI, K_2CO_3, CuI, acetone, reflux, 1.5 h, 70%; (g) H_2, Pd/$BaSO_4$, EtOH/EtOAc, 35 °C, 4 h; (h) DMF, 120 °C, 1 h, 65% (over two steps).

Isomorellin (**1**) would be constructed from compound **2** via double alkylation, hydrogenation, and regioselective Claisen rearrangement. Compound **2** could be obtained from compound **3** via oxidation and selective deprotection of hydroxyl. Through a sequence of hydrogenation and Claisen/Diels–Alder cascade, cage compound **3** could be generated from bisalkylated xanthone **4**, which was derived from xanthone **5** via a series of protection, deprotection, and alkylation. Xanthone **5** was easily prepared from the condensation of 2,3,4-trihydroxybenzoic acid and 1,3,5-trihydroxybenzene.[14]

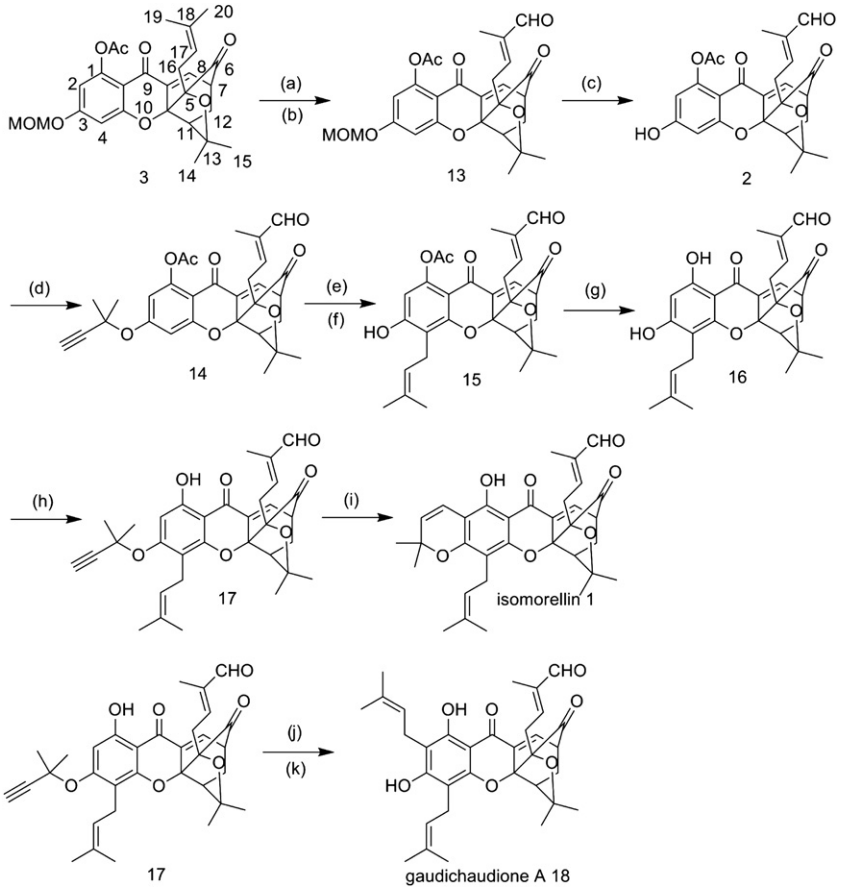
Synthetic route of the key intermediate **3** was shown in Scheme 2. Our synthetic studies commenced with a $ZnCl_2$ mediated condensation of phloroglucinol (**6**) and 2,3,4-trihydroxybenzoic acid (**7**) in $POCl_3$ to produce xanthone **5** in 45% yield.[14] Identifying the protection step is yield limiting step for the synthetic route, then we propose that the Ac on 1-hydoxyl of xanthone might have some impact, then tried, then get better yield. Xanthone **10** was obtained from xanthone **5** via selective protection of 5,6-dihydroxyl with Ph_2CCl_2, 3-hydroxyl with MOMCl (Methyl chloromethyl ether), and 1-hydroxyl with Ac_2O in 76% yield over three steps. Xanthone **10** was transformed to **11** via hydrogenolysis at the presence of Pd/C (95%). With the electron-withdrawing effect of Ac at 1-hydroxyl, the activities of 5,6-dihydroxy groups were enhanced. So 5,6-dihydroxy groups were alkylated simultaneously with 2-chloro-2-methylbutyne in the presence of KI and K_2CO_3 with catalytic amount of CuI in 70% yield. By contrast, when the 1-hydroxyl group of the xanthone was free or protected with MOM or Me, our attempts to alkylate 5,6-dihydroxyl groups under the same conditions were fruitless. We also attempted to protect 1-hydroxyl with other electron-withdrawing groups, such as MsCl. Unfortunately, compound **9** could not fully react with MsCl and the yield was below 60%. Compound **3** was easily formed from compound **4** via hydrogenolysis at the presence of Pd/$BaSO_4$ and

Claisen/Diels–Alder cascade reaction in 65% yield over two steps. Generally, caged and isocaged compounds would be produced but isocaged compound was not monitored in our experiments.

