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Synthetic Study of 1,3-Butadiene-Based IMDA Approach to Construct a [5−7−6] Tricyclic Core and Its Application to the Total Synthesis of C8-*epi*-Guanacastepene O

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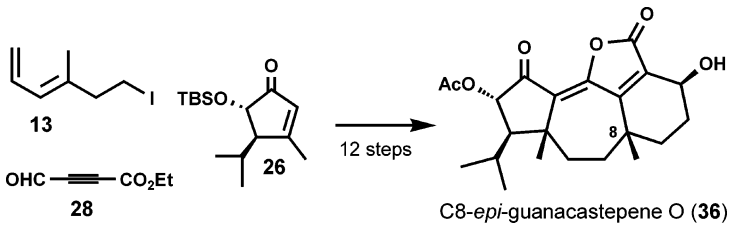
Received May 12, 2006



An efficient intramolecular Diels−Alder (IMDA) strategy for the construction of the [5−7−6] tricyclic core (**18**) of guanacastepenes has been developed from *cis*- and *trans*-1,3-butadiene-tethered 4-oxopent-2-ynoic acid ethyl esters **10** and **11**. This method facilitates the synthesis of C8-*epi*-guanacastepene O (**36**) in a very efficient manner.

Introduction

The widespread occurrence of bacterial resistance to most common antibiotics,[1] including the last resort antibiotics, the vancomycin group (glycopeptide) antibiotics, has generated a pressure to develop effective counter measures.[2] In this regard, a novel class of diterpenoid guanacastepenes (**1**−**6** in Figure 1) identified by Clardy and co-workers in 2000[3] provides an opportunity to develop small-molecule-based anti-bacterial agents because some of the guanacastepenes (such as guanacastepene A) are known to be effective against the methicillin-resistant strain of *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus faecalis* (VREF).[4] However, their hemolytic activity against human red blood cells prevents them from being directly used as therapeutics.

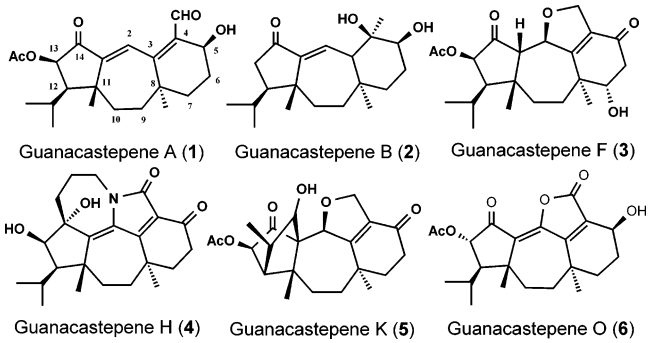


FIGURE 1. Naturally occurring guanacastepenes.

Structurally, guanacastepenes present two conformers in a dynamic equilibrium at room temperature.[3] Thus, development

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(1) Neu, H. C. *Science* **1992**, *257*, 1064.

(2) (a) O'Brien, D. P.; Entress, R. M. H.; Cooper, M. A.; O'Brien, S. W.; Hopkinson, A.; Williams, D. H. *J. Am. Chem. Soc.* **1999**, *121*, 5259. (b) Nicolaou, K. C.; Hughes, R.; Cho, S. Y.; Wingssinger, N.; Smethurst, C.; Labischinski, H.; Endermann, R. *Angew. Chem., Int. Ed.* **2000**, *39*, 3823. (c) Chiosis, G.; Boneca, I. G. *Science* **2001**, *293*, 1484. (d) Liu, H. T.; Sadamoto, R.; Sears, P. S.; Wong, C. H. *J. Am. Chem. Soc.* **2001**, *123*, 9916. (e) Kohli, R. M.; Walsh, C. T.; Burkart, M. D. *Nature* **2002**, *418*, 658.

(3) (a) Brady, S. F.; Singh, M. P.; Janso, J. E.; Clardy, J. *J. Am. Chem. Soc.* **2000**, *122*, 2116. (b) Brady, S. F.; Bondi, S. M.; Clardy, J. *J. Am. Chem. Soc.* **2001**, *123*, 9900.

(4) Singh, M. P.; Janso, J. E.; Luckman, S. W.; Brady, S. F.; Clardy, J.; Greenstein, M.; Maiese, W. M. *J. Antibiot.* **2000**, *53*, 256.

10.1021/jo060996h CCC: $33.50
Published on Web 08/10/2006

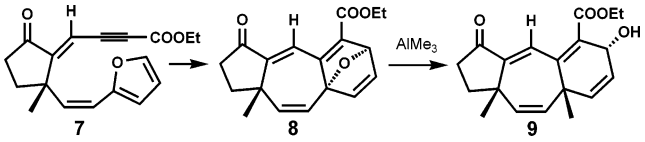


FIGURE 2. Furan-based IMDA to make the guanacastepene core.

of efficient accesses to the structurally diverse analogues is essential to their structure−activity relationship (SAR) studies.

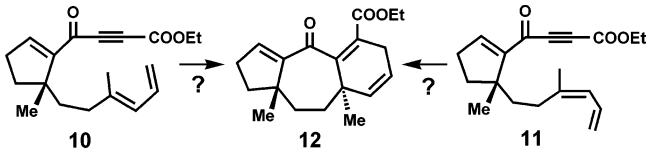
There have been numerous efforts to derive efficient syntheses of this novel class of natural products,[5] recently culminating in the total synthesis of guanacastepene A[6a] by the laboratory of Danishefsky in 2002 and two formal total syntheses[6b,c] by the laboratories of Snider in 2003 and Hanna in 2004.

