JOC The Journal of Organic Chemistry

ARTICLE

pubs.acs.org/joc

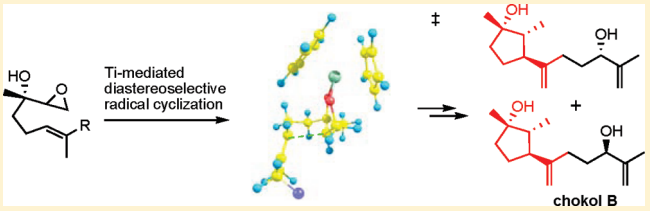
Protecting-Group-Free Synthesis of Chokols

Carmen Pérez Morales, Julieta Catalán, Victoriano Domingo, José A. González Delgado, José A. Dobado, M. Mar Herrador, José F. Quílez del Moral,* and Alejandro F. Barrero*

Department of Organic Chemistry, University of Granada, Avda. Fuentenueva, 18071 Granada, Spain

Supporting Information

ABSTRACT: As a result of a combined theoretical and experimental study, we describe a two-step protocol for the preparation of an optically pure, multifunctional, cyclopentanic core shared by a number of natural products. This process is based on a hitherto unreported Ti(III)-mediated diastereoselective cyclization in which the hydroxy-directed template effect played by the Ti(III) species was found to be crucial for the stereoselective outcome of the reaction. The viability of this concept was confirmed with the first protecting-group free synthesis of three enantiopure chokols, namely, chokols K, E, and B.



INTRODUCTION

A number of terpenoid compounds of different origin share a common structural motif consisting of a cyclopentanic unit with contiguous asymmetric centers (Figure 1).[1] These structures include sesquiterpenes in the form of chokols. Chokols are 2,6-cyclofarnesanes isolated from the stroma of the timothy-grass *Phleum pratense* infected by the endophytic fungus *Epichloe typhina* and have been reported to have antifungal properties. They have thus attracted significant interest over the years, and in fact the enantioselective synthesis of chokols A, C, and G has already been achieved.[2]

Although cyclopentanes are common structural motifs in natural compounds, the synthesis of these structures is often lengthy and tedious, especially when these blocks are highly functionalized, although noteworthy synthetic efforts have been recently published.[3] Within this context, we believe that structure **1**, which contains suitable functionalities to lead to further synthetic steps, may well serve as a versatile building block for the stereoselective synthesis of these kinds of compounds. Consequently we embarked on a project aimed at developing an expedient, practical route to **1**[4] and its application to the synthesis of bioactive chokols.

RESULTS AND DISCUSSION

Bearing in mind the concept of step economy,[5] our approach to this cyclopentanic structure involved as a single step a Ti(III)-mediated,[6] stereocontrolled cyclization of the 1,2-monoepoxy derivative of commercially available enantiopure (−)-linalool (**2**). Taking into account the Lewis acid character of titanocene(III) and its reported ability to exert a template effect during pinacol couplings[7] and in the regioselective opening of 2,3-epoxy alcohols,[8] we anticipated that this effect might play a determining role in the stereochemical outcome of the key 5-*exo*-*trig* cyclization,[9] in which the cyclic complex **A** is proposed to be involved (Scheme 1). Since two stereogenic centers are formed in the cyclization of **I** to **II**, apart from the desired cyclopentanic core **1**, three other distereomers may be well created.

To evaluate the feasibility of our approach, theoretical studies[10] through DFT methods (UM05/Ahlrichs-pVDZ)[11] were undertaken to provide the crucial reaction and activation energies of the key cyclization process leading from the acyclic radicals **Ia**−**d** to the cyclopentane radicals **IIa**−**d**.[12] These studies are summarized in Figure 2, which also sets out the relative energies of the four possible cyclic radicals **IIa**−**d**. In summary, these calculations showed that the process involving intermediate **Ia**, which should finally lead to compound **1**, presents the most favorable thermodynamic and kinetic data in support of our hypothesis.

Encouraged by the computational results, we went on to address the experimental studies that should corroborate the applicability of our synthetic proposal. We started by subjecting the commercially available (−)-linalool **2** to Sharpless experimental conditions to epoxidize chemoselectively the terminal double bond,[13] thus giving a diastereomeric mixture of monoepoxides **3** in a molecular ratio close to unity. We then allowed this mixture to react with a 0.3 equiv of Cp_2TiCl_2, an excess of Mn, and a collidine/TMSCl mixture as regenerator.[6] In this way, we found six products, that is, **1** and **4**−**8**, (Table 1, entry 1), with the *cis*-tetrahydrofuran **6**[14] and the desired cyclopentane **1** obtained as major products. These compounds were isolated with the help of the semi/preparative HLPC, and their structure and stereochemistry unequivocally assigned by mass and exhaustive NMR spectroscopy, including bidimensional NOE-DIFF experiments. Noteworthy here is the fact that under these experimental conditions, where the excess of TMSCl precludes the formation of the cyclic Ti(IV) complex **A**

Received: November 16, 2010
Published: March 10, 2011

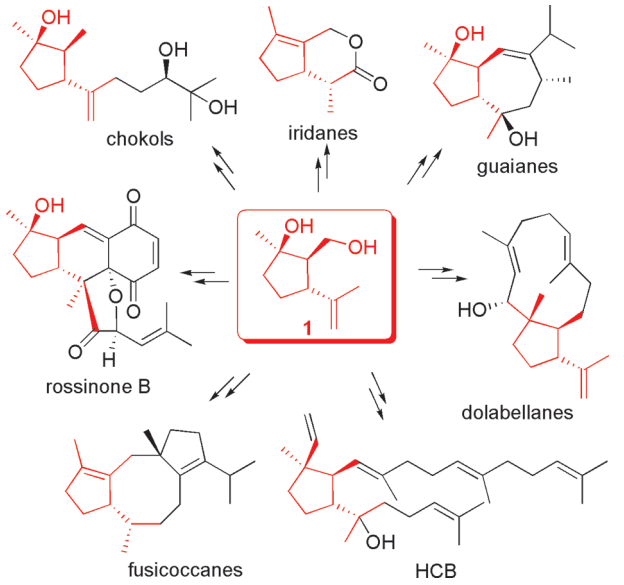


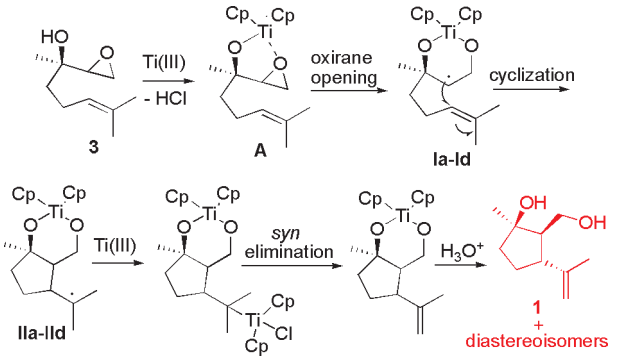
Figure 1. Natural products sharing the cyclopentanic core **1**.

