Chemical Transformation of Deacylsubexpinnatin into the Natural Oxetane Lactone Subexpinnatin C[1]

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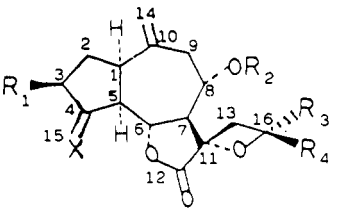
Subexpinnatin C (**5**), a secondary metabolite isolated from *Centaurea canariensis* Brouss. (var. *subexpinnata* Burch.), has been regio- and stereoselectively synthesized from deacylsubexpinnatin (**11**). This transformation involves a photoaddition reaction and a new method of obtaining the oxetane ring.

The four-membered oxetane ring is uncommon in nature,[2] but it occurs in some biologically interesting compounds. In previous we reported the isolation of five new sesquiterpene lactones with an 11,13-oxetane ring from *Centaurea clementei* D.C. and *Centaurea canariensis* Brouss. (var. *subexpinnata* Burch.), clementein (**1**), clementein B (**2**), clementein C (**3**), subexpinnatin B (**4**), and subexpinnatin C (**5**).[3-6] These compounds can be derived from the corresponding α-methylene γ-lactones by cycloaddition of acetaldehyde (Chart I).

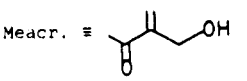
The oxetane ring placed at the α-position of a γ-lactone was found to have an enhanced reactivity. For instance, the ring is easily opened by nucleophiles under very mild conditions.[4,5] Again, these products are very interesting, since the C_{11}–C_{13} double bond in sesquiterpene lactones, which is related to their biological properties,[7,8] is "masked" as the acetaldehyde adduct.

These features prompted us to carry out the synthesis of the aforementioned oxetane lactones from their hypothetical precursors, the α-methylene γ-lactones, according to the retrosynthetic analysis shown in Scheme I. In order to find out if direct conversion of α-methylene γ-lactones grouping into the oxetane ring was possible, we attempted a photocycloaddition between deacylsubexpinnatin (**11**)[9] and acetaldehyde. Instead of the methyloxetane compound, we obtained the product of conjugated addition of the acyl radical to the C_{11}–C_{13} double bond. This reaction[10] permits access to compounds such as **9**, a key synthon in the aforementioned retrosynthetic analysis.

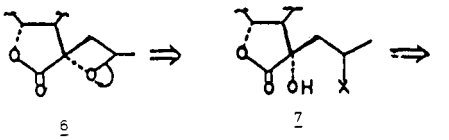
Chart I

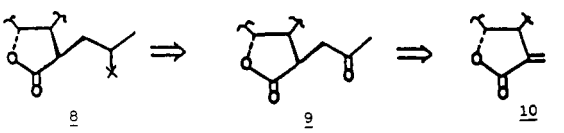


	X	R_1	R_2	R_3	R_4
1	$=CH_2$	OH	Meacr.	CH_3	H
2	$=CH_2$	OH	Meacr.	H	CH_3
3	$H\beta, CH_3\alpha$	OH	Meacr.	H	CH_3
4	$=CH_2$	H	Meacr.	H	CH_3
5	$=CH_2$	H	H	H	CH_3



Scheme I





Results and Discussion

Photochemical treatment of **11** with acetaldehyde in a modified Hanovia reactor,[11] with a Ni(II) and Co(II) aqueous solution as filter (Scheme II), gave 70% yield, c.a. 7:1 mixture of **12** and **13** on the basis of their isolated acetates derivatives **14** and **15**, respectively. Compound **13** proved to be a mixture of epimeric alcohols at C-16, for in the ^1H NMR of **15**, double signals are observed for C_{16}-H, C_{16}-$OCOCH_3$, and C_8-$OCOCH_3$ protons. The formation of **12** could be explained through a radical mechanism (Scheme III)[12] and compound **13** can be derived from **12** by a photoreduction reaction.

