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Synthetic Studies Toward Natural Furanosesquiterpenoids from Santonin. Synthesis of (+)-1,2-Dihydrotubipofuran

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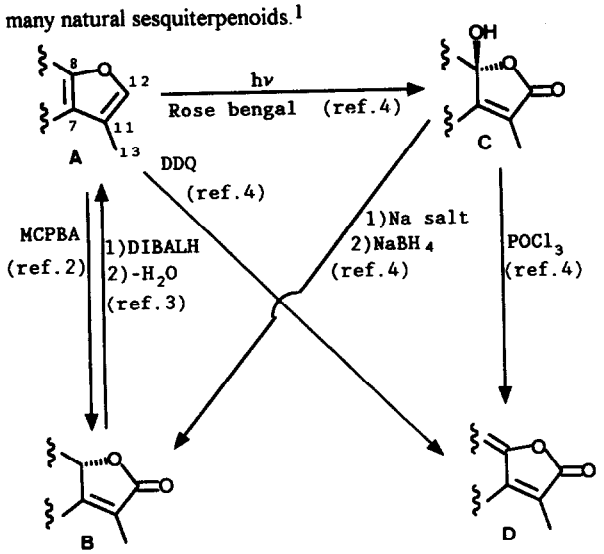
Abstract: Santonin **(1)** was converted into (+)-1,2-dihydrotubipofuran **(13)** via a synthetic pathway involving a very easy preparation of 7,11-ene-8,12-olide and 8,12-furan moieties and A-ring elaboration on the eudesmane framework.

Sesquiterpenoids possessing an 8,12-furan moiety (A) on various skeletons, including eudesmane, guaiane, germacrane and elemane are a rapidly expanding group of natural products.[1] Related functionalities[2-4] such as 7,11-ene-8,12-olide (B), 7,11-ene-8-hydroxy-8,12-olide (C) and 7(11),8-dien-8,12-olide (D) are also present in many natural sesquiterpenoids.[1]

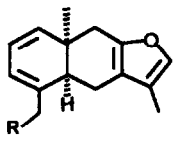


Compounds with these kinds of functionalities have considerable biological activity such as antiinflammatory,[5] ichtyotoxic and cytotoxic,[6] seed germination inhibitory[7] and molluscicidal activities,[7,8] and consequently efficient synthesis of these compounds are a synthetic challenge which has received much attention during the recent years.[9]

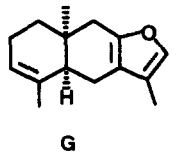
In a previous paper[10], starting from santonin **(1)** we have synthesized the trienone **2**, which by allylic oxidation (SeO_2/ dioxane, under reflux) allowed us to prepare ketol ester **3**, a key intermediate to the synthesis of 8,12-eudesmanolides.[10,11]

Continuing with our research programme directed toward the synthesis of biologically active sesquiterpenoids, we show in this paper, the utility of compound **3** in a very easy preparation of 7,11-ene-8,12-olide (B) and 8,12-furan (A) moieties and report the first synthesis of (+)-1,2-dihydrotubipofuran **(13)**. Tubipofuran[6] (E) is an *ent*-furanoeudesmane with *cis*-stereochemistry between the angular C-5 and C-10 positions, which was isolated, along with its 15-acetoxyderivative (F) from the stolonifer *Tubipora musica*

Linnaeus.[6] These compounds show ichtyotoxicity toward a killi-fish *Orizias latipes* and compound (F) shows citotoxicity against B-16 melanoma cells *in vitro*.[6]



