An Efficient Stereoselective Synthesis of Stypodiol and Epistypodiol

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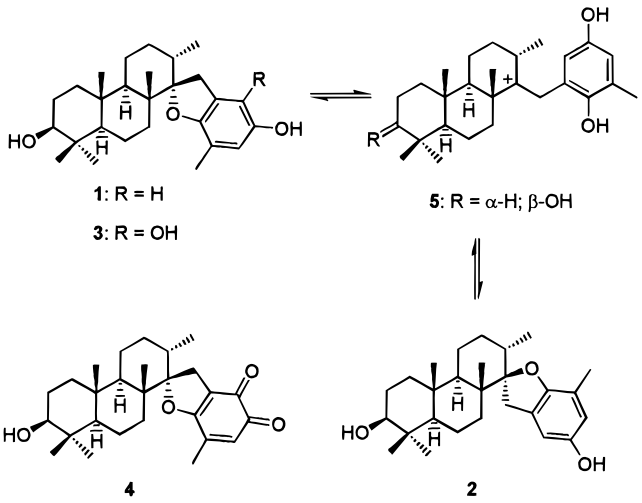
An efficient synthesis of stypodiol (**1**) and its epimer at C-14, epistypodiol (**2**), was accomplished starting from (*S*)-(+)-carvone (**7**). The synthesis of both epimeric compounds proceeds through common intermediates using an IMDA reaction, a sonochemical Barbier reaction, and an acid-catalyzed quinol−tertiary alcohol cyclization as key synthetic steps.

Introduction

Stypodiol (**1**), epistypodiol (**2**), and stypotriol (**3**) are secondary diterpene metabolites identified as the major compounds excreted by the tropical brown algae *Stypopodium zonale* (Lamouroux) Papenfuss.[1] These compounds display diverse biological properties, particularly toxic and strong narcotic and hyperactive effects upon the reef-dwelling fish, *Eupomacentrus leucostictus*.[1a,b,2] The nonnatural but related *o*-quinone stypoldione (**4**), rapidly formed by air oxidation of stypotriol (**3**), has also been found to show pronounced cytotoxic properties and to inhibit cell division in marine embryos and in mammalian cell cultures, through a mechanism that appears to inhibit polymerization of tubulin into microtubes.[3] This interesting biological activity together with their novel structures has made these compounds desirable targets for synthesis and for structure−activity studies.

Two successful syntheses of stypoldione (**4**), *via* stypodiol (1), have been reported.[4,5] In addition, stypotriol (**3**) has also been prepared by reduction of stypoldione (**4**).[1b] To date, however, the synthesis of epistypodiol (**2**) has never been achieved and no chemical methods have been found to relate it to stypodiol (**1**), although it could be likely that both epimers might be interconverted through a carbocation such as **5**, which has been considered as a common intermediate in their biosynthesis.[6] Herein we describe a very efficient and stereoselective synthesis of both epimeric spirobenzofuran compounds, stypodiol (**1**) and epistypodiol (**2**), through common intermediates.[7]



Results and Discussion

The synthesis of stypodiol (**1**), our initial target in this work, commences with the preparation of the enantiomerically pure tricyclic intermediate **6** (Scheme 1), which represents the ABC ring system of **1**. This compound has the necessary functionality already present for further elaboration of rings A and C, and in particular, the carbonyl group could be utilized for introducing the spirobenzofuranyl unit (DE rings) of the target compound. The preparation of **6** is effected using (*S*)-(+)-carvone (**7**) as a C-ring synthon which is incorporated into the tricyclic framework following a C → ABC annulation strategy, using an intramolecular Diels−Alder (IMDA) reaction as the key step.[8]

The synthesis of key intermediate **6** is summarized in Scheme 2. The known methyl carvone **8**,[9] which was

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(1) (a) Gerwick, W. H.; Fenical, W.; Fritsch, N.; Clardy, J. *Tetrahedron Lett.* **1979**, 145. (b) Gerwick, W. H.; Fenical, W. *J. Org. Chem.* **1981**, *46*, 22. (c) Rovirosa, J.; Sepúlveda, M.; Quezada, E.; San-Martin, A. *Phytochemistry* **1992**, *31*, 2679.

(2) (a) Gerwick, W.; Fenical, W.; Norris, J. *Phytochemistry* **1985**, *24*, 1279. (b) Gerwick, W. H.; Whatley, G. J. *J. Chem. Ecol.* **1989**, *15*, 677.

(3) (a) White, S. J.; Jacobs, R. S. *Mol. Pharmacol.* **1983**, *24*, 500. (b) Jacobs, R.; Culver, P.; Langdon, R.; O'Brien, T.; White, S. *Tetrahedron* **1985**, *41*, 981. (c) O'Brien, E. T.; Asai, D. J.; Jacobs, R. S.; Wilson, L. *Mol. Pharmacol.* **1989**, *35*, 635.

(4) (a) Mori, K.; Koga, Y. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 391. (b) Mori, K.; Koga, Y. *Liebigs Ann. Chem.* **1991**, 769. (c) Mori, K.; Koga, Y. *Liebigs Ann. Chem.* **1995**, 1755. (d) Falck, J. R.; Chandrasekhar, S.; Manna, S.; Chiu, C.-C., S. *J. Am. Chem. Soc.* **1993**, *115*, 11606.

(5) For related synthetic work, see: (a) Begley, M. J.; Fish, P. V.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2263. (b) Fish, P. V.; Pattenden, G.; Hodgson, S. T. *Tetrahedron Lett.* **1988**, *29*, 3857. (c) Spanevello, R. A.; Gonzalez-Sierra, M.; Rúveda, E. A. *Synth. Commun.* **1986**, *16*, 749.

(6) (a) Gonzalez, A. G.; Alvarez, M. A.; Martín, J. D.; Norte, M.; Pérez, C.; Rovirosa, J. *Tetrahedron* **1982**, *38*, 719. (b) Kato, T.; Kumanireng, A. S.; Ichinose, I.; Kitahara, Y.; Kaminuna, Y., Kato, Y. *Chem. Lett.* **1975**, 335. (c) Gonzalez, A. G.; Martín, J. D.; Rodriguez, M. L. *Tetrahedron Lett.* **1973**, 3657.

(7) The preparation of stypodiol (**1**) and its conversion into stypoldione (**4**) was published previously as a preliminary communication: Abad, A.; Agulló, C.; Arnó. M.; Cuñat, A. C.; Meseguer, B.; Zaragozá, R. J. *Synlett* **1996**, 913.

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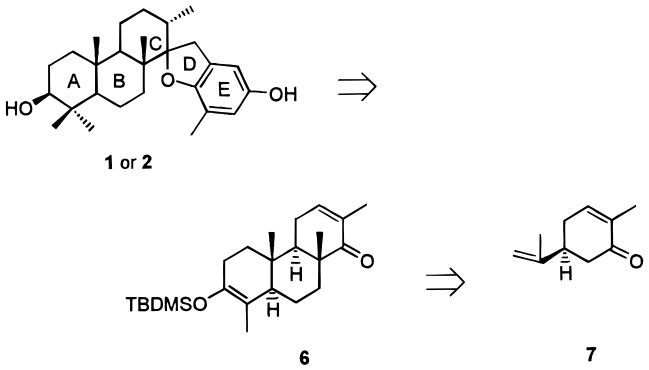
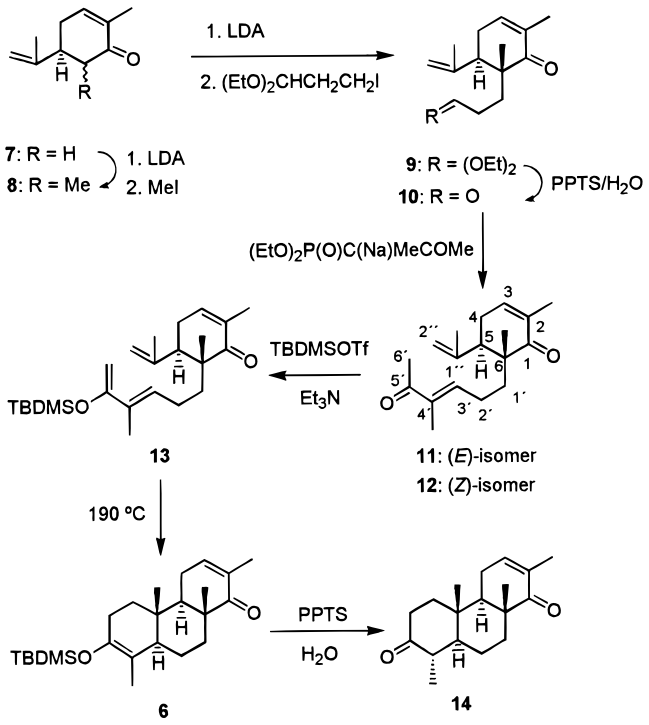
Scheme 1