(1) Studies on Terpene Syntheses. 1.
(2) Searles, S. *Comprehensive Heterocyclic Compounds*; Pergamon: Oxford, England, 1984; Vol. 7, pp 363–402, and references cited therein.
(3) Massanet, G. M.; Collado, I. G.; Macias, F. A.; Bohlmann, F.; Jakupovic, J. *Tetrahedron Lett.* **1983**, *24*, 1640.
(4) González Collado, I.; Macías, F. A.; Massanet, G. M.; Rodríguez Luis, F. *Phytochemistry* **1985**, *24*, 2107.
(5) González Collado, I.; Macías, F. A.; Massanet, G. M.; Rodríguez Luis, F. *Tetrahedron* **1986**, *42*, 3611.
(6) Clementein (**1**) was obtained at first as the only oxetane lactone from *C. clementei*. In a further study two closely related lactones, **2** and **3**, were isolated. It was thought that the series of names clementein, clementein B, and clementein C introduced less confusion than the corresponding clementein, clementein A, and clementein B.
(7) Hoffmann, H. M. R.; Rabe, J. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 94.
(8) Petragnani, N.; Ferraz, M. C.; Silva, G. V. J.; *Synthesis* **1986**, *3*, 157.
(9) Lactone **11** was obtained by the saponification of subexpinnatin, its 8-hydroxymethacrylate. *Phytochemistry* **1982**, *21*, 895.
(10) Work is currently under way to explore the utility and scope of this reaction. Photochemical experiments carried out with different α,β-unsaturated substrates (ketones, carboxylic acids, esters, and lactones) gives the corresponding adducts. The yields obtained indicate that this reaction is a useful synthetic route to 1,4-diketones.
(11) Wagner, P. J.; Hammond, G. S. *J. Am. Chem. Soc.* **1966**, *88*, 1245.
(12) (a) Vogel, H. *Synthesis* **1970**, 99–140. (b) Walling, C.; Huyser, E. S. *Org. React. (N.Y.)* **1963**, *13*, 108–149.

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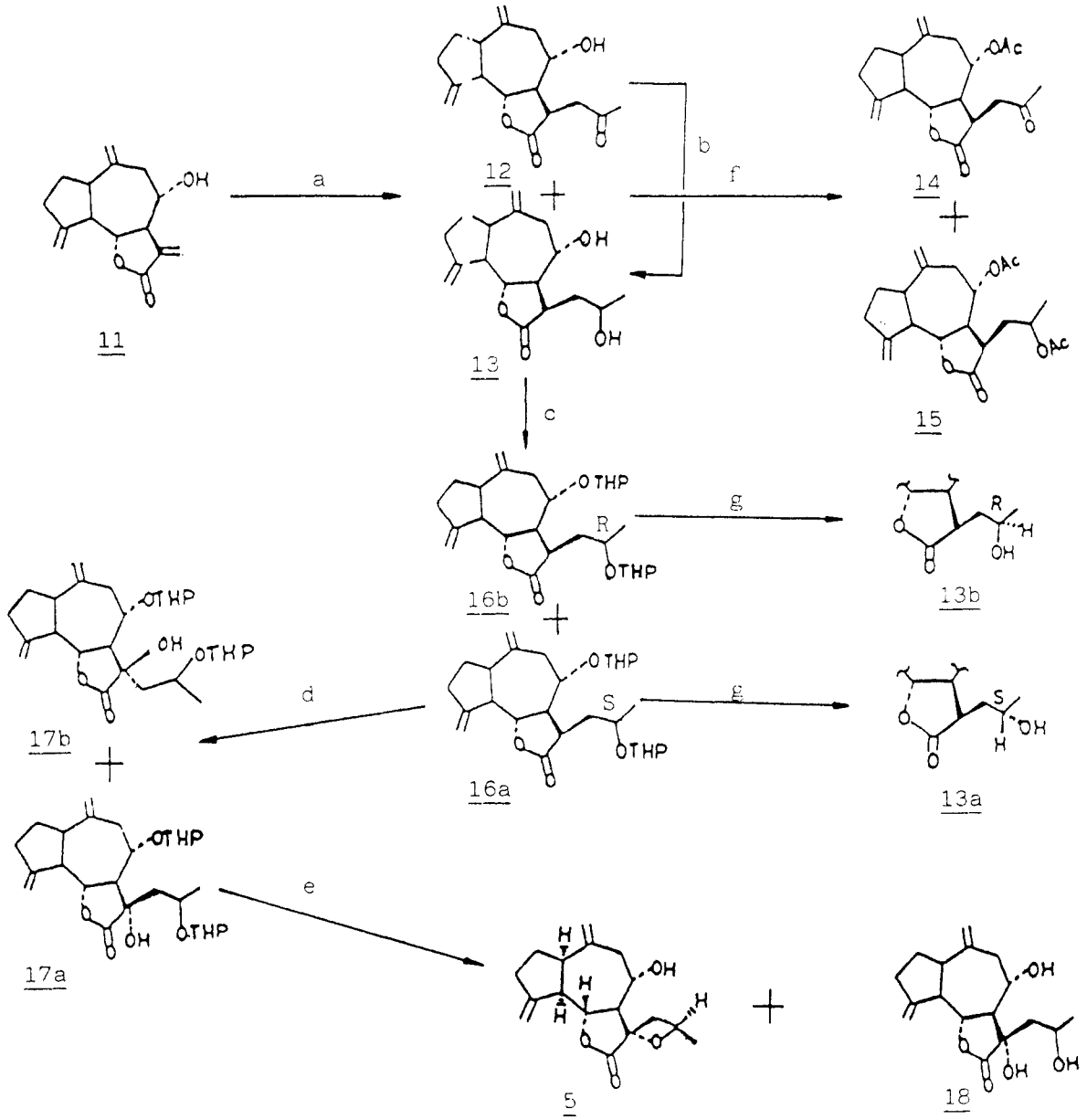
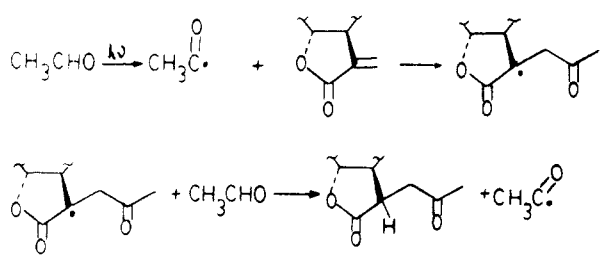
Scheme II[a]