E: R=H
F: R=OAc

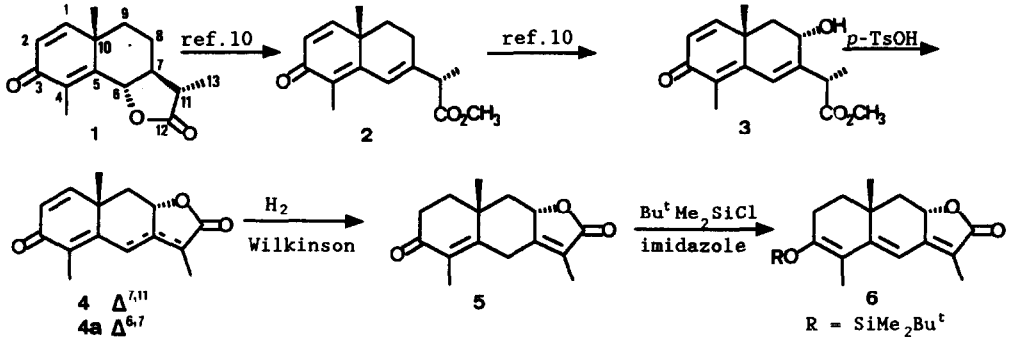


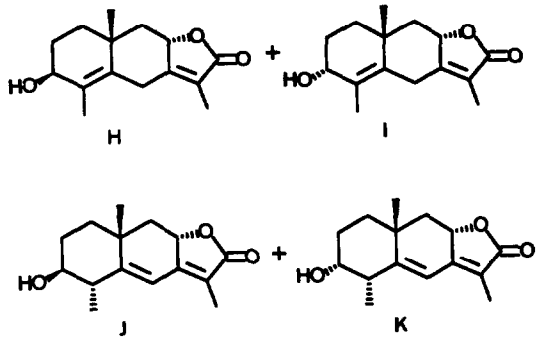
G
1,2-Dihydrotubipofuran

RESULTS AND DISCUSSION

It is known that treatment of γ-hydroxyesters with catalytic acid results in cyclization to the corresponding γ-lactones.[10-12] On the other hand isomerization of double bonds is carried out also by acid catalysis.[13] Consequently compound **3** was heated with benzene and *p*-toluenesulfonic acid under reflux with the hope of obtaining directly the butenolide **4**. In a first assay (40 mg of acid / gr of substrate), although the reaction product was homogeneous on TLC, its ^{1}H NMR showed the presence of two products **4** and **4a** in a 3:7 ratio. In the ^{1}H NMR spectrum of this mixture two multiplets at δ 5.25 and 5.07 in **4a** and **4** respectively was observed for H-8, a singlet at δ 6.13 in **4a** and AB system at δ 3.99 and 3.23 in **4** for H-6 and a doublet at δ 1.48 in **4a** and a triplet (J 1.8 Hz) a δ 1.86 in **4** for H-13.With a double amount of *p*-toluenesulfonic acid compound **4** was obtained as the only product in a 93% yield. The structure of **4** was fully supported by the ^{1}H and ^{13}C NMR spectra as shown in the Experimental Section and Table.

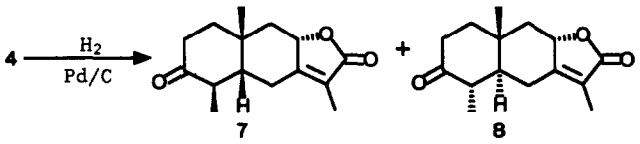
With this easy preparation of the butenolide moiety in hand we focused our efforts on the elaboration of the 3,4-double bond present, as such or as derivatives, in A ring of several natural products. Our first approach was based on the Corey's basic decomposition of allylic tosylhydrazines.[14] Towards this end a solution of the dienone **4** in benzene-ethanol was chemoselectively hydrogenated using the Wilkinson catalyst under medium pressure of hydrogen for 2 days giving 90% yield of a homogeneous TLC 1,2-dihydroderivative **5**. Its ^{1}H NMR spectrum indicated however the existence of a keto-enol equilibrium (1 : 1 ratio in acetone-d_6): an AB system at δ 3.78 and 3.07 (J = 17.5 Hz) for the H-6 protons of the keto form and a singlet a δ 5.98 for the H-6 proton of the enol form.[15] This one was trapped as *tert*-butyldimethylsilylether **6** (*t*-BuMe$_2$SiCl, imidazole, DMF)[16] with a 75% yield and suitably characterized.





