Synthesis of the Putative Structure of 15-Oxopuupehenoic Acid

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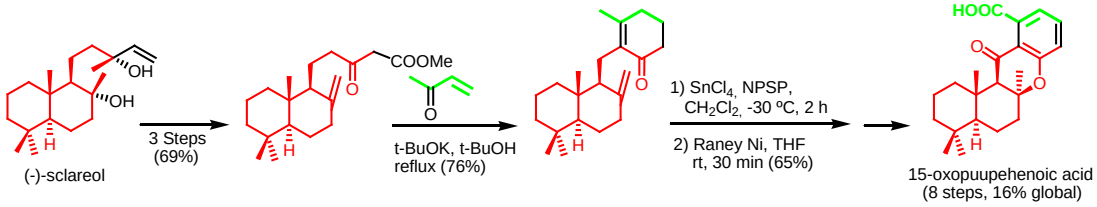


ABSTRACT: A synthesis of the putative structure of the marine natural 15-oxopuupehenoic acid has been achieved starting from commercial (-)-sclareol. Key steps of the synthetic sequence are the Robinson annulation of a β-ketoester and methyl vinyl ketone and the unprecedented cyclization of the resulting α,β-enone, mediated by tin (IV) chloride in the presence of N-phenylselenophthalimide. The physical properties of synthetic compound have some differences with those reported for the natural product.

The interesting biological activity of certain merosesquiterpenes, particularly those having a bicyclic sesquiterpene fragment joined to a phenol or quinone moiety, as the 15-human lipoxygenase (15-HLO) inhibitor jaspic acid (**1**),[1] and related benzopyran derivatives, as the antibacterial hongoquercin A (**2**) and B (**3**),[2] and oxopuupehenoic acid (**4**),[3] has driven research procedures for carrying out their synthesis.

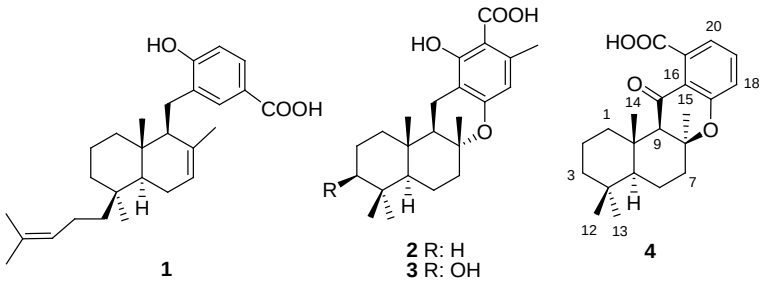
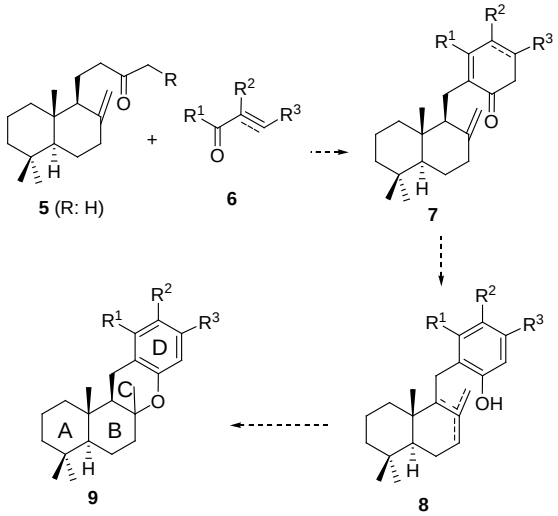


FIGURE 1. Representative bioactive merosesquiterpenes.

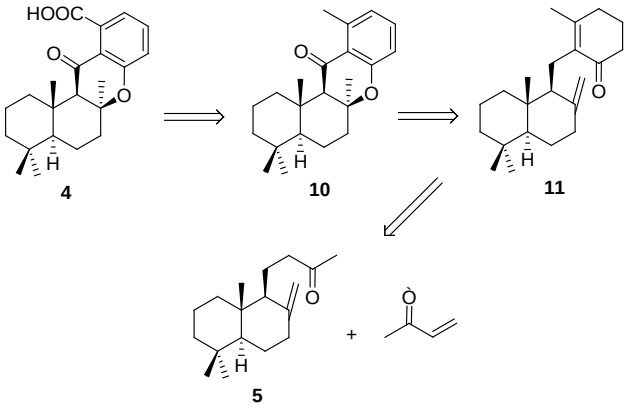
In most cases, the processes used involve the condensation of a sesquiterpene derivative, usually with an electrophilic character, with an aromatic derivative of nucleophilic nature.[4] In certain cases, the preparation of the latter involves some difficulty, due to either its substitution pattern or to the presence in the aromatic ring of electrophilic groups (such as CN, COR, COOR, etc..), with the consequent lengthening of the synthetic sequence. It is therefore of interest to investigate new processes that allow the ellaboration of the aromatic fragment of the target compounds in an alternative way.

SCHEME 1. A Robinson annulation based strategy toward merosesquiterpenes.



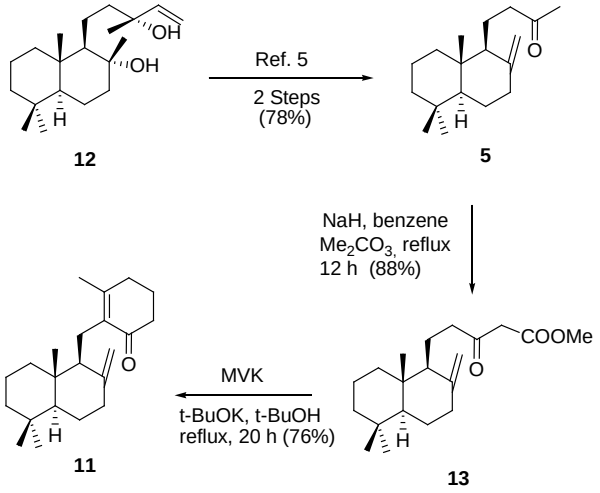
Considering the above arguments a new synthetic strategy toward this type of merosesquiterpenes has been planned (Scheme 1). The aromatic ring of target compounds **8** and **9** will be elaborated after the Michael addition of kinetic enolate of methyl ketone **5**[5] to the suitable electron-deficient alkene or alkyne **6**, and the subsequent intramolecular aldol condensation. This procedure could allow to prepare compounds similar to **8** and **9** having a function in the A or B ring; it must to point out that A or B ring functionalized methyl ketones similar to **5** have been obtained in good yields from different diterpenes, such as communic acids,[6] larixol[7] and abietic acid.[8] The regiocontrol in the formation of suitable enol derived from compound **5** can be achieved by utilizing the corresponding β-ketoester (R: COOMe), which under the reaction conditions undergoes decarboalkoxylation.[9]

SCHEME 2. Retrosynthesis of 15-oxopuupehenoic acid (4).