(Scheme 1), no relevant diastereoselectivity was observed. At this point, to ensure the generation of the type **A** complex, a mixture of epoxides **3**[15] was allowed to react with 2.1 equiv of Cp_2TiCl_2 and 8 equiv of Mn at room temperature. To our delight, we found that compounds **4** (53% yield) and **1** (12% yield), both of them sharing the same desired stereochemistry at the two contiguous stereogenic centers generated in the cyclization, were then the main products (Table 1, entry 2). No traces of compounds **7** and **8** were detected, whereas tetrahydrofuran **6**, the main compound when substoichiometric Ti(III) was used, was found only in very minor quantities. The remarkable difference in the results obtained when either substoichiometric or 2 equiv of Ti(III) was employed confirmed the determining role played by Cp_2TiCl in driving the stereochemical outcome of the reaction, as suggested by the theoretical calculations.

Encouraged by the highly diasteroselective formation of **4** and **1** in the stoichiometric version and bearing in mind that the unsaturation present in the olefinic derivative **1** would guarantee further bond forming events at this site in the molecule, we then turned our efforts to diminishing the quantity of the product formed from a reductive termination step (protonation of the alkyltitanium intermediate in Scheme 1), namely, **4**. To this end, and bearing in mind that the formation of **4** may be due to the presence of the HCl generated in the synthesis of complex **A**, the cyclization was carried out in the presence of three different bases: triethylamine, 2,4,6-collidine, and DBU (Table 1, entries 3−7). In the event, the addition of 1 equiv of Et_3N meant a significant improvement in the formation of the unsaturated **1**. The quantity of base required in this process was optimized, the best results being obtained when 2 equiv of Et_3N was used. When cyclization was carried out in the presence of 2,4,6-collidine, compound **4** turned out to be the main product. Finally, the results obtained with DBU were comparable to those obtained with Et_3N, although the latter proved to be slightly more efficient. Furthermore, compound **1** was found to crystallize from a hexane/ether solution of the mixture of the reaction products, which further facilitates the preparation in multigrams scale of this versatile cyclopentanic fragment.

Once we had developed a way of gaining access to this building block in only two steps, we focused our efforts on confirming the

Scheme 1. Synthetic Approach for 1: Mechanistic Details



viability of its use in the synthesis of chokols K, E and B as representative examples of the natural structures included in Figure 1. To the best of our knowledge, no previous asymmetric synthesis of either chokol K, E, or B[16] (**9**, **10** and **15**) has been published. Herein we present a stereoselective route to the enantiomers of these compounds using the approach described and without the assistance of protecting groups,[17] a method that might compete favorably with previous efforts to synthesize this kind of compounds.[18]

Since the targeted chokols contain 15 carbon atoms, our plan to synthesize these cyclopentanic structures included the use as starting material of the naturally occurring (+)-nerolidol **12**,[19] the C15 homologue of (−)-linalool, in the hope that the key Ti(III)-mediated cyclization of the corresponding 1,2-monoepoxy derivative (**13**) would proceed with similar efficiency and diastereoselectivity to those obtained with (−)-linalool. In the event, exposure of **13** to 2 equiv of Cp_2TiCl_2, 2 equiv of Et_3N, and an excess of Mn led to a 68% yield of the desired cyclopentanic structure **14**, isolated easily by crystallization from the crude of the reaction, with its three stereogenic centers possessing the requisite stereochemistry (Scheme 2). From compound **14**, the completion of the synthesis of chokol K requires only the deoxygenation of the primary alcohol. After a good deal of experimentation we found that this conversion could be efficiently achieved without the need of orthogonal protecting groups by using the chemoselective conversion of the primary alcohol to its xanthate derivative, which was then reduced with Bu_3SnH in the presence of AIBN to furnish chokol K (**9**). Synthetic **9** was found to display identical spectroscopic properties when compared to natural chokol K.[16] Nevertheless, the optical rotation $[\alpha]_D$ value of synthetic **9** (+28.7°, *c* 1.0, EtOH) was found to be opposite to that of natural chokol K (−32.8°, *c* 0.05, EtOH), which although allowing us to confirm the absolute configuration of the natural product, proved that our synthesis leads to its enantiomer. Once the synthesis of (+)-chokol K was achieved, we decided to address the synthesis of its congeners chokol E and B. At this point it should be remarked that, as indicated in ref 16, some controversy exits concerning the configuration at C-10 of chokol B; thus, although Tajimi et al. did not assign this configuration in the paper reporting the isolation of this compound,[20] later on it was reported that the natural product consisted of *ca.* 1:1 mixture of diastereisomers. Then, to contribute to the solution of this discrepancy, the synthesis of the two possible epimers constituting (+)-chokol B (**11a** and **11b**) was addressed (Scheme 2). In our approach to **11a** and **11b**, we

