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Remarkable Selectivity in Addition of Alcohols to Epoxydienes of 5,7 Bicyclic and 5,7,6 Tricyclic Systems

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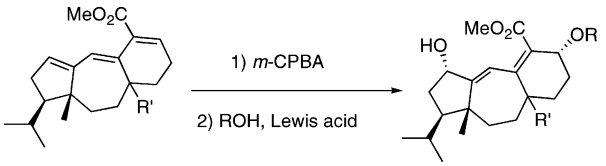
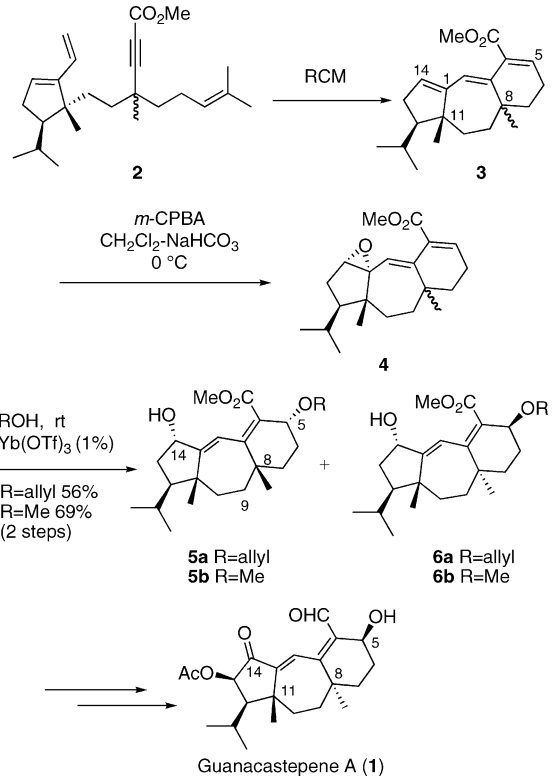


Acid-catalyzed addition of alcohols to tricyclic dienyl epoxides such as **4** or bicyclic vinyl oxiranes such as **17** exclusively occurred at the vinyl terminus of unsaturated system through a typical S_N2' process affording 1,6- and 1,4-dioxygenated derivatives, respectively.

Vinyl epoxides are versatile building blocks in organic synthesis, and their behavior as electrophiles is well documented.[1] Nucleophilic addition to these substrates may occur at the vinyl terminus through a typical conjugated addition (1,4 or S_N2' process) and/or at the allylic position through a direct 1,2-addition (S_N2 process).[2] While transition-metal-catalyzed reactions preferably proceed via an S_N2' process affording 1,4-adducts,[3,4] in the presence of Lewis acid, carbon and oxygen nucleophiles add in a 1,2-manner, presumably because of their ability to coordinate to the oxirane oxygen to help deliver the nucleophile to the adjacent carbon.[5]

SCHEME 1



Recently, we described a concise formal synthesis[6] of guanacastepene A (**1**), an antibacterial diterpenoid natural product with a novel carbon skeleton.[7−9] Our approach was based on the simultaneous construction of the seven- and six-membered rings through a tandem ring-closing metathesis (RCM), i.e., **2** → **3** (Scheme 1). Among the issues that had to be addressed to complete the synthesis of **1** was the stereoselective incorporation of oxygen functionalities. In the course of this study, to our surprise, we found that dienyl epoxide **4** underwent facile 1,6-addition of alcohols through a S_N2' type process in the presence of Lewis acid. In this reaction, palladium catalyst is not required: simply stirring **4** in allyl alcohol in the presence of catalytic ytterbium triflate [$Yb(OTf)_3$]

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(1) Hudlicky, T.; Reed, J. W. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 5; p 931.

(2) For a recent example on the S_N2 versus S_N2' addition of dithiane anions to vinyl epoxides, see: Smith, A. B.; Pitram, S. M.; Boldi, A. M.; Gaunt, M. J.; Sfouggatakis, C.; Moser, W. H. *J. Am. Chem. Soc.* **2003**, *125*, 14435.

