ORGANIC LETTERS

2011
Vol. 13, No. 17
4554–4557

Enantioselective Synthesis of (−)-Jiadifenin, a Potent Neurotrophic Modulator

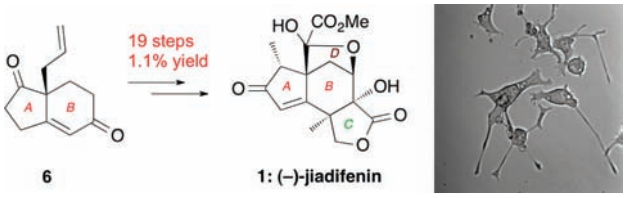
Lynnie Trzoss,[†] Jing Xu,*[,†] Michelle H. Lacoske,[†] William C. Mobley,[‡] and Emmanuel A. Theodorakis*[,†]

Department of Chemistry and Biochemistry, University of California, San Diego, 9500 Gilman Drive, La Jolla, California 92093-0358, United States, and Department of Neurosciences, University of California, San Diego, 9500 Gilman Drive, La Jolla, California 92093-0752, United States

etheodor@ucsd.edu; jix001@ucsd.edu

Received June 28, 2011

ABSTRACT



The first enantioselective synthesis of (−)-jiadifenin (1), a potent neurite outgrowth promoter isolated from the *Illicium* species, is described. The synthetic strategy builds upon bicyclic motif 6, which represents the AB ring of the natural product and proceeds in 19 steps and 1.1% overall yield. Key to our approach is a Mn(III)-mediated oxidation reaction of A ring that, following a regio- and diastereoselective α-hydroxylation and methylation sequence, produces the desired functionalities of (−)-jiadifenin. The effect of synthetic 1 in NGF-mediated neurite outgrowth was also measured in PC-12 cells.

Nerve growth factor (NGF) and related members of the neurotrophin family of proteins are essential for the survival and differentiation of sensory and sympathetic neurons.[1] Studies over past decades have demonstrated the great therapeutic potential in using NGF to prevent, slow down, or even reverse the progression of neurodegenerative disorders, including Alzheimer's and Parkinson's disease.[2] Like many polypeptides, NGF is rapidly degraded in the body and is incapable of crossing the blood−brain barrier. Its poor pharmacokinetic profile has prompted the scientific community to explore alternative therapeutic strategies based on small molecules that can mimic neurotrophins, promote their biosynthesis, or regulate their cellular signaling.

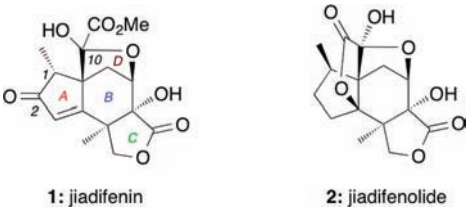


Figure 1. Structures of jiadifenin (**1**) and jiadifenolide (**2**).

In 2002, Fukuyama and co-workers reported the isolation of a novel seco-prezizaane-type sesquiterpene, jiadifenin (**1**) (Figure 1), from *Illicium jiadifengpi*.[3] Initial evaluation of its biological profile showed that **1** promotes

[†] Department of Chemistry and Biochemistry, University of California.
[‡] Department of Neurosciences, University of California.

(1) (a) Sofroniew, M. V.; Howe, C. L.; Mobley, W. C. *Annu. Rev. Neurosci.* **2001**, *24*, 1217–1281. (b) Skaper, S. D.; Walsh, F. S. *Mol. Cell. Neurosci.* **1998**, *12*, 179–193. (c) Hefti, F. *Annu. Rev. Pharmacol. Toxicol.* **1997**, *37*, 239–267. (d) Skaper, S. D. *CNS Neurol. Disord.: Drug Targets* **2008**, *7*, 46–62. (e) Greene, L. A.; Shooter, E. M. *Annu. Rev. Neurosci.* **1980**, *3*, 353–402.