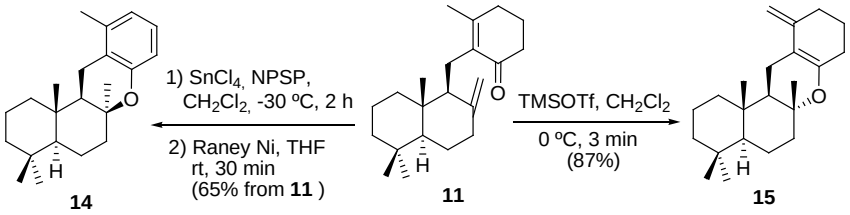
We then investigated the preparation of 15-oxopuupehenoic acid (**4**), a marine sponge metabolite that has not yet been synthesized, utilizing this strategy. Scheme 2 shows the retrosynthesis of acid **4** from methyl ketone **5**, easily otained from commercial (-)-sclareol (**12**). Compound **4** will be obtained after successive benzylic oxidation of benzopyran resulting from the cyclization of phenol prepared after aromatization of α,β-enone **11**. This ketone will be obtained after the Robinson annulation of methyl ketone **5** with methyl vinyl ketone.

SCHEME 3. Construction of the merosesquiterpene skeleton. Synthesis of α,β-enone 11.



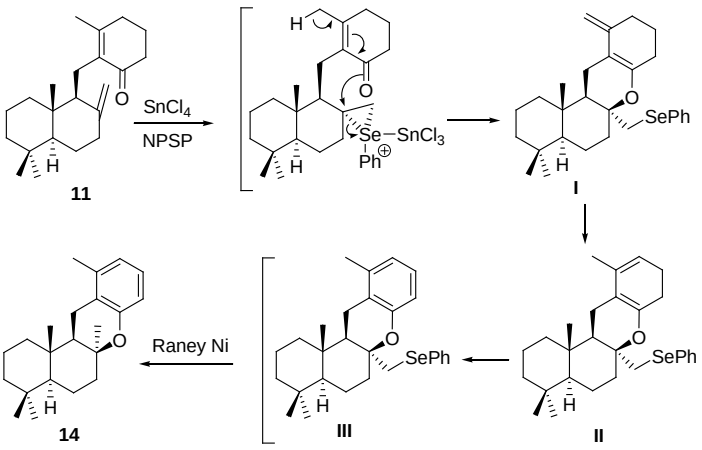
Scheme 3 shows the construction of the merosesquiterpene skeleton starting from commercial (-)-sclareol (**12**). This was converted into methyl ketone **5** in a two-step sequence, in 78% global yield, utilizing a procedure previously developed in our laboratory.[5] The treatment of β-ketoester **13** with methyl vinyl ketone and t-BuOK in t-BuOH under reflux gave the α,β-enone **11** directly in 76% yield.

SCHEME 4. Cyclization of enone 11. Synthesis of benzopyrans 14 and 15.



The next step was to address the transformation of enone **11** into the tetracyclic benzopyran framework of the target compound. The most usual method to achieve this type of tetracyclic skeleton involves the diastereoselective cyclization of a drimenyl phenol;[10] however all attempts of converting compound **11** into the corresponding drimenyl phenol, after dehydrogenation of the enone moiety, were unsuccessful. Interestingly, it was observed that this enone undergoes cyclization directly, without previous aromatization. Thus, the benzopyran **14** was obtained in 65% yield when ketone **11** was treated with $SnCl_4$ and N-phenylselenophthalimide (NPSP) in dichloromethane and subsequently with Raney nickel in THF (Scheme 4).[11] Compound **14** is probably formed after the cyclization of a dienol derived from enone **11** and the further aromatization of the tetracyclic diene. A possible mechanism for this transformation is depicted in scheme 5. Under the acid conditions diene **I** isomerizes to give **II**, which then undergoes in situ air oxidation leading to selenide **III**. A result which supports this mechanism is the formation of unstable diene **15** after treatment of enone **11** with TMSOTf in dichloromethane at 0 ºC. The *R* configuration on C-8 of compound **15** was confirmed by the NOE effect observed between Me-15 (singlet at 1.12 ppm) and Me-14 (singlet at 0.85 ppm).[12]

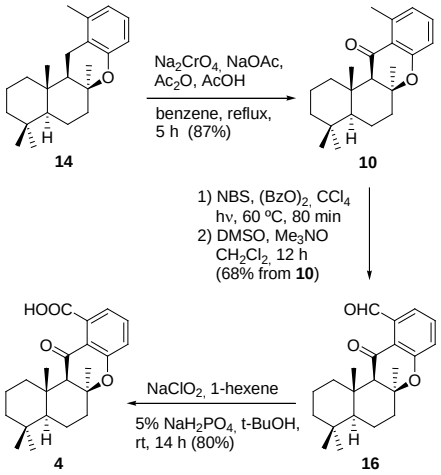
SCHEME 5. A possible mechanism for the direct transformation of α,β-enone 11 into benzopyran 14.



Finally, benzylic oxidation of compound **14** to achieve acid **4** was undertaken (Scheme 6). The treatment of benzopyran **14** with sodium chromate, in the presence of sodium acetate, acetic acid and acetic anhydride, gave ketone **10**.[13] This was transformed into aldehyde **16**, by reacting it with NBS in the presence of benzoyl peroxide, under light irradiation, and subsequent treatment with DMSO and trimethylamine N-

oxide in CH_2Cl_2 of the resulting crude. Finally, aldehyde **16** was converted into acid **4**, after oxidation with $NaClO_2$. The *S* configuration on C-8 was confirmed by the NOE correlation between Me-15 (singlet at 1.21 ppm) and H-9 (singlet at 1.96 ppm).

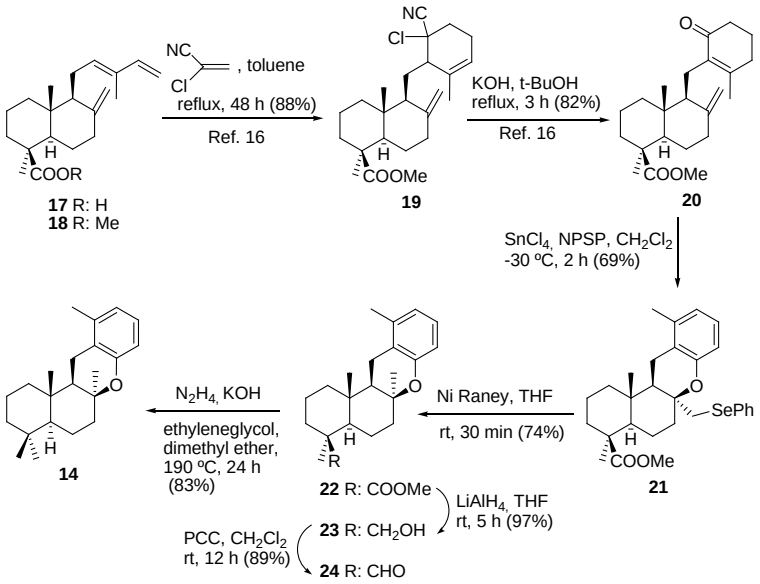
SCHEME 6. Synthesis of 15-oxopuupehenoic acid (4).