With compound **3** in hand, the most important task was the introduction of diverse substituent groups to C2 and C20 to construct other caged xanthones outlined in Scheme 3. C20 was selectively oxidized to aldehyde with SeO_2 and PCC (pyridinium chlorochromate). Considering that the Ac at 1-hydroxyl was unstable, we chose the reaction conditions of NaI in acetone with one drop HCl (2 N) as catalyst to selectively deprotect MOM. Compound **2** was alkylated with 2-chloro-2-methylbutyne (**16**) in the presence of KI and K_2CO_3 under CuI catalysis to afford compound **14** in 85% yield. Compound **15** was firstly hydrogenated under Pd/$BaSO_4$ catalysis in EtOAc and then rearranged in DMF at 120 °C to get compound **16** in 80% yield over two steps. Because the caged structure was unstable in basic aqueous solution, Ac at 1-hydroxyl was deprotected under the reaction conditions of HCl (6 N) in acetone and the yield was 75%. After compound **17** was obtained, gaudichaudione A (**18**) was easily constructed in the same procedure from compound **14** to **15** in 68% yield over three steps. Compound **17** was heated in DMF at 120 °C via Claisen reaction to form isomorellin (**1**) in 85% yield.

hydroxyl and acetic anhydride at 1-hydroxyl in 78% yield over two steps. The subsequent hydrogenolysis of the three benzyl groups led to xanthone **20** (95%). Then the next steps were similar to Theodorakis's method.[14]

During our research work, we found 1-hydroxyl in xanthone **5** played an important role for the reaction capabilities of 5,6-dihydroxyl and the regioselectivity of Claisen rearrangement. Xanthone without 1-hydroxyl would be bialkylated at 5,6-dihydroxy groups with 1,1-dimethylpropenyl isobutyl carbonate under Pd(0) catalysis.[17] However, the bisalkylation could barely happen under the same reaction conditions when there existed 1-hydroxyl, no matter it was protected or exposed. As shown in Scheme 4, the reaction capabilities of 5,6-dihydroxy groups in compound **11b** and **11c** were too low to be bialkylated. The yield of compound **21b** was only 25% when 1-hydroxy was exposed.[12] Furthermore, compound **4b** and **4c** were not observed on TLC. These above results may be explained by the electronic effects of the C9 carbonyl group and the 1-hydroxyl. The electron-withdrawing effect of the carbonyl group was increased by the presence of the 1-*o*-acetyl but attenuated by the presence of the 1-*O*-methoxymethyl.

