Stereoselective Synthesis of 8,12-Furanoeudesmanes from Santonin. Absolute Stereochemistry of Natural Furanoeudesma-1,3-diene and Tubipofurane†

Gonzalo Blay, Luz Cardona, Begoña García, José R. Pedro,* and Juan J. Sánchez

Departament de Química Orgànica, Facultat de Química, Universitat de València, E- 46100 Burjassot (València), Spain

Received December 4, 1995⊗

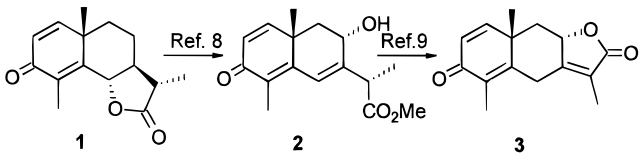
Ketobutenolide **3**, easily obtained from santonin (**1**), has been transformed into two natural furanoeudesmanes **4** and **5**, isolated from *Commiphora molmol* and *Tubipora musica*, respectively. *trans*- And *cis*-decalin systems were obtained by stereoselective reduction of the C_4-C_5 double bond in **3** in the following way: hydrogenation of **3** over Pd/C followed by acidic treatment gave the *cis* isomer **10** as the major product; selective hydrogenation of the C_1-C_2 double bond with the Wilkinson's catalyst followed by reduction with NaTeH yielded mainly the *trans* isomer **9**. Compounds **9** and **10** were transformed into **4** and **5** in parallel sequences. Optical rotation and CD measurements of the synthetic products revealed that the stereochemistry of both natural products should be revised to their enantiomeric form.

In recent years, many furanosesquiterpenoids have been isolated from different natural sources, mainly from marine organisms and higher plants.[1] These products show unique structures, and some of them have potent biological activities, including antifeedant and ichtiotoxic,[2] ixodicidic,[3] cell-division inhibitor,[4] fungistatic and antibacterial,[5] or predator deterrent[6] among others. Because of these features, much effort has been devoted to the synthesis of these products.[7]

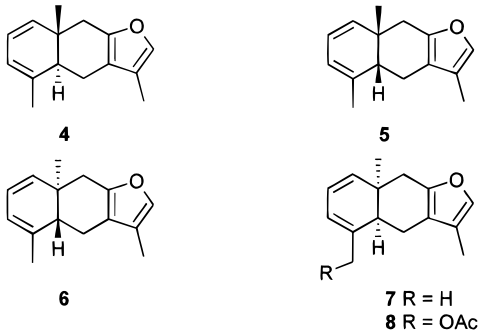
In a previous paper,[8] we described an efficient method for the functionalization of C_8 in santonin (**1**) to give alcohol **2** (Scheme 1). On treatment of **2** with *p*-toluenesulfonic acid (*p*-TsOH), lactone ring closure takes place with concomitant migration of the double bond from C_6-C_7 to C_7-C_{11} leading to butenolide **3**.[9] Compound **3** was envisaged as an excellent material for the synthesis of several 8,12-furanosesquiterpenes and other sesquiterpenes bearing related functionalities such as 7(11)-en-8,12-olide, 8-hydroxy 7(11)-en-8,12-olide, and 8(11)-dien-8,12-olide.[10−12]

In the present work we describe the synthesis of two furanoeudesmanes **4** and **5** (Scheme 2) using the readily available **3** as starting material. Structure **4** was reported for a natural product isolated first from *Commiphora molmol*[13] and later from *Commiphora myrrh* oil.[14]

Scheme 1



Scheme 2



Structure **5** is the enantiomer form of the reported structure of tubipofurane (**7**), an *ent*-furanoeudesmane with *cis*-stereochemistry between the angular C_5 and C_{10} positions, which was isolated along with its 15-acetoxy derivative **8** from the stolonifer *Tubipora musica*.[15] These compounds show ichtiotoxicity toward a killifish *Orizias latipes*, and compound **8** shows cytotoxicity against B-16 melanoma cells in vitro.

During the course of our experimental work, a total synthesis of racemic tubipofurane (**7**) and its derivative **8** was reported.[16]

In our previous paper,[9] we synthesized the supposed enantiomer of 1,2-dihydrotubipofurane and established that the signs of optical rotation of our synthetic product and natural tubipofurane were coincident. Although this coincidence is not necessarily conclusive, the similarity between both structures made us think of a possible error

† In memoriam of Professor Félix Serratosa.

⊗ Abstract published in *Advance ACS Abstracts,* April 15, 1996.

(1) Roberts, J. S.; Bryson, I. *Nat. Prod. Rep.* **1984**, *1*, 105. Fraga, B. M. *Nat. Prod. Rep.* **1985**, *2*, 147; **1986**, *3*, 273; **1987**, *4*, 473; **1988**, *5*, 497; **1990**, *7*, 515; **1992**, *9*, 217; **1992**, *9*, 557; **1993**, *10*, 397; **1994**, *11*, 533; **1995**, *12*, 303.

(2) Thompson, J. E.; Walker, R. P.; Wratten, S. J.; Walker E. J. *Tetrahedron* **1982**, *38*, 1865.

(3) Maradufu, A. *Phytochemistry* **1982**, *21*, 677.

(4) Tanaka, J.; Miki, H.; Higa, T. *J. Nat. Prod.* **1992**, *55*, 1522.

(5) Roussis, V.; Fenical, W.; Miralles, J.; Kornprobst, J. M. *New J. Chem.* **1991**, *15*, 959.

(6) Fontana, A.; Avila, C.; Martínez, E.; Ortea, J.; Trivellone, E.; Cimino, G. *J. Chem. Ecol.* **1993**, *19*, 339.