(2) (a) Price, R. D.; Milne, S. A.; Sharkey, J.; Matsuoka, N. *Pharmacol. Ther.* **2007**, *115*, 292–306. (b) Longo, F. M.; Xie, Y.; Massa, S. M. *Curr. Med. Chem.: Cent. Nerv. Syst. Agents* **2005**, *5*, 29–41. (c) Martin, J. B. N. *Eng. J. Med.* **1999**, *340*, 1970–1980. (d) O'Neill, M. J.; Messenger, M. J.; Lakics, V.; Murray, T. K.; Karran, E. H.; Szekeres, P. G.; Nisenbaum, E. S.; Merchant, K. M. *Int. Rev. Neurobiol.* **2007**, *77*, 179–217. (e) Wilson, R. M.; Danishefsky, S. J. *Acc. Chem. Res.* **2006**, *39*, 539–549.

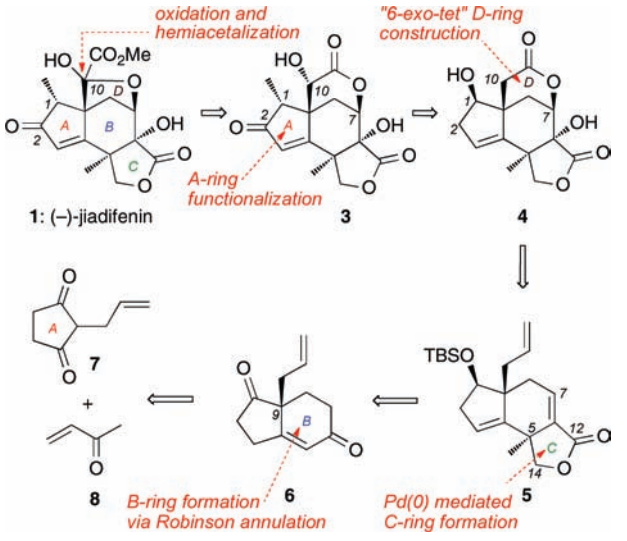
(3) Yokoyama, R.; Huang, J.-M.; Yang, C.-S.; Fukuyama, Y. *J. Nat. Prod.* **2002**, *65*, 527–531.

10.1021/ol201742j
Published on Web 08/03/2011

significant neurite outgrowth in primary cultures of fetal rat cortical neurons in concentrations as low as 0.1 μM. More recently, from the same plant species the Fukuyama group isolated jiadifenolide (**2**), another structurally related and more potent neurotrophic agent.[4] Their complex fused-ring system, along with their significant therapeutic potential, provide very intriguing and challenging targets. Synthetic studies toward these compounds[5] culminated a racemic synthesis of jiadifenin by the Danishefsky group.[6] These efforts also allowed preliminary SAR studies that highlighted clearly the medicinal value of this family of small molecules.

We have recently reported the first enantioselective synthesis of jiadifenolide (**2**).[7] Our strategy offers the opportunity to diversify our chemistry toward other members of this family. Herein, we report the first enantioselective synthesis of jiadifenin (**1**).

Scheme 1. Retrosynthetic Analysis of (−)-Jiadifenin



Scheme 1 illustrates the retrosynthetic analysis toward (−)-jiadifenin. The target molecule was envisioned to ultimately arise from oxidation and hemiacetalization of **3**. A sequential diastereoselective C-10 α-hydroxylation and C-1 methylation could be used to install the desired functional groups on the jiadifenin framework. Moreover, the A ring of **3** was projected to arise from selective manipulation at the C-1 and C-2 centers of motif **4**. In turn, **4** could be formed from tricyclic structure **5**,[7] via a sequence that includes oxidative cleavage of the terminal alkene, regio- and diastereoselective epoxide formation, and acid-induced "6-exo-tet" epoxide opening, thus constructing the D ring lactone. Access to **5** would be accomplished from "Hajos-Parrish-like"[7,8] diketone **6**,[9] via a sequential Stiles carboxylation[10] and installation of the quaternary methyl moiety, followed by a Pd(0)-mediated carbomethoxylation[11] and TFA-assisted C ring formation. Lastly, diketone **6** would be produced via an asymmetric Robinson annulation[12] using compounds **7** and **8** as starting materials.

