First Diastereoselective Synthesis of (−)-Methyl Thyrsiflorin A, (−)-Methyl Thyrsiflorin B Acetate, and (−)-Thyrsiflorin C

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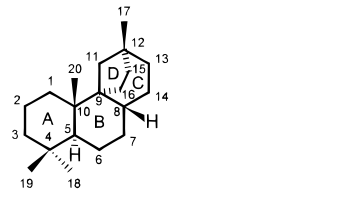
Received October 7, 1999

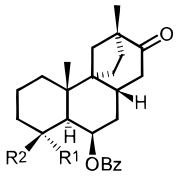
An efficient procedure for the synthesis of scopadulan diterpenes, using (+)-podocarp-8(14)-en-13-one **13** as starting material, is reported. This procedure has been used for the diastereoselective synthesis of (−)-methyl thyrsiflorin A (**8**), (−)-methyl thyrsiflorin B acetate (**9**), and (−)-thyrsiflorin C (**7**). Key steps in our strategy are the intramolecular cyclopropanation of diazoketone **19** and the regioselective cleavage of the cyclopropane ring.

Introduction

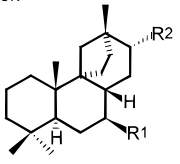
The plant *Scoparia dulcis* has long been used in Paraguay, India, and Taiwan as an alternative medicine for the treatment of stomach disease, hepatosis, and hypertension. Investigating biologically active substances from Paraguayan medicinal plants (*S. dulcis* L., Scrophulariaceae), Hayashi and co-workers isolated a number of structurally unique tetracyclic diterpenes.[1] These diterpenes, which had a novel skeleton (**1**), were named scopadulcic acid A (**2**), scopadulcic acid B (**3**), and scopadulciol (**4**) and revealed interesting antiviral and antitumor properties.[2] During the past several years, new scopadulan diterpenes such as thyrsiflorin A (**5**), thyrsiflorin B (**6**), and thyrsiflorin C (**7**) have been isolated from *Calceolaria thyrsiflora*[3] and *Calceolaria dentata*,[4] and the acids were identified as the corresponding methyl esters.



1 Scopadulan skeleton

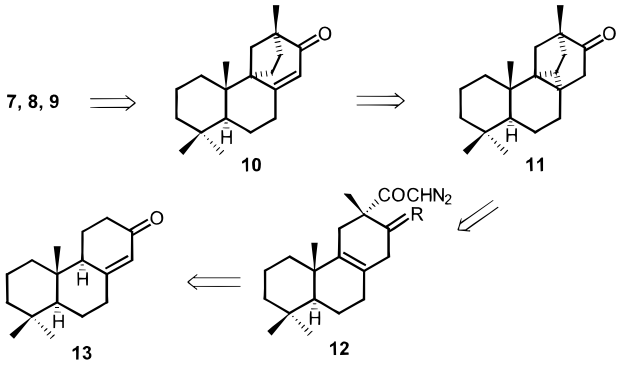


2 R^1=CH_2OH, R^2=CO_2H
3 R^1=CO_2H, R^2=CH_3
4 R^1=CH_2OH, R^2=CH_3



5 R^1=H, R^2=$OCOCH_2CO_2H$
6 R^1=OH, R^2=$OCOCH_2CO_2H$
7 R^1=OH, R^2=OH
8 R^1=H, R^2=$OCOCH_2CO_2Me$
9 R^1=OAc, R^2=$OCOCH_2CO_2Me$

Scheme 1



Despite the pharmacological properties shown by these diterpenes and their interesting skeleton structure, only a few cases of synthesis have been reported; most of them were racemic,[5] and only the enantiodivergent total synthesis of (+)- and (−)-scopadulcic acid A has recently been described.[6] This paper reports a diastereoselective approach for the synthesis of these tetracyclic diterpenes, using as starting material (+)-podocarp-8(14)-en-13-one **13**, easily available in optically active form from natural sources.[7]

The utility of this procedure has been proved by preparing (−)-methyl thyrsiflorin A (**8**, MTA),[8] (−)-methyl thyrsiflorin B acetate (**9**, MTBA), and (−)-thyrsiflorin C (**7**, TC).

Results and Discussion

The retrosynthetic analysis of MTA (**8**), MTBA (**9**), and TC (**7**) is described in Scheme 1. The versatility of our

(1) Hayashi, T.; Kishi, M.; Kawasaki, M.; Arisawa, M.; Shimizu, M.; Suzuki, S.; Yoshizaki, M.; Morita, N.; Tezuka, Y.; Kikuchi, T.; Berganza, L. H.; Ferro, E.; Basualdo, I. *Tetrahedron Lett*. **1987**, *28*, 3693. Hayashi, T.; Kishi, M.; Kawasaki, M.; Arisawa, M.; Morita, N. *J. Nat. Prod*. **1988**, *51*, 360. Hayashi, T.; Asano, S.; Mizutani, M.; Takeguchi, N.; Kojima, T.; Okamura, K.; Morita, N. *J. Nat. Prod*. **1991**, *54*, 802.

(2) Hayashi, K.; Niwayama, S.; Hayashi, T.; Nago, R.; Ochiai, H.; Morita, N. *Antivir. Res*. **1988**, *9*, 345.

(3) Chamy, M. C.; Piovano, M.; Garbarino, J. A.; Miranda, C.; Gambaro, V.; Rodriguez, M. L.; Ruiz-Perez, C.; Brito, I. *Phytochemistry* **1991**, *30*, 589.

(4) Chamy, M. C.; Piovano, M.; Garbarino, J. A.; Vargas, C. *Phytochemistry* **1995**, *40*, 1751.

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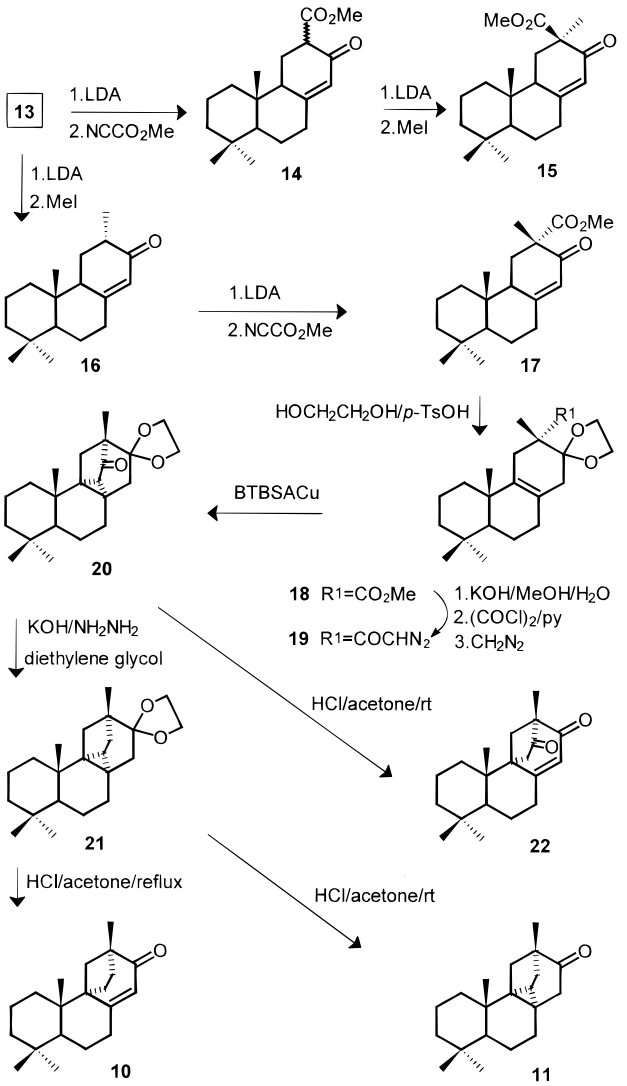
(6) Fox, M. E.; Li, C.; Marino, J. P., Jr.; Overman, L. E. *J. Am. Chem. Soc*. **1999**, *121*, 5467.