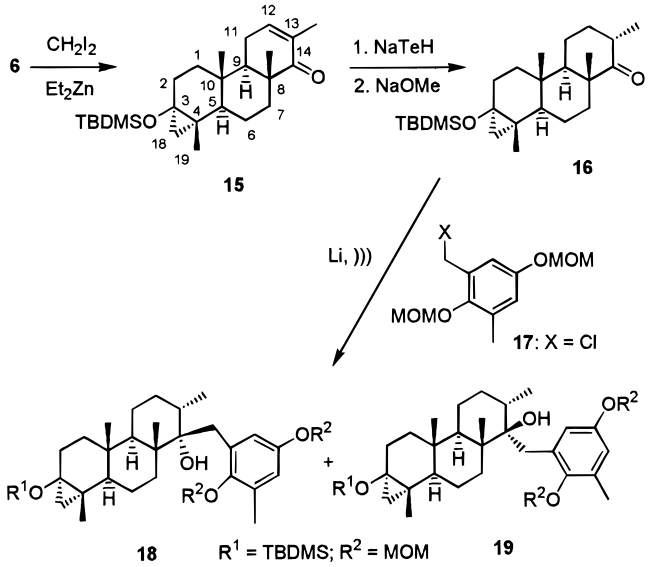


Scheme 2



obtained as a mixture of epimers by methylation of the kinetic enolate of **7** with methyl iodide in an improved 86% yield, was deprotonated at low temperature with LDA and treated with 3-iodopropanaldehyde diethyl acetal[10] to afford diastereoselectively compound **9** in an excellent 80% yield. Removal of the acetal protecting group with pyridinium *p*-toluenesulfonate (PPTS) in aqueous acetone provided the aldehyde **10** in 92% yield. Homologation of aldehyde **10** with the α-phosphonate carbanion generated from diethyl 2-oxobutane-3-phosphonate[11] and NaH in THF at room temperature gave the desired (*E*)-enone **11** in 86% yield after column chromatography, together with the corresponding (*Z*)-isomer **12** in 5% yield. The synthesis of the IMDA precursor **13** was completed in nearly quantitative yield by treatment of enone **11** with TBDMS triflate and triethylamine in dichloromethane at −78 °C.

Scheme 3



Heating a solution of **13** in toluene and a small amount of propylene oxide in a sealed tube at 190 °C for 7 days afforded the *trans*−*anti*−*trans* fused adduct **6** in 97% yield after column chromatography. In the absence of propylene oxide as proton scavenger, partial isomerization of the double bond was observed and a chromatographycally inseparable 1:1 mixture of the adduct **6** and its $\Delta^{2,3}$-isomer[12] was obtained. The stereochemistry of **6**, the only identifiable stereoisomer formed in the IMDA reaction, was confirmed by a detailed spectroscopic analysis effected on the diketone **14**, formed by hydrolysis of the *tert*-butyldimethylsilyl moiety of **6**. Of particular significance was the enhancement observed at the signals corresponding to the axial hydrogens at C-6, C-4, C-2, and C-11 and the axial methyl group at C-8 upon irradiation of the 10*β*-Me at *δ* 1.16, in a NOE experiment. In the same way, irradiation of the 8*β*-Me signal at *δ* 1.06 gave NOE enhancement for H-6*β*, H-7*β*, H-11*β*, and 10*β*-Me. The overall yield for the preparation of the key tricyclic intermediate **6** from carvone was 52% (six steps).

With the tricyclic enone **6** readily at hand, we turned our attention to the required modification of the A-ring functionality and introduction of the spirobenzofuranyl unit. Toward this end, the enone **6** was transformed into compound **15** (Scheme 3). First the tricyclic ketone **6** was submitted to Simmons−Smith cyclopropanation conditions to stereoselectively cyclopropanate the ring A double bond, necessary for the introduction of the geminal dimethyl group at C-4 in the natural compound. An NOE enhancement observed between the α hydrogen atom of the methylene group of the cyclopropane ring at *δ* 0.21 and the axial hydrogen atoms at C-5 and C-1 supported the stereochemistry assigned to the cyclopropane ring. The reduction of the enone **15** using sodium tellurium hydride[13] prepared a mixture of epimeric ketones which was transformed into the saturated ketone **16** by sodium methoxide equilibration.[14] This ketone, obtained in 85%

(8) The route followed for the preparation of **6** parallels one described previously by us for the preparation of a related system, see: Abad, A.; Agulló, C.; Arnó, M.; Cuñat, A. C.; Meseguer, B.; Zaragozá, R. J. *Synlett* **1994**, 733.

(9) Cory, R. M.; Renneboog, R. M. *J. Org. Chem*. **1984**, *49*, 3898.

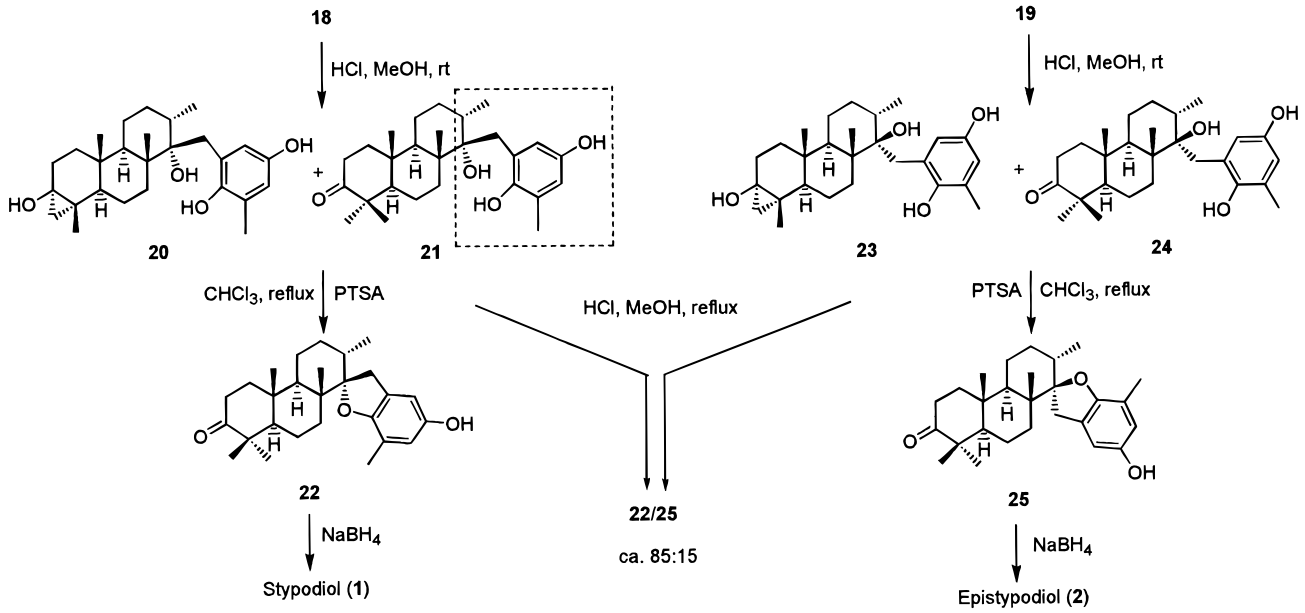
(10) Larson, G. L.; Klesse, R. *J. Org. Chem*. **1985**, *50*, 3627.