The reduction of the dihydroderivative **5** to the corresponding allylic alcohols was difficult: The starting product was not changed upon treatment with $LiAlH(O\text{-}t\text{-}Bu)_3$ in THF in the usual conditions and only with a great excess of $NaBH_4$ in ethanol (12 mol/mol of substrate) could the reduction of the carbonyl group be carried out giving a 75% yield of an inseparable mixture of four alcohols: C_3-epimers allylic and homoallylic (H-K).

In view of these results we decided to explore an alternative approach involving a chemoselective hydrogenation of **4** to the corresponding tetrahydroderivative keeping unchanged the butenolide moiety and subsequent A-ring elaboration.[11] With this prospect in mind and on the basis of the previous results obtained in the hydrogenation of several dienones[10-12,17,18] we decided to carry out this reaction with carbon-supported palladium in acetone and epimerization with *p*-toluenesulfonic acid/benzene. However, the major product in this case was the *cis*-fused isomer **7** (75%) contrarialy to that reported in similar cases.[10-12,17,18] With $Rh\text{-}Al_2O_3$, which is described as reversing the stereochemistry results[19] we obtained with our substrate similar results to that Pd/C, being the yield of the reaction lower than before. The structures of **7** and **8** were fully supported by the ^1H and ^{13}C NMR spectra. The *cis* ring fusion for **7** was deduced by the observed coupling constant between H-6 and H-5. The proton H-6α appears at δ 2.84 as a double doublet with H-6β geminal (J = 14.6 Hz) and H-5β equatorial-equatorial (J = 1.9 Hz) couplings and the proton H-6β arises at δ 2.51 as a double double quadruplet with H-6α geminal, H-5β axial-equatorial (J = 5.1 Hz) and H-13 homoallylic (J = 1.3 Hz) couplings. In the trans ring fusion isomer **8**, the proton H-6α appears at δ 2.81 as a double doublet with H-6β geminal (J = 14.0 Hz) and H-5α equatorial-axial (J = 4.1 Hz) while the proton H-6β arises at δ 2.08 as a double double quadruplet with geminal, H-5α axial-axial (J = 11.6 Hz) and H-13 homoallylic (J = 1.4 Hz) couplings.



This result thwarted our initial purpose to synthesize the most abundant naturally *trans*-fused furanosesquiterpenoids and obligated us to direct our work toward the synthesis of the (+)-1,2-dihydrotubipofuran (**13**). Reduction of the ketone group of **7** was carried out with $NaBH_4$ in ethanol yielding the epimeric alcohols **9** and **10** (1.7:1, 94% yield) or with $LiAlH(O\text{-}t\text{-}Bu)_3$ in THF, which increased remarkablely the diastereoselectivity of the reaction (7:1, 88% yield). Conversion of the alcohol **9** into its 3β-chloro derivative **11** with $SOCl_2$-pyridine[20] at 80°C (64% yield) or with $POCl_3$-pyridine[21] at room temperature (86% yield) followed by elimination of the chloride[22] with $LiBr/Li_2CO_3$/DMF at 80-90°C for 12 hours yielded **12** exclusively (68% yield). At higher temperatures (100°C) the reaction times was shorter, however there was important loss of product probably due to its volatility. Finally the reduction of butenolide **12** to lactol[3,23] with

DIBALH in toluene at -20°C and dehydration in the isolation process afforded directly the furane **13** (80% yield).The ^{1}H NMR spectrum of synthetic product was consistent with structure **13** and identical with literature data for the 1,2-dihydroderivative of the natural tubipofuran.[6,24]

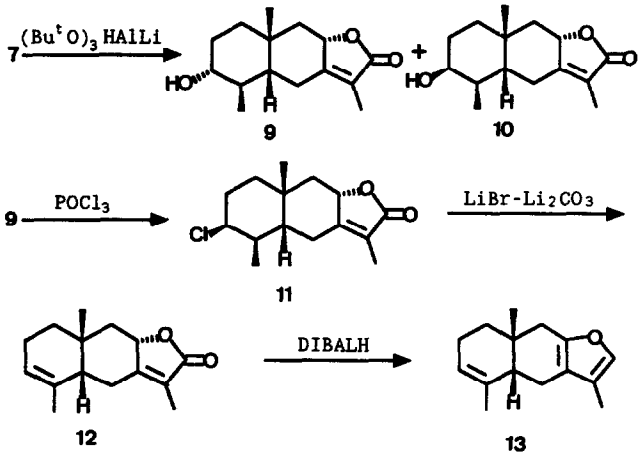


Table. ^{13}C NMR Data of Compounds 4 and 6-13 (δ, $CDCl_3$)

