DOI: 10.1002/cjoc.201500295

Synthesis of Two Coumarins Isolated from *Aster praealtus*

Bo Wang,[a,b] Huijun Chen,[a] Yikang Wu,*[,a] and Bo Liu*[,b]

[a] *State Key Laboratory of Bioorganic and Natural Products Chemistry, Collaborative Innovation Center of Chemistry for Life Sciences, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, China*

[b] *Key Laboratory of Green Chemical Technology of College of Heilongjiang Province, School of Chemical and Environmental Engineering, Harbin University of Science and Technology, Harbin 150040, China*

Two coumarins isolated from *Aster praealtus* were synthesized via a direct coupling of the corresponding cyclohexyl carbinol with a coumarin-derived aryl bromide or iodide, a very difficult etherification due to the excess steric congestion around the carbinol and the low reactivity of the aryl halide that frustrated many seemingly feasible protocols. Unequivocal ^{1}H and ^{13}C NMR data for these compounds were thus made available for the first time. Uncertainty and errors in ^{1}H and ^{13}C NMR data in previous reports are also eliminated and revealed, respectively.

Keywords alcohols, condensation, natural products, stereochemistry, ethers

Introduction

During our recent study[1] on the synthesis of peroxy chamigranoids[2] (such as **1**, Figure 1), enantioselective cyclization of geraniol **2** was once considered as a possible approach for construction of the cyclohexane ring with the geminal dimethyl groups in the target structures. Alternatives involving the potentially exploitable intermediate cyclohexyl carbinol **3** were also examined.

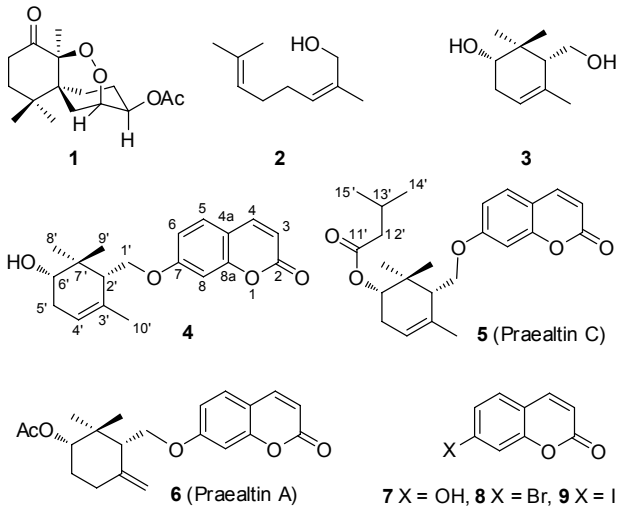


Figure 1 The structures for talaperoxide A **1**, geraniol **2**, the carbinol **3**, natural coumarins **4**—**6** and the building blocks **7**—**9**.

As an extension of the work on the peroxy chamigranoids, we also explored the synthesis of two other natural products[3] related to **3**, *i.e.* coumarins **4** and **5**. These two natural products were documented in the literature since 1968 and 1989,[4,5] respectively. Racemic **4** was also reported[6,7,8a] as a side/minor products of Lewis acid mediated cyclization of a geranyl epoxide (with the coumarin moiety already connected to the primary OH of geraniol). Recently, a coumarin sharing the same planar structure with **4** was also isolated[8b] from roots of *Cleme viscosa* (L.).

Compound **5** (Praealtin C) was only obtained[5] as an inseparable mixture with an acyl isomer (carrying a 2-methylbutanoyl instead of the 3-methylbutanoyl group on the secondary hydroxyl group); its NMR hence has never been secured to date. Therefore, it appeared warranted to carry out a synthetic study of the natural coumarins **4** and **5**.

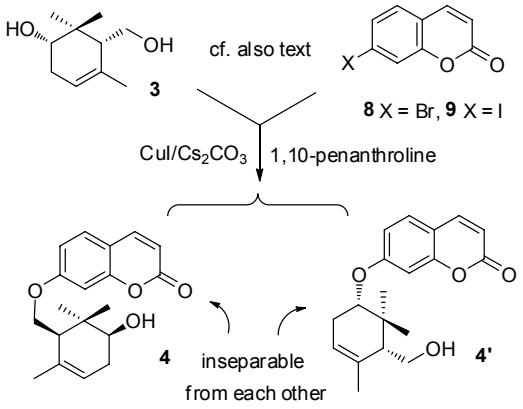
Results and Discussion

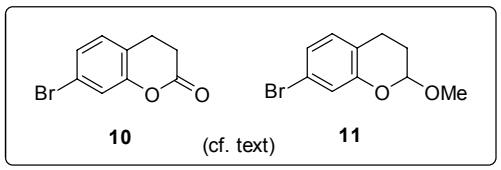
Given optically active **3** (prepared using a literature[9] procedure) already available, direct coupling with a coumarin-related species such as **8** and **9** (Scheme 1) appeared to be a straightforward entry to the target compounds **4** and **5**. However, to date there has been no precedent for coupling of **8** or **9** with any aliphatic alcohols, although substituted phenols did undergo smooth coupling[10] with **8**; attachment of any alkyl groups to the C-7 position of coumarin can be achieved only either via alkylation of the OH of **7** with a halide (often unhindered or activated) or a Mitsunobu reaction with an unhindered alcohol.[11] These documented literature cases, when taken together, seemed to indicate