(11) Corbel, B.; Medinger, L.; Haelters, J. P.; Sturtz, G. *Synthesis* **1985**, 1048.

(12) The numbering system as given in structure **15** (see Scheme 3) will be followed throughout the text of this paper for all polycyclic compounds (diterpene and steroid numbering). Systematic *Chemical Abstracts* names are used for title compounds in the Experimental Section.

(13) Yamashita, M.; Tanaka, Y.; Arita, A.; Nishida, M. *J. Org. Chem*. **1994**, *59*, 3500.

Scheme 4



overall yield from enone **6**, was the optimal precursor for the spiroannulation.

Our strategy for the construction of the spirobenzofuran unit of stypodiol (**1**) from **16** was based on the preparation of a hydroquinone tertiary alcohol moiety (as in compound **21**, Scheme 4), which was expected to undergo a stereoselective cyclization process to afford the desired portion (DE rings) of the natural compound. Thus, we attempted the coupling of the ketone **16** with the C_7-aromatic part **17**,[15] by addition of the corresponding benzylic organometallic derivative of **17** to the carbonyl group of **16**. Despite many attempts, we were initially not able to produce the desired tertiary alcohol. For instance, treatment of **16** with the lithium[16] or magnesium[17] reagent derived from **17** always afforded the unreacted ketone **16** together with the cross-coupling product of **17** and the protonated organometalic species (**17**, X = H). Other alternative procedures implying traditional Barbier reaction conditions,[16a] SmI_2-promoted coupling,[18] or organocerium reagents[19] also failed to give any addition product.

These disappointing results contrast with the easy addition of other nucleophilic reagents to the carbonyl group of **16**, for example, smooth and clean β-stereoselective addition of vinylmagnesium bromide and dimethylsulfonium methylide to the carbonyl group of **16** takes place in THF at low temperature and must be attributed to the higher steric requirements of the benzylic organometallic reagent.

Fortunately and after some experimentation, it was found that this decisive step could be promoted by sonication.[20] Thus, treatment of ketone **16** with the benzyl chloride **17** and lithium in THF at 0 °C under sonication in a 150 W cleaning bath afforded a 3:7 mixture of epimeric tertiary alcohols **18** and **19**, respectively, in 70% combined yield together with 2−5% of the unreacted starting material. These two alcohols were easily separated by flash chromatography, and their stereochemistries were assigned by intramolecular NOE studies. In particular, irradiation of the Me-8β of the less polar isomer **18** at δ 0.96 gave NOE enhancements for the benzylic hydrogens at δ 2.83 and 2.94, the aromatic hydrogens at δ 6.71 and 6.77, and the Me-Ar group at δ 2.24, which strongly supported the β disposition of the benzylic moiety in this isomer. Contrarily, irradiation of the same methyl group of the more polar isomer **19** gave an NOE enhancement to 14-OH at δ 3.35, which indicated the α orientation of the benzylic unit in this epimer.

The 3:7 ratio of **18** and **19** obtained from the above sonochemical Barbier reaction was somewhat disappointing and contrary to our initial expectations.[21] However, the availability of both epimeric tertiary alcohols allowed us to independently study the construction of the spirodihydrofuran unit from each epimer, to gain some insight into the mechanism operating in this process, and to complete finally the synthesis not only of stypodiol (**1**) but also of its epimer epistypodiol (**2**).

We started by treating the minor alcohol **18**, with the hydroxyl group axially disposed, with hydrochloric acid in MeOH at room temperature to remove the methoxymethyl (MOM) and *tert*-butyldimethylsilyl (TBDMS)

(14) Reduction of the conjugated double bond could also be effected by catalytic hydrogenation (H_2, Pd/C, or Rh/Al_2O_3) without affecting the cyclopropane ring but in slightly lower yield since partial reduction (ca. 10%) of the carbonyl group also occurs.

(15) Prepared in 60−70% overall yield from 1-bromo-2,5-bis-(methoxymethoxy)-3-methylbenzene as described in the Supporting Information.

(16) The organolithium compound was prepared by the reaction of benzyl mesylate **17** (X = OMs) or benzyl thioether **17** (X = SPh) with lithium/naphthalene, see: (a) Guijarro, D.; Mancheño, B.; Yus, M. *Tetrahedron* **1992**, *48*, 4593. (b) Screttas, C. G.; Micha-Screttas, M. *J. Org. Chem*. **1978**, *43*, 1064.

(17) Generated from **17** (X = Cl) and [Mg(anthracene)$(THF)_3$], see: (a) Gallagher, M. J.; Harvey, S.; Raston, C. L.; Sue, R. E. *J. Chem. Soc., Chem. Commun*. **1988**, 289. (b) Bogdanović, B.; Janke, N.; Kinzelmann, H. G. *Chem. Ber*. **1990**, *123*, 1507.

(18) Souppe, J.; Namy, J. L.; Kagan, H. B. *Tetrahedron Lett*. **1982**, *23*, 3497.

(19) Imanoto, T.; Kusumoto, T.; Tawarayama, Y.; Sugiura, Y.; Mita, T.; Hatanaka, Y.; Yokoyama, M. *J. Org. Chem*. **1984**, *49*, 3904.

(20) (a) Luche, J. L.; Damiano, J. C. *J. Am. Chem. Soc*. **1980**, *102*, 7927. (b) Einhorn, C.; Einhorn, J.; Luche, J. L. *Synthesis* **1989**, 787.

(21) A completely opposite stereochemical result was obtained in the addition of other organometallic species to the carbonyl group of **16**. Meseguer, B. Ph.D. Thesis, Universidad de Valencia, February 1997.

protecting groups (Scheme 4). Not unexpectedly, partial acid-induced ring cleavage of the cyclopropane moiety of the initially formed cyclopropanol **20** also occurred under these conditions, affording after 2 h a mixture of cyclopropanol **20** and ketone **21**. Although both compounds could be easily separated by chromatography, the separation proved to be unnecessary because subsequent exposure of the mixture to catalytic *p*-toluenesulfonic acid (PTSA) in refluxing chloroform for 1.30 h completed the cleavage of the cyclopropanol and resulted in simultaneous cyclization to produce solely the desired spirodihydrofuran **22** in an excellent 72% overall yield for the whole process. It is interesting to note that prolonging the hydrochloric acid treatment of **18** for 2 days, under the conditions mentioned above, also led to the spirodihydrofuran **22** as the only identifiable product, albeit in considerably lower yield.[22]

Similarly, the reaction of the major equatorial alcohol **19** with hydrochloric acid in MeOH at room temperature for 2 h afforded a mixture of cyclopropanol **23** and ketone **24**. Exposure of this mixture to catalytic PTSA in chloroform at reflux resulted in smooth cyclization to produce exclusively the spirodihydrofuran **25** in 75% overall yield for the two steps. One interesting observation was that prolonged treatment of **19** with hydrochloric acid in MeOH did not yield, in contrast to the axial alcohol **18**, the corresponding spirodihydrofuran, ketone **24** being the main product identified in the reaction mixture after several days of stirring at room temperature.

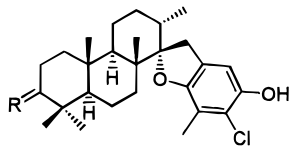
Both epimeric spirodihydrofurans **22** and **25** showed ^{1}H and ^{13}C NMR spectroscopic data which were superimposable on all of the signals associated with the CDE ring portions of the corresponding natural products stypodiol (**1**) and epistypodiol (**2**), respectively. A significant difference in the chemical shift of the angular methyl group at C-8 of both compounds is observed in their ^{1}H NMR spectra; this methyl group resonates at 0.25 ppm downfield in **25** compared with **22** (1.18 and 0.93 ppm in **25** and **22**, respectively), due to the gauche interaction with the equatorial oxygen atom in the former. Also in agreement with the assigned stereochemistry to both epimers, the signal for the benzylic carbon atom in the ^{13}C NMR spectrum of **25** is quite shifted upfield relative to that of **22** ($\Delta\delta$ −4.4 ppm) due to the cooperative γ interaction with C-7, C-9, and C-12.