Among the synthetic methods disclosed, the approach based on the IMDA reaction[7] is particularly attractive in light of its concise and convergent nature to construct the [5−7−6] tricyclic core of guanacastepenes. However, application of this important approach to the synthesis of guanacastepenes has not yet been reported.[8]

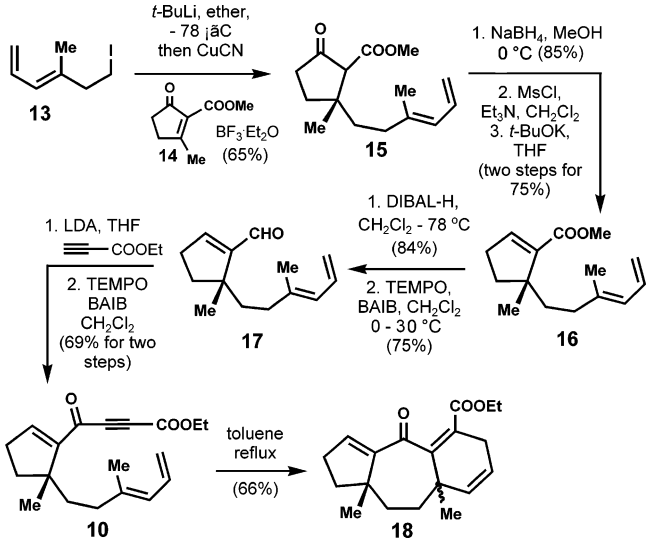
In our previous communication,[7] we reported an efficient approach to construct the [5−7−6] tricyclic core **8** of guanacastepene using the IMDA reaction and Me_3Al-mediated ring opening of its oxabridge as the key synthetic steps (Figure 2). However, an X-ray study[9] revealed that the oxabridge oriented in the undesired direction. As a result, the Me_3Al-mediated ring opening of the oxabridge led to **9** with the unnatural stereochemistry at C8.

Since the furan-based DA adduct is notoriously susceptible to retro-Diels−Alder reaction,[10] we are intrigued to explore whether the generation of **8** from **7** is also thermodynamically controlled. We could, in principle, design some nonreversible DA reactions that can generate DA adducts with our desired conformations. On the basis of this consideration, we decided to synthesize substrates **10** and **11** and to test their DA reactions in hopes of getting kinetically controlled product **12** with the right stereochemistry at C8 (Scheme 1), although it is difficult to predict which isomer (**10** or **11**) could give the desired adduct **12**.

SCHEME 1. Synthetic Analysis



SCHEME 2. Synthesis of Substrate 10 and Its IMDA Reaction to Make 18



We report herein the details of this study and the results generated from this investigation, which eventually led to the synthesis of C8-*epi*-guanacastepene O in a very efficient manner.

Results and Discussion

Synthetically, the *trans*- and *cis*-1,3-butadienes **13** and **19** were made by the well-established methods[11] (see Supporting Information for detail). Their applications use the key intermediates **10** and **11**, and the evaluation of their IMDA reactions are described in Schemes 2 and 3.

The synthesis of intermediate **10** started from **13** (Scheme 2). Accordingly, **13** was first treated with *t*-BuLi at −78 °C in Et_2O, followed by reaction with CuCN,[12] to form its corresponding copper reagent,[13] which was subjected to 1,4-addition to **14** in the presence of $BF_3{\bullet}Et_2O$[14] to afford **15** in 65% yield. The conversion of **15** to **16** was achieved by a standard protocol of reduction−mesylation−elimination. Thus, ester **16** could be converted to its aldehyde **17** by sequential reduction−oxidation.

To make the key intermediate **10**, aldehyde **17** was reacted with the lithium salt of ethyl propiolate, followed by TEMPO/BAIB[15]-mediated oxidation.

(5) (a) Snider, B. B.; Hawryluk, N. A. *Org. Lett.* **2001**, *3*, 569. (b) Magnus, P.; Waring, M. J.; Ollivier, C.; Lynch, V. *Tetrahedron Lett.* **2001**, *42*, 4947. (c) Dudley, G. B.; Danishefsky, S. J. *Org. Lett.* **2001**, *3*, 2399. (d) Dudley, G. B.; Tan, D. S.; Kim, G.; Tanski, J. M.; Danishefsky, S. J. *Tetrahedron Lett.* **2001**, *42*, 6789. (e) Snider, B. B.; Shi, B. *Tetrahedron Lett.* **2001**, *42*, 9123. (f) Dudley, G. B.; Danishefsky, S. J. *Tetrahedron Lett.* **2002**, *43*, 5605. (g) Mehta, G.; Umarye, J. D. *Org. Lett.* **2002**, *4*, 1063. (h) Gradl, S. N.; Kennedy-Smith, J. J.; Kim, J.; Trauner, D. *Synlett* **2002**, *3*, 411. (i) Shipe, W. D.; Sorensen, E. J. *Org. Lett.* **2002**, *4*, 2063. (j) Nguyen, T. M.; Seifert, R. J.; Mowrey, D. R.; Lee, D. *Org. Lett.* **2002**, *4*, 3959. (k) Nakazaki, A.; Sharma, U.; Tius, M. A. *Org. Lett.* **2002**, *4*, 3363. (l) Boyer, F.-D.; Hanna, I. *Tetrahedron Lett.* **2002**, *43*, 7469. (m) Du, X.-H.; Chu, H. V.; Kwon, O. *Org. Lett.* **2003**, *5*, 1923. (n) Brummond, K. M.; Gao, D. *Org. Lett.* **2003**, *5*, 3491. (o) Hughes, C. C.; Kennedy-Smith, J. J.; Trauner, D. *Org. Lett.* **2003**, *5*, 4113. (p) Srikrishna, A.; Dethe, D. H. *Org. Lett.* **2004**, *6*, 165. (q) Chiu, P.; Li, S. *Org. Lett.* **2004**, *6*, 613. (r) Mandal, M.; Danishefsky, S. J. *Tetrahedron Lett.* **2004**, *45*, 3831. (s) Hughes, C. C.; Miller, A. K.; Trauner, D. *Org. Lett.* **2005**, *7*, 3425.

(6) (a) Lin, S.; Dudley, G. B.; Tan, D. S.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 2188. (b) Shi, B.; Hawryluk, N. A.; Snider, B. B. *J. Org. Chem.* **2003**, *68*, 1030. (c) Boyer, F.-D.; Hanna, I.; Richard, L. *Org. Lett.* **2004**, *6*, 1817.