[a] (a) CH_3CHO, $h\nu$, 25 °C; (b) $NaBH_4$, MeOH, 25 °C; (c) DHP, *p*-TsOH; (d) LDA, THF, −70 °C, then O_2, 0 °C and H^+; (e) aqueous HCl–MeOH; (f) Ac_2O, Py; (g) aqueous HCl–MeOH.

Scheme III



The structure of **12** was fully supported by the MS spectrum [*m/e* 290 (M^+), 43, ($C_2H_3O^+$)] and the ^1H NMR spectrum [δ 3.20 (2 H, m, C_{13}-H_2), 2.19 (3 H, s, C_{16}-CH_3)].

Reduction of the mixture of **12** and **13** with sodium borohydride gave **13** in 98% yield. The stereochemistry at C_{11} is difficult to assign from the value of $J_{7,11}$ (9.5 Hz). Nevertheless, the β-orientation of the aliphatic chain in C_{11} may be inferred from the chemical shifts of C_{11}-H and C_7-H, similar to those found for other 8α-hydroxy-7αH,11αH-guaianolides.[13,14]

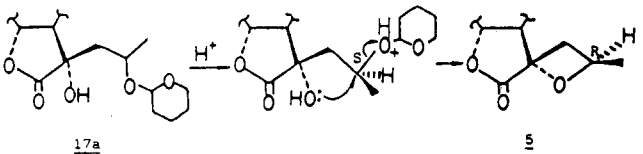
Protection of the hydroxy group by reaction with DHP and *p*-toluenesulfonic acid as catalyst gave two C_{16} epimeric mixtures of diastereoisomers **16a** (51%) and **16b** (24%). This mixture was carefully chromatographed and subsequent deprotection of the separated compounds gave the pure alcohols **13a** and **13b**.

The stereochemistry of C_{16} was proposed on the basis of subsequent chemical transformations. Reaction of **16a** with LDA at −70 °C and trapping of the resulting enolate with gaseous O_2 at 0 °C afforded the corresponding C_{11}-hydroxy derivatives **17a** (48%) and **17b** (15%).[15]

(13) (a) Bohlmann, F.; Ziesche, J. *Phytochemistry* **1980**, *19*, 692. (b) Bohlmann, F.; Singh, P.; Borthakur, N.; Jakupovic, J. *Phytochemistry* **1981**, *20*, 2379. (c) Singhal, A. K.; Chowdhury, P. K.; Sharma, R. P.; Baruah, J. N.; Herz, W. *Phytochemistry* **1982**, *21*, 462. (d) Sarg, T. M.; Omar, A. A.; Khafagy, S. M.; Grenz, M.; Bohlmann, F. *Phytochemistry* **1982**, *21*, 1163. (e) Bohlmann, F.; Hartono, L.; Jakupovic, J.; Hunec, S. *Phytochemistry* **1985**, *24*, 1003.