Although the formation of the equatorial alcohol **19** as the major isomer in the above sonochemical Barbier reaction allowed us to obtain **25**, direct precursor of epistypodiol (**2**), in acceptable global yield from the tricyclic ketone **16** (ca. 37% overall yield), the formation of the axial alcohol **18** as the minor isomer limited the global yield obtained for the conversion of ketone **16** into **22**, direct precursor of stypodiol (**1**). This situation prompted us to explore alternative ways for increasing the production of **22** from **16**. An obvious way of achieving this objective was to find a procedure to transform the alcohol **19** (or the correspondent phenols **23** or **24**) into **22**.[23] After several unsuccessful trials,[24] a simple solution was found. Heating at reflux the mixture of cyclopropanol **23** and ketone **24** in hydrochloric acid and methanol for 15 h led to an 85:15 mixture of **22** and **25**, respectively, from which the desired spirodihydrofuran **22** could be easily separated by chromatography. In practice, the conversion of alcohol **19** into **22** could be effected without isolation of intermediates **23** and **24**, since its treatment with hydrochloric acid in methanol, first stirring at room temperature for 2 h and then heating at reflux for another additional 15 h, afforded the above-mentioned mixture of **22** and its epimer at C-14. From this mixture the spirodihydrofuran **22** was obtained in 68% yield after column chromatography. Thus, the global yield for the conversion of the tricyclic ketone **16** into **22**, via both epimeric tertiary alcohols, was 48%.[25]

The results obtained in the above cyclization reactions deserve some mechanistic considerations. Evidently, a carbonium ion similar to that proposed as intermediate in the biosynthesis of stypodiol (**1**) and epistypodiol (**2**) (e.g., **5**, R = O, *vide supra*) is a discrete intermediate in the reaction of both epimeric alcohols when hydrochloric acid in MeOH at reflux is used to promote the cyclization (Scheme 5). For the same reasons discussed by Pattenden[5a] for a related monocyclic system, this carbonium ion experiences preferential nucleophilic α-attack by the phenolic hydroxyl group to afford the spirodihydrofuran **22**. On the contrary, the stereochemical outcome followed by the cyclization reaction catalyzed by PTSA in refluxing chloroform, in which cyclization occurs without affecting the stereochemical integrity of the carbinol center, excludes the participation of such a cationic intermediate. In this case, a plausible mechanism could involve as key step the nucleophilic addition of the tertiary hydroxyl group to the keto tautomeric form of the phenolic moiety.

Completion of the synthesis of stypodiol (**1**) only required stereoselective reduction of the carbonyl group of **22**. This end was readily achieved in 86% yield by

(22) The use of an oxygen-free atmosphere and a high-quality hydrochloric acid in this prolonged acid treatment was essential to reproduce this result. We obtained the best result with Aldrich HCl, 37 wt % in water, 99.999%. Treatment of **18** in MeOH for 2 days with the habitual hydrochloric acid used in the laboratory led to a different compound that was presumed to be the ketone i. Further support for the structure assigned to i was obtained after its reduction to the alcohol ii ($NaBH_4$, CH_2Cl_2−MeOH, −10 °C) and comparison of the spectroscopic data of this with that of stypodiol (**1**). Both compounds had nearly superimposable ^{1}H NMR spectra with the exception of the signal attributed to the aromatic moiety. Thus, compound ii showed only an aromatic hydrogen and the signal corresponding to Me-Ar was moved 0.1 ppm downfield with respect the same signal of **1** [^{1}H NMR of ii ($CDCl_3$, 200 MHz): δ 6.60 (s, 1H), 3.20 (m, 1H), 3.19 (d, J = 16.5 Hz), 2.74 (d, J = 16.5 Hz, 1H), 2.24 (s, 3H), 0.91 (s, 6H), 0.83 (s, 3H), 0.74 (s, 3H), 0.64 (d, J = 6.5 Hz, 3H)]. Conclusive evidence of the presence of the chlorine atom in ii was obtained from its HRMS (calcd for $C_{27}H_{39}ClO_3$ 446.2588, found 446.2607).



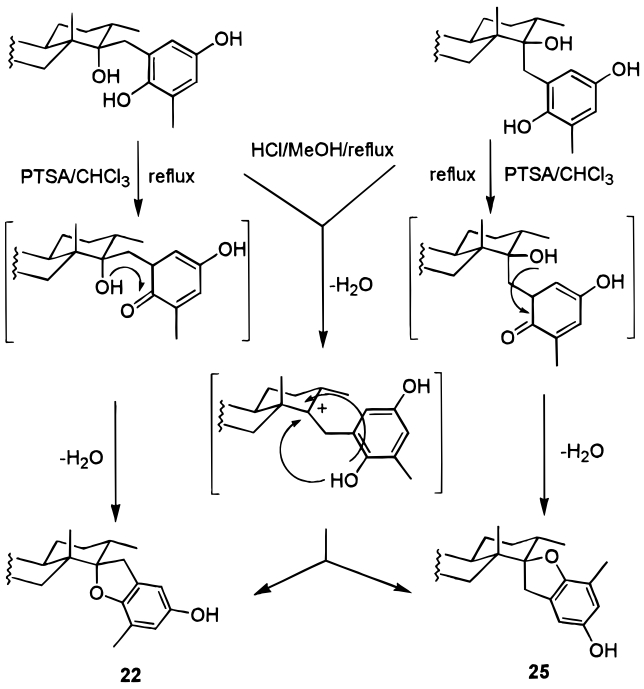
i: R = O
ii: R = β-OH, α-H

(23) The possible epimerization of the spirodihydrofuran **25** to **22** was also attempted. Several acidic (e.g., PTSA/C_6H_6, reflux; PTSA, THF/H_2O, 150 °C; AcOH/HBr, reflux; HCl/MeOH, reflux) and basic conditions (e.g., KOH, MeOH, reflux) were assayed without success. For experimental conditions and related isomerizations, see: (a) Reference 6a. (b) Paquette, L. A.; Ezquerra, J.; He, W. *J. Org. Chem.* **1995**, *60*, 1435. (c) González, A. G.; Alvarez, M. A.; Darias, J.; Martín, J. D. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2637.

(24) These included some attempts for forcing the formation of a carbonium ion at C-14, via transformation of the OH into a better leaving group, that could react with the MOM ether moiety. Examples of formation of cyclic ethers by a related process are known, see: Ziegler, F. E.; Wallace, O. B. *J. Org. Chem.* **1995**, *60*, 3626.

(25) As expected, treatment of the axial alcohol **18**, or even the mixture of **18** and **19**, under the same conditions as used for **19** also led to a similar mixture of the epimeric spirodihydrofurans **22** and **25**.