The synthetic effort departed from lactone **4** that was enantioselectively and efficiently synthesized from diketone **6** in 13 steps with a 15% overall yield (> 90% ee,[13] Scheme 2). With an abundant amount of **4** in hand (> 3 g), the elimination of C-1 hydroxyl moiety became the first challenge. Various trials of the C-1 alcohol deoxygenation under standard or modified Barton−McCombie conditions[14] proved unsuccessful. Moreover, mesylation of **4** followed by treatment with a variety of bases failed to produce the corresponding alkene **9**. The dehydration proceeded smoothly using Martin sulfurane,[15] and the derived crude diene **9** was hydrogenated selectively at the C-1-C-2 centers with H_2(1 atm)/Pd/C to produce compound **10** (72% yield over 2 steps).

The ensuing allylic oxidation at the C-2 position of **10** proved to be difficult, presumably due to the sensitive 6-membered lactone moiety. Several standard or modified conditions were evaluated, including SeO_2,[16] CrO_3/TBHP,[17]

(4) Kubo, M.; Okada, C.; Huang, J.-M.; Harada, K.; Hioki, H.; Fukuyama, Y. *Org. Lett.* **2009**, *11*, 5190–5193.

(5) Harada, K.; Imai, A.; Uto, K.; Carter, R. G.; Kubo, M.; Hioki, H.; Fukuyama, Y. *Org. Lett.* **2011**, *13*, 988–991.

(6) (a) Cho, Y. S.; Carcache, D. A.; Tian, Y.; Li, Y.-M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2004**, *126*, 14358–14359. (b) Carcache, D. A.; Cho, Y. S.; Hua, Z.; Tian, Y.; Li, Y.-M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2006**, *128*, 1016–1022.

(7) Xu, J.; Trzoss, L.; Chang, W. K.; Theodorakis, E. A. *Angew. Chem., Int. Ed.* **2011**, *50*, 3672–3676.

(8) (a) Rapson, W. S.; Robinson, R. *J. Chem. Soc.* **1935**, 1285–1288. (b) Wieland, P.; Miescher, K. *Helv. Chim. Acta* **1950**, *33*, 2215–2228. (c) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615–1621.

(9) (a) Ruprah, P. K.; Cros, J.-P.; Pease, J. E.; Whittingham, W. G.; Williams, J. M. J. *Eur. J. Org. Chem.* **2002**, 3145–3152. (b) Lacoste, E.; Vaique, E.; Berlande, M.; Pianet, I.; Vincent, J.-M.; Landais, Y. *Eur. J. Org. Chem.* **2007**, 167–177. (c) Zhang, X.-M.; Wang, M.; Tu, Y.-Q.; Fan, C.-A.; Jiang, Y.-J.; Zhang, S.-Y.; Zhang, F.-M. *Synlett* **2008**, 2831–2835.

(10) (a) Finkbeiner, H. L.; Stiles, M. *J. Am. Chem. Soc.* **1963**, *85*, 616–622. (b) Micheli, R. A.; Hajos, Z. G.; Cohen, N.; Parrish, D. R.; Portland, L. A.; Sciamanna, W.; Scott, M. A.; Wehrli, P. A. *J. Org. Chem.* **1975**, *40*, 675–681. (c) Frie, J. L.; Jeffrey, C. S.; Sorensen, E. J. *Org. Lett.* **2009**, *11*, 5394–5397.

(11) (a) Cowell, A.; Stille, J. K. J. *Am. Chem. Soc.* **1980**, *102*, 4193–4198. (b) Cacchi, S.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1985**, *26*, 1109–1112.

(12) For selected natural product syntheses from our group using asymmetric Robinson annulations see: (a) Ling, T. T.; Xiang, A. X.; Theodorakis, E. A. *Angew. Chem., Int. Ed.* **1999**, *38*, 3089–3091. (b) Ling, T. T.; Poupon, E.; Rueden, E. J.; Kim, S. H.; Theodorakis, E. A. *J. Am. Chem. Soc.* **2002**, *124*, 12261–12267. (c) Brady, T. P.; Kim, S. H.; Wen, K.; Theodorakis, E. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 739–742. (d) Ghosh, S.; Rivas, F.; Fischer, D.; González, M. A.; Theodorakis, E. A. *Org. Lett.* **2004**, *6*, 941–944. (e) Brady, T. P.; Kim, S. H.; Wen, K.; Kim, C.; Theodorakis, E. A. *Chem.—Eur. J.* **2005**, *11*, 7175–7190.

