First synthesis of (-)-isoambreinolide, (+)-vitexifolin D and (+)-vitedoin B

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A very efficient method for synthesizing spirolactones is reported. The treatment of δ,ε-unsaturated carboxylic acids with iodine and triphenylphosphine under mild conditions leads to the corresponding spiro γ-lactones in high yield and with complete stereoselectivity. Utilizing this, the first synthesis of the terpene spirolactones (-)-isoambreinolide, (+)-vitexifolin D and (+)-vitedoin B has been achieved.

Introduction

Compounds bearing a spiro-carbon are widely found in nature. Among these, spirolactone derivatives are of particular interest, mainly due to the important biological properties exhibited by some of them.[1] Recently, some trinorlabdane-type spirolactones, such as isoambreinolide (**1**),[2] vitexifolin D (**2**)[2] and vitedoin B (**3**),[3] whose biological activities have not yet been investigated, have been isolated from different vegetal species.

The biological importance of the above-mentioned compounds and the presence of the sterically-constrained spiro structure in these substances have motivated many research groups to investigate the synthesis of this type of compounds. However, the stereoselective synthesis of spirocompounds is a challenging task, requiring good control in the construction of the quaternary carbon. In this respect, many strategies involve the creation of the spirolactone concomitant to cyclization with the fused quaternary centre. *p*-Spiroquinones have been synthesized through an iodine (III)-induced dearomatization of phenols to quinones[4] or *via* a cerium (IV)-mediated oxidative coupling of 2,6-dibromophenol derivatives.[5] Spirolactones have also been synthesized *via* radical-based approaches[6] and reductive cross-coupling processes.[7] Other strategies utilized for synthesizing this type of compounds include cationic rearrangements,[8] halolactonization processes[9] and furanyl dienolate-based cyclizations.[10]

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† Electronic Supplementary Information (ESI) available: Copies of ^{1}H and ^{13}CNMR spectra for compounds **1-3** and **6-19**. See http://dx.doi.org/

Pericyclic-type reactions, including electrocyclizations,[11] [2+2] cycloadditions[12] and Diels-Alder reactions[13], have also been employed for this purpose.

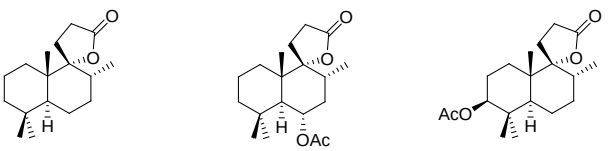


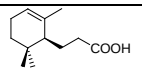
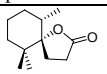
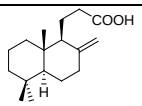
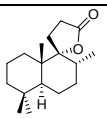
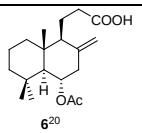
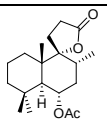
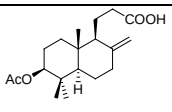
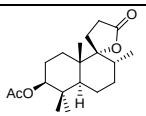
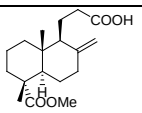
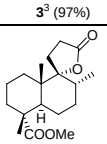
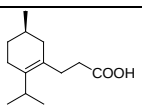
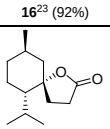
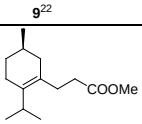
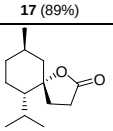
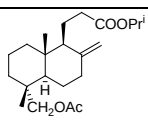
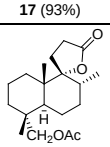
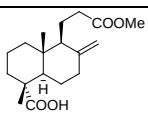
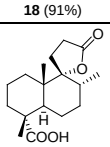
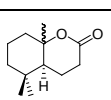
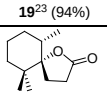
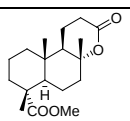
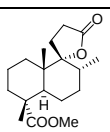
Fig. 1 Trinorlabdane-type spirolactones.

However, the most immediate method to access spirolactones involves an intramolecular esterification reaction[14] (favoured for entropic reasons), a strategy that requires the prior installation of the tertiary alcohol. Another direct route towards spirolactones such as terpenes **1-3** could involve the cyclization of the appropiate unsaturated carboxylic acid under suitable reaction conditions. Very recently, our group reported the preparation of spirodihydrobenzofuran derivatives by the cyclization of *o*-allyl phenols mediated by NIS-PPh_3.[15] The I_2-PPh_3 mediated spirocyclization of unsaturated β-dicarbonyl compounds, with complete regio- and stereoselectivity, was also communicated very recently by the present authors.[16]

Results and discussion

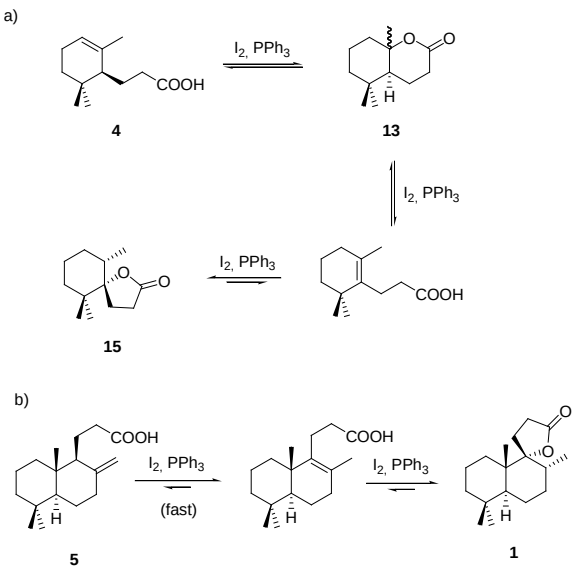
δ,ε-Unsaturated carboxylic acids show a similar behaviour to that of β-dicarbonyl compounds when treated with I_2-PPh_3. The treatment of α-cyclogeranyl acetic acid (**4**)[17] with 1.0 eq. of I_2 and 1.0 eq. of PPh_3 in dichloromethane at room temperature for 72 h afforded, with complete regio- and stereoselectivity, the spiro γ-butyrolactone **15**[18] in 96% yield (Table 1). In a similar way, acid **5**[19] was transformed into isoambreinolide (**1**) after 48 h of reaction, and acetoxy acid **6**[20] led to vitexifolin D (**2**), a *nor*-labdane spirolactone,