(7) Abad, A.; Arno, M.; Domingo, L. R.; Zaragoza, R. J. *Tetrahedron* **1985**, *41*, 4937. Manh, D. D. K.; Fetizon, M.; Flament, J. P. *Tetrahedron* **1975**, *31*, 1879 and references cited herein.

(8) The preparation of (−)-methyl thyrsiflorin A (**8**) was published previously as a preliminary communication: Abad, A.; Agullo; C.; Arno, M.; Marín, M. L.; Zaragoza, R. J. *Synlett* **1997**, 574.

10.1021/jo991561f CCC: $19.00
Published on Web 01/20/2000

Scheme 2



approach is based on the preparation of a tetracyclic intermediate **10**, which already possesses the scopadulan skeleton and a suitable functionality, able to be converted into the three target scopadulan diterpenes. The intermediate **10** would be the result of regioselective cleavage of a cyclopropane ring existing between C-8, C-9 and C-16 in compound **11**. This cyclopropane moiety could arise from an intramolecular cyclopropanation of the convenient diazoketone **12**. Finally, this diazoketone could be obtained by alkylation and acylation of podocarpenone **13**.

The synthetic route begins with the alkylation of podocarpenone **13** using LDA/THF at −25 °C followed by the addition of MeI in order to yield stereoisomer **16** in 94% yield (Scheme 2). Assignment of the stereochemistry of the C-12 Me group was supported by its spectroscopic data, in particular from the *J* values of the signal due to H-12 (δ 2.45). This signal collapsed to a double doublet with *J* 5.8 and 5.5 Hz when C-12 Me was irradiated; these coupling constants are consistent with an equatorial (β) orientation of H-12 that establishes the α-disposition of C-12 Me group.

By treatment of a solution of **16** in THF at −15 °C with LDA followed by addition of $NCCO_2Me$, using Mander's methoxycarbonylation procedure,[9] introduction of the methoxycarbonyl group occurred stereoselectively from the less hindered α side of the molecule to give **17** in 80% yield. It is interesting to note that reversing the order of the last two steps yielded, via the compound **14**, the keto ester epimer **15** as the sole identifiable product. The ester **14** was obtained as a 7:3 mixture of 12β-ester and its 12α-epimer, respectively. The assigned stereochemistries at C-12 in both keto esters **15** and **17** were supported by their spectroscopic data. Of special significance were the NOE enhancements to H-11α and H-11β when the C-17 methyl of isomer **17** was irradiated and the NOE effect observed between the C-17 methyl of isomer **15** (irradiated) and protons H-11α and H-9.

After the introduction of the substituents at C-12, our attention was focused on the ring closure between the α-side chain at C-12 and C-9 in order to complete the tetracyclic structure. It was envisaged that the cyclization could be achieved by intramolecular cyclopropanation of the corresponding diazoketone and subsequent regioselective cleavage of the cyclopropane ring. However, before applying this methodology three transformations had to be made. First of all, the methyl ester had to be converted into the corresponding α-diazoketone. In addition, the double bond between C-8 and C-14 had to migrate to positions C-8 and C-9. Furthermore, after completion of the cyclization two carbonyl groups would exist simultaneously in the molecule; therefore, protection of the carbonyl group at C-13 at this stage was considered to be appropriate.

To this end, migration of the double bond and protection of the carbonyl group could be accomplished simultaneously if using the convenient protective group and the suitable acidic catalyst. Therefore, both transformations were achieved using ethylene glycol and *p*-toluenesulfonic acid (*p*-TsOH) as a catalyst,[10] to give **18** in 83% yield and recovering a 9% of starting material. Ester **18** was then converted into diazoketone **19** using a standard procedure[11] in 92% crude yield.

Initial attempts to effect the cyclization of α-diazoketone **19**, $Rh_2(OAc)_4$,[12] $BF_3{\cdot}OEt_2$,[13] trifluoroacetic acid/$HClO_4$,[14] and $HClO_4$,[15] all gave disappointing results. Eventually, the desired intramolecular insertion was successfully carried out by a slow addition of diazoketone **19** over a refluxing solution of bis(*N*-*tert*-butylsalicylaldiminato)copper(II) (BTBSACu) in toluene[16] to give ketone **20** in 82% yield.

With ketone **20** in hand, we turned our attention to effect the regioselective opening of cyclopropane ring. Ring cleavage of cyclopropyl moieties caused by the enolic form of ketones and assisted by another carbonyl group in the α′-position to the cyclopropane ring has already

(9) Mander, L. N.; Sethi, S. P. *Tetrahedron Lett.* **1983**, *24*, 5425. Carbtree, S. R.; Chu, W. L. A.; Mander, L. N. *Synlett* **1990**, 169.
(10) Greene, T. W.; Wuts, P. G. M. *Protective groups in Organic Chemistry*, John Wiley ans Sons: New York, 1991; pp 188−189. Kocienski, P. J. *Protecting Groups*; G. Thieme Verlag: Germany, 1994; pp 161−162.
(11) Abad, A.; Agullo; C.; Arno, M.; Cuñat, A. C.; Domingo, L. R.; Zaragoza, R. J. *An Quim.* **1991**, *87*, 116.
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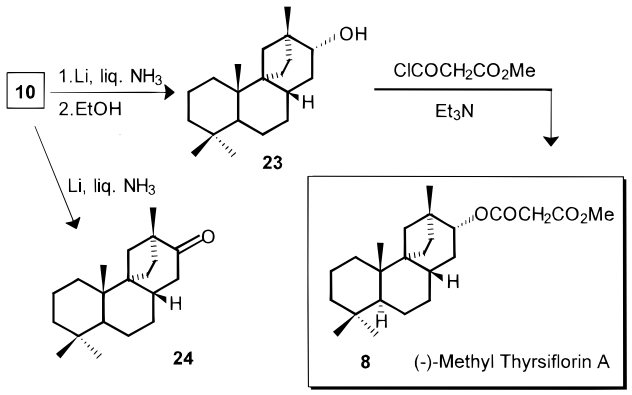
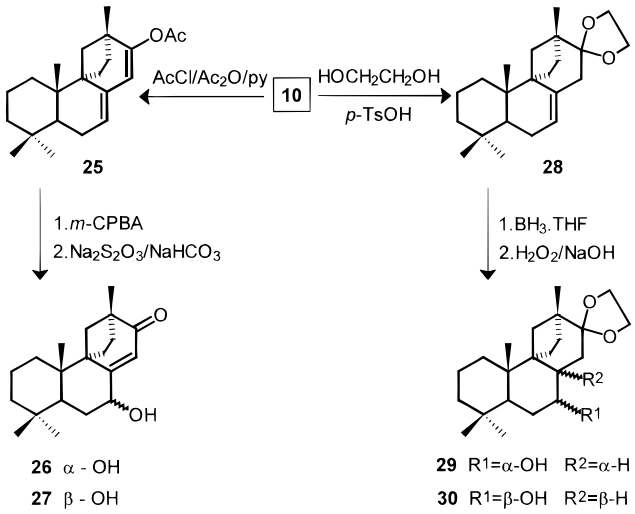
(15) Ghatak, U. R.; Sanyal, B.; Satyanarayana, G. O. S. V.; Ghosh, S. *J. Chem. Soc., Perkin Trans I* **1981**, 1203.
(16) Charles, R. G.*J. Org. Chem.* **1957**, *22*, 677. Corey, E. J.; Myers, A. G. *Tetrahedron Lett.* **1984**, *25*, 3559.

Scheme 3



Scheme 4



been reported in the literature.[17] After testing different experimental conditions, the enone **22** was obtained in 90% yield by treatment of ketone **20** with acetone/HCl 5:1 at room temperature for 2.5 h.

However, this method results in the existence of two carbonyl groups simultaneously in the molecule. To arrive at target compound **10**, the carbonyl group at C-15 needs to be reduced, which involves two additional steps, the first being protection of the carbonyl group at C-13 selectively and the second being deprotection after the reduction. To reduce the number of steps in the sequence, we explored the possibility of reducing the saturated ketone **20** first and then producing the regioselective cleavage of the cyclopropane ring.