(7) Li, C.-C.; Liang, S.; Zhang, X.-H.; Xie, Z.-X.; Chen, J.-H.; Wu, Y.-D.; Yang, Z. *Org. Lett.* **2005**, *7*, 3709.

(8) It is of note that Kwon and MacMillan groups revealed their efforts to generate the [5−7−6] core by an IMDA reaction (see refs 5m and http://etd.caltech.edu/etd/available/etd-10282003-135857/).

(9) See Supporting Information for details.

(10) Kappe, C. O.; Murphree, S. S.; Padwa, A. *Tetrahedron* **1997**, *53*, 14179.

(11) (a) Ukai, J.; Ikeda, Y.; Ikeda, N.; Yamamoto, H. *Tetrahedron Lett.* **1983**, *24*, 4029. (b) Ma, S.; Negishi, E.-I. *J. Org. Chem.* **1997**, *62*, 784.

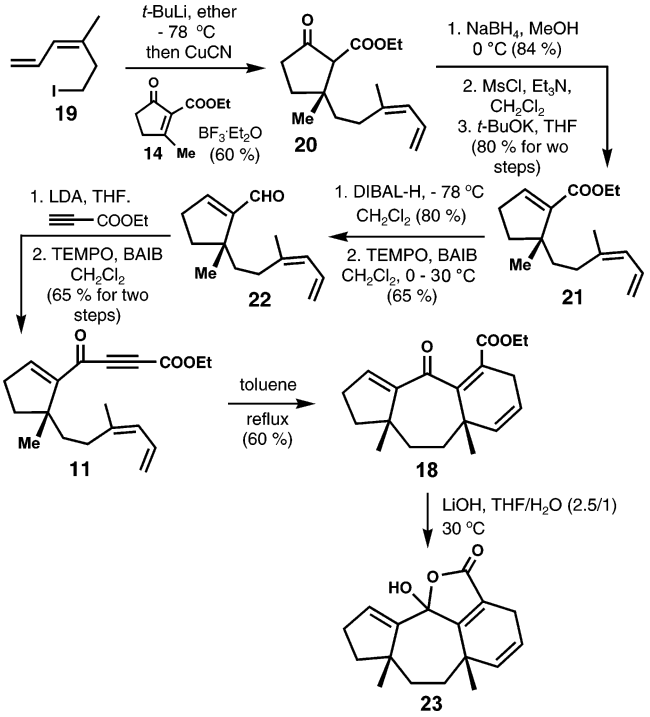
(12) (a) Bertz, S. H. *J. Am. Chem. Soc.* **1991**, *113*, 5470. (b) Stemmler, T.; Penner-Hahn, J. E.; Knochel, P. *J. Am. Chem. Soc.* **1993**, *115*, 384. (c) Underiner, T. L.; Goering, H. L. *J. Org. Chem.* **1990**, *55*, 2757.

(13) (a) Lipshutz, B. H.; Sengupta, S. *Org. React.* **1992**, *41*, 135. (b) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon Press: Oxford, 1992. (c) Chapdelaine, M. J.; Hulce, M. *Org. React.* **1990**, *38*, 225.

(14) Yamamoto, Y. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 947.

(15) Mico, A. D.; Margarita, R.; Parlanti, L.; Vescovi, A.; Pinacatelli, G. *J. Org. Chem.* **1997**, *62*, 6974.

SCHEME 3. Syntheses of 11, 18, and 23



With **10** in hand, we carried out its IMDA reaction in refluxing toluene, and the tricyclic-core-based adduct **18** was obtained in 66% yield, together with some unidentified products.

We then turned our attention to the synthesis of the [5−7−6] tricyclic core from substrate **11**. In an analogous way, compound **11** was smoothly made from iodide **19** (Scheme 3).

With **11** in hand, we started to test its cyclization to make the [5−7−6] tricyclic core of guanacastepenes by the IMDA reaction. Thus, under refluxing conditions in toluene, substrate **11** was indeed converted into its cyclized product in 60% yield, and no other adducts were identified. However, after examining its ^{1}H NMR and ^{13}C NMR spectra, we surprisingly found that the product generated from substrate **11** was identical to the one derived from substrate **10**.

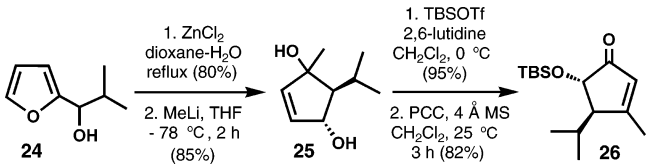
To determine the relative stereochemistry of the newly generated [5−7−6] tricyclic core from both **10** and **11**, ester **18** was converted to its lactone **23** as a pair of enantiomers. An X-ray study of **23** revealed that the tricyclic core system was in place as expected; however, the stereochemistry at C8 was opposite to the configuration of the natural form (see Supporting Information for details).

Although we have carried out an investigation for the IMDA reactions with substrates **10** and **11** by systematically changing the reaction conditions (such as reaction temperature, solvents, with or without Lewis acids), no product with the desired stereochemistry at C8 was identified.