(7) For a review, see: Allen, A. J.; Vaillancourt, V.; Albizati, K. F. *Org. Prep. Proced. Int.* **1994**, *26*, 1.

(8) Blay, G.; Cardona, L.; García, B.; Pedro, J. R. *J. Org. Chem.* **1991**, *56*, 6172.

(9) Cardona, L.; García, B.; Pedro, J. R.; Ruiz, D. *Tetrahedron* **1994**, *50*, 5527.

(10) Takeda, K.; Horibe, I.; Minato, H. *J. Chem. Soc. C* **1968**, 569.

(11) Minato, H.; Nagasaki, T. *J. Chem. Soc. C* **1966**, 1866.

(12) Moriyama, Y.; Takahashi, T. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 3196.

(13) Brieskorn, C. H.; Noble, P. *Phytochemistry* **1983**, *22*, 187.

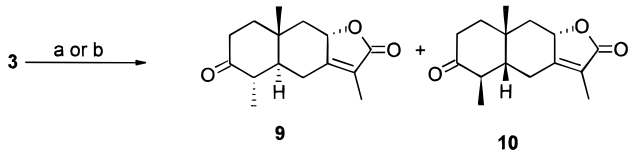
(14) Maradufu, A.; Warthen, J. D., Jr. *Plant Sci.* **1988**, *57*, 181.

(15) Iguchi, K.; Mori, K.; Suzuki, M.; Takahashi, H.; Yamada, Y. *Chem. Lett.* **1986**, 1789.

(16) Ojida, A.; Tanoue, F.; Kanematsu, K. *J. Org. Chem.* **1994**, *59*, 1970.

S0022-3263(95)02145-1 CCC: $12.00

Scheme 3



a) 1.H_2, Pd/C; 2. *p*-TsOH	5%	75%
b) 1.H_2, Wilkinson; 2. NaTeH	78%	-

in the stereochemistry assigned to natural tubipofurane.[15] Thus, corroboration of the absolute stereochemistry of compounds **7** and **8** in a stereocontrolled way made our goal more attractive.

Results and Discussion

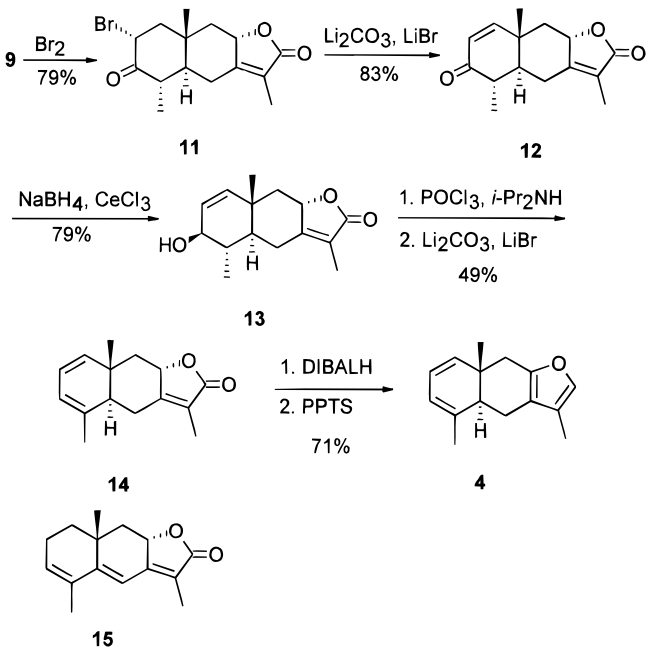
Since compounds **4** and **5** only differ in the stereochemistry of C_5 and therefore in the junction of the two rings in the decalin system, our first goal was to find conditions to carry out the stereoselective reduction of the C_4-C_5 double bond present in **3**.

Hydrogenation of **3** over 5% Pd/C in acetone by standard conditions, followed by acidic treatment with *p*-TsOH in benzene at reflux, gave the *cis*-fused ketobutenolide **10** as the main product (75%) together with a minor amount of the *trans*-isomer **9** (5%) (Scheme 3). This result was satisfactory to carry out the synthesis of *cis*-eudesmanolides. However, the yield of the *trans*-isomer was too low to achieve an efficient synthesis of *trans*-eudesmanolides. Therefore, we searched for alternative reduction methods. All attempts of hydrogenation, changing solvents, catalysts, or conditions, gave **10** as the main product. Other methods using metals such as Na in HMPA/THF,[17] Al−$NiCl_2$ in THF,[18] and ultrasound assisted Zn−$NiCl_2$ in EtOH−water,[19] and hydride or hydrogen donors such as Et_3SiH/CF_3CO_2H,[20] NaTeH,[21] or Ph_3PSnH,[22] were unsuccessful as either they did not give reduction, or under forcing conditions they reacted with the lactone ring or they gave intractable mixtures. Probably the inertness of this compound was due to the cross-conjugation of the carbonyl group in the dienone system. Therefore, the C_1−C_2 double bond was selectively hydrogenated with Wilkinson's catalyst and the resulting enone subjected to reduction. After some trials, treatment of the enone with NaTeH in an AcOH/NaOAc-buffered medium gave the *trans*-isomer **9** in 78% yield. No traces of **10** were found in the reaction mixture.

After the problem of the C_5 configuration was solved, we attempted the synthesis of furanoeudesmanes **4** and **5** in parallel sequences starting from **9** and **10** respectively.