To this end, ketone **20** was subjected to Wolff−Kishner conditions giving **21** in 92% yield. Then treatment of **21** under the ring cleavage conditions used above succeeded only in deprotecting ketal moiety without opening the ring, to give the saturated ketone **11**. This fact confirmed that the absence of carbonyl moiety α′ to the cyclopropane ring makes cleavage more difficult. Fortunately, treatment of **21** under more forcing conditions (refluxing 9:1 acetone/HCl for 3.5 h) provided the desired enone **10** in an optimized 81% yield accompanied by ketone **11** (12%). All efforts to complete the conversion of the intermediate ketone **11** into enone **10**, including longer reaction time, led to poorer yields. It should be noted that to our knowledge this ring opening, without the assistance of a second carbonyl group α′ to the cyclopropane ring, has not been described previously. A mechanism to explain this cleavage is proposed in Scheme 5 (see below).

At this point, we had already prepared the key intermediate **10**, able to be converted into the three target scopadulan diterpenes. Then, to fulfill the synthesis of MTA, MTBA and TC, modification of B and C-ring functionalities was necessary. The transformation of enone **10** into MTA is detailed in Scheme 3. This transformation required stereoselective reduction of the double bond to give the B/C ring trans-juncture characteristic of the scopadulan skeleton and also stereoselective reduction of the carbonyl group followed by esterification of the resulting α-hydroxy group. Birch reduction was chosen to effect both stereoselective reductions. Thus, treatment of **10** under Birch's conditions using a proton donor (Li/NH_3−THF/EtOH) caused reduction on both carbonyl and double bond affording alcohol **23** in 86% yield. The assignment of the α-configuration of the hydroxy group at C-13 was based on the *J* values of the H-13 signal at δ 3.36 (J = 10.4 and 5.5 Hz) corresponding to an axial-axial and an axial−equatorial couplings with H-14α and H-14*β*, respectively. When enone **10** was subjected to Birch reduction without using a protic donor (Li/NH_3−THF), the carbonyl moiety at C-13 remained unchanged affording **24** in 89% yield. Since this functionalization is present in other scopadulan diterpenes the sequence developed here is also applicable to the preparation of such natural compounds. To reach completion of MTA (**8**), esterification of the secondary alcohol of **23** was accomplished with $ClCOCH_2CO_2CH_3$ /Et_3N in 76% yield.

After having successfully accomplished the synthesis of the simplest member of the three target scopadulan diterpenes, our efforts were next focused on the oxidation of B ring of enone **10** to reach the other goals of the synthesis of MTBA and TC. Preliminary attempts to introduce an additional hydroxyl group at C-7 met with troubles, since direct allylic oxidation of **10** with PDC/*t*-BuOOH on Celite[18] led to complex mixtures of products. An alternative sequence to obtain the 7*β*-hydroxy enone **27** was conversion of enone **10** into the corresponding 7,13-dienyl acetate **25**, stereoselective epoxidation of the double bond between C-7 and C-8 and subsequent cleavage of the oxirane ring. Thus, treatment of enone **10** under standard conditions ($AcCl/py/Ac_2O$) afforded its dienyl acetate (**25**) (80% yield); however, oxidation of **25** with *m*-CPBA[19] yielded the 7α-hydroxy enone **26** (67% yield) (Scheme 4). Since the opposite stereochemistry was obtained in this epoxidation a different route was sought.

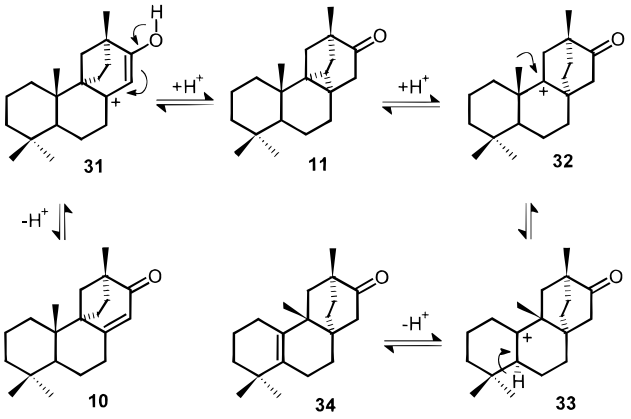
It was envisaged that the hydroxyl group at C-7 could be introduced by hydroboration-oxidation of a double bond existing between C-7 and C-8. This double bond would be the result of the acidic isomerization during transformation of enone **10** into the ketal **28**. To this end, **10** was subjected to similar conditions to those used in the synthesis of ketal **18** (*p*-TsOH, 2.1×10^{-3} M in benzene); however, only unreacted enone **10** was recovered after long reaction time. This unexpected result can

(17) Lafontain, J.; Mongrain, M.; Sergent-Guay, M.; Ruest, L.; Deslongchamps, P. *Can. J. Chem.* **1980**, *58*, 2460. Beames, D. J.; Halleday, J. A.; Mander, L. N. *Aust. J. Chem.* **1972**, *25*, 137. Stipanovic, R. D.; Turner, R. B. *J. Org. Chem.* **1968**, *33*, 3261.

(18) Chandrasekaran, S.; Chidambaram, N. *J. Org. Chem.* **1987**, *52*, 5048.

(19) Abad, A.; Agulló, C.; Arno, M.; Domingo, L. R.; Zaragoza, R. J. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1875.

Scheme 5

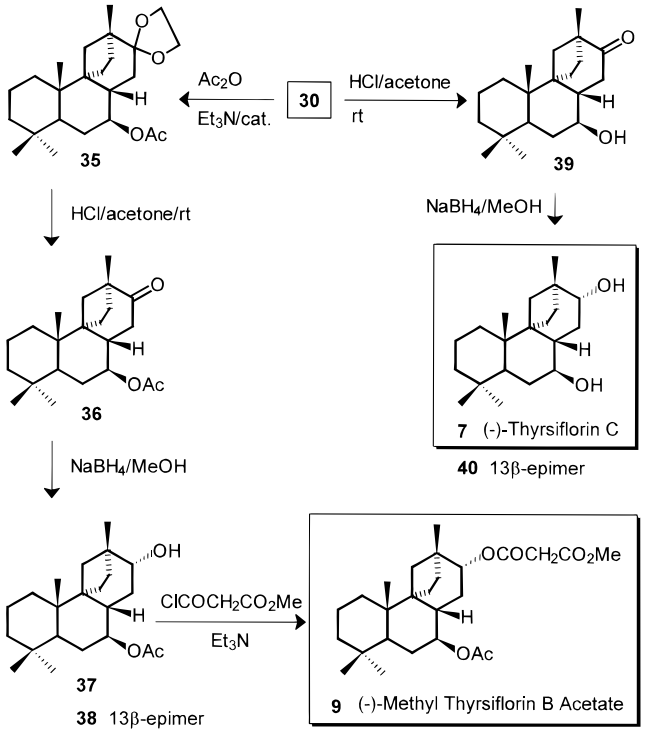


be explained by the low concentration of catalyst, which only permits ketalization of the carbonyl group without isomerization of the double bond. That molecule would be extremely sensitive to hydrolysis and would restore the starting enone during the workup stage.[20] Eventually, this ketalization was best accomplished using *p*-TsOH (5.5×10^{-3} M in benzene) to afford the unconjugated ketal **28** in 72% yield and 20% of starting enone **10**.

Further attempts were made in order to optimize the efficiency of this transformation. However, when higher concentrations of *p*-TsOH (4.0×10^{-2} M in benzene) were used, instead of obtaining the predictable ketal **28**, the reaction followed a different reaction pathway leading to the formation of a new product which was identified, after deketalization, as the rearranged ketone **34** (Scheme 5). To our knowledge, this molecule displays a novel carbon framework, which is a new tetracyclic diterpene skeleton. We confirmed that this new ketone **34** could be obtained directly from enone **10**, using the same conditions, without the presence of ethylene glycol. A reasonable mechanism to explain this rearrangement is proposed in Scheme 5, and it is very related with the cyclopropane ring opening of **11** that produces enone **10**. In fact, this last transformation may be explained through regioselective protonation of C8−C16 bond to give the tertiary carbocation **31**, which assisted by the enolic form of the carbonyl group at C-13 would evolve to the enone **10**. On the other hand, the rearrangement of enone **10** to give ketone **34** implies, in the first stage, the equilibrium between **10** and **11**. Then, regioselective protonation of C9−C16 bond would afford the carbocation **32**, which after 1,2-methyl shift[21] would evolve to the tertiary carbocation **33**. Finally, proton elimination would give the, probably more stable, rearranged ketone **34**. When cyclopropane **11** was treated under the same conditions as enone **10**, ketone **34** was obtained, supporting the contribution of **11** in this proposed reaction pathway. A complete study of this mechanism is currently in progress.