dx.doi.org/10.1021/jo102280n |*J. Org. Chem.* 2011, 76, 2494–2501

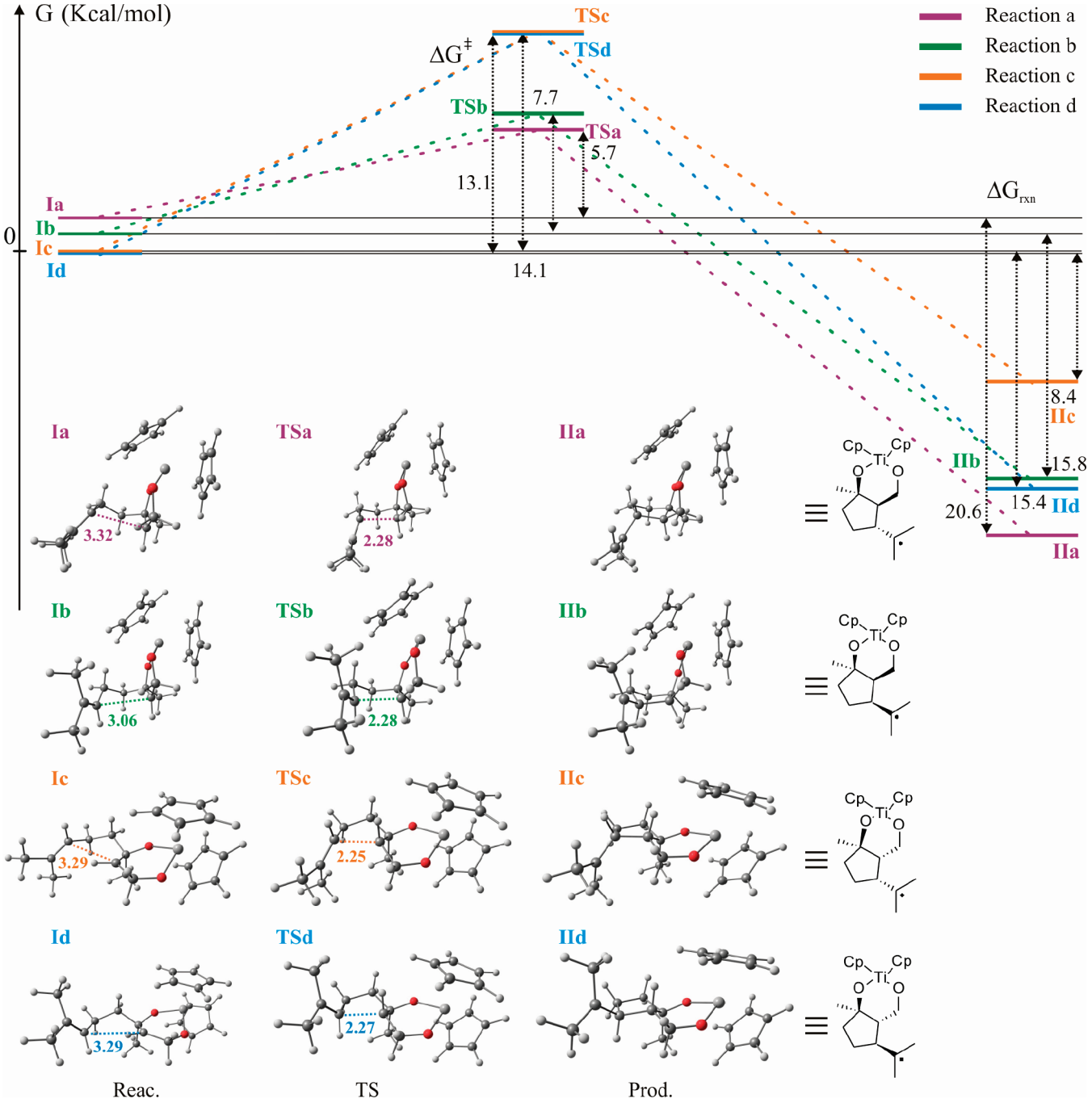


Figure 2. Gibbs free energies of activation ($\Delta G^{\ddagger}$), energies of reaction (ΔG_{rxn}), and relative energy (E_{rel}) of the products for the ring closing leading from **I** to **II**, at the M05/Ahlrichs-pVDZ theoretical level.

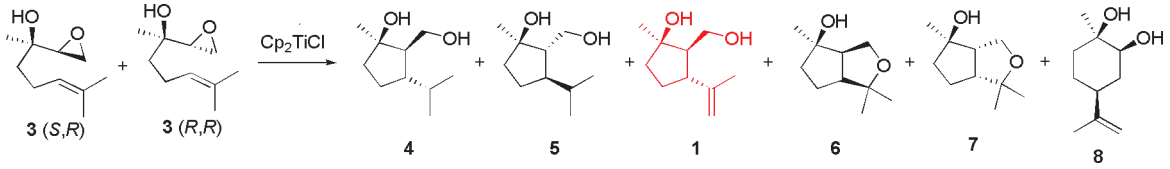
also prepared not only chokol E (**10**) but also its epimer at C-10 (**15**), which also allowed us to confirm the stereochemistry assigned to this natural compound.

To conclude the synthesis of chokol E from chokol K, the chemo- and diastereoselective dihydroxylation of **9** was required. To this end, and considering the usual selective outcome of Sharpless asymmetric dihydroxylation,[21] diene **9** was treated with AD-mix α. Unfortunately, the reaction proceeded with no diastereoselectivity, and (+)-chokol E (**10**) was obtained together with its C-10 epimer (**15**) at 1:1 ratio. However, when chokol K (**9**) was treated with AD-mix *β*, compound **15** was produced as the only detectable stereoisomer. Although the NMR data of compounds **10** and **15** and those reported for natural chokol E were almost superimposable (see Table 2 in Supporting Information), slight differences in the ^{1}H NMR chemical shift of the methylene protons (in natural chokol E: *δ* 4.78 and 4.82 ppm) led us to confirm the stereochemical assignment of chokol E (Figure 3). Finally, and as expected the signs of the optical rotation $[\alpha]_D$ of our synthetic (+)-**10** and of the natural compound were opposite.[20]

Conversion of triols **10** and **15**, respectively, into the two possible epimers that should constitute chokol B, namely,

dx.doi.org/10.1021/jo102280n |*J. Org. Chem.* 2011, 76, 2494–2501

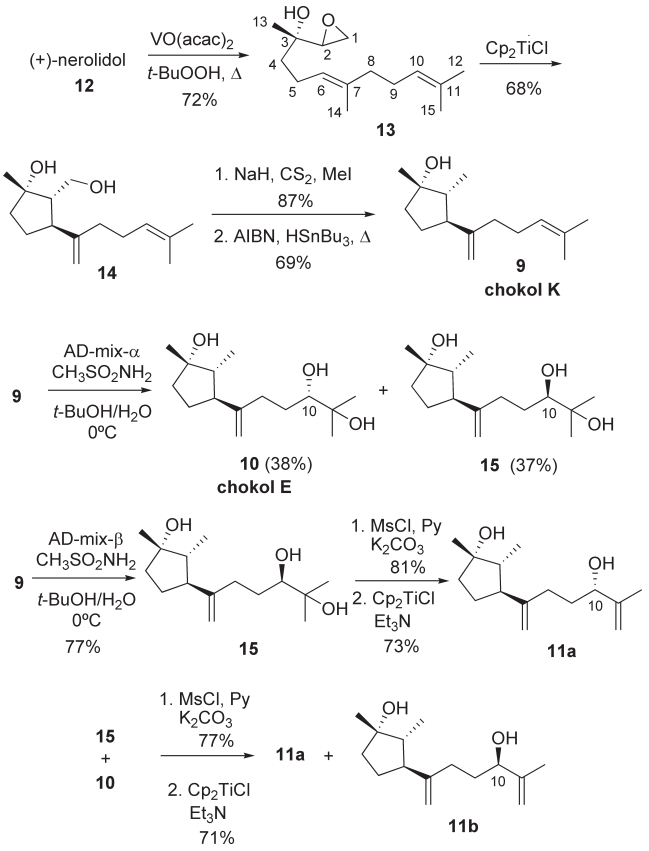
Table 1. Ti(III)-Mediated Diastereoselective Cyclization of 3



			yield (%)					
entry	Ti(III) (equiv)	base (equiv)	4	5	1	6	7	8
1[a]	0.3		5	9	20	22	3	7
2	2.1		53	*c*	12	*c*		
3	2.1	Et_3N (1)	13	*c*	55	*c*		
4	2.1	Et_3N (2)	10	*c*	66	*c*		
5	2.1	Et_3N (4)	8	*c*	60	*c*		
6[b]	2.1	collidine (2)	35	10	22	*c*		
7	2.1	DBU (2)	9	*c*	56	*c*		

[a] An excess of Mn and a collidine/TMSCl mixture as regenerator were also added to the reaction mixture. [b] An approximate 10% yield of a nonassigned stereoisomer of **1** was also formed. [c] Minor quantities (~5%) of the corresponding isomers were detected.