For the reintroduction of the C_1−C_2 double bond, ketone **9** was treated with Br_2 to give bromo ketone **11** in 79% yield, which upon elimination with Li_2CO_3−LiBr in DMF afforded enone **12** in 83% yield (Scheme 4).[23]

Scheme 4



In order to form the C_3−C_4 double bond, the carbonyl group had to be reduced. That was carried out by treatment of **12** with $NaBH_4$ in the presence of $CeCl_3 \cdot 7H_2O$, which avoids the 1,4-reduction of enones.[24] The reaction took place with total regio- and stereoselectivity, and only alcohol **13** was obtained in 79% yield.

The direct elimination of allylic alcohols with basic alumina has been described,[23] but it occurs in low yield. An attempted elimination by treatment of **13** with *p*-TsOH did not lead to the desired product. Instead, the highly conjugated triene **15** was obtained. Therefore, the elimination was carried out in two steps: treatment of **13** with $POCl_3$ in the presence of *i*-Pr_2NH gave a mixture of two epimeric allylic chlorides which where subjected without separation to elimination by Li_2CO_3−LiBr. In this way the diene **14** was obtained in 49% overall yield from **13**.

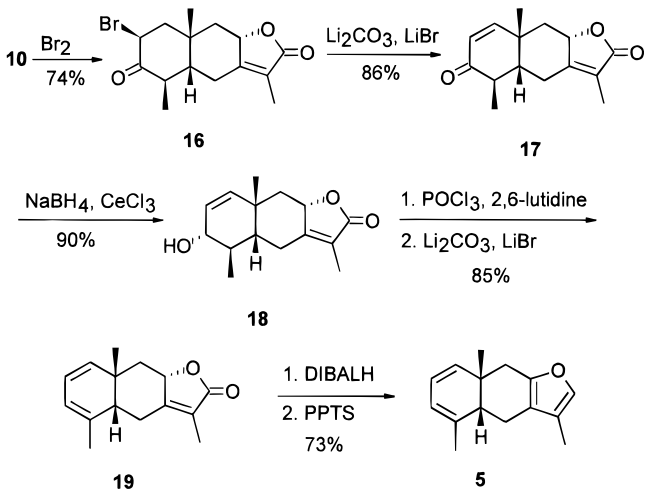
Finally, transformation of the butenolide moiety in the furan ring was achieved by Minato and Nagasaki's procedure.[25] Treatment of **14** with DIBAL-H gave a mixture of two epimeric lactols that were dehydrated with PPTS[26] at 0 °C to give the expected furanoeudesmane **4** in 71% overall yield.

The spectral and physical constants of synthetic **4** were fully coincident with those described for the natural furanoeudesma-1,3-diene isolated from *C. molmol*.[13] However, **4** showed an $[\alpha]^{21}_D$ of −200 whereas the reported value for the natural product was +59. Although we do not have a satisfactory explanation for this difference of the absolute values, the observed opposite sign indicates that the products are enantiomers.

Because the absolute stereochemistry of our synthetic products is established by unambiguous chemical synthesis from santonin (**1**) (the stereochemistry of C_{10} is maintained unchanged through the entire sequence), whose stereochemistry has been unambiguously established by X-ray analysis,[27] we can conclude that the

(17) Bower, K. W.; Giese, R. W.; Grimshaw, J.; House, H. O.; Kolodny, N. H.; Konberger, K.; Roe, D. K. *J. Am. Chem. Soc.* **1970**, *92*, 2783.
(18) Hazarika, M.; Barva, N. *Tetrahedron Lett.* **1989**, *30*, 5567.
(19) Petrier, C.; Luche, J. L. *Tetrahedron Lett.* **1987**, *28*, 2347.
(20) Bulloc, M.; Rappoli, B. J. *J. Chem. Soc., Chem. Commun.* **1989**, *110*, 291.
(21) (a) Yamashita, M.; Kato, Y.; Suemitsu, R. *Chem. Lett.* **1980**, 847. (b) Yamashita, M.; Tanaka, Y.; Arita, A.; Nishida, M. *J. Org. Chem.* **1994**, *59*, 3500.
(22) (a) Levsink, A. J.; Naltes, J. G. *Tetrahedron Lett.* **1966**, 2221. (b) Wolf, H. R.; Zink, M. P. *Helv. Chim. Acta* **1973**, *56*, 1062.
(23) Corey, E. J.; Hortmann, A. J. *J. Am. Chem. Soc.* **1965**, *87*, 5736.
(24) Luche, J. L. *J. Am. Chem. Soc.* **1978**, *100*, 2226.
(25) Minato, H.; Nagasaki, T. *J. Chem. Soc. C* **1971**, 1070.
(26) Miyashita, M.; Yoshikoshi, A.; Grieco, P. A. *J. Org. Chem.* **1977**, *42*, 3772.

Scheme 5



stereochemistry of the natural product isolated from *C. molmol* should be revised to its enantiomeric form **6**.

Experimental reinforcement for this conclusion is given by the negative Cotton effect displayed by synthetic **4**, which is in good agreement with that predicted for a *cisoid* diene chromophore twisted in the sense of a right-handed helix in a *trans*-eudesma-1,3-diene like **4**, according to the helicity rule.[28,29]

By a similar synthetic sequence with slight experimental modifications, *cis*-fused ketobutenolide **10** was transformed via **16** (74%), **17** (86%), **18** (90%), and **19** (85%) into **5** (73%) (Scheme 5).

Compound **5** displayed spectral data identical to those of the natural product isolated from *T. musica*.[15] Also, both compounds exhibited an identical sign of optical rotations (+33 for our synthetic product and +5.6 for its natural counterpart). Our synthesis suggests that the stereochemistry of natural tubipofurane should be revised to **5**.