Following our research toward the functionalization at C-7, we investigated the hydroboration−oxidation of the double bond in ketal **28**. Previous hydroboration−oxidation studies on similar compounds[22] had showed preferential hydroboration from the less hindered α-side. However, in this case the presence of the cyclopentane

Scheme 6



D-ring increases the hindrance of the α-side. Therefore, hydroboration of the double bond could predominantly occur from the *β*-side permitting the synthesis of alcohol **30** with the required stereochemistry at C-7 and C-8. Then, treatment of olefin **28** with $BH_3 \cdot SMe_2$, followed by oxidation (H_2O_2, NaOH),[23] afforded a complex mixture of compounds, from which the desired *β*-alcohol **30** was only isolated in 25% yield accompanied by a 20% of a new product which resulted to be, after deketalization, the ketone **24**. This product is the result of an unusual double bond reduction. Fortunately, further experiments with $BH_3 \cdot THF$[24] modifying the amount of hydroborating agent,[25] provided the desired *β*-alcohol **30** in an optimized 71% yield along with a 22% of the α-alcohol **29**. The splitting pattern showed for H-7 of alcohol **30** (δ 3.40, ddd, J = 10.8, 10.8, and 5.5 Hz) is in agreement with an axial orientation, thus, coupling with two axial (H-8*β* and H-6*β*) and an equatorial (H-6α) protons.

Once the correct functionalization at C-7 and stereochemistry at C-8 have both successfully been achieved, our attention was next turned to modify the functionalization present in **30**, completing the synthesis of MTBA and TC as outlined in Scheme 6. Treatment of **30** with Ac_2O/Et_3N and 4-pyrrolidinopyridine[26] yielded the acetate **35** in 92% yield, and then subsequent deketalization of **35** gave ketone **36** in almost quantitative yield. Reduction of **36** using $NaBH_4$/MeOH occurred preferentially on *β*-side, giving alcohol **37** (77%) accompanied by the minor

(20) Petersen, Q. R.; Sowers, E. E. *J. Org. Chem.* **1964**, *29*, 1627.
(21) For related migrations, see: Delmond, B.; Taran, M. *J. Chem. Soc., Chem. Commun.* **1984**, 716.
(22) Jeffs, P. W.; Mahajan, J. R.; Wenkert, E. *J. Am. Chem. Soc.* **1964**, *86*, 2218.
(23) Lane, C. F. *J. Org. Chem.* **1974**, *39*, 1437.
(24) Kabalka, G. W.; Hedgecock, H. C., Jr. *J. Org. Chem.* **1975**, *40*, 1776.
(25) It should be pointed out that 4 mol of $BH_3 \cdot THF$ per mol of olefin was required to effect this conversion. When either longer reaction times or higher concentration of hydroborating agent were used lower yields were obtained, due probably to the reduction of the ketal moiety.[29] Likewise the use of a more bulky hydroborating agent, such as 9-BBN,[30] to increase the stereoselectivity of the reaction, was unsuccessful.
(26) Hassner, A.; Krepski, L. R.; Alexanian, V. *Tetrahedron* **1978**, *34*, 2069.

epimer **38** (21%). Finally, esterification of **37** with $ClCOCH_2CO_2CH_3/Et_3N$ afforded the second scopadulan diterpene (−)-methyl thyrsiflorin B acetate (**9**) in 73% yield.

To obtain the (−)-thyrsiflorin C (**7**), ketal **30** was subjected to deketalization providing ketone **39** in 82% yield. Subsequent treatment of **39** with $NaBH_4$/MeOH furnished as major compound the (−)-thyrsiflorin C (**7**) in 78% yield together with 20% of 13*β*-epimer **40**.

Synthetic scopadulan diterpenes **7**, **8**, **9** and also alcohol **23** and ketone **24** showed spectroscopic and physical data similar to those previously reported in the literature.[27] Also specific optical rotations recorded here for **7**, **8**, and **9** are in good accord with those reported previously, confirming the absolute stereochemistry of these scopadulan diterpenes.

In conclusion, a diastereoselective synthetic route to the scopadulan diterpenes whose key steps are an intramolecular cyclopropanation and a regioselective cyclopropane ring opening, has been designed and demonstrated, using a chiral podocarpenone **13** as a starting material. This route permits the synthesis of an advanced intermediate such as enone **10**, which already possesses the scopadulan skeleton, in seven steps (31% overall yield) from podocarpenone **13**. The utility of this sequence has been proved by preparing (−)-methyl thyrsiflorin A **8** (65%, two steps), (−)-methyl thyrsiflorin B acetate **9** (27%, six steps), and (−)-thyrsiflorin C **7** (33%, four steps) from the intermediate **10**.

Experimental Section

General Experimental Details. Melting points are uncorrected. Optical rotations were determined using a 5-cm pathlength cell. $[\alpha]_D$ values are given in 10^{-1} deg·cm^2·g^{-1}. IR spectra were measured as KBr pellets or as films on NaCl plates. NMR spectra were recorded on 250, 300 or 400 MHz spectrometers. The signal of the deuterated solvent ($CDCl_3$) was taken as the reference (the singlet at δ 7.24 for ^{1}H and the triplet centered at δ_c 77.00 for ^{13}C NMR data). Complete assignments of ^{13}C NMR multiplicities were made on the basis of DEPT experiments. HMQC and NOE experiments were used in some ^{1}H NMR assignments. *J* values are given in Hz. In all compounds, NMR assignments are given with respect to the numbering scheme shown in structure 1. Mass spectra were run by electron impact (EI) at 70 eV. Elemental analyses were performed by Servei de Microanalisi del CSIC (Barcelona). Purifications were performed by flash chromatography on Si gel (230−400 mesh). All nonaqueous reactions were carried out in an argon atmosphere in oven-dried glassware. Commercial reagent grade solvents and chemicals were used as received unless otherwise noted. THF was distilled from sodium benzophenone ketyl under argon atmosphere. Organic extracts were washed with brine, dried over sodium sulfate and concentrated under vacuum.

12α-Methyl-8(14)-podocarpen-13-one (16). A solution of LDA in THF (0.5 M, 9.76 mL, 4.88 mmol) was slowly added (ca. 2 h) to a solution of podocarpenone **13** (1.09 g, 4.43 mmol) and *o*-phenanthroline (used as indicator) in THF (35.9 mL) at −25 °C, until persistence of red color. Then, HMPA (0.77 mL, 4.43 mmol) and MeI (0.83 mL, 13.29 mmol) were successively added via syringe, and the resulting yellow solution was allowed to warm to room temperature for 1.25 h. The reaction mixture was quenched with saturated NH_4Cl (5 mL), poured into saturated aqueous NH_4Cl solution, and extracted with ether. Workup afforded an oily residue which was purified by column chromatography, using hexanes−ethyl acetate (from 95:5 to 9:1) as eluent, to give the unreacted enone **13** (35 mg, 3%) and the methyl podocarpenone **16** as a colorless oil (1.088 g, 94%): $[\alpha]^{23}_D$ −25.4 (*c* 2.2, $CHCl_3$); IR (KBr) 1671 cm^{-1}; ^{1}H NMR (300 MHz; $CDCl_3$) δ 5.78 (1H, dd, J = 2.1, 1.8, H-14), 2.45 (1H, m, H-12), 1.06 (3H, d, J = 7.2, H-17), 0.91, 0.86 and 0.84 (3H each, each s, H-18, H-19 and H-20); ^{13}C NMR (75 MHz; $CDCl_3$) δ_C 203.28 (s), 164.54 (s), 123.93 (d), 54.36 (d), 48.38 (d), 41.83 (t), 39.62 (s), 39.57 (d), 39.39 (t), 35.81 (t), 33.65 (q), 33.42 (s), 27.57 (t), 22.52 (t), 21.95 (q), 18.80 (t), 16.70 (q), 15.40 (q); MS (EI) *m*/*z* 260 (M$^+$, 82), 245 (33), 123 (100); HRMS $C_{18}H_{28}O$ requires 260.2140, found 260.2151.