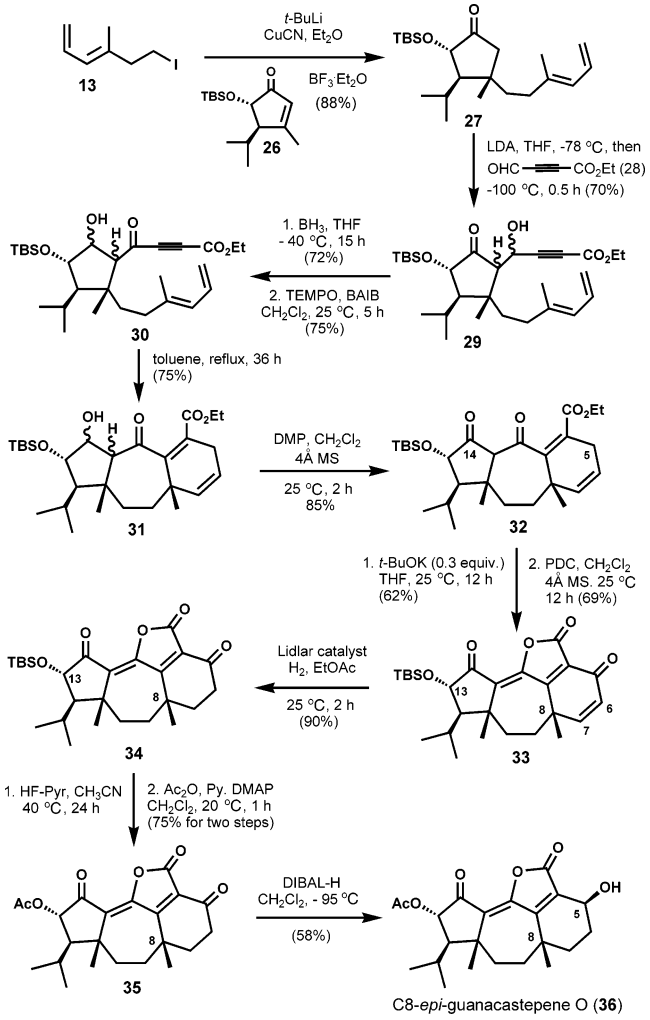
Interestingly, unlike naturally occurring guanacastepenes, which present two conformers at room temperature,[3] the synthesized compounds **18** and **23** show distinguished peaks in their NMR spectra. This important observation inspired us to synthesize some unnatural guanacastepenes with a defined conformational feature, like **18** and **23**, and to test their biological activities accordingly. We hoped that such an investigation could find a correlation between the conformation and anti-bacterial or hemolytic activities of guanacastepenes.

Our first target for the total synthesis of the guanacastepene derivative was C8-*epi*-guanacastepene O **35** (Scheme 5), in consideration of its structural similarity to compounds **18** and **23**. To this end, we needed to make compound **26** (Scheme 4). Accordingly, furan **24** was first treated with $ZnCl_2$ in dioxane−H_2O as a cosolvent to give a cyclopentenone,[16] which then underwent 1,2-addition of MeLi to afford **25** in 68% yield for two steps. The secondary alcohol in **25** was first protected as the TBS ether and then transferred to the key intermediate **26** by PCC-mediated oxidative rearrangement.[17]

SCHEME 4. Synthesis of Compound 26



SCHEME 5. Total Synthesis of C8-*epi*-Guanacastepene O (36)



Substrates **13** and **26** were utilized to make **27** in 88% yield (Scheme 5). Thus after treatment of ketone **27** with LDA at −78 °C, the formed enolate was reacted with aldehyde **28**, and product **29** was obtained as a mixture of diastereoisomers.

Guided by our previous experience in model studies,[7] we envisioned that **30** (Scheme 5) could be an ideal precursor to build the tricyclic core of guanacastepene O **31** by the IMDA reaction.

(16) Csaky, A. G.; Mba, M.; Phumet, J. *Synlett* **2003**, 2092.
(17) Dauben, W. G.; Michno, D. M. *J. Org. Chem.* **1977**, *42*, 682.

To verify this prediction, ketone **29** was first subjected to a chemoselective reduction with BH_3•THF,[18] and the formed propargylic alcohol was then oxidized to its ketone form by TEMPO/BAIB to give **30**. It is worthwhile to note that this BH_3-mediated ketone reduction proceeded in a chemoselective manner, presumably due to the formation of borate from propargylic alcohol and BH_3•THF at first, followed by an intramolecular hydride transfer.

Thus, we began to test the formation of the [5−7−6] tricyclic core **31** by the IMDA reaction. As expected, the desired cyclization product was obtained in 75% yield under refluxing conditions in toluene, which is in agreement with the observation in our previous model study.[7] Compound **31** was oxidized with Dess−Martin periodinane (DMP) to yield a dione **32** in 85% yield. Compound **32** was cyclized with a catalytic amount of *t*-BuOK, followed by PDC oxidation to install oxygen at C5 to give lactone **33** in 43% yield for two steps.

To make compound **35**, enone **33** was subjected to hydrogenation to remove the double bond between C6 and C7. The generated product **34** then underwent sequential desilylation and acetylation to afford **35** in 75% yield for two steps, and the presence of the tricyclic core was tentatively confirmed through X-ray crystallography; however, the data were of insufficient quality to allow a definitive determination of the structure.

To complete the total synthesis of C8-*epi*-guanacastepene O (**36**), compound **35** was treated with DIBAL-H in CH_2Cl_2 at −95 °C, and the expected product **36** was obtained in 58% yield.[19] Interestingly, unlike its natural counterparts, C8-*epi*-guanacastepene O (**36**) has a distinct structural conformation according to its NMR spectra.

In summary, we have synthesized the *cis*- and *trans*-1,3-butadiene-tethered 4-oxopent-2-ynoic acid ethyl esters **10** and **11** and examined their cyclizations to make the [5−7−6] tricyclic core of guanacastepene by the IMDA reaction. Although both substrates gave the same product **18** with wrong stereochemistry at C8, the developed chemistry has been successfully applied to the total synthesis of C8-*epi*-guanacastepene O (**36**). Further study regarding the synthesis of guanacastepenes with the right stereochemistry at C8 is currently underway in our laboratory.

Experimental Section

The experimental detail for the syntheses of intermediates **10** and **11**, as well as their Diels−Alder adduct **18**, is provided in the Supporting Information.

Synthesis of 5-(*tert*-Butyldimethylsilanyloxy)-4-isopropyl-3-methyl-cyclopent-2-enone (26): To a solution of **24**[20] (5.2 g, 37 mmol) in 1,4-dioxane (440 mL) was added a solution of $ZnCl_2$ (20.3 g, 150 mmol) in H_2O (230 mL), and the formed mixture was adjusted to pH = 5.5 with a 0.5 M solution of HCl and then heated for 48 h. After removal of the solvent, the residue (30 mL) was extracted with EtOAc (3 × 50 mL), and the combined organic layers were dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by a silica gel chromatography (EtOAc/hexanes = 1/2) to give the product **25a** (4.16 g) in 80% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.59−7.56 (m, 1H), 6.18−6.16 (m, 1H), 4.82 (br, 1H), 4.02 (br, 1H), 2.34−2.24 (m, 2H), 1.11 (d, J = 6.6 Hz, 3H), 0.85 (d, J = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 209.1, 163.3, 134.2, 72.3, 60.4, 26.9, 20.4, 18.0. MS [$C_8H_{12}O_2$], (EI) m/z (M+), calcd 140, found 140.

