Synthesis of a Truncated Tetradenolide

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Abstract: The enantiopure synthesis of a truncated tetradenolide is presented. Starting from the versatile chiron 7,3-lactone xylofuranose derivative (7,3-LXF), the enantiomerically pure synthesis of the title compound is obtained in six steps with a 40% overall yield.

Introduction

A number of 6-substituted 5,6-dihydro-α-pyrones have been shown to exhibit relevant pharmacological activities. For instance, Goniodiol[1] **1**, Pectinolides A-C[2] **2**, Passifloricin A[3] **3** and (–)-Pironetin **4**, [4] (Figure 1) belong to this important class of compounds. Interestingly, it has been observed that the most active compounds are those that possess hydroxyl groups in the side and an aliphatic chain at the C3' position. In this regard, *Tetradenia riparia*, [5] plays an important role in ethnomedicine and traditional medicine in Madagascar and southern Africa; among the active compounds extracted from this plant are ibozol, a diterpene diol, and various similar diterpenoids, and an α-pyrone, *Tetradenolide*, this last which was first isolated by Puyvelde, [6] has attracted much attention, not only because of Its biological activity but also for the controversial analysis of its molecular structure. [7]

In this regard, we report here the synthesis of a new 6-substituted 5,6-dihydro-α-pyrone (which we termed as truncated Tetradenolide) starting from the Chiron 7,3-LXF.

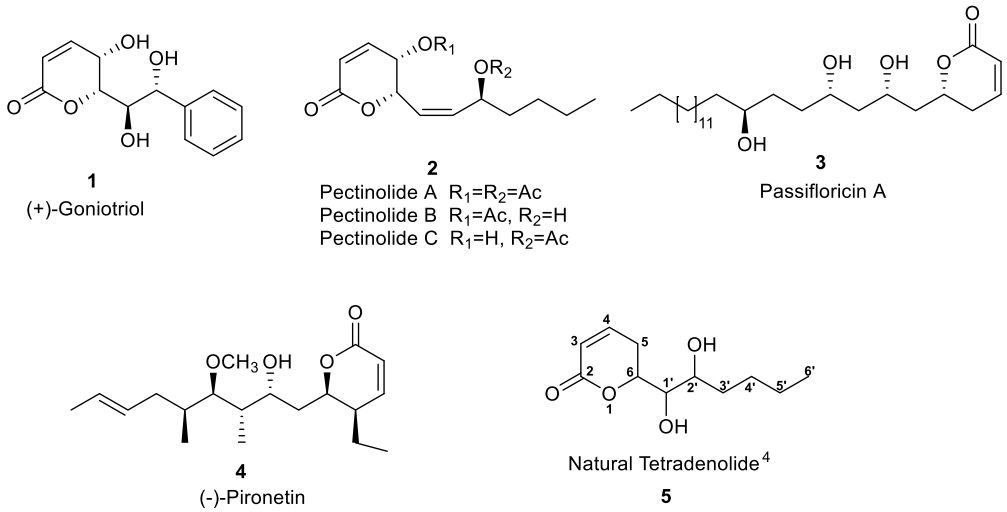

Figure 1. 6-hydroxysubstituted 5,6-dihydro-α-pyrones

Results and Discussion

We have achieved the synthesis of the 7,3-lactone-xylofuranose derivative (7,3-LXF) from diacetone D-glucose in grams' scale, [8] and has been applied to the synthesis of the metabolites produced by *Trichoderma spp* and *Penicillium isolates*. [9] (Scheme 1).