* E-mail: yikangwu@sioc.ac.cn
Received April 10, 2015; accepted April 23, 2015; published online June 2, 2015.
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/cjoc.201500295 or from the author.

that for some reasons the coupling of **8** or **9** with alcohols might be experimentally unfeasible.

Scheme 1 Coupling of **3** with coumarin-related aryl halides





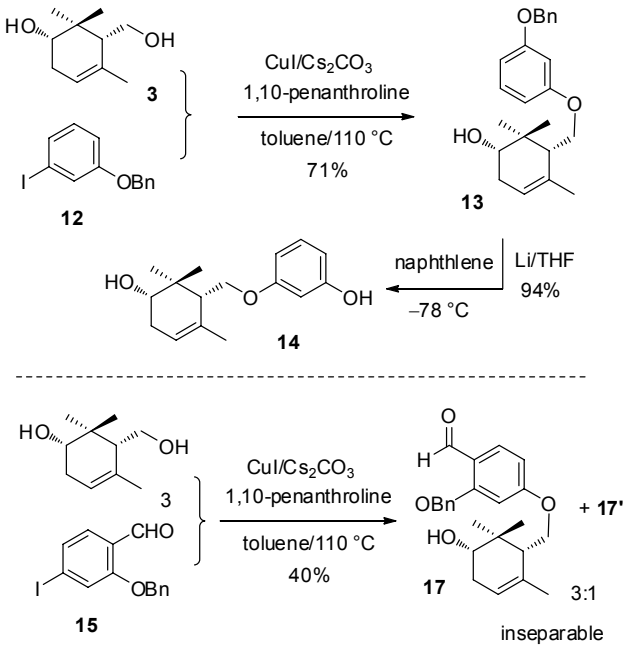
Nevertheless, prompted by the potential advantage such a direct coupling may offer to the coumarin synthesis, also by the availability of **3**, we decided to take the challenge of the seemingly hopeless coupling anyway.

The initial experiment was performed under the Buchwald's[12] conditions, which were effective for connection of a range of alcohols (even sterically hindered ones) to different phenols. Thus, the bromide **8** (prepared according to a literature[13] procedure from the commercially available coumarin **7**) was treated with alcohol **3** in the presence of $Pd_2(dba)_2$/BINAP and Cs_2CO_3 in toluene at 90 ℃. Unfortunately, no reactions could be detected even after 24 h. Addition of a co-solvent such as $MeO(CH_2)_2OMe$ or EtOAc did not give any improvement. Use of $Pd(OAc)_2/K_3PO_4$[14] instead of $Pd_2(dba)_2/Cs_2CO_3$ to run the reaction under the otherwise the same conditions also failed to lead to any discernible changes.

Because of the repeated failures with the Pd-catalyzed coupling under the conditions exemplified above, we next turned to Cu-catalyzed ones, which in many cases effectively catalyzed[15] the coupling of aryl halides with alcohols. Buchwald CuI/Cs_2CO_3/1,10-phenanthroline/toluene/110 ℃[16] conditions, which were effective for even secondary alcohols, were then tested. However, with either **8** or **9** as the aryl halide no reactions occurred at elevated temperatures up to 110 ℃ after 24 h. Increasing the amount of the added CuI to 1 mol equivalent (with respect to **3**) or more did not result in any discernible changes. Use of 8-hydroxyquinoline to replace the 1,10-phenanthroline as the ligand with K_3PO_4 as the base instead of Cs_2CO_3 as reported[17] by Xu and Hu also failed to result any reactions.

However, under the CuI/Cs_2CO_3/1,10-phenanthroline/toluene/110 ℃ conditions[16] the coupling of **12**[18] with **3** proceeded smoothly (Scheme 2), affording the corresponding coupling product **11** in 71% isolated yield. Debenzylation of **13** could also be achieved satisfactorily under Liu's[19] Li/naphthalene conditions. Encouraged by this model reaction, we next used **15**[20a] (which might allow for a late stage construction of the coumarin ring through the aldehyde group) to run the coupling under the same conditions. But unfortunately, the yield for the expected **17** turned out to be only 40%. And the product was no longer predominated by a single isomer (containing a regio-isomer **17'**, where the aryl group was on the secondary OH, cf. the discussion below for **4'** in Scheme 1). All these made this route much less attractive than expected. The planned[20b] subsequent steps were therefore not carried out.

