Synthesis of Kaempferol 3-*O*-[2″,3″- and 2″,4″-Di-*O*-(*E*)-*p*-coumaroyl]-α-L-rhamnopyranosides

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Dedicated to Professors Xiyan Lu and Lixin Dai

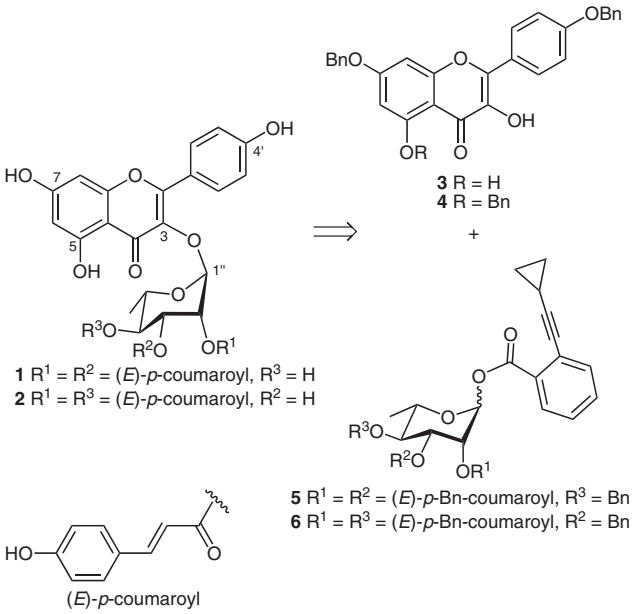
Abstract: Kaempferol 3-*O*-[2″,3″- and 2″,4″-di-*O*-(*E*)-*p*-coumaroyl]-α-L-rhamnopyranoside, two acylated flavonol 3-*O*-glycosides with potent inhibitory activity against methicillin-resistant *Staphylococcus aureus*, were synthesized for the first time, employing glycosyl *o*-cyclopropylethynylbenzoates as donors and $Ph_3PAuNTf_2$ as a catalyst for the construction of the flavonol glycosidic linkages.

Key words: flavonol glycosides, glycosylation, glycosyl *o*-alkynylbenzoate, antibacterial activity

Kaempferol 3-*O*-[2″,3″-di-*O*-(*E*)-*p*-coumaroyl]-α-L-rhamnopyranoside (**1**), named platanoside, has been isolated from *Platanus acerifolia* (Platanaceae),[1] *P. orientalis*,[2] *P. occidentalis*,[3] *Pentachondra pumila* (Epacridaceae),[4a] *Faeniculum vulgare* (Apiaceae), and *F. dulce*.[4b] Recently, this compound was found to have selective and potent activity against methicillin-resistant *Staphylococcus aureus* (MRSA) with an IC_{50} of 2.0 μg/mL.[3] MRSA is a serious pathogen with significant patient mortality.[5] Hospital-acquired infections of MRSA have shown resistance to multiple antibiotics. Daptomycin is currently the most useful anti-MRSA drug, however, various side effects have been registered, including an increase in blood creatine phosphokinase, rhabdomyolysis, skin exfoliation, and skin ulcers. Thus, development of new anti-MRSA drugs is a matter of great urgency.

Kaempferol 3-*O*-[2″,4″-di-*O*-(*E*)-*p*-coumaroyl]-α-L-rhamnopyranoside (**2**), the regioisomer of compound **1**, has been identified from *Ocotea vellosiana* (Lauraceae),[6] *Laurus nobilis* (Lauraceae),[7] *Mammea longifolia* (Guttiferae),[8] *Eriobotrya japonica* (Rosaceae),[9] *Cinnamomum kotoense* (Lauraceae),[10] *Epimedium sagittatum* (Berberidaceae),[11] and *Machilus philippinensis* (Lauraceae).[12] Independently, compound **2** was also found to be a potent anti-MRSA agent, with the minimum inhibitory concentrations (MICs) being 0.5–2.0 μg/mL.[13] In addition, compound **2** could suppress proliferation of human peripheral blood mononuclear cells induced by phytohemagglutinin, with an IC_{50} of ca. 6.0 μM.[10]