(14) (a) Bohlmann, F.; Borthakur, N.; Jakupovic, J.; Pickard, J. *Phytochemistry* **1982**, *21*, 1357. (b) Bohlmann, F.; Singh, P. *Phytochemistry* **1982**, *21*, 2119. (c) Bohlmann, F.; Singh, P.; Jakupovic, J.; Huneck, S. *Planta Med.* w1985, *51*, 74.

Scheme IV



17a 5

The stereochemistries of **17a** and **17b** were deduced from their ^1H NMR spectra. Thus, the C_7-H undergoes a deshielding effect of 0.45 ppm in **17a** with respect to **13a**, which is consistent with an α-orientation for the hydroxyl group in this compound. Similarly, the isomer **17b**, which has β-orientation in the hydroxyl group, shows a deshielding effect of 0.44 ppm on C_6-H.[16]

Mild acid treatment of **17a** gave **5** (40%) and **18** (25%). Melting point and spectral properties (IR, ^1H NMR) of **5** were in complete agreement with those of subexpinnatin C.[5,17] The stereoselectivity of this cyclization could be explained by a S_N2 attack of the hydroxy group of C_{11} (Scheme IV) on C_{16} to displace the THP group. Preparation of **5** indicated that **13a** must have the *S* configuration.

This cyclization reaction, of which no previous report could be found, represents, to our knowledge, the first example of cyclization of 1,3-diols to form the oxetane ring under mild acid conditions.

Thus, the regio- and stereoselective synthesis of subexpinnatin C has been achieved in five steps with an overall yield of 7%.

Experimental Section

Melting points were taken on a Kofler hot stage apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 257 spectrometer in film. ^1H NMR and ^{13}C NMR spectra were made on Bruker WB-360, Varian FT-300, or Bruker WB-200 spectrometers using $SiMe_4$ as an internal standard. Mass spectra were recorded on a VG-Micromass ZAB-2F spectrometer.

Chromatographic separations were made on silica gel (Merck). The starting material, subexpinnatin, was isolated from the $CHCl_3$ fraction obtained from the ethanolic extract of *Centaurea canariensis* Brouss. (var. *subexpinnata* Burch.). Saponification of subexpinnatin was effected by following the procedure previously described.[9]

13-Acetyl-8α-hydroxy-11-epicostus Lactone (12). A solution of **11** (300 mg) in fresh acetaldehyde (100 mL), with continuous stirring in a modified Hanovia reactor with a Ni(II) and Co(II) aqueous solution and Pyrex jacket as filter, was irradiated with a 125-W Hg/medium pressure lamp at 25 °C for 60 min. The filter solution contained 46 g of $NiSO_4 \cdot 6H_2O$ and 14 g of $CoSO_4 \cdot 7H_2O$ per 100 mL of water.

The reaction mixture was concentrated under reduced pressure with addition of a very small amount of benzene. After chromatography ($HCCl_3$/hexane, 3:1) it yielded 245 mg (70%) of a mixture of **12** and **13**, ca. 7:1 ratio. Ketone **12** is a colorless gum: IR (film) 1760, 1710, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.21 (d, 1 H, $J_{3,15}$ = 2 Hz, C_{15}-H), 5.04 (d, 1 H, $J_{3,15'}$ = 2 Hz, C_{15}-H′), 4.94 (s br, 1 H, C_{14}-H), 4.89 (s br, 1 H, C_{14}-H′) 3.93 (dd, 1 H, $J_{5,6} = J_{6,7}$ = 10 Hz, C_6-H), 3.73 (ddd, 1 H, $J_{7,8}$ = 7, $J_{8,9}$ = 8, and $J_{8,9'}$ = 5 Hz, C_8-H), 3.20 (m, 2 H, C_{13}-H_2), 2.98–2.84 (m, 2 H, C_1-H and C_5-H), 2.68 (m, 1 H, C_{11}-H), 2.65 (dd, 1 H, $J_{8,9}$ = 8 and $J_{9,9'}$ = 13 Hz, C_9-H), 2.54–2.40 (m, 2 H, C_3-H_2), 2.25 (ddd, 1 H, $J_{6,7}$ = 10, $J_{7,8} = J_{7,11}$ = 9.5 Hz, C_7-H), 2.19 (s, 3 H, C_{16}-CH_3), 2.13 (dd, 1 H, $J_{8,9'}$ = 5 and $J_{9,9'}$ = 13 Hz, C_9-H′), and 1.94–1.74 (m, 2 H, C_2-H_2); MS, *m/e* (relative intensity) 290 (M^+) (1.7), 272 ($M - H_2O^+$) (14.9), 43 ($C_2H_3O^+$) (100).