Since Yamada's group assigned the total stereochemistry of tubipofurane on the basis of CD measurements by application of the helicity rule,[28,29] we decided to carry out a similar study with our synthetic product in order to compare results. Identical signs of Cotton effects at 264 nm ($\Delta\epsilon$ +2.8 for the synthetic product in EtOH and hexane, and +0.56 for the natural product in hexane) were found for both compounds, giving reinforced support for the identity of both compounds.

Application of the helicity rule in *cis*-eudesmanes can be troublesome. Because of the flexibility of the decalin system, two conformations—nonsteroidal and steroidal—are possible, the helicity sign of the skewed diene changing from one conformation to the other. Therefore independent determination of the conformation must be done.

Yamada's group assigned the nonsteroidal conformation for tubipofurane on the basis of a W-shaped long-range coupling between H_1 and H_5 observed in a $^1H-^1H$ long-range correlation 2D-NMR spectrum of natural 15-acetoxytubipofurane **8**, which would be explainable only in the case of a nonsteroidal conformation for **8**, and therefore **7**. Consequently by application of the helicity rule they assigned the *ent*-stereochemistry for C_{10} in tubipofurane.

Indeed, although we were not able to observe coupling between H_1 and H_5 in two-dimensional $^1H-^1H$ COSY experiments with our synthetic material, decoupling experiments (irradiating H-1 at δ 5.43 caused sharpening of the signal of H_5 at δ 2.02) showed this long-range coupling. Moreover, by irradiation of H_{14} at δ 1.14, NOEs were observed with H_5 at δ 2.02, $H_{9\beta}$ at δ 2.47, $H_{9\alpha}$ (weaker) at δ 2.64, and H_1 at δ 5.48. Equally, the absence of a NOE with $H_{6\beta}$ was found. These results seem to indicate that C_{14} is equatorial (or near-equatorial) with respect to ring B. However, the J values of H_5 (J = 5.7 and 8.7 Hz) differ from the standard values for either a steroidal or nonsteroidal conformation, indicating a rather distorted molecule. Probably because of the flattening caused by the C_7-C_8 furan moiety, ring B must adopt a boatlike conformation that can affect ring A, changing the skew angle of the diene or the disposition of carbons attached to this ring (i.e. C_6, C_9, and C_{14}). Because of the difficulties in determining the actual conformation of the tubipofurane molecule, it is understandable that application of the helicity rule in the simplest way may lead to erroneous results. Furthermore, nonapplicability of the diene helicity rule may also arise by a larger controlling effect of the allylic bonds in the Cotton effect and/or by interactions with the furan ring diene.

In summary, (a) compound **3** has been shown to be an excellent intermediate for the synthesis of *cis*- or *trans*-eudesma-8,12-furans from santonin (**1**) and (b) as a consequence of the synthesis of enantiomerically pure **4** and **5**, the stereochemistry of natural furanoeudesma-1,3-diene **4** and tubipofurane (**7**) has been revised to their enantiomer forms **6** and **5**, respectively.[30]

Experimental Section

All melting points are uncorrected. Column chromatography was performed on silica gel (Merck, silica gel 60, 230−400 mesh). IR spectra were recorded as liquid films for oils and as KBr disks for solids. Specific rotations were measured in $CHCl_3$. CD experiments were performed in EtOH and hexane. UV spectra were measured in EtOH. NMR were run in $CDCl_3$ at 399.95 MHz for ^1H and at 50.3, 75.43, or 100.58 MHz for ^{13}C. The carbon type (methyl, methylene, methine, or quaternary) was determined by DEPT experiments. ^{13}C NMR spectra of compounds **4**, **5**, **11**−**14**, and **16**−**19** are listed in Table 1. Mass spectra were run by electron impact at 70 eV.

3-Oxo-5α*H*,4,8*β*H-eudesma-7(11)-en-8,12-olide (9). A solution of 580 mg (2.38 mmol) of **3** in 55 mL of benzene and 2 mL of EtOH was added via syringe to a solution of 300 mg of tris(triphenylphosphine)rhodium(I) chloride under argon. The resulting mixture was stirred overnight under a H_2 atmosphere. The solvents were removed under reduced pressure, and the residue was chromatographed (6:4 hexane/EtOAc) to give 560 mg (95%) of a yellow solid that was immediately used in the next step.

A suspension of tellurium powder (1.0 g, 7.83 mmol) and $NaBH_4$ (0.71 g, 14.6 mmol) in 30 mL of deoxygenated EtOH was refluxed under argon for 45 min. After this time, the resulting deep purple solution was cooled at −20 °C and a solution of 1.1 mL of glacial AcOH in 4.5 mL of EtOH was added, followed by a solution of the solid obtained in the previous step (560 mg) in 8 mL of EtOH. The resulting mixture was stirred at room temperature for 1 h. After this time, the reaction flask was open to air, water was added, and

(27) Kitabayashi, C.; Matsuura, Y.; Tanaka, N.; Katsube, Y.; Matsuura, T. *Acta Crystallogr. C* **1985**, *41*, 1779.

(28) Moscowitz, A.; Charney, E.; Weiss, U.; Ziffer, H. *J. Am. Chem. Soc.* **1961**, *83*, 4661.

(29) Gawronsky, J. K.; Walborsky, H. M. In *Circular Dicroism. Principles and Applications. Chapter 11: Diene Chirality*; Nakanishi, K., Berova, N., Woody R. W., Eds.; VCH Publishers, Inc.: New York, 1994.

(30) Authentical samples of the natural products for direct comparison with our synthetic materials were not available.