Table 1. Treatment of unsaturated carboxylic acids and esters, and δ-lactones with I_2-PPh_3. Synthesis of γ-spirolactones

Entry	Acid or ester[a]	Time	Spirolactone[a]
1	 **4**[17]	72 h	 **15**[18] (96%)
2	 **5**[19]	48 h	 **1**[2] (91%)
3	 **6**[20]	24 h	 **2**[2] (61%)
4	 **7**[21]	48 h	 **3**[3] (97%)
5	 **8**[21]	48 h	 **16**[23] (92%)
6	 **9**[22]	12 h	 **17** (89%)
7	 **10**[22]	24 h	 **17** (93%)
8	 **11**	48 h	 **18** (91%)
9	 **12**	4 days	 **19**[23] (94%)
10	 **13**[17]	24 h	 **15**[18] (89%)
11	 **14**[24]	24 h	 **16**[23] (95%)

[a]All the above acids and esters are enantiopure substances, except acid **4** and esters **13** and **15**, which are racemic compounds.

recently isolated from the fruits of *Vitex rotundifolia*[2] and not yet synthesized. Acids **7**[21] and **8**[21] showed a similar behaviour to that observed for compounds **5** and **6**, leading to the corresponding spirolactones, vitedoin B (**3**), a compound recently isolated from the seeds of *Vitex negundo*[3] and not yet synthesized, and **16**.[23] On the other hand, the γ,δ-unsaturated acid **9** gave the spiro γ-lactone **17**, under the above conditions. Under the same reaction conditions, unsaturated esters led to the corresponding spiro γ-lactones after prolonged reaction times. Thus, the methyl ester **10** afforded lactone **17** after 24 h, and the isopropyl ester **11** was converted into lactone **18** after 48 h. The treatment of the δ,ε-unsaturated methyl ester **12** with I_2-PPh_3 for 4 days gave the spiro γ-lactone **19**. Interestingly, the transformation of δ-valerolactones into the corresponding spiro γ-butyrolactones, under these reaction conditions, has also been observed (entries 10 and 11). Thus, the treatment of lactones **13**[17] and **14**[24] with I_2 and PPh_3 in CH_2Cl_2 at room temperature for 24 h led to spiro γ-lactones **15** and **16**, respectively, in high yield and with complete stereoselectivity.[25] These results suggest that, at least in some cases, these δ-valerolactones could be intermediates in the formation of final spiro γ-butyrolactones. In fact, acid **4** was transformed into a mixture of lactones **13** and **15** after treatment with I_2 and PPh_3 for 12 h. This probably occurs because the initial δ-lactone undergoes ring opening to give the stable γ,δ-unsaturated acid, which is finally transformed into the thermodynamically more stable spiro γ-lactone (Scheme 1a). In the case of unsaturated acids bearing an exocyclic carbon-carbon double bond, such as compounds **5-8**, the formation of δ-valerolactones is not observed. These compounds, in the presence of I_2 and PPh_3, undergo the fast isomerization to the more stable tetrasubstituted alkene,[26] which is inmediately transformed into the corresponding spiro γ-lactone (Scheme 1b).



Scheme 1 a) Spirolactonization of acid **4**, *via* δ-lactone **13**. b) Direct spirolactonization of compounds type **5-8**.

The relative stereochemistry of the above spirolactones was established on the basis of NOE experiments. The spectroscopic properties of synthetic compounds **1**-**3** were identical to those reported for the natural products. The optical rotation of synthetic vitedoin B (**3**) ($[\alpha]_D^{25}$ = + 5.2; c = 1.0, $CHCl_3$) was similar to that reported for the natural product ($[\alpha]_D^{29}$ = + 4.7; c = 0.9, $CHCl_3$).[3] The optical rotation of synthetic vitexifolin D (**2**) ($[\alpha]_D^{25}$ = + 15.5; c = 2.8, acetone) was different to that reported for the natural product ($[\alpha]_D^{17}$ = - 4.4; c = 2.8, acetone).[2] The optical rotation of natural isoambreinolide (**1**) has not yet been reported.[2]

Conclusions

In summary, a very efficient method for synthesizing spiro γ-lactones is reported. The treatment of γ,δ- and δ,ε-unsaturated carboxylic acids and esters with iodine and triphenylphosphine under mild conditions leads to the corresponding spiro γ-lactones in high yield and with complete stereoselectivity. Utilizing this new methodology, the first synthesis of the terpene spirolactones (-)-isoambreinolide (**1**), (+)-vitexifolin D (**2**) and (+)-vitedoin B (**3**) has been achieved.

Experimental

General procedure for the preparation of spirolactones from carboxylic acids or esters.

To a solution of triphenylphosphine (1 mmol) in dry CH_2Cl_2 (10 mL) was added iodine (1 mmol). The mixture was stirred at room temperature for 5 min and a solution of starting material (1 mmol) in dry CH_2Cl_2 (10 mL) was added. The resulting mixture was stirred at room temperature for the specified time, after which TLC showed no starting material. The solvent was removed under vacuum and the crude product was diluted with Et_2O – water (90 – 30 mL) and the phases were shaken and separated. The organic phase was washed with water, brine and dried over anhydrous Na_2SO_4. Removal of the solvent under vacuum afforded a crude product which was directly purified by flash chromatography on silica gel (5% ether/hexanes) to give the corresponding spirolactone.