13-Acetyl-8α-acetoxy-11-epicostus Lactone (14) and 13-(1′-Hydroxyethyl)-8α,16-diacetoxy-11-epicostus Lactone (15). A mixture of **12** and **13** (8 mg) was acetylated with 1 mL of Ac_2O/pyridine (3:1) for 24 h, room temperature. After purification column by chromatography (hexane/EtOAc, 9:1), this afforded 7.5 mg of **14** and 1 mg of **15**. **14** was isolated as a colorless gum: IR (film) 1770, 1740, 1715, 1640, 1240 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.18 (d, 1 H, $J_{3,15}$ = 2 Hz, C_{15}-H), 5.01 (d, 1 H, $J_{3,15'}$ = 2 Hz, C_{15}-H′), 4.92 (s br, 1 H, C_{14}-H), 4.87 (s br, 1 H, C_{14}-H′), 4.75 (ddd, 1 H, $J_{7,8}$ = 10, $J_{8,9}$ = 8.5, and $J_{8,9'}$ = 5.5 Hz, C_8-H), 3.94 (dd, 1 H, $J_{5,6} = J_{6,7}$ = 9.5 Hz, C_6-H), 2.95–2.81 (m, 2 H, C_1-H and C_5-H), 2.92 (dd, 1 H, $J_{11,13}$ = 5.5 and $J_{13,13'}$ = 14 Hz, C_{13}-H), 2.85 (dd, 1 H, $J_{11,13'}$ = 4 and $J_{13,13'}$ = 14 Hz, C_{13}-H′), 2.70 (ddd, 1 H, $J_{7,11}$ = 10, $J_{11,13}$ = 5.5 and $J_{11,13'}$ = 4 Hz, C_{11}-H), 2.69 (dd, 1 H, $J_{8,9}$ = 8.5 and $J_{9,9'}$ = 13.5 Hz, C_9-H), 2.55 (ddd, 1 H, $J_{6,7}$ = 9.5 and $J_{7,8} = J_{7,11}$ = 10 Hz, C_7-H), 2.47–2.41 (m, 2 H, C_3-H_2), 2.13 (s, 3 H, C_{16}-CH_3), 2.03 (dd, 1 H, $J_{8,9'}$ = 5.5, $J_{9,9'}$ = 13.5 Hz, C_9-H′), 1.98 (s, 3 H, C_8-OCOCH_3); MS, *m/e* (relative intensity) 272 ($M - 60^+$) (19.5), 43 ($C_2H_3O^+$) (100). **15** was isolated as a colorless gum: IR (film) 1760, 1730, 1250 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.18 (d, 1 H, $J_{13,15}$ = 2 Hz, C_{15}-H), 5.14 and 5.10 (m, 1 H, C_{16}-H), 5.05 (d, 1 H, $J_{13,15'}$ = 2 Hz, C_{15}-H′), 5.00 and 4.96 (s br, 1 H, C_{14}-H), 4.92 (s br, 1 H, C_{14}-H′), 4.85 (m, 1 H, C_8-H), 3.95 and 3.93 (dd, 1 H, $J_{5,6} = J_{6,7}$ = 10 Hz, C_6-H), 2.90 (d br, 1 H, C_1-H), 2.83 (d br, 1 H, $J_{5,6}$ = 10 Hz, C_5-H), 2.71 (dd, 1 H, $J_{8,9}$ = 5 and $J_{9,9'}$ = 12 Hz, C_9-H), 2.75–2.65 (m, 1 H, C_{11}-H), 2.57-2.42 (m, 2 H, C_3-H_2), 2.28 (m, 1 H, C_7-H), 2.22–1.95 (m, 2 H, C_{13}-H_2), 2.17 (dd, 1 H, $J_{8,9'}$ = 4 and $J_{9,9'}$ = 12 Hz, C_9-H′), 2.11 and 2.12 (s, 3 H, OCOCH_3), 2.02 and 2.03 (s, 3 H, OCOCH_3), 1.95–1.75 (m, 2 H, C_2-H_2), 1.23 (d, 3 H, $J_{16,17}$ = 6 Hz, C_{16}-CH_3); MS, *m/e* (relative intensity) 316 ($M - 60^+$) (1.8), 256 ($M - 120^+$) (7.9).