12α-Methoxycarbonyl-12*β*-methyl-8(14)-podocarpen-13-one (17). In a similar manner as above, a solution of LDA in THF (0.5 M, 9.30 mL, 4.65 mmol) was slowly added (ca. 2.5 h) to a solution of methyl podocarpenone **16** (1.098 g, 4.22 mmol) and a small amount of *o*-phenanthroline in THF (38 mL) at −15 °C. After cooling to −78 °C, HMPA (0.73 mL, 4.22 mmol) and $CNCO_2Me$ (1.0 mL, 12.66 mmol) were successively added via syringe. The reaction mixture was allowed to warm to −30 °C for 2.5 h, then quenched by addition of saturated NH_4Cl (6 mL), poured into aqueous NH_4Cl and extracted with ether. Workup gave a residue, which was purified by chromatography, using hexanes−ethyl acetate (from 9:1 to 8:2) as eluent, to afford the methyl ester **17** as a white solid (1.065 g, 80%): mp 102−103 °C (needles, from hexane); $[\alpha]^{23}_D$ +40.2 (*c* 2.0, $CHCl_3$); IR (KBr) 1729, 1685, 1621 cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 5.85 (1H, dd, J = 2.1, 1.8, H-14), 3.59 (3H, s, OMe), 2.45 (1H, ddd, J = 15.7, 5.3, 1.9, H-7*β*), 2.35 (1H, dd, J = 13.8, 5.3, H-11α), 1.46 (from NOE) (1H, dd, J = 13.8, 10.4, H-11*β*), 1.29 (3H, s, H-17), 0.86 (3H, s, H-18), 0.81 (3H, s, H-19), 0.69 (3H,s, H-20); ^{13}C NMR (75 MHz; $CDCl_3$) δ_C 196.08 (s), 173.14 (s), 165.17 (s), 124.84 (d), 53.53 (d), 52.40 (q), 49.56 (d), 41.63 (t), 38.88 (t), 38.71 (s), 35.13 (t), 33.53 (q), 33.34 (s), 32.01 (t), 21.97 (q), 21.86 (t), 21.22 (q), 18.60 (t), 14.66 (q), the signal of a quaternary carbon was hidden by another carbon signal; MS (EI) *m*/*z* 318 (M$^+$, 73), 303 (40), 243 (23), 137 (100); HRMS $C_{20}H_{30}O_3$ requires 318.2195, found 318.2197. Anal. Calcd for $C_{20}H_{30}O_3$: C, 75.42; H, 9.50. Found: C, 75.54; H, 9.63.

13,13-Ethylenedioxy-12α-methoxycarbonyl-12*β*-methyl-8-podocarpene (18). A mixture of podocarpenone **17** (1.065 g, 3.35 mmol), ethylene glycol (1.48 mL, 26.47 mmol), *p*-TsOH monohydrate (18 mg, 0.095 mmol), and benzene (44 mL) was refluxed in a Dean−Stark system for 31 h. After this time the reaction mixture was diluted with hexane, washed with 10% aqueous $NaHCO_3$ solution and brine, dried and concentrated to give a semisolid. Chromatography of the crude with hexanes−ethyl acetate (from 9:1 to 8:2) gave the ketal **18** as a white solid (1.0 g, 83%) and 95 mg (9%) of starting material. For **18**: mp 96−97 °C (from hexane); $[\alpha]^{24}_D$ +22.2 (*c* 1.4, $CHCl_3$); IR (KBr) 1727 cm^{-1}; ^{1}H NMR (300 MHz; $CDCl_3$) δ 3.98−3.72 (4H, m, ketal), 3.67 (3H, s, OMe), 2.80 (1H, br d, J = 17.5, H-14), 1.19 (3H, s, H-17), 0.92 (3H, s, H-20), 0.85 (3H, s, H-18), 0.81 (3H, s, H-19); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 175.07 (s), 135.75 (s), 122.91 (s), 110.13 (s), 64.98 (t), 64.90 (t), 51.88 (q), 51.07 (d), 48.41 (s), 41.55 (t), 39.31 (t), 37.28 (s), 35.94 (t), 33.40 (t), 33.17 (s), 33.05 (q), 31.15 (t), 21.51 (q), 18.93 (q), 18.73 (q), 18.71 (t), 18.49 (t); MS (EI) *m*/*z* 362 (M$^+$, 97), 347 (100), 315 (28); HRMS $C_{22}H_{34}O_4$ requires 362.2457, found 362.2456.

Preparation of Diazoketone 19 from Ketal 18. A mixture of ketal **18** (1.0 g, 2.76 mmol), KOH (85%, 4.0 g, 60.71 mmol), distilled water (8.7 mL), and methanol (51 mL) was refluxed for 18 h. The reaction mixture was then cooled, poured into cold aqueous HCl (1.2 M, 70 mL) and extracted once with CH_2Cl_2 and further three times with ether. Workup as usual gave 933 mg of a yellowish solid crude acid which was used in the following step without further purification.

To a solution of the crude acid in dry benzene (23.9 mL), pyridine (337 μL, 4.14 mmol) and $(COCl)_2$ (98%, 1.46 mL, 33.12 mmol) were successively added. When the addition was

(27) For spectroscopic and physical data see refs 3 and 4. Although some typographical errors have been found in the cited references. The corrected values have been given to us by a personal communication from Prof. Garbarino and are as follows. For (−)-methyl thyrsiflorin B acetate: $[\alpha]^{25}_D$ = −4.7 (*c* 0.8) (ref 3) and $[\alpha]^{25}_D$ = −7.63 (*c* 1.0) (ref 4). For (−)-thyrsiflorin C (ref 3): mp 166−168 °C and $[\alpha]^{25}_D$ = −12.3 (*c* 1.2).

complete a white suspension appeared. After the mixture was stirred for 27 h at room temperature, the solvent was removed in vacuo (Teflon vacuum pump). The crude was cooled in an ice bath, and an excess of an ethanol-free CH_2N_2/ether solution[28] (0.35 M, 32 mL) was added. The reaction mixture was stirred for 24 h at 4 °C before evaporation of the solvent. The obtained residue was filtered through a pad of neutral alumina, using hexanes−ethyl acetate (9:1) as eluent, to give the α-diazoketone **19** (959 mg, 92%) as a yellowish foam containing a 10% of ketal **18**. This diazoketone was not purified due to its instability and then used directly in the next step. NMR data for crude diazoketone **19**: ^{1}H NMR (400 MHz; C_6D_6) δ 5.28 (1H, s, $COCHN_2$), 3.48−3.35 (4H, m, ketal), 3.16 (1H, br d, J = 17.3, H-14), 1.16 (3H, s, H-17), 0.91, 0.84 and 0.81 (3H each, each s, H-18, H-19 and H-20); ^{13}C NMR (75 MHz; C_6D_6) δ_C 196.09 (s), 136.96 (s), 122.54 (s), 110.85 (s), 64.65 (t), 64.66 (t), 53.52 (d), 52.30 (s), 51.31 (d), 41.89 (t), 39.67 (t), 37.73 (s), 36.28 (t), 33.36 (t), 33.32 (q), 33.28 (s), 31.67 (t), 21.77 (q), 19.36 (q), 19.28 (q), 19.14 (t), 18.99 (t).