3-((1*S*,4*S*,4a*S*,8a*R*)-4-Acetoxy-5,5,8a-trimethyl-2-methylene-decahydronaphthalen-1-yl)propanoic acid (6).

Colourless oil. $[\alpha]_D^{25}$ = + 33.5 (c = 0.6, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): 0.76 (s, 3H), 0.89 (s, 3H), 1.02 (s, 3H), 1.12 (ddd, *J*= 12.4, 12.4, 4.1 Hz, 1H), 1.20 - 1.77 (m, 9H), 1.92 (dt, *J*= 12.0, 8.1 Hz, 1H), 2.05 (s, 3H), 2.20 (m, 1H), 2.55 (m, 1H), 2.70 (dd, *J*= 12.3, 5.1 Hz, 1H), 4.62 (s, 1H), 4.96 (s, 1H), 5.05 (ddd, *J*= 11.1, 11.1, 5.1 Hz, 1H), 6.02 (br s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm): 15.9 (CH_3), 18.3 (CH_2), 19.2 (CH_2), 21.9 (CH_3), 22.4 (CH_3), 33.2 (C), 33.5 (CH_2), 39.0 (CH_2), 39.6 (C), 43.3 (CH_2), 44.0 (CH_2), 55.3 (CH), 57.4 (CH), 73.1 (CH), 109.4 (CH_2), 143.6 (C), 170.1 (C), 179.05 (C). IR (film) $\nu_{máx}$: 1735, 1647, 1459, 1377, 1242, 1025, 971, 897, cm^{-1}. HRMS (APcI) *m/z*: calcd for $C_{19}H_{30}O_4Na$ ($M+Na^+$) 345.2042, found: 345.2036.

3-((1*S*,4a*R*,6*S*,8a*R*)-6-Acetoxy-5,5,8a-trimethyl-2-methylene-decahydronaphthalen-1-yl)propanoic acid (7).

Colourless syrup. $[\alpha]_D^{25}$ = + 26.5 (c = 1.0 $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.72 (s, 3H), 0.85 (s, 3H), 0.87 (s, 3H), 1.26 - 1.45 (m, 3H), 1.56-1.92 (m, 7H), 1.97 (ddd, *J* = 12.9, 12.9, 5.0 Hz, 1H), 2.05 (s, 3H), 2.20 (m, 1H), 2.40 (ddd, *J* = 13.0, 4.1, 2.5 Hz, 1H), 2.52 (m, 1H), 4.52 (dd, *J* = 11.9, 4.4 Hz, 1H), 4.51 (s, 1H), 4.87 (s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 14.4 (CH_3), 16.5 (CH_3), 19.0 (CH_2), 21.3 (CH_3), 23.8 (CH_2), 24.2 (CH_2), 28.2 (CH_3), 32.7 (CH_2), 36.6 (CH_2), 37.9 (CH_2), 38.0 (C), 39.2 (C), 54.6 (CH), 55.7 (CH), 80.6 (CH), 107.0 (CH_2), 147.0 (C), 171.0 (C), 179.1 (C). IR (film) $\nu_{máx}$: 1733, 1709, 1369, 1244, 1030, 894, 757 cm^{-1}. HRMS (APcI) *m/z*: calcd for $C_{19}H_{30}O_4Na$ ($M+Na^+$) 345.2042, found: 345.2050.

3-((1*S*,4a*R*,5*R*,8a*R*)-5-Methoxycarbonyl-5,8a-dimethyl-2-methylene-decahydronaphthalen-1-yl)propanoic acid (8).

Colourless oil. $[\alpha]_D^{25}$ = + 25.3 (c = 0.7 $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.71 (s, 3H), 1.13 (s, 3H), 1.20 (m, 1H), 1.44 (ddd, *J* = 12.9, 12.9, 4.4 Hz, 1H), 1.52 - 1.69 (m, 4H), 1.69 - 1.83 (m, 4H), 1.85 - 1.97 (m, 2H), 2.01 (ddd, *J* = 12.9, 12.9, 5.1 Hz, 1H), 2.20 (m, 1H), 2.33 (ddd, *J* = 12.7, 3.9, 2.1 Hz, 1H), 2.52 (ddd, *J* = 16.4, 9.2, 4.7 Hz, 1H), 3.65 (s, 3H), 4.50 (s, 1H), 4.81 (s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 14.6 (CH_3), 16.5 (CH_3), 18.4 (CH_2), 18.6 (CH_2), 26.8 (CH_2), 32.8 (CH_2), 36.9 (CH_2), 37.7 (CH_2), 37.9 (CH_2), 39.0 (C), 47.7 (C), 49.7 (CH), 51.9 (CH_3), 56.0 (CH), 107.1 (CH_2), 147.1 (C), 179.3 (C), 180.1 (C). IR (film): 1726, 1709, 1445, 1245, 1130, 1048, 893 cm^{-1}. HRMS (APcI) *m/z*: calcd for $C_{18}H_{28}O_4Na$ ($M+Na^+$) 331.1885, found: 331.1899.

(*R*)-3-(2-Isopropyl-5-methylcyclohex-1-enyl)propanoic acid (9).

Colourless oil. $[\alpha]_D^{25}$ = + 27.7 (c = 0.7, $CHCl_3$).^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm) 0.934 (d, *J*= 5.0 Hz, 3H), 0.936 (d, *J*= 6.8, 6H), 1.26 (br s, 1H), 1.56 - 1.72 (m, 4H), 1.99 (d, *J*= 12.7, 1H), 2,15 - 2.40 (m, 5H), 2.84 (h, *J*= 6.86 Hz, 1H), 6.34 (br s, 1H).^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm): 20.6 (CH_3), 21.1 (CH_3), 21.8 (CH_3), 23.0 (CH_2), 28.3 (CH_2), 28.9 (CH), 29.0 (CH), 31.4 (CH_2), 34.4 (CH_2), 38.4 (CH_2), 136.4 (C), 179.1 (C). IR (film) ν_{max}: 3421, 2870, 1708, 1542, 1457, 1260, 1096, 1025, 800 cm^{-1}. HRMS (APcI) *m/z*: calcd for $C_{13}H_{22}O_2Na$ ($M+Na^+$) 233.1517, found: 233.1532.