(13) The ee of this reaction was determined by the chiral shift agent Eu(hfc)$_3$. For related references see: (a) Corey, E. J.; Virgil, S. C. *J. Am. Chem. Soc.* **1990**, *112*, 6429–6431. (b) Nguyen, T. X.; Dakanali, M.; Trzoss, L.; Theodorakis, E. A. *Org. Lett.* **2011**, *13*, 3308–3311.

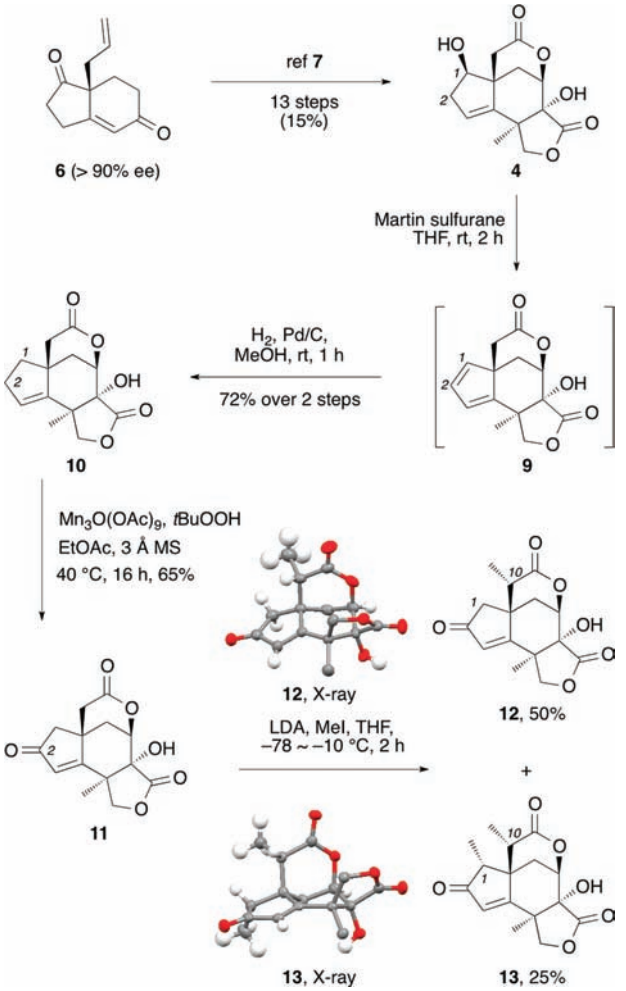
(14) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, *16*, 1574–1585.

(15) (a) Martin, J. C.; Arhart, R. J. *J. Am. Chem. Soc.* **1971**, *93*, 4327–4329. (b) Arhart, R. J.; Martin, J. C. *J. Am. Chem. Soc.* **1972**, *94*, 5003–5010. (c) Martin, J. C.; Franz, J. A.; Arhart, R. J. *J. Am. Chem. Soc.* **1974**, *96*, 4604–4611. Some recent examples using Martin sulfurane in natural product total synthesis:(d) Nicolaou, K. C.; Zhang, H.-J.; Ortiz, A.; Guella, G. *Angew. Chem., Int. Ed.* **2008**, *47*, 8605–8610. (e) Movassaghi, M.; Hunt, D. K.; Tjandra, M. *J. Am. Chem. Soc.* **2006**, *128*, 8126–8127. (f) Baran, P. S.; Richter, J. M. *J. Am. Chem. Soc.* **2004**, *126*, 7450–7451.

(16) Warpehoski, M. A.; Chabaud, B.; Sharpless, K. B. *J. Org. Chem.* **1982**, *47*, 2897–2900.