(3) For leading references on palladium(0)-catalyzed reactions, see: (a) Trost, B. M.; Molander, G. A. *J. Am. Chem. Soc.* **1981**, *103*, 5969. (b) Tsuji, J.; Kataoka, H.; Kobayashi, Y. *Tetrahedron Lett.* **1981**, *22,* 257. For a review on S_N2' addition of organocuprates to vinyl epoxides, see: Marshall, J. A. *Chem. Rev*. **1989**, *89*, 1503.

(4) For S_N2' palladium-catalyzed addition of alkoxides, see: (a) Deardorff, D. R.; Myles, D. C.; MacFerrin, K. D. *Tetrahedron Lett.* **1985**, *26*, 5615. (b) Deardorff, D. R.; Myles, D. C. *Organic Synthesis*; Wiley & Sons: New York, 1993; Collect. Vol. 8, p 13. (c) Trost, B. M.; Ito, N.; Greenspan, P. D. *Tetrahedron Lett.* **1993**, *34,* 1421. (d) Snider, B. B.; Hawryluk, N. A. *Org. Lett.* **2001**, *3*, 569.

(5) (a) For Lewis acid promoted S_N2 addition of alkyllithiums, see: Alexakis, A.; Vranken, E.; Mangenay, P.; Chemla, F. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3352. (b) For 1,2-addition of alcohols, see: Prestat, G.; Baylon, C.; Heck, M.-P.; Mioskowski, C. *Tetrahedron Lett.* **2000**, *41*, 3829. (c) For rhodium-catalyzed 1,2-ring opening of vinyl epoxides, see: Fagnou, K.; Lautens, M. *Org. Lett.* **2000**, *2*, 2319.

(6) Boyer, F.-D.; Hanna, I.; Ricard, L. *Org. Lett*. **2004**, *6*, 1817.

(7) Isolation and biological activity: (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. (c) Singh, M. P.; Janso, J. E.; Luckman, S. W.; Brady, S. F.; Clardy, J.; Greenstein, M.; Maiese, W. M. *J. Antibiot.* **2000**, *53*, 256.

(8) Total and formal syntheses: (a) Tan, D. S.; Dudley, G. B.; Danishefsky, S. J. *Angew. Chem., Int. Ed*. **2002**, *41*, 2185. (b) Lin, S.; Dudley, G. B.; Tan, D. S.; Danishefsky, S. J. *Angew. Chem., Int. Ed*. **2002**, *41*, 2188. (c) Shi, B.; Hawryluk, N. A.; Snider, B. B.; *J. Org. Chem.* **2003**, *68*, 1030.

(9) For recent synthetic studies related to guanacastepene, see, inter alia: (a) Magnus, P.; Ollivier, C. *Tetrahedron Lett.* **2002**, *43*, 9605. (b) Shipe, W. D.; Sorensen, E. J. *Org. Lett.* **2002**, *4,* 2063 (c) Nguyen, T. M.; Seifert, R. J.; Mowrey, D. R.; Lee, D. *Org. Lett.* **2002**, *4,* 3959. (d) Nakazaki, A.; Sharma, U.; Tius, M. A. *Org. Lett.* **2002**, *4*, 3363. (e) Mehta, G.; Umarye, J. D.; Srinivas, K. *Tetrahedron Lett.* **2003**, *44*, 4233. (f) Du, X.; Chu, H. V.; Kwon, O. *Org. Lett.* **2003**, *5*, 1923. (g) Brummond K. M.; Gao, D. *Org. Lett.* **2003**, *5*, 3491. (h) Hughes, C. C.; Kennedy-Smith, J. J.; Trauner, D. *Org. Lett.* **2003**, *5*, 4113. (i) Srikrishna, A.; Dethe, D. H. *Org. Lett.* **2004**, *6*, 168. (j) Chiu, P.; Li, S. *Org. Lett.* **2004**, *6*, 613.