Preparation of Cyclopropane 20 from Diazoketone 19. To a refluxing solution of bis(*N-tert*-butylsalicylaldiminato)-copper(II) (24 mg, 0.06 mmol) in dry toluene (30 mL), a solution of the diazoketone **19** (90%, 237 mg, 0.57 mmol) in dry toluene (10 mL) was slowly added for 6 h (syringe pump). After the addition was complete, the reaction mixture was stirred for a further 30 min before evaporation of the solvent. Chromatography of the crude using hexanes−ethyl acetate (8:2) afforded 23 mg of the unreacted ketal impurity **18** and the ketone **20** as a white solid (162 mg, 82%): mp 185−186 °C (from ether); $[\alpha]^{20}_D$ −17.4 (*c* 1.4, $CHCl_3$); IR (KBr) 1725 cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 3.98−3.65 (4H, m, ketal), 2.28 (1H, d, J = 14.8, H-14), 2.11 (1H, d, J = 12.3, H-11), 2.04 (1H, d, J = 14.8, H-14′), 1.80 (1H, s, H-16), 1.68 (1H, d, J = 12.3, H-11′), 1.06 (3H, s, H-20), 0.90 (3H, s, H-17), 0.80 (3H, s, H-19), 0.79 (3H, s, H-18); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 210.99 (s), 112.24 (s), 65.24 (t), 64.94 (t), 52.29 (s), 47.98 (s), 47.48 (d), 41.82 (t), 41.59 (t), 39.47 (d), 36.56 (t), 34.06 (s), 33.71 (q), 33.05 (s), 32.20 (s), 31.89 (t), 29.19 (t), 21.37 (q), 18.41 (t), 17.75 (t), 17.53 (q), 10.97 (q); MS (EI) *m*/*z* 344 (M$^+$, 100), 316 (15); HRMS $C_{22}H_{32}O_3$ requires 344.2351, found 344.2352. Anal. Calcd for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 76.82; H, 9.45.

Preparation of Compound 21 from Ketone 20. A solution of the ketone **20** (190 mg, 0.55 mmol), KOH (85%, 1.2 g, 18.21 mmol), hydrazine monohydrate (98%, 0.6 mL, 12.12 mmol), and di(ethylene glycol) (7.6 mL) was refluxed at 120 °C for 2 h. Then, the resulting yellow solution was heated at 220 °C and the excess of reactants distilled for 2 h. The yellow-brown mixture was cooled to room temperature, poured into saturated aqueous NH_4Cl and extracted with hexane. Workup as usual furnished a solid residue that was purified by column chromatography, using hexane−diethyl ether (from 95:5 to 9:1) as eluent, to afford ketal **21** as a white solid (167 mg, 92%): mp 76−77 °C (from methanol); $[\alpha]^{24}_D$ +23.1 (c 1.9, $CHCl_3$); IR (KBr) 3008, 1109 cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 3.90−3.74 (4H, m, ketal), 1.03 (3H, s, H-17), 0.86 (3H, s, H-20), 0.78 (3H, s, H-19), 0.77 (3H, s, H-18); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 111.34 (s), 64.72 (t), 64.62 (t), 48.18 (d), 43.86 (s), 42.56 (t), 42.00 (t), 41.71 (s), 36.86 (t), 36.14 (t), 35.32 (t), 33.91 (q), 33.64 (s), 33.08 (s), 30.54 (t), 26.53 (d), 21.51 (q), 19.77 (q), 19.70 (s), 18.80 (t), 18.27 (t), 17.72 (q); MS (EI) *m*/*z* 330 (M$^+$, 100), 316 (7); HRMS $C_{22}H_{34}O_2$ requires 330.2559, found 330.2551. Anal. Calcd for $C_{22}H_{34}O_2$: C, 79.95; H, 10.37. Found: C, 79.96; H, 10.36.

8(14)-Scopadulen-13-one (10). A solution of ketal **21** (107 mg, 0.32 mmol) in acetone/HCl 12M (9:1, 6.2 mL) was refluxed for 3.5 h. The mixture was cooled to room temperature, diluted with ether and washed with 10% aqueous $NaHCO_3$ solution. Workup gave a residue, which after chromatography, using hexanes−ethyl acetate (9:1), afforded the cyclopropane **11** (13 mg, 12%) followed by the enone **10** (75 mg, 81%): mp 97−98 °C (from hexane); $[\alpha]^{23}_D$ +164.1 (c 1.5, $CHCl_3$); IR (KBr) 3007, 1664, 1601 cm^{-1}; ^{1}H NMR (300 MHz; $CDCl_3$) δ 5.72 (1H, dd, J = 2.2, 0.5, H-14), 2.56 (1H, dddd, J = 17.7, 5.8, 2.4, 0.5, H-7β), 2.44 (1H, dddd, J = 17.7, 12.1, 6.8, 2.2, H-7α), 1.16 (3H, s, H-17), 0.93, 0.90 and 0.88 (3H each, each s, H-18, H-19 and H-20); ^{13}C NMR (75 MHz; $CDCl_3$) δ_C 204.50 (s), 171.12 (s), 124.37 (d), 58.94 (s), 50.39 (s), 47.22 (d), 44.12 (t), 41.91 (t), 37.46 (s), 35.29 (t), 33.76 (q), 33.43 (s), 32.79 (t), 30.80 (t), 29.27 (t), 22.66 (q), 20.97 (t), 20.86 (q), 20.22 (q), 18.40 (t); MS (EI) *m*/*z* 286 (M$^+$, 68), 271 (24); HRMS $C_{20}H_{30}O$ requires 286.2297, found 286.2297. Anal. Calcd for $C_{20}H_{30}O$: C, 83.85; H, 10.56. Found: C, 83.92; H, 10.61.

13α-Scopadulanol (23). To an intense blue solution of Li (20 mg, 2.90 mmol) in NH_3 (8 mL) at −35 °C a solution of **10** (37 mg, 0.13 mmol) in THF (1.2 mL) was added. After being stirred for 1 h, a mixture of EtOH/THF (1:4, 0.5 mL) was slowly added for 30 min and the reaction mixture was allowed to stir for further 30 min. The lithium excess was then destroyed by addition of solid NH_4Cl and the NH_3 excess was evaporated under argon atmosphere. The crude mixture was poured into water and extracted with ether. Usual workup afforded a solid residue which was purified by chromatography, using hexanes−ethyl acetate (9:1) to give 3.0 mg (8%) of ketone **27** and 32.3 mg (86%) of alcohol **23**: mp 133−134 °C (from hexanes−ethyl acetate) (lit.[3] mp 140−141 °C, from MeOH−H_2O); $[\alpha]^{23}_D$ −30.3 (c 1.5, $CHCl_3$) (lit.[3] $[\alpha]^{25}_D$ −38.3, c 1.0); IR (KBr) 3250 cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 3.36 (1H, dd, J = 10.4, 5.5, H-13), 0.97 (3H, s, H-17), 0.94 (3H, s, H-20), 0.79 (3H, s, H-18), 0.78 (3H,s, H-19); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 76.32 (d), 52.41 (s), 47.91 (d), 44.44 (t), 44.05 (s), 42.14 (t), 38.46 (s), 38.11 (t), 37.33 (d), 33.56 (q), 33.06 (s), 32.51 (t), 30.63 (t), 30.08 (t), 24.37 (t), 23.24 (q), 21.99 (q), 21.77 (t), 18.73 (t), 17.28 (q); MS (EI) *m*/*z* 290 (M$^+$, 100), 275 (10), 272 (9), 261 (12); HRMS $C_{20}H_{34}O$ requires 290.2610, found 290.2615.

(−)-Methyl Thyrsiflorin A (8). To a solution of alcohol **23** (29.3 mg, 0.102 mmol) in diethyl ether (1.2 mL) cooled in an ice bath, dry Et_3N (143 μL, 1.02 mmol) and $ClCOCH_2CO_2CH_3$ (110 μL, 1.02 mmol) were successively added. After being stirred for 40 min at room temperature, the reaction mixture was diluted with hexane. Workup as usual gave an oily residue, which was purified by flash chromatography with hexanes−ethyl acetate (95:5) to afford (−)-methyl thyrsiflorin A (**8**) as a colorless oil (29.9 mg, 76%): $[\alpha]^{20}_D$ −47.6 (c 2.1, $CHCl_3$) (lit.[3] −50.0, c 1.5); IR (KBr) 1755, 1734 cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 4.64 (1H, ddd, J = 11.0, 6.1, 1.2, H-13), 3.71 (3H, s, $COOCH_3$), 3.33 (2H, s, $COCH_2CO$), 0.94 (3H, s, H-20), 0.89 (3H, s, H-17), 0.86 (1H, dd, J = 12.1, 2.8, H-5), 0.79 (3H, s, H-18), 0.77 (3H, s, H-19); ^{13}C NMR (300 MHz; $CDCl_3$) δ_C 167.17 (s), 166.21 (s), 80.00 (d), 52.49 (s), 52.34 (q), 47.94 (d), 44.47 (t), 43.05 (s), 42.16 (t), 41.70 (t), 38.52 (s), 37.14 (d), 34.19 (t), 33.60 (q), 33.10 (s), 32.49 (t), 31.94 (t), 29.94 (t), 24.36 (t), 23.11 (q), 22.02 (q), 21.77 (t), 18.72 (t), 17.31 (q); MS (EI) *m*/*z* 390 (M$^+$, 12), 306 (7), 272 (100); HRMS $C_{24}H_{38}O_4$ requires 390.2770, found 390.2775.