The ^1H and the ^{13}C NMR data of synthetic 15-oxopuupehenoic acid (**4**) were similar to those reported for the natural compound, but significative differences were observed for the aromatic protons in the ^1H NMR. In the case of synthetic acid, these protons appear at δ 7.38 (dd, *J* = 8.4, 7.6 Hz, 1H), 7.03 (d, *J* = 7.6 Hz, 1H) and 6.88 (d, *J* = 8.4 Hz, 1H), whereas the data reported by Crews et al for the natural acid were δ 7.48 (dd, *J* = 8.0, 7.5 Hz, 1H), 7.27 (dd, *J* = 7.5, 1.5 Hz, 1H) and 7.01 (dd, *J* = 8.0, 1.5 Hz, 1H) . The optical rotation was also different: $[\alpha]_D^{25}$ -21.2 (c 0.3, $CHCl_3$), for the synthetic acid, and $[\alpha]_D^{25}$ +27 (c 0.1, $CHCl_3$), for the natural product.[3]

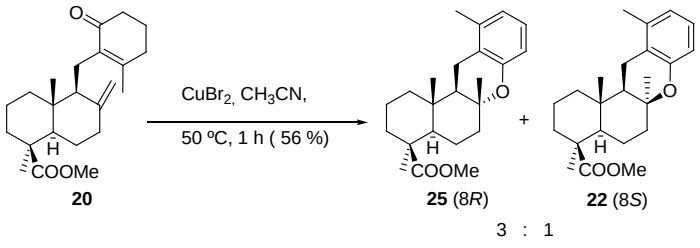
Even though the structure of synthetic 15-oxopuupehenoic acid (**4**), based on the well known diastereoselectivity of cyclization and on the NOE effects observed in the ^1H NMR spectra, seems not to be doubtful, we have developed an alternative route towards this compound starting from the labdane diterpene (+)- *trans*-communic acid (**17**),[14] which has also been utilized in the synthesis of a variety of terpenoids.[15] Scheme 7 shows the synthesis of intermediate **14** from acid **17**. The key intermediate was the α,β-enone **20**, obtained after the Diels-Alder cycloaddition of ester **18** with 2-chloroacrylonitrile and the subsequent alkalyne treatment of adduct **19**.[16] When compound **20** was treated with $SnCl_4$ in the presence of *N*-phenylselenophthalimide (NPSP) at -30 ºC for 2 h, the selenoderivative **21** was obtained. The ^1H NMR spectrum of this compound shows a characteristic AB system (doublets at 3.03 and 3.08 ppm, *J* = 12.2 Hz), due to the CH_2-Se group.[17] Further treatment of this compound with Raney nickel afforded ester **22**. These results are in agreement with the mechanism depicted in scheme 5. After succesive reductions, the expected compound **14** was obtained.

SCHEME 7. Alternative synthesis of benzopyran 14 from *trans*-communic acid (17).



As it could be expected, compound **25**, the 8*R* epimer of benzopyran **22**, was obtained after acid cyclization of α,β-enone **20**. Thus, the treatment of this with $CuBr_2$ in acetonitrile at 50 ºC for 1 h gave a mixture of epimers **25** and **22**, in a 3 : 1 ratio (Scheme 8). The ^1H NMR spectrum of compound **25 s**hows a NOE correlation of Me-14 (singlet at 0.75) and Me-15 (singlet at 1.18). The above results, depicted in scheme 7 and 8, are consistent with those previously reported for the cyclization of drimenyl phenols and confirm the diastereoselectivity of these processes.[10-12]

SCHEME 8. Acid cyclization of α,β-enone 20.



All above commented results allowed us to establish unequivocally the structure of synthetic 15-oxopuupehenoic acid (**4**). At this point it coul be noted that the last stage of the structure determination of natural oxopuupehenoic acid by Crews' group involves establishing the susbtitution pattern on the aromatic ring. These authors proposed four alternative structures for the natural compound, including two acids regioisomers and two seven-membered lactones, and finally they decide in favour of structure **4**, on the basis of J_{HC} gHMBC correlations. The results reported here makes it advisable to revise the structure of natural compound.

In summary, the enantiospecific synthesis of the putative structure of 15-oxopuupehenoic acid (**4**), starting from commercial (-)-sclareol (**12**), has been achieved, utilizing a new synthetic strategy. Key steps of this are the Robinson annulation of a β-ketoester and methyl vinyl ketone and the unprecedented cyclization of the resulting α,β-enone, mediated by tin (IV) chloride in the presence of *N*-phenylselenophthalimide. The unstable tetracyclic dienol ether **15** was isolated when the cyclization of enone **11** was carried out with TMSOTf. An alternative route starting from (+)-*trans*-communic acid (**17**) has also been developed. The synthetic acid **4** showed physical properties different to those reported for the natural compound.

EXPERIMENTAL SECTION

General Methods. Reactions were performed under an argon atmosphere using dry solvents. Dichloromethane was dried over calcium hydride, benzene and tetrahydrofuran were dried over sodium-benzophenone. Thin-layer chromatography (TLC) was performed using silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV fluorescence quenching and phosphomolybdic acid solution staining. Chromatography separations were carried out by conventional column on silica gel 60 (230-400 Mesh), using Hexanes-MeOtBu (hexanes/ether) mixtures of increasing polarity. ^{1}H and ^{13}C NMR spectra were recorded at 500 MHz and 125 MHz, respectively. $CDCl_3$ was treated with K_2CO_3. Chemical shifts are expressed in parts per million (δ scale) downfield from tetramethylsilane. Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration), with the abbreviations s, br s, d, br d, t, q, and m denoting singlet, broad singlet, doublet, broad doublet, triplet, quartet and multiplet respectively. *J* = coupling constant in Hertz (Hz). The signals of the ^{13}C NMR were assigned utilizing DEPT experiments and on the basis of heteronuclear correlations. Infrared spectra (IR) were recorded as thin films on a FTIR spectrophotometer with samples between sodium chloride plates and are reported in frequency of absorption (cm^{-1}). Only selected absorbances (ν max) are reported. $[\alpha]_D$ measurements were carried out in a polarimeter, utilizing a 1 dm length cell and $CHCl_3$ as a solvent. Concentration is expressed in mg/mL. Mass spectra: HRMS were recorded on an spectrometer, utilizing a quadrupole MS/MS analyzer, and using FAB with thioglicerol or glycerol matrix doped in NaI 1%.

