CHEMISTRY
A EUROPEAN JOURNAL

COMMUNICATION

DOI: 10.1002/chem.201204292

Total Syntheses of Ainsliadimer B and Gochnatiolides A and B

Dongliang Xia,[a] Yu Du,[a] Zhi Yi,[a] Hao Song,[a] and Yong Qin*[a, b]

Dedicated to Professor Zhitang Huang on the occasion of his 85th birthday

The genus *Ainsliaea* is an important herbal resource in traditional Chinese medicine for treating various diseases, including rheumatism, traumatic injuries, edema, stomach ache, and anorexia.[1] Phytochemistry studies in recent decades have shown that the major secondary metabolites isolated from these plant species are monomeric, dimeric and trimeric guaianolides,[2] such as dehydrozaluzanin C (**1**),[3] ainsliadimer B (**2b**),[4] the gochnatiolides A (**3**),[5] B (**4**),[5,6] and C (**5**),[5] and the ainsliatrimers A (**6**) and B (**7**;[4] Figure 1). These compounds exhibit micro- to nanomolar activity against a variety of human cancer cell lines.[4]

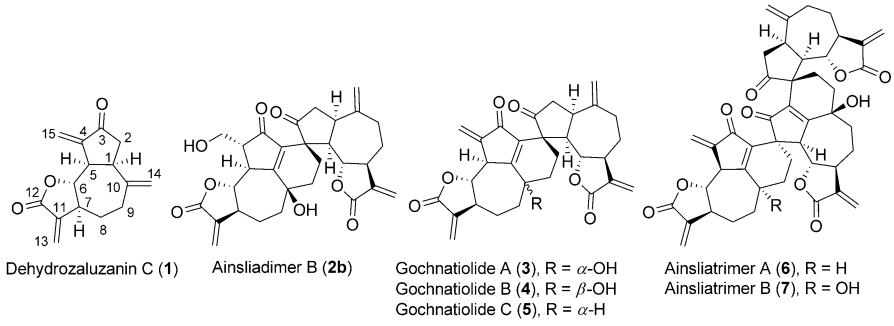


Figure 1. Structures of dimeric and trimeric guaianolides.

These dimeric and trimeric guaianolides were proposed to be accessible through the biosynthetic assembly of the monomeric guaianolide unit of dehydrozaluzanin C analogues by Diels–Alder cycloaddition.[4,7] This approach has guided biomimetic syntheses of dimeric ainsliadimers A and B[8,9] and gochnatiolides A–C[9] by the Lei group by using a Diels–Alder reaction of monomeric guaianolide units. However, efficiently assembling a dimeric skeleton and precisely controlling the regio- and stereoselectivity of individual syntheses of dimeric gochnatiolides remains challenging.

In this communication, we report the total syntheses of ainsliadimer B and gochnatiolides A and B by using a pathway in which the key reaction is a cross Diels–Alder cycloaddition of dehydrozaluzanin C with its analogues. Precise modification of the monomeric guaianolide unit for the Diels–Alder reaction allows highly regio- and stereoselective assembly of the skeletons of dimeric guaianolides.

The retrosynthetic analysis of dimeric guaianolides is shown in Scheme 1. We envisioned that the double bond at C4′–C15′ of gochnatiolides A and B (**3** and **4**) could be derived from 10′-*epi*-ainsliadimer B (**2a**) and ainsliadimer B (**2b**), respectively, by C15′-β-hydroxyl elimination. 10′-*epi*-Ainsliadimer B (**2a**) and ainsliadimer B (**2b**), in turn, could be synthesized from intermediate **8** by regio- and stereoselective epoxidation on the C1′–C10′ double bond, followed by a base-catalyzed epoxide ring-opening reaction. Compound **8** could be constructed by a regio- and stereoselective intermolecular Diels–Alder reaction between the precisely modified electron-rich diene **9** and the electron-deficient dienophile dehydrozaluzanin C (**1**). Both monomeric diene **9** and dienophile **1** could be synthesized from the same intermediate **10** by multi-step functional transformation. Intermediate **10** could be readily derived from the known intermediate **11**, which itself could be produced by the photoirradiation-induced rearrangement of naturally abundant α-santonin.