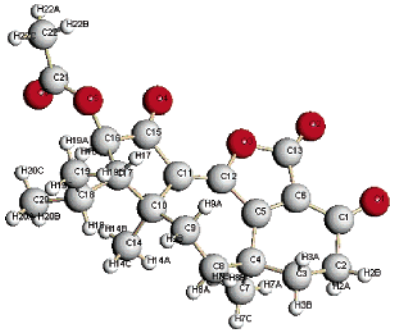
To a solution of **25a** (3.5 g, 25 mmol) in THF (50 mL) was added MeLi (1.6 M in Et_2O, 46 mL, 75 mmol) dropwise at −78 °C, and the reaction mixture was stirred at −78 °C for 2 h. The reaction was quenched by addition of a saturated aqueous NH_4Cl solution (20 mL), and the formed organic layer was first separated; the aqueous layer was then extracted with EtOAc (3 × 30 mL), and the combined organic layers were dried over $MgSO_4$. The solvent was removed under vacuum, and the residue was purified by a column chromatography on silica gel (hexane/EtOAc = 1/1) to give product **25** (3.32 g) in 85% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.84−5.82 (m, 1H), 5.78−5.76 (m, 1H), 4.71−4.69 (m, 1H), 1.99−1.91 (m, 1H), 1.48 (s, 3H), 1.40−1.35 (m, 1H), 1.09 (d, J = 6.3 Hz, 3H), 1.03 (d, J = 6.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.7, 135.4, 82.4, 81.1, 63.4, 29.5, 28.1, 22.9, 22.2. MS [$C_9H_{16}O_2$], (EI) m/z (M^+), calcd 156, found 156.

To a solution of **25** (1.56 g, 10 mmol) in CH_2Cl_2 (30 mL) were added 2,6-lutidine (1.28 g, 12 mmol) and TBSOTf (2.64 g, 2.3 mL, 10 mmol) at −78 °C, and the reaction mixture was then stirred at the same temperature for 1 h. The reaction was quenched by addition of a saturated aqueous NH_4Cl solution (5 mL) at −78 °C, and the formed mixture was then diluted with water (20 mL) and extracted with Et_2O (3 × 30 mL). The organic phase was first washed with brine (2 × 10 mL) and then dried over Na_2SO_4. The solvent was removed under vacuum to afford the crude tertiary alcohol (2.56 g, 9.5 mmol), which was used in next step without further purification.

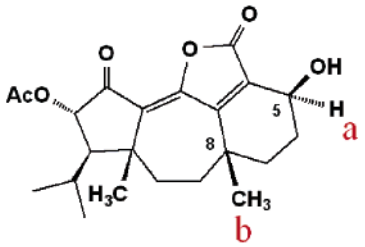
To a slurry of PCC (3.87 g, 18 mmol) and 4 Å molecular sieves (3.0 g) in CH_2Cl_2 (30 mL) was added the crude alcohol made above in CH_2Cl_2 (20 mL) at room temperature, and the resulting reddish mixture was stirred at the same temperature for 3 h. The reaction was worked up by addition of ether (30 mL), and the formed mixture was first filtered through a silica gel pad and then washed with Et_2O (3 × 40 mL). The combined ether phases were washed

(18) Brown, H. C.; Zaidlewics, M. *Encyclopedia of Reagents for Organic Synthesis*; Wiley: New York, 1995; Vol. 1, p 638.

(19) Reduction of keto ester **35** proceeded with a good selectivity, and we believed the molecular conformation of **35** might play a major role in this outcome. Compound **35** shows a certain type of ball-shape, especially the axial methyl group at C8, which will guide the reducing agent to approach the C5 ketone from its top face at −95 °C (see its crystal structure of compound **35** listed below), leading to the formation of the desired stereochemistry at C5. The stereochemistry for the *trans*-relationship between the proton (a) at C5 and the protons (b) of the methyl group at C8 was confirmed by 1D NOESY study of compound **36** (see Supporting Information for details).



X-ray structure of compound **35**



C8-*epi*-guanacastepene O (**36**)

(20) Csaky, A. G.; Mba, M.; Plumet, J. *Synlett* **2003**, 2092.

successively with aqueous solutions of 5% NaOH (2 × 20 mL), $NaHCO_3$ (2 × 20 mL), and then dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by a flash chromatography to give **26** (1.90 g) in 71% for two steps. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.90 (br, 1H), 3.98 (d, J = 2.1 Hz, 1H), 2.63 (br, 1H), 2.24−2.18 (m, 1H), 2.06 (s, 3H), 1.12 (d, J = 6.9 Hz, 3H), 0.89 (s, 9H), 0.75 (d, J = 6.9 Hz, 3H), 0.18 (d, J = 4.5 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 206.8, 177.9, 129.18, 73.1, 58.6, 26.7, 25.8, 21.5, 18.2, 17.9, 16.5, −3.5, −5.2. HRMS *m*/*z* calcd for $C_{15}H_{28}O_2Si$ [M^+ + 1] 269.1931, found [M^+ − 1] 269.1927.