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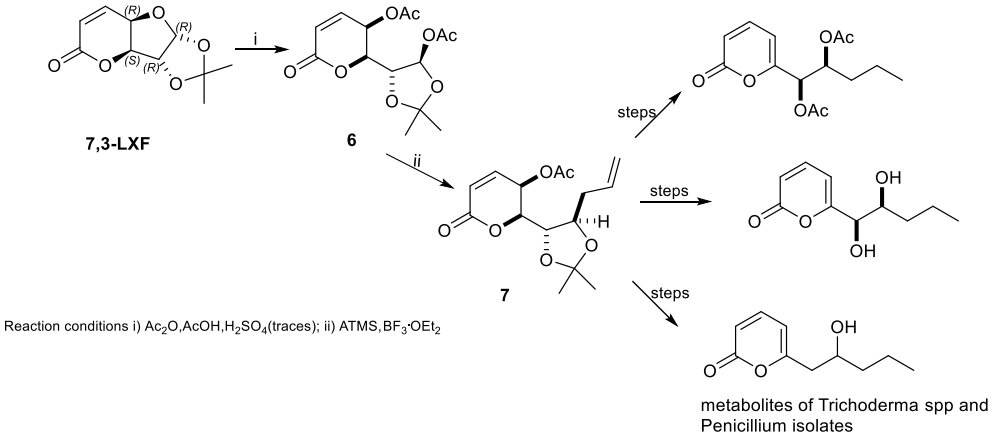
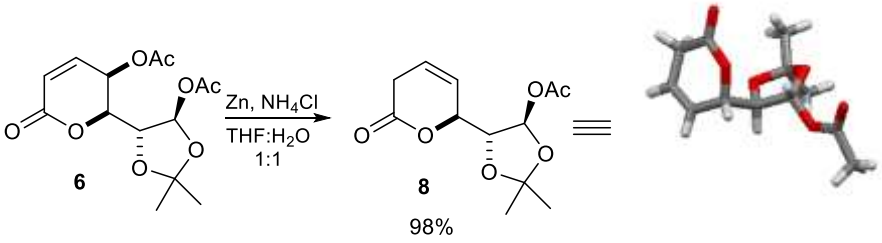


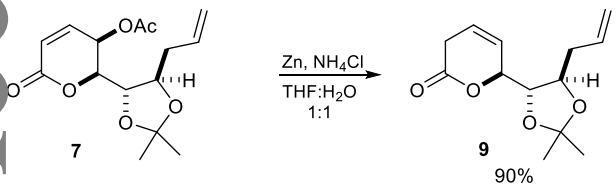
Scheme 1 Synthesis of the allylated pyrone **7**

The synthesis of the title compound begun by testing a reductive deacetoxylation of **6** with Zinc and NH_4Cl. [10] The reductive elimination afforded compound **8** which provided crystalline material suitable for x-ray studies. [11] This compound crystallizes in space group $P2_12_12_1$, and the absolute configuration was determined as (6*S*,1'*R*,2'*R*). It is worth to mention that the short non-bonding separation of 3.442(3) Å between the lactone O atom and the dioxolane O atom bonded to C2' is related to the spatial pre-organization for a latent C6–O/C2´–OH *syn* arrangement. (Scheme 2).



Scheme 2 Selective deacetoxylation of **6**

The same procedure was then applied to the allylated derivative **7**, giving the expected product **9** (Scheme 3).



Scheme 3 Selective deacetoxylation of **7**

Attempts for selective hydrogenation of the side chain of acetylated compound **7** were unsuccessful, exhaustive hydrogenation occurred giving compound **10**, from which the crystal structure was determined. [12] Compound **10** crystallizes in space group $P2_12_12_1$, and the absolute configuration was determined as (5*R*,6*R*,1'*S*,2'*R*). Consistent C–C bond lengths are observed along the alkyl chain, 1.512(5), 1.459(6) and 1.581(7) Å. In this way, we proved that the addition of the allyl group is favored on the *Re* face of the oxocarbenium ion. [8] (Figure 2) Similarly, the hydrogenation of the C=C double bonds in **9** was not selective and compound **11** was obtained (Scheme 4).

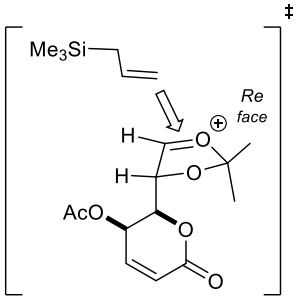


Figure 2. Selective allylation of oxocarbeniun ion *Re* face for the synthesis of **7**