Scheme 2. Synthesis of 9, 10, 11, and 15



11a and **11b**, was undertaken via the titanocene(III)-mediated epoxide opening of the oxirane derived from treating **10** and **15** with mesyl chloride and base, following a procedure recently described by Justicia et al.[22] According to this work, olefins **11a** and **11b** were formed via a mixed disproportation process of the β-titanoxy radical originated after the homolytic opening of the oxirane. As a result of this process, diol **11a** (from **15**) and the mixture of epimers **11a** and **11b** (from **15** + **10**) were satisfactory obtained with yields up to 70%. Unfortunately, the proton NMR spectrum of **11a** and **11b** were undistinguishable, and only a few carbons presented differences in their ^{13}C NMR spectrum, none of them higher than 0.2 ppm (Figure 4). These overlappings, together with the fact that no optical rotations were reported for the natural product,[20] made it impossible to clarify the ambiguity regarding the C-10 configuration of chokol B, the most active of these fungitoxic sesquiterpenes.

In summary, via a combined theoretical and experimental study we have developed an expedient two-step procedure for the distereoselective preparation of an optically pure cyclopentanic core **1**, with (−)-linalool serving as chiral pool precursor. This process is based on the hydroxy-directed template effect played by the Ti(III) species in the radical cyclization of the corresponding acyclic precursor. The addition of Et_3N was found to be crucial for increasing the quantities of products deriving from an oxidative termination step. Cyclopentane **1** contains peripheral functional groups suitable for appending additional substituents, thus rendering the strategy viable for the synthesis of different natural products. The feasibility of this concept has been established with the first synthesis of three enantiomers of natural chokols. Most notably, the synthesis of these sesquiterpenes has been achieved in four, five, and seven steps, respectively, without the use of protecting groups, and apart from the deoxygenation of the primary alcohol, the oxidation states of the intermediates gradually rose from beginning to end.

EXPERIMENTAL SECTION

General Procedure for the Stoichiometric Cyclization of 3 Using Different Bases. A mixture of Cp_2TiCl_2 (522 mg, 2.50 mmol) and Mn dust (523 mg, 9.51 mmol) in strictly deoxygenated THF (6.63 mL) was stirred at room temperature until the red solution turned green. Then, a solution of **3** (200 mg, 1.19 mmol) and the corresponding base in strictly deoxygenated THF (2.84 mL) was added to the solution of Cp_2TiCl. After starting material consumption (TLC analysis), the

dx.doi.org/10.1021/jo102280n |J. Org. Chem. 2011, 76, 2494–2501

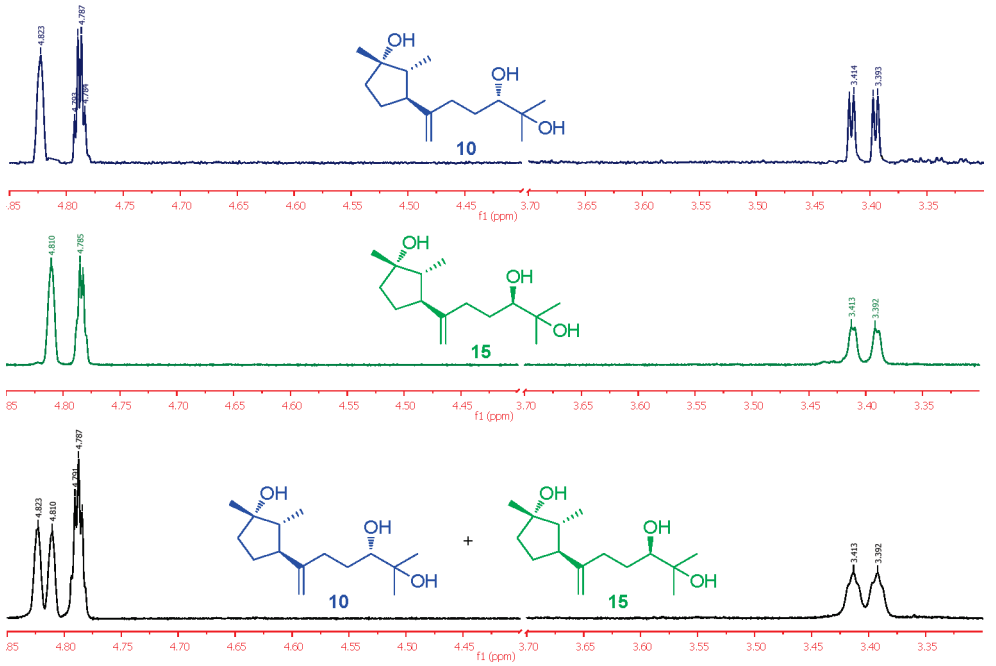


Figure 3. Comparison between the ^{1}H NMR spectra of **10**, **15**, and **10** + **15** (range 3.30−4.85 ppm).

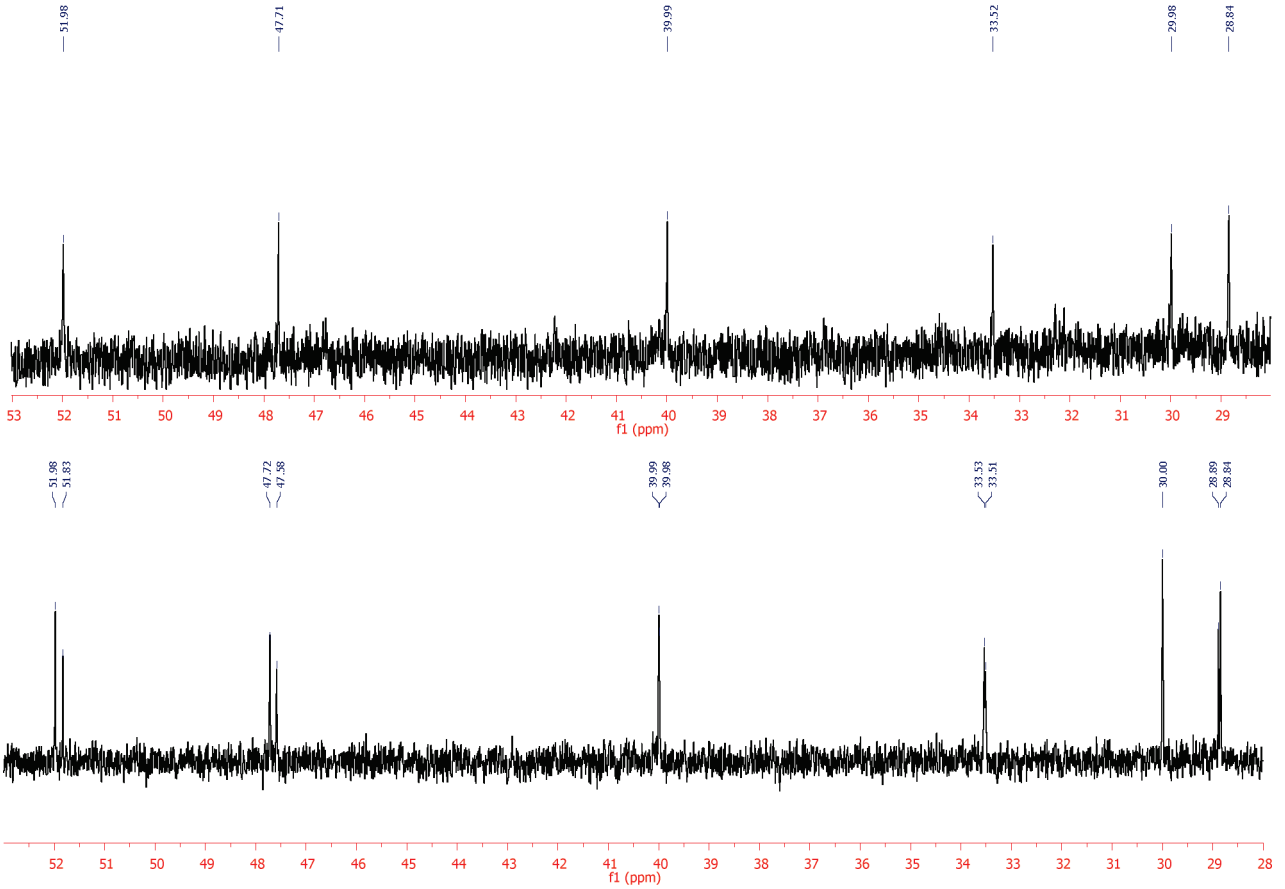


Figure 4. Comparison between the ^{13}C NMR spectra of **11a** and **11a** + **11b** (range 28−52 ppm).