Scheme 5



treatment of **22** with $NaBH_4$ at low temperature. The spectral and physical data of **1** were identical with those previously reported for the natural compound.[1b] Similarly, reduction of ketone **25** under the same conditions as for **22** afforded epistypodiol (**2**) in 90% yield. The spectral data (^1H and ^{13}C NMR, IR, and MS) of **2** were also identical with those of the natural product.[1b,26]

In conclusion, we have completed the stereoselective synthesis of stypodiol (**1**) and epistypodiol (**2**) from (*S*)-(+)-carvone (**7**), *via* the tricyclic ketone **6**, in 13 synthetic steps and in ca. 20% and 14% overall yields, respectively. A relevant step of the synthesis of both epimeric spirodihydrofurans is the acid-catalyzed cyclization of the quinol−tertiary alcohol **19** (and also of the axial epimer **18**). In the case of **19**, the stereochemical outcome of this process depends on the acid conditions used. It can take place with inversion or retention of the configuration at C-14 to afford the pentacyclic framework of stypodiol (**1**) or epistypodiol (**2**), respectively. The synthesis of **1** represents a considerable improvement, in both number of steps and overall yield, with respect to previous syntheses described for this product while the synthesis of **2** constitutes the first synthesis of this natural compound.[27]

Experimental Section

General. All melting points were determined using a Kofler hot-stage apparatus and are uncorrected. Optical rotations were determined using a 5 cm path length cell. $[\alpha]_D$ values are given in units of 10^{-1} deg cm^2 g^{-1}. IR spectra were measured as KBr pellets or liquid films. All ^1H spectra were recorded at 300 or 400 MHz, and all ^{13}C at 75 MHz. The signal of the deuterated solvent ($CDCl_3$) was taken as the reference (the singlet at δ 7.24 for ^1H and the triplet centered at δ_C 77.00 for ^{13}C NMR data). Complete assignment of most of the products was made on the basis of a combination of homonuclear COSY, DEPT, and inverse-detected heteronuclear multiple quantum coherence (HMQC) experiments. In all compounds NMR assignments are given with respect to the numbering scheme shown in structures **11** and **15** for monocyclic and polycyclic systems, respectively. Mass spectra were obtained by electron impact (EI) at 70 eV. Column chromatography refers to flash chromatography and was performed on Merck silica gel 60, 230−400 mesh. Silica gel 60 (Macherey Nagel, 0.015−0.04 mm) was used for medium-pressure liquid chromatography (MPLC). All reaction were carried out under an inert atmosphere of dry argon using oven-dried glassware and freshly distilled and dried solvents. The ampules used for the Diels−Alder reactions were previously treated during at least 48 h with a 5% solution of 1,1,1,3,3,3-hexamethyldisilazane in ether, washed with acetone, and dried at 120 °C overnight. Unless stated otherwise, reaction mixtures were worked up by addition of water and extraction with the appropriated solvent (indicated), the organic extracts being washed with water and brine and dried using anhydrous sodium sulfate. Evaporation was performed under reduced pressure.

(5*R*,6*R*)-6-(3,3-Diethoxypropyl)-2,6-dimethyl-5-(1-methylethenyl)-2-cyclohexen-1-one (9). To a solution of LDA in THF (0.8 M solution; 4.9 mL, 3.92 mmol) at −78 °C was slowly added (ca. 1 h) a solution of methyl carvone (**8**; mixture of epimers at C-6) (500 mg, 3.05 mmol) and HMPA (0.848 mL, 4.88 mmol) in THF (4 mL). After the reaction mixture had been allowed to warm to room temperature and then stirred at this temperature for 1 h, it was cooled to −78 °C and treated with 3-iodopropanaldehyde diethyl acetal (1.18 g, 4.57 mmol). The reaction mixture was then slowly allowed to warm to room temperature during 3 h, poured into a cooled saturated aqueous NH_4Cl solution, and extracted with a 1:1 mixture of hexanes−ethyl ether. Workup afforded an oily residue, which was purified by MPLC, using 95:5 hexane−ethyl acetate as eluent, to give the ketone ketal **9** (709 mg, 80%) as a colorless oil: $[\alpha]^{21}_D$ +25 (*c* 7.3, $CHCl_3$); IR (film) 3070, 2990−2800, 1668, 1376, 1063, 897 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.51 (1 H, m, H-3), 4.72 (1 H, s, H-2″), 4.67 (1 H, s, H′-2″), 4.37 (1 H, dd, J = 5.5, 5.0, H-3′), 3.56 (2 H, m, OCH_2CH_3), 3.41 (2 H, m, OCH'_2CH_3), 2.66 (1 H, dd, J = 6.0, 6.0, H-5), 2.56 (1 H, m, H-4), 2.25 (1 H, m, H′-4), 1.71 (3 H, m, Me-2), 1.59 (3 H, s, Me-1″), 1.14 (6 H, two overlapped t, J = 6.5, 2 × OCH_2CH_3), 0.97 (3 H, s, Me-6); MS (EI) *m*/*z* 294 (M^+, 5), 249 (7), 202 (25), 187 (20), 85 (100); HRMS $C_{18}H_{30}O_3$ requires 294.2195, found 294.2192.

3-[(1*R*,6*R*)-1,3-Dimethyl-6-(1-methylethenyl)-2-oxo-3-cyclohexenyl]-1-propanal (10). PPTS (306 mg, 1.2 mmol) was added to a solution of ketal **9** (588 mg, 1.98 mmol) in 4% aqueous acetone (40 mL), and the resulting mixture was heated at reflux for 1 h and then poured into water. Extraction of the resulting mixture with ether and workup of the extract afforded a residue, which was purified by MPLC, using 9:1 hexanes−ethyl acetate as eluent, to afford aldehyde **10** (402 mg, 92%) as an oil: $[\alpha]^{21}_D$ +20 (*c* 4.25, $CHCl_3$); IR (film) 3070, 3040, 2724, 1724, 1665, 997, 900 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.7 (1 H, s, CHO), 6.58 (1 H, m, H-3), 4.8 (1 H, s, H-2″), 4.71 (1 H, s, H′-2″), 2.65 (1 H, dd, J = 6.0, 6.0, H-5), 2.25−2.6 (4 H, m, H-4 and H-2′), 1.85 (2H, m, H-1′), 1.72 (3 H, m, Me-2), 1.62 (3 H, s, Me-1″), 1.00 (3 H, s, Me-6); MS (EI) *m*/*z* 220 (M^+, 2), 163 (35), 123 (25), 109 (20), 93 (20), 82 (100); HRMS $C_{14}H_{20}O_2$ requires 220.1463, found 220.1459.

(5*R*,6*R*)-2,6-Dimethyl-5-(1-methylethenyl)-6-[(*E*)-4-methyl-5-oxo-3-hexenyl]-2-cyclohexen-1-one (11). To a stirred slurry of prewashed NaH (55% dispersion oil; 113 mg, 2.60 mmol) in THF (12 mL) at 0 °C was added, dropwise via syringe, diethyl 2-oxobutane-3-phosphonate (557 mg, 0.49 mL, 2.68 mmol) during 45 min. After hydrogen evolution had

(26) The specific rotation of the synthetic product, an amorphous solid, was $[\alpha]^{19}_D$ +4.5 (*c* 0.44, $CHCl_3$), while the literature value of the natural compound, an oil, was $[\alpha]_D$ −4.5 (*c* 1.35, $CHCl_3$). We believe that the difference in the value of the specific rotation of synthetic and natural epistypodiol (**2**) should be attributable to a different degree of purity of both samples, since this compound (and also **1**) decomposes on exposure to air and is difficult to keep in a high degree of purity. The pertinence of **1** and **2**, both isolated from the same natural source, to different enantiomeric series seems improbable. Unfortunately, the specific rotation of **2** has only be described on one occasion. Its corresponding diacetate, prepared by us by treatment of **2** with excess pyridine and acetic anhydride at rt for 48 h, had $[\alpha]_D$ −7.9 (*c* 0.76, $CHCl_3$).

(27) Although not described here, we have also prepared stypoldione (**4**) by oxidation of stypodiol (**1**) with Fremy's salt (see preliminary communication[7]).

ceased, the mixture was warmed to room temperature and stirred for 10 min. To the resulting mixture was added a solution in THF (4 mL) of the aldehyde **10** (190 mg, 0.87 mmol). After being stirred at room temperature for 30 min, the mixture was treated with a saturated aqueous NH_4Cl solution and poured into water. Extraction with ethyl ether and workup as usual afforded an oil, which was purified by chromatography, using 85:15 hexanes−ethyl acetate as eluent, to give the (*Z*)-olefin **12** (11.6 mg, 5%) followed by the (*E*)-olefin **11** (203 mg, 86%).

