ORGANIC LETTERS

2005
Vol. 7, No. 14
2917−2920

A Novel Stereocontrolled Approach to Eudesmanolides: Total Synthesis of (±)-Gallicadiol and (±)-Isogallicadiol

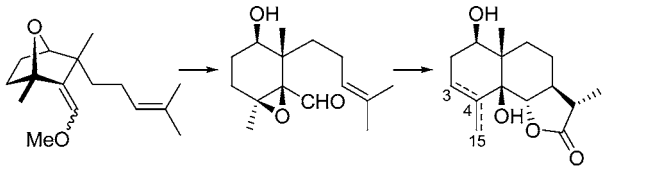
Wei-Dong Z. Li*,†,‡ and Zhang-Hua Gao†

State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000, China, and State Key Laboratory of Elemento-organic Chemistry, Nankai University, Tianjin 300071, China

liwd@lzu.edu.cn; wdli@nankai.edu.cn

Received April 18, 2005

ABSTRACT



6, Gallicadiol ($\Delta^{3,4}$)
7, Isogallicadiol ($\Delta^{4,15}$)

A novel approach for the stereocontrolled synthesis of eudesmanolides was developed based on a quasi-biomimetic strategy starting from a functionalized oxabicyclic template, as shown above, by which the first total syntheses of gallicadiol (6) and isogallicadiol (7) were achieved. The key elements of the synthesis include: (1) a facile and stereospecific synthesis of a functionalized epoxy aldehyde intermediate; (2) a mild Lewis acid-mediated stereoselective ene cyclization; and (3) a stereocontrolled γ-lactonization.

Eudesmanolides are structurally characteristic, naturally occurring sesquiterpene lactones (i.e., α-santonin) exhibiting a wide range of biological activities.[1] The chemical synthesis of this class of biologically significant compounds has drawn a great deal of attention.[2] Although some semisynthetic (i.e., from readily available α-santonin)[3] and total synthetic[4] approaches have been developed over the past decades, it is still highly desirable to explore a more general and highly stereocontrolled total synthetic method. In continuation of our study on the synthesis of bioactive sesquiterpenoids,[5] we report here the development of a novel and highly stereocontrolled approach for the total synthesis of C-1 hydroxylated eudesmanolides, which culminated in the first chemical synthesis of (±)-gallicadiol (**6**)[6] and (±)-isogallicadiol (**7**),[7] which were first isolated from the medicinal

* Fax/Phone: 0086-(0)22-23494613.
† Lanzhou University.
‡ Nankai University.

(1) For general review, see: (a) Munoz, O.; Penazola, A.; Gonzales, A. G.; Ravelo, A. G.; Bazzocchi, I. L.; Alvarenga, N. L. In *Studies in Natural Product Chemistry*; Atta-ür-Rahman, Ed.; Elsevier Science Publisher: Amsterdam, 1996; Vol. 18, pp 739−783. For recent examples, see: (b) Goren, N. *Phytochemistry* **1996**, *42*, 747. (c) Massanet, G. M.; Guerra, F. M.; Jorge, Z. D.; Astorga, C. *Phytochemistry* **1997**, *45*, 1645. (d) Cho, J. Y.; Park, J.; Yoo, E. S.; Baik, K. U.; Jung, J. H.; Lee, J.; Park, M. H. *Planta Med.* **1998**, *64*, 594. (e) Cantrell, C. L.; Franzblau, S. G.; Fischer, N. H. *Planta Med.* **2001**, *67*, 685.

(2) For general reviews on sesquiterpene syntheses, see: (a) Heathcock, C. H. In *The Total Synthesis of Natural Products*; ApSimon, J., Ed.; John Wiley and Sons: New York, 1973; Vol. 2, pp 197−558. (b) Heathcock, C. H.; Graham, S. L.; Pirrung, M. C.; Plavac, F.; White, C. T. *The Total Synthesis of Natural Products*; ApSimon, J., Ed.; John Wiley and Sons: New York, 1983; Vol. 5. (c) Spivey, A. C.; Weston, M.; Woodhead, S. *Chem. Soc. Rev.* **2002**, *31*, 43.