Methyl 3-oxo-5-((1'*S*,4'a*S*,8'a*S*)-5',5',8'a-trimethyl-2'-methylene-decahydronaphthalen-1'-yl) pentanoate (13).

Dimethyl carbonate (855 g, 9.5 mmol) and 60% NaH (190 mg, 4.75 mmol) is added to a solution of ketone **5** (250 mg, 0.95 mmol) in anhydrous benzene (25 mL) and the mixture was kept stirring at reflux under argon atmosphere for 12 h. Then, The reaction mixture was carefully quenched with water (0.3 mL), and ether (30 mL) was added. The organic solution was washed with water (4 x 10 mL), brine, dried over anhydrous Na_2SO_4 and evaporated to afford a crude product which was purified by flash chromatography on silica gel (20% ether/hexanes) to yield **13** (267 mg, 88%) as a colorless syrup. $[\alpha]_D^{25}$ = + 18.0 (c = 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 4.81 (d, *J* = 0.86 Hz, 1H), 4.41 (s, 1H), 3.71 (s, 3H), 3.40 (s, 2H), 2.67 (m, 1H), 2.46 - 2.33 (m, 2H), 1.99 - 1.00 (m, 13H), 0.85 (s, 3H), 0.79 (s, 3H), 0.67

(s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 203.1 (C), 167.7 (C), 148.3 (C), 106.3 (CH_2), 56.1 (CH), 55.5 (CH), 52.3 (CH_3), 49.2 (CH_2), 42.2 (CH_2), 42.1 (CH_2), 39.8 (C), 39.0 (CH_2), 38.3 (CH_2), 33.67 (CH_3), 33.63 (C), 24.5 (CH_2), 21.7 (CH_3), 19.4 (CH_2), 17.3 (CH_2), 14.3 (CH_3). IR (film): 1749, 1717, 1646, 1457, 1437, 1318, 1236, 889, 667 cm^{-1}. HRMS(FAB) *m/z*: calcd for $C_{20}H_{32}O_3Na$ ($M+Na^+$) 343.2249, found: 343.2253.

3-Methyl-2-(((4'a*S*,8'a*S*)-5',5',8'a-trimethyl-2'-methylene-decahydronaphthalen-1-yl) methyl) cyclohex-2-enone (11).

t-BuOK (16 mg, 0.14 mmol) is added to a solution of ketoester **13** (900 mg, 2.81 mmol) and methyl vinyl ketone (200 mg, 2.85 mmol) in t-BuOH (10 mL) and the mixture is stirred at room temperature for 30 min. Then, aditional t-BuOK (64 mg, 0.56 mmol) is added and the mixture is refluxed with stirring for 20 h. Then, 1N HCl (10 mL) is added and the mixture is extracted with ether (60 mL). The organic phase is washed with water (5 x 20 mL), dried over anhydrous Na_2SO_4 and evaporated to give a crude residue, which after column chromatography on silica gel (5% ether/hexanes) afforded enone **11** (670 mg, 76%) $[\alpha]_D^{25}$ = - 21.6 (c = 0.4, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 4.68 (s, 1H), 4.53 (s, 1H), 2.51 (dd, *J* = 14.3, 9.1 Hz, 1H), 2.43 (m, 1H), 2.39 – 2.24 (m, 4H), 2.11 (dd, *J* = 8.8, 4.2 Hz, 1H), 1.95 (s, 3H), 1.93 – 1.10 (m, 13H), 0.85 (s, 3H), 0.80 (s, 3H), 0.76 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 199.2 (C), 155.0 (C), 149.6 (C), 136.7 (C), 106.9 (CH_2), 55.7 (CH), 55.7 (CH), 42.3 (CH_2), 40.6 (C), 38.9 (CH_2), 38.7 (CH_2), 38.2 (CH_2), 33.8 (CH_3), 33.7 (C), 33.4 (CH_2), 24.7 (CH_2), 22.2 (CH_3), 22.0 (CH_2), 21.9 (CH_3), 20.7 (CH_2), 19.6 (CH_2), 14.3 (CH_3). IR (film): 1718, 1663, 1618, 1543, 1509, 1458, 1378, 882, 756 cm^{-1}. HRMS(FAB) *m/z*: calcd for $C_{22}H_{34}ONa$ ($M+Na^+$) 337.2507, found: 337.2509.

(4a*S*,6a*S*,12b*S*)-4,4,6a,11,12b-Pentamethyl-2,3,4,4a,5,6,6a,12,12a,12b-decahydro-1H-benzo[a]xanthene (14).

To a solution of *N*-phenylselenophthalimide (NPSP) (318 mg, 1.04 mmol) in anhydrous CH_2Cl_2 (5 mL) was added $SnCl_4$ (0.3 mL) at – 30 ºC and the mixture was stirred for 5 min, then a solution of enone **11** (300 mg, 0.95 mmol) in CH_2Cl_2 (5 mL) was added and the mixture was kept stirring at this temperature for 2 h, at which time TLC showed no starting material. Then, ether (30 mL) was added and the organic phase was washed with water (3 x 10 mL), brine, dried over anhydrous Na_2SO_4 and evaporated to afford a crude product. A 60-70% aqueous dispersion of Raney nickel (2 mL) was then added to a solution of the above residue in THF (10 mL) and the mixture was stirred at room temperature for 30 min. After this, the mixture was filtered through a silica gel/anhydrous Na_2SO_4 pad and evaporated to afford a crude product. Flash cromatography column on silica gel (2% ether/hexanes), afford pure **14** (125 mg, 65% from 11). $[\alpha]_D^{25}$= -13.9 (c = 0.4, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 6.96 (dd, *J* = 8.1, 7.3 Hz, 1H), 6.68 (d, *J* = 7.3 Hz, 1H), 6.60 (d, *J* = 8.1 Hz, 1H), 2.68 (d, *J* =18.3 Hz, 1H), 2.64 (dd, *J* =18.3, 6.7 Hz, 1H), 2.21 (s, 3H), 2.15 (m, 1H), 1.85 (br d, *J* = 8.7 Hz, 1H), 1.67– 1.52 (m, 5H), 1.50– 1.37 (m, 3H), 1.17 (m, 1H), 1.15 (s, 3H), 0.94 (dd, *J*= 11.9, 2.7 Hz, 1H), 0.90 (s, 3H), 0.81 (s, 3H), 0.68 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ:154.6 (C), 136.3 (C), 126.0 (CH), 121.4 (C), 121.1 (CH), 114.8 (CH), 74.8 (C), 55.3 (CH), 49.8 (CH), 41.9 (CH_2), 40.7 (CH_2), 40.2 (CH_2), 38.4 (C), 33.7 (CH_3), 33.3 (C), 27.1 (CH_3),

21.9 (CH_3), 20.7 (CH_2), 19.2 (CH_3), 18.5 (CH_2), 18.3 (CH_2), 14.2 (CH_3). IR (film): 2924, 1586, 1467, 1260, 774, 665 cm^{-1}. HRMS(FAB) *m/z*: calcd for $C_{22}H_{32}ONa$ ($M+Na^+$) 335.2351, found: 335.2346.