	4	**6**$^+$	**7**	**8**	**9**	**10**	**11**	**12**	**13**
C_1	153.6	43.3^a	37.3^a	36.7^a	30.0^a	28.4^a	29.4^a	24.3^a	24.5^a
C_2	126.3	27.8^a	25.5^a	26.8^a	24.2^a	23.9^a	23.6^a	22.0^a	23.2^a
C_3	185.1	112.8^b	211.2	210.4	75.0	71.0	67.5	123.7	119.4
C_4	131.7^a	100.5^b	51.0^b	50.9^b	37.3^b	33.4^b	34.0^b	132.4	136.9
C_5	152.3^a	157.5^b	43.0^b	45.1^b	48.3^b	42.7^b	42.8^b	45.8	43.7
C_6	28.6	108.3	39.8^a	46.7^a	37.8^a	33.2^a	33.5^a	36.0^a	35.1^a
C_7	158.2	153.5^b	158.5	160.5	160.5	160.5	160.0	160.3	119.2^b
C_8	76.3	75.7	78.0	77.5	78.4	78.5	78.2	78.4	149.8
C_9	42.4	36.8^a	38.4^a	39.3^a	38.7^a	38.3^a	38.8	37.8^a	29.8^a
C_{10}	40.0	35.6	34.8	34.6	34.3	34.5	34.5	33.6	33.1
C_{11}	121.8	115.0^b	123.0	120.7	121.0	121.1	121.2	120.3	114.4^b
C_{12}	173.7	175.5	174.0	174.3	174.5	174.4	174.2	174.7	136.9
C_{13}	8.4	8.2	8.4	8.1	8.0	8.2	8.3	8.7	8.0
C_{14}	24.2	23.2	26.9	16.3	27.5	27.6	27.5	26.9	26.7
C_{15}	11.0	11.6	12.1	11.2	15.7	16.9	18.4	21.8	22.7

$^+$ Bu^{t}Me$_2$Si- group: δ -3.4 and -3.6 for *Me*$_2$Si, 18.3 for Me$_3$*C*-Si and 25.7 for *Me*$_3$C-Si.

^{a,b} These signals may be interchangeables within the corresponding spectrum.

EXPERIMENTAL

All melting points are uncorrected. TLC was carried out on Merck 0.25 mm silica gel 60 HF_{254} analytical aluminum plates. 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 $CHCl_3$. NMR spectra were run in $CDCl_3$ at 200.1, 299.95 or 399.95 MHz for ^1H and 50.3, 75.43, or 100.58 MHz for ^{13}C. The carbon type (methyl, methylene, methine, or quaternary) was determined by DEPT experiments. Mass spectra were run by electron impact at 70 eV.

3-Oxo-8βH-eudesma-1,4,7(11)-trien-8,12-olide **(4)**. A solution containing 463 mg (1.68 mmol) of hydroxyester **3** and *p*-toluenesulfonic acid (40 mg) in 30 mL of benzene was heated under reflux for 2 h. The reaction mixture was filtered through silica gel, and the filtrate was concentrated *in vacuo*. The residue was chromatographed on silica gel (hexane-ether) to give 383 mg (93%) of compound **4**: m.p. 190-193°C dec. (CH_2Cl_2); $[\alpha]^{24}_D$ +167° (c 0.65); IR (KBr) 1750, 1690, 1650, 1630, 1040, 840, 760, 740 cm^{-1}; MS *m/e* 245 (M^++1, 14), 244 (M^+, 100), 229 (M^+-CH_3, 33), 216 (23), 215 (12), 201 (32), 187 (10); HMRS: 244.1090, $C_{15}H_{16}O_3$ required 244.1095; ^1H NMR δ 6.47 (d, 1H, J = 9.8 Hz, H-1), 6.25 (d, 1H, J = 9.8 Hz, H-2), 5.07 (ddt, 1H, J = 1.8, 6.1, 12.0 Hz, H-8), 3.99 (d, 1H, J = 15.8 Hz, H-6α), 3.23 (dq, 1H, J = 1.7, 15.8 Hz, H-6β), 2.51 (dd, 1H, J = 6.1, 12.0 Hz, H-9β), 1.97 (d, 3H, J = 1.2 Hz, H-15), 1.86 (t, 3H, J = 1.8 Hz, H-13), 1.41 (s, 3H, H-14), 1.23 (t, 1H, J = 12.0 Hz, H-9α).