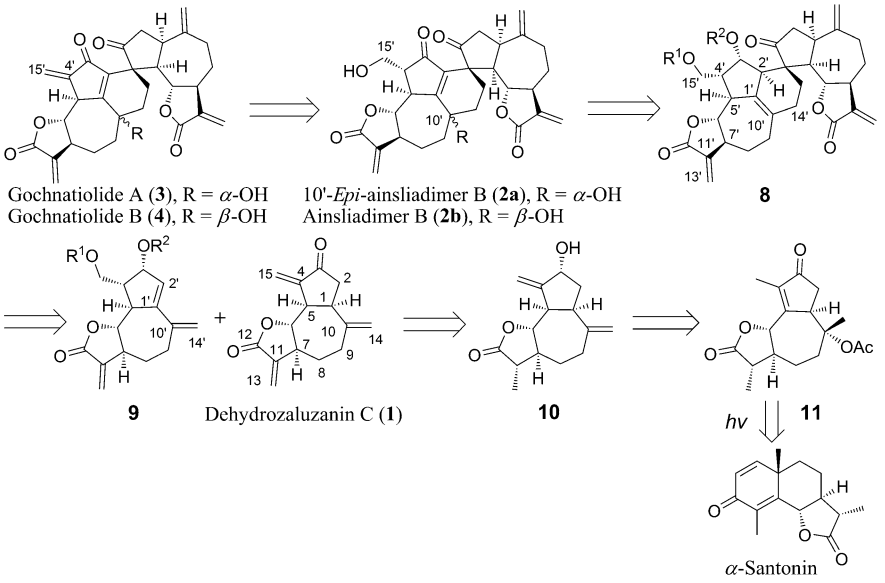
The total syntheses of dimeric guaianolides commenced with the preparation of **14** from **11**. The alkene **12** was prepared in approximately 40% yield by using a known five-step procedure (Scheme 2).[10] Regioselective epoxidation of the double bond within the cyclopentene ring was realized by using *meta*-chloroperbenzoic acid (*m*CPBA) in $CHCl_3$ to provide epoxide **13** in 84% yield. Epoxide ring opening in **13** with $Al(OiPr)_3$ in toluene at high temperature gave inter-

[a] D. Xia,[+] Y. Du,[+] Z. Yi, H. Song, Prof. Dr. Y. Qin
Key Laboratory of Drug Targeting and Drug Delivery Systems of the Ministry of Education, West China School of Pharmacy
and State Key Laboratory of Biotherapy
Sichuan University, Chengdu, 610041 (P.R. China)
Fax: (+86) 28-85503842
E-mail: yongqin@scu.edu.cn

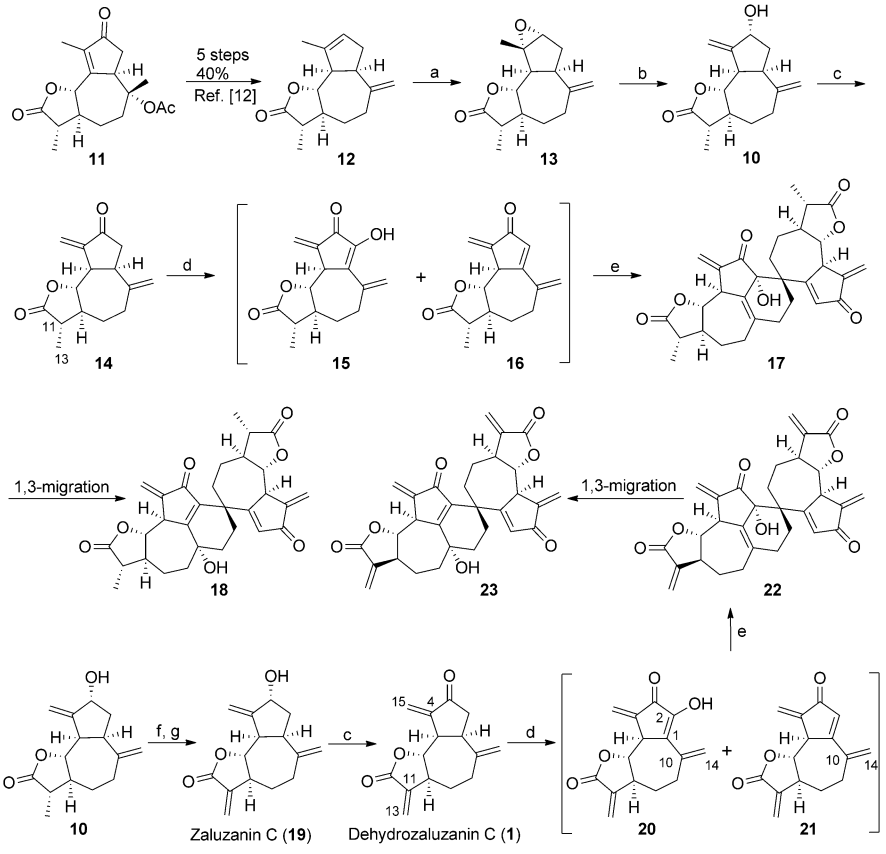
[b] Prof. Dr. Y. Qin
Innovative Drug Research Centre and
College of Chemistry and Chemical Engineering
Chongqing University, Chongqing, 401331 (P.R. China)
Fax: (+86) 23-65678750
E-mail: qinyong@cqu.edu.cn