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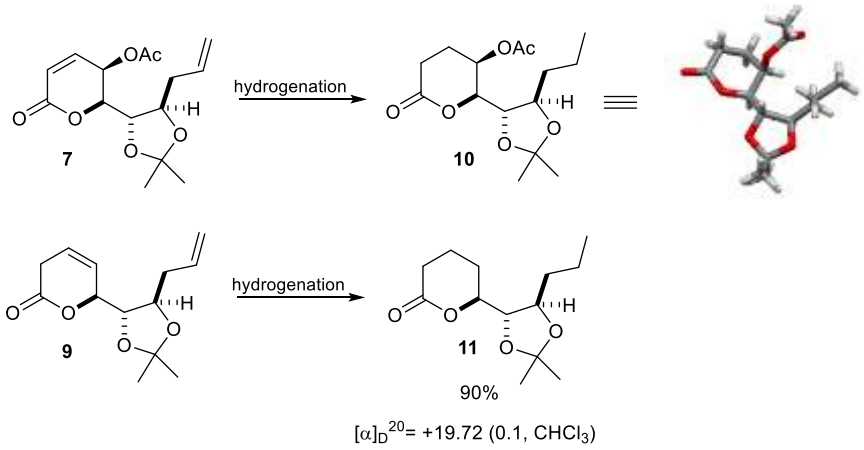
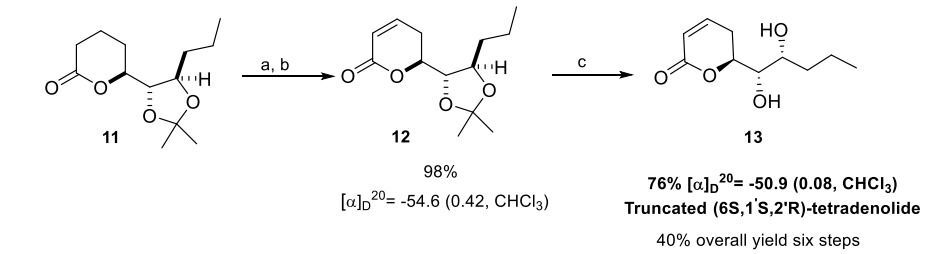


Scheme 4. Non-selective hydrogenation of the allylated pyrones **7** and **9**

Due to the lack of selectivity for the hydrogenation reaction, a further step was required to regenerate the double bond in the δ-lactone. This was done through a sequential reaction of α-phenylselenation of **11**, using phenyl selenium bromide, followed by oxidative elimination with hydrogen peroxide in DCM, to obtain **12** in quantitative yield. Finally, the isopropylidene protecting group was removed by acid hydrolysis giving the target product the enantiomerically pure truncated (6*S*,1'*S*,2'*R*)-tetradenolide **13** in 76% yield (Scheme 5).



a) LDA, PhSeBr (3eq),THF -78°C, 3h. b) H_2O_2, DCM, rt, 15 min. c) H_2O: AcOH:H_2SO_4 (38:46:16%v/v)

Scheme 5. Synthesis of Truncated Tetradnolide **13**

Conclusions

In conclusion, we have synthesized in an enantiopure and concise way, a truncated Tradenolide **13** from Chiron *7,3-LXF* in six-steps with 40% overall yield, featuring a reductive deacetoxylation step under mild conditions. This route has allowed us to develop a new venue for accessing both natural and synthetic 6-substituted-5,6-dihydro-α-pyrones, which are currently evaluated for their biological properties.

Experimental Section

Lactone *7,3-LXF* is obtained following the SHOWO (sequential hydrolysis oxidation Wittig olefination) protocol. (Supporting Information)

1.2 equivalents of H_5IO_6 (4.20 g, 18.44 mmol) and 30 ml anhydrous ethyl acetate are placed in a dry flask equipped with a magnetic bar and under an argon atmosphere. Then a solution of 1:2.5:6-di-*O*-isopropylidene-*α*-*D*-glucose (4g, 15.39 mmol) in 30 mL of anhydrous ethyl acetate is added. It is kept under stirring for 2 hours, the reaction is monitored by TLC, once the reaction is finished it is filtered and concentrated under reduced pressure obtaining

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aldehyde **A** which is used without prior purification in the following reaction.

In a flask contained aldehyde **A**, it was dissolved with 100 ml of a system composed of EtOH: H_2O (3:7), then 4.147 g (18.44 mmol, 1.2 eq) of $Br^-[PPh_3CH_2CO_2CH_3]^+$ (previously prepared with PPh_3 and $BrCH_2CO_2CH_3$) were added; left stirring for solvation. Once the salt had dissolved, KOH flakes were added until pH≈14 was reached and stirred 3 h. Then we made an extraction with CH_2Cl_2 (40 ml x3), in order to be able to remove the triphenylphosphine oxide (Ph_3PO) formed, the aqueous phase was again subjected to stirring; an HCl solution was added until pH≈3 was reached, stirring was continued for approximately 10 more minutes; at the end of the time it was extracted with AcOEt (40 ml x 4). The organic phase was dried over anhydrous Na_2SO_4, filtrated and concentrated under reduced pressure obtaining 3.04 g of acid **A1**, with a yield of 86%.