Table 1. ^{13}C NMR Data of Compounds 4, 5, 11−14, and 16−19 (δ, $CDCl_3$)

carbon	4[a]	5[a]	11	12	13	14	16	17	18	19
C_1	135.6	117.8	51.2	126.9	137.6	136.0	51.7	153.3	136.7	121.9
C_2	122.1	124.1	52.1[b]	159.7	128.6	132.0	52.3[b]	126.7	128.8	122.5
C_3	119.9	134.8	200.8	199.7	74.2	120.6	201.9	199.5	73.6	134.6
C_4	137.5	140.8	51.2[b]	48.6	37.3	127.1	50.9[b]	47.3	45.7	135.2
C_5	42.8	44.1	44.9	42.4	47.1	46.5	42.9	40.3	35.9	45.2
C_6	19.8	23.0	26.7	26.2	25.4	24.2	25.3	24.7	23.5	24.3
C_7	116.7[b]	118.2[b]	159.2	121.5	120.1	134.1	157.5	158.3	160.3	160.4
C_8	149.9	149.7	77.0	77.3	78.0	78.1	77.5	76.9	77.8	77.5
C_9	36.6	35.0	46.1	44.4	44.9	44.4	25.3	24.7	23.5	24.3
C_{10}	35.5	35.8	37.3	37.3	36.4	35.8	37.7	37.4	36.5	35.9
C_{11}	119.9[b]	119.1[b]	121.7	156.9	162.0	161.9	123.5	122.9	120.8	120.6
C_{12}	137.0	136.4	174.1	174.1	174.7	174.5	173.8	173.9	174.5	174.8
C_{13}	8.2	8.1	8.4	8.3	8.0	8.2	8.1	8.5	8.4	8.9
C_{14}	15.4	25.9	12.1	11.9	15.1	14.8	26.5	25.3	26.8	25.2
C_{15}	20.5	23.0	17.0	17.8	19.7	19.9	12.8	12.2	15.6	20.9

[a] Assignment by heteronuclear $^1H-^{13}C$ NMR correlation. [b] These signals may be interchanged within the corresponding spectrum.

the mixture was stirred for 1 h. The reaction mixture was filtered through Celite and eluted with EtOAc. The resulting solution was washed to neutrality with brine, dried, concentrated, and chromatographed (7:3 hexane/EtOAc) to afford 470 mg (78%) of compound **9**. For physical and chemical features of compound **9**, see ref 9.

2α-Bromo-3-oxo-5α*H*,4,8*βH*-eudesma-7(11)-en-8,12-olide (11). To a 0 °C precooled solution of ketone **9** (0.408 mg, 1.64 mmol) in $CHCl_3$ was added 17.5 mL of a 0.1 M solution of Br_2 in CCl_4. The addition of the reagent took 100 min, and stirring was continued for 30 min. The reaction mixture was diluted with water and extracted with three portions of CH_2Cl_2. The combined organic layers were washed with aqueous $NaHCO_3$ and aqueous NaCl, dried with $MgSO_4$, and concentrated. Chromatography of the residue (6:4 hexane/EtOAc) gave 423 mg (79%) of bromo ketone **11**: mp 126−127 °C (hexane/EtOAc); $[\alpha]^{21}_D$ +61 (*c* 1.15); IR (KBr) 1730, 1680 cm^{-1}; MS *m/e* 247 (M^+ − Br, 17), 246 (M^+ − HBr, 100), 218 (M^+ − CHO, 8), 151 (10), 135 (11), 95 (68); HRMS 247.1297 $C_{15}H_{19}O_3$ (M^+ − Br) required 247.1334; ^1H NMR δ 1.06 (1H, t, J = 12.5 Hz), 1.17 (3H, d, J = 6.4 Hz), 1.35 (3H, s), 1.39 (1H, td, J = 4.2, 12.5 Hz), 1.81 (3H, t, J = 1.6 Hz), 1.95 (1H, t, J = 13.5 Hz), 2.13 (1H, td, J = 1.7, 12.5 Hz), 2.35 (1H, dd, J = 6.1, 12.5 Hz), 2.47 (1H, dd, J = 6.3, 13.5 Hz), 2.54 (1H, qd, J = 6.4, 12.5 Hz), 2.84 (1H, dd, J = 4.2, 12.5 Hz), 4.85 (1H, dd, J = 6.3, 13.5 Hz), 4.88 (1H, dd, J = 6.1, 12.5 Hz).

3-Oxo-5α*H*,4,8*βH*-eudesma-1,7(11)-dien-8,12-olide (12). A suspension of **11** (373 mg, 1.15 mmol), Li_2CO_3 (245 mg), and LiBr (178 mg) in dry DMF (13 mL) was heated under argon at 120 °C for 2 h. The reaction mixture was cooled in an ice bath, quenched with aqueous NH_4Cl, and extracted with EtOAc (three times). After the usual workup, chromatography (6:4 hexane/EtOAc) gave 234 mg (83%) of **12**: mp 183−184 °C (hexane/EtOAc); $[\alpha]^{21}_D$ +166 (*c* 0.72); IR (KBr) 3010, 1750, 1740 cm^{-1}; MS *m/e* 246 (M^+, 100), 218 (M^+ − CO, 8), 215 (M^+ − CHO, 6), 152 (10), 151 (11), 135 (13), 123 (11), 122 (12), 95 (77); HRMS 246.1256, $C_{15}H_{18}O_3$ required 246.1256; ^1H NMR δ 1.22 (3H, d, J = 6.8 Hz), 1.27 (3H, s), 1.30 (1H, t, J = 11.5 Hz), 1.70 (1H, dt, J = 4.0, 13.0 Hz), 1.83 (3H, t, J = 1.3 Hz), 2.20 (1H, dt, J = 1.3, 13.0 Hz), 2.42 (1H, qd, J = 6.8, 13.0 Hz), 2.43 (1H, dd, J = 6.3, 11.5 Hz), 2.90 (1H, dd, J = 4.0, 13.0 Hz), 4.90 (1H, dd, J = 6.3, 11.5 Hz), 5.90 (1H, d, J = 10.0 Hz), 6.70 (1H, d, J = 10.0 Hz).