PDC/TBHP,[18] $PhI(OAc)_2$/TBHP,[19] $Pd(O_2CCF_3)_2$/BQ[20] and $Rh_2(cap)_4$/TBHP,[21] but none of them could yield a satisfactory result. Gratifyingly, Mn(III) acetate/TBHP[22,23] produced traces of **11** after 72 h at ambient temperature. To avoid side reactions and accelerate the desired transformation, the reaction temperature was then raised to 40 °C, which significantly improved the yield to 65% and shortened the reaction time to 16 h. With **11** in hand, we attempted to methylate the C-1 center. We hypothesized that this reaction would install the methyl group α- to the enone in a chemoselective fashion. To our surprise, lithiation (LDA) and methylation of **11** with 1.2 equiv of MeI afforded the C-10 methylated adduct **12**. The C-1 position could be methylated only upon excess amount of MeI, producing the dimethylated product **13** together with **12**. The structures of compounds **12** and **13** were unambiguously confirmed via single crystal X-ray analysis (Scheme 2).[24] Other related alkylation attempts gave us similar or worse results.

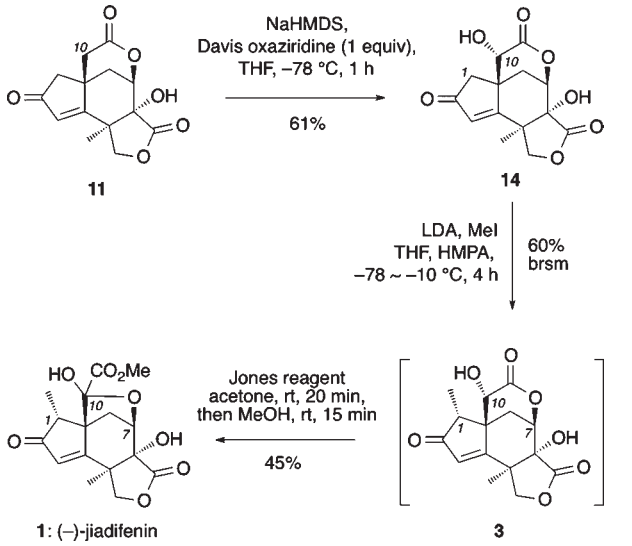
Scheme 2. Synthesis of **11**



(17) (a) Dauben, W. G.; Lorber, M. E.; Fullerton, D. S. *J. Org. Chem.* **1969**, *34*, 3587–3592. (b) Pearson, A. J.; Chen, Y. S.; Hsu, S. Y.; Ray, T. *Tetrahedron Lett.* **1984**, *25*, 1235–1238.

On the basis of these observations, it became obvious that the C-10 center is more sterically accessible than the C-1 position. Thus, an alternative sequence for the A-ring functionalization was developed. Treating **11** with NaHMDS and quenching of the C-11 enolate with Davis oxaziridine[25] (1 equiv) produced α-hydroxylated lactone **14** as a single diastereomer in 61% yield. Alkylation of **14** with LDA/MeI/HMPA furnished the desired C-1 methylated product **3** with the desired stereochemistry. Without extensive purification, alcohol **3** was oxidized and rearranged under Jones conditions[6] giving rise, after methanolic work up, to (−)-jiadifenin (**1**) as the major product in 45% yield (C-10 anomeric mixture, major anomer/minor anomer ≈ 2.5:1; Scheme 3). Synthetic jiadifenin was found to have identical spectroscopic and analytical properties (^{1}H NMR, ^{13}C NMR, HRMS) and similar optical rotation values (measured $[\alpha]^{24}_D$ −123.8 (c 0.17, EtOH), literature[3] $[\alpha]^{22}_D$ −152.9 (c 0.24, EtOH)).

Scheme 3. Completion of the Synthesis of (−)-Jiadifenin



Validation of the biological profile of synthetic (−)-jiadifenin (**1**) with regard to the stimulation of NGF-mediated neurite outgrowth was carried out using a PC-12 cellular assay.[6a,26] As shown in Figure 2, a significant increase of neuronal differentiation could be observed upon 72 h of incubation with NGF (50 ng/mL) and **1** (0.3 and 0.5 μM). Specifically, jiadifenin at 0.3 μM induced 21% of neurite bearing cells compared to 12% found in the control containing only NGF and DMSO (Figure 3A). A 28% of neurite bearing cells was observed at 0.5 μM of **1**