Scheme 2 Model reactions



Nevertheless, the smooth coupling of **12** seemed to suggest that the inertness of **8** or **9** in the coupling might not be all caused by the steric crowding of the hydroxyl group in **3**; perhaps the electronic effects of the lactone carbonyl group also contributed. It followed that breaking up the conjugate system by saturating the C—C double bond might eliminate the possible negative influence of the carbonyl group on the aromatic ring and thus improve the reactivity. With this thought in mind, we next used **10** to replace **8** to perform the reaction under the same conditions.

To our disappointment, the outcome was still negative, with no desired **4** could be detected. But somewhat different from the situation with the reaction using **8** (where the starting **8** remained intact), the added **10**

completely disappeared in the end. We reasoned that this was because the non-conjugate lactone was more sensitive to base-mediated hydrolysis than the conjugate one. To exclude the possibility of a failed coupling being caused by hydrolysis of **10**, we next used **11** (which should be reasonably stable to the basic conditions) to re-run the coupling reaction.

Without the interference from the hydrolysis, the coupling of **11** with **3** indeed occurred, but only to a negligible extent (＜3%) after heating at 110 ℃ for 37 h; the starting **3** and **11** were recovered in 95% and 85%, respectively.

Up to this point, it seemed that use of a direct coupling of **3** to afford **4** would be a mission impossible;[21] lack of similar coupling precedents in the literature indeed had its reasons. However, with all the reactants still in hand, before giving up we decided to run the reaction under more forcing conditions despite the very likely excessive side reactions.

Thus, with *m*-xylene to replace toluene as the reaction solvent, we re-examined the coupling of **3** with **8** in a sealed tube at 160 ℃ (bath) under otherwise the same conditions. To our gratification, the desired **4** was finally formed in 11% isolated yield (along with 50% of recovered **3**) after 24 h. If using **9** instead of **8**, the yield for **4** was 20% (along with 40% of recovered **3**).

Careful examination of the ^{1}H NMR of the **4** revealed co-existence of two species (inseparable on silica gel) in an approximately 5.9∶1 ratio. In the beginning the possibility of epimerization under the high temperature was considered. However, acylation of the remaining hydroxyl group indicated (through the changes in the ^{1}H NMR) that the unexpected isomer was more likely to be the regio-isomer **4'** (Scheme 1).

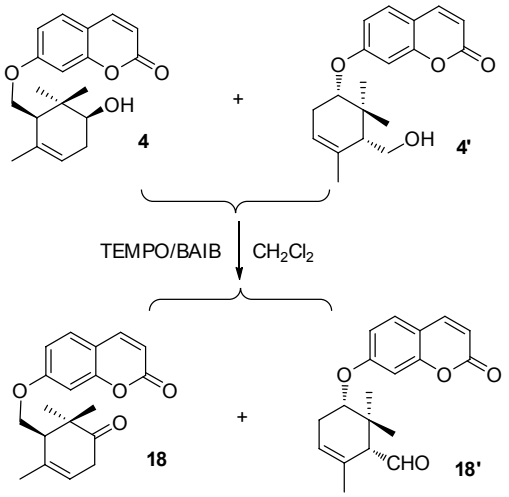
To confirm this, the coupling product was subjected to oxidation of TEMPO/BAIB[22] (Scheme 3); the product mixture did show an aldehyde signal in ^{1}H NMR. If only a limited amount of TEMPO was employed with the reaction time carefully controlled, only **4'** was oxidized while most of the **4** remain intact. The unreacted **4** could be easily separated from **18'**.

It is noteworthy that as shown by the formation of **4'**, the reactivity difference between the primary and the secondary OH groups in **3** appeared much less than one might expect. This unexpected phenomenon may stem from a substantially increased steric congestion around the primary OH caused by the additional (allylic) methyl group.

Using pure **4** as the substrate, target compound **5** was readily obtained via a simple acylation (Scheme 4).

The synthetic samples of **4** and **5** allowed for collection of unambiguous ^{1}H and ^{13}C NMR data as well as the optical rotations for the first time. Although direct data comparison for **4** is not possible,[23] the ^{1}H and ^{13}C NMR recorded on a mixture of **5** and its (acyl) isomer allowed for unequivocal confirmation of the previously assigned structure and relative configuration for **5**. Some uncertainty (because the sample was a mixture of two compounds) in the signals in the previous assignments is also cleared. Since **4** and **5** co-exist in the same plant, the two compounds are very likely to share the same relative configuration.