(*R*)-Methyl 3-(2-isopropyl-5-methylcyclohex-1-enyl)propanoate (10).

Colourless syrup. $[\alpha]_D^{25}$ = - 31.4 (c = 0.7, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): 0.93 (d, *J*= 5.0 Hz, 3H), 0.94 (d,

J= 6.8, 6H), 1.30 (m, 1H), 1.56 - 1.71 (m, 4H), 1.97 - 2.01 (m, 2H), 2,26 - 2.32 (m, 4H), 2.83 (h, *J*= 6.8 Hz, 1H), 3.67 (s, 1H).^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm): 20.6 (CH_3), 21.1 (CH_3), 21.7 (CH_3), 22.9 (CH_2), 28.2 (CH_2), 28.8 (CH), 28.9 (CH), 31.3 (CH_2), 33.4 (CH_2), 38.3 (CH_2), 51.4 (CH_3), 136.47 (C), 174.1 (C). IR (film) ν_{max}: 1741, 1639, 1458, 1436, 1363, 1256, 1170 cm^{-1}. HRMS (APcI) *m/z*: calcd for $C_{14}H_{24}O_2Na$ ($M+Na^+$) 247.1674, found: 247.1659.

Isopropyl 3-((1*S*,4a*R*,5*R*,8a*R*)-5-(acetyloxymethyl)-5,8a-dimethyl-2-methylene-decahydronaphthalen-1-yl)propanoate (11).

Colourless oil. $[\alpha]_D^{25}$ = + 25.6 (c = 16.8 $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.72 (s, 3H), 0.81 (s, 3H), 1.08 (ddd, *J* = 12.4, 12.4, 4.9 Hz, 1H), 1.21 (d, *J* = 6.3 Hz, 3H), 1.21 (d, *J* = 6.3 Hz, 3H), 1.34 - 1.39 (m, 4H), 1.53 - 1.67 (m, 5H), 1.79 (ddd, *J* = 12.7, 3.2, 3.2 Hz, 1H), 1.84 - 1.97 (m, 2H), 2.06 (s, 3H), 2.13 (m, 1H), 2.33 - 2.45 (m, 2H), 3.64 (d, *J* = 10.9 Hz, 1H), 3.84 (d, *J* = 10.9 Hz, 1H), 4.50 (s, 1H), 4.84 (s, 1H), 4.99 (h, *J* = 6.3 Hz, 1H). ^{13}C RMN ($CDCl_3$, 125 MHz) δ: 14.7 (CH_3), 17.5 (CH_3), 18.5 (CH_2), 19.1 (CH_2), 21.0 (CH_3), 21.84 (CH_3), 21.89 (CH_3), 24.3 (CH_2), 33.5 (CH_2), 35.9 (CH_2), 36.8 (C), 37.9 (CH_2), 38.4 (CH_2), 39.5 (C), 49.4 (CH), 56.1 (CH), 67.3 (CH), 72.9 (CH_2), 106.8 (CH_2), 147.4 (C), 171.2 (C), 173.7 (C). IR (film) $\nu_{máx}$: 1733, 1467, 1379, 1239, 1110, 1038, 891 cm^{-1}. HRMS (APcI) *m/z*: calcd for $C_{22}H_{36}O_4Na$ ($M+Na^+$) 387.2511, found: 387.2499.

(1*R*,4a*R*,5*S*,8a*R*)-5-(2-Methoxycarbonylethyl)-1,4a-dimethyl-6-methylene-decahydronaphthalene-1-carboxylic acid (12).

Colourless solid, mp 124 ºC (methanol); $[\alpha]_D^{25}$ = + 7.9 (c = 0.8 $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.75 (s, 3H), 1.14 (m, 1H), 1.23 (s, 3H), 1.33 - 1.48 (m, 2H), 1.53 - 1.67 (m, 3H), 1.67 - 1.81 (m, 4H), 1.87 (m, 1H), 2.08 (ddd, *J* = 12.6, 12.6, 5.7 Hz, 1H), 2.10 - 2.19 (m, 2H), 2.32 (br d, *J* = 12.7 Hz, 1H), 2.45 (ddd, *J* = 16.0, 9.3, 4.7 Hz, 1H), 3.64 (s, 3H), 4.49 (s, 1H), 4.82 (s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 14.8 (CH_3), 18.6 (CH_2), 18.9 (CH_2), 19.0 (CH_3), 27.0 (CH_2), 33.0 (CH_2), 35.8 (CH_2), 37.6 (CH_2), 37.9 (CH_2), 39.4 (C), 46.9 (C), 49.9 (CH), 51.4 (CH_3), 56.4 (CH), 106.7 (CH_2), 147.7 (C), 174.5 (C), 178.4 (C). IR (KBr) $\nu_{máx}$: 1737, 1624, 1440, 1357, 1254, 1166, 1042, 891 cm^{-1}. HRMS (APcI) *m/z*: calcd for $C_{18}H_{28}O_4Na$ ($M+Na^+$) 331.1885, found: 331.1888.

(4a*S*)-5,5,8a-Trimethyl-octahydrochromen-2-one (13).