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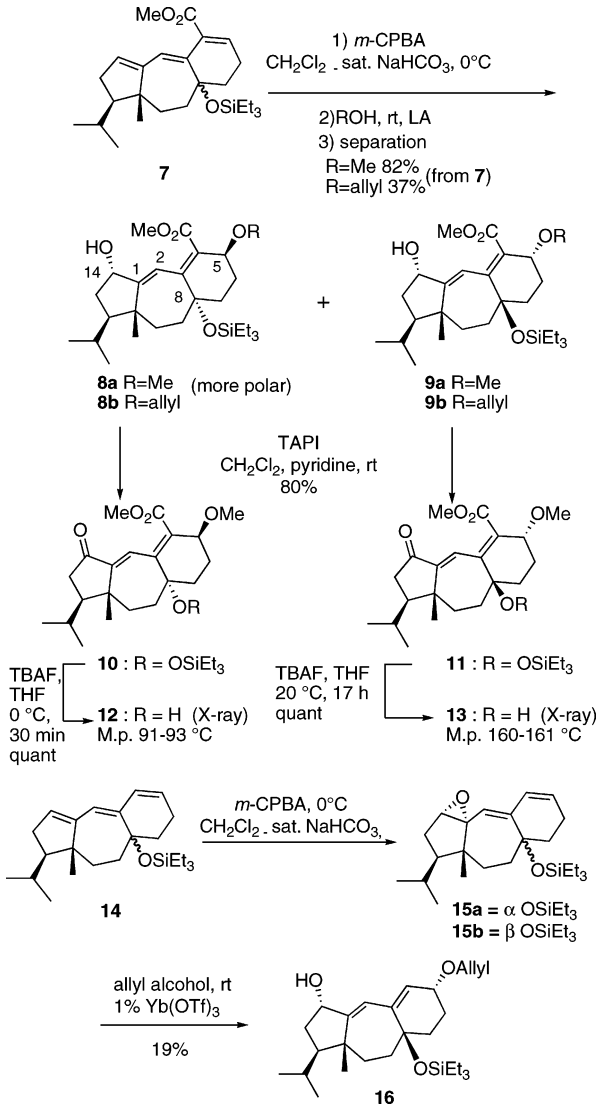
SCHEME 2



for 1 h at room temperature produced a 3:2 separable mixture of alcohols **5a** and **6a** in 56% overall yield from **3**. Under these conditions none of the 1,2-adduct was isolated. This reaction proceeded with high stereoselectivity: the nucleophilic attack of alcohol took place exclusively on the opposite face to the angular methyl group at C8 (guanacastepene numbering). When methanol was used instead allyl alcohol, **4** was converted to **5b** and **6b** (1:1.1 ratio) in 69% combined yield. To our knowledge 1,6-addition of alcohols to epoxydiene such as **4** is hitherto unprecedented.[10] This prompted us to further investigate the scope of this reaction. We report herein our finding.

To assess the effect of substituents on the tricyclic framework, trienes **7** and **14** were first studied. When epoxide derived from **7**[11] was treated with methanol in the presence of $CeCl_3$ or $Yb(OTf)_3$ a similar transformation was observed providing **8a** and **9a** (Scheme 2). The structure of these compounds was deduced from spectroscopic data,[12] and assignment of the relative configuration at C5, C8, and C14 was unambiguously established on the basis of the following transformations. Alcohols **8a** and **9a** were separately oxidized with Dess–Martin's periodinane reagent[13] to ketones **10** and **11,** respectively, and the protecting silyl group was cleaved to afford hydroxyketones **12** and **13**.[14] These compounds are crystalline, and their structures were confirmed by X-ray crystallographic analysis. In the same way, triene **7** furnished allyl ethers **8b** and **9b** albeit in lower yield (37%).[15] Thus, replacing the methyl group by $OSiEt_3$ at C8 has no effect on the regio- and stereoselectivity of the reaction. As for **4**, the stereochemical outcome of this S_N2' process is governed by the substituent at C8.

In an attempt to explore the effect of the ester group at C4, triene **14**[11] was submitted to the above-described conditions. As in preceding examples, oxidation of **14** with *m*-CPBA at 0 °C in CH_2Cl_2 and saturated aqueous $NaHCO_3$ was chemo- and stereoselective producing a mixture of two diastereomeric epoxides **15a** and **15b** as deduced from NMR spectra. However, treatment of the crude epoxide with allyl alcohol in the presence of catalytic $Yb(OTf)_3$ led to a mixture from which only one isomer, alcohol **16**, was isolated in low yield (19%).[15] A similar result was obtained with methanol as nucleophile. Thus, removal of the electron-withdrawing ester group presumably destabilizes the dienyl system and may explain the low yield and the loss of the other isomer.