Compounds **1** and **2** are typical naturally occurring acylated flavonol 3-*O*-glycosides.[14] A key step to synthesize this type of natural metabolites is the construction of the phenolic 3-O-glycosidic linkage, which has been mainly resorted to the glycosylation protocol with glycosyl bromides as donors under phase-transfer-catalysis conditions[15] (PTC) or under the action of silver salts.[16] Recently, we disclosed an efficient alternative to the synthesis of this type of linkage with glycosyl *o*-alkynylbenzoates as donors and gold(I) complex as a catalyst.[17] Herein, we report the synthesis of compounds **1** and **2** employing this new protocol for the flavonol 3-*O*-glycoside formation (Scheme 1).



Scheme 1 Acylated flavonol 3-*O*-glycosides **1** and **2** and their retrosynthetic perspective

We have described recently the synthetic routes toward 7,4′-di-*O*-benzyl-kaempferol (**3**) and 5,7,4′-tri-*O*-benzyl-kaempferol (**4**).[17] Worth mentioning is that direct benzylation of kaempferol (2.5 equiv BnBr, K_2CO_3, DMF, r.t.) led to 3,7-di-*O*-benzyl-kaempferol (instead of the desired 7,4′-di-*O*-benzyl-kaempferol) as the major product in ca. 30% yield.[18] In the present synthesis of **4**, the transformation from methyl ketone **7** to bromide **8** was greatly im-

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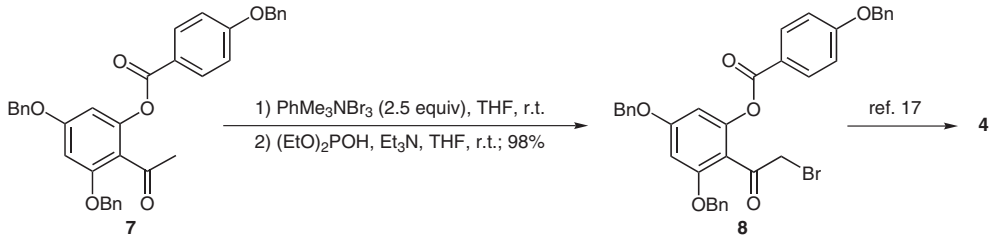


Scheme 2 Improved synthesis of 5,7,4′-tri-*O*-benzyl-kaempferol (**4**)