3-Oxo-8βH-eudesma-4,7(11)-dien-8,12-olide **(5).** 100 mg (0.11 mmol) of freshly prepared Wilkinson catalyst were suspended in 6 mL of dry benzene and stirred under H_2 atmosphere until complete dissolution. A solution of compound **4** (192 mg, 0.786 mmol) in 18 mL of dry benzene and 0.6 mL of absolute ethanol was then added via syringe. After stirring (*ca.* 3.5 atm) for 2 days at room temperature, the hydrogenation mixture was filtered through silica gel and concentrated *in vacuo* to give 185 mg (95%) of compound **5.**

3-t-Butyldimethylsilyloxy-8βH-eudesma-3,5,7(11)-trien-8,12-olide **(6).** Compound **(5)** (26 mg, 0.105 mmol) in DMF (0.8 mL) was treated with *t*-butyldimethylsilyl chloride (59 mg, 0.391 mmol) and imidazole (72 mg, 1.05 mmol) at room temperature over 12 h. The reaction mixture was chromatographed on silica gel giving 26 mg (75%) of compound **6**: mp 96-99°C (CH_2Cl_2), $[\alpha]^{22}_D$ -605° (c 0.655); IR (KBr) 1740, 1600, 1240, 1220, 1100, 890, 840 cm^{-1}; MS *m/e* 246 (M^++1-[Bu^tMe_2Si], 1), 244 (M^+-[Bu^tMe_2SiH], 0.7), 220 (11), 219 (40), 149 (15), 49 (100); HMRS: 246.1253, $C_{15}H_{18}O_3$ (M^++1-[Bu^tMe_2Si]) required 246.1251; ^1H NMR δ 6.10 (s, 1H, H-6), 5.01 (ddd, 1H, J = 1.3, 4.9, 13.0 Hz, H-8), 2.47 (broad ddd, 1H, J = 7.8, 9.7, 17.6 Hz, H-2), 2.16 (dd, 1H, J = 4.9, 11.5 Hz, H-9β), 2.3-2.1 (m, 1H, H-2' overlapped with H-9β), 1.88 (d, 3H, J = 1.3 Hz, H-13), 1.84 (s, 3H, H-15), 1.7-1.6 (m, 2H, 2H-1), 1.42 (dd, 1H, J = 11.5, 13.0 Hz, H-9α), 1.17 (s, 3H, H-14), 0.96 (s, 9H, $(CH_3)_3CSi$), 0.17 (s, 6H, $2CH_3Si$).

3-Oxo-4αH,5,8βH-eudesm-7(11)-en-8,12-olide **(7)** ***and 3-oxo-5αH,4,8βH-eudesm-7(11)-en-8,12-olide*** **(8)**. 0.875 g (3.59 mmol) of butenolide **4** in 88 mL of acetone was hydrogenated over a 5% Pd/C catalyst (95 mg) over 1.5 h. After removal of the catalyst by filtration through a pad of silica gel, the filtrate was concentrated *in vacuo*. A solution of the oily residue and *p*-toluenesulfonic acid (88 mg) in 36 mL of benzene