To gain insight into the effect of the cyclic structure, we have designed vinyl epoxides allowing the selective incorporation of alkoxy substituents into various bicyclic frameworks. First epoxides derived from dienes **17**[8c] and **18**[16] were submitted to the conditions described above. As shown in Scheme 3, while both substrates undergo exclusively 1,4-addition, a reversal of stereoselectivity was observed. In contrast to tricyclic epoxides, additions occurred preferably *anti* to the leaving group producing mainly *trans* 1,4-dioxygenated compounds. In the event, addition of either methanol or allyl alcohol to the epoxide derived from **17** in the presence of $Yb(OTf)_3$ (1%) furnished a 7:3 separable mixture of **19 (21)** and **20 (22)** in 68–76% overall yield. Roughly the same result was obtained in the presence of catalytic cerium chloride. Similarly, **18** gave diastereomers **23 (25)** and **24 (26)** in

(10) For palladium-catalyzed alkylation of dienyl epoxides, see: Trost, B. M.; Urch, C. J.; Hung, M.-H. *Tetrahedron Lett.* **1986**, *27*, 4949.

(11) Boyer, F.-D.; Hanna, I. *Tetrahedron Lett.* **2002**, *43*, 7469.

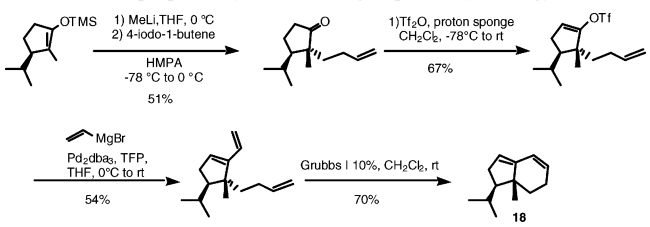
(12) As for **5** and **6**,[6] diastereomers **8** and **9** exhibit strike differences in their NMR spectra. In particular, while **9** showed sharp signals for all carbon atoms, many of its diastereomer were broad or hardly observed (see the Supporting Information).

(13) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155. Meyer, S. D.; Schreiber, S. L. *J. Org. Chem.* **1994**, *59*, 7549.

(14) While cleavage of the silyl ether in **10** with TBAF in THF was very easy (0 °C, 30 min, quantitative yield), complete conversion of **11** to **13** necessitated longer time and higher temperature (17 h, rt).

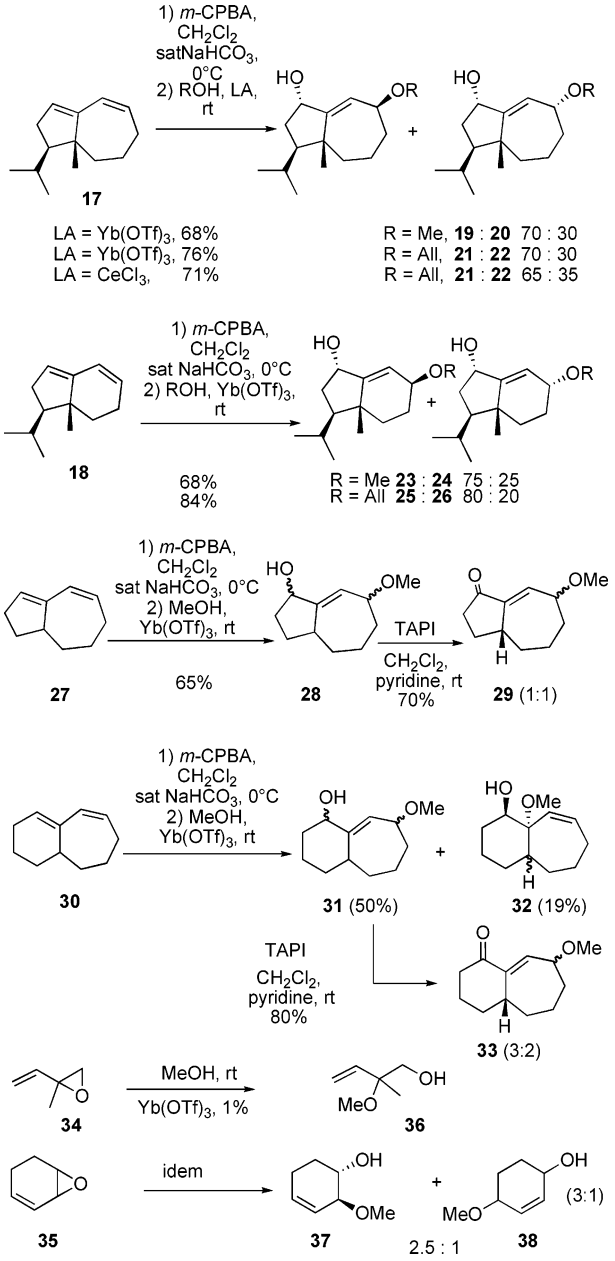
(15) The structure of **16** were deduced from its NMR spectra in comparison with those **8** and **9** (see ref 12).