Compound **11**, an oil: $[\alpha]^{24}_D$ +51 (*c* 2.10, $CHCl_3$); IR (film) 3071, 1666, 1639, 1371, 1279, 1084, 897 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.60 (1 H, m, H-3), 6.56 (1 H, ddd, J = 8.0, 8.0, 1.5, H-3′), 4.83 (1 H, m, H-2″), 4.76 (1 H, br s, H′-2″), 2.75 (1 H, dd, J = 7.5, 7.5, H-5), 2.55 (1 H, m, H-4), 2.38 (1 H, H′-4), 2.28 (3 H, s, H-6′), 1.77 (3 H, m, Me-2), 1.73 (3 H, m, Me-4′), 1.67 (3 H, s, Me-1″), 1.06 (3 H, s, Me-6); MS (EI) *m*/*z* 274 (M^+, 2), 247 (2), 206 (2), 177 (3), 164 (100); HRMS calcd for $C_{18}H_{26}O_2$ 274.1933, found 274.1934.

Compound **12**, an oil: IR (film) 3071, 3030, 1686, 1665, 1369, 895 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.56 (1 H, m, H-3), 5.63 (1 H, ddd, J = 7.0, 3.0, H-3′), 4.77 (1 H, m, H-2″), 4.72 (1 H, br s, H′-2″), 2.73 (1 H, dd, J = 5.0, 5.0, H-5), 2.62 (1 H, m, H-4), 2.31 (1 H, H′-4), 2.23 (3 H, s, H-6′), 1.90 (3 H, m, Me-4′), 1.76 (3 H, s, Me-2), 1.63 (3 H, s, Me-1″), 1.02 (3 H, s, Me-6); MS (EI) *m*/*z* 274 (M^+, 7), 247 (1), 231 (2), 206 (3), 177 (6), 164 (100); HRMS calcd for $C_{18}H_{26}O_2$ 274.1933, found 274.1931.

(5*R*,6*R*)-6-[(3*E*)-5-[(*tert*-Butyldimethylsilyl)oxy]-4-methyl-3,5-hexadienyl]-2,6-dimethyl-5-(1-methylethenyl)-2-cyclohexen-1-one (13). Enone **11** (171 mg, 0.63 mmol) in dry CH_2Cl_2 (7 mL) was cooled to −78 °C and treated sequentially with triethylamine (0.26 mL, 1.88 mmol) and *tert*-butyldimethylsilyl triflate (0.21 mL, 0.94 mmol). After 1 h at −78 °C, the reaction mixture was quenched with a 5% aqueous $NaHCO_3$ solution and poured into water and the mixture was extracted with ether. Workup as usual furnished an oily residue which was purified by MPLC on silica gel, using 95:5 hexanes−ethyl acetate as eluent, to give compound **13** as a colorless oil (237 mg, 98%): $[\alpha]^{25}_D$ +28 (*c* 1.94, C_6H_6); IR (film) 3075, 1669, 1593, 1298, 1012, 836, 780 cm^{-1}; ^1H NMR (C_6D_6) δ 6.29 (1 H, dd, J = 7.5, 7.5, H-3′), 5.92 (1 H, s, H-3), 4.72 (1 H, s, H-2″), 4.65 (1 H, s, H′-2″), 4.48 (1 H, s, H-6′), 4.36 (1 H, s, H′-6′), 2.50 (1 H, dd, J = 6.0, 6.0, H-5), 1.88 (1 H, m, H-4), 1.77 (3 H, m, Me-2), 1.76 (3 H, s, Me-4′), 1.50 (3 H, s, Me-1″), 1.06 (3 H, s, Me-1), 1.01 (9 H, s, Me_3CSi), 0.17 (6 H, s, Me_2Si); MS (EI) *m*/*z* 388 (M^+, 5), 331 (4), 226 (21), 225 (100), 199 (3), 164 (62); HRMS calcd for $C_{24}H_{40}O_2Si$ 388.2798, found 388.2799.

[4a*R*-(4aα,4b*β*,8aα,10a*β*)]-7-[(*tert*-Butyldimethylsilyl)oxy]-2,4b,8,10a-tetramethyl-4a,4b,5,6,8a,9,10,10a-octahydro-1(4*H*)-phenanthrenone (6). A toluene solution (10 mL) of **13** (205 mg, 0.53 mmol) and a small amount of propylene oxide (2 drops) was sealed in a tube under argon and heated at 190−195 °C during 168 h. After cooling, the tube was opened and the solvent removed in vacuo to give an oily residue. This was purified by chromatography, using 9:1 hexanes−ethyl acetate 9:1 as eluent, to give enone **6** as a white solid (199 mg, 97%): mp 140−141 °C (from pentane); $[\alpha]^{24}_D$ +32 (*c* 0.75, C_6H_6); IR (film) 1670, 1256, 1199, 838, 778 cm^{-1}; ^1H NMR (C_6D_6) δ 6.13 (1 H, m, H-12), 1.84 (3 H, m, Me-13), 1.63 (3 H, br s, Me-4), 1.03 (9 H, s, Me_3CSi), 0.95 (3 H, s, Me-8), 0.73 (3 H, s, Me-10), 0.13 (6 H, s, Me_2Si); MS (EI) *m*/*z* 389 (M^+ + 1, 30), 388 (M^+, 100), 373 (35), 331 (35), 274 (15), 237 (23), 197 (7); HRMS calcd for $C_{24}H_{40}O_2Si$ 388.2798, found 388.2788.

[4a*R*-(4aα,4b*β*,8*β*,8aα,10a*β*)]-4a,4b,5,6,7,8,8a,9,10,10a-decahydro-2,4b,8,10a-tetramethyl-7-oxo-1(4*H*)-phenanthrenone (14). In the same manner as above, a solution of **13** (195 mg, 0.50 mmol) in toluene (10 mL) was heated at 190−195 °C for 168 h. The residue obtained after evaporation of the solvent was dissolved in 4% aqueous acetone (16 mL), PTSA (20 mg, 0.1 mmol) was added, and the resulting mixture was heated at reflux for 1 h and then poured into water. Extraction with ether and workup of the extract afforded a residue, which was purified by chromatography, using 8:2 hexanes−ethyl acetate as eluent, to give diketone **14** (110 mg, 80%) as a white solid: mp 164−165 °C (from ether); $[\alpha]^{25}_D$ +48 (*c* 3.27, $CHCl_3$); IR (film) 1706, 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.62 (1 H, m, H-12), 2.42 (1 H, ddd, J = 14.5, 14.5, 7.0, H-2*β*), 2.32 (3 H, m, H-2α, 2H-11), 2.28 (1 H, dq, J = 12.5, 6.0, H-4), 1.99 (1 H, ddd, J = 13.0, 9.5, 2.5, H-1*β*), 1.95 (1 H, ddd, J = 14.0, 3.0, 3.0, H-7*β*), 1.72 (3 H, m, Me-13), 1.55 (1 H, dd, J = 10.0, 5.6, H-9), 1.16 (3 H, s, Me-10), 1.06 (3 H, s, Me-8), 0.99 (3 H, d, J = 7.0, Me-4).

[1a*S*-(1aα,1b*β*,3aα,7a*β*,7bα,9aα)]-9a-[(*tert*-Butyldimethylsilyl)oxy]-1,1a,1b,2,3,3a,7,7a,7b,8,9,9a-dodecahydro-1a,3a,5,7b-tetramethyl-4*H*-cyclopropa[*a*]phenanthren-4-one (15). A solution of compound **6** (159 mg, 0.41 mmol) in dry toluene (6 mL) was treated with diethylzinc (2.5 mL of 1 M in hexane, 2.46 mmol). Diiodomethane (0.39 mL, 4.9 mmol) was introduced dropwise, and the mixture was stirred for 2 h, poured into a saturated aqueous NH_4Cl solution, and extracted with ether. Workup as usual gave a residue, which was purified by chromatography, using 97.5:2.5 hexanes−ethyl acetate as eluent, to afford cyclopropane **15** as a white solid (151 mg, 92%): mp 138−139 °C (from methanol); $[\alpha]^{25}_D$ +62 (*c* 6.0, $CHCl_3$); IR (KBr) 3080, 3050, 1660, 1200, 1010, 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.61 (1 H, m, H-12), 1.70 (3 H, m, Me-13), 1.63 (1 H, dd, J = 12.5, 7.5, H-9), 1.03 and 1.02 (3 H each, each s, Me-4 and Me-8), 0.91 (3 H, s, Me-10), 0.83 (9 H, s, Me_3-CSi), 0.53 (1 H, ddd, J = 14.0, 14.0, 6.5, H-1α), 0.49 (1 H, d, J = 4.5, H-18*β*), 0.21 (1 H, d, J = 4.5, H-18α), 0.08 and 0.02 (3H each, each s, Me_2Si); MS (EI) *m*/*z* 403 (M^+ + 1, 10), 402 (M^+, 40), 346 (25), 345 (90), 317 (5), 288 (7), 253 (12), 211 (100); HRMS calcd for $C_{25}H_{42}O_2Si$ 402.2954, found 402.2954.