Colourless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): 0.85 (s, 3H), 0.89 (s, 3H), 0.95 (s, 3H), 0.99 (s, 3H), 1.20-1.35 (m, 2H), 1.40 - 1.77 (m, 10H), 1.37 (s, 3H), 1.38 (s, 3H), 1.84 – 2.00 (m, 4H), 2.32 (t, *J*= 8.1 Hz, 1H), 2.15 (m, 1H), 2.53 - 2.63 (m, 3H), 2.70 (m, 1H). ^{13}C NMR ($CDCl_3$, 500 MHz) δ (ppm), Signals asignables to the major product: 16.9 (CH_3), 17.7 CH_2), 20.6 (CH_3), 22.0 (CH_3), 26.1 (CH_2), 31.9 (CH_3), 33.7 (C), 39.2 (CH_2), 40.6 (CH_2), 44.3 (CH_2), 82.2 (CH), 171.7 (C). Signals asignables to the minor product: 16.5 (CH_3), 19.7 CH_2), 20.6 (CH_3), 22.6 (CH_3), 29.4 (CH_2), 32.1 (CH_3), 33.8 (C), 40.2 (CH_2), 41.1 (CH_2), 49.0 (CH_2), 83.8 (CH), 172.9 (C). IR (film) $\nu_{máx}$: 1728, 1461, 1263, 1148, 1097, 1041, 973 cm^{-1}.HRMS (APcI) *m/z*: calcd for $C_{12}H_{20}O_2Na$ ($M+Na^+$) 219.1361, found: 219.1373.

(4a*R*,6a*R*,7*R*,10a*S*,10b*R*)-Methyl 4a,7,10a-trimethyl-3-oxo-dodecahydro-1*H*-benzo[f]chromene-7-carboxylate (14).

Colourless solid, mp 196-197 ºC (methanol); $[\alpha]_D^{25}$ = + 35.0 (c = 0.9 $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.85 (s, 3H), 1.06 (ddd, *J* = 12.6, 12.6, 3.8 Hz, 1H), 1.14 (s, 3H), 1.23 (br d, *J* = 13.8 Hz, 1H), 1.35 (s, 3H), 1.39 (ddd, *J* = 13.9, 13.9, 3.3 Hz, 1H), 1.51 - 1.88 (m, 10H), 1.95 (br d, *J* = 12.7 Hz, 1H), 2.53 (m, 1H), 2.66 (ddd, *J* = 18.8, 8.4, 2.5 Hz, 1H), 3.65 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 15.3 (CH_3), 15.6 (CH_2), 16.3 (CH_3), 17.4 (CH_2), 22.1 (CH_2), 22.9 (CH_3), 28.9 (CH_2), 36.7 (CH_2), 36.7 (C), 38.2 (CH_2), 40.7 (CH_2), 47.2 (C), 50.2 (CH), 52.0 (CH_3), 53.5 (CH), 83.5 (C), 171.2 (C), 178.6 (C). IR (KBr) $\nu_{máx}$: 1714, 1460, 1246, 1107, 1067, 987, 957, 771 cm^{-1}. HRMS (APcI) *m/z*: calcd for $C_{18}H_{29}O_4$ ($M+H^+$) 309.2066, found: 309.2048.

(1*S*,6*S*)-6,6,10-Trimethyl-1-oxaspiro[4.5]decan-2-one (15).

Colourless syrup; ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): 0.86 (d, *J*= 6.7 Hz, 3H), 0.88 (s, 3H), 0.95 (s, 3H), 1.24 (m, 1H), 1.41 - 1.45 (m, 2H), 1.49 - 1.53 (m, 2H), 1.67 (m, 1H), 1.86 (ddd, *J*= 13.6, 11.2, 5.1 Hz, 1H), 2.18 (ddd, *J*= 13.5,11.5, 8.4 Hz, 1H), 2.49 (ddd, *J*= 18.7, 11.3, 5.1 Hz, 1H), 2.56 (ddd, *J*= 18.7, 11.2, 8.4 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm): 15.5 (CH_3), 21.2 (CH_2), 22.0 (CH_3), 24.6 (CH_3), 25.3 (CH_2), 29.7 (CH_2), 30.5 (CH_2), 36.2 (CH_2), 36.8 (CH), 92.6 (C), 177.7 (C). IR (Film) $\nu_{máx}$: 1766, 1481, 1452, 1390, 1369, 1275, 1202, 969 cm^{-1}. HRMS (APcI) *m/z*: calcd for $C_{12}H_{21}O_2$ ($M+H^+$) 197.1542, found: 197.1538.

Isoambreinolide (1).

Colourless solid, mp 97 ºC (methanol); $[\alpha]_D^{25}$ = - 4.3 (c = 0.84, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): 0.82 (s, 3H), 0.84 (d, *J*= 6.6 Hz, 3H), 0.85 (s, 3H), 0.92 (s, 3H), 1.18 (ddd, *J*= 13.6, 13.6, 4.0 Hz, 1H), 1.25 - 1.64 (m, 10H), 1.76 - 1.85 (m, 2H), 2.19 (ddd, *J*= 13.5, 11.7, 7.8 Hz, 1H), 2.45 (ddd, *J*= 18.7, 11.6, 5.1 Hz, 1H), 2.53 (ddd, *J*= 18.7, 11.3, 7.8 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm): 15.6 (CH_3), 15.7 (CH_3), 18.3 (CH_2), 21.3 (CH_2), 21.9 (CH_3), 24.7 (CH_2), 29.5 (CH_2), 30.9 (CH_2), 31.2 (CH_2), 33.1 (CH_3), 33.3 (C), 36.8 (CH), 41.3 (CH_2), 42.2 (C), 46.6 (CH), 94.0 (C), 177.8 (C). IR (film) $\nu_{máx}$: 1768, 1462, 1388, 1219, 1176, 1116, 971 cm^{-1}. HRMS (APcI) *m/z*: calcd for $C_{17}H_{29}O_2$ ($M+H^+$) 265.2168, found: 265.2176.

Vitexifolin D (2).