(4a*S*,6a*R*,12b*S*)-4,4,6a,12b-Tetramethyl-11-methylene-1,3,4,4a,5,6,6a,8,9,10,11,12,12a,12b -tetradecahydro-1H-benzo[a]xanthene (15).

Trimethylsilyl trifluoromethanesulfonate (TMSOTf) (0.5 mL, 2.76 mmol) was added to a solution of enone **11** (264 mg, 0.84 mmol) in anhydrous CH_2Cl_2 (10 mL) at 0 ºC under argon atmosphere and the mixture was stirred at room temperature for 3 min, at which time TLC showed no **11**. Then ether (20 mL) was added and the organic phase was washed with water (3 x 20 mL), brine, dried over anhydrous Na_2SO_4 and evaporated to give the unstable diene **15** (228 mg, 87%). ^1H NMR (500 MHz, CD_3COCD_3) δ: 4.57 (s, 1H), 4.44 (s, 1H), 2.50–0.90 (m, 20H), 1.12 (s, 3H), 0.90 (s, 6H), 0.85 (s, 3H). ^{13}C NMR (CD_3COCD_3, 125 MHz) δ: 150.6 (C), 144.4 (C), 105.5 (C), 100.4 (CH_2), 76.2 (C), 56.1 (CH), 52.6 (C), 41.7 (CH_2), 40.8 (CH_2), 39.0 (CH_2), 36.6 (C), 32.9 (C), 32.9 (CH_3), 28.8 (CH_2), 25.9 (CH_2), 22.5 (CH_2), 21.0 (CH_3), 19.8 (CH_3), 19.5 (CH_2), 18.4 (CH_2), 18.1 (CH_2), 14.4 (CH_3).

(4a*S*,6a*S*,12b*S*)-4,4,6a,11,12b-Pentamethyl-1,2,3,4,4a,5,6,6a-octahydro-12aH-benzo[a] xanthen-12(12bH)-one (10).

Na_2CrO_4 (71 mg , 0.44 mmol) was added to a solution of compound **14** (55 mg, 0.176 mmol), sodium acetate (30 mg, 0.36 mmol), acetic acid (0.3 mL) and acetic anhydride (0.3 mL) in benzene (5 mL) and the mixture was kept stirring at reflux for 5 h, at which time TLC showed no **14**. Then, were added successively water (10 mL) and ether (25 mL) and the phases were shaken. The organic phase was washed with water (4 x 10 mL), brine, dried over anhydrous Na_2SO_4 and evaporated to give a crude product which after flash chromatography column on silica gel (15% hexanes/ether) afforded pure ketone **10** (50 mg, 87%). $[\alpha]_D^{25}$= -23.4 (c = 0.4, $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz) δ: 7.25 (dd, *J* = 8.3, 7.4 Hz, 1H), 6.74 (dd, *J* = 8.3, 0.7 Hz, 1H), 6.72 (dd, *J* = 7.4, 0.7 Hz, 1H), 2.61 (s, 3H), 2.22 (dt, *J* = 6.1, 3.3 Hz, 1H), 1.93 (s, 1H), 1.76–1.67 (m, 2H), 1.66– 1.46 (m, 3H), 1.45– 1.37 (m, 2H), 1.32– 1.25 (m, 1H), 1.24 (s, 3H), 1.21– 1.14 (m, 1H), 0.91 (s, 3H), 0.89 (dd, *J* = 5.5, 2.6 Hz, 1H), 0.83 (s, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 196.6 (C), 161.3 (C), 141.0 (C), 134.1 (CH), 123.8 (CH), 120.8 (C), 116.0 (CH), 79.1 (C), 66.1 (CH), 54.2 (CH), 41.7 (CH_2), 40.3 (CH_2), 39.8 (CH_2), 38.1 (C), 33.8 (CH_3), 33.4 (C), 26.5 (CH_3), 23.1 (CH_2), 22.0 (CH_3), 18.4 (CH_2), 18.1 (CH_2), 15.5 (CH_3). IR (film): 2927, 1674, 1599, 1315, 1270, 777, 665 cm^{-1}. HRMS(FAB) *m/z*: calcd for $C_{22}H_{30}O_2Na$ ($M+Na^+$) 349.2143, found: 349.2150.

(4a*S*,6a*S*,12b*S*)-4,4,6a,12b-Tetramethyl-12-oxo-2,3,4,4a,5,6,6a,12,12a,12b-decahydro-1H-benzo[a]xanthene-11-carbaldehyde (16).

N-Bromosuccinimide (NBS) (40 mg; 0.225 mmol) and benzoyl peroxyde (3 mg) was added to a solution of ketone **10** (60 mg, 0.184 mmol) in carbon tetrachloride (8 mL), and the mixture was stirred under light irradiation at 60 ºC in argon atmosphere for 80 min. After evaporation under vacuum, the resulting crude product was purified by column chromatography on silica gel (20% hexanes/ether) affording a solid residue