mixture was diluted with MTBE, filtered, quenched with 2 N HCl, extracted with MTBE, washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The resulting crude was purified by column chromatography (hexane/MTBE, 1:1) on silica gel

dx.doi.org/10.1021/jo102280n |*J. Org. Chem.* 2011, 76, 2494–2501

to give the corresponding cyclization products specified in Table 1 (see article body).

Extraction and Isolation of (+)-Nerolidol from *Inula viscosa*. *Inula viscosa* (also known as olivarda) was collected in the northwestern outskirts of the city of Granada (Spain), in May 2009. The aerial parts of the plant (8 kg) were macerated in MTBE for 20 min resulting in 60 g of extract. A 30 g fraction was dissolved in MTBE (1250 mL) and extracted with 1 N NaOH solution (4 × 150 mL) to yield 8.7 g of neutral fraction and 19.5 g of acid fraction. The neutral fraction was column chromatographed using mixtures of hexane/MTBE of increasing polarity. The fraction eluted with hexane/MTBE (1:2) consisted of 1.550 g of (+)-nerolidol **12**. Colorless oil, $[\alpha]^{20}_D = +12.2$ (*c* 1.0, $CHCl_3$).[23]

(+)-1,2-Epoxy-1,2-dihydronerolidol (13). A mixture of (+)-nerolidol **12** (2.98 g, 13.40 mmol) and $VO(acac)_2$ (172 mg, 0.67 mmol) in benzene (178 mL) was refluxed for 10 min under argon. Addition of *t*-BuOOH 5−6 M in decane (5 mL) followed, and stirring continued at this temperature for 10 min. After cooling, the mixture was diluted with EtOAc, washed with saturated $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The resulting crude was purified by column chromatography (hexane/MTBE, 3:1) on silica gel to afford 2.30 g (72% overall yield) of mixture of epimers **13**.

(+)-1-Hydroxychokol K (14). A mixture of Cp_2TiCl_2 (1.54 mg, 6.17 mmol) and Mn dust (1.29 g, 23.51 mmol) in strictly deoxygenated THF (23.17 mL) was stirred at room temperature until the red solution turned green. Then, a solution of the corresponding mixture of **13** (700 mg, 2.93 mmol) and Et_3N (0.82 mL, 5.87 mmol) in strictly deoxygenated THF (9.87 mL) was added to the solution of Cp_2TiCl. The reaction mixture was stirred until disappearance of the starting material (15 min). After starting material consumption (TLC analysis), the mixture was diluted with MTBE, filtered, and quenched with 2 N HCl, extracted with MTBE, washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The resulting crude was purified by column chromatography (hexane/MTBE, 1:1) on silica gel to afford 476 mg (68% overall yield) of **14**. Colorless oil, $[\alpha]^{20}_D = +36.69$ (*c* 1.0, CH_2Cl_2); IR (film) 3367, 2963, 2927, 1640, 1453, 1376, 1057, 1057, 889 cm^{-1}; ^{1}HNMR (500 MHz, $CDCl_3$) δ 5.11 (t, *J* = 6.9 Hz, 1H), 4.82 (bs, 1H), 4.78 (bs, 1H), 3.89 (dd, *J* = 11.3, 2.9 Hz, 1H), 3.70 (dd, *J* = 11.3, 5.0 Hz, 1H), 2.82 (q, *J* = 9.5 Hz, 1H), 2.50 (bs, 2OH), 2.14 (m, 2H), 2.04−1.94 (m, 3H), 1.82−1.63 (m, 3H), 1.68 (s, 3H), 1.61 (s, 3H), 1.50−1.43 (m, 1H), 1.39 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.3, 131.6, 124.1, 108.5, 81.5, 61.8, 53.2, 46.1, 41.6, 38.8, 29.0, 28.5, 26.7, 25.6, 17.7 ppm; HRCIMS calcd for $C_{15}H_{26}O_2$ $[M - H]^+$ 237.1855, found 237.1852.

(+)-Chokol K (9). A mixture of **14** (200 mg, 0.84 mmol) and carbon disulfide (0.2 mL, 3.36 mmol) was dissolved in tetrahydrofuran (4 mL). A solution of sodium hydride 60% in mineral oil (40 mg, 1.01 mmol) in tetrahydrofuran (6 mL) was added to the solution of alcohol to 0 °C. This mixture was stirred for 1 h 30 min under argon atmosphere at room temperature. Then, methyl iodide (0.42 mL, 6.71 mmol) was added, and the mixture was stirred for 5 min. The reaction mixture was diluted with MTBE and washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The resulting crude was purified by column chromatography (hexane/MTBE, 3:1) on silica gel to afford 239 mg (87% overall yield) of the corresponding xanthate. A mixture of the xanthate (140 mg, 0.43 mmol), AIBN (7 mg, 0.04 mmol), and $HSn(Bu)_3$ (372 mg, 0.34 mmol) in strictly deoxygenated toluene (27 mL) was refluxed for 10 min under argon. The reaction mixture was purified directly by column chromatography (hexane/MTBE, 1:1) on silica gel to afford 64 mg (69% overall yield) of (+)-chokol K **9**. Colorless oil, $[\alpha]^{20}_D = +36.1$ (*c* 1.0, CH_2Cl_2), + 28.7 (*c* 1.0, EtOH), for natural chokol K: −32.8. (*c* 0.05, EtOH); IR (film) 3436, 2963, 2361, 2342, 1639, 1452, 1376, 917, 886 cm^{-1}; ^{1}HNMR (500 MHz, $CDCl_3$) δ 5.13 (t, *J* = 6.9 Hz, 1H), 4.77 (bs, 1H), 4.76 (bs, 1H), 2.38 (q, *J* = 9.1 Hz, 1H), 2.13 (q, *J* = 7.5 Hz, 2H), 2.00−1.92 (m, 3H), 1.75 (t, *J* = 7.8 Hz, 2H), 1.69 (s, 3H), 1.61 (s, 3H), 1.55 (sextuplet, *J* = 6.6 Hz, 1H), 1.42 (dq, *J* = 8.1, 5.0 Hz, 1H), 1.28 (s, 3H), 0.87 (d, *J* = 6.5 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.7, 131.6, 124.4, 108.2, 80.4, 52.1, 47.6, 40.1, 33.8, 28.7, 26.9, 26.7, 25.8, 17.8, 10.7 ppm; HRCIMS calcd for $C_{15}H_{26}O$ $[M - H]^+$ 221.1905, found 221.1895.