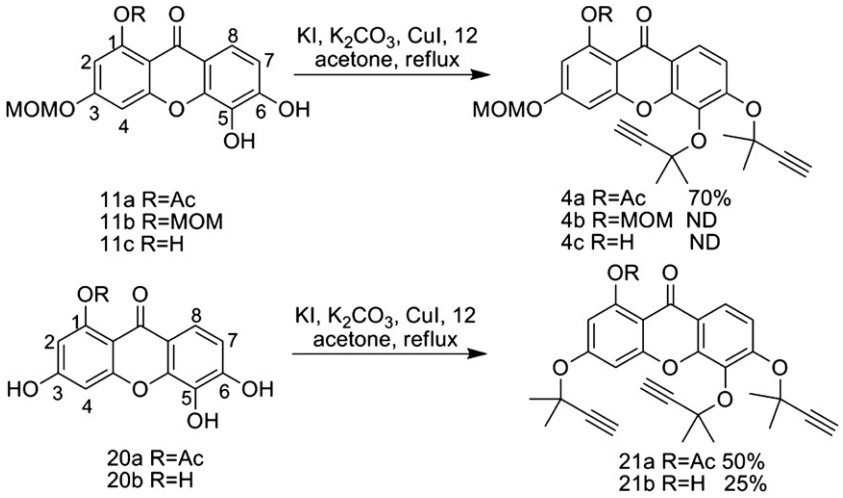


Scheme 3. Synthetic route of isomorellin (**1**) and gaudichaudione A (**18**). Reagents and conditions: (a) SeO_2, *t*-BuOOH, DCM, 25 °C, 24 h; (b) PCC, DCM, 25 °C, 2 h, 60% (over two steps); (c) HCl (2 N), NaI, acetone, 40 °C, 4 h, 75%; (d) $(CH_3)_2CClC{\equiv}CH$, KI, K_2CO_3, CuI, acetone, reflux, 1.5, 85%; (e) H_2, Pd/$BaSO_4$, EtOAc, 25 °C, 10 min; (f) DMF, 120 °C, 1 h, 80% (over two steps); (g) HCl(6 N), acetone, 50 °C, 75%; (h) $(CH_3)_2CClC{\equiv}CH$, KI, K_2CO_3, CuI, acetone, reflux, 1.5, 85%; (i) DMF, 120 °C, 4 h, 85%; (j) H_2, Pd/$BaSO_4$, EtOAc, 25 °C, 10 min; (k) DMF, 120 °C, 1 h, 80% (over two steps).

Based on the fact that 1-acetoxyl enhanced the reaction abilities of 5,6-dihydroxyl at xanthone **5**, an efficient synthetic route for the caged xanthone analogues was provided as shown in Supplementary data. Xanthone **5**[14] was protected with benzyl chloride at 3,5,6-

3. Summary and conclusions

In conclusion, we reported the first total syntheses of isomorellin and gaudichaudione A and provided a more efficient



Scheme 4. Effect of C1 group on alkylation.

synthesis of forbesione, gambogin, desoxygaudichaudione A, and desoxymorelin. Our strategy highlighted the selective protection of the different hydroxyls of xanthone to increase the reactivity of 5,6-O-bisalkylation and regioselectivity of Claisen/Diels–Alder cascade reaction. Our exploration of such effects could lead to the synthesis of other *Garcinia* natural products as well as designed analogues.

4. Experimental section

4.1. General

For ^{1}H NMR data the chemical shifts are based on TMS peak at δ=0.00 ppm for proton NMR and $CDCl_3$ peak at δ=77.00 ppm (t) in carbon NMR. When the middle peak of the triplet is not marked at δ=77.00 ppm, it is taken to this value and the subsequent difference is added or subtracted from all other peaks. HRMS were recorded using Electrospray Ionization (ESI) using a Time of Flight mass spectrometer.

*4.1.1. 1,3,5,6-Tetrahydroxy-9H-xanthen-9-one (**5**).* To a round-bottomed flask containing phloroglucinol (10.0 g, 79.3 mmol), 2,3,4-trihydroxybenzoic acid (13.5 g, 79.3 mmol), and $ZnCl_2$ (70.0 g, 515 mmol) was added $POCl_3$ (150 mL). The reaction mixture was stirred for 3.5 h at 65 °C under N_2. It was then cooled to 25 °C and poured into a beaker of ice. The reaction mixture was filtered and the filter cake was washed with saturated NaCl to get the crude material, which was purified by silica gel column chromatography (EtOAc) to yield compound **5** (9.1 g, 40%): yellow solid; mp>200 °C; EI-MS (*m*/*z*) 259 $(MH)^+$.

*4.1.2. 7,9-Dihydroxy-2,2-diphenyl-6H-[1,3]dioxolo[4,5-c]xanthen-6-one (**8**).* Compound **5** (0.13 g, 0.5 mmol) was added to diphenyl ether (10 mL) and then dichlorodiphenylmethane (0.18 g, 0.75 mmol) was added. The reaction mixture was heated to 175 °C for 0.5 h under N_2. The reaction mixture was cooled to room temperature and poured into petroleum ether (100 mL). The precipitate was collected by filtration and washed with petroleum ether, which was purified by silica gel column chromatography (petroleum ether/EtOAc 8:1). Compound **8** (0.18 g, 85%) was obtained: light yellow solid; mp: 212–214 °C; ^{1}H NMR (300 MHz, CD_3COCD_3): δ 6.26 (d, *J*=2.2 Hz, 1H), 6.46 (d, *J*=2.2 Hz, 1H), 7.13 (d, *J*=8.5 Hz, 1H), 7.48 (m, 6H), 7.66 (m, 4H), 7.82 (d, *J*=8.5 Hz, 1H), 9.83 (s, 1H), 12.99 (s, 1H); EI-MS (*m*/*z*) 424 $(M)^+$.

*4.1.3. 7-Hydroxy-9-(methoxymethoxy)-2,2-diphenyl-6H-[1,3]dioxolo[4,5-c]xanthen-6-one (**9**).* At room temperature K_2CO_3 (1.1 g, 8 mmol) was added to the solution of compound **8** (1.70 g, 4 mmol) in acetone (50 mL). After stirred for 15 min, to this mixture was added MOMCl (0.46 mL, 6 mmol). The reaction mixture was stirred for 6 h and poured into H_2O (150 mL). The precipitate was collected by filtration and washed with water, which was purified by silica gel column chromatography (petroleum ether/EtOAc 8:1) to give the compound **9** (1.68 g, 90%) as a white solid: mp 125–127 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.50 (s, 3H), 5.24 (s, 2H), 6.45 (d, *J*=2.2 Hz, 1H), 6.65 (d, *J*=2.2 Hz, 1H), 6.97 (d, *J*=8.5 Hz, 1H), 7.40 (m, 6H), 7.64 (m, 4H), 7.87 (d, *J*=8.5 Hz, 1H), 12.89 (s, 1H); EI-MS (*m*/*z*): 468 $(M)^+$.