(3) For examples, see: (a) Ando, M.; Akahane, A.; Takase, K. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 283. (b) Garcia-Granados, A.; Martinez, A.; Parra, A.; Rivas, F.; Onorato, M. E.; Arias, J. M. *Tetrahedron* **1993**, *49*, 1091. (c) Miyashita, M.; Suzuki, T.; Yoshikoshi, A. *Chem. Lett.* **1987**, 2387. (d) Bargues, V.; Blay, G.; Garcia, B.; Garcia, C. L.; Pedro, J. R. *Tetrahedron* **1995**, *51*, 5609.

(4) For examples, see: (a) Abe, Y.; Harukawa, T.; Ishikawa, H.; Miki, T.; Sumi, M.; Toga, T. *J. Am. Chem. Soc.* **1956**, *78*, 1422. (b) Van Hijfte, L.; Vandewalle, M. *Tetrahedron* **1984**, *40*, 4371. (c) Macias, F. A.; Aguilar, J. M.; Molinillo, J. M. G.; Rodriguez-Luis, F.; Collado, I. G.; Massanet, G. M.; Fronczek, F. R. *Tetrahedron* **2000**, *56*, 3409.

(5) For previous studies from this laboratory, see: (a) Zhou, G.; Gao, X.-L.; Li, W.-D. Z.; Li, Y.-L. *Tetrahedron Lett.* **2001**, *42*, 3101. (b) Li, W.-D. Z.; Zhou, G.; Gao, X.-L.; Li, Y.-L. *Tetrahedron Lett.* **2001**, *42*, 4649. (c) Zhang, Z.; Li, W.-D. Z.; Li, Y.-L. *Org. Lett.* **2001**, *3*, 2555.

10.1021/ol050850p CCC: $30.25
Published on Web 06/15/2005

plant *Artemisia maritima gallica* Willd and represent a rare yet biogenetically interesting class of $C_{5,10}$ *cis*-eudesmanolide.

Biosynthetically, C-1 hydroxylated eudesmane sesquiterpenoids (eudesmanoids) are generally derived from the common biogenetic precursor farnesyl pyrophosphate (FPP) via a mild acid-promoted transannular cationic cyclization of a 1,10-epoxygermacrane derivative and further oxygenative derivatization of the resulting intermediate **i** (Figure 1).[8] This general biosynthetic pathway was manifested in

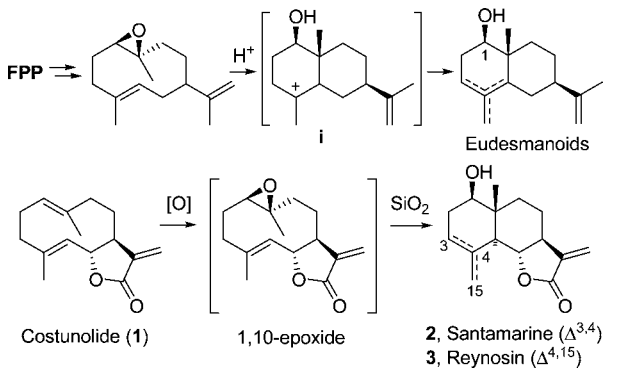


Figure 1. Biogenesis of C-1 hydroxylated eudesmanoids.

an ingenuous biomimetic conversion[9] of naturally occurring costunolide (**1**) into santamarine (**2**) and reynosin (**3**), two typical antitumor eudesmanolides,[10] as shown in Figure 1.

Inspired by this biogenetic knowledge,[8,9,11] we hypothesized an allylic cationic intermediate **ii** (Figure 2) to mimic the transient biogenetic intermediate **i** (Figure 1) for the construction of the eudesmane skeleton, which we envisioned to be generated from a substituted oxabicyclic precursor **4** by an acid-promoted ring-opening process (Figure 2). This quasi-biomimetic strategy has been proven to be effective in our previous concise and stereocontrolled total synthesis of balanitol (**5**), via a formic acid-mediated tandem ring-