13-(1′-Hydroxyethyl)-8α-hydroxy-11-epicostus Lactone (13). The mixture of **12** and **13** (225 mg) was dissolved in 22 mL of methanol. Sodium borohydride (45 mg) was added in portions at 25 °C with continuous stirring over a period of 4 min. After 1 min the reaction mixture was then diluted with water. The solution was extracted with ethyl acetate, obtaining 223 mg (98%) of **13** as a crystalline compound: mp 123–125 °C; IR (KBr) 3400, 1760, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.20 (s br, 1 H, C_{15}-H), 5.06 (s br, 1 H, C_{15}-H′), 4.97 (s br, 1 H, C_{14}-H), 4.89 (s br, 1 H, C_{14}-H′), 4.10 (m, 1 H, C_{16}-H), 3.91 and 3.88 (dd, 1 H, $J_{5,6} = J_{6,7}$ = 9.5 Hz, C_6-H), 3.75 (m, 1 H, C_8-H), 2.92 (d br, 1 H, C_1-H), 2.87 (d br, 1 H, $J_{5,6}$ = 9.5 Hz, C_5-H), 2.75 and 2.65 (m, 1 H, C_{11}-H), 2.71 (dd, 1 H, $J_{8,9}$ = 8.5 and $J_{9,9'}$ = 13 Hz, C_9-H), 2.55–2.44 (m, 2 H, C_3-H_2), 2.32 (m, 1 H, C_7-H), 2.22–2.11 (m, 2 H, C_{13}-H_2), 2.19 (dd, 1 H, $J_{8,9'}$ = 5 and $J_{9,9'}$ = 13 Hz, C_9-H′), 1.97–1.77 (m, 2 H, C_2-H_2), 1.29 (d, 3 H, $J_{16,17}$ = 6 Hz, C_{16}-CH_3); MS, *m/e* (relative intensity) 292 (M^+) (2.6), 277 ($M - 15^+$) (3.4), 274 ($M - 18^+$) (8.1), 256 ($M - 2 \times H_2O^+$) (12.5).

(16*S*)-8,16-Bis(2″-tetrahydropyranyl)-13-(1′-hydroxyethyl)-8α-hydroxy-11-epicostus Lactone (16a) and (16*R*)-8,16-Bis(2″-tetrahydropyranyl)-13-(1′-hydroxyethyl)-8α-hydroxy-11-epicostus Lactone (16b). **13** (200 mg) was dissolved in 2 mL of freshly distilled dihydropyran, followed by a few crystals of *p*-toluenesulfonic acid. After 2 h, anhydrous potassium carbonate was added and the mixture allowed to stand overnight. The salts were removed by filtration and excess dihydropyran was removed by distillation under reduced pressure. The reaction mixture was chromatographed (hexane/EtOAc, 9:1) and **16a** (160 mg, 51%) and **16b** (74 mg, 24%) were separated. **16a** was isolated as a yellowish gum: IR (film) 1780, 1650, 1085 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.21 (s br, 1 H, C_{15}-H), 5.03 (s br, 1 H, C_{15}-H′), 4.89 (s br, 1 H, C_{14}-H), 4.83 (s br, 1 H, C_{14}-H′), 4.69 (m, 1 H, $C_{2'}$-H), 4.54 (m, 1 H, $C_{2''}$-H), 4.23 (m, 1 H, C_{16}-H), 3.95–3.25 (m, 6 H, C_6-H, C_8-H, $C_{6'}$-H_2, and $C_{6''}$-H_2), 2.94–2.50 (m, 4 H, C_1-H, C_5-H, C_9-H, and C_{11}-H), 2.50-2.37 (m, 2 H, C_3-H_2), 2.37–2.12 (m, 2 H, C_7-H and C_9-H′), 2.10–1.34 (m, 14 H), 1.30–1.15 (m, 3 H, C_{16}-CH_3); MS, *m/e* (relative intensity) 292 ($M - 2 \times C_5H_8O^+$) (6.7), 85 ($C_5H_9O^+$) (100). **16b** was isolated as a yellowish gum: IR (film) 1780, 1650, 1085 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.20 (s br, 1 H, C_{15}-H), 5.03 (s br, 1 H, C_{15}-H′), 4.99 (s br, 1 H, C_{14}-H), 4.85 (s br, 1 H, C_{14}-H′), 4.72 (m, 1 H, $C_{2'}$-H), 4.58 (m, 1 H, $C_{2''}$-H), 4.24 (m, 1 H, C_{16}-H), 3.90–3.40 (m, 6 H, C_6-H, C_8-H, $C_{6'}$-H_2, and $C_{6''}$-H_2), 2.94–2.64 (m, 3 H, C_1-H, C_5-H, and C_9-H), 2.56 (m, 1 H, C_7-H), 2.45 (m, 3 H, C_3-H_2 and C_{11}-H), 2.25 (m, 1 H, C_9-H′), 2.10–1.80 (m, 2 H, C_{13}-H_2), 1.80–1.40 (m, 14 H), 1.30–1.15 (m, 3 H, C_{16}-CH_3); MS, *m/e* (relative