(+)-10-*Epi*-chokol E (15). A mixture of **9** (65 mg, 0.29 mmol), *tert*-butyl alcohol (2.6 mL), and water (2.6 mL) was cooled to 0 °C. Then, we added $CH_3SO_2NH_2$ (28 mg, 0.29 mmol) and ADmix-β (408 mg, 0.41 mmol). The reaction mixture was stirred vigorously at 0 °C for 28 h. While the mixture was stirred at 0 °C, solid sodium thiosulfate (394 mg) was added, and the mixture was allowed to warm to room temperature and stirred for 30−60 min. Ethyl acetate and NaOH 5 M were added to the reaction mixture, and after separation of the layers, the aqueous phase was further extracted with ethyl acetate three times. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The resulting crude was purified by column chromatography (hexane/MTBE, 1:3) on silica gel to afford 57 mg (77% overall yield) of **15**. Colorless oil, $[\alpha]^{20}_D = +28.7$ (*c* 1.0, CH_2Cl_2); IR (film) 3408, 2964, 2932, 2874, 1639, 1458, 1377, 1159, 1079, 918 cm^{-1}; ^{1}HNMR (500 MHz, $CDCl_3$) δ 4.79 (bs, 1H), 4.77 (bs, 1H), 3.32 (d, *J* = 10.5 Hz, 1H), 2.32 (bq, *J* = 9.8 Hz, 1H), 2.22 (ddd, J = 14.8, 10.8, 5.1 Hz, 1H), 2.02−1.88 (m, 2H), 1.70 (m, 2H), 1.62−1.48 (m, 2H), 1.44−1.32 (m, 2H), 1.21 (s, 3H), 1.15 (s, 3H), 1.10 (s, 3H), 0.80 (d, *J* = 7.0 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.5, 108.1, 80.3, 78.2, 73.1, 51.5, 47.4, 39.8, 31.0, 29.8, 28.8, 26.6, 26.6, 23.2, 10.7 ppm; HRFABMS calcd for $C_{15}H_{28}O_3Na$ $[M + Na]^+$ 279.1936, found 279.1942.

(+)-Chokol E (10). A mixture of **9** (98 mg, 0.45 mmol), *tert*-butyl alcohol (4.0 mL), and water (4.0 mL) was cooled to 0 °C. Then, we added $CH_3SO_2NH_2$ (41 mg, 0.89 mmol) and ADmix-α (0.66 g, 0.16 mmol). The reaction mixture was stirred vigorously at 0 °C for 14 h. While the mixture was stirred at 0 °C, solid sodium thiosulfate (0.60 g) was added and the mixture was allowed to warm to room temperature and stirred for 30−60 min. Ethyl acetate and NaOH 5M, was added to the reaction mixture, and after separation of the layers, the aqueous phase was further extracted with ethyl acetate three times. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The resulting crude was purified by column chromatography (hexane/MTBE, 1:3) on silica gel to afford 85 mg (75% overall yield) of the mixture 1:1 of compounds **10**:**15**

A fraction enriched in compound **10** was subjected to HPLC (normal phase, hexane/MTBE, 1:1.5, t_R = 39.2 min) to give 5 mg of (+)-chokol E **10**. Colorless oil, $[\alpha]^{20}_D = +17.2$ (*c* 0.5, CH_2Cl_2), for natural chokol E: −15.8 (*c* 0.67, EtOH); IR (film) 3408, 2964, 2932, 2874, 1639, 1458, 1377, 1159, 1079, 918 cm^{-1}; ^{1}HNMR (500 MHz, $CDCl_3$) δ 4.82 (bs, 1H), 4.78 (bs, 1H), 3.40 (d, *J* = 10.5 Hz, 1H), 2.40 (bq, *J* = 9.8 Hz, 1H), 2.28 (ddd, J = 14.8, 10.8, 5.1 Hz, 1H), 2.08−1.93 (m, 2H), 1.77 (bt, 2H), 1.69−1.40 (m, 4H), 1.28 (s, 3H), 1.23 (s, 3H), 1.18 (s, 3H), 0.88 (d, *J* = 6.5 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.8, 108.4, 80.4, 78.5, 73.2, 52.1, 47.9, 40.1, 31.1, 30.1, 28.9, 26.7, 26.7, 23.4, 10.7 ppm.

Compound 11a. To a mixture of **15** (19 mg, 0.085 mmol), catalytic DMAP, and 1.2 mL of pyridine was added MsCl (0.04 mL, 0.51 mmol) at 0 °C. After stirring for 35 min at this temperature, the reaction mixture was diluted with MTBE, and saturated $NaHCO_3$ was added. Then, the aqueous phase was extracted three times with MTBE, and the organic phase was washed with HCl 2 N and with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude was dissolved in MeOH (1.29 mL), and K_2CO_3 (46 mg, 0.34 mmol) was added with stirring at room temperature for 20 min. Then, the reaction was diluted with MTBE, washed with HCl 2 N, saturated $NaHCO_3$, and brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The resulting crude was purified by column chromatography (hexane/MTBE, 1:1.5) on silica gel to afford 14 mg (81% overall yield)

of the corresponding epoxide. A mixture of Cp_2TiCl_2 (61.47 mg, 0.25 mmol) and Mn dust (51.72 mg, 0.94 mmol) in strictly deoxygenated THF (0.47 mL) was stirred at room temperature until the red solution turned green. Then, a solution of the corresponding epoxide (14 mg, 0.058 mmol) and Et_3N (0.032 mL, 0.23 mmol) in strictly deoxygenated THF (0.19 mL) was added to the solution of Cp_2TiCl. The reaction mixture was stirred until consumption of the starting material (1 h). The mixture was diluted with MTBE, filtered through a Büchner, and washed with 2 N HCl and brine, and the resultant organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting crude was purified by column chromatography (hexane/MTBE, 1:3) on silica gel to afford 10 mg (73% overall yield) of **11a**. Colorless oil, $[\alpha]^{20}_D = +8.15$ (*c* 1.0, CH_2Cl_2); IR (film) 3392, 3076, 2962, 2874, 1715, 1640, 1456, 1375, 1196, 1089, 919, 889 cm^{-1}; ^{1}HNMR (500 MHz, $CDCl_3$) δ 4.95 (bs, 1H), 4.85 (bs, 1H), 4.79 (bs, 1H), 4.78 (bs, 1H), 4.09 (t, *J* = 6.5 Hz, 1H), 2.39 (bq, *J* = 10.1 Hz, 1H), 2.11−2.05 (m, 2H), 2.02−1.94 (m, 2H), 1.78−1.64 (m, 3H), 1.74 (s, 3H) 1.46−1.39 (m, 2H), 1.28 (s, 3H), 0.80 (d, *J* = 6.5 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.5, 147.6, 111.2, 108.3, 80.4, 75.9, 52.0, 47.7, 40.0, 33.5, 30.0, 28.9, 26.7, 17.7, 10.7 ppm; HRCIMS calcd for $C_{15}H_{26}O_2$ $[M - H]^+$ 237.1855, found 237.1865.