(18) Fousteris, M. A.; Koutsourea, A. I.; Nikolaropoulos, S. S.; Riahi, A.; Muzart, J. *J. Mol. Catal. A: Chem.* **2006**, *250*, 70–74.
(19) Zhao, Y.; Yeung, Y. Y. *Org. Lett.* **2010**, *12*, 2128–2131.
(20) McMurry, J. E.; Kočotovský, P. *Tetrahedron Lett.* **1984**, *25*, 4187–4190.
(21) Catino, A. J.; Forslund, R. E.; Doyle, M. P. *J. Am. Chem. Soc.* **2004**, *126*, 13622–13623.
(22) Shing, T. K. M.; Yeung, Y.-Y.; Su, P. L. *Org. Lett.* **2006**, *8*, 3149–3151.

(Figure 3A). In terms of total neurite outgrowth, the neurite lengths enhanced by **1**, at 0.3 and 0.5 μM, were 148% ($p < 0.001$) and 172% ($p < 0.001$), respectively, compared to the DMSO+NGF control (Figure 3B). No neurite outgrowth was observed in the absence of NGF,[27] in agreement with previous findings.[6a]

In summary, we describe here an efficient and enantioselective approach to (−)-jiadifenin (**1**), a potent promoter of neurite outgrowth. This approach departs from readily available diketone **6** and proceeds in 19 steps and 1.1% overall yield. In addition, we have shown that synthetic jiadifenin induces significant neurite outgrowth in PC-12 cells in the presence of NGF. Along these lines, our strategy paves the way for the synthesis of several natural products of this family[28] and designed analogs thereof that could shine light into the unexplored biological mode of action of these compounds.

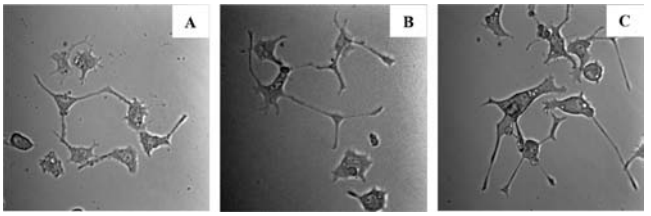


Figure 2. Images of neurons after 72 h treatment with (A) DMSO (1% v/v) + NGF (50 ng/mL), (B) compound **1** (0.3 μM) + DMSO + NGF, and (C) compound **1** (0.5 μM) + DMSO + NGF.

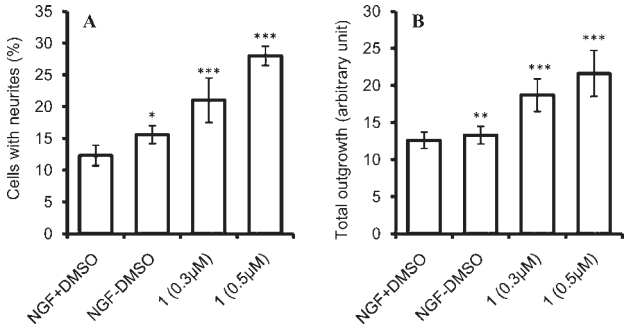


Figure 3. NGF-enhancement in the PC-12 assay for 72 h. (A) Percentage of cells with longer processes than two cell body lengths and (B) total neurite outgrowth length. Values are reported as means ± SE of triplicate experiments: * $P < 0.03$, ** $P < 0.01$, *** $P < 0.001$.

Acknowledgment. We gratefully acknowledge the National Institutes of Health (NIH) for financial support of this work through Grant Number R01 GM-081484. We thank the National Science Foundation for instrumentation grants CHE9709183 and CHE0741968. We also thank Dr. Anthony Mrse (UCSD NMR Facility), Dr. Yongxuan Su (UCSD MS Facility), and Dr. Arnold L. Rheingold and Dr. Curtis E. Moore (UCSD X-ray Facility). We appreciate the technical support from Ms. Kristine N. Wright (Dept. of Neurosciences, UCSD).