(55 mg). This was dissolved in dichloromethane – dimethylsulfoxide (3 ml : 3 mL) and trimethylamine *N*-oxide dihydrate (45 mg, 0.40 mmol) was added at 0 ºC. After stirring at room temperature for 12 h, ether was added (20 mL) and the organic phase was washed with water (3 x 30 mL), brine, dried over anhydrous Na_2SO_4 and evaporated to give a crude product, which after column chromatography on silica gel (30% hexanes/ether) afforded pure aldehyde **16** (42 mg, 68%). $[\alpha]_D^{25}$= +1.3 (c = 0.3, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 10.68 (s, 1H), 7.51 (dd, *J* = 8.3, 7.6 Hz, 1H), 7.31 (dd, *J* = 7.6, 1.1 Hz, 1H), 7.13 (dd, *J* = 8.3, 1.1 Hz, 1H), 2.29 (dt, *J* = 14.4, 3.0 Hz, 1H), 2.05 (s, 1H), 1.75– 1.66 (m, 2H), 1.56– 1.54 (m, 3H), 1.52– 1.41 (m, 2H), 1.27 (s, 3H), 1.26– 1.21 (m, 2H), 0.93 (s, 3H), 0.92 (dd, *J* = 11.8, 2.5 Hz, 1H), 0.89 (s, 3H), 0.85 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 196.4 (C), 193.8 (CH), 160.7 (C), 138.2 (C), 135.0 (CH), 123.1 (CH), 121.1 (C), 120.3 (CH), 80.6 (C), 65.5 (CH), 54.1 (CH), 41.5 (CH_2), 40.2 (CH_2), 39.6 (CH_2), 38.5 (C), 33.8 (CH_3), 33.4 (C), 26.5 (CH_3), 22.0 (CH_3), 18.3 (CH_2), 18.1 (CH_2), 15.5 (CH_3). IR (film): 2924, 1673, 1589, 1466, 1283, 773, 665 cm^{-1}. HRMS(FAB) *m/z*: calcd for $C_{22}H_{28}O_3Na$ ($M+Na^+$) 363.1936, found: 363.1941.

15-Oxopuupehenoic acid (4).

A solution of sodium chlorite (13 mg, 0.14 mmol) in aqueous 5% NaH_2PO_4 (3 mL), was added to a solution of aldehyde **16** (20 mg, 0.059 mmol) and 1-hexene (0.4 mL) in t-BuOH (6 mL), and the mixture was stirred at room temperature under argon atmosphere for 14 h. After evaporation the solvent under vacuum, ether -Water (20: 5 mL) were added to the residues and the phase were shaken. The organic phase was extracted with satd $NaHCO_3$ (3 x 10 mL). Combined aqueous phases were acidified by addition of 2N HCl and extracted with ether (3 x 10 mL). The organic phase was dried over anhydrous Na_2SO_4 and evaporated to give pure acid **4** (17 mg, 80%). $[\alpha]_D^{25}$= -21.2 (c = 0.3, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.38 (dd, *J* = 8.4, 7.6 Hz, 1H), 7.03 (d, *J* = 7.6 Hz, 1H), 6.88 (d, *J* = 8.4 Hz, 1H), 2.23 (dt, *J* = 14.7, 3.3 Hz, 1H), 1.96 (s, 1H), 1.74 - 1.59 (m, 2H), 1.56 - 1.32 (m, 3H), 1.31- 1.22 (m, 2H), 1.21 (s, 3H), 1.20 - 1.08 (m, 2H), 0.90 (s, 3H), 0.87 (dd, *J* = 9.0, 1.9 Hz, 1H), 0.85 (s, 3H), 0.82 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 195.8 (C), 174.0 (C), 160.5 (C), 135.4 (C), 135.4 (CH), 120.1 (CH), 118.9 (CH), 118.3 (C), 80.1 (C), 65.0 (CH), 54.2 (CH), 41.6 (CH_2), 39.8 (CH_2), 39.7 (CH_2), 38.6 (C), 33.8 (CH_3), 33.4 (C), 26.4 (CH_3), 22.0 (CH_3), 18.3 (CH_2), 18.2 (CH_2), 15.4 (CH_3). IR (film): 3417, 2923, 1685, 1579, 1474, 772, 666 cm^{-1}. HRMS(FAB) *m/z*: calcd for $C_{22}H_{28}O_4Na$ ($M+Na^+$) 379.1885, found: 379.1882.

(4*S*,4a*R*,6a*S*,12a*R*,12b*S*)-methyl 4,11,12b-trimethyl-6a-(phenylselanylmethyl)-2,3,4,4a,5,6,6a,12,12a,12b-decahydro-1H-benzo[a]xanthene-4-carboxylate (21).

To a solution of *N*-phenylselenophthalimide (NPSP) (350 mg, 1.16 mmol) in anhydrous CH_2Cl_2 (7 mL) was added $SnCl_4$ (0.3 mL) at – 30 ºC and the mixture was stirred for 5 min, then a solution of ester **20** (300 mg, 0.837 mmol) in CH_2Cl_2 (5 mL) was added and the mixture was kept stirring at this temperature for 2 h, at which time TLC showed no starting material. Then, ether (30 mL) was added and the organic phase was washed with water (3 x 10 mL), brine, dried over anhydrous Na_2SO_4 and evaporated to give a crude product which was puri-

fied by flash cromatography column (5% ether/hexanes), to afford selenide **21** (295 mg, 69 %). $[\alpha]_D^{25}$= +29.4 (c = 9.0, $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz) δ: 7.47– 7.43 (m, 2H), 7.22– 7.18 (m, 3H), 6.95 (dd, *J* = 7.4, 7.3 Hz, 1H), 6.68 (d, *J* = 7.4 Hz, 1H), 6.60 (d, *J* = 7.3 Hz, 1H), 3.57 (s, 3H), 3.08 (d, *J* =12.2 Hz, 1H), 3.03 (d, *J* =12.2 Hz, 1H), 2.52 (d, *J* =18.2 Hz, 1H), 2.39 (dd, *J* =18.2, 7.5 Hz, 1H), 2.23– 2.13 (m, 2H), 2.12 (s, 3H), 2.05 (m, 1H), 1.92– 1.72 (m, 3H), 1.50– 0.75 (m, 6H), 1.21 (s, 3H), 1.20– 0.83 (m, 3H), 0.45(s, 3H). ^{13}C NMR **(**$CDCl_3$, 125 MHz) δ: 177.8 (C), 153.7 (C), 136.3 (C), 133.0 (2CH), 130.9 (C), 129.1 (2CH), 127.0 (CH), 126.4 (CH), 121.7 (CH), 120.9 (C), 115.1 (CH), 76.6 (C), 55.8 (CH), 51.2 (CH_3), 45.9 (CH), 43.8 (C), 40.5 (CH_2), 38.7 (C), 38.0 (CH_2), 38.0 (CH_2), 37.7 (CH_2), 28.7 (CH_3), 20.5 (CH_2), 19.4 (CH_2), 19.1 (CH_3), 19.1 (CH_2), 13.0 (CH_3). IR (film): 2922, 1720, 1585, 1466, 1002, 773, 665 cm^{-1}.

(4*S*,4a*R*,6a*S*,12a*R*,12b*S*)- Methyl 4,6a,11,12b-tetramethyl-2,3,4,4a,5,6,6a,12,12a,12b-decahydro-1H-benzo[a]xanthene-4-carboxylate (22).