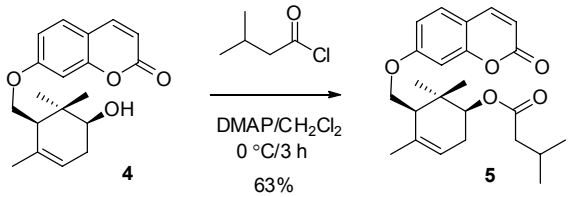
Scheme 3 The TEMPO/BAIB oxidation



BAIB = bis(acetoxy)iodobenzene

TEMPO = 2,2,6,6-tetramethyl-1-piperidinyloxy

Scheme 4 Acylation of **4**



It should be noted that the two[4,7] existing sets of ^{1}H NMR data for the synthetic **4** either were incomplete or contained some errors. As for the recently reported[8b] natural product that was assigned the same planar structure as **4**, its ^{1}H NMR is partially incompatible with that for the **4** from this work (a signal at *ca.* δ 3.5 was missing and the two geminal methyl groups appeared at *ca.* δ 0.3 to the downfield; cf. the tabular data comparison in the Supporting Information).

More definite rejecting evidence is found in the ^{13}C NMR, where practically all signals from the aliphatic moiety of the natural sample are completely incompatible with those for the synthetic **4**. Therefore that[8b] natural product and **4** (of the *cis* configuration) must be different compounds. And as the ^{1}H NMR for the natural product[8b] is also incompatible with those reported[4] for the *anti* isomer (*e.g.*, the geminal methyl groups), it is concluded that even the planar structure assigned for that natural sample is incorrect.

Conclusions

In summary, synthesis of naturally-occurring coumarins, *i.e.* compounds **4** and **5** were attempted through a direct coupling reaction between a cyclohexyl carbinol

of unequivocal relative and absolute configurations and a proper coumarin-derived aryl bromide or iodide. Because of the excess steric congestion of the alcohol and the reduced reactivity of the halides, the coupling did not occur under the literature conditions. The seemingly impossible coupling was eventually achieved in a sealed tube at 160 ℃. The synthetic samples of **4** and **5** not only provided clear-cut spectroscopic data for these two long-known compounds for the first time, but also revealed some errors and ambiguity in the previous studies. A recently reported natural product, which was reportedly to have the same planar structure as **4**, is also proven to be erroneously assigned.

Experimental

The NMR spectra were recorded on either an Agilent 500/54 NMR spectrometer (operating at 500 MHz for ^{1}H) or an Agilent 400/54 instrument (operating at 400 MHz for ^{1}H). IR spectra were measured on a Nicolet 380 Infrared spectrophotometer. ESI-MS data were acquired on a Shimadzu LCMS-2010EV mass spectrometer. EI-MS were collected using an Agilent Technologies 5973N instrument. ESI-HRMS data were obtained with a Thermo Fisher Scientific LTQ FT Ultra spectrometer. EI-HRMS were recorded on a Waters Micromass GCT Premier. Optical rotations were measured on a Jasco P-1030 polarimeter. Melting points were uncorrected (measured on a hot stage melting point apparatus equipped with a microscope). Toluene, *m*-xylene and CH_2Cl_2 were dried with activated 4 Å MS (molecular sieves). All chemicals were reagent grade and used as purchased. Column chromatography was performed on silica gel (300−400 mesh) under slightly positive pressure. PE＝petroleum ether (b.p. 60−90 ℃).

Synthesis of 8[13]

With cooling (ice-water bath) and stirring, concd. H_2SO_4 (1.3 mL, 0.024 mmol) was added dropwise to a mixture of malic acid (520 mg, 3.9 mmol) and *m*-bromo-phenol (1.0 g, 5.8 mmol) in a flask (equipped with a condenser). After completion of the addition, the mixture was heated (with magnetic stirring) in a 120 ℃ bath for 6 h. The dark mixture was then cooled to ambient temperature. The mixture was extracted with EtOAc (50 mL×3). The combined organic layers were washed with water (10 mL) and brine (10 mL) before being dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography [*V*(PE)/*V*(EtOAc)＝7∶1] on silica gel gave **8** as a white solid (338 mg, 1.52 mmol, 39%): M.p. 121−123 ℃ (lit.[13a] m.p. 121−123 ℃, lit.[13b] m.p. 123.5 ℃). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.66 (d, *J*＝9.6 Hz, 1H), 7.52 (d, *J*＝1.7 Hz, 1H), 7.42 (dd, *J*＝8.3, 1.8 Hz, 1H), 7.35 (d, *J*＝8.3 Hz, 1H), 6.44 (d, *J*＝9.6 Hz, 1H).

Synthesis of 9

The same procedure for the preparation of **8** given above was employed. Yield: 7%. Data for **9**: M.p. 178−180 ℃ (lit.[24] m.p. 172 ℃). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.72 (d, *J*＝1.2 Hz, 1H), 7.65 (d, *J*＝9.6 Hz, 1H), 7.62 (dd, *J*＝8.1, 1.6 Hz, 1H), 7.19 (d, *J*＝8.1 Hz, 1H), 6.45 (d, *J*＝9.6 Hz, 1H); EI-MS *m/z* (%): 272 (M^+, 100), 244 (52), 127 (6), 117 (17), 89 (32).