was stirred at room temperature overnight. The reaction mixture was filtered through silica gel, and the filtrate concentrated *in vacuo*. Column chromatography (hexane-ethyl acetate) of the residue gave 664 mg of compound **7** (75%) and 45 mg of compound **8** (5%). Compound **7** had the following features: mp 137-139°C (hexane-ether), $[\alpha]^{21}_D$ +176° (c 1.36); IR (KBr) 1740, 1700, 1680, 1090, 1040, 760 cm^{-1}; MS *m/e* 249 (M^++1, 18), 248 (M^+, 100), 233 (M^+-CH_3, 27), 230 (48), 219 (24), 202 (18), 191 (34); HMRS: 248.1403, $C_{15}H_{20}O_3$ required 248.1407; ^1H NMR δ 4.94 (broad dd, 1H, J = 6.5, 10.0 Hz, H-8), 2.84 (dd, 1H, J = 1.9, 14.6 Hz, H-6α), 2.51 (ddq, 1H, J = 1.3, 5.1, 14.6 Hz, H-6β), 2.39 (td, 1H, J = 6.2, 14.0 Hz, H-2α), 2.26 (ddd, 1H, J = 2.8, 5.3, 14.0 Hz, H-2β), 2.07 (dd, 1H, J = 6.5, 12.6 Hz, H-9β), 2.07 (dq, 1H, J = 6.5, 12.2 Hz, H-4 overlapped with H-9β), 1.88 (dd, 1H, J = 10.0, 12.6 Hz, H-9α), 1.82 (t, 3H, J = 1.3 Hz, H-13), 1.8-1.6 (m, 3H, 2H-1, H-5), 1.21 (s, 3H, H-14), 1.04 (d, 3H, J = 6.5 Hz, H-15). Compound **8** had the following features. mp 125-129°C (CH_2Cl_2), $[\alpha]^{22}_D$ +139° (c 0.66); IR (KBr) 1740, 1700, 1690, 1100, 1050 cm^{-1}; MS *m/e* 249 (M^++1, 17), 248 (M^+, 100), 233 (M^+-CH_3, 5), 230 (7), 220 (14), 219 (13), 192 (15), 191 (12); HMRS: 248.1402, $C_{15}H_{20}O_3$ required 248.1407; ^1H NMR δ 4.86 (broad dd, 1H, J = 6.0, 11.6 Hz, H-8), 2.81 (dd, 1H, J = 4.1, 14.0 Hz, H-6α), 2.51 (td, 1H, J = 6.4, 14.0 Hz, H-2β), 2.2-2.4 (m, 2H, H-2α, H-4), 2.29 (dd, 1H, J = 6.0, 12.0 Hz, H-9β overlapped with H-2α, H-4), 2.08 (ddq, 1H, J = 1.4, 11.6, 14.0 Hz, H-6β), 1.7-1.8 (m, 1H, H-1β), 1.76 (t, 3H, J = 1.4 Hz, H-13 overlapped with H-1β), 1.50 (td, 1H, J = 5.2, 14.0 Hz, H-1α), 1.27 (dt, 1H, J = 4.1, 12.4 Hz, H-5), 1.25 (s, 3H, H-14), 1.04 (d, 3H, J = 6.5 Hz, H-15), 0.96 (dd, 1H, J = 11.6, 12.0 Hz, H-9α).