[+] These authors contributed equally to this work

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201204292.



Scheme 1. Retrosynthetic analysis of dimeric guaianolides.



Scheme 2. Model reactions to assemble a dimeric skeleton. Reagents and conditions: a) *m*CPBA, $CHCl_3$, −20 °C to 0 °C, 2 h, 84 %; b) $Al(OiPr)_3$, toluene, sealed, 140 °C, 5 h, 65 %; c) Dess–Martin reagent, CH_2Cl_2, 0 °C, 1 h, 90 %; d) $(PhSeO)_2O$, PhCl, 70 °C, 0.5 h; e) neat, 25 °C, 24 h, 10 % for **14** to **18** over two steps, 19 % for **1** to **23** over two steps; f) lithium diisopropyl amide (LDA), $(PhSe)_2$, hexamethylphosphoramide (HMPA), THF, −78 °C to −30 °C, 2.5 h, 75 %; g) H_2O_2, AcOH, THF, 0 °C→25 °C, 0.5 h, 82 %.

mediate **10** in 65 % yield. Oxidation of **10** with Dess–Martin reagent provided **14** in excellent yield.

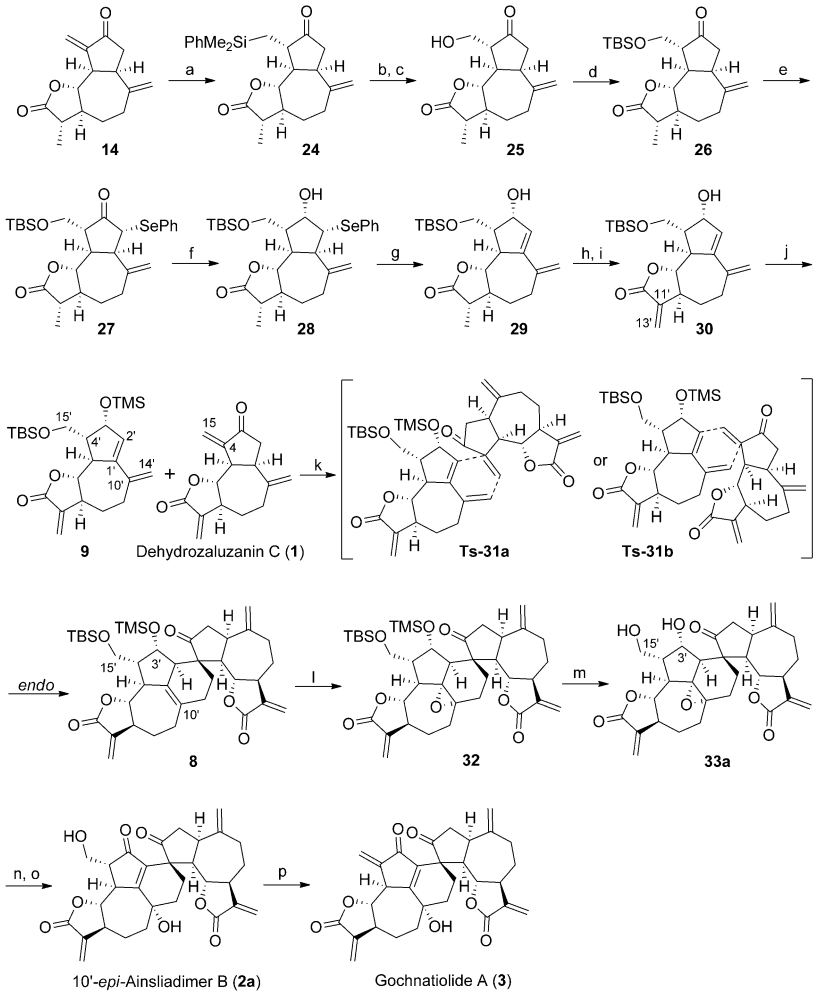
With **14** in hand, we tested the feasibility of a proposed biomimetic Diels–Alder reaction[4,7] of **14** with its oxidized enol **15** or diene **16**, to directly yield a gochnatiolide-type skeleton (Scheme 2). Oxidation of **14** with $(PhSeO)_2O$,[11] followed by removal of the excess oxidant $(PhSeO)_2O$ by using rapid flash chromatography, gave a crude mixture of the unstable oxidized product **15** and partially oxidized diene **16**. When this mixture was treated with 2 equivalents of **14** under various conditions, dimer **18** was always isolated as the sole detectable dimer in approximately 10 % yield. This dimer most likely resulted from a cross Diels–Alder reaction of enol **15** with diene **16**, followed by a 1,3-hydroxyl migration in the resulting adduct **17**. We suspected that the reaction of **14** with its oxidized enol **15** or diene **16** failed to yield a gochnatiolide-type skeleton because these compounds lack a C11−C13 double bond, leading to an unfavorable conformation that prevents the desired Diels–Alder reaction between them.