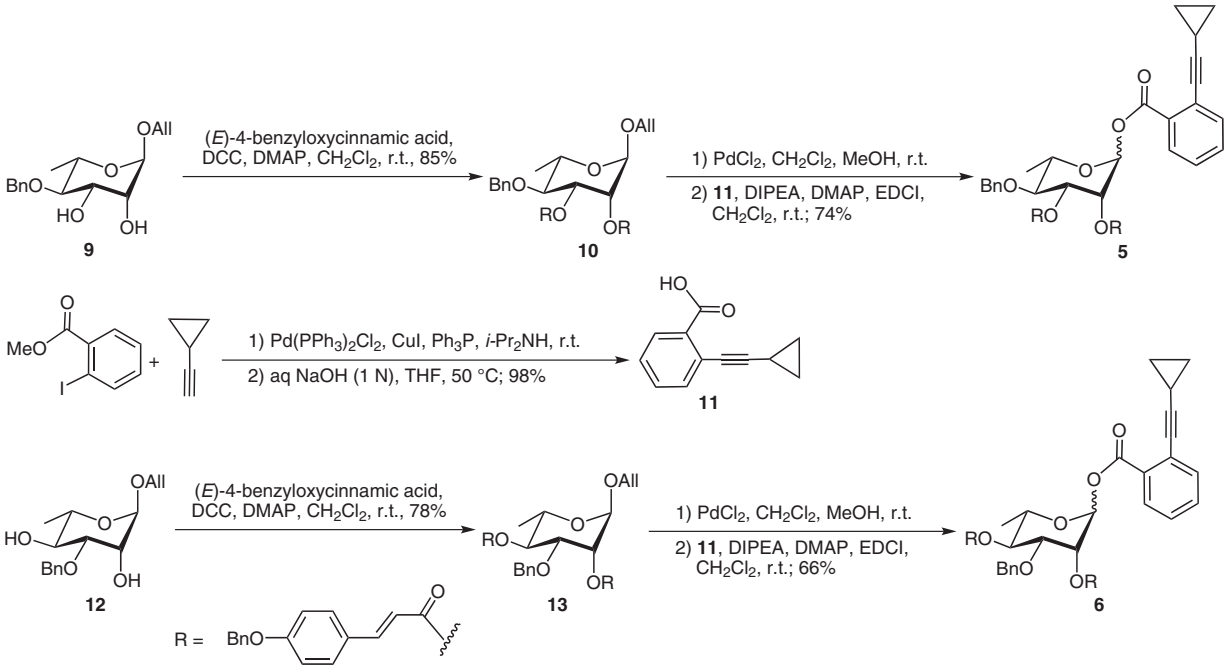
proved by dibromination (with 2.5 equiv of $PhMe_3NBr_3$) first followed by selective debromination [$(EtO)_2POH$, Et_3N, THF, r.t.],[19] providing bromide **8** in an excellent 98% yield (Scheme 2); previous attempts in direct monobromination of **7** led to **8** in less than 49% yield (1 equiv of $PhMe_3NBr_3$, THF, r.t.).[17]

The required rhamnosyl donors **5** and **6** were prepared as shown in Scheme 3. Here we used *o*-cyclopropylethynylbenzoate as the anomeric leaving group instead of the previous *o*-hexynylbenzoate.[20] Although the preparation procedure is similar,[20c] this small variation brings two dividends: the reagent ethynyl cyclopropane is cheaper than 1-hexyne, in addition, *o*-cyclopropylethynylbenzoic acid (**11**) is a crystalline solid (mp 79–82 °C) while *o*-hexynylbenzoic acid is a liquid at room temperature.

Thus, allyl 4-*O*-benzyl-α-L-rhamnopyranoside (**9**)[21] was condensed with (*E*)-4-benzyloxycinnamic acid under the action of DCC and DMAP to provide compound **10** (85%). Removal of the anomeric allyl group on **10** was effected with $PdCl_2$, the resulting lactol was then directly subjected to condensation with *o*-cyclopropylethynylbenzoic acid (**11**, DIPEA, DMAP, EDCI, CH_2Cl_2, r.t.)[20] to afford the desired rhamnosyl donor **5** in 74% yield (two steps). Employing similar transformations, rhamnosyl donor **6** was prepared from allyl 3-*O*-benzyl-α-L-rhamnopyranoside (**12**)[22] in three steps and 51% overall yield.

The glycosidic coupling of 7,4′-di-*O*-benzyl-kaempferol (**3**) with rhamnosyl *o*-cyclopropylethynylbenzoate (**5**) under the action of $Ph_3PAuNTf_2$ led unexpectedly to a complex mixture (Scheme 4). In contrast, the coupling of 5,7,4′-tri-*O*-benzyl-kaempferol (**4**) with **5** under similar conditions (0.2 equiv $Ph_3PAuNTf_2$, 4 Å MS, CH_2Cl_2, r.t.) proceeded smoothly, providing the desired 3-*O*-α-L-rhamnoside (**14**) in a good 74% yield. Similarly, glycosylation of **4** with *o*-cyclopropylethynylbenzoate donor **6** gave α-L-rhamnoside (**15**) in 89% yield. Finally, removal of the six *O*-benzoyl groups on **14**/**15** was achieved with an excess amount of BBr_3 (18 equiv) in CH_2Cl_2 at low temperature (–78 °C), furnishing the target flavonol glycosides **1** and **2** in 68% yield, respectively. The spectroscopic data of the synthetic compounds are identical to those reported for the natural products.[23]