Compounds 11a and 11b. To a mixture 1:1 of **10** + **15** (23 mg, 0.10 mmol), catalytic DMAP, and 1.4 mL of pyridine was added MsCl (0.05 mL, 0.62 mmol) at 0 °C. After stirring for 35 min at this temperature, the reaction mixture was diluted with MTBE, and saturated $NaHCO_3$ was added. Then, the aqueous phase was extracted three times with MTBE, and the organic phase was washed with HCl 2 N and with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude was dissolved in MeOH (1.56 mL), and K_2CO_3 (57 mg, 0. 41 mmol) was added with stirring at room temperature for 20 min. Then, the reaction was diluted with MTBE, washed with HCl 2 N, saturated $NaHCO_3$, and brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The resulting crude was purified by column chromatography (hexane/MTBE, 1:1.5) on silica gel to afford 17 mg (77% overall yield) of the corresponding epoxides.

A mixture of Cp_2TiCl_2 (43.90 mg, 0.18 mmol) and Mn dust (36.90 mg, 0.67 mmol) in strictly deoxygenated THF (0.33 mL) was stirred at room temperature until the red solution turned green. Then, a solution of the corresponding epoxides (10 mg, 0.04 mmol) and Et_3N (0.023 mL, 0.17 mmol) in strictly deoxygenated THF (0.13 mL) was added to the solution of Cp_2TiCl. The reaction mixture was stirred until consumption of the starting material (35 min). The mixture was diluted with MTBE, filtred through a Büchner, and washed with 2 N HCl and brine, and the resultant organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting crude was chromatographed on silica gel (hexane/MTBE, 1:3) to afford 7 mg (71% overall yield) of **11a** + **11b**. Colorless oil; IR (film) 3392, 3076, 2962, 2874, 1715, 1640, 1456, 1375, 1196, 1089, 919, 889 cm^{-1}; ^{1}HNMR (500 MHz, $CDCl_3$) δ 4.95 (bs, 1H), 4.84 (bs, 1H), 4.79 (bs, 1H), 4.78 (bs, 1H), 4.09 (t, *J* = 6.5 Hz, 1H), 2.39 (bq, *J* = 10.1 Hz, 1H), 2.11−2.05 (m, 2H), 2.02−1.93 (m, 2H), 1.78−1.64 (m, 3H), 1.74 (s, 3H) 1.46−1.39 (m, 2H), 1.28 (s, 3H), 0.87 (d, *J* = 6.5 Hz, 3H) ppm. Signals assignable to **11a**: ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.52, 147.63, 111.13, 108.27, 80.32, 75.83, 51.98, 47.72, 39.99, 33.51, 30.00, 28.84, 26.64, 17.65, 10.71 ppm. Signals assignable to **11b**: ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.5, 147.6, 111.0, 108.2, 80.3, 75.7, 51.8, 47.6, 40.0, 33.5, 30.0, 28.9, 26.7, 17.7, 10.7 ppm.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information. Preparation of **3** and its catalytic cyclization, computational methods, and ^{1}H, NOEDIFF, ^{13}C and two-dimensional NMR spectra of **1**, **4**−**7**; and ^{1}H and ^{13}C NMR spectra of **8**−**11** and **14**−**15**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: jfquilez@ugr.es; afbarre@ugr.es.

■ ACKNOWLEDGMENT

This research was supported by the Spanish Ministry of Science and Technology, Project CTQ2006-15575-C02-01. The authors thank A. L. Tate for revising their English text. V. D. and C.P.M. thank the Spanish MICINN for two predoctoral grants enabling them to pursue these studies.

■ REFERENCES

(1) Examples of terpenoids containing in their structure a cyclopentane core with contiguous asymmetric centers: (a) Rossinone, B; Appleton, D. R.; Chuen, C. S.; Berridge, M. V.; Webb, V. L.; Copp, B. R. *J. Org. Chem.* **2006**, *74*, 9195–9198. (b) Guaianes:Blay, G.; García, B.; Molina, E.; Pedro, J. R. *J. Org. Chem.* **2006**, *71*, 7866–7869. (c) Dobellanes: Wang, Y.; Harrison, L. J.; Tan, B. C. *Tetrahedron* **2009**, *65*, 4035–4043. (d) Hydroxylcyclopentylbotryococcene: Pan, J.-J.; Bugni, T. S.; Poulter, C. D. *J. Org. Chem.* **2009**, *74*, 7562–7565. (e) Iridanes: Barrero, A. F.; Arseniyadis, S.; Herrador, M. M.; Quilez del Moral, J. F.; Arteaga, J. F.; Sánchez, E. M. *Synlett* **2005**, 591–594. (f) Fusicoccanes: Kato, N. S.; Zhang, C.-S.; Matsui, T.; Iwabuchi, H.; Mori, A.; Ballio, A.; Sassa, T. *J. Chem. Soc., Perkin Trans. 1: Org, Biomol. Chem.* **1998**, *16*, 2473–2474.

(2) For a recent review: (a) Barrero, A. F.; Quílez del Moral, J. F.; Herrador, M. M.; Rodríguez, H.; Pérez Morales, C. *Curr. Org. Chem.* **2009**, *13*, 1164–1181. For asymmetric synthesis of chokols, see: (b) Groth, U.; Kesenheimer, C; Kreye, P. *Synlett* **2006**, 2223–2226. (c) Kanada, R. M.; Ogasawara, K. *Chem. Commun.* **1998**, *16*, 1755–1756. (d) Urban, E.; Knuehl, G.; Helmchen, G. *Tetrahedron* **1995**, *51*, 13031–13038.

(3) For recent papers involving synthesis of cyclopentanes, see: (a) Zhao, G.-L.; Ibrahem, I.; Dziedzic, P.; Sun, J.; Bonneau, C.; Cordova, A. *Chem.—Eur. J.* **2008**, *14*, 10007–10011. (b) Dake, G. R.; Fenster, E. E.; Patrick, B. O. *J. Org. Chem.* **2008**, *73*, 6711–6715. (c) Lentsch, C.; Rinner, U. *Org. Lett.* **2009**, *11*, 5326–5328. (d) Kaeobamrung, J.; Bode, J. W. *Org. Lett.* **2009**, *11*, 677–680. (e) Qu, J.-P.; Deng, C.; Zhou, J.; Sun, X.-L.; Tang, Y. *J. Org. Chem.* **2009**, *74*, 7684–7689. (f) Beckett, J. S.; Beckett, J. D.; Hofferberth, J. E.. *Org. Lett.* **2010**, *12*, 1408–1411. (g) Kiss, L.; Forró, E.; Sillanpää, R.; Fülöp, F. *Synthesis* **2010**, 153–160. (h) Davies, J. J.; Krulle, T. M.; Burton, J. W. *Org. Lett.* **2010**, *12*, 2738–2741.