1a*S*-(1aα,1b*β*,3aα,5*β*,7a*β*,7bα,9aα)]-9a-[(*tert*-Butyldimethylsilyl)oxy] tetradecahydro-1a,3a,5,7b-tetramethyl-4*H*-cyclopropa[a]phenanthren-4-one (16). A mixture of powdered tellurium (148 mg, 2.76 mmol), anhydrous ethanol (4 mL), and $NaBH_4$ (104 mg, 1.16 mmol) was heated and stirred under argon at 80 °C. After 30 min the mixture was cooled to room temperature and a solution of enone **15** (117 mg, 0.29 mmol) in a 3:1 mixture of ethanol−pentane (3 mL) was added. After refluxing for about 1.5 h, the mixture was cooled and filtered through a short pad of silica gel, eluting with 9:1 hexanes−ether. Evaporation of the solvent afforded a mixture of C-13 epimeric methyl ketones (116 mg). A solution of this mixture in THF (1.5 mL) was treated with 5% NaOMe in MeOH (4 mL). The reaction mixture was stirred for 1 h and poured into water. Extraction with CH_2Cl_2 and workup as usual afforded a residue, which was purified by chromatography, using 99:1 hexanes−ethyl acetate as eluent, to give the ketone **16** (108 mg, 92%) as a white solid: mp 144−143 °C (from methanol); $[\alpha]^{25}_D$ +40 (*c* 2.87, $CHCl_3$); IR (KBr) 1705, 1250, 1185, 825 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.64 (1 H, m, H-13), 2.08 (1H, m, H-1*β*), 2.04 (1H, m, H-2α), 1.90 (1 H, ddd, J = 13.5, 13.5, 7.5, H-2*β*), 1.15 (3 H, s, Me-8), 1.02 (3 H, s, Me-4), 0.93 (3 H, d, J = 7.0, Me-13), 0.87 (3 H, s, Me-10), 0.83 (9 H, s, Me_3CSi), 0.51 (1 H, ddd, J = 13.5, 13.5, 6.0, H-1α), 0.48 (1 H, d, J = 5.0, H-18*β*), 0.20 (1 H, d, J = 5.0, H-18α), 0.08 and 0.02 (3 H each, each s, Me_2Si); MS (EI) *m*/*z* 405 (M^+ + 1, 6), 404 (M^+, 25), 348 (12), 347 (47), 255 (15), 212 (17), 211 (100); HRMS calcd for $C_{25}H_{44}O_2Si$ 404.3111, found 404.3111.

1a*S*-(1aα,1b*β*,3aα,4α,5*β*,7a*β*,7bα,9aα)]-9a-[(*tert*-Butyldimethylsilyl)oxy]-4-[[2,5-bis(methoxymethoxy)-3-methylphenyl]methyl]tetradecahydro-1a,3a,5,7b-tetramethyl-1H-cyclopropa[*a*]phenanthren-4-ol (18) and 1a*S*-(1aα,1b*β*,3aα,4*β*, 5*β*,7a*β*,7bα,9aα)]-9a-[(*tert*-butyldimethylsilyl)oxy]-4-[[2,5-bis(methoxymethoxy)-3-methylphenyl]-methyl]tetradecahydro-1a,3a,5,7b-tetramethyl-1*H*-cyclopropa[*a*]phenanthren-4-ol (19). A mixture of ketone **16** (120 mg, 0.29 mmol), benzyl chloride **17** (X = Cl) (161 mg, 0.61 mmol), lithium (20 mg, 2.9 mmol), and THF (8.8 mL) was sonicated in a cleaning bath (150 W) for 1 h between 0 and 5 °C. After this time the reaction mixture was quenched by addition of a saturated aqueous NH_4Cl solution (2 mL) and poured into water. Extraction with CH_2Cl_2 and workup as usual gave an oily residue that was purified by MPLC eluting with 96:4 hexanes−ethyl acetate, to afford the unreacted ketone **16** (3.3 mg, 3%) and the epimeric alcohols **18** and **19**.

18 (axial alcohol; less polar isomer): 39 mg (21%); an oil; $[\alpha]^{22}_D$ +19 (*c* 0.95, $CHCl_3$); IR (film) 3500, 3055, 1590, 1460, 1150, 1030, 830, 770 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.77 (1 H, d, *J* = 2.5, H−Ar), 6.71 (1 H, d, *J* = 2.5, H′-Ar), 5.08 (2 H, s, OCH_2O), 4.90 (2 H, dd, *J* = 5.5, OCH'_2O), 3.57 (3 H, s, MeO), 3.44 (3 H, s, Me′O), 2.94 and 2.83 (1 H each, AB system, *J* = 14.5, CH_2-Ar), 2.24 (3 H, s, Me-Ar), 1.08 (3 H, s, Me-4), 0.96 (3 H, s, Me-8), 0.82 (9 H, s, Me_3CSi), 0.76 (3 H, d, *J* = 7.0, Me-13), 0.75 (3 H, s, Me-10), 0.41 (1 H, d, *J* = 5.0, H-18β), 0.18 (1 H, d, *J* = 5.0, H-18α), 0.07 and 0.01 (3H each, each s, Me_2Si); MS (EI) *m*/*z* 630 (M^+, 2), 568 (5), 466 (2), 405 (15), 295 (2), 255 (12), 227 (12), 226 (100); HRMS calcd for $C_{37}H_{62}O_6Si$ 630.4316, found 630.4320.

19 (equatorial alcohol; more polar isomer): 91 mg (49%); an oil; $[\alpha]^{20}_D$ +22 (*c* 2.0, $CHCl_3$); IR (film) 3490, 3050, 1695, 1590, 1150, 1035, 830, 770, 730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.78 (1 H, d, *J* = 2.5, H-Ar), 6.70 (1 H, d, *J* = 2.5, H′-Ar), 5.07 (2 H, s, OCH_2O), 4.89 (2 H, br s, OCH'_2O), 3.58 (3 H, s, MeO), 3.44 (3 H, s, Me′O), 3.35 (1 H, br s, OH), 3.05 and 2.87 (1 H each, AB system, *J* = 14.5, CH_2-Ar), 2.24 (3 H, s, Me-Ar), 1.06 (3 H, s, Me-4), 0.99 (3 H, s, Me-8), 0.84 (9 H, s, Me_3CSi), 0.79 (3 H, s, Me-10), 0.66 (3 H, d, *J* = 7.0, Me-13), 0.46 (1 H, d, *J* = 5.0, H-18β), 0.21 (1 H, d, *J* = 5.0, H-18α), 0.09 and 0.03 (3H each, each s, Me_2Si); MS (EI) *m*/*z* 630 (M^+, 7), 568 (9), 466 (4), 436 (3), 405 (13), 296 (2), 255 (12), 227 (12), 226 (100); HRMS calcd for $C_{37}H_{62}O_6Si$ 630.4316, found 630.4329.