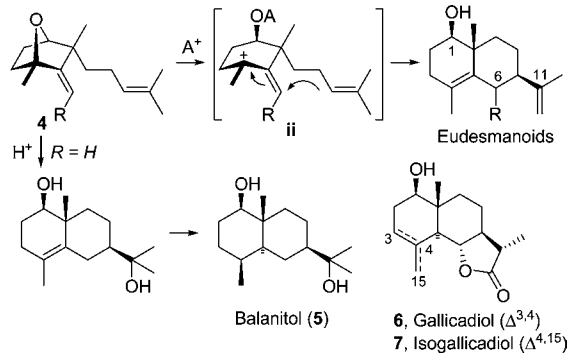


Figure 2. General quasi-biomimetic strategy to eudesmanoids.

opening cyclization of the oxabicyclic precursor **4a** (**4**, R = H) as the key step (Figure 2).[12] A logical extension of this approach for the synthesis of both C-1 and C-6 hydroxylated eudesmanoids, that is, eudesmanolides **2**, **3**, **6**, and **7**, would be the incorporation of an oxygenated (or equivalent)[13] substituent R in **4**.

After considerable experimentation, we found that the methoxyvinylation of the bisalkylated oxabicyclic ketone **8** to the corresponding methoxy vinylic ether **4b** (**4**, R = OMe) was realized by employing the Magnus protocol[14] via the Peterson olefination reaction. Thus, the addition of (methoxy(trimethylsilyl)methyl)lithium (Magnus reagent)[14] to ketone **8** (−78 → −60 °C, 1 h) was followed by in situ treatment with *t*-BuOK (−78 °C → rt) of the resulting adduct to give an isomeric mixture of methoxy vinylic ethers **4b** (*E*/*Z* 4:3, 87%), which could be separated by chromatography on silica gel.[15] Other conventional olefination methods, including the Corey−Tius protocol[16] or the use of (diazomethyl)phosphonate,[17] have all failed due to considerable steric hindrance of the keto carbonyl in **8**.

With the designated oxabicyclic methoxy vinylic ether **4b** in hand, we next studied the anticipated cationic cyclization under acidic conditions. Treatment of **4b** with a protic acid (i.e., formic or acetic acid) resulted in a rapid hydrolytic ring-opening of the oxabicyclic ring system, leading to a cyclohexenal derivative **12** (vide infra, Scheme 2) in good yield. The use of $ZnBr_2$ as a mild Lewis acid in anhydrous CH_2Cl_2 produced a major cyclization product (54%), which was fully characterized spectroscopically as decalinic diene **9**, along with a small amount of dealkylated diene **10** (Scheme 1). Treatment with a stronger Lewis acid (i.e., TMSOTf) afforded a demethoxylated hydroxy diene **11** in moderate yield.

Apparently, although the action of Lewis acid promoted the tandem ring-opening cationic cyclization of **4b**, leading

(6) Gonzalez, A. G.; Galindo, A.; Mansilla, H.; Kesternich, V. H.; Palenzuela, J. A.; Lopez, M. *Tetrahedron* **1988**, *44*, 6750.

(7) (a) Gonzalez, A. G.; Galindo, A.; Hansilla, H.; Kesternich, V. H.; Palenzuela, J. A.; Rodriguez, M. L. *J. Nat. Prod.* **1990**, *53*, 462. (b) Trendafilova, A. B.; Todorova, M. N.; Gussev, C. V. *Phytochemistry* **1996**, *42*, 469.

(8) For general reviews, see: (a) Cane, D. E. *Chem. Rev.* **1990**, *90*, 1089. (b) Banthorpe, D. V. In *Natural Products: Their Chemistry and Biological Significance*; Mann, J., Davidson, R. S., Hobbs, J. B., Banthorpe, D. V., Harborne, J. B., Eds.; Longman Scientific & Technical: Essex, U.K., 1994; pp 316−327. (c) Marco, J. A.; Sanz-Cervera, J. F.; Garcia-Lliso, V.; Domingo, L. R.; Carda, M.; Rodriguez, S.; Lopez-Ortiz, F.; Lex, J. *Liebigs Ann.* **1995**, 1837. (d) Minnaard, A. J.; Stork, G. A.; Wijnberg, J. B. P. A.; De Groot, A. *J. Org. Chem.* **1997**, *62*, 2344. (e) Steele, C. L.; Crock, J.; Bohlmann, J.; Croteau, R. *J. Biol. Chem.* **1998**, *273*, 2078. (f) Seemann, M.; Zhai, G.; Umezawa, K.; Cane, D. E. *J. Am. Chem. Soc.* **1999**, *121*, 591.