To test this idea, compound **10** was converted to natural zaluzanin C (**19**)[12] by a two-step procedure of phenylselenation and dephenylselenation. Zaluzanin C (**19**) was further oxidized with Dess–Martin reagent to give dehydrozaluzanin C (**1**), which possesses a C11−C13 double bond. As before, in the case of oxidation of **1** by $(PhSeO)_2O$, excess oxidant $(PhSeO)_2O$ was removed by using rapid flash chromatography and 2 equivalents of **1** were added. Only adduct **23**,[9] rather than a gochnatiolide-type adduct, was isolated in 19 % yield. Analogously to **18**, com-

pound **23** should form through a cross Diels–Alder reaction between the two oxidized intermediates enol **20** and diene **21**, followed by 1,3-hydroxyl migration of the adduct **22** (Scheme 2).

Because both the dienophile functionality in **1** and the diene functionality in **20** and **21** are electron-deficient, the Diels–Alder reaction of **1** at the C4−C15 double bond with **20** or **21** is theoretically unfavorable because it requires overcoming a high energy barrier. In order to force the Diels–Alder reaction of **1** to occur at the electron-deficient C4−C15 double bond and thereby form a gochnatiolide-type adduct, we prepared a precisely modified electron-rich diene functionality at C14′, C10′, C1′, and C2′ in a guaianolide unit such as **9** (Scheme 3). We also preinstalled a 15′-silyloxy substituent in **9** because performing a direct enone hydration at a later stage to generate a β-hydroxyl group for synthesizing ainsliadimer B (**2**) is quite challenging.[9,13] Temporarily protecting the C4′−C15′ double bond with a 15′-silyloxy group has the added advantage of reducing the number of reactive sites and therefore the risk of undesired reaction pathways other than the planned Diels–Alder reaction of **9** with **1**.