(16) **18** was prepared by the following sequence by analogy with **17**[8c]:



Details concerning the preparation of bicylic dienes **27** and **30** will be reported shortly.

SCHEME 3



good overall yield. None of the 1,2-adducts were isolated (Scheme 3). It is noteworthy that palladium-catalyzed addition of oxygen nucleophiles to vinyl epoxide prepared from **17** proceeded with the opposite stereoselectivity.[17]

Subjecting the vinyl epoxide derived from **27** to the ring-opening conditions with methanol afforded **28** as a mixture of stereoisomers, which upon oxidation led to α,β-unsaturated ketone **29** as a mixture of two diastereomers in a 1:1 ratio (Scheme 3). As with precedent examples, a complete regioselectivity was observed: nucleophilic attack occurred exclusively at the vinyl epoxide terminus. However, lack of methyl and isopropyl groups in the starting diene led to a complete loss of stereoselectivity.

In contrast to the above epoxides, the nucleophilic addition regioselectivity was marginal when the five-membered ring was replaced with a six membered-ring as in diene **30**. In this case, both 1,4- and 1,2-addition products **31** and **32**, respectively, were obtained in a 2.5:1 ratio. The structure of the major regioisomer was deduced from its spectroscopic data and confirmed by its oxidation to the corresponding α,β-unsaturated ketone **33** (ν_{max} 1685 cm^{-1}).

Lewis acid catalyzed addition of alcohols to simple vinyloxiranes such as isoprene monooxide **34** and cyclohexadiene monooxide **35** proceeded mainly via an S_N2 process. While **34** led exclusively to 1,2-addition product **36**,[18] cyclic epoxide **35** gave a mixture of 3,4- and 3,6-dioxygenated cyclohexenes **37** and **38** (3:1), respectively, in a 2.5:1 ratio (Scheme 3).[19] These results are best in accord with the known behavior of vinyl epoxides in the presence of acids.

In summary, we have shown that, unlike simple vinyloxiranes, Lewis acid catalyzed addition of alcohols to tricyclic dienyl epoxides such as **4** or bicyclic vinyl oxiranes such as **17** exclusively occurred at the vinyl terminus of unsaturated system through a typical S_N2' process. This regioselectivity is the result of the domination of steric factors at the cyclopentene part which direct the attack at the most remote end of the unsaturated system. These findings bear directly on synthetic efforts toward guanacastepene and highlight the variability of region- and stereoselectivity of oxygen nucleophiles in various triene monoepoxides.

Experimental Section

Representative Procedure for the Preparation and the Ring Opening of Epoxides.

Allyl Ethers 5a and 6a. *m*-CPBA (80%, 80 mg) was added to a biphasic mixture of **3** (116 mg, 0.369 mmol), CH_2Cl_2 (1.5 mL), and saturated aqueous sodium bicarbonate (1.5 mL) at 0 °C. The heterogeneous mixture was stirred vigorously for 30 min and then quenched with saturated sodium sulfite (0.2 mL). The mixture was stirred for 15 min while slowly warming to room temperature. The CH_2Cl_2 layer was separated, and the aqueous layer was extracted three times with CH_2Cl_2. The combined organic layers were washed with saturated $NaHCO_3$ and brine, dried ($MgSO_4$), and evaporated under reduced pressure to give 132 mg of crude epoxide **4**, which was used without further purification in the next reaction.