Supporting Information Available. Experimental procedures and characterization data of key intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

(23) For more examples of metal-based allylic oxidation, see Bi-based: (a) Salvador, J. A. R.; Silvestre, S. M. *Tetrahedron Lett*. **2005**, *46*, 2581–2584. Cr-based:(b) Muzart, J. *Chem. Rev*. **1992**, *92*, 113–140. Co-based:(c) Salvador, J. A. R.; Clark, J. H. *Chem. Commun*. **2001**, *6*, 33–34. (d) Jurado-Gonzalez, M.; Sullivan, A. C.; Wilson, J. R. H. *Tetrahedron Lett*. **2003**, *44*, 4283–4286. Cu-based:(e) Salvador, J. A. R.; Sáe Melo, M. L.; Campos Neves, A. S. *Tetrahedron Lett*. **1997**, *38*, 119–122. (f) Arsenou, E. S.; Koutsourea, A. I.; Fousteris, M. A.; Nikolaropoulos, S. S. *Steroids* **2003**, *68*, 407–414. Fe-based: (g) Barton, D. R. H.; Le Gloahec, V. N. *Tetrahedron* **1998**, *54*, 15457–15468. Pd-based:(h) Yu, J. Q.; Corey, E. J. *J. Am. Chem. Soc*. **2003**, *125*, 3232–3233. (i) Yu, J. Q.; Wu, H. C.; Corey, E. *J. Org. Lett*. **2005**, *7*, 1415–1417. (j) Chen, M. S.; White, M. C. *J. Am. Chem. Soc*. **2004**, *126*, 1346–1347. (k) Chen, M. S.; Prabagaran, N.; Labenz, N. A.; White, M. C. *J. Am. Chem. Soc*. **2005**, *127*, 6970–6971. (l) Fraunhoffer, K. J.; Prabagaran, N.; Sirois, L. E.; White, M. C. *J. Am. Chem. Soc*. **2006**, *128*, 9032–9033. (m) Delcamp, J. H.; White, M. C. *J. Am. Chem. Soc*. **2006**, *128*, 15076–15077. (n) Covell, D. J.; White, M. C. *Angew. Chem., Int. Ed*. **2008**, *47*, 6448–6451. (o) Stang, E. M.; White, M. C. *Nature Chem*. **2009**, *1*, 547–551. Rh-based:(p) Catino, A. J.; Nichols, J. M.; Choi, H.; Gottipamula, S.; Doyle, M. P. *Org. Lett*. **2005**, *7*, 5167–5170. (q) Choi, H.; Doyle, M. P. *Org. Lett*. **2007**, *9*, 5349–5352. (r) McLaughlin, E. C.; Doyle, M. P. *J. Org. Chem*. **2008**, *73*, 4317–4319. (s) McLaughlin, E. C.; Choi, H.; Wang, K.; Chiou, G.; Doyle, M. P. J. *Org. Chem*. **2009**, *74*, 730–738. Sodium chlorite:(t) Silvestre, S. M.; Salvador, J. A. R. *Tetrahedron* **2007**, *63*, 2439–2445.

(24) CCDC831791 and CCDC831792 contain the supplementary crystallographic data for compound **12** and **13**, respectively. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/products/csd/request/. In our schemes, some hydrogen atoms were omitted for clarity.

(25) (a) Davis, F. A.; Chattopadhyay, S.; Towson, J. C.; Lal, S.; Reddy, T. *J. Org. Chem*. **1988**, *53*, 2087–2089. (b) Vishwakarma, L. C.; Stringer, O. D.; Davis, F. A. *Org. Synth*. **1993**, *8*, 546. (c) Davis, F. A.; Chen, B.-C. *Chem. Rev*. **1992**, *92*, 919–934.

(26) (a) Chen, A. P.-J.; Müller, C.; Cooper, H. M.; Williams, C. M. *Tetrahedron* **2010**, *66*, 6842–6850. (b) Jessen, H. J.; Barbaras, D.; Hamburger, M.; Gademann, K. *Org. Lett*. **2009**, *11*, 3446–3449.

(27) In these experiments **1** was used in concentrations of 0.3 and 0.5 μM over 72 h.

(28) For recent reviews on the chemistry and chemical biology of natural products from Illicium species, see: (a) Urabe, D.; Inoue, M. *Tetrahedron* **2009**, *65*, 6271–6289. (b) Fukuyama, Y.; Huang, J.-M. *Studies in Natural Products Chemistry*, Vol 32; Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, 2005; pp 395−429.