Aqueous Raney nickel (60-70%, 1.5 mL) was added to a solution of selenide **21** (160 mg, 0.31 mmol) in THF (10 mL) and the mixture was stirred at room temperature for 30 min. Then it was filtered through a silicagel-anhydrous Na_2SO_4 pad and evaporated under vacuum to give ester **22** (83 mg, 74%). $[\alpha]_D^{25}$= +7.39 (c = 24.04, $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz) δ: 6.96 (dd, *J* = 8.1, 7.3 Hz, 1H), 6.68 (d, *J* = 7.3 Hz, 1H), 6.61 (d, *J* = 8.1 Hz, 1H), 3.57 (s, 3H), 2.70 (dd, *J* = 18.1, 7.4 Hz, 1H), 2.64 (d, *J* = 18.1 Hz, 1H), 2.21 (s, 3H), 2.17 (dt, *J* = 13.6, 2.9 Hz, 1H), 2.08 (m, 1H), 1.92 (m, 1H), 1.86– 1.76 (m, 2H), 1.63 (m, 1H), 1.56– 1.41 (m, 2H), 1.40 (dd, *J* = 12.9, 1.5 Hz, 1H), 1.21 (s, 3H), 1.34– 0.87 (m, 3H), 1.16 (s, 3H), 0.46 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 177.8 (C), 154.4 (C), 136.3 (C), 126.1 (CH), 121.2 (CH), 120.8 (C), 114.9 (CH), 74.3 (C), 56.0 (CH), 51.2 (CH), 48.9 (CH_3), 43.8 (C), 40.7 (CH_2), 40.5 (CH_2), 38.5 (C), 38.1 (CH_2), 28.7 (CH_3), 27.0 (CH_3), 20.9 (CH_2), 19.6 (CH_2), 19.2 (CH_3), 19.0 (CH_2),12.8 (CH_3). IR (film): 2934, 1720, 1459, 1466, 1108, 773, 662 cm^{-1}. HRMS(FAB) m/z: calcd for $C_{23}H_{32}O_3Na$ ($M+Na^+$) 379.2249, found: 379.2257.

((4*S*,4a*R*,6a*S*,12a*R*,12b*S*)-4,6a,11,12b-Tetramethyl-2,3,4,4a,5,6,6a,12,12a,12b-decahydro-1H-benzo[a]xanthen-4-yl)methanol (23).

To a solution of ester **22** (200 mg, 0.56 mmol) in THF(15 mL) was added $LiAlH_4$ (85 mg, 2.23 mmol) at 0 ºC, and the mixture was stirred at room temperature, under argon atmosphere, for 5 h, at which time TLC, showed no **22**. Then, 2N HCl (1 mL) was added slowly at 0 ºC and the mixture was dileted with ether (25 mL). The organic phase was washed with water (3 x 10 mL), brine, dried over anhydrous Na_2SO_4 and evaporated to give pure alcohol **23** (180 mg, 97%). $[\alpha]_D^{25}$= -15.5 (c =15.46, $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz) δ: 6.96 (dd, *J* = 8.1, 7.3 Hz, 1H), 6.68 (d, *J* = 7.3 Hz, 1H), 6.59 (d, *J* = 8.1 Hz, 1H), 3.75 (d, *J* = 11.0 Hz, 1H), 3.42 (dd, *J* = 11.0, 1.0 Hz, 1H), 2.66 (dd, *J* = 18.2, 7.2 Hz, 1H), 2.60 (d, *J* = 18.2 Hz, 1H), 2.21 (s, 3H), 2.15 (dt, *J* = 13.7, 3.0 Hz, 1H), 1.96– 1.61 (m, 4H), 1.60– 1.47 (m, 2H), 1.48– 1.32 (m, 2H), 1.15 (s, 3H), 1.10 (m, 1H), 1.01 (s, 3H), 1.00–0.91 (m, 2H), 0.65 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 154.6 (C), 136.3 (C), 126.1 (CH), 121.3 (CH), 121.2 (C), 114.8 (CH), 74.6 (C), 65.2 (CH_2), 55.9 (CH), 50.0 (CH), 41.0 (CH_2), 40.1 (CH_2), 38.6 (C), 38.3 (C), 35.3 (CH_2), 27.1 (CH_3),

27.0 (CH_3), 20.8 (CH_2), 19.2 (CH_3), 18.3 (CH_2), 18.2 (CH_2), 15.0 (CH_3). IR (film): 3372, 2926, 1585, 1468, 1261, 1002, 755, 665 cm^{-1}. HRMS(FAB) m/z: calcd for $C_{22}H_{32}O_2Na$ ($M+Na^+$) 351.2300, found: 351.2294.

(4*S*,4a*R*,6a*S*,12a*R*,12b*S*)-4,6a,11,12b-Tetramethyl-2,3,4,4a,5,6,6a,12,12a,12b-decahydro-1H-benzo[a]xanthene-4-carbaldehyde (24).

PDC (345 mg, 0.98 mmol) was added to a solution of alcohol **23** (130 mg, 0.396 mmol) in dichloromethane (6 mL), under an argon atmosphere, and the mixture was stirred at room temperature for 12 h, at which time TLC showed no **23**. Then, the mixture was diluted with eter (20 mL), filtered on siligel, washed with éter (5 mL). The filtrate was whased with 2N HCl (2 x 5 mL), water, brine and dried over anhydrous Na_2SO_4. The solvent was removed under vaccum and to give aldehyde **24** (115 mg, 89%). $[\alpha]_D^{25}$= -14.72 (c =23.76, $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz) δ: 9.73 (s, 1H), 6.97 (dd, *J* = 8.2, 7.4 Hz, 1H), 6.69 (d, *J* = 7.4 Hz, 1H), 6.60 (d, *J* = 8.2 Hz, 1H), 2,70 (dd, *J* = 18.1, 7.5 Hz, 1H), 2.63 (d, *J* = 7.5 Hz, 1H), 2.20 (m, 1H), 2.21 (s, 3H), 2.06 (m, 1H), 1.93– 1.82 (m, 2H), 1.63– 1.38 (m, 3H), 1.32 (dd, *J* = 12.9, 1.8 Hz, 1H), 1.18 (s, 3H), 1.16 (m, 1H), 1.04 (s, 3H), 1.03– 0.92 (m, 2H), 0.54 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 205.3 (C), 154.2 (C), 136.3 (C), 126.2 (CH), 121.4 (CH), 120.8 (C), 114.9 (CH), 74.3 (C), 55.6 (CH), 48.3 (C), 48.3 (CH), 40.7(CH_2), 39.6 (CH_2), 38.4 (C), 33.9 (CH_2), 26.8 (CH_3), 24.3 (CH_3), 20.8 (CH_2), 19.2 (CH_3), 18.3 (CH_2), 17.6 (CH_2), 13.5 (CH_3). IR (film): 2931, 1716, 1467, 1261, 1168, 755, 665 cm^{-1}. HRMS(FAB) m/z: calcd for $C_{22}H_{30}O_2Na$ ($M+Na^+$) 349.2143, found: 349.2150.