In summary, two acylated flavonol 3-*O*-glycosides **1** and **2** with potent anti-MRSA activities were synthesized for the first time. The synthesis features formation of the flavonol 3-*O*-glycosidic linkages with glycosyl *o*-alkynylbenzoates as donors under the catalysis of a gold(I) complex. This is especially advantageous for the present



Scheme 3 Preparation of rhamnosyl *o*-cyclopropylethynylbenzoates **5** and **6**

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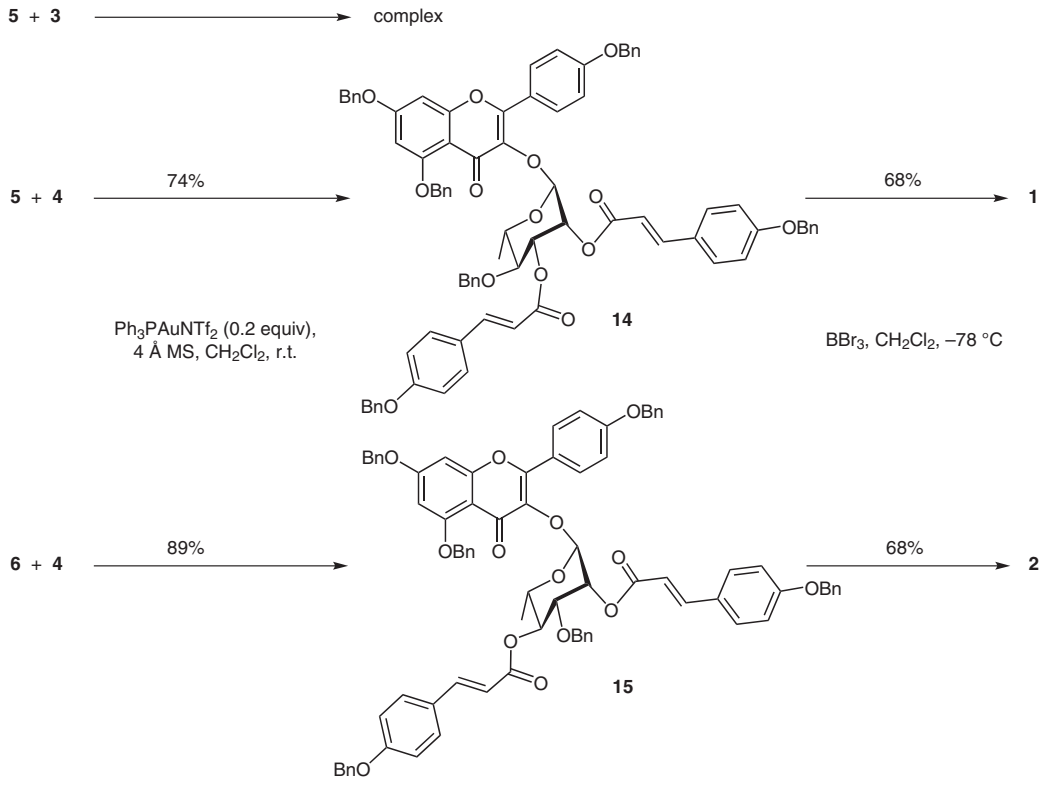

Scheme 4 Completion of the synthesis of compounds **1** and **2**

synthesis of the flavonol 3-*O*-α-L-rhamnosides; the previous methods involve unstable rhamnosyl bromides and stochiometric amount of silver salts.[24] Additionally, glycosyl *o*-cyclopropylethynylbenzoates have been used for the first time as glycosyl donors instead of the previous *o*-hexynylbenzoates. The advantage of this slight variation lies in the more convenient and cheaper preparation of the reagent *o*-cyclopropylethynylbenzoic acid.