(9) (a) Rodrígues, A. A. S.; García, M.; Rabi, J. A. *Phytochemistry* **1978**, *17*, 953. (b) El-Feraly, F. S.; Benigni, D. A.; McPhail, A. T. *J. Chem. Soc., Perkin Trans. 1* **1983**, 355. (c) Barrero, A. F.; Sánchez, J. F.; Barrón, A.; Ramírez, A. *Phytochemistry* **1992**, *31*, 332.

(10) Ogura, M.; Cordell, G. A.; Farnsworth, N. R. *Phytochemistry* **1978**, *17*, 957.

(11) Gonzalez, A. G.; Galindo, A.; Mansilla, H.; Gutierrez, A. *J. Chem. Soc., Perkin Trans. 1* **1982**, 881.

(12) For other cationic cyclization approaches to decaline ring system, see: Cooper, J. L.; Harding, K. E. *Tetrahedron Lett.* **1977**, *18*, 3321 and references therein.

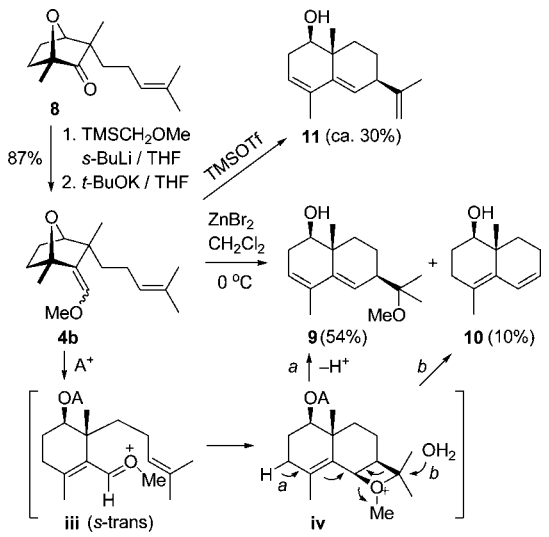
(13) Other substituents bearing a heteroatom, such as S, Si, or Cl, would be alternative choices.

(14) (a) Magnus, P.; Roy, G. *Organometallics* **1982**, *1*, 553. (b) For an applicable example in synthesis, see: Kende, A. S.; Blacklock, T. J. *Tetrahedron Lett.* **1980**, *21*, 3119.

(15) See Supporting Information-1 for experimental details.

(16) Corey, E. J.; Tius, M. A. *Tetrahedron Lett.* **1980**, *21*, 3535.