Synthesis of 14 via coupling of 3 with 12 followed by debenzylation of 13

Alcohol **3**[24] ($[\alpha]_D^{26}$ −52.0 (*c* 2.0, CH_2Cl_2) (lit.[25] $[\alpha]_D^{20}$ −51.7 (*c* 2, CH_2Cl_2)), (100 mg, 0.59 mmol), *m*-benzy-loxy-iodo-benzene (182 mg, 0.59 mmol), Cs_2CO_3 (385 mg, 1.18 mmol), 1,10-phenanthroline (22 mg, 0.118 mmol), CuI (11 mg, 0.059 mmol) and a magnetic stirring bar were added to a thick wall/heavy-duty reusable sealed tube equipped with a Teflon screw cap. Dry toluene (2 mL) was then added. The flask was flushed with argon and sealed with the screw cap. The flask was placed in in a 110 ℃ bath for 24 h (with magnetic stirring). After being cooled to ambient temperature, water was added (10 mL). The mixture was extracted with EtOAc (80 mL×3). The combined organic layers were washed with water (10 mL) and brine (10 mL) before being dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography [*V*(PE)/*V*(EtOAc)＝7∶1] on silica gel furnished **13** as a colorless oil (147 mg, 0.42 mmol, 71%), from which the following data were collected: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.50−7.27 (m, 5H), 7.18 (t, *J*＝8.1 Hz, 1H), 6.60 (dd, *J*＝7.9, 2.3 Hz, 1H), 6.57 (t, *J*＝1.9 Hz, 1H), 6.54 (dd, *J*＝8.1, 2.7 Hz, 1H), 5.46 (s, 1H), 5.03 (s, 2H), 4.23 (dd, *J*＝9.8, 3.7 Hz, 1H), 4.03 (dd, *J*＝9.9, 2.9 Hz, 1H), 3.45−3.39 (m, 1H), 3.22 (d, *J*＝9.2 Hz, 1H), 2.38 (d, *J*＝18.0 Hz, 1H), 2.17 (d, *J*＝17.7 Hz, 1H), 2.04 (s, 1H), 1.75 (s, 3H), 1.07 (s, 3H), 1.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.0, 159.3, 136.9, 131.7, 130.0, 128.6, 128.0, 127.6, 120.7, 107.7, 107.4, 102.1, 72.7, 70.1, 66.1, 48.9, 37.2, 32.0, 29.7, 28.1, 22.4, 21.9. ESI-MS *m/z*: 375.4 ($[M+Na]^+$).

A solution of the above obtained **13** (117 mg, 0.33 mmol) in dry THF (2 mL) was added to a mixture of Li/naphthalene (prepared by stirring Li cuts (5 mg, 2.02 mmol) and naphthalene (168 mg, 1.34 mmol) in dry THF (2 mL) at ambient temperature under argon for 30 min before use) and stirred at −25 ℃ under argon (balloon). After the addition, the mixture was stirred at −25 ℃ for 3 h (when TLC showed completion of the reaction). Aq. sat. NH_4Cl (10 mL) was added carefully. The mixture was extracted with EtOAc (80 mL×3). The combined organic layers were washed with water (10 mL) and brine (10 mL) before being dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography [*V*(PE)/*V*(EtOAc)＝5∶1] on silica gel furnished **14** as a colorless oil (82 mg, 0.31 mmol, 94%): $[\alpha]_D^{25}$ −66.5 (*c* 0.5, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.11 (t, *J*＝8.2 Hz, 1H), 6.57 (s, 1H), 6.49−6.44 (m, 2H), 6.40 (t, *J*＝2.2 Hz, 1H), 5.49 (s, 1H), 4.21 (dd, *J*＝9.8, 3.6 Hz, 1H),

4.13－4.02 (a lump, 1H, OH), 4.04 (dd, J＝9.8, 2.5 Hz, 1H), 3.44 (s, 1H), 2.40 (ddd, J＝18.3, 4.8, 2.4 Hz, 1H), 2.22 (d, J＝17.2 Hz, 1H), 2.20 (s, 1H), 1.75 (s, 3H), 1.10 (s, 3H), 1.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 158.7, 157.8, 131.0, 130.2, 120.7, 109.5, 104.8, 102.7, 72.2, 65.5, 48.7, 37.1, 31.9, 28.6, 23.1, 22.4; FT-IR (film) ν_{max}: 3378, 2961, 2924, 1597, 1483, 1466, 1287, 1174, 1149, 1075, 1010, 906, 769, 689 cm^{-1}; EI-MS *m/z* (%): 262 (M^+, 3), 149 (16), 135 (18), 121 (15), 110 (100). EI-HRMS calcd for $C_{16}H_{22}O_3$ (M^+) 262.1569, found 262.1571.