To a solution of the above crude in allyl alcohol (1.0 mL) was added at room temperature ytterbium triflate hydrate [$Yb(OTf)_3$] (3 mg, 4.8 μmol, 0.013 equiv). After being stirred at room temperature for 1 h, allyl alcohol was removed under reduced pressure and the residue was purified by flash chromatography on silica gel (EtOAc/PE 1:4). Concentration of the appropriate fractions afforded 32 mg (22%) of **5a** as colorless oils and 48 mg (34%) of **6a** (major, more polar isomer). **Allyl Ether 5a.** Colorless oil. R_f: 0.35 (EtOAc/PE 1:4). ^1H NMR: δ

(17) In their study on the synthesis of guanacastepene, Snider and co-workers reported preparation of an analogue to **20** (R = OAc) using palladium-catalyzed (Pd_2dba_3 and dppb) opening of the epoxide ring.[8c]

(18) For 1,2-asymmetric additions of alcohols to isoprene monoepoxide, see: Trost, B. M.; McEachern, E. J.; Toste, F. D. *J. Am. Chem. Soc.* **1998**, *120*, 12702.

(19) NMR spectra of **31** are identical to those described in ref 4c. The regio- and stereochemistry of **33** was determined as follows: oxidation of the inseparable mixture of diastereomers afforded a single enone whose structure was deduced from spectroscopic data.

6.07 (br s, 1 H), 5.95−5.85 (m, 1 H), 5.23 (d, J = 17.2 Hz, 1 H), 5.13 (d, J = 10.3 Hz, 1 H), 4.55 (d, J = 9.6 Hz, 1 H), 4.30 (t, J = 5.9 Hz, 1 H), 4.09 (dd, J = 12, 5.6 Hz, 1 H), 3.96 (dd, J = 12, 5.6 Hz, 1 H), 3.72 (s, 3 H), 2.15−1.50 (m, 8 H), 1.43 (t, J = 7.8 Hz, 1 H), 1.35−1.15 (m, 3 H), 1.14 (s, 3 H), 1.10−1.00 (m, 1 H), 0.98 (s, 3 H), 0.92 (d, J = 6.6 Hz, 3 H), 0.85 (d, J = 6.6 Hz, 3 H). ^{13}C NMR: δ 169.0 (C), 155.6 (C), 149.6 (C), 135.4 (CH), 129.0 (C), 117.9 (CH_2), 116.5 (CH), 73.6 (CH), 71.3 (CH_2), 70.3 (CH), 53.3 (CH), 51.3(CH_3), 48.8 (C), 41.0 (C), 38.0 (CH_2), 36.3 (CH_2), 36.2 (CH_2), 35.9 (CH_2), 30.6, 29.2, 24.1 (CH_2), 23.3 (CH_3), 22.1 (CH_3), 15.9 (CH_3). IR (CCl_4): 3612, 1720 cm^{-1}.

Allyl Ether 6a. Colorless oil. R_f: 0.45 (EtOAc/PE 1:4). ^{1}H NMR: δ 6.04 (br s, 1 H), 5.95−5.84 (m, 1 H), 5.23 (d, J = 17.2 Hz, 1 H), 5.13 (d, J = 10.3 Hz, 1 H), 4.41 (br s, 1 H), 4.32 (br s, 1 H), 4.07 (dd, J = 12, 5.6 Hz, 1 H), 3.99 (dd, J = 12, 5.6 Hz, 1 H), 3.70 (s, 3 H), 2.15−1.50 (m, 10 H), 1.45−1.15 (m, 3 H), 1.04 (s, 3 H), 0.97 (d, J = 6.6 Hz, 3 H), 0.94 (s, 3 H), 0.91 (d, J = 6.6 Hz, 3 H). ^{13}C NMR: δ 135.5 (CH), 116.5 (CH_2), 74.8 (br), 72.7 (br), 70.2 (CH_2), 51.3 (CH_3), 39.3, 37.5, 37.0, 36.6, 34.8, 29.7, 28.1, 23.7, 22.4. The remains of the carbons gave signals that were too broad to be observed. IR (CCl_4): 3612, 1720 cm^{-1}.

Acknowledgment. We gratefully thank Dr. Louis Ricard (Ecole Polytechnique) for the X-ray structure determination of compounds **12** and **13**.

Supporting Information Available: Experimental procedure, characterization data of compounds **5**, **6**, **8**−**13**, **16**, **19**−**23**, **25**, **29**, and **33**, X-ray analysis of **12** and **13,** and copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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