Colourless needles, mp 100-101 °C (hexane-EtOAc); $[\alpha]_D^{25}$ = + 18.7 (c = 0.33, $CHCl_3$); $[\alpha]_D^{25}$ = + 15.5 (c = 0.28, acetone) [lit.[2]: $[\alpha]_D^{17}$ = - 4.4 (c = 2.8, acetone)]. ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): 0.88 (d, *J*= 6.5 Hz, 3H), 0.90 (s, 3H), 1.00 (s,

3H), 1.04 (s, 3H), 1.28 - 1.66 (m, 6H), 1.81 - 1.88 (m, 2H), 1.98 (m, 1H), 1.91 (br d, *J*= 11.6 Hz, 1H), 2.03 (s, 3H), 2.19 (ddd, *J*= 13.9, 11.5, 7.5 Hz, 1H), 2.48 (ddd, *J*= 19.0, 11.6, 5.6 Hz, 1H), 2.55 (ddd, *J*= 19.0, 11.3, 7.3 Hz, 1H), 5.13 (ddd, *J*= 11.4, 11.4, 4.8 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm): 15.1 (CH_3), 16.9 (CH_3), 18.0 (CH_2), 21.9 (CH_3), 22.6 (CH_3), 24.6 (CH_2), 29.3 (CH_2), 31.8 (CH_2), 33.2 (C), 35.0 (CH), 36.0 (CH_3), 37.0 (CH_2), 42.8 (CH_2), 43.9 (C), 48.9 (CH), 71.5 (CH), 92.6 (C), 170.5 (C), 177.3 (C). IR (film) $\nu_{máx}$: 1771, 1732, 1652, 1457, 1245, 1220, 1097, 1023, 966, 801, 774, 660, 615 cm^{-1}. HRMS (APcI) *m/z*: calcd for $C_{19}H_{31}O_4$ ($M+H^+$) 323.2222, found: 323.2213.

Vitedoin B (3).

Colourless solid, mp 94-95 ºC (hexane-EtOAc); $[\alpha]_D^{25}$ = + 5.2 (c = 1.0, $CHCl_3$) [lit.[3]: $[\alpha]_D^{29}$ = + 4.7 (c = 0.9, $CHCl_3$)]. ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm) 0.85 (d, *J*= 6.6 Hz, 3H), 0.87 (s, 3H), 0.88 (s, 3H), 0.95 (s, 3H), 1.25 (br s, 2H), 1.40 - 1.47 (m, 2H), 1.50 - 1.66 (m, 5H), 1.83 (m, 1H), 1.86 (ddd, *J*= 13.7, 11.6, 5.0 Hz, 1H), 2.04 (s, 3H), 2.18 (ddd, *J*= 13.4, 11.8, 8.1 Hz, 1H), 2.46 (ddd, *J*= 18.7, 11.7, 5.0 Hz, 1H), 2.54 (ddd, *J*= 18.7, 11.3, 8.0 Hz, 1H), 4.48 (dd, *J*= 11.5, 4.4 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm): 15.4 (CH_3), 15.8 (CH_3), 16.6 (CH_3), 20.9 (CH_2), 21.3 (CH_3), 23.2 (CH_2), 24.9 (CH_2), 27.8 (CH_3), 29.36 (CH_2), 29.44 (CH_2), 30.7 (CH_2), 36.7 (CH), 37.7 (C), 41.8 (C), 46.1 (CH), 80.0 (CH), 93.3 (C), 170.7 (C), 177.3 (C). IR (film) $\nu_{máx}$: 1767, 1733, 1462, 1366, 1242, 1199, 1177, 1111, 1281, 1091, 1032, 972, 954, 668 cm^{-1}. HRMS (APcI) *m/z*: calcd for $C_{19}H_{31}O_4$ ($M+H^+$) 323.2222, found: 323.2233.

(1*S*,2*R*,4a*R*,5*R*,8a*R*)- 2',5',8'a-Trimethyl-5'-methoxycarbonyl-spiro[furan-2(5*H*),1'(2'*H*)-decahydro naphthalen]-5-one (16).

Colourless oil. $[\alpha]_D^{25}$ = + 28.4 (c = 0.9, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): 0.83 (d, *J*= 6.6 Hz, 3H), 0.92 (s, 3H), 1.14 (s, 3H), 1.10 (m, 1H), 1.35 - 1.49 (m, 6H), 1.71 - 1.78 (m, 2H), 1.83 (ddd, *J*= 13.7, 11.5, 4.9 Hz, 1H), 2.17 (m, 1H), 2.31 (m, 1H), 2.46 (ddd, *J*= 18.7, 11.7, 5.0 Hz, 1H), 2.51 (ddd, *J*= 18.7, 11.2, 8.0 Hz, 1H), 3.62 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm): 15.4 (CH_3), 15.9 (CH_3), 16.8 (CH_3), 17.6 (CH_2), 23.8 (CH_2), 24.8 (CH_2), 29.5 (CH_2), 30.4 (CH_2), 30.5 (CH_2), 36.1 (CH_2), 36.9 (CH), 41.6 (CH), 41.7 (C), 47.4 (C), 51.8 (CH_3), 93.5 (C), 177.5 (C), 178.6 (C). IR (film) $\nu_{máx}$: 1764, 1720, 1462, 1391, 1243, 1200, 1102, 961, 760, 616 cm^{-1}. HRMS (APcI) *m/z*: calcd for $C_{18}H_{28}O_4Na$ ($M+Na^+$) 331.1885, found: 331.1885.

(1*S*,2*R*,5*R*)-6-Isopropyl-10-methyl-1-oxaspiro[4,5]decan-2-one (17).