3*β*-Hydroxy-5α*H*,4,8*βH*-eudesma-1,7(11)-dien-8,12-olide (13). A solution of **12** (204 mg, 0.83 mmol) and $CeCl_3 \cdot 7H_2O$ (308 mg, 0.83 mmol) in MeOH (7 mL) was treated with $NaBH_4$ (35 mg, 0.93 mmol) at 0 °C. After 15 min, the reaction was quenched with aqueous NH_4Cl. The usual workup and chromatography (6:4 hexane/EtOAc) afforded 165 mg (80%) of compound **13**: mp 157−158 °C (hexane/EtOAc); $[\alpha]^{21}_D$ +177 (*c* 0.82); IR (KBr) 3480, 1720, 1670 cm^{-1}; MS *m/e* 248 (M^+, 100), 233 (M^+ − CH_3, 30), 215 (8), 165 (67), 137 (13), 124 (13), 123 (14), 110 (20), 107 (17), 97 (15); HRMS 248.1415, $C_{15}H_{20}O_3$ required 248.1412; ^1H NMR δ 1.12 (3H, s), 1.13 (4H, d, J = 6.4 Hz), 1.27 (1H, ddd, J = 3.7, 11.8, 13.5 Hz), 1.55 (1H, d, J = 6.8 Hz), 1.65 (1H, qdd, J = 6.4, 8.8,11.8 Hz), 1.83 (3H, t, J = 1.6 Hz); 2.06 (1H, tt, J = 1.6, 13.5 Hz), 2.31 (1H, dd, J = 6.4, 12.4 Hz), 2.84 (1H, dd, J = 3.7, 13.5 Hz), 3.77 (1H, br t, J = 8.8 Hz), 4.86 (1H, dd, J = 6.4, 11.2 Hz), 5.53 (1H, dd, J = 2.0, 10.0 Hz), 6.70 (1H, d, J = 1.2, 10.0 Hz).

5α*H*,8*βH*-Eudesma-1,3,7(11)-trien-8,12-olide (14). A solution of **13** (100 mg, 0.41 mmol) in CH_2Cl_2 (3 mL) containing diisopropylamine (0.57 mL) was treated with $POCl_3$ (76 μL, 0.82 mmol) under argon at 0 °C. The reaction mixture was stirred at this temperature for 1 h and then quenched with aqueous NH_4Cl. The mixture was extracted with CH_2Cl_2, dried, and concentrated to give an oil which according to ^1H NMR analysis consisted of a mixture of two epimeric chlorides. A solution of this mixture, LiBr (63 mg), and Li_2CO_3 (86 mg) in DMF (5 mL) was heated under argon at 70 °C for 7 h. After this time, the reaction mixture was worked up (ether) as described above and chromatographed (1:1 hexane/ether) to give 48 mg (50%) of **14** as an oil: $[\alpha]^{22}_D$ +22 (*c* 0.82); IR (NaCl) 1750, 1680 cm^{-1}; MS *m/e* 230 (M^+, 58), 215 (M^+ − CH_3, 32), 201 (M^+ − CHO, 11), 173 (11), 171 (17), 159 (25), 157 (24), 135 (20), 120 (19), 119 (100); HRMS 230.1306, $C_{15}H_{18}O_2$ required 230.1307; ^1H NMR δ 1.00 (3H, s), 1.39 (1H, t, J = 12.0 Hz), 1.85 (3H, s), 1.87 (3H, s), 2.32 (1H, dd, J = 6.4, 12.0 Hz), 3.35 (2H, s), 2.98 (1H, d, J = 9.4 Hz), 4.85 (1H, dd, J = 6.2, 12.0 Hz), 5.53 (1H, d, J = 9.4 Hz), 5.75 (1H, br m, $W_{1/2}$ J = 5.2, 9.4 Hz).

5α*H*-8,12-Furanoeudesma-1,3-diene (4). To a solution of compound **14** (55 mg, 0.23 mmol) in 4.7 mL of dry THF at −35 °C under argon was dropwise added via syringe a solution of 1 M DIBAL-H in hexane (0.28 mL, 0.28 mmol). After stirring at −35 °C for 20 min the reaction was quenched by adding via syringe 1.5 mL of a 1:6:1 mixture of 2-propanol, toluene, and water. The mixture was diluted with ethyl acetate (1.2 mL), treated with anhydrous Na_2SO_4 (225 mg) and Celite (90 mg), and vigorously stirred (under argon) for 30 min. After this time, the mixture was filtered through neutral alumina and the solvent removed in vacuo. The resulting oil was diluted in 1,2-dichloroethane (7.5 mL), and PPTS (5.9 mg) was added under argon. The mixture was stirred at room temperature for 2 h. The usual workup (ether) and flash chromatography (under argon, 100:1 hexane/ether) yielded 38 mg (72%) of **4** as a colorless oil which solidified on standing overnight in the freezer: mp 45−46 °C (lit.[14] mp 46 °C); $[\alpha]^{22}_D$ −200 (*c* 0.93) (lit.[13] $[\alpha]^{21}_D$ +59); IR (KBr) 3010, 1640, 1580, 1550, 1430, 1130, 1080, 720 cm^{-1}; MS *m/e* 214 (M^+, 100), 199 (M^+ − CH_3, 37), 181 (11), 119 (13), 118 (27), 109 (13), 108 (88), 106 (17); UV λ_{max} 263 (ϵ = 3440), 219 (ϵ = 6150) nm [lit.[14] UV λ_{max} 263 (ϵ = 4200), 217 (ϵ = 7200) nm]; CD λ_{max} 264 nm ($\Delta\epsilon$ −9.4); HRMS 214.1360, $C_{15}H_{18}O$ required 214.1358; ^1H NMR δ 0.80 (3H, s), 1.85 (3H, s), 1.93 (3H, d, J = 1.2 Hz), 2.28 (1H, qdd, J = 13.8, 15.2, 16.0 Hz), 2.41 (1H, dd, J = 1.6, 16.0 Hz), 2.53 (1H, md, J = 1.6, 13.8 Hz), 2.65 (1H, ddd, J = 1.2, 5.2, 15.2 Hz), 2.73 (1H, d, J = 16.0 Hz), 5.53 (1H, d, J = 9.4 Hz), 5.70 (1H, br m, $W_{1/2}$ = 13.0 Hz), 7.06 (1H, s).