Scheme 1. Cyclization of Oxabicyclic Methoxy Vinylic Ether **4**

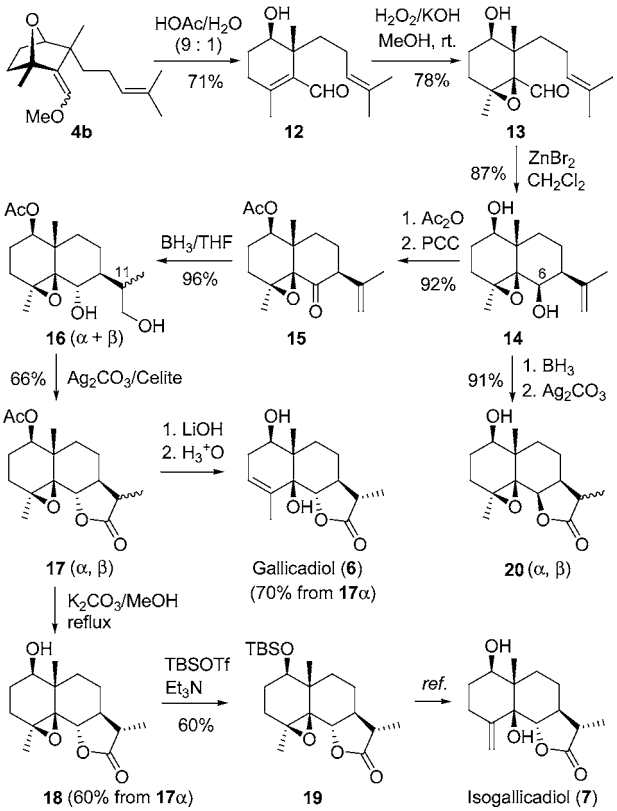


to the eudesmane skeleton (**9** and **11**), intriguingly, the methoxy group, which we deliberately introduced in **4b** for C-6 oxygenation of eudesmane skeleton, migrated to the peripheral alkyl chain instantaneously. The probable mechanistic rationale for this unusual methoxy 1,3-shift is depicted in Scheme 1, in which a metastable methyloxonium intermediate **iii** with a favorable *s-trans* configuration may be generated initially, which undergoes a deprotonative C−O bond cleavage[18] (pathway *a*) to give the methoxy-migrated diene **9** preferentially.[19] One evident fact is that submission of either *E* or *Z* isomer (or a mixture) of **4b** to the above cyclization conditions afforded the single diastereomeric **9** in comparable yield. The minor dealkylative product **10** may be attributed to an alternative nucleophilic attack (pathway *b*) at the C-11 by residual H_2O.

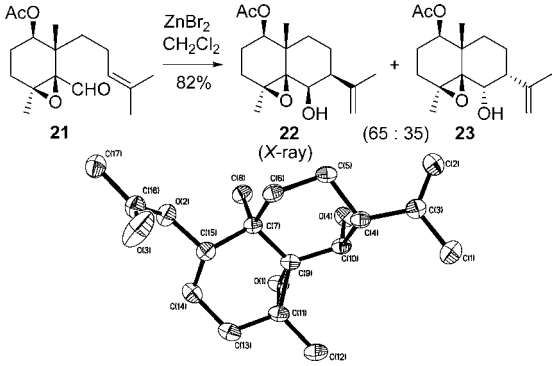
Although we have not been able to tune the cationic cyclization of **4b** as anticipated (arrows in **ii**), presently,[20] we decided to employ the readily available α,β-unsaturated aldehyde **12** as a valuable intermediate for our target synthesis.

As shown in Scheme 2, epoxidation (30% H_2O_2, KOH, MeOH) of hydroxy aldehyde **12** afforded β-epoxide **13** as a single diastereomer in 78% yield, which was subjected to ene cyclization[21] mediated by a mild Lewis acid. To our delight, the desired ene cyclization proceeded smoothly in the presence of 0.95 equiv of $ZnBr_2$ in anhydrous CH_2Cl_2 to give an epoxy diol **14** as the major diastereomer in 87% isolated yield. The stereochemistry of **14** was unambiguously confirmed by a single-crystal X-ray diffraction analysis (Scheme 3) of the corresponding C-1 acetate **22** (mp 111−112 °C).[22] Two minor diastereomeric products,[23] **14a** and **14b**, were also obtained in a total yield of 13% in a ratio of

Scheme 2. Total Synthesis of Gallicadiol and Isogallicadiol



Scheme 3. Ene Cyclization of C-1 Acetoxy Aldehyde **21**



(17) (a) Ohira, S. *Synth. Commun.* **1989**, *19*, 561. (b) Surprenant, S.; Chan, W. Y.; Berthelette, C. *Org. Lett.* **2003**, *5*, 4851.

(18) Blay, G.; Cardona, L.; Garcia, B.; Garcia, C. L.; Pedro, J. R. *Tetrahedron Lett.* **1994**, *35*, 931.

(19) For relevant examples of this type of 1,3-shift, see: (a) Finnerty, J.; Andraos, J.; Yamamoto, Y.; Wong, M. W.; Wentrup, C. *J. Am. Chem. Soc.* **1998**, *120*, 1701. (b) Fulloon, B. E.; Wentrup, C. *J. Org. Chem.* **1996**, *61*, 1363. Further study of this mechanistic pathway is underway.