*4.1.4. 9-(Methoxymethoxy)-6-oxo-2,2-diphenyl-6H-[1,3]dioxolo[4,5-c]xanthen-7-yl acetate (**10**).* Ac_2O (1.7 g, 16.7 mmol) was added to a solution of compound **9** (6.0 g, 12.8 mmol) and DMAP (2.35 g, 0.193 mmol) in dichlormethane (100 mL). The reaction mixture was stirred for 0.5 h at room temperature. Another dichlormethane (100 mL) was added to dilute and the reaction mixture was washed with H_2O (100 mL×3). The organic layer was dried with Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether/EtOAc 4:1) to give the compound **10** (5.9 g, 91%) as a white solid: mp 192–193 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.46 (s, 3H), 3.51 (s, 3H), 5.27 (s, 2H), 6.67 (d, *J*=2.1 Hz, 1H), 6.94 (d, *J*=8.4 Hz, 1H), 7.09(d, *J*=2.1 Hz, 1H), 7.26 (m, 6H), 7.41 (m, 4H), 7.87 (d, *J*=8.4 Hz, 1H); EI-MS (*m*/*z*): 510 $(M)^+$.

*4.1.5. 5,6-Dihydroxy-3-(methoxymethoxy)-9-oxo-9H-xanthen-1-yl acetate (**11**).* To a solution of compound **10** (5.9 g, 11.6 mmol) in THF/MeOH (40 mL/40 mL) was added 10% Pd/C (0.59 g). The reaction mixture was stirred at 50 °C under an atmosphere of hydrogen overnight. The reaction mixture was filtered and concentrated under reduced pressure. The residue was pulped with petroleum ether/EtOAc (50 mL/10 mL) and filtered to give the compound **11** (3.6 g, 90%) as white solid: mp 149–151 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.50 (s, 3H), 3.51 (s, 3H), 5.22 (s, 2H), 6.65

(d, J=2.4 Hz, 1H), 6.86 (d, J=9 Hz, 1H), 6.94 (d, J=2.4 Hz, 1H) 7.64 (d, J=9 Hz, 1H); EI-MS (m/z): 346 $(M)^+$.

*4.1.6. 3-(Methoxymethoxy)-5,6-bis(2-methylbut-3-yn-2-yloxy)-9-oxo-9H-xanthen-1-yl acetate (**4**).* To a solution of xanthone **11** (0.55 g, 1.6 mmol) in dried acetone (5 mL) was added KI (0.79 g, 4.8 mmol), K_2CO_3 (0.66 g, 4.8 mmol), CuI (0.03 g, 0.16 mmol), and 2-chloro-2-methylbut-3-yne (1.6 g, 16 mmol). The reaction mixture was heated at reflux for 1.5 h under nitrogen. It was then cooled to 25 °C and filtered. The filtration was concentrated and the residue was purified by silica gel column chromatography (petroleum ether/EtOAc 8:1) to give the compound **4** (0.56 g, 70%) as a light yellow solid: mp 133–136 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.75 (s, INS> 6H), 1.80 (s, 6H), 2.34(s, 1H), 2.48(s, 3H), 2.64 (s, 1H), 3.51 (s, 3H), 5.26 (s, 2H), 6.69 (d, J=2.1 Hz, 1H), 7.03 (d, J=2.1 Hz, 1H), 7.57 (d, J=9 Hz, 1H), 7.93 (d, J=9 Hz, 1H); ESI-MS (m/z): 479 $M+H^+$.