(4a*S*,6a*S*,12b*S*)-4,4,6a,11,12b-Pentamethyl-2,3,4,4a,5,6,6a,12,12a,12b-decahydro-1H-benzo[a]xanthene (14).

Solid KOH (30 mg) and hydrazine hydrate (0.6 mL) were added to a solution of aldehyde **24** (117 mg, 0.359 mmol) in ethyleneglycol dimethylether (5 mL) and the mixture was heated at 190 ºC under stirring for 24 h, at which time TLC showed no **24**. Then, ether (25 mL) was added and the organic phase was washed with water (10 x 10 mL), brine, dried over anhydrous Na_2SO_4 and evaporated to give a crude product, which after column chromatography on silica gel (2% ether/hexanes) afforded benzopyran **14** (93 mg, 83%).

Treatment of ester 20 with $CuBr_2$.

$CuBr_2$ (800 mg, 3.62 mmol) was added to a solution of ester **20** (650 mg, 1.81 mmol) in acetonitrile (10 mL) and the mixture was stirred at 50 ºC for 1 h. After evaporation under vacuum, ether (40 mL) was added and the organic solution was washed with 2N HCl (3 x 10 mL), water (3 x 10 mL), brine, dried over anhydrous Na_2SO_4 and evaporated to give a crude product. Column chromatography of this crude on silica gel (5% ether/hexanes) gave a mixture of benzopyrans **25** and **22** (361 mg, 56%) ratio 3:1. Another column chromatography of this mixture on silica gel (1% ether/hexanes) give pure **25.**

(4S,4aR,6aR,12aR,12bS)-methyl 4,6a,11,12b-tetramethyl-2,3,4,4a,5,6,6a,12,12a,12b-decahydro-1H-benzo[a]xanthene-4-carboxylate (25). ^1H NMR ($CDCl_3$, 500 MHz) δ: 6.99 (dd, *J* = 8.1, 7.3 Hz, 1H), 6.70 (d, *J* = 7.3 Hz, 1H), 6.63 (d, *J* = 8.1 Hz, 1H), 3.67 (s, 3H), 2.56 (dd, *J*

= 16.7, 5.1 Hz, 1H), 2.33 (dd, *J* = 16.7, 13.4 Hz, 1H), 2.22 (s, 3H), 2.21 (m, 1H), 2.10 (dt, *J*=12.7, 3.3 Hz, 1H), 2.04 (m, 1H), 1.97– 1.67 (m, 3H), 1.66– 1.48 (m, 4H), 1.23 (s, 3H), 1.18 (s, 3H), 1.19– 0.97 (m, 2H), 0.75 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 177.48 (C), 152.71 (C), 137.17 (C), 126.33 (CH), 120.94 (CH), 120.76 (C), 114.53 (CH), 75.61 (C), 56.39 (CH_3), 51.28 (CH), 51.05 (CH), 43.57 (C), 40.89 (CH_2), 39.30 (CH_2), 37.60 (CH_2), 37.09 (C), 28.45 (CH_3), 21.04 (CH_2), 20.13 (CH_2), 19.97 (CH_3), 18.91 (CH_3), 18.85 (CH_2), 12.42 (CH_3). HRMS(FAB) m/z: calcd for $C_{23}H_{32}O_3Na$ ($M+Na^+$) 379.2249, found: 379.2242.

ASSOCIATED CONTENT

Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the internet at http://pubs.acs.org.

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The manuscript was written through contributions of all authors. / All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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(11) The obtention of the 8*S* configuration, which exhibits compound **14**, has been previously achieved through selenium or palladium induced cyclization. The cyclization of a drimenyl phenol utilizing $SnCl_4$ and N-phenylselenophthalimide (NPSP) was first reported by our group in the first synthesis of (+)-puupehenone (reference 4c). This method has been utilized latter by other groups, see : (a) Hua, D. H.; Huang, X.; Chen, Y.; Battina, S. K.; Tamura,M.; Noh, S. K.; Koo, S. I.; Namatame,I.; Tomoda, H.; Perchellet, E. M.; Perchellet, J. – P. *J. Org. Chem*. **2004**, *69*, 6065-6078. (b) Gansäuer, A.; Rosales, A.; Justicia. J. *Synlett* **2006**, 927–929. At this point, it must be noted that rearrangement has never been observed during this cyclization process.

(12) Previous investigations have revealed that acid cyclization of drimenyl phenols take place in high diastereoselectivity, affording as the major, or even as the only, isomer the epimer benzopyran with the 8*R* configuration, which exhibits compound **15**. For a study on this subject see reference 4d.

(13) A similar benzylic oxidation has been utilized in the synthesis of 15-oxopuupehenol, which has the same absolute stereochemistry that compounds **10**, **16** and **4**. This process takes places without isomerization. See reference 4h.

(14) (+)-*trans*-Communic acid (**17**) is a labdane diterpene very abundant in some species of *Juniperus* and *Cupressus*. See: (a) Pascual Teresa, J. de; San Feliciano, A.; Miguel del Corral, J. M.; Barrero, A. F. *Phytochemistry* **1983**, *22*, 300-301. (b) Ahond, A.; Carnero, P.; Gastambide, B. *Bull. Soc. Chim. Fr*. **1964**, 348-349.

(15) For recent examples of the use of (+)-*trans*-communic acid (**17**) in the synthesis of terpenoids see: (a) Barrero, A. F.; Alvarez-Manzaneda, E. J.; Alvarez-Manzaneda, R.; Chahboun, R.; Meneses, R.; Cuerva, J. M.; Aparicio, M.; Romera, J. L. *Org. Lett.* **2001**, *3*, 647-650. (b) Barrero, A. F.; Arseniyadis, S.; Quilez Del Moral, J. F.; Herrador, M. M.; Valdivia, M.; Jimenez, D. *J. Org. Chem.* **2002**, *67*, 2501-2508. (c) Katoh, T.; Tanaka, R.; Takeo, M.; Nishide, K.; Node, M. *Chem. Pharm. Bull.* **2002**, *50*, 1625-1629. (d) Alvarez-Manzaneda, E.; Chahboun, R.; Cabrera, E.; Alvarez, E.; Alvarez-Manzaneda, R.; Lachkar, M.; Messouri, I. *Synlett* **2007**, 2425-2429.

(16) Alvarez-Manzaneda, E.; Chahboun, R.; Cabrera, E.; Alvarez, E.; Haidour, A.; Ramos, J. M.; Alvarez-Manzaneda, R.; Romera, J. L.; Escobar, M. A. ; Messouri, I.. *Synthesis* **2008**, 4019-4027.

(17) A similar AB system has been previously described for related selenoderivatives. See references 4c and 11a.