Colourless syrup; $[\alpha]_D^{25}$ = -3.6 (c = 0.7, $CHCl_3$), ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): 0.83 (s,3H) ,0.84 (d, *J*= 7.0 Hz, 3H), 0.88 (d, *J*= 6.26, 3H), 0.96 (d, *J*= 6.93, 3H), 1.11 - 1.21 (m, 4H), 1.45 - 1.65 (m, 2H), 1.75 - 1.89 (m, 3H), 1.98 (h, *J*= 6.8, 1H), 2.34 (ddd, *J*= 13.2, 10.7, 7.0 Hz, 1H), 2.5 (ddd, *J*= 18.3, 10.67, 6.9 Hz, 1H), 2.63 (ddd, *J*= 18.4, 10.9, 7.1 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm): 17.8 (CH_3), 21.7 (CH_2), 22.0 (CH_3), 23.8 (CH_3), 26.3 (CH), 28.6 (CH), 29.0 (CH_2), 31.2 (CH_2), 34.6 (CH_2), 49.3 (CH_2), 49.8 (CH), 89.37 (C), 177.04 (C). IR (film) $\nu_{máx}$: 2868, 1770, 1465, 1216, 1139, 947, 917 cm^{-1}. HRMS (APcI) *m/z*: calcd for $C_{13}H_{22}O_2Na$ ($M+Na^+$) 233.1517, found: 233.1524.

(1*S*,2*R*,4a*R*,5*R*,8a*R*)-5'-Acetyloxymethyl-2',5',8'a-trimethyl-spiro[furan-2(5*H*),1'(2'*H*)-decahydronaphthalen]-5-one (18).

Colourless syrup; $[\alpha]_D^{25}$ = + 15.9 (c = 2.6 $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.83 (s, 3H), 0.84 (d, *J* = 6.1 Hz, 3H), 0.94 (s, 3H), 1.22 - 1.40 (m, 6H), 1.47 - 1.62 (m, 4H), 1.72 - 1.80 (m, 2H), 1.83 (ddd, *J* = 13.9, 11.7, 5.2 Hz, 1H), 2.06 (s, 3H), 2.19 (ddd, *J* = 13.7, 11.8, 8.0 Hz, 1H), 2.45 (ddd, *J* = 18.7, 11.6, 5.0 Hz, 1H), 2.53 (ddd, *J* = 18.7, 11.6, 7.8 Hz, 1H), 3.68 (d, *J* = 10.9 Hz, 1H), 3.81 (d, *J* = 10.9 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 15.4 (CH_3), 16.0 (CH_3), 17.4 (CH_2), 17.5 (CH_3), 21.0 (CH_3), 21.3 (CH_2), 24.8 (CH_2), 29.5 (CH_2), 30.58 (CH_2), 30.64 (CH_2), 35.3 (CH_2), 36.6 (CH), 36.6 (C), 41.3 (CH), 42.0 (C), 72.7 (CH_2), 93.7 (C), 171.3 (C), 177.6 (C). IR (film) $\nu_{máx}$: 1766, 1738, 1464, 1383, 1240, 1038, 967 cm^{-1}. HRMS (APcI) *m/z*: calcd for $C_{19}H_{30}O_4Na$ ($M+Na^+$) 345.2042, found: 345.2031.

(1*S*,2*R*,4a*R*,5*R*,8a*R*)-2',5',8'a-Trimethyl-spiro[furan-2(5*H*),1'(2'*H*)-decahydronaphthalen]-5-oxo-5'-carboxylic acid (19).

Colourless solid, mp 198-199 ºC (methanol); $[\alpha]_D^{25}$ = + 17.6 (c = 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.85 (d, *J* = 6.6 Hz, 3H), 0.95 (s, 3H), 1.17 (s, 3H), 1.25 (s, 3H), 1.23 - 1.33 (m, 4H), 1.35 - 1.44 (m, 2H), 1.44 - 1.55 (m, 2H), 1.55-1.65 (m, 2H), 1.78 (m, 1H), 1.85 (ddd, *J* = 13.7, 11.5, 4.9 Hz, 1H), 2.20 (ddd, *J* = 13.6, 11.7, 8.1 Hz, 1H), 2.33 (m, 1H), 2.47 (ddd, *J* = 18.7, 11.6, 5.0 Hz, 1H), 2.55 (ddd, *J* = 18.7, 11.6, 8.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 15.5 (CH_3), 15.9 (CH_3), 16.6 (CH_3), 17.6 (CH_2), 23.8 (CH_2), 24.7 (CH_2), 29.5 (CH_2), 30.3 (CH_2), 30.5 (CH_2), 36.2 (CH_2), 36.9 (CH), 41.6 (C), 41.7 (CH), 47.2 (C), 93.6 (C), 177.5 (C), 183.5 (C). IR (KBr) $\nu_{máx}$: 1763, 1695, 1464, 1390, 1242, 962, 759 cm^{-1}. HRMS (APcI) *m/z*: calcd for $C_{17}H_{26}O_4Na$ ($M+Na^+$) 317.1729, found: 317.1727.

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References

1 For recent studies concerning biologically active spirolactones see: *(a)* T. Asai, T. Taniguchi, T. Yamamoto; K. Monde and Y. Oshima, *Org. Lett.* 2013, **15**, 4320-4323; *(b)* M. Liu, S. Lin, M. Gan, M. Chen, L. Li, S. Wang, J. Zi, X. Fan; Y. Liu, Y. Si, Y. Yang, X. Chen and J. Shi, *Org. Lett.* 2012, **14**, 1004-1007; *(c)* A. Bartoli, F. Rodier, L. Commeiras, J.-L. Parrain and G. Chouraqui, *Nat. Prod. Rep.* 2011, **28**, 763-782.