*4.1.7. Caged xanthone (**3**).* To a solution of xanthone **4** (0.22 g, 0.46 mmol) in alcohol (10 mL) was added 10% Pd/$BaSO_4$ (22 mg). The reaction mixture was degassed using hydrogen and stirred under an atmosphere of hydrogen for 0.5 h at room temperature. The reaction mixture was filtered and concentrated under reduced pressure. The residue need not be purified and dissolved in DMF (5 mL). The solution was heated at 120 °C for 1 h under N_2. DMF was removed under reduced pressure and the residue was purified by silica gel column chromatography (petroleum ether/EtOAc 8:1) to give the compound **4** (0.14 g, 65%) as a yellow solid: mp 169–171 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.41 (s, 3H), 1.31 (s, 3H), 1.35 (d, 1H, J=9.9 Hz), 1.53 (s, 3H), 1.69 (s, 3H), 2.30 (dd, 1H, J=13.5, 4.5 Hz), 2.38 (s, 3H), 2.42 (d, 1H, J=9.6 Hz), 2.60 (d, 2H, J=8.1 Hz), 3.49 (m, 4H), 4.47–4.48 (m, 1H), 5.22 (s, 2H), 6.41 (d, 1H, J=2.4 Hz), 6.58 (d, 1H, J=2.4 Hz), 7.30 (d, 1H, J=6.9 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 17.0, 21.1, 25.4, 29.0, 30.4, 46.8, 48.7, 56.6, 83.3, 84.4, 90.5, 94.2, 102.1, 106.3, 107.3, 118.3, 133.1, 135.1, 135.1, 152.3, 162.1, 163.2, 169.4, 173.9, 203.1; m/z (EI): 505 $M+Na^+$, 483 $M+H^+$; HRMS(ESI-TOF) found 505.1834 (calcd for $C_{27}H_{30}O_8+Na^+$ 505.1838).

*4.1.8. Caged xanthone (**13**).* To dichloromethane (5 mL) was added SeO_2 (0.5 mg, 0.00455 mmol), 2-hydroxybenzoic acid (3.2 mg, 0.023 mmol), 75% *t*-BuOOH (993.6 mg, 8.28 mmol). The mixture was stirred for 0.5 h at room temperature and then caged xanthone **5** (110 mg, 0.23 mmol) was added. The reaction mixture was stirred for 24 h and washed with a solution of Na_2SO_3 (3 g) in water (15 mL). The organic layer was dried with Na_2SO_4 and concentrated under reduced pressure. The residue was dissolved in dichloromethane (3 mL) and PCC (98 mg, 0.46 mmol) was added. The reaction mixture was stirred for 2 h and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether/EtOAc 5:1) to give the compound **13** (68 mg, 60% over two steps) as a light yellow solid; mp 148–149 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.30–1.35 (m, 7H), 1.73 (s, 3H), 2.31–2.40 (m, 5H), 2.53 (d, J=9.6 Hz, 2H), 3.49 (s, 4H), 5.21 (s, 2H), 6.42 (m, 2H), 6.51 (m, 1H), 7.46 (d, J=6.9 Hz, 1H), 9.30 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 8.8, 21.1, 25.03, 29.7, 30.2, 30.9, 46.7, 48.7, 56.7, 83.2, 84.1, 91.1, 94.4, 101.8, 106.7, 107.0, 134.5, 135.7, 140.2, 147.0, 152.5, 161.8, 163.9, 169.2, 173.6, 194.7, 202.5; m/z (ESI): 519 $M+Na^+$, 497 $M+H^+$; HRMS(ESI-TOF) found 519.1625 (calcd for $C_{27}H_{28}O_9+Na^+$ 519.1631).

*4.1.9. Caged xanthone (**2**).* To a solution of caged xanthone **13** (60 mg, 0.12 mmol) in acetone (5 mL) was added NaI (36 mg, 0.24 mmol) and 2 N HCl (one drop). The mixture was stirred at 40 °C for 6 h and diluted by 15 mL EtOAc, which was washed with saturated $NaHCO_3$ (3×10 mL). The organic layer was dried with anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether/EtOAc 4:1) to give the compound **2** (41 mg, 75%) as a yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.28–1.35 (m, 7H), 1.71 (s, 3H), 2.30–2.37 (m, 4H), 2.78–2.86 (m, 2H), 2.82 (dd, 1H, J=16.0, 5.6 Hz), 3.48–3.51 (m, 1H), 6.21 (d, 1H, J=2.2 Hz), 6.25 (d, 1H, J=2.2 Hz), 6.60–6.65 (m, 1H), 7.45 (d, 1H, J=6.9 Hz), 8.67 (br, 1H), 9.26 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 8.8, 21.1, 25.0, 28.9, 28.9, 30.0, 46.6, 48.7, 62.2, 83.4, 84.3, 91.0, 101.8, 106.6, 134.5, 135.6, 139.9, 149.1, 152.66, 162.0, 164.4, 169.7, 173.6, 196.1, 202.7; m/z (ESI): 451 $M-H^+$; HRMS(ESI-TOF) found 451.1399 (calcd for $C_{25}H_{24}O_8-H^+$ 451.1393).