Coupling of 3 with 8 to afford 4

Alcohol **3** (34 mg, 0.20 mmol), **8** (54 mg, 0.24 mmol), Cs_2CO_3 (130 mg, 0.40 mmol), 1,10-phenanthroline (8 mg, 0.04 mmol), CuI (8 mg, 0.04 mmol) and a magnetic stirring bar were added to a thick wall/heavy-duty reusable sealed tube equipped with a Teflon screw cap. Dry *m*-xylene (2 mL) was then added. The flask was flushed with argon and sealed with the screw cap. The flask was placed in a 160 ℃ bath for 24 h (with magnetic stirring). After being cooled to ambient temperature, water was added (10 mL). The mixture was extracted with EtOAc (80 mL×3). The combined organic layers were washed with water (10 mL) and brine (10 mL) before being dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography [V(PE)/V(EtOAc)＝3∶1] on silica gel furnished an approximately 5.9∶1 (as shown by ^{1}H NMR) inseparable mixture of **4** and **4'** as a colorless oil (8 mg, 0.025 mmol, 11%), along with recovered **3** (50%).

Coupling of 3 with 9 to afford 4

The same procedure given above for the coupling of **3** with **8** was used. Yield (**4**/**4'**＝5.9∶1): 20%, along with 40% of recovered **3**.

Removal of 4' in 4 by TEMPO oxidation

A solution of the mixture of **4** and **4'** (18 mg, 0.05 mmol), BAIB (21 mg, 0.066 mmol) and TEMPO (5 mg, 0.028 mmol) in dry CH_2Cl_2 (1 mL) was stirred at ambient temperature for 3 h. The mixture was concentrated on a rotary evaporator. The residue was purified by column chromatography [V(PE)/V(EtOAc)＝3∶1] on silica gel to give pure **4** as a colorless oil (14 mg, 0.038 mmol, 77%). Data for **4** (after removal of **4'** by TEMPO oxidation): $[\alpha]_D^{27}$ −75.5 (c 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.64 (d, J＝9.6 Hz, 1H), 7.37 (d, J＝8.7 Hz, 1H), 6.87－6.83 (m, 2H), 6.26 (d, J＝9.4 Hz, 1H), 5.47 (br s, 1H), 4.34 (dd, J＝9.8, 3.9 Hz, 1H), 4.12 (dd, J＝9.9, 3.5 Hz, 1H), 3.48 (t, J＝5.0 Hz, 1H), 2.76－2.46 (br s, 1H), 2.39 (br d, J＝18.4 Hz, 1H), 2.19－2.10 (m, 2H), 1.76 (s, 3H), 1.06 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.4 (quat.), 161.1 (quat.), 155.8 (quat.), 143.3 (CH), 131.9 (quat.), 128.8 (CH), 120.7 (CH), 113.3 (CH), 113.1 (CH), 112.8 (quat.), 101.4 (CH), 73.0 (CH), 67.3 (CH_2), 48.7 (CH), 37.1 (quat.), 31.9 (CH), 27.3 (CH_3), 22.4 (CH_3), 20.9 (CH_3); FT-IR (film) ν_{max}: 3473 (br), 2964, 2914, 1732, 1614, 1555, 1508, 1403, 1280, 1231, 1125, 835 cm^{-1}; ESI-MS *m/z*: 315.2 ($[M+H]^+$); ESI-HRMS calcd for $C_{19}H_{23}O_4$ ($[M+H]^+$) 315.1596, found 315.1590.

Acylation of 4 to furnish 5

A solution of isopentanoyl chloride (470 μL, 0.038 mmol, of a stock solution prepared by dissolving 100 μL of isopentanoyl chloride in 10 mL of CH_2Cl_2) was added to a solution of **4** (8 mg, 0.025 mmol) and DMAP (12 mg, 0.10 mmol) in dry CH_2Cl_2 (0.5 mL) stirred in an ice-water bath for 3 h (TLC showed completion of the reaction). The mixture was diluted with EtOAc, washed with water (5 mL) and brine (5 mL) before being dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography [V(PE)/V(EtOAc)＝5∶1] on silica gel furnished **5** as a white wax (6 mg, 0.017 mmol, 62%): $[\alpha]_D^{25}$ −53.0 (c 0.5, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.64 (d, J＝9.1 Hz, 1H), 7.37 (d, J＝8.8 Hz, 1H), 6.84 (dd, J＝8.8, 2.3 Hz, 1H), 6.81 (d, J＝1.9 Hz, 1H), 6.25 (d, J＝9.6 Hz, 1H), 5.39 (br s, 1H), 4.76 (t, J＝5.5 Hz, 1H), 4.37 (dd, J＝9.8, 4.4 Hz, 1H), 4.08 (dd, J＝9.8, 4.8 Hz, 1H), 2.42－2.34 (m, 1H), 2.28 (br s, 1H), 2.19 (br d, J＝6.7 Hz, 2H), 2.14－2.07 (m, 2H), 1.79 (s, 3H), 1.04 (s, 3H), 1.03 (s, 3H), 0.96 (d, J＝6.0 Hz, 3H), 0.95 (d, J＝6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 172.6, 162.0, 161.2, 156.0, 143.4, 133.4, 128.7, 119.7, 113.10, 113.07, 112.5, 101.3, 75.5, 68.5, 48.9, 44.0, 35.8, 28.8, 26.1, 25.9, 22.7, 22.5, 22.4, 20.1; FT-IR (film) ν_{max}: 2962, 2929, 2866, 1735, 1613, 1406, 1292, 1230, 1121, 834 cm^{-1}; EI-MS *m/z* (%): 398 (M^+, 1.05), 296 (13), 176 (23), 162 (15), 135 (100), 121 (53), 119 (34), 107 (31), 93 (51), 85 (37); EI-HRMS calcd for $C_{24}H_{30}O_5$ (M^+) 398.2093, found 398.2096.