(*Z*)-3-(6-hydroxy-2,2-dimethyl-dihydro-5*H*-furo[3,2-*d*] [1,3] dioxol-5-yl) acrylic acid.

*Analytical data of **A1**:*

White solid with m.p. = 152-154°C

IR(cm^{-1}) 3445.6, 2988.4, 1703.9, 1651.1, 1427.9

^{1}H NMR ($CHCl_3$, 300 MHz) δ ppm 1.37 (s, 3H), 1.54 (s, 3H), 4.65 (dd, 1H, *J*=3 Hz, *J*=5.7 Hz), 4.84 (d, 2H, *J*=3.3Hz), 6.03 (d, 1H, *J*=3.3 Hz), 6.25 (d, 1H, *J*=9.6Hz), 6.99 (dd, 1H, *J*=5.4 Hz, *J*=9.6 Hz).

^{13}C NMR ($CHCl_3$, 75 MHz) δ ppm 160.66, 138.55, 125.03, 112.25, 105.00, 83.61, 82.16, 67.31, 35.89, 26.46

In a flask containing 3.04g of acid **A1**, 3 g (14.54 mmol, 1.1 eq) of DCC were added, dissolved with anhydrous CH_2Cl_2, stirred for 4 h under an inert atmosphere. The reaction has a milky appearance ranging from whitish to very faint yellow. At the end of the reaction time, it was filtered over a silica bed to eliminate the urea derivative generated by the DCC, it was concentrated in rotavapor at atmospheric pressure and it was purified by column chromatography packed with silica (stationary phase), in a system 4:1 Hexane: AcOEt (as mobile phase), yielding 2.41 g with an 86% yield.

*Analytical data of **7,3-LXF**:*

Viscous colorless liquid, $[\alpha]_D^{25}$ = +15.0 ° (1.0, $CHCl_3$).

^{1}H NMR ($CDCl_3$/TMS, 400 MHz) δ: 1.35 (3H, s), 1.54 (3H, s), 4.63 (1H, dd, *J* = 6.4, 3.6 Hz), 4.38 (2H, m), 6.02 (1H, d, *J* = 4.0 Hz), 6.25 (1H, d, *J* = 10 Hz), 6.97 (1H, dd, *J* = 10.0, 6.0 Hz).

^{13}C NMR (100 MHz, $CDCl_3$) δ 160.89, 138.69, 125.37, 112.56, 105.27, 83.87, 82.41, 67.57, 26.72, 26.17

(2*S*,3*R*)-2-((4*R*,5*R*)-5-acetoxy-2,2-dimethyl-1,3-dioxolan-4-yl)-6-oxo-3,6-dihydro-2H-pyran-3-yl acetate, 6.

A solution of 7,3-LXF (2.2 g, 10.37 mmol) in acetic anhydride (3.13 mL, 32.79 mmol) was cooled to -10 ° C, then acetic acid (0.59 mL, 10.32 mmol) was added followed by sulfuric acid as a catalyst (0.07 mL) and it was left under stirring for 1.5 hours, at the same temperature. After the reaction time was complete, the mixture was neutralized with $NaHCO_3$ solution and extracted with ethyl acetate (3x15 mL). The organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure.

The crude reaction was purified by column chromatography with 4: 1 hexane-AcOEt eluent system, to obtain 2.6 g of diacetylated **6** with 80% yield.

*Analytical data of **6**:*

Colorless syrup, $[\alpha]_D^{25}$ = -134.2 (1.0, $CHCl_3$)

HRMS-EI (m/z): $[M]^+$ calculated for $C_{14}H_{18}O_8$ 314.1002, found 314.0419

^{1}H NMR ($CDCl_3$, 500 MHz), δ: 6.95 (dd, *J*= 9.5, 5.5 Hz, 1H), 6.45 (d, *J*= 3 Hz, 1H), 6.24 (d, *J*= 10 Hz, 1H), 5.50 (dd, *J*= 5.5, 2.5 Hz, 1H), 4.75 (dd, *J*= 5.5, 3.0 Hz, 1H), 4.54 (dd, *J*= 5.5, 3.0 Hz, 1H), 2.12 (s, 3H), 2.10 (s, 3H), 1.50 (s, 3H), 1.46 (s, 3H) ppm.