(5α,13α)-14,17-Epoxy-23-hydroxy-4,4,8-trimethyl-16,24-cyclo-13,17-secochola-16,20(22),23-trien-3-one (22). To a stirred solution of alcohol **18** (38 mg, 0.06 mmol) in MeOH (4 mL) was added hydrochloric acid (0.3 mL, 37 wt % in water) under an argon atmosphere. After the mixture was stirred for 2.5 h at room temperature, the reaction was quenched with 5% aqueous $NaHCO_3$ solution and stirred until CO_2 evolution ceased. Water was added, and the mixture was worked up to give an oil, a mixture of cyclopropanol **20** and ketone **21**. A solution of this oil and PTSA (1 mg, 0.005 mmol) in chloroform (4 mL) was heated at reflux during 1.5 h. The reaction mixture was treated with a 5% aqueous $NaHCO_3$ solution, poured into water, and then worked up using ether to extract. Purification by chromatography, using 8:2 hexanes−ethyl acetate as eluent, afforded the spirodihydrofuran **22** (18 mg, 72% overall for the two steps) as an amorphous solid: $[\alpha]^{21}_D$ +12 (*c* 1.18, $CHCl_3$); IR (film) 3390, 3015, 1695, 1475, 1230, 1130, 845, 820 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.39 (1 H, s, H-Ar), 6.37 (1 H, s, H′-Ar), 4.23 (1 H, br s, OH), 3.18 and 2.75 (1 H each, AB system, *J* = 16, CH_2-Ar), 2.50 (2 H, m, H-2), 2.14 (3 H, s, Me-Ar), 1.02 (3 H, s, Me-4β), 1.00 (3 H, s, Me-10), 0.95 (3 H, s, Me-4α), 0.93 (3 H, s, Me-8), 0.67 (3 H, d, *J* = 6.5, Me-13); MS (EI) *m*/*z* 411 (M^+ + 1, 32), 410 (M^+, 100), 273 (31); HRMS calcd for $C_{27}H_{38}O_3$ 410.2821, found 410.2827.

(5α,13α14β)-14,17-Epoxy-23-hydroxy-4,4,8-trimethyl-16,24-cyclo-13,17-secochola-16,20(22),23-trien-3-one (25). This compound was prepared by successive treatment of **19** (38 mg, 0.06 mmol) with HCl/MeOH/rt (1.5 h) and PTSA/$CHCl_3$/reflux (2.5 h), as described above for the synthesis of **22**. Chromatography of the crude product, using 8:2 hexanes−ethyl acetate as eluent, yielded **25** (18.5 mg, 75%) as an amorphous solid: $[\alpha]^{19}_D$ +31 (*c* 1.18, $CHCl_3$); IR (film) 3460, 3010, 1695, 1470, 1230, 845, 725 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.45 (1 H, s, H-Ar), 6.35 (1 H, s, H′-Ar), 4.3 (1 H, br s, OH), 3.05 and 2.92 (1 H each, AB system, *J* = 16.5, CH_2-Ar), 2.52 (1 H, ddd, *J* = 15.5, 10.5, 7.5, H-2β), 2.37 (1 H, ddd, *J* = 16.5, 7.0, 4.0, H-2α), 2.11 (3 H, s, Me-Ar), 1.18 (3 H, s, Me-8), 1.02 (3 H, s, Me-4β), 1.00 (3 H, s, Me-10), 0.97 (3 H, s, Me-4α), 0.71 (3 H, d, *J* = 6.5, Me-13); MS (EI) *m*/*z* 411 (M^+ + 1, 27), 410 (M^+, 100), 273 (26), 231 (2), 205 (4); HRMS calcd for $C_{27}H_{38}O_3$ 410.2821, found 410.2828.

Preparation of Spirodihydrofuran 22 from Alcohol 19. A solution of alcohol **19** (32 mg, 0.05 mmol) in MeOH (4 mL) under an atmosphere of argon was treated with hydrochloric acid (0.3 mL, 37 wt % in water) and stirred at room temperature for 1.5 h. After this time, the reaction mixture was refluxed overnight (ca. 15 h), cooled to room temperature, treated with a 5% aqueous $NaHCO_3$ solution, and poured into water. Workup using ether as extract gave an oil that was purified by chromatography (8:2 hexanes−ethyl acetate, as eluent) to give spirodihydrofurans **22** (14 mg, 68%), which was identical with the compound obtained from alcohol **18** (see above), and **25** (2.5 mg, 12%).

(3β,5α,13α)-14,17-Epoxy-4,4,8-trimethyl-16,24-cyclo-13,17-secochola-16,20(22),23-triene-3,23-diol (Stypodiol, 1). $NaBH_4$ (7.8 mg, 0.21 mmol) was slowly added to a solution of ketone **22** (18 mg, 0.042 mmol) in a 1:1 mixture of CH_2Cl_2−MeOH (4.5 mL) at −60 °C. The reaction mixture was stirred for 1 h from −60 to −10 °C; then acetone (0.1 mL, 1.37 mmol) was added and the mixture allowed to warm to room temperature. Water was added, and the mixture was extracted with CH_2Cl_2. Usual workup followed by column chromatography of the residue on silica gel, using 6:4 hexanes−ethyl acetate as eluent, afforded (−)-stypodiol (**1**) (15.5 mg, 86%) as a solid: mp 260−265 °C (dec) (from $CHCl_3$); $[\alpha]^{21}_D$ −7.6 (*c* 0.59, $CHCl_3$) (lit.[1b] $[\alpha]_D$ −3.1); IR (film) 3420, 3010−2800, 1475, 1370, 1225, 1020 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.39 (1 H, s, H-Ar), 6.37 (1 H, s, H′-Ar), 4.18 (1 H, br s, OH), 3.22 (1 H, dd, *J* = 11.0, 5.5, H-3), 3.18 and 2.73 (1 H each, AB system, *J* = 16, CH_2-Ar), 2.15 (3 H, s, Me-Ar), 0.93 (3 H, s, Me-8), 0.92 (3 H, s, Me-10), 0.84 (3 H, s, Me-4β), 0.75 (3 H, s, Me-4α), 0.66 (3 H, d, *J* = 6.5, Me-13); MS (EI) *m*/*z* 413 (M^+ + 1, 27), 412 (M^+, 100), 328 (2), 275 (4), 257 (25), 215 (4), 189 (5); HRMS calcd for $C_{27}H_{40}O_3$ 412.2977, found 412.2974.

(3β,5α,13α,14β)-14,17-Epoxy-4,4,8-trimethyl-16,24-cyclo-13,17-secochola-16,20(22),23-triene-3,23-diol (Epistypodiol, 2). Following the same procedure used to prepare **1** from **22**, the ketone **25** (15 mg, 0.035 mmol) was converted to (+)-epistypodiol (**2**) (13.5 mg, 90%) as an amorphous solid that could not be induced to crystallize: $[\alpha]^{25}_D$ +4.5 (*c* 0.35, $CHCl_3$) [lit.[1b] −4.5]; IR (film) 3460, 3010−2800, 1475, 1375, 1230, 1015 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.44 (1 H, s, H-Ar), 6.35 (1 H, s, H′-Ar), 4.35 (1 H, br s, OH), 3.18 (1 H, dd, *J* = 11.0, 5.0, H-3), 3.06 and 2.91 (1 H each, AB system, *J* = 17, CH_2-Ar), 2.11 (3 H, s, Me-Ar), 1.14 (3 H, s, Me-8), 0.91 (3 H, s, Me-10), 0.85 (3 H, s, Me-4β), 0.74 (3 H, s, Me-4α), 0.70 (3 H, d, *J* = 6.5, Me-13); MS (EI) *m*/*z* 413 (M^+ + 1, 31), 412 (M^+, 100), 395 (8), 379 (5), 351 (2), 276 (7), 257 (50), 215 (4), 189 (8); HRMS calcd for $C_{27}H_{40}O_3$ 412.2977, found 412.2974.

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Supporting Information Available: ^1H NMR spectra of compounds **1**, **2**, **6**, **8**−**11**, **13**−**19**, **22,** and **25** tables of ^{13}C NMR data of compounds **8**−**13** (Table 1) and **1**, **2**, **6**, **14**−**16**, **18**, **19**, **22**, and **25** (Table 2), and spectroscopic data and experimental procedures for the preparation of 3-iodopropanaldehyde diethyl acetal and compound **17** (X = Cl) from 1-bromo-2,5-bis-(methoxymethoxy)-3-methylbenzene (21 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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