(4) The preparation of racemic **1** has been previously reported as a mixture of diastereomers in eight steps: Tanimori, S.; Ueda, T.; Nakayama, M. *Biosci. Biotechnol. Biochem.* **1993**, *57*, 1713–1715.

(5) Wender, P. A.; Croatt, M. P.; Witulski, B. *Tetrahedron* **2006**, *62*, 7505–7511.

(6) For pioneering work in this field, see: (a) Nugent, W. A.; RajanBabu, T. V. *J. Am. Chem. Soc.* **1988**, *110*, 8561–8562. (b) RajanBabu, T. V.; Nugent, W. A. *J. Am. Chem. Soc.* **1989**, *111*, 4525–4527. (c) RajanBabu, T. V.; Nugent, W. A.; Beattie, M. S. *J. Am. Chem. Soc.* **1990**, *112*, 6408–6409. (d) RajanBabu, T. V.; Nugent, W. A. *J. Am. Chem. Soc.* **1994**, *116*, 986–997. For reviews, see: (e) Gansäuer, A.; Bluhm, H. *Chem. Rev.* **2000**, *100*, 2771–2788. (f) Gansäuer, A.; Pierobon, M. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, Germany, 2001; Vol. 2, pp 207−220. (g) Gansäuer, A.; Rinker, B. *Tetrahedron* **2002**, *58*, 7017–7026. (h) Gansäuer, A.; Narayan, S. *Adv. Synth. Catal.* **2002**, *344*, 465–475.(i) Gansäuer, A.; Rinker, B. In *Titanium and Zirconium in Organic Synthesis*; Marek, I., Ed.; Wiley-VCH: Weinheim, Germany,

2002; pp 435−450. (j) Gansäuer, A.; Lauterbach, T.; Narayan, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 5556–5573. (k) Cuerva, J. M.; Justicia, J.; Oller-Lopez, J. L.; Bazdi, B.; Oltra, J. E. *Mini-Rev. Org. Chem.* **2006**, *3*, 23–35. (l) Cuerva, J. M.; Justicia, J.; Oller-Lopez, J. L.; Oltra, J. E. *Top. Curr. Chem.* **2006**, *264*, 63–91. (m) Barrero, A. F.; Quilez del Moral, J. F.; Sanchez, E. M.; Arteaga, J. F. *Eur. J. Org. Chem.* **2006**, 1627–1641. For references of the catalytic version, see:(n) Gansäuer, A.; Bluhm, H. *Chem. Commun.* **1998**, 2143–2144. (o) Gansäuer, A.; Pierobon, M.; Bluhm, H. *Angew. Chem., Int. Ed.* **1998**, *37*, 101–103. (p) Gansäuer, A.; Bluhm, H.; Pierobon, M. *J. Am. Chem. Soc.* **1998**, *120*, 12849–12859. (q) Barrero, A. F.; Rosales, A.; Cuerva, J. M.; Oltra, J. E. *Org. Lett.* **2003**, *5*, 1935–1938.

(7) Chakraborty, T. K.; Das, S. *Tetrahedron Lett.* **2002**, *43*, 2313–2315.

(8) Enemærke, R. J.; Larsem, J.; Hjøluund, G. H.; Skrydstrup, T.; Daasbjerg, K. *Organometallics* **2005**, *24*, 1252–1262.

(9) Diastereoselective epoxide openings were already described by Nugent and RajanBabu, including cases with functionalized carbohydrate-derived epoxyalkenes; see ref 6d.

(10) Frisch, M. J. et al. *Gaussian 03, revision B.05*; Gaussian, Inc.: Wallingford, CT, 2004.

(11) (a) Zhao, Y.; Schultz, N. E.; Truhlar, D. G. *J. Chem. Phys.* **2005**, *123*, 161103–1611103−4. (b) Schafer, A.; Horn, H.; Ahlrichs, R. *J. Chem. Phys.* **1992**, *97*, 2571–2577.

(12) Acyclic radicals **Ia**−**d** should be considered as conformers since according to the theoretical data the geometry of the carbon where the radical is located is trigonal (note that the *x*, *y*, and *z* Cartesian coordinates for all theoretically calculated species are provided in Supporting Information). On the other hand, the cyclic radicals **IIa**−**d** resulting from the cyclization (two stereocenters are created) are diastereomers.

(13) Sharpless, K. B.; Michaelson, R. C. *J. Am. Chem. Soc.* **1973**, *95*, 6136–6137.

(14) The preference for the formation of *cis*-adduct **6**, via a homolytic substitution of the Cp_2TiCl radical, has been reported in related systems where no template effect can be involved: Gansäuer, A.; Rinker, B.; Pierobon, M.; Grimme, S.; Gerenkamp, M.; Mück-Lichtenfeld, C. *Angew. Chem., Int. Ed.* **2003**, *42*, 3687–3690.

(15) When **3a** and **3b** were subjected separately to the reaction conditions, the same mixture of products were obtained. Consequently, a balance between the axially and equatorially disposed radicals initially generated in each case should occur via a planar structure where the electron would be located in a p orbital. The theoretically calculated planar or quasi-planar disposition of the corresponding carbon in the acyclic radicals **Ia**−**d** supports this hypothesis.

(16) Chemical conversions of chokol G to chokol K and chokol B, the latter as a mixture of diastereoisomers, has been previously reported: Tanimori, S.; Ueda, T.; Nakayama, M. *Biosci. Biotechnol. Biochem.* **1994**, *58*, 1174–1176.

(17) For a review on this subject, see: Young, I. S.; Baran, P. S. *Nature* **2009**, *1*, 193–205.

(18) For previous synthetic reports on this type of compounds, see ref 1. The last synthesis of chokols reported was the Groth asymmetric preparation of chokol A: Groth, U.; Kesenheimer, C; Kreye, P. *Synlett* **2006**, 2223–2226. The overall yield of this convergent approach was 27% over 6 steps, starting from a chiral ester and a high order cuprate, which in turn were prepared in 3 and 5 steps, respectively.

(19) (+)-Nerolidol can be obtained directly in multigram quantities from *Inula viscosa*. For details see the Experimental Section.

(20) Koshino, H.; Togiya, S.; Terada, S.; Yoshihara, T.; Sakamura, S.; Shimanuki, T.; Sato, T.; Tajimi, A. *Agric. Biol. Chem.* **1989**, *53*, 789–796.

(21) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K. S.; Kwong, H. L.; Morikawa, K.; Wang, Z. M. *J. Org. Chem.* **1992**, *10*, 2768–2771.

(22) Justicia, J.; Jiménez, T.; Morcillo, S. P.; Cuerva, J. M.; Oltra, J. E. *Tetrahedron* **2009**, *65*, 10837–10841.

(23) The optical rotatory power of our (+)-natural compound (+12.2°) is comparable to that of (−)-nerolidol (−12.5°) obtained synthetically from (−)-linalool: David, E.; Cane, D. E.; Ha, H.-J.; McIlwaine, D: B.; Pascoe, K. O. *Tetrahedron Lett.* **1990**, *31*, 7553–7554. These values suggest a high optical richness for our (+)-nerolidol.