As shown in Scheme 3, the diene **9** was prepared from compound **14**. The enone group in **14** was subjected to a Michael addition of $(PhMe_2Si)_2Cu(CN)Li_2$ to give silane **24**.[14] After fluoridation of the silyl group with $HBF_4{\cdot}Et_2O$ and oxidation with H_2O_2 to convert the silyl group to a hydroxyl group, the resulting hydroxyl group was protected with a TBS group to afford compound **26**. Both phenylselenation (**26** to **27**) and reduction of the ketone functionality (**27** to **28**) proceeded in high yield with excellent stereoselectivity, with each step yielding a single stereomer. After converting the phenylselenyl group to a double bond (**28** to **29**) without protection of the hydroxyl group, the lactone ring in **29** was modified with a C11′−C13′ double bond by two steps of phenylselenation and dephenylselenation to provide compound **30**. Protection of the hydroxyl group in **30** with TMS afforded the diene **9** in high yield. As expected, when 1 equivalent of **9** was mixed with 2 equivalents of **1** under neat conditions at 60 °C for 10 h, an electron-demanding Diels–Alder reaction occurred to provide the desired adduct **8** in 66 % yield (Scheme 3). Although the Diels–Alder reaction of **9** with **1** could theoretically occur via several pathways, **8** was isolated as the sole gochnatiolide-type adduct, indicating that the reaction proceeds through a dominant endo-addition transition state (**Ts-31a**) rather than through an exo-addition transition state (**Ts-31b**). This is probably because the bottom face of the diene in **9** is completely blocked by two silyloxy groups, and the upper face of the dienophile in **1** is completely blocked by the seven-membered ring. The reaction had to be conducted in a solid phase in order to obtain reasonable yields. In the pres-



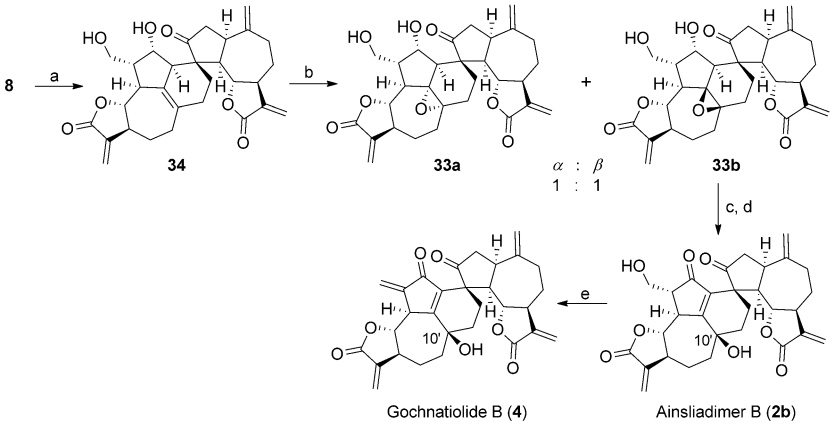
Scheme 3. Synthesis of gochnatiolide A. Reagents and conditions: a) $PhMe_2SiLi$, CuCN, THF, −78 °C, 2.5 h, 88 %; b) $HBF_4{\cdot}Et_2O$, CH_2Cl_2, 0 °C, 5 min; c) H_2O_2, KF, $NaHCO_3$, MeOH/THF (1:1), 0 °C to 30 °C, 1.5 h, 96 % over two steps; d) *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf), 2,6-lutidine, CH_2Cl_2, 0 °C, 0.5 h, 95 %; e) lithium hexamethyldisilazide (LiHMDS), PhSeBr, THF, −78 °C to −55 °C, 2.5 h, 78 %; f) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, 0 °C, 1.5 h, 83 %; g) H_2O_2, THF, 0 °C to 25 °C, 1.5 h, 94 %; h) LDA, $(PhSe)_2$, HMPA, THF, −78 °C to −30 °C, 1.5 h; i) H_2O_2, AcOH, THF, 0 °C to 25 °C, 1.5 h, 73 % over two steps; j) TMSCl, Et_3N, CH_2Cl_2, 0 °C to 10 °C, 92 %; k) neat, 60 °C, 10 h, 66 %; l) *m*CPBA, CH_2Cl_2, 0 °C, 0.5 h, 97 %; m) TBAF, THF, 0 °C, 0.5 h, 97 %; n) PCC, CH_2Cl_2, 0 °C, 1 h; o) Et_3N, CH_2Cl_2, 25 °C, 3 h, 85 % over two steps; p) DCC, CuCl, CH_2Cl_2, reflux, 4 h, 92 %.

ence of a variety of solvents, the Diels–Alder reaction proceeded very slowly to give **8** in less than 15% yield. The addition of weak acids, such as ceric ammonium sulfate (CAS), pyridinium *p*-toluenesulfonate (PPTS), TsOH, and AcOH, to the Diels–Alder reaction caused the decomposition of **1**, exclusively.