*4.1.10. Caged xanthone (**14**).* To a solution of xanthone **2** (20 mg, 0.044 mmol) in dried acetone (3 mL) was added KI (14.7 mg, 0.088 mmol), K_2CO_3 (12.1 mg, 0.088 mmol), and CuI (0.88 mg, 0.0044 mmol). Then 2-chloro-2-methylbut-3-yne (9.02 mg, 0.088 mmol) was added, and the reaction mixture was heated to reflux for half hour. The reaction was then cooled to 25 °C and filtered. The filtration was concentrated and the residue was purified by silica gel column chromatography (petroleum ether/EtOAc 8:1) to give the compound **14** (22 mg, 85%) as a light yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.21 (s, 3H), 1.25–1.31 (m, 4H), 1.64–1.71 (s, 9H), 2.23–2.30 (m, 4H), 2.46 (d, 1H, J=9.6 Hz), 2.57–2.74 (m, 3H), 3.45 (m, 1H), 6.33–6.37 (m, 1H), 6.70 (d, J=2.4 Hz, 1H), 6.62 (d, J=2.4 Hz, 1H), 7.37 (d, 1H, J=6.9 Hz), 9.19 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 7.8, 20.1, 24.1, 27.9, 28.1, 28.3, 28.6, 29.0, 45.6, 47.5, 72.1, 74.8, 75.7, 82.0, 83.1, 89.8, 103.4, 105.8, 107.5, 133.6, 134.5, 139.3, 145.8, 150.8, 160.2, 161.8, 168.2, 172.7, 193.7, 201.6; m/z (ESI): 541 $M+Na^+$, 519 $M+H^+$; HRMS(ESI-TOF) found 541.1841 (calcd for $C_{30}H_{30}O_8+Na^+$ 541.1838).

*4.1.11. Caged xanthone (**15**).* To a solution of xanthone **14** (0.22 g, 0.04 mmol) in EtOAc (10 mL) was added 10% Pd/$BaSO_4$ (22 mg). The reaction mixture was degassed using hydrogen and stirred under an atmosphere of hydrogen for 10 min. The reaction mixture was filtered and concentrated under reduced pressure. The residue does not need purification and dissolved in DMF (2 mL). The solution was heated to 120 °C for 1 h under nitrogen. DMF was removed under reduced pressure and the residue was purified by silica gel column chromatography (petroleum ether/EtOAc 6:1) to give the compound **3** (0.20 g, 80% over two steps) as a light yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.19–1.24 (m, 7H), 1.65–1.68 (m, 9H), 2.23–2.31 (m, 4H), 2.50–2.64 (m, 3H), 3.30 (m, 2H), 3.42 (m, 1H), 5.11 (t, 1H, J=6.9 Hz), 6.20 (s, 1H), 6.36 (t, 1H, J=7.2 Hz), 7.39 (d, 1H, J=6.9 Hz), 9.15 (s, 1H); ^{13}C NMR (CD_3COCD_3, 75 MHz) δ 8.7, 18.2, 21.2, 23.0, 25.8, 26.0, 28.3, 28.6, 29.2, 47.8, 49.8, 84.4, 84.5, 92.1, 106.1, 106.8, 114.5, 122.9, 132.8, 135.3, 136.4, 140.7, 147.0, 151.3, 160.7, 162.7, 169.4, 174.5, 194.6, 204.0; m/z (ESI):519 $M-H^+$; HRMS(ESI-TOF) found 519.2023 (calcd for $C_{30}H_{32}O_8-H^+$ 519.2019).

*4.1.12. Caged xanthone (**16**).* HCl (1 mL, 6 N) was added to the solution of compound **3** (17 mg, 0.03 mmol) in THF/MeOH (1 mL/1 mL). The reaction mixture was heated to 50 °C. After 5 h, EtOAc (10 mL) was added to the reaction mixture, which was washed with brine (10 mL×3). Organic layer was dried with Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether/EtOAc 4:1) to give the compound **16** (12 mg, 80%) as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.28–1.32 (m, 7H), 1.71–1.77 (m, 9H), 2.38 (dd, 1H, J=14.4, 6 Hz), 2.57–2.64 (m, 2H), 2.66–2.78 (m, 1H), 3.30–3.37 (m, 2H), 3.53–3.57 (m, 1H), 5.12 (t, 1H, J=6 Hz), 6.06 (s, 1H), 6.46 (t, 1H, J=7.2 Hz), 7.02 (s, 1H), 7.58 (d, 1H, J=6.9 Hz), 9.23 (s, 1H), 12.53 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 8.7, 18.1, 25.1, 28.8, 29.1, 29.7, 30.1, 32.0, 46.8, 49.1, 70.6, 84.1, 90.9, 97.0, 100.6, 106.9, 121.3, 127.3, 133.2, 136.1, 139.9, 147.7, 157.8, 163.5, 163.7, 178.9, 195.3,

202.8; *m*/*z* (ESI):477 M−H$^+$; HRMS(ESI-TOF) found 477.1908 (calcd for $C_{28}H_{30}O_7$−H$^+$ 477.1913).