***3α-Hydroxy-4α,5,8βH-eudesm-7(11)-en-8,12-olide* (9) *and 3β-hydroxy-4α,5,8βH-eudesm-7(11)-en-8,12-olide* (10).** Compound **7** (292 mg, 1.29 mmol) in dry THF (50 mL) was added to a suspension of LiAlH(O-*t*-Bu)$_3$ (380 mg, 1.49 mmol) in dry THF (10 mL) at 0°C and stirred at this temperature for 15 min. The reaction was quenched with 1M aqueous HCl, diluted with brine and extracted with ethyl acetate. Usual work up and chromatography (hexane-ether) eluted 35 mg (11%) of alcohol **10**: m.p. 137-141°C (CH_2Cl_2); $[\alpha]^{22}_D$ +179° (c 1.65); IR (KBr) 3600-3300, 1745, 1710, 1660, 1090, 1030, 960 cm^{-1}; MS *m/e* 251 (M^++1, 17), 250 (M^+, 100), 235 (M^+-CH_3, 67), 233 (13), 232 (M^+-H_2O, 64), 221 (33), 217 (41); HMRS: 250.1559, $C_{15}H_{22}O_3$ required 250.1563; ^1H NMR δ 4.84 (broad dd, 1H, J = 7.3, 10.9 Hz, H-8), 3.75 (broad dd, 1H, J = 2.6, 5.0 Hz, H-3), 2.74 (dd, 1H, J = 1.9, 14.6 Hz, H-6α), 2.50 (ddq, 1H, J = 1.3, 5.6, 14.6 Hz, H-6β), 1.80 (t, 3H, J = 1.3 Hz, H-13), 1.9-1.7 (m, 2H, H-5, H-9β overlapped with H-13), 1.7-1.5 (m 1H, H-2β), 1.64 (dd, 1H, J = 10.9, 12.6 Hz, H-9α overlapped with H-2β), 1.4-1.2 (m, 1H, H-4), 1.15 (s, 3H, H-14), 0.99 (d, 3H, J = 6.6 Hz, H-15).

A second eluted product was alcohol **9** (248 mg, 77%) with the following features: m.p. 142-143°C (CH_2Cl_2); $[\alpha]^{20}_D$ +141° (c 1.54); IR (KBr) 3500, 1745, 1680, 1100, 1040, 770, 750, 640 cm^{-1}; MS *m/e* 250 (M^+, 6), 235 (M^+-CH_3, 25), 232 (M^+-H_2O, 100), 217 (51), 204 (19), 203 (43), 194 (20); HMRS: 250.1560, $C_{15}H_{22}O_3$ required 250.1563; ^1H NMR δ 4.84 (broad dd, 1H, J = 7.2, 10.5 Hz, H-8), 3.11 (ddd, 1H, J = 5.2, 7.3, 11.5 Hz, H-3), 2.86 (dd, 1H, J = 1.8, 14.5 Hz, H-6α), 2.48 (ddt, 1H, J = 1.2, 5.2, 14.5 Hz, H-6β), 1.85 (dd, 1H, J = 7.2, 12.0 Hz, H-9β overlapped with H-13), 1.79 (t, 3H, J = 1.7 Hz, H-13), 1.74 (dd, 1H, J = 10.5, 12.0 Hz, H-9α), 1.12 (s, 3H, H-14), 1.04 (d, 3H, J = 1.1 Hz, H-15).

***3β-chloro-4αH,5,8βH-eudesm-7(11)-en-8,12-olide* (11).** To a solution of 0.453 g (1.81 mmol) of compound **9** in dry pyridine (1 mL) was added a solution of $POCl_3$ (0.55 mL, 5.90 mmol). After stirring 18 h a room temperature, the reaction was quenched by adding aqueous 1M NH_4Cl. The mixture was extracted with

ethyl acetate and the combined organic layers washed with brine, dried and concentrated *in vacuo*. The reaction product was chromatographed on silica gel (hexane-ethyl acetate) yielding 0.412 (86%) of compound **11**: mp 136-140°C (CH_2Cl_2), $[\alpha]^{20}_D$ +200° (c 1.62); IR (KBr) 1740, 1680, 1080, 1030 cm^{-1}; MS *m/e*, 270, 268 (M^+, 11, 30), 255, 253 (M^+-CH_3, 23, 68), 241 (11), 240 (13), 239 (23), 234 (18), 233 (M^+-Cl, 100); HMRS: 268.1221, $C_{15}H_{21}O_2Cl$ required 268.1225; ^1H NMR δ 4.85 (broad dd, 1H, J = 6.5, 10.9 Hz, H-8), 4.24 (dd, 1H, J = 2.2, 2.7 Hz, H-3), 2.75 (dd, 1H, J = 1.4, 14.5 Hz, H-6α), 2.51 (broad dd, 1H, J = 6.5, 14.5 Hz, H-6β), 2.0-1.8 (m, 3H, H-2, H-5, H-9β), 1.81 (broad s, 3H, H-13), 1.61 (dd, 1H, J = 10.9, 12.5 Hz, H-9α), 1.55 (ddq, 1H, J = 2.2, 6.4, 12.0 Hz, H-4), 1.4-1.2 (m, 1H, H-2'), 1.18 (s, 3H, H-14), 1.01 (d, 3H, J = 6.4 Hz, H-15).