Compound **8** possesses a gochnatiolide-type skeleton and suitable functionalities at C10′ and C15′, allowing us to begin synthesizing gochnatiolide A (**3**). To our delight, treating **8** with 2 equivalents of *m*CPBA in CH_2Cl_2 at 0°C for 0.5 h regio- and stereoselectively created an α-epoxide ring, giving compound **32** in 97% yield as a single stereomer. After the removal of both silyl protecting groups in **32**, the secondary hydroxyl group at C3′ in **33a** was selectively oxidized with pyridinium chlorochromate (PCC) to yield a ketone functionality without affecting the primary hydroxyl group at C15′. The epoxide ring was then opened with Et_3N to give 10′-*epi*-ainsliadimer B (**2a**) in 85% yield over two steps (**33a** to **2a**). Dehydration of **2a** with *N*,*N*′-dicyclohexylcarbodiimide (DCC)/CuCl in CH_2Cl_2 completed the synthesis of gochnatiolide A (**3**; Scheme 3).

The tertiary hydroxyl group at C10′ in both ainsliadimer B (**2b**) and gochnatiolide B (**4**) has an inverted configuration relative to the same group in gochnatiolide A (**3**), and direct epoxidation of **8** provides only an α-epoxide ring. Thus, it would be advantageous to find an alternative way to generate the β-epoxide ring necessary for the syntheses of ainsliadimer B (**2b**) and gochnatiolide B (**4**; Scheme 4). Fortunately, after removing both silyl groups in **8** with *tert*-butyl ammonium fluoride (TBAF), epoxidation of the resulting **34** with *m*CPBA provided separable α-epoxide **33a** and β-epoxide **33b** in 95% yield in a 1:1 ratio. Selective oxidation of the secondary hydroxyl group in **33b** with PCC, followed by epoxide ring opening with the Hünig base, gave ainsliadimer B (**2b**) in 88% yield over two steps. Dehydration of ainsliadimer B (**2b**) with DCC/CuCl in CH_2Cl_2 completed the total synthesis of gochnatiolide B (**4**; Scheme 4).

In summary, the total syntheses of dimeric ainsliadimer B (**2b**), and gochnatiolides A and B (**3** and **4**) from α-santonin have been accomplished in 25 steps with approximately 1% overall yield. A well-designed Diels–Alder reaction of natural dehydrozaluzanin C (**1**) with the precisely modified monomeric guaianolide derivative **9** allows stereoselective assembly of a dimeric gochnatiolide-type skeleton **8** with the required stereochemistry. Efficient construction of **8** with preinstalled functionalities guarantees the synthesis of dimeric ainsliadimer B (**2b**) and gochnatiolides A and B (**3** and **4**) through multi-step, regio- and stereoselective manipulation of functionalities. The successful synthesis of dimeric gochnatiolides provides the starting material for further synthesis of complex trimeric ainsliatrimers.



Scheme 4. Syntheses of ainsliadimer B and gochnatiolide B. Reagents and conditions: a) TBAF, THF, 0°C to 25°C, 0.5 h, 99%; b) *m*CPBA, CH_2Cl_2, 0°C, 1 h, 95%; c) PCC, CH_2Cl_2, 0°C, 1 h; d) iPr_2NEt, CH_2Cl_2, 25°C, 3 h, 88% over two steps; e) DCC, CuCl, CH_2Cl_2, reflux, 5 h, 83%.

Acknowledgements

We are grateful for financial support from the NSFC (20825207, 20972100, 21021001, and 21132006) and the National Basic Research Program of China (973 program, 2010CB833200). We thank Prof. Weidong Zhang, Second Military University, Shanghai, China, for providing NMR spectra for comparison.