Synthesis of 2-(*tert*-Butyldimethylsilanyloxy)-3-isopropyl-4-methyl-4-(3-methylhexa-3,5-dienyl)-3,5-dienyl]cyclopentanone (27): To a solution of iodide **13** (1.47 g, 6.6 mmol) in Et_2O (40 mL) was added ^{t}BuLi (1.5 M in pentane, 8.8 mL, 13.2 mmol) dropwise at −78 °C, and the mixture was stirred at the same temperature for 30 min. then copper(I) cyanide (646 mg, 7.26 mmol) was added. The reaction mixture was first warmed to −30 °C for 5 min and then cooled back to −78 °C. To this solution was slowly added a mixture of cyclopentenone **26** (708 mg, 2.64 mmol) and BF_3•Et_2O (0.99 mL, 6.6 mmol) in precooled Et_2O (20 mL), and the formed mixture was stirred at −78 °C for 30 min. The reaction was worked up by sequential addition of aqueous solutions of NH_4-Cl (5 mL) and $NaHCO_3$ (5 mL), and formed suspension was filtered through a Celite pad and washed with Et_2O (100 mL). The filtrate was concentrated under vacuum, and the residue was purified by a flash chromatography on silica gel (EtOAc/hexanes = 1/20) to give product **27** as a colorless oil (845 mg) in 88% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.60−6.52 (m, 1H), 5.85 (d, J = 10.2 Hz, 1H), 5.12−4.96 (m, 2H), 4.15 (d, J = 11.1 Hz, 1H), 2.20−1.95 (m, 5H), 1.76 (s, 3H), 1.74−1.67 (m, 1H), 1.44−1.38 (m, 1H), 1.11 (d, J = 7.2 Hz, 3H), 1.06 (d, J = 6.9 Hz, 3H), 0.99 (s, 3H), 0.90 (s, 9H), 0.19 (s, 3H), 0.12 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 215.9, 138.9, 133.1, 125.6, 114.9, 77.0, 56.9, 48.9, 39.9, 37.4, 34.6, 26.0, 25.1, 22.1, 19.2, 18.3, 16.7, −3.3, −5.1. HRMS *m*/*z* calcd for $C_{22}H_{40}O_2Si$ [M^+] 364.2798, found [M^+] 364.2791.

Synthesis of 4-[4-(*tert*-Butyldimethylsilanyloxy)-3-isopropyl-2-methyl-2-(3-methylhexa-3,5-dienyl)-3,5-dienyl]-5-oxocyclopentyl]4-hydroxybut-2-ynoic Acid Ethyl Ester (29): To a solution of diisopropylamine (0.28 mL, 2.0 mmol) in THF (10 mL) was added ^{n}BuLi (2.5 M in hexanes, 0.8 mL, 2.0 mmol) at −78 °C, and the solution was then warmed to 0 °C and stirred for 20 min. To this solution was added cyclopentanone **27** (728 mg, 2.0 mmol) in THF (11 mL) at −78 °C, and the mixture was stirred at the same temperature for 40 min. The mixture was then cooled −100 °C; to this solution was added dropwise a precooled solution of aldehyde **28** (378 mg, 3.0 mmol) in THF (12.0 mL), and the formed mixture was stirred at the same temperature for additional 20 min. The reaction was quenched by addition of a saturated aqueous NH_4-Cl solution (20 mL), and the mixture was extracted with Et_2O (3 × 50 mL). The combined organic phases were washed with brine (2 × 15 mL) and dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by a flash chromatography on silica gel (EtOAc/PE = 1/10) to give product **29** (686 mg) in 70% yield. Since product **29** is a mixture of diastereoisomers, we did not assign its ^{1}H NMR and ^{13}C NMR. HRMS *m*/*z* calcd for $C_{28}H_{45}O_5Si$ [M^+ − 1] 489.3018, found [M^+ − 1] 489.3033.

Synthesis of 4-[4-(*tert*-Butyldimethylsilanyloxy)-5-hydroxy-3-isopropyl-2-methyl-2-(3-methylhexa-3,5-dienyl)cyclopentyl]-4-oxobut-2-ynoic Acid Ethyl Ester (30): To a solution of **29** (686 mg, 1.4 mmol) in THF (30 mL) was added dropwise BH_3−THF complex in THF (1.0 M, 1.4 mL, 1.4 mmol) at −78 °C, and the mixture was then stirred at −40 °C for 15 h. The reaction was worked up by addition of a saturated aqueous NH_4Cl solution (10.0 mL); the organic layer was first separated, and the aqueous layer was then extracted with Et_2O (3 × 10 mL), and the combined organic layers were dried over $MgSO_4$. The solvent was removed under vacuum, and the residue was purified by a flash chromatography on silica gel (EtOAc/PE = 1/5) to give a diol (496 mg) in 72% yield as a mixture of diastereoisomers.

To a solution of the diol (496 mg, 1.0 mmol) made above in CH_2Cl_2 (15 mL) were added 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO) (28 mg, 0.18 mmol) and [bis(acetoxy)iodo]benzene (BAIB) (354 mg, 1.1 mmol) at room temperature, and the reaction mixture was stirred at the same temperature for 5 h. The reaction was quenched by sequential addition of a saturated aqueous NH_4-Cl solution (5 mL) and water (20 mL), and the formed mixture was first extracted with Et_2O (2 × 40 mL) and then dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by a flash chromatography on silica gel (EtOAc/PE = 1/20) to give product **30** (368 mg) in 75% yield as a mixture of diastereoisomers. The spectra data for one of the isomers are listed below. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.61−6.52 (m, 1H), 5.89 (d, J = 11.1 Hz, 1H), 5.12 (dd, J_1 = 1.6 Hz, J_2 = 16.8 Hz, 1H), 5.01 (dd, J_1 = 1.4 Hz, J_2 = 9.9 Hz, 1H), 4.35−4.26 (m, 3H), 4.12−4.08 (m, 1H), 3.12 (d, J = 6.1 Hz, 1H), 2.44 (d, J = 5.6 Hz, 1H), 2.25−2.12 (m, 2H), 1.87−1.85 (m, 1H), 1.79 (s, 3H), 1.78−1.70 (m, 3H), 1.33 (t, J = 7.1 Hz, 3H), 1.06 (d, J = 7.0 Hz, 3H), 0.98 (d, J = 6.8 Hz, 3H), 0.94 (s, 9H), 0.88 (s, 3H), 0.17 (d, J = 5.7 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 186.7, 151.8, 138.6, 133.0, 125.5, 114.6, 81.0, 79.2, 73.9, 71.7, 66.3, 62.7, 55.8, 45.1, 40.6, 34.2, 25.6, 25.1, 24.7, 19.9, 19.3, 17.7, 16.6, 13.65, −4.5, −4.6. HRMS *m*/*z* calcd for $C_{28}H_{46}O_5Si$ [M^+ − 1] 489.3042, found [M^+ − 1] 489.3038.