(20) Further studies are ongoing to restrain this seemingly inevitable migration by attaching an electron-donating group (i.e., trimethylsilyl) at the allylic terminal of the homoprenyl chain in **4b**.

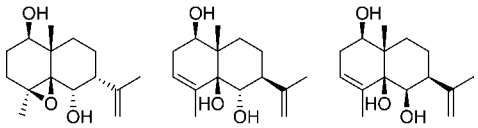
(21) (a) Marshall, J. A.; Wuts, P. G. M. *J. Am. Chem. Soc.* **1978**, *100*, 1627. (b) Schwartz, M. A.; Crowell, J. D.; Musser, J. H. *J. Am. Chem. Soc.* **1972**, *94*, 4361.

(22) X-ray crystallographic data of **22**: $C_{17}H_{26}O_4$, FW 294.38, monoclinic, space group *C*2/*c*, a = 16.846(8) Å, b = 18.842(8) Å, c = 11.732(5) Å, β = 121.761(5)°, Z = 6, d_{calcd} = 1.235 g/cm^3, R_1 ($I > 2\sigma(I)$) = 0.0375, wR_2 (all data) = 0.1048. See Supporting Information-1 for more details.

(23) Stereostructures were characterized spectroscopically.

ca. 1:2. It is noteworthy that treatment of **14** with $ZnBr_2$ (1.0 equiv) in CH_2Cl_2 resulted in a facile regioselective epoxy ring-opening to give eudesmane triol **14c** (mp 118−119 °C) quantitatively. This interesting reactivity of the $C_{4,5}$ β-epoxy function appears to be general as protic acid could also promote a similar epoxy ring-opening process (vide infra).

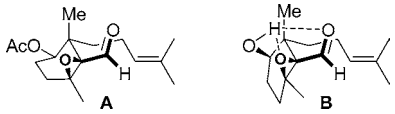
Apparently, the 6β-hydroxy of **14** needed to be inverted



14a **14b** **14c**

at this stage for the synthesis of the more common *trans*-configurated eudesmane $C_{6,7}$ γ-lactones. Thus, PCC oxidation of the C-1 acetate **22** gave the epoxy ketone **15** (mp 100−102 °C) in 92% yield from diol **14**, which was then subjected to hydroboration using BH_3 in THF to furnish, after usual oxidative workup, the epoxy diol **16** as a diastereomeric mixture (α/β 65:35) in 96% yield with a stereospecific inversion of the 6β-hydroxy configuration.[24] Oxidative γ-lactonization of the epoxy diol **16** (α and β) with Ag_2CO_3/Celite (Fetizon reagent)[25] in refluxing benzene afforded the epoxy γ-lactones 11α-**17** (mp 139−141 °C) and 11β-**17** (mp 154−156 °C) in 66% yield (ratio 65:35), which were separated readily by silica gel chromatography. Alkaline hydrolysis of lactone 11α-**17** in an aqueous LiOH in THF followed by treatment with 2 N HCl (rt, 2 h)[26] gave the title gallicadiol (**6**) in 70% overall yield. The total synthetic (±)-**6** (mp 170−172 °C) exhibits[27] spectroscopic properties identical to those of natural **6** reported.[6] 6β-Hydroxy diol **14** was similarly converted to the $C_{6,7}$ *cis*-eudesmanolide **20** (α/β 53:47) in 91% overall yield.[28] Alternatively, when 11α-**17** was treated with anhydrous K_2CO_3 in refluxing methanol and followed by acidic workup, epoxy lactone 11α-**18** (mp 89−90 °C) was isolated in 60% yield.[29] Treatment of 11α-**18** with TBSOTf in CH_2Cl_2 in the presence of Et_3N afforded the corresponding siloxy lactone **19** (60%),[30] a known[7] semisynthetic intermediate en route to isogallicadiol (**7**).