Keywords: Diels–Alder reactions · dimeric guaianolides · natural products · regioselectivity · stereoselectivity · total synthesis

[1] Y. P. Luo, X. T. Zhao, X. D. Yang, J. F. Zhao, L. Li, *Asia-Pacific Trad. Med.* **2009**, *5*, 158–161.
[2] For recent reviews on guaianolides, see: a) Z. J. Zhan, Y. M. Ying, L. F. Ma, W. G. Shan, *Nat. Prod. Rep.* **2011**, *28*, 594–629; b) B. M. Fraga, *Nat. Prod. Rep.* **2010**, *27*, 1681–1708; c) B. M. Fraga, *Nat. Prod. Rep.* **2008**, *25*, 1180–1209.
[3] B. R. Chhabra, N. M. Ahuja, M. K. Bhullar, P. S. Kalsi, *Fitoterapia* **1998**, *69*, 274–275.
[4] Y. Wang, Y. H. Shen, H. Z. Jin, J. J. Fu, X. J. Hu, J. J. Qin, J. H. Liu, M. Chen, S. K. Yan, W. D. Zhang, *Org. Lett.* **2008**, *10*, 5517–5520.
[5] a) F. Bohlmann, M. Ahmed, J. Jakupovic, R. M. King, H. Robinson, *Phytochemistry* **1983**, *22*, 191–195; b) F. Bohlmann, C. Zdero, G. Hirschmann-Schmeda, J. Jakupovic, X. A. Dominguez, R. M. King, H. Robinson, *Phytochemistry* **1986**, *25*, 1175–1178.
[6] The original incorrect assignment of 2-α-OH was corrected to be 10-α-OH during the total synthesis by Lei et al. (see refs. [5] and [9]).
[7] Z. J. Wu, X. K. Xu, Y. H. Shen, J. Su, J. M. Tian, S. Liang, H. L. Li, R. H. Liu, W. D. Zhang, *Org. Lett.* **2008**, *10*, 2397–2400.
[8] C. Li, X. L. Yu, X. G. Lei, *Org. Lett.* **2010**, *12*, 4284–4287.
[9] C. Li, X. Y. Dian, W. D. Zhang, X. G. Lei, *J. Am. Chem. Soc.* **2012**, *134*, 12414–12417.
[10] For synthetic studies on monomeric guaianolides, see: a) V. Bargues, G. Blay, L. Cardona, B. Garcia, J. R. Pedro, *J. Nat. Prod.* **2002**, *65*, 1703–1706; b) G. Blay, L. Cardona, B. Garcia, L. Lahoz, J. R.

Pedro, *J. Org. Chem.* **2001**, *66*, 7700–7705; c) V. Bargues, G. Blay, L. Cardona, B. Garcia, J. R. Pedro, *Tetrahedron* **1998**, *54*, 1845–1852; d) M. Ando, K. Ibayashi, N. Minami, T. Nakamura, K. Isogai, *J. Nat. Prod.* **1994**, *57*, 433–434; e) M. Ando, H. Kusaka, H. Ohara, K. Takase, H. Yamaoka, Y. Yanagi, *J. Org. Chem.* **1989**, *54*, 1952–1960; f) D. H. R. Barton, J. E. D. Levisalles, J. T. Pinhey, *J. Chem. Soc.* **1962**, 3472–3482; g) D. H. R. Barton, P. D. Mayo, M. Shafiq, *J. Chem. Soc.* **1957**, 929–935.

[11] a) J. W. Morzycki, J. Obidzinska, *Can. J. Chem.* **1991**, *69*, 790–793; b) H. J. Reich, I. L. Reich, J. M. Renga, *J. Am. Chem. Soc.* **1973**, *95*, 5813–5815.

[12] a) R. D. de Vivar, A. Cabrera, A. Ortega, J. Romo, *Tetrahedron* **1967**, *23*, 3903–3907; b) S. Nagumo, K. Izawa, K. Higashiyama, M. Nagai, *Yakugaku Zasshi* **1980**, *100*, 427–433.

[13] a) P. Marqués-Gallego, J. Reedijk, *Chem. Eur. J.* **2010**, *16*, 12860–12864; b) A. J. Boersma, D. Coquiere, D. Geerdink, F. Rosati, B. L. Feringa, G. Roelfes, *Nat. Chem.* **2010**, *2*, 991–995; c) I. C. Stewart, R. G. Bergman, F. D. Toste, *J. Am. Chem. Soc.* **2003**, *125*, 8696–8697.

[14] Y. Murata, D. Yamashita, K. Kitahara, Y. Minosako, A. Nakazaki, S. Kobayashi, *Angew. Chem.* **2009**, *121*, 1428–1431; *Angew. Chem. Int. Ed.* **2009**, *48*, 1400–1403.

Received: December 3, 2012
Published online: February 28, 2013