(15) Macías, F. A.; Massanet, G. M.; Rodríquez Luis, F., unpublished results.

(16) González, A. G.; Bermejo, J.; Bretón, J. L.; Galindo, A.; Massanet, G. M. *Rev. Latinoam. Quim.* **1978**, *9*, 78.

(17) ^{13}C NMR chemical shift of C_{11}, C_{13}, C_{16}, and C_{17} support the assignation of an *R* configuration for the C_{16} in **5**.

intensity) 292 (M - 2 × $C_5H_8O^+$) (8.7), 85 ($C_5H_9O^+$) (100).

(16*S*)-13-(1′-Hydroxyethyl)-8α-hydroxy-11-epicostus Lactone (13a). **16a** (5 mg) was dissolved in 25 mL of MeOH/HCl(aq) (0.05 N) (3:1) and allowed to stand for 72 h. The solution was neutralized with NaOH(aq) (0.1 N). Acetone was added. The salts were removed by filtration and the solvent was removed by distillation under reduced pressure. Purification by preparative TLC (three times in hexane/EtOAc, 7:1) yielded 2 mg of **13a** as a crystalline compound: mp 124–126 °C; ^1H NMR ($CDCl_3$) δ 3.88 (dd, 1 H, $J_{5,6} = J_{6,7} = 9.5$ Hz, C_6-H), 2.65 (m, 1 H, C_{11}-H), 2.32 (m, 1 H, C_7-H), 2.22–2.11 (m, 2 H, C_{13}-H).

(16*R*)-13-(1′-Hydroxyethyl)-8α-hydroxy-11-epicostus Lactone (13b). Deprotection of **16b** (5 mg) as described for **16a**, after purification by preparative TLC (three times in hexane/EtOAc, 7:1) gave 2 mg of **13b** as a crystalline compound: mp 122–124 °C; ^1H NMR ($CDCl_3$) δ 3.91 (dd, 1 H, $J_{5,6} = J_{6,7} = 9.5$ Hz, C_6-H), 2.75 (m, 1 H, C_{11}-H), 2.32 (m, 1 H, C_7-H), 2.22–2.11 (m, 2 H, C_{13}-H).