We further examined the $ZnBr_2$-mediated ene cyclization of acetylated epoxy aldehyde **21**, and two major isomeric cyclization products, **22** and **23**,[31] were obtained in 82% yield in a ratio of 65:35 (Scheme 3). Apparently, the 1β-hydroxy group of **13** directs the highly stereoselective ene cyclization to **14**. The above facts would suggest favorable conformers **A** and **B** for ene cyclization precursors **21** and **13**, respectively. The concave conformer **B** may be more favorable owing to intramolecular hydrogen bonding.



In summary, we have developed a novel highly stereocontrolled[32] total synthetic approach for eudesmanolides, which features the assembly of a functionalized oxabicyclic template **4b** and a highly stereoselective ene cyclization under mild Lewis acid promotion. As demonstrated here in the total synthesis of gallicadiol (**6**) and isogallicadiol (**7**), this general quasi-biomimetic strategy would be of great potential in the stereocontrolled synthesis of other types of sesquiterpenoids.[33] Further derivatization of the readily accessible eudesmane diene intermediates **9** and **11** to eudesmanoids[34] can be envisioned, as well. Studies along these lines are ongoing in this laboratory.

Acknowledgment. This paper is dedicated to Professor Philip Magnus. We are grateful to Mr. Bing Liu for his kind assistance in the preparation of compound **4b**. We thank the National Natural Science Foundation (Distinguished Youth Fund 29925204 and QT 20021001) for financial support. The Cheung Kong Scholars program and the Outstanding Scholars program of Nankai University are gratefully acknowledged.

Supporting Information Available: Experimental procedures, spectral data, copies of spectrum for compounds **4b**, **6**, **7**, **9**−**20**, and **22**, and crystallographic information file (CIF) for compound **22**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL050850P

(24) Obviously, hydroboration of the terminal olefin of **15** took place first and was followed by intramolecular face-specific hydride transfer from boron to the C-6 carbonyl, leading to 6α-hydroxy.

(25) For leading references, see: (a) Balogh, V.; Fetizon, M.; Golfier, M. *J. Org. Chem.* **1971**, *36*, 1339. (b) Fetizon, M.; Golfier, M.; Louis, J.-M. *Tetrahedron* **1975**, *31*, 171. For alternative hydroboration−oxidative γ-lactonization sequences, see: (c) Jefford, C. W.; Wang, Y. *J. Chem. Soc., Chem. Commun.* **1988**, 634. (d) Chavan, S. P.; Zubaidha, P. K.; Dhondge, V. D. *Tetrahedron* **1993**, *49*, 6429.

(26) Both relactonization and acid-mediated epoxy ring-opening of the resulting deacetylation intermediate took place at this stage.

(27) Authentic sample of **6** is not available for direct comparison.

(28) Epimers separated readily by silica gel chromatography after C-1 O-silylation (TBSOTf, Et_3N), which were fully characterized spectroscopically; see Supporting Information-1 for details.

(29) The corresponding ring-opening product of γ-lactone, dihydroxy methyl ester, was obtained in ca. 20% yield.

(30) A minor product (ca. 10%) was identified as the C-1 O-silylated gallicadiol (**6**).

(31) Corresponding to C-1 acetates of **14** and **14a**, respectively.

(32) Enantioselective synthesis is achievable in view of the accessibility of the chiral starting oxabicyclic ketone.[5c] See: Guan, Y.-K.; Li, Y.-L. *Chirality* **2005**, *17*, 113.

(33) For examples, see: (a) Heathcock, C. H.; Ratcliffe, R.; Van, J. *J. Org. Chem.* **1972**, *37*, 1796. (b) Minnaard, A. J.; Wijnberg, J. B. P. A.; De Groot, A. *Tetrahedron* **1994**, *50*, 4755.

(34) For examples, see: (a) Xu, F.; Morikawa, T.; Matsuda, H.; Ninomiya, K.; Yoshikawa, M. *J. Nat. Prod.* **2004**, *67*, 569. (b) Kawaguchi, Y.; Ochi, T.; Takaishi, Y.; Kawazoe, K.; Lee, K.-H. *J. Nat. Prod.* **2004**, *67*, 1893. (c) Sun, Z.; Chen, B.; Zhang, S.; Hu, C. *J. Nat. Prod.* **2004**, *67*, 1975.