Acknowledgement

This work was supported by the National Natural Science Foundation of China (Nos. 21172247, 21372248) and the Chinese Academy of Sciences.

References and Notes

[1] Chen, H.-J.; Wu, Y.-K. *Org. Lett*. **2015**, *17*, 592.
[2] (a) Liu, D.-A.; Dong, Z.-J.; Wang, F.; Liu, J.-K. *Tetrahedron Lett*. **2010**, *51*, 3152; (b) Chokpaiboon, S.; Sommit, D.; Teerawatananond, T.; Muangsin, N.; Bunyapaiboonsri, T.; Pudhom, K. *J. Nat. Prod*. **2010**, *73*, 1005; (c) Liu, D.-Z.; Luo, M.-H. *Fitoterapia* **2010**, *81*, 1205; (d) Li, H.; Huang, H.; Shao, C.; Huang, H.; Jiang, J.; Zhu, X.; Liu, Y.; Liu, L.; Lu, Y.; Li, M.; Lin, Y.; She, Z. *J. Nat. Prod*. **2011**, *74*, 1230; (e) Chokpaiboon, S.; Sommit, D.; Bunyapaiboonsri, T.; Matsubara, K.; Pudhom, K. *J. Nat. Prod*. **2011**, *74*, 2290; (f) Wibowo, M.; Prachyawarakorn, V.; Aree, T.; Wiyakrutta, S.; Mahidol, C.; Ruchirawat, S.; Kittakoop, P. *Eur. J. Org. Chem*. **2014**, 3976; For use of merulin A for the treatment of African sleeping sickness, see: (g) Navarro, G.; Chokpaiboon, S.; De Muylder, G.; Bray, W. M.; Nisam, S. C.; McKerrow, J. H.; Pudhom, K.; Linington, R. G. *PLoS One* **2012**, *7*, e46172; (h) Linington, R.; Navarro, G.; Pudhom, K.;

McKerrow, J. *WO 2013019686 A2* [*Chem. Abstr*. **2013**, *158*, 302292].

[3] The relative configurations for **4** and **5** depicted in this work are adopted from those in the literature (ref 5 below), which presumably were deduced on the basis of the single crystal X-ray crystallographic analysis of **6** (Praealtin A) isolated at the same time.

[4] Bohlmann, F.; Zdero, C.; Kapteyn, H. *Liebig. Ann. Chem*. **1968**, *717*, 186.

[5] Wilzer, K. A.; Fronczek, F. R.; Urbatsch, L. E.; Fischer, N. H. *Phytochemistry* **1989**, *28*, 1729.

[6] Coates, R. M.; Melvin, L. S., Jr. *Tetrahedron* **1970**, *26*, 5699.

[7] Aziz, M.; Rouessac, F. *Tetrahedron* **1988**, *44*, 101 (in Frehch. Cf. the ^{1}H NMR data for the compounds "**8** (1)" and "**8** (2)" therein). It appears that the data sets therein were switched by mistake—while the planar structure for the"**8** (2)" matched the **4** in this work, the corresponding data were given for the exocyclic alkenic isomer "**8** (1)" therein. For detailed tabular comparisons, see: the Supporting Information.

[8] For an epimer of **4** (with the relative configuration depicted as *anti*), see: (a) Bohlmann, F.; Gerke, T.; King, R. M.; Robinson, H. *Liebig. Ann. Chem*. **1983**, 714 (the compound **6** therein, without any accompanying data); (b) Almahy, H. A.; Alagimi, A. A. *Arabian J. Chem*. **2012**, *5*, 241 [*Chem. Abstr.* **2012**, *158*, 295655]; relative configuration unknown); For importance and bioactivities of some oxygenated coumarins, see *e.g.*: (c) Riveiro, M. E.; De Kimpe, N.; Moglioni, A.; Vazquez, R.; Monczor, F.; Shayo, C.; Davio, C. *Curr. Med. Chem*. **2010**, *17*, 1325; (d) Riveiro, M. E.; Maes, D.; Vazquez, R.; Vermeulen, M.; Mangelinckx, S.; Jacobs, J.; Debenedetti, S.; Shayo, C.; De Kimpe, N.; Davio, C. *Biorg. Med. Chem*. **2009**, *17*, 6547; (e) Maes, D.; Vervisch, S.; Debenedetti, S.; Davio, C.; Mangelinckx, S.; Giubellina, N.; De Kimpe, N. *Tetrahedron* **2005**, *61*, 2505.