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References and Notes

(1) (a) Kaouadji, M. *Phytochemistry* **1990**, *29*, 2295. (b) Kaouadji, M.; Morand, J.-M.; Garcia, J. *J. Nat. Prod.* **1993**, *56*, 1618.
(2) Mitrokotsa, D.; Mitaku, S.; Demetzos, C.; Harvala, C.; Mentis, A.; Perez, S.; Kokkinopoulos, D. *Planta Med.* **1993**, *59*, 517.
(3) Ibrahim, M. A.; Mansoor, A. A.; Gross, A.; Ashfaq, M. K.; Jacob, M.; Khan, S. I.; Hamann, M. T. *J. Nat. Prod.* **2009**, *72*, 2141.
(4) (a) Bloor, S. J. *Phytochemistry* **1995**, *38*, 1033. (b) Soliman, F. M.; Shehata, A. H.; Khaled, A. E.; Ezzat, S. M. *Molecules* **2002**, *7*, 245.
(5) (a) Diekema, D. J.; Boots Miller, B. J.; Vaughn, T. E.; Woolson, R. F.; Yankey, J. W.; Ernst, E. J.; Flach, S. D.; Ward, M. M.; Franciscus, C. L.; Pfaller, M. A.; Doebbeling, B. N. *Clin. Infect. Dis.* **2004**, *38*, 78. (b) Mahamat, A.; MacKenzie, F. M.; Brooker, K.; Monnet, D. L.; Daures, J. P.; Gould, I. M. *Int. J. Antimicrob. Agents* **2007**, *30*, 169.
(6) Garcez, W. S.; Yoshida, M.; Gottlieb, O. R. *Phytochemistry* **1995**, *39*, 815.
(7) Fiorini, C.; David, B.; Fouraste, I.; Vercauteren, J. *Phytochemistry* **1998**, *47*, 821.
(8) Rao, L. J. M.; Yada, H.; Ono, H.; Yoshida, M. *J. Agric. Food Chem.* **2002**, *50*, 3143.
(9) Kawahara, N.; Satake, M.; Goda, Y. *Chem. Pharm. Bull.* **2002**, *50*, 1619.
(10) Kuo, Y.-C.; Lu, C.-K.; Huang, L.-W.; Kuo, Y.-H.; Chang, C.; Hsu, F.-L.; Lee, T.-H. *Planta Med.* **2005**, *71*, 412.
(11) Wang, G.-J.; Tsai, T.-H.; Lin, L.-C. *Phytochemistry* **2007**, *68*, 2455.
(12) Lee, S.-S.; Lin, H.-C.; Chen, C.-K. *Phytochemistry* **2008**, *69*, 2347.
(13) Otsuka, N.; Liu, M.-H.; Shiota, S.; Ogawa, W.; Kuroda, T.; Hatano, T.; Tsuchiya, T. *Biol. Pharm. Bull.* **2008**, *31*, 1794.
(14) (a) Harborne, J. B.; Williams, C. A. *Nat. Prod. Rep.* **1995**, *12*, 639. (b) Harborne, J. B.; Williams, C. A. *Nat. Prod. Rep.* **1998**, *15*, 631. (c) Harborne, J. B.; Williams, C. A. *Nat. Prod. Rep.* **2001**, *18*, 310. (d) Veitch, N. C.; Grayer, R. J. *Nat. Prod. Rep.* **2008**, *25*, 555.
(15) For early reports, see: (a) Demetzos, C.; Skaltsounis, A.-L.; Tillequin, F.; Koch, M. *Carbohydr. Res.* **1990**, *207*, 131. (b) Razanamahefa, B.; Demetzos, C.; Skaltsounis, A.-L.; Andriantisiferana, M.; Tillequin, F. *Heterocycles* **1994**, *38*, 357. (c) Demetzos, C.; Skaltsounis, A.-L.; Razanamahefa, B.; Tillequin, F. *J. Nat. Prod.* **1994**, *57*, 1234. (d) Li, M.; Han, X.; Yu, B. *Tetrahedron Lett.* **2002**, *43*, 9467.
(16) For early reports, see: (a) Wagner, H.; Danninger, H.; Seligmann, O.; Nogradi, M.; Farkas, L.; Farnsworth, N. *Chem. Ber.* **1970**, *103*, 3678. (b) Vermes, B.; Farkas, L.; Nógrádi, M. In *Topics in Flavonoid Chemistry and*