^{13}C NMR ($CDCl_3$, 125 MHz) δ: 169.89, 161.49, 140.09, 125.02, 113.44, 95.89, 80.09, 76.32, 61.17, 26.65, 26.22, 21.16, 20.60 ppm.

(2S,3R)-2-((4S,5R)-5-allyl-2,2-dimethyl-1,3-dioxolan-4-yl)-6-oxo-3,6-dihydro-2H-pyran-3-yl acetate, 7.

Ally trimethyl silane (3.14 mL, 19.75 mmol) was added to a solution in stirring of **6** (1.0 g, 3.18 mmol) in dry CH_2Cl_2 (12 mL); the reaction was allowed to stir for 10 min and then was cooled to (-40 ° C). Then BF_3OEt_2 (1.4 mL, 14.8 mmol) was added dropwise. After 10 min, the reaction mixture was allowed to warm at room temperature and the stirring continued for 1.5 h. After that, the reaction was quenched with $NaHCO_3$ solution and extracted with CH_2Cl_2 (3 x 20 mL). The organic phase was dried over anhydrous Na_2SO_4, filtrated and concentrated under reduced pressure.

The crude reaction was purified by FCC with a 4:1 hexane-AcOEt eluting mixture to afford 0.8 g of **7** with 85% yield.

*Analytical data of **7**:*

Colorless oil, $[\alpha]_D^{20}$= -99.2 (1.0, $CHCl_3$)

HRMS-FAB (m/z): $[M+1]^+$ Calculated for $C_{15}H_{20}O_6$ 297.1338, found 297.1332

^{1}H NMR ($CDCl_3$, 500 MHz), δ: 6.85 (dd, *J*= 10.0, 5.0 Hz, 1H), 6.20 (dd, *J*= 9.5, 0.5 Hz, 1H), 5.84 (m, 1H), 5.53 (m, 1H), 5.13 (m, 1H), 4.24 (dt, *J*= 12.0, 6.0, 2.0 Hz, 1H), 3.96 (dd, *J*= 8.5, 3.5 Hz, 1H), 2.10 (s, 3H), 2.37 (m, 2H),1.40 (d, *J*= 7.5 Hz, 6H) ppm.

^{13}C NMR ($CDCl_3$, 125 MHz) δ: 170.18, 161.96, 140.11, 133.19, 124.67, 118.23, 109.84, 78.04, 75.92, 75.40, 62.43, 37.04, 27.28, 26.48, 20.73, ppm.

(4R,5R)-2,2-dimethyl-5-((S)-6-oxo-5,6-dihydro-2H-pyran-2-yl)-1,3-dioxolan-4-yl acetate, 8.

To a solution of diacetoxylated **6** (1g, 3.18 mmol) in THF (10 mL) was added powder zinc (3.66 g, 56 mmol) followed by the addition of a saturated NH_4Cl solution (5 mL), and the mixture was stirred for 1h. After that, was added water, and the product was extracted with AcOEt (3 x 20mL). The organic phase was dried with Na_2SO_4, filtrated and concentrated under reduced pressure. The crude product was purified by FCC with a system 4:1 hexane: AcOEt to afford 0.8 g of deacetoxylated compound with a 98% yield.

*Analytical data of **8**:*

Crystalline white solid, m. p. = 82-85°C; $[\alpha]_D^{20}$ = -13.3 (1.0, $CHCl_3$)

HRMS-FAB (m/z): $[M+1]^+$ calculated for $C_{12}H_{16}O_6$ 257.1020, found 257.1025;

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^{1}H NMR ($CDCl_3$, 500 MHz) δ: 6.29 (d, *J* = 2.7 Hz, 1H), 6.03 – 5.99 (m, 1H), 5.87 (dddd, *J* = 10.1, 3.7, 2.3, 1.6 Hz, 1H), 5.26 (dt, *J* = 6.3, 2.4 Hz, 1H), 4.31 (dd, *J*= 2.7, 2.0 Hz, 1H), 3.19 – 3.06 (m, 2H), 2.11 (s, 3H), 1.50 (s, 3H), 1.48 (s, 3H) ppm.