2 M. Ono, T. Yanaka, M. Yamamoto, Y. Ito and T. Nohara, *J. Nat. Prod.* 2002, **65**, 537-541.

3 M. Ono, Y. Nishida, C. Masuoka, J.-C. Li, M. Okawa, T. Ikeda and T. Nohara, *J. Nat. Prod.* 2004, **67**, 2073-2075.

4 Y. Tamura, T. Yakura, J. I. Haruta and Y. Kita, *J. Org. Chem.* 1987, **52**, 3927-3931.

5 N. Kotoku, H. Tsujita, A. Hiramtsu, C. Mori, N. Koizumi and M. Kobayashi, *Tetrahedron* 2005, **61**, 7211-7218.

6 *(a)* D. P. Curran, M. –H. Chen, E. Spletzeir, C. M. Seong and C. T. Chang, *J. Am. Chem. Soc.* 1989, **111**, 8872-8878; *(b)* W. Zhang and G. Pugh, *Tetrahedron Lett.* 2001, **42**, 5617-5620.

7 *(a)* S. Fukuzawa, T. Nakanishi, T. Fujinami and S. Sakai, *J. Chem. Soc., Chem. Commun.* 1986, 624-625; *(b)* C. A. Merlic and J. C. Walsh, *J. Org. Chem.* 2001, **66**, 2265-2274.

8 *(a)* R. A. Abramovitch, J. A. Hawi, J. A. Rodrigues and T. R. Trombetta, *J. Chem. Soc.. Chem. Commun*. 1986, 283-284 ; *(b)* M.-C. Yeh, Y.-C. Lee and T.-C. Young, *Synthesis* 2006, 3621-3624.

9 B.-X. Tang, Q. Yin, R.-Y. Tang and J.-H. Li, *J. Org. Chem.* 2008, **73**, 9008-9011.

10 *(a)* N. Maulide and I. E. Markó, *Org. Lett.* 2006, **8**, 3705-3707. *(b)* M. Nomiya, T. Murakami, N. Takada, T. Okuno, Y. Harada and M. Hashimoto, *J. Org. Chem.* 2008, **73**, 5039-5047.

11 R. D. Miller, W. Theis, G. Heilig and S. Kirchmeyer, *J. Org. Chem.* 1991, **56**, 1453-1463.

12 B. Doroh and G. A. Sulikowski, *Org. Lett.* 2006, **8**, 903-906.

13 *(a)* C. W. Zapf, B. A. Harrison, C. Drahl and E. J. Sorensen, *Angew. Chem. Int. Ed.* 2005, **44**, 6533-6537. *(b)* K. C. Nicolaou and S. T. Harrison, *Angew. Chem. Int. Ed*. 2006, **45**, 3256-3260. *(c)* K. C. Nicolaou, R. M. Denton, A. Lenzen, D. J. Edmonds, A. Li, R. R. Milburn and S. T. Harrison, *Angew. Chem. Int. Ed.* 2006, **45**, 2076-2081. *(d)* R. Blanc, V. Heran, R. Rahmani, L. Commeiras and J.-L. Pawain, *Org. Biomol. Chem.* 2010, **8**, 5490-5494.

14 For some selected synthesis utilizing the intramolecular esterification reaction see: *(a)* C. H. Heathcock and T. W. Vougeldern, *Heterocycles* 1987, **25**, 75-78. *(b)* L. Barriault and D. H. Deon, *Org. Lett.* 2001, **3**, 1925-1927. *(c)* T. Taniguchi and H. Ishibashi, *Tetrahedron* 2008, **64**, 8773-8779. *(d)* T. Taniguchi, G. Tanabe, O. Muraoka and H. Ishibashi, *Org. Lett*. 2008, **10**, 197-199. *(e)* P. Liu, S. Hong and S. M. Weinreb, *J. Am. Chem. Soc.* 2008, **130**, 7562-7564.

15 M. J. Cano, H. Bouanou, R. Tapia, E. Alvarez, R. Alvarez-Manzaneda, R. Chahboun and E. Alvarez-Manzaneda, *J. Org. Chem.* 2013, **78**, 9196-9204.

16 R. Tapia, M. J. Cano, H. Bouanou, E. Alvarez, R. Alvarez-Manzaneda, R. Chahboun and E. Alvarez-Manzaneda, *Chem. Commun.* 2013, **49**, 10257-10259.

17 R. Buchecker, R. Egli, H. Regel-Wild, C. Tscharner, C. H. Eugster, G. Uhde and G. Ohloff, *Helv. Chim. Acta* 1973, **56**, 2548-2563.

18 V. Jäger, W. Kuhn and J. Buddrus, *Tetrahedron Lett.* 1986, **27**, 2587-2590.

19 R. J. Peters, M. M. Ravn, R. M. Coates and R. B. Croteau, *J. Am. Chem. Soc.* 2001, **123**, 8974-8978.

20 C. Morin and N. Nedjar, *Tetrahedron Lett.* 1996, **37**, 4705-4706.

21 Compounds **7** and **8** were synthesized from abietic acid. R. Tapia, PhD Thesis, University of Granada, 2012.

22 Compounds **9** and **10** were synthesized from (-)-menthol. H. Bouanou, PhD Thesis, University of Granada, 2013.

23 For a brief description of the corresponding carboxylic acid, see: D. Burn and W. Rigby, *J. Chem. Soc.* 1957, 2964-74.

24 The corresponding carboxylic acid has been recently isolated. See: G. Cioffi, A. Bader, A. Malafronte, F. Dal Piaz and N. De Tommasi, *Phytochemistry* 2008, **69**, 1005-1012.

25 During their studies on the stereochemistry of marrubiin, McCrindle et al reported the conversion of ambreinolide into isoambreinolide by treatment with sulphuric acid. These authors indicate a low yield, which is not specified, for this transformation and did not provide evidence for the configurations on the C-8 and C-9 of final compound. See: R. A. Appleton, J. W. B. Fulke, M. S. Henderson and R. McCrindle, *J. Chem. Soc.* (C), 1967, 1943-1947.

26 For a recent example of this I_2-PPh_3 mediated isomerization see reference 15.