3-Oxo-4α*H*,5,8*βH*-eudesma-7(11)-en-8,12-olide (10). A suspension of recrystallized **3** (875 mg, 3.59 mmol) in acetone (90 mL) was hydrogenated over a 5% Pd/C catalyst for 90 min.

After this time, the catalyst was removed by filtration through a pad of silica gel and the filtrate concentrated in vacuo. A solution of the residue and *p*-toluenesulfonic acid (90 mg) in 35 mL of benzene was stirred overnight at room temperature. The reaction mixture was filtered through silica gel and, after evaporation of the solvent, chromatographed with hexane−EtOAc to give 665 mg (75%) of compound **10** followed by 45 mg (5%) of compound **9**. For physical and chemical features of compound **10**, see ref 9.

2*β*-Bromo-3-oxo-4α*H*,5,8*β*H-eudesma-7(11)-en-8,12-olide (16). By the same procedure used in the synthesis of **11** (4.5 h), from compound **5** (410 mg, 1.65 mmol) was obtained 400 mg (74%) of compound **16**: mp 119−120 °C (hexane/EtOAc); $[\alpha]^{12}_D$ +78 (*c* 1.1); IR (KBr) 1740, 1720, 1680 cm^{-1}; MS *m*/*e* 328 (M^+(^{81}Br), 28), 326 (M^+(^{79}Br), 30), 313 (16), 311 (15), 310 (9) 308 (8), 299 (20), 297 (19), 247 (M^+ − HBr,100), 229 (12), 163 (18), 135 (23), 123 (17), 110 (31), 82 (15); HRMS 328.0496, $C_{15}H_{19}O_3Br$ required 328.0497; ^{1}H NMR δ 1.14 (3H, d, J = 6.4 Hz), 1.26 (3H, s), 1.78 (1H, ddd, J = 1.6, 5.2, 13.0 Hz), 1.84 (3H, t, J = 1.6 Hz), 1.87 (1H, t, J = 12.0 Hz), 2.12 (1H, t, J = 13.6 Hz), 2.22 (1H, dd, J = 6.8, 12.0 Hz), 2.29 (1H, qd, J = 6.4, 13.0 Hz), 2.44 (1H, dd, J = 6.0, 13.6 Hz), 2.59 (1H, broad dd, J = 5.2, 14.8 Hz), 2.86 (1H, dd, J = 1.6, 14.8 Hz), 4.69 (1H, dd, J = 6.0, 13.6 Hz), 4.93 (1H, broad dd, J = 6.8, 12.0 Hz).

3-Oxo-4α*H*,5,8*β*H-eudesma-1,7(11)-dien-8,12-olide (17). A suspension of compound **16** (200 mg, 0.61 mmol), LiBr (96 mg), and Li_2CO_3 in DMF was heated at 110 °C for 2 h. The usual workup and chromatography afforded 130 mg (86%) of compound **17**: mp 150−151 °C; $[\alpha]^{22}_D$ +217 (*c* 0.8); IR (KBr) 1746, 1672 cm^{-1}, MS *m*/*e* 246 (M^+, 40), 231 ($M^+ - CH_3$, 17), 217 (22), 136 (16), 135 (100), 124 (58), 122 (67), 119 (28), 95 (99), 82 (83), 67 (38); HRMS 246,1256, $C_{15}H_{18}O_3$ required 246.1256; ^{1}H NMR δ 1.19 (3H, d, J = 6.4 Hz), 1.39 (3H, s), 1.48 (1H, t, J = 12.2 Hz), 1.87 (3H, t, J = 1.6 Hz), 2.04 (1H, dd, J = 4.8, 13.4 Hz), 2.14 (1H, qd, J = 6.4, 13.4 Hz), 2.32 (1H, dd, J = 6.4, 12.2 Hz), 2.63 (1H, tdd, J = 1.2, 4.8, 14.8 Hz), 2.94 (1H, dd, J = 1.2, 14.8 Hz), 4.86 (1H, dd, J = 6.4, 12.2 Hz), 5.91 (1H, d, J = 10.0 Hz), 6.55 (1H, d, J = 10.0 Hz).