13,13-Ethylenedioxy-7-scopadulene (28). A mixture of enone **10** (49 mg, 0.17 mmol), ethylene glycol (238 μL, 4.26 mmol), *p*-TsOH monohydrate (14 mg, 0.074 mmol), and benzene (13.1 mL) was refluxed in a Dean−Stark system for 2.5 h. The reaction mixture was poured into water and extracted with hexane. The combined extracts were washed with 10% aqueous $NaHCO_3$ solution and brine, dried and concentrated to give a solid. Chromatography of the crude using hexanes−ethyl acetate (95:5) gave the ketal **28** as a white solid (41 mg, 72%) followed by 9.9 mg (20%) of starting material. For **28**: mp 124−125 °C (from methanol); $[\alpha]^{24}_D$ −106.4 (c 1.9, $CHCl_3$); IR (KBr) 1115 cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 5.20 (1H, m, H-7), 4.00−3.75 (4H, m, ketal), 2.50 (1H, dddd, J = 16.1, 5.8, 2.9, 2.9, H-14), 2.30 (1H, d, J = 16.1, H-14′), 2.12 (1H, ddd, J = 16.4, 16.4, 5.8), 1.66 (1H, br d, J = 11.5, H-11), 0.97 and 0.93 (3H each, each s, H-17 and H-20), 0.89 (3H, s, H-19), 0.83 (3H,s, H-18); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 140.19 (s), 118.08 (d), 113.05 (s), 65.45 (t), 65.02 (t), 54.80 (s), 46.85 (s), 45.44 (d), 42.56 (t), 41.20 (t), 40.28 (t), 37.16 (s), 34.05 (t), 33.79 (q), 33.21 (t), 32.88 (s), 31.28 (t), 24.08 (t),

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23.16 (q), 19.83 (q), 18.79 (q), 18.72 (t); MS (EI) *m/z* 330 (M^+, 100), 315 (6); HRMS $C_{22}H_{34}O_2$ requires 330.2559, found 330.2560.

13,13-Ethylenedioxy-7β-scopadulanol (30). A solution of BH_3·THF (1 M in THF, 344 μL, 0.344 mmol) was slowly added to the olefin **28** (28.4 mg, 0.086 mmol) cooled in an ice-bath. Once the addition was complete the reaction mixture was allowed to warm to room temperature, stirred for 50 min, and cooled in an ice-bath again. Then, a mixture of NaOH 6M/H_2O_2 35% (1:1.25, 100 μL) was carefully added dropwise. After 35 min at room temperature, the resulting mixture was heated to 60 °C for 1 h, cooled, quenched with saturated aqueous NH_4-Cl and diluted with diethyl ether. Usual workup gave an oily residue which was purified by chromatography, using hexanes−ethyl acetate (from 7:3 to 6:4) as eluent, to afford the α-alcohol **29** (6.5 mg, 22%) followed by the β-alcohol **30** (21.2 mg, 71%) as a white solid: mp 161−162 °C (from hexane−diethyl ether); $[\alpha]^{23}_D$ +8.3 (*c* 1.2, $CHCl_3$); IR (KBr) 3398, 1121 cm^{-1}; ^1H NMR (300 MHz; $CDCl_3$) δ 4.00−3.75 (4H, m, ketal), 3.40 (1H, ddd, *J* = 10.8, 10.8, 5.5, H-7), 2.10 (1H, dd, *J* = 13.9, 5.1, H-14β), 1.00 (3H, s, H-20), 0.91 (3H, s, H-17), 0.82 and 0.81 (3H each, each s, H-18 and H-19); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 112.81 (s), 73.83 (d), 65.30 (t), 64.96 (t), 53.06 (s), 47.16 (s), 46.17 (d), 44.46 (d), 42.58 (t), 41.97 (t), 38.49 (s), 35.22 (t), 35.07 (t), 33.53 (q), 33.05 (s), 32.41 (t), 32.13 (t), 25.24 (t), 22.07 (q), 19.44 (q), 18.67 (t), 17.67 (q); MS (EI) *m/z* 348 (M^+, 100), 330 (6), 316 (6); HRMS $C_{22}H_{36}O_3$ requires 348.2664, found 348.2666.

7β-Acetoxy-13,13-ethylenedioxyscopadulane (35). To a solution of alcohol **30** (14.7 mg, 0.042 mmol) and 4-pyrrolidinopyridine (98%, 0.6 mg, 0.004 mmol) as a catalyst in dry Et_3N (155 μL) cooled in an ice bath, acetic anhydride (9 μL, 0.084 mmol) was added dropwise. After stirring for 20 min, the reaction mixture was diluted with hexane. Workup as usual followed by column chromatography, using hexanes−ethyl acetate (from 8:2 to 7:3) as eluent, yielded the acetate **35** (15.1 mg, 92%) as an amorphous solid that could not be induced to crystallize: $[\alpha]^{24}_D$ +5.5 (c 2.9, $CHCl_3$); IR (KBr) 1726, 1124 cm^{-1}; ^1H NMR (250 MHz; $CDCl_3$) δ 4.67 (1H, ddd, *J* = 11.0, 11.0, 5.5, H-7), 4.00−3.72 (4H, m, ketal), 2.02 (3H, s, $COCH_3$), 1.00 (3H, s, H-20), 0.90 (3H, s, H-17), 0.80 and 0.79 (3H each, each s, H-18 and H-19); ^{13}C NMR (62.5 MHz; $CDCl_3$) δ_C 170.89 (s), 112.61 (s), 76.35 (d), 65.37 (t), 65.03 (t), 53.09 (s), 47.24 (s), 45.83 (d), 42.43 (t), 41.90 (t), 41.12 (d), 38.30 (s), 35.07 (t), 34.93 (t), 33.49 (q), 33.13 (s), 32.21 (t), 27.95 (t), 25.10 (t), 21.99 (q), 21.38 (q), 19.48 (q), 18.60 (t), 17.55 (q); MS (EI) *m/z* 390 (M^+, 42), 348 (48), 331 (27), 330 (100); HRMS $C_{24}H_{38}O_4$ requires 390.2770, found 390.2762.

7β-Acetoxy-13-scopadulanone (36). A solution of ketal **35** (20.5 mg, 0.052 mmol) in acetone/HCl 12 M (9:1, 1.2 mL) was stirred at room temperature for 30 min. The mixture was diluted with diethyl ether and washed with a 10% aqueous $NaHCO_3$ solution. Workup as usual gave a residue, which was purified by chromatography using hexanes−ethyl acetate (8:2) to furnish the ketone **36** (17.8 mg, 98%) as a colorless oil: $[\alpha]^{25}_D$ +32.5 (c 1.5, $CHCl_3$); IR (NaCl) 1733, 1710 cm^{-1}; ^1H NMR (300 MHz; $CDCl_3$) δ 4.82 (1H, ddd, *J* = 10.7, 10.7, 5.6, H-7), 2.43 (1H, dd, *J* = 15.4, 5.6, H-14β), 2.21 (1H, ddd, *J* = 11.5, 10.5, 5.6, H-8), 2.01 (3H, s, $COCH_3$), 1.04 and 1.02 (3H each, each s, H-17 and H-20), 0.84 and 0.81 (3H each, each s, H-18 and H-19); ^{13}C NMR (75 MHz; $CDCl_3$) δ_C 213.19 (s), 170.82 (s), 76.02 (d), 53.71 (s), 52.39 (s), 46.11 (d), 45.11 (t), 44.19 (d), 41.80 (t), 39.84 (t), 38.69 (s), 36.62 (t), 33.48 (q), 33.17 (s), 32.19 (t), 27.92 (t), 25.47 (t), 21.86 (q), 21.15 (q), 19.60 (q), 18.53 (t), 17.40 (q); MS (EI) *m/z* 346 (M^+, 1), 304 (4), 287 (17), 286 (74), 271 (100); HRMS $C_{22}H_{34}O_3$ requires 346.2508, found 346.2507.