Synthesis of 2-(*tert*-Butyldimethylsilanyloxy)-3-hydroxy-1-isopropyl-8a,10a-dimethyl-4-oxo-1,2,3,3a,4,6,8a,9,10,10a-decahydrobenzo[*f*]azulene-5-carboxylic Acid Ethyl Ester (31): The mixture of **30** (368 mg, 0.75 mmol) was dissolved in toluene (150 mL), and the solution was heated at 120 °C for 36 h. After removal of the solvent under vacuum, the residue was purified by a flash chromatography on silica gel (EtOAc/PE = 1/20) to give product **31** (276 mg, in 75% yield) as a mixture of diastereoisomers. Since **31** is a mixture of diastereoisomers, we did not assign its H NMR and ^{13}C NMR. HRMS *m*/*z* calcd for $C_{28}H_{46}O_5Si$ [M^+ − 1] 489.3042, found [M^+ − 1] 489.3062.

Synthesis of 9-(*tert*-Butyldimethylsilanyloxy)-8-isopropyl-5a,7a-dimethyl-5a,6,7,7a,8,9-hexahydro-3*H*-1-oxabenzo[*cd*]cyclopenta[*h*]azulene-2,10-dione (32): To a solution of **31** (274 mg, 0.56 mmol) and 4 Å molecular sieves (500 mg) in CH_2Cl_2 (15 mL) was added Dess−Martin periodinane (2.21 g, 5.0 mmol) at room temperature in one portion, and the formed mixture was continually stirred at the same temperature for 1 h. The reaction was quenched by addition of petroleum ether (50 mL), and the formed precipitate was filtered off, and the filter was concentrated under vacuum. The residue was purified by a flash chromatography on silica gel (EtOAc/PE = 1/10) to give dione **32** (232 mg) in 85% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.89−5.85 (m, 1H), 5.57 (dd, J_1 = 2.8 Hz, J_2 = 9.6 Hz, 1H), 4.36−4.31 (m, 1H), 4.20−4.15 (m, 1H), 3.83 (d, J = 7.6 Hz, 1H), 3.58 (s, 1H), 3.10−3.04 (m, 1H), 2.85−2.79 (m, 1H), 2.05−1.47 (m, 8H), 1.27 (t, J = 7.1 Hz, 3H), 1.15 (s, 3H), 1.08 (d, J = 6.8 Hz, 3H), 1.04 (d, J = 6.8 Hz, 3H), 0.85 (s, 9H), 0.83 (s, 3H), 0.17 (s, 3H), 0.10 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 204.5, 199.4, 165.6, 157.7, 136.2, 124.5, 123.87, 70.4, 61.7, 60.7, 42.3, 38.3, 35.6, 35.4, 28.6, 26.9, 26.1, 25.9, 25.9, 24.9, 21.6, 18.1, 15.8, 14.2, −3.9, −5.2. HRMS *m*/*z* calcd for $C_{28}H_{44}O_5Si$ [M^+ + 1] 489.3030, found [M^+ + 1] 489.3017.

Synthesis of 9-(*tert*-Butyldimethylsilanyloxy)-8-isopropyl-5a,-7a-dimethyl-5a,6,7,7a,8,9-octahydro-1-oxabenzo[*cd*]cyclopenta-[*h*]azulene-2,3,10-trione (33): To a solution of dione **32** made above (232 mg, 0.48 mmol) in THF (50.0 mL) at −78 °C was added dropwise a solution of *t*-BuOK in THF (0.1 M solution, 1.4 mL), and the mixture was slowly warmed to room temperature and then continually stirred for 12 h. The reaction was quenched with a saturated aqueous NH_4Cl solution (10.0 mL), and the organic layer was separated; the aqueous layer was then extracted with Et_2O (3 × 10 mL). The combined organic layers were first washed sequentially with aqueous solutions of HCl (5%, 10 mL), $NaHCO_3$

(2 × 10 mL), and NH_4Cl (20 mL) and then dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by a flash chromatography on silica gel (EtOAc/PE = 1/10) to give lactone **33a** (132 mg) in 62% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.77−5.70 (m, 2H), 4.29 (d, J = 11.6 Hz, 1H), 3.06−2.91 (m, 2H), 2.05−1.96 (m, 4H), 1.81−1.70 (m, 2H), 1.34 (s, 3H), 1.24 (s, 3H), 1.13 (d, J = 6.8 Hz, 6H), 0.91 (s, 9H), 0.28 (s, 3H), 0.19 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.1, 167.9, 157.1, 147.6, 137.3, 130.4, 126.4, 119.7, 76.1, 57.9, 42.5, 37.5, 37.2, 35.9, 32.0, 26.1, 25.9, 24.4, 22.6, 21.1, 19.1, 18.4, −3.0, −5.1. MS [$C_{26}H_{38}O_4Si$], (EI) m/z (M^+), calcd 442, found 442.

To a stirred slurry of **33a** (115 mg, 0.26 mmol) and 4 Å molecular sieves (250 mg) in CH_2Cl_2 (10 mL) was added PDC (650 mg, 2.6 mmol) in one portion at room temperature, and the dark-reddish mixture was stirred at room temperature for 12 h. The reaction was worked up by filtration of the mixture through a silica gel pad and washed with EtOAc (50 mL). The filtrate was concentrated under vacuum, and the residue was purified by a flash chromatography on silica gel (EtOAc/PE = 1/2) to give diketone **33** (82 mg) in 69% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.04 (d, J = 10.0 Hz, 1H), 6.29 (d, J = 10.0 Hz, 1H), 4.32 (d, J = 11.7 Hz, 1H), 2.22−1.95 (m, 4H), 1.76−1.60 (m, 2H), 1.61 (s, 3H), 1.31 (s, 3H), 1.15−1.12 (m, 6H), 0.91 (s, 9H), 0.27 (s, 3H), 0.19 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.6, 178.4, 171.4, 162.7, 156.7, 145.3, 132.6, 126.9, 124.1, 75.7, 57.8, 43.4, 41.8, 37.1, 33.9, 32.1, 26.1, 25.9, 24.8, 19.7, 19.2, 18.4, −3.0, −4.9. HRMS m/z calcd for $C_{26}H_{36}O_5Si$ [$M^+ - 1$] 455.2259, found [$M^+ - 1$] 455.2251.