*4.1.13. Caged xanthone (**17**).* To a solution of caged xanthone **16** (21 mg, 0.044 mmol) in dried acetone (3 mL) was added KI (14.7 mg, 0.088 mmol), K_2CO_3 (12.1 mg, 0.088 mmol), and CuI (0.88 mg, 0.0044 mmol). Then 2-chloro-2-methylbut-3-yne (9.02 mg, 0.088 mmol) was added, and the reaction mixture was heated to reflux for half hour, which was then cooled to 25 °C and filtered. The filtration was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (petroleum ether/EtOAc 8:1) to give the compound **17** (20 mg, 85%) as a light yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.28 (s, 4H), 1.30 (s, 3H), 1.65–1.71 (m, 6H), 1.73–1.74 (m, 9H), 2.34(dd, 1H, *J*=13.5, 4.5 Hz), 2.60 (d, 1H, *J*=6.4 Hz), 2.62–2.68 (m, 3H), 3.16–3.53 (m, 2H), 3.53–3.57 (m, 1H), 5.06–5.08 (m, 1H), 6.38 (t, 1H, *J*=6.6 Hz), 6.89 (s, 1H), 7.58 (d, 1H, *J*=6.9 Hz), 9.22 (s, 1H), 12.48 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 8.5, 18.2, 22.1, 25.3, 25.7, 29.0, 29.1, 29.9, 30.0, 46.9, 49.0, 73.0, 75.5, 83.5, 84.0, 84.0, 90.67, 97.2, 101.5, 110.4, 122.2, 131.8, 132.5, 136.0, 140.1, 146.5, 156.4, 162.8, 164.2, 179.1, 194.5, 202.8; *m*/*z* (ESI): 567 M+Na$^+$, 545 M+H$^+$; HRMS(ESI-TOF) found 567.2363 (calcd for $C_{33}H_{36}O_7$+Na$^+$ 567.2359).

*4.1.14. Isomorellin (**1**).* A solution of caged xanthone **17** (10 mg, 0.018 mmol) in DMF (2 mL) was heated to 120 °C for 4 h under nitrogen. DMF was removed under reduced pressure and the residue was purified by silica gel column chromatography (petroleum ether/EtOAc 10:1) to give isomorellin **1** (8.5 mg, 85%) as a yellow solid: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.19 (s, 3H), 1.22 (s, 4H), 1.40–1.42 (m, 6H), 1.52 (s, 3H), 1.59 (s, 3H), 1.70 (s, 3H), 2.34 (dd, 1H, *J*=13.5, 4.5 Hz), 2.60 (d, 1H, *J*=6.4 Hz), 2.63 (m, 2H), 3.24 (m, 2H), 3.50 (m, 1H), 5.06 (t, 1H, *J*=6 Hz), 5.47 (d, 1H, *J*=9.9 Hz), 6.35 (t, 1H, *J*=6.6 Hz), 6.56 (d, 1H, *J*=9.9 Hz), 7.52 (d, 1H, *J*=6.9 Hz), 9.19 (s, 1H), 12.70 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 8.6, 18.2, 21.7, 25.8, 27.8, 28.5, 29.0, 29.0, 29.7, 30.0, 46.9, 49.1, 83.4, 83.5, 84.0, 90.3, 97.4, 101.3, 108.1, 115.3, 121.9, 126.4, 132.9, 133.4, 135.6, 140.1, 146.4, 157.5, 157.6, 157.8, 178.9, 194.4, 203.0; *m*/*z* (ESI): 567 M+Na$^+$, 545 M+H$^+$; HRMS(ESI-TOF) found 567.2354 (calcd for $C_{33}H_{36}O_7$+Na$^+$ 567.2359).