3α-Hydroxy-4α*H*,5,8*β*H-eudesma-1,7(11)-dien-8,12-olide (18). By the same procedure used in the synthesis of **13**, from compound **17** (200 mg, 0.81 mmol) was obtained 146 mg (90%) of **18**: mp 81−82 °C; $[\alpha]^{22}_D$ +121 (*c* 0.81); MS *m*/*e* 248 (M^+, 20), 233 ($M^+ - CH_3$, 13), 230 (94), 215 (16), 165 (100), 84 (34); IR (KBr) 3460, 1726, 1680 cm^{-1}; HRMS 248.1412, $C_{15}H_{20}O_3$ required 248.1412; ^{1}H NMR δ 1.08 (3H, d, J = 6.4 Hz), 1.23 (3H, s), 1.34 (1H, qdd, J = 6.4, 7.8, 11.8 Hz), 1.40 (1H, t, J = 12.0 Hz), 1.58,1(H, d, J = 7.8 Hz), 1.65 (1H, dd, J = 6.3, 11.8 Hz), 1.84 (3H, t, J = 1.6 Hz), 2.16 (1H, dd, J = 6.7, 12.0 Hz), 2.52 (1H, dd, J = 6.3, 14.6 Hz), 2.72 (1H, d, J = 14.6 Hz), 3.74 (1H, broad t, J = 7.8 Hz), 4.75 (1H, dd, J = 6.7, 12.0 Hz), 5.43 (1H, dd, J = 1.6, 10.0 Hz), 5.52 (1H, dd, J = 1.6, 10.0 Hz).

5,8*β*H-Eudesma-1,3,7(11)-trien-8,12-olide (19). A solution of **18** (71 mg, 0.23 mmol) and 2,6-lutidine (0.33 mL, 2.8 mmol) in CH_2Cl_2 (2.5 mL) was treated with $POCl_3$ (52 μL, 0.56 mmol) at 0 °C. After 1 h, additional $POCl_3$ (13 μL, 0.14 mmol) was added and the mixture stirred at 0 °C for 2.5 h. After this time, the mixture was treated as described for the synthesis of **14**. The resulting mixture of chlorides, LiBr (44 mg), and Li_2CO_3 (59 mg) in DMF was heated at 100 °C for 2 h and 40 min. Usual workup and chromatography (4:1 hexane/EtOAc) gave 56 mg (85%) of **19**: mp 150−151 °C (hexane/EtOAc); $[\alpha]^{21}_D$ +164 (*c* 0.65); IR (KBr) 3027, 1733 , 1681 cm^{-1}; MS *m*/*e* 230 (M^+, 22), 215 ($M^+ - CH_3$, 6), 197 (5), 185 (12), 119 (100), 105 (16), 91 (12); UV λ_{max} 218 (ϵ = 13 130), 162 (ϵ = 4000) nm; HRMS 230.1307 $C_{15}H_{18}O_2$ required 230.1307; ^{1}H NMR δ 1.30 (3H, s), 1.52 (1H, t, J = 12.0 Hz), 1.84 (3H, s), 1.85 (3H, t, J = 1.6 Hz), 1.95 (1H, dd, J = 6.2, 12.0 Hz), 2.53 (1H, dd, J = 6.4, 14.9 Hz), 2.62 (1H, broad s, $W_{1/2}$ = 11.2 Hz), 3.05 (1H, dd, J = 2.0, 14.9 Hz), 4.72 (1H, dd, J = 6.2, 12.0 Hz), 5.39 (1H, d, J = 9.3 Hz), 5.66 (1H, broad s, $W_{1/2}$ = 10.0 Hz), 5.73 (1H, dd, J = 5.4, 9.3 Hz).

Tubipofurane (5). By the same procedure used in the synthesis of **4**, compound **19** (81 mg, 0.35 mmol) gave compound **5** (55 mg, 73%): $[\alpha]^{25}_D$ +33 (*c* 0.89) [lit.[15] $[\alpha]^{25}_D$ +5.7 (*c* 0.6)]; IR (NaCl) 3027, 1644, 1581, 1563 cm^{-1}; MS *m*/*e* 214 (M^+, 5), 199 (M^+ − Me, 2), 108 (100); UV λ_{max} (EtOH) 219 (ϵ = 6650), 264 (ϵ = 4470) nm [lit.[15] UV λ_{max} (EtOH) 216 (ϵ = 5400), 263 (ϵ = 3900) nm]; CD λ_{max} 264 nm ($\Delta\epsilon$ +2.8) [lit.[15] λ_{max} 263 ($\Delta\epsilon$ +0.6)]; HRMS 214.361,$C_{15}H_{18}O$ required 214.1358; ^{1}H NMR δ 1.13 (3H, s), 1.87 (3H, d, J = 0.4 Hz), 1.91 (3H, d, J = 0.8 Hz), 2.02 (1H, dd, J = 5.7, 8.7 Hz), 2.20 (1H, dddd, J = 1.8, 4.0, 8.7, 16.0 Hz), 2.45 (1H, d, J = 16.8 Hz), 2.54 (1H, dd, J = 5.7, 15.6 Hz), 2.64 (1H, d, J = 16.8 Hz), 5.43 (1H, d, J = 9.4 Hz), 5.63 (1H, broad d, J = 5.0 Hz), 5.82 (1H, dd, J = 5.0, 9.4 Hz), 7.00 (1H, s, H_{12}).

Acknowledgment. Financial support from Dirección General de Investigación Científica y Técnica (DGICYT, Grant PB 94-0985) is acknowledged. We thank Prof. Dr. Luis Franco and Dr. Esteban Ballestar (Department of Biochemistry, University of Valencia) for measuring CD experiments and Dr. C. H. Brieskorn for sending us copies of ^{1}H NMR spectra of natural furanoeudesma-1,3-diene.

Supporting Information Available: ^{1}H NMR spectra of compounds **4**, **5**, **11**−**14**, and **16**−**19** (10 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.

JO9521458