^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.55, 168.34, 124.48, 121.88, 113.73, 97.25, 83.85, 77.21, 30.38, 26.49, 26.29, 21.25 ppm.

(S)-6-((4S,5R)-5-allyl-2,2-dimethyl-1,3-dioxolan-4-yl)-3,6-dihydro-2H-pyran-2-one, 9.

To a solution of **7** (0.7 g, 2.36 mmol) in THF (10 mL) was added Zn powder (1.4 g, 22 mmol), followed by a saturated solution of NH_4Cl (10 mL), the reaction was stirred for 1 h. In the end, the solution was filtered to remove the solids, and extracted with AcOEt (3 x 5 mL). The organic phase was dried over anhydrous Na_2SO_4, filtrated and concentrated under reduced pressure.

The crude product was purified by FCC with a 4: 1 hexane-AcOEt eluting mixture to afford 0.51 g of **9** with a 90% yield.

*Analytical data of **9**:*

Colorless oil, $[\alpha]_D^{20}$ = -5.8 (0.3, $CHCl_3$)

HRMS-FAB (m/z): $[M+1]^+$ calculated for $C_{13}H_{19}O_4$ 239.1283, found 239.1289

^{1}H NMR ($CDCl_3$, 500 MHz), δ: 6.00 – 5.96 (m, 1H), 5.91 – 5.81 (m, 2H), 5.17 (ddd, J = 13.7, 11.4, 1.3 Hz, 2H), 4.96 – 4.93 (m, 1H), 4.33 (dt, J = 8.4, 6.1 Hz, 1H), 3.77 (dd, J = 8.4, 1.1 Hz, 1H), 3.21 – 3.05 (m, 2H), 2.50 – 2.37 (m, 2H), 1.41 (s, 3H), 1.37 (s, 3H) ppm.

^{13}C NMR ($CDCl_3$, 125 MHz) δ: 169.12, 133.16, 123.59, 123.02, 118.31, 109.46, 81.89, 76.56, 74.45, 36.96, 30.47, 27.51, 26.28 ppm.

(2S,3R)-2-((4S,5R)-2,2-dimethyl-5-propyl-1,3-dioxolan-4-yl)-6-oxotetrahydro-2H-pyran-3-yl acetate, 10.

The reaction was performed in a 25 mL hydrogenator equipped with a Teflon-coated magnetic stirrer bar, the reactor was charged with a solution of **7** (0.3 g, 0.1 mmol) in AcOEt (5 mL), was added $Pd(OH)_2$/C (8 mg, 20% / g), the reaction was stirred at 25°C for 12 hours under hydrogen pressure of 10 atm. At the end of the reaction, the mixture was filtered and concentrated under reduced pressure.

The residue was purified by FCC with a 7: 3 hexanes: AcOEt mixture to afford 0.25 g of hydrogenated compound **10** with an 83% yield.

*Analytical data of **10**:*

Crystalline white solid, m. p. = 63-65 °C, $[\alpha]_D^{20}$= +70.1 (0.1, $CHCl_3$)

^{1}H NMR ($CDCl_3$, 500 MHz) δ: 5.28 (dt, *J* = 7.9, 4.0 Hz, 1H), 4.34 (ddd, *J* = 3.3, 2.3, 0.9 Hz, 1H), 4.10 (td, *J* = 8.2, 3.4 Hz, 1H), 3.82 (dd, *J* = 8.5, 2.2 Hz, 1H), 2.76 (m, 1H), 2.62 (ddd, *J* = 18.3, 7.8, 6.9 Hz, 1H), 2.23 (m, 1H), 2.09(s, 3H), 2.07(m, 1H), 1.59 (m, 2H), 1.56 (m, 3H), 1.39 (d, *J* = 11.4 Hz, 6H), 0.95 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C NMR ($CDCl_3$, 125 MHz) δ: 170.04, 169.33, 109.76, 78.61, 76.48, 76.35, 65.84, 34.63, 27.58, 26.80, 26.40, 23.70, 21.03, 19.23, 14.09 ppm.

(S)-6-((4S,5R)-2,2-dimethyl-5-propyl-1,3-dioxolan-4-yl)-tetrahydro-2H-pyran-2-one, 11.