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Biochemistry; Farkas, L.; Gábor, M.; Kállay, F., Eds.; Elsevier: Amsterdam, **1975**, 162–170. (c) Farkas, L.; Vermes, B.; Mihály, N.; Kálmán, A. *Phytochemistry* **1976**, *15*, 1184.

(17) Yang, W.; Sun, J.; Lu, W.; Li, Y.; Shan, L.; Han, W.; Zhang, W.-D.; Yu, B. *J. Org. Chem.* **2010**, *51*, 1504.

(18) **3,7-Di-*O*-benzyl-kaempferol**
^{1}H NMR (300 MHz, $CDCl_3$): δ = 12.72 (s, 1 H), 10.29 (s, 1 H), 7.93 (d, *J* = 8.8 Hz, 2 H), 7.47–7.32 (m, 9 H), 6.92 (d, *J* = 8.8 Hz, 2 H), 6.74 (d, *J* = 2.0 Hz, 1 H), 6.42 (d, *J* = 2.0 Hz, 1 H), 5.19 (s, 2 H), 5.03 (s, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.0, 164.0, 161.0, 160.2, 156.5, 156.1, 136.6, 136.4, 136.0, 130.3, 128.4, 128.3, 128.2, 128.0, 127.7, 120.5, 115.4, 105.2, 98.3, 93.0, 73.3, 69.9, 40.1, 39.9, 39.7, 39.5, 39.3, 39.1, 38.9.

(19) Diwu, Z.; Beachdel, C.; Klaubert, D. H. *Tetrahedron Lett.* **1998**, *39*, 4987.

(20) (a) Li, Y.; Yang, Y.; Yu, B. *Tetrahedron Lett.* **2008**, *49*, 3604. (b) Yang, Y.; Li, Y.; Yu, B. *J. Am. Chem. Soc.* **2009**, *131*, 12076. (c) Li, Y.; Yang, X.; Liu, Y.; Zhu, C.; Yang, Y.; Yu, B. *Chem. Eur. J.* **2010**, *16*, 1871. (d) Yang, Y.; Li, Y.; Yu, B. *Tetrahedron Lett.* **2010**, *51*, 1504. (e) Li, Y.; Yu, B. *Chem. Commun.* **2010**, *46*, 6060.

(21) Zhang, Z.; Mao, J.; Chen, H.; Cai, M. *Tetrahedron Asymmetry* **1994**, *5*, 2283.

(22) Fürstner, A.; Jeanjean, F.; Razon, P.; Wirtz, C.; Mynott, R. *Chem. Eur. J.* **2003**, *9*, 307.