(16*S*)-8,16-Bis(2″-tetrahydropyranyl)-13-(1′-hydroxyethyl)-8α,11α-dihydroxycostus Lactone (17a) and (16*S*)-8,16-Bis(2″-tetrahydropyranyl)-13-(1′-hydroxyethyl)-8α,11β-dihydroxycostus Lactone (17b). A solution of **16a** (90 mg) in dry THF (4.5 mL) was dripped into a mixture containing 0.2 mL of diisopropylamine, 0.5 mL of a hexane solution of butyllithium (15%), and 1 mL of THF and stirred continuously for 30 min at −70 °C under a dry nitrogen atmosphere. After the mixture had been stirred for 40 min, it reached 0 °C and then dry oxygen was bubbled through for 30 min. It was carefully neutralized with HCl(aq) (1 N). The mixture was extracted with ethyl acetate, and after purification by CC (hexane/EtOAc, 9:1), it yielded 43 mg (48%) of **17a** and 12 mg (13%) of **17b**. **17a** was isolated as a colorless gum: IR (film) 3350, 1760, 1640, 1080 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.20 (s br, 1 H, C_{15}-H), 5.03 (s br, 1 H, C_{15}-H′), 4.97–4.75 (m, 4 H, C_{14}-H_2, $C_{2'}$-H, and $C_{2''}$-H), 4.56 (m, 1 H, C_{16}-H), 4.26–3.40 (m, 6 H, C_6-H, C_8-H, $C_{6'}$-H_2, and $C_{6''}$-H_2), 2.98–2.82 (m, 2 H, C_1-H and C_5-H), 2.70 (m, 1 H, C_7-H), 2.65 (m, 1 H, C_9-H), 2.55–2.40 (m, 2 H, C_3-H_2), 2.28 (dd, 1 H, $J_{8,9} = 8$ and $J_{9,9'} = 12$ Hz, C_9-H′), 2.10–1.37 (m, 14 H), 1.30–1.10 (m, 3 H, C_{16}-CH_3). **17b** was isolated as a colorless gum: IR (film) 3350, 1760, 1640, 1080 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.19 (s br, 1 H, C_{15}-H), 5.08 (s br, 1 H, C_{15}-H′), 5.01–4.84 (m, 4 H, C_{14}-H_2, $C_{2'}$-H, and $C_{2''}$-H), 4.56 (m, 1 H, C_{16}-H), 4.36 (dd, 1 H, $J_{5,6} = J_{6,7} = 10$ Hz, C_6-H), 4.05–3.37 (m, 5 H, C_8-H, $C_{6'}$-H_2, and $C_{6''}$-H_2), 2.95–2.82 (m, 2 H, C_1-H and C_5-H), 2.71 (dd, 1 H, $J_{8,9} = 5$ and $J_{9,9'} = 12$ Hz, C_9-H), 2.53–2.12 (m, 4 H, C_3-H_2, C_7-H, and C_9-H′), 2.12-1.40 (m, 14 H), 1.30–1.18 (m, 3 H, C_{16}-CH_3).

Subexpinnatin C (5) and 8α,11α-Dihydroxy-13-(1′-hydroxyethyl)-11-epicostus Lactone (18). **17a** (35 mg) was treated as described for the deprotection of **16a**, and 8 mg (40%) of **5** and 5 mg (25%) of **18** were obtained after purification by preparative TLC (six times in $HCCl_3$/*t*-BuOH, 19:1). **5** was isolated as a crystalline compound: mp 186–188 °C; IR (KBr) 3400, 1770, 1630; ^{13}C NMR ($CDCl_3$/MeOH-d_4 1:1) δ 178.9 (C-12), 151.6 (C-4), 145.1 (C-10), 115.0 (C-14), 110.4 (C-15), 79.7 (C-6), 76.5 (C-11), 68.0 (C-8), 64.4 (C-16), 55.5 (C-7), 53.3 (C-5), 44.5 (C-1)*, 44.1 (C-13)*, 32.3 (C-9), 30.5 (C-2)*, 30.2 (C-3)*, 24.3 (C-17). (Assignments denoted with asterisks may be interchanged.)

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Synthesis of (*R*)-Serine-*2-d* and Its Conversion to the Broad Spectrum Antibiotic Fludalanine

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A novel and practical synthesis of (*R*)-serine-*2-d* that is stoichiometric in its use of deuterium is described. Isopropyl (*R,S*)-2-phenyl-2-oxazoline-4-carboxylate is metalated, deuteriated, resolved, and hydrolyzed to provide the optically pure (>99.8%) unnatural amino acid with >98% isotopic purity. Fluorination of the primary hydroxyl with SF_4 produces (*S*)-3-fluoroalanine-*2-d* (Fludalanine).

(*S*)-3-Fluoroalanine-*2-d* (Fludalanine, 1) in combination with the 2,4-pentanedione enamine of cycloserine sodium salt constitutes a novel, uniquely synergistic bacteriacidal antimicrobial (MK-641/642).[1] The introductions of deuterium and fluorine present unique problems which have been previously solved by the photofluorination of (*R*)-alanine-d^2 or the reductive amination of lithium fluoropyruvate using $NaBD_4$ followed by resolution.[3] With the advent of the requirement for large quantities of Fludalanine (1, MK-641) we had to address the practical and economical introduction of deuterium into an organic molecule. Neither of the original routes had addressed this critical issue, although the latter has been run on a multikilo scale.

In approaching the synthesis of 1 there are three prime criteria for a good route: (1) the specific introduction of

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