5,8βH-eudesm-3,7(11)-dien-8,12-olide (12). A suspension of compound **11** (0.114 mg, 0.42 mmol), LiBr (0.100 g, 1.15 mmol) and Li_2CO_3 (0.119 g, 1.60 mmol) in dry DMF (1.2 mL) was heated at 80-90°C for 12 h. The reaction was quenched with water and the mixture extracted with ethyl acetate. By the usual work up and chromatography with hexane-ether as eluent 67 mg (68%) of compound **12** and 5 mg (4%) of starting product were obtained. Compound **12**: mp 96-99°C (CH_2Cl_2), $[\alpha]^{22}_D$ +120° (c 0.48); IR (KBr) 1740, 1685, 1080, 1040, 1025, 770 cm^{-1}; MS *m/e* 233 (M^++1, 2), 232 (M^+, 3), 205 (5), 167 (3), 149 (7), 121 (6); HMRS: 232.1460, $C_{15}H_{20}O_2$ required 232.1458; ^1H NMR δ 5.37 (broad s, 1H, H-3), 4.82 (broad dd, 1H, J = 6.5, 11.6 Hz, H-8), 2.96 (dd, 1H, J = 1.9, 14.7 Hz, H-6α), 2.53 (broad dd, 1H, J = 6.5, 14.7 Hz, H-6β), 2.28 (broad s, 1H, H-5), 2.1-1.8 (m, 3H, 2H-2, H-9β), 1.80 (t, 3H, J = 1.3 Hz, H-13), 1.62 (broad s, 3H, H-15), 1.6-1.4 (m, 2H, 2H-1), 1.45 (t, 1H, J = 11.6 Hz, H-9α overlapped with H-1), 1.17 (s, 3H, H-14).

***(+)-1,2-dihydrotubipofuran* (13).** To a solution of 48 mg (0.207 mmol) of compound **12** in dry toluene (5 mL) at -20°C was added via syringe a solution of 1M DIBALH in hexane (0.25 ml, 0.25 mmol). After stirring at -20°C for 30 min the reaction was quenched adding via syringe 1.5 mL of a 2M solution of isopropanol in toluene and 0.2 mL of water. The mixture was diluted with ethyl acetate (1.5 mL) and treated with anhydrous Na_2SO_4 (400 mg) and kieselguhr (160 mg) and vigorously stirred (under argon) for 30 min. Flash chromatography (under argon, neutral alumina, ethyl acetate) yielded 36 mg (80%) of (+)-dihydrotubipofuran (**13**): an oil, $[\alpha]^{26}_D$ +38° (c 1.05); IR (NaCl) 3040, 1660, 1575, 810, 740 cm^{-1}; MS *m/e* 216 (M^+, 12), 201 (M^+-CH_3, 6), 108 (100), 91 (5); HMRS: 216.1505, $C_{15}H_{20}O$ required 216.1509; ^1H NMR δ 7.03 (broad s, 1H, H-12), 5.25 (broad s, 1H, H-3), 2.69 (broad dd, 1H, J = 6.0, 16.4 Hz, H-6), 2.49 (d, 1H, J = 17.0 Hz, H-9), 2.37 (broad d, 1H, J = 17.0 Hz, H-9'), 2.17 (broad dd, 1H, J = 7.6, 16.4 Hz, H-6'), 2.6-2.1 (m, 2H, 2H-2), 1.91 (dd, 1H, J = 6.0, 7.6 Hz, H-5), 1.90 (s, 3H, H-13 overlapped with H-5), 1.71 (broad d, 3H, J = 1.6 Hz, H-15), 1.8-1.6 (m, 1H, H-1), 1.3-1.2 (m, 1H, H-1'), 1.00 (s, 3H, H-14).

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