*4.1.15. Gaudichaudione A (**18**).* To a solution of xanthone **17** (10 mg, 0.018 mmol) in EtOAc (3 mL) was added 10% Pd/$BaSO_4$ (1 mg). The reaction mixture was degassed using hydrogen and stirred under an atmosphere of hydrogen for 10 min. The reaction mixture was filtered and concentrated under reduced pressure. The residue does not need purification and dissolved in DMF (2 mL). The solution was heated to 120 °C for 0.5 h under nitrogen. DMF was removed under reduced pressure and the residue was purified by silica gel column chromatography (petroleum ether/EtOAc 8:1) to give gaudichaudione A **18** (8 mg, 80% over two steps) as a yellow solid: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.28–1.32 (m, 7H), 1.71–1.82 (m, 15H), 2.34 (dd, 1H, *J*=13.5, 4.5 Hz), 2.55 (d, 1H, *J*=9.3 Hz), 2.68 (d, 2H, *J*=7.5 Hz), 3.31–3.36 (m, 4H), 3.51–3.54 (m, 1H), 5.13 (m, 1H), 5.22 (m, 1H), 6.38 (m, 1H), 6.55 (s, 1H), 7.57 (d, 1H, *J*=6.9 Hz), 9.23 (s, 1H), 12.80 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 8.7, 17.9, 18.1, 21.3, 22.2, 25.4, 25.8, 25.9, 28.9, 29.1, 30.0, 47.0, 49.0, 83.3, 83.9, 90.7, 100.7, 106.4, 107.7, 121.2, 121.6, 133.5, 134.4, 135.8, 135.8, 140.3, 146.5, 155.8, 163.8, 168.6, 179.1, 194.5, 203.1; *m*/*z* (ESI):545 M−H$^+$; HRMS(ESI-TOF) found 545.2546 (calcd for $C_{33}H_{38}O_7$−H$^+$ 545.2539).

Acknowledgements

This work was supported by 2008ZX09401-001, 2009ZX09501-003 and 2010ZX09401-401 of National Major Science and Technology Project of China (Innovation and Development of New Drugs), 90713038 and 21072231 of National Natural Science Foundation of China (Key Program).

Supplementary data

Preparation of the caged xanthone analogues is provided. Copies of ^{1}H and ^{13}C NMR spectra are provided. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2011.05.029. These data include MOL files and InChIKeys of the most important compounds described in this article.

References and notes

1. Thoison, O.; Fahy, J.; Dumontet, V.; Chiaroni, A.; Riche, C.; Tri, M. V.; Sevenet, T. *J. Nat. Prod.* **2000**, *63*, 441–446.
2. Zhang, H.-Z.; Kasibhatla, S.; Wang, Y.; Herich, J.; Guastella, J.; Tseng, B.; Drewe, J.; Cai, S. X. *Bioorg. Med. Chem.* **2004**, *12*, 309–317.
3. Guo, Q. L.; You, Q. D.; Wu, Z. Q.; Yuan, S. T.; Zhao, L. *Acta Pharmacol. Sin.* **2004**, *25*, 769–774.
4. Guo, Q. L.; Lin, S. S.; You, Q. D.; Gu, H. Y.; Yu, J.; Zhao, L.; Qi, Q.; Liang, F.; Tan, Z.; Wang, X. *Life Sci.* **2006**, *78*, 1238–1245.
5. Tao, Z.; Zhou, Y.; Lu, J.; Duan, W.; Qin, Y.; He, X.; Lin, L.; Ding, J. *Cancer Biol. Ther.* **2007**, *6*, 691–696.
6. Cao, S.-G.; Wu, X.-H.; Sim, K.-Y.; Tan, B. K. H.; Pereira, J. T.; Wong, W. H.; Hew, N. F.; Goh, S. H. *Tetrahedron Lett.* **1998**, *39*, 3353–3356.
7. Wu, X.; Cao, S.; Goh, S.; Hsu, A.; Tan, B. K. *Planta Med.* **2002**, *68*, 198–203.
8. Asano, J.; Chiba, K.; Tada, M.; Yoshii, T. *Phytochemistry* **1996**, *41*, 815–820.
9. Quillinan, A. J.; Scheinmann, F. *J. Chem. Soc., Chem. Commun.* **1971**, 966–967.
10. Nicolaou, K. C.; Jim, Li. *Angew. Chem., Int. Ed.* **2001**, *40*, 4264–4268.
11. Tisdale, E. J.; Chowdhury, C.; Vong, B. G.; Li, H.; Theodorakis, E. A. *Org. Lett.* **2002**, *4*, 909–912.
12. Tisdale, E. J.; Slobodov, I.; Theodorakis, E. A. *Org. Biomol. Chem.* **2003**, *1*, 4418–4422.
13. Tisdale, E. J.; Li, H.; Vong, B. G.; Kim, S. H.; Theodorakis, E. A. *Org. Lett.* **2003**, *5*, 1491–1494.
14. Tisdale, E. J.; Theodorakis, E. A. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 12030–12035.
15. Nicolaou, K. C.; Xu, H.; Wartmann, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 756–761.
16. Li, N.-G.; Wang, J.-X.; Liu, X.-R.; Lin, C.-J.; You, Q.-D.; Guo, Q.-L. *Tetrahedron Lett.* **2007**, *48*, 6586–6589.
17. Chantarasriwong, O.; Cho, W. C.; Batova, A.; Chavasiri, W.; Moore, C.; Rheingold, A. L.; Theodorakis, E. A. *Org. Biomol. Chem.* **2009**, *7*, 4886–4894.