Synthesis of 9-(*tert*-Butyldimethylsilanyloxy)-8-isopropyl-5a,7a-dimethyl-4,5,5a,6,7,7a,8,9-octahydro-1-oxabenzo[*cd*]cyclopenta[*h*]azulene-2,3,10-trione (34): To a solution of diketone **33** made above (50 mg, 0.11 mmol) in ethyl acetate (15 mL) was added Lindlar catalyst (5 mg), and the mixture was stirred at 25 °C for 2 h under a balloon pressure of hydrogen. The reaction was worked up by filtration of the mixture through a silica gel pad, and the filtrate was concentrated under vacuum, and the residue was purified by a flash chromatography on silica gel (EtOAc/PE = 1/2) to give product **34** (45.5 mg) in 90% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.30 (d, J = 11.4 Hz, 1H), 2.83−2.61 (m, 2H), 2.21−1.79 (m, 8H), 1.50 (s, 3H), 1.28 (s, 3H), 1.15 (d, J = 2.9 Hz, 3H), 1.13 (d, J = 2.5 Hz, 3H), 0.91 (s, 9H), 0.26 (s, 3H), 0.19 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.7, 190.9, 174.8, 162.8, 144.8, 133.1, 123.2, 75.7, 57.2, 43.4, 39.1, 36.8, 36.1, 35.7, 35.4, 26.3, 26.0, 25.9, 24.7, 23.6, 19.3, 18.3, −3.2, −5.1. HRMS m/z calcd for $C_{26}H_{38}O_5Si$ [M^+] 457.2416, found [M^+] 457.2395.

Synthesis of Acetic Acid 8-(isopropyl-5a,7a-dimethyl-2,3,10-trioxo-3,4,5,5a,6,7,7a,8,9,10-decahydro-2*H*-1-oxabenzo[*cd*]cyclopenta[*h*]azulene-9-yl Ester (35): To a solution of **34** (25 mg, 0.055 mmol) in CH_3CN (10 mL) were added pyridine (1.0 mL) and an aqueous HF solution (42%, 1.0 mL) at room temperature, and the reaction mixture was stirred at 40 °C for 24 h. The reaction was worked up by filtration of the mixture through a silica gel pad and washed with EtOAc (25 mL). The filtrate was concentrated under vacuum, and the residue was immediately used for the next step without purification.

To a solution of the crude product made above (17 mg, 0.05 mmol) in CH_2Cl_2 (5.0 mL) were added pyridine (0.10 mL), Ac_2O (0.10 mL), and DMAP (0.3 mg) at room temperature, and the reaction mixture was stirred at room temperature for 1 h. The reaction was worked up by addition of water (5 mL), and the mixture was then extracted with EtOAc (3 × 15 mL); the combined organic phase was washed with brine (10 mL) and dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by a flash chromatography on silica gel (EtOAc/PE = 1/1) to give product **35** (16 mg) in 75% yield in two steps. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.42 (d, J = 11.6 Hz, 1H), 2.79−2.60 (m, 2H), 2.30−2.15 (m, 2H), 2.13 (s, 3H), 2.06−1.88 (m, 6H), 1.51 (s, 3H), 1.36 (s, 3H), 1.07 (d, J = 4.2 Hz, 3H), 1.06 (d, J = 4.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.5, 190.9, 174.4, 169.6, 162.5, 145.6, 132.2, 123,4, 75.5, 54.2, 44.1, 39.0, 36.8, 36.1, 35.9, 35.4, 26.4, 25.6, 25.3, 23.5, 20.7, 20.0. HRMS m/z calcd for $C_{22}H_{26}O_6$ [M^+] 386.1729, found [M^+] 386.1724.

Synthesis of C8-*epi*-Guanacastepene O (36): To a solution of **35** (7.7 mg, 0.02 mmol) in CH_2Cl_2 (4 mL) was added DIBAL-H (1.0 M in toluene, 40 μL, 0.04 mmol) at −95 °C, and the reaction mixture was stirred at the same temperature for 30 min. The reaction was quenched by slow addition of MeOH (0.1 mL) at −95 °C, and the mixture was warmed to room temperature. The formed mixture was first diluted with EtOAc (10 mL) and then mixed with a saturated solution of Rochelle salt (2 mL), and the formed mixture was stirred at room temperature for 2 h. The organic layer was separated, and the aqueous phase was extracted with EtOAc (3 × 5 mL); the combined organic phases were washed with brine (2 × 2 mL) and then dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by a flash chromatography on silica gel (EtOAc/PE/$CHCl_3$ = 3/2/1) to give **36** (4.5 mg) in 58% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.45 (d, J = 11.8 Hz, 1H), 4.71−4.66 (m, 1H), 2.28−2.20 (m, 1H), 2.14 (s, 3H), 2.13−1.66 (m, 9H), 1.40 (s, 3H), 1.33 (s, 3H), 1.05 (d, J = 1.7 Hz, 3H), 1.04 (d, J = 1.7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.0, 169.8, 167.8, 160.2, 147.9, 133.3, 125.4, 75.7, 63.4, 54.9, 43.5, 39.0, 36.8, 36.7, 35.7, 27.9, 27.4, 25.8, 25.2, 22.8, 20.9, 20.0. HRMS m/z calcd for $C_{22}H_{28}O_6$ [M^+] 388.1886, found [M^+] 388.1885.

Acknowledgment. Financial support from the NSFC (20325208, 20225318, 20521202) and the RGC of Hong Kong (HKUST6193/00P) is acknowledged.

Supporting Information Available: Experimental procedure for preparation of compounds **13b** and **19b**, ^{1}H and ^{13}C NMR spectra for the selected compounds, as well as single-crystal data of **8a**, **23**, and **36** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

JO060996H