[9] Bovolenta, M.; Castronovo, F.; Vadala, A.; Zanoni, G.; Vidari, G. *J. Org. Chem*. **2004**, *69*, 8959.

[10] (a) Belluti, F.; Perozzo, R.; Lauciello, L.; Colizzi, F.; Kostrewa, D.; Bisi, A.; Gobbi, S.; Rampa, A.; Bolognesi, M. L.; Recanatini, M.; Brun, R.; Scapozza, L.; Cavalli, A. *J. Med. Chem*. **2013**, *56*, 7516; (b) Reisch, J.; Wickramasinghe, A.; Kumar, V. *Monatshefte Chem*. **1988**, *119*, 1333.

[11] (a) Sevestre, A.; Helaine, V.; Guyot, G.; Martin, C.; Hecquet, L. *Tetrahedron Lett*. **2003**, *44*, 827; (b) Clarke, D. J.; Robinson, R. S. *Tetrahedron* **2002**, *58*, 2831; (c) Kosiova, I.; Kovackova, S.; Kois, P. *Tetrahedron* **2007**, *6*, 312; (d) Tobe, M.; Isobe, Y.; Goto, Y.; Obara, F.; Tsuchiya, M.; Matsui, J.; Hirota, K.; Hayashi, H. *Bioorg. Med. Chem*. **2000**, *8*, 2037; (e) Liu, M.-M.; Chen, X.-Y.; Huang, Y.-Q.; Feng, P.; Guo, Y.-L.; Yang, G.; Chen, Y. *J. Med. Chem*. **2014**, *57*, 9343.

[12] Palucki, M.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc*. **1997**, *119*, 3395.

[13] For synthesis of **8** from *m*-bromo-phenol and malic acid, see: (a) Belluti, F.; Perozzo, R.; Lauciello, L.; Colizzi, F.; Kostrewa, D.; Bisi, A.; Gobbi, S.; Rampa, A.; Bolognesi, M. L.; Recanatini, M.; Brun, R.; Scapozza, L.; Cavalli, A. *J. Med. Chem*. **2013**, *56*, 7516 (where NMR data for **8** were incompatible with those in ref 12b); (b) Mitteilung, K.; Reisch, J.; Rosenthal, B. H. W. *Monatshefte Chem*. **1987**, *118*, 871; For an alternative route to **8** from **7**, see (c) Thompson, A. L. S.; Kabalka, G. W.; Akula, M. R.; Huffman, J. W. *Synthesis* **2005**, 547.

[14] Vorgushin, A. V.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc*. **2005**, *127*, 8146.

[15] Ma, D.; Cai, Q. *Acc. Chem. Res*. **2008**, *41*, 1450.

[16] Wolter, M.; Nordmann, G.; Job, G. E.; Buchwald, S. L. *Org. Lett*. **2002**, *4*, 973.

[17] Niu, J.; Guo, P.; Kang, J.; Li, Z.; Xu, J.; Hu, S. *J. Org. Chem*. **2009**, *74*, 5075.

[18] Bassoli, A.; Borgonovo, G.; Busnelli, G.; Morini, G. *Eur. J. Org. Chem*. **2006**, 1656.

[19] Liu, H.-J.; Yip, J. *Tetrahedron Lett*. **1997**, *38*, 2253.

[20] (a) Morriello, G. J.; Devita, R. J.; Moyes, C. R. **2008**, *WO 2008057336 A2* [*Chem. Abstr.* **2008**, *148*, 561711]; (b) Such plans were rather common in synthesis of coumarins, see *e.g.*: Maes, D.; Riveiro, M. E. ; Shayo, C.; Davio, C.; Debenedetti, S.; De Kimpe, N. *Tetrahedron* **2008**, *64*, 4438; (c) Gong, D.-H.; Li, C.-Z.; Yuan, C.-Y. *Chin. J. Chem*. **2001**, *19*, 517.

[21] Attachment of **3** or the epoxy (of the tri-substituted C—C double bond) geraniol onto coumarin core via Mitsunobu reaction with **7** was unsuccessful.

[22] Vatèle, J.-M. *Tetrahedron Lett*. **2006**, *47*, 715.

[23] The ref 5 above did not provide any data for **4**, only referred to the ref 4 above.

[24] Thakar, K. A.; Goswami, D. D. *J. Ind. Chem. Soc*. **1972**, *49*, 707 [*Chem. Abstr.* **1972**, *77*, 139506.]

[25] Bovolenta, M.; Castronovo, F.; Vadalà, A.; Zanoni, G.; Vidari, G. *J. Org. Chem*. **2004**, *69*, 8959.

(Zhao, X.)