(23) **Spectroscopic Data for Synthetic Compounds**
Compound **1**: $[\alpha]_D^{25}$ 72.1 (*c* 0.2, MeOH); lit.[4] [α] 89.6. ^{1}H NMR (400 MHz, CD_3OD): δ = 7.87 (d, *J* = 8.8 Hz, 2 H), 7.62 (d, *J* = 15.8 Hz, 1 H), 7.60 (d, *J* = 15.8 Hz, 1 H), 7.46 (d, *J* = 8.6 Hz, 1 H), 7.38 (d, *J* = 8.5 Hz, 1 H), 6.99 (d, *J* = 8.7 Hz, 1 H), 6.81 (d, *J* = 8.6 Hz, 1 H), 6.75 (d, *J* = 8.5 Hz, 1 H), 6.41 (d, *J* = 2.0 Hz, 1 H), 6.38 (d, *J* = 15.8 Hz, 1 H), 6.29 (d, *J* = 15.8 Hz, 1 H), 6.21 (d, *J* = 2.0 Hz, 1 H), 5.82 (dd, *J* = 1.5, 3.2 Hz, 1 H), 5.60 (s, 1 H), 5.28 (dd, *J* = 3.2, 9.5 Hz, 1 H), 3.64 (t, *J* = 9.8 Hz, 1 H), 3.51–3.58 (m, 1 H), 1.05 (d, *J* = 6.0 Hz, 3 H). ^{13}C NMR (100 MHz, CD_3OD): δ = 179.4, 168.5, 167.8, 165.9, 163.4, 161.8, 161.5, 161.3, 159.1, 158.6, 147.8, 147.0, 135.5, 131.9, 131.4, 131.2, 127.1 (d), 122.4, 116.9, 116.8 (d), 114.9, 114.4, 105.9, 100.3, 99.9, 94.8, 73.0, 72.2, 71.0, 70.9, 17.8. ESI-HRMS: *m/z* calcd for $C_{39}H_{31}O_{14}$ $[M - H]^-$: 723.1719; found: 723.1740.
Compound **2**: $[\alpha]_D^{25}$ –36.6 (*c* 0.3, MeOH); lit.[10] [α] –44.8. ^{1}H NMR (500 MHz, CD_3OD): δ = 7.81 (d, *J* = 8.7 Hz, 2 H), 7.69 (d, *J* = 15.6 Hz, 1 H), 7.58 (d, *J* = 15.6 Hz, 1 H), 7.53 (d, *J* = 8.7 Hz, 2 H), 7.50 (d, *J* = 8.7 Hz, 2 H), 7.04 (d, *J* = 8.7 Hz, 2 H), 6.84 (d, *J* = 8.7 Hz, 2 H), 6.81 (d, *J* = 8.7 Hz, 2 H), 6.43 (d, *J* = 16.1 Hz, 1 H), 6.40 (d, *J* = 1.4 Hz, 1 H), 6.32 (d, *J* = 15.6 Hz, 1 H), 6.20 (d, *J* = 1.8 Hz, 1 H), 5.76 (s, 1 H), 5.43 (t, *J* = 1.4 Hz, 1 H), 4.98 (t, *J* = 9.9 Hz, 1 H), 4.55 (s, 1 H), 4.16 (dd, *J* = 3.2, 9.7 Hz, 1 H), 3.29–3.26 (m, 1 H), 0.86 (d, *J* = 6.0 Hz, 3 H). ^{13}C NMR (125 MHz, CD_3OD): δ = 179.3, 168.5, 168.4, 166.0, 163.3, 161.9, 161.4, 159.5, 158.6, 147.5, 147.0, 134.7, 132.0, 131.4, 131.3, 127.2, 122.5, 116.8, 116.7, 115.0, 114.7, 106.0, 100.0, 99.2, 94.9, 74.7, 73.2, 69.8, 68.5, 17.7.

(24) (a) Maloney, D. J.; Hecht, S. M. *Org. Lett.* **2005**, *7*, 1097. (b) Smith, J. A.; Maloney, D. J.; Clark, D. E.; Xu, Y.; Hecht, S. M.; Lannigan, D. A. *Bioorg. Med. Chem.* **2006**, *14*, 6034. (c) Smith, J. A.; Maloney, D. J.; Hecht, S. M.; Lannigan, D. A. *Bioorg. Med. Chem.* **2007**, *15*, 5018.

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