7β-Acetoxy-13α-scopadulanol (37). To a solution of ketone **36** (17.8 mg, 0.051 mmol) in MeOH (1.9 mL) at 0 °C, $NaBH_4$ (98%, 20 mg, 0.51 mmol) was added. The reaction mixture was stirred for 50 min and then diluted with diethyl ether. Usual workup followed by column chromatography, using hexanes−ethyl acetate (from 8:2 to 6:4) as eluent, yielded the β-alcohol **38** (3.8 mg, 21%) followed by the α-alcohol **37** (13.8 mg, 77%) as a white solid: mp 181−183 °C (from MeOH−H_2O); $[\alpha]^{24}_D$ +3.4 (*c* 1.8, $CHCl_3$); IR (KBr) 3306, 1732 cm^{-1}; ^1H NMR (250 MHz; $CDCl_3$) δ 4.68 (1H, ddd, *J* = 11.0, 11.0, 5.6, H-7), 3.35 (1H, dd, *J* = 10.6, 5.9, H-13), 2.02 (3H, s, $COCH_3$), 0.99 (6H, s, H-17 and H-20), 0.81 and 0.79 (3H, s, H-18 and H-19); ^{13}C NMR (62.5 MHz; $CDCl_3$) δ_C 170.86 (s), 76.28 (d), 76.00 (d), 53.10 (s), 45.86 (d), 44.49 (t), 44.11 (s), 41.99 (d), 41.88 (t), 38.34 (s), 33.99 (t), 33.47 (s), 33.12 (q), 32.27 (t), 30.58 (t), 27.94 (t), 25.83 (t), 23.08 (q), 21.94 (q), 21.30 (q), 18.61 (t), 17.49 (q); MS (EI) *m/z* 348 (M^+, 7), 289 (13), 288 (61), 273 (100); HRMS $C_{22}H_{36}O_3$ requires 348.2664, found 348.2651.

(−)-Methyl Thyrsiflorin B Acetate (9). In the same manner as described to obtain (−)-methyl thyrsiflorin A (**8**), alcohol **37** (13.6 mg,0.039 mmol) was converted, after chromatography using hexanes−ethyl acetate (from 9:1 to 8:2) as eluent, into (−)-methyl thyrsiflorin B acetate (**9**) (12.8 mg, 73%) as a colorless oil: $[\alpha]^{24}_D$ −12.0 (*c* 0.5, $CHCl_3$) (lit.[27] −7.6, *c* 1.0 and −4.7, *c* 0.8, respectively); IR (NaCl) 1750, 1740, 1735 cm^{-1}; ^1H NMR (300 MHz; $CDCl_3$) δ 4.75−4.60 (2H, m, H-7 and H-13), 3.72 (3H, s, CO_2Me), 3.34 (2H, s, CH_2CO_2Me), 2.02 (3H, s, $COCH_3$), 0.99 (3H, s, H-20), 0.91 (3H, s, H-17), 0.81 and 0.79 (3H each, each s, H-18 and H-19); ^{13}C NMR (75 MHz; $CDCl_3$) δ_C 170.95 (s), 167.04 (s), 166.23 (s), 79.31 (d), 75.97 (d), 53.20 (s), 52.37 (q), 45.87 (d), 44.48 (t), 43.13 (s), 41.89 (t), 41.80 (d), 41.65 (t), 38.40 (s), 33.47 (q), 33.14 (s), 32.25 (t), 31.87 (t), 30.30 (t), 27.98 (t), 25.82 (t), 22.90 (q), 21.93 (q), 21.34 (q), 18.58 (t), 17.50 (q); MS (EI) *m/z* 448 (M^+, 10), 388 (28), 373 (42), 270 (100); HRMS $C_{26}H_{40}O_6$ requires 448.2825, found 448.2846.

7β-Hydroxy-13-scopadulanone (39). In the same manner as described for the synthesis of **36**, ketal **30** (28.4 mg, 0.04 mmol) was converted, after chromatography using hexanes−ethyl acetate (from 7:3 to 5:5) as eluent, into the ketone **39** (20.2 mg, 82%) as a colorless oil: $[\alpha]^{25}_D$ +45.0 (*c* 1.4, $CHCl_3$); IR (NaCl) 3570−3110, 1701 cm^{-1}; ^1H NMR (300 MHz; $CDCl_3$) δ 3.53 (1H, ddd, *J* = 11.0, 10.5, 5.4, H-7), 2.72 (1H, dd, *J* = 15.6, 5.9, H-14β), 1.87 (1H, ddd, *J* = 12.4, 5.7, 2.5), 1.04 and 1.00 (3H each, each s, H-17 and H-20), 0.85 and 0.83 (3H each, each s, H-18 and H-19); ^{13}C NMR (75 MHz; $CDCl_3$) δ_C 213.77 (s), 73.91 (d), 53.62 (s), 52.46 (s), 47.34 (d), 46.34 (d), 45.19 (t), 41.84 (t), 40.13 (t), 38.81 (s), 36.73 (t), 33.50 (q), 33.08 (s), 32.33 (t), 32.02 (t), 25.57 (t), 21.91 (q), 19.69 (q), 18.59 (t), 17.47 (q); MS (EI) *m/z* 304 (M^+, 100), 289 (17), 286 (13), 271 (14); HRMS $C_{20}H_{32}O_2$ requires 304.2402, found 304.2402.

(−)-Thyrsiflorin C (7). In the same manner as described for alcohol **37**, ketone **39** (9 mg, 0.0296 mmol) was treated. Chromatography of the crude product, using hexanes−ethyl acetate (from 6:4 to 3:7) as eluent, afforded the dialcohol **40** (1.9 mg, 20%) and (−)-Thyrsiflorin C (**7**) (7.1 mg, 78%) as a white solid: mp 167−169 °C (from MeOH−H_2O) (lit.[27] 166−168 °C); $[\alpha]^{24}_D$ −8.8 (*c* 0.8, $CHCl_3$) (lit.[27] −12.3, *c* 1.2); IR (KBr) 3337, 1036 cm^{-1}; ^1H NMR (300 MHz; $CDCl_3$) δ 3.45−3.35 (2H, m, H-7 and H-13), 2.31 (1H, ddd, *J* = 12.9, 5.9, 5.1), 0.99 and 0.97 (3H each, each s, H-17 and H-20), 0.82 and 0.81 (3H each, each s, H-18 and H-19); ^{13}C NMR (75 MHz; $CDCl_3$) δ_C 76.22 (d), 73.80 (d), 53.04 (s), 46.12 (d), 45.18 (d), 44.59 (t), 44.14 (s), 41.96 (t), 38.53 (s), 34.28 (t), 33.50 (q), 33.06 (s), 32.45 (t), 31.85 (t), 30.67 (t), 25.97 (t), 23.13 (q), 22.01 (q), 18.68 (t), 17.58 (q); MS (EI) *m/z* 306 (M^+, 59), 289 (22), 288 (100), 273 (41); HRMS $C_{20}H_{34}O_2$ requires 306.2559, found 306.2549.

Acknowledgment. This work was financially supported by DGICYT (Research Program PB95-1088). M.A.G. thanks the Conselleria d'Educació i Ciència de la Generalitat Valenciana for a research fellowship.

Supporting Information Available: Representative data and experimental procedures for the preparation of **15** and **22.** Representative data for **11**, **24**−**26**, **29**, **34**, **38**, and **40**. ^1H NMR spectra for **7**−**10**, **17**, **20**, and **30**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO991561F