The reaction was performed in a 25 mL hydrogenator equipped with a Teflon-coated magnetic stirrer bar, the reactor was charged with a solution of **9** (0.4 g, 1.68 mmol) in AcOEt (5 mL), was added $Pd(OH)_2$/C (8 mg, 20% / g), the reaction was stirred at 25°C for 12 hours under hydrogen pressure of 10 atm. At the end of the reaction, the mixture was filtered and concentrated under reduced pressure.

The residue was purified by FCC with a 7: 3 hexanes: AcOEt mixture to afford 0.35 g of hydrogenated compound **11** with an 87% yield.

*Analytical data of **11**:*

Colorless oil, $[\alpha]_D^{20}$= +19.72 (0.1, $CHCl_3$)

HRMS-FAB (m/z): $[M+1]^+$ calculated for $C_{13}H_{23}O_4$ 243.1564, found 243.1596

^{1}H NMR ($CDCl_3$, 500 MHz) δ: 4.33 (ddd, J = 9.1, 4.5, 2.1 Hz, 1H), 4.20 (dd, J = 7.9, 3.9 Hz, 1H), 3.61 (dd, J = 8.3, 2.1 Hz, 1H), 2.61 (ddd, J = 17.8, 9.2, 3.4 Hz, 1H), 2.50 (ddd, J = 17.9, 8.9, 6.8 Hz, 1H), 2.08 – 2.01 (m, 1H), 1.95 – 1.76 (m, 3H), 1.58 – 1.50 (m, 3H), 1.44 (d, J = 7,5 Hz, 1H), 1.41 (s, 3H), 1.39 (s, 3H), 0.95 (t, J = 4.8 Hz, 3H) ppm.

^{13}C NMR ($CDCl_3$, 125 MHz) δ: 170.98, 109.15, 82.46, 77.17, 75.76, 35.06, 29.97, 27.56, 26.53, 25.30, 19.31, 18.50, 14.16 ppm.

(6S)-6-((4S,5R)-2,2-dimethyl-5-propyl-1,3-dioxolan-4-yl)-3-(phenylselanyl) tetrahydro-2H-pyran-2-one

A solution of LDA was prepared with n-BuLi (1.0 mmol) and DIPA (1.2 mmol) in anhydrous THF (3 mL) at 0°C, the mixture reaction was cooled to -78 ° C for 30 min, and then a solution of hydrogenated compound **11** (0.1 g, 0.41 mmol) in THF (3 ml) was added. After 30 min of stirring, PhSeBr (0.2 g, 0.85 mmol) dissolved in anhydrous THF (1 mL) was added. The reaction mixture was allowed to stir for 4 hours at -78 ° C, once the reaction was finished, it was neutralized with an NH_4Cl saturated solution and extracted with AcOEt (3 x 5 mL). The organic phase was dried over anhydrous Na_2SO_4, filtrated and concentrated under reduced pressure.

The crude product was purified by FCC with 100% hexane eluent (10 mL), followed by a mixture of 95:5 of hexanes: AcOEt (10 mL) to afford 0.119 g of the compound with 72.57 % yield.

Analytical data of phenylselenated compound:

Yellow syrup

HRMS-FAB (m/z): [M]+ Calculated for $C_{19}H_{26}O_4Se_1$ 398.0996, found 398.0984

^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.68 – 7.64 (m, 2H), 7.40 – 7.30 (m, 3H), 4.37 (ddd, J = 8.3, 4.3, 1.8 Hz, 1H), 4.17 (td, J = 8.1, 4.2 Hz, 1H), 4.00 (t, J = 6.6 Hz, 1H), 3.55 (dd, J = 8.4, 1.9 Hz, 1H), 2.52 – 2.45 (m, 2H), 2.06 – 1.96 (m, 1H), 1.90 – 1.82 (m, 1H), 1.57 – 1.48 (m, 3H), 1.44 – 1.40 (m, 1H), 1.39 (s, 3H), 1.36 (s, 3H), 0.95 (t, J = 7.0 Hz, 3H) ppm.

^{13}C NMR ($CDCl_3$, 125 MHz) δ: 169.97, 135.88, 129.32, 128.94, 127.73, 109.30, 82.74, 76.31, 75.82, 38.79, 34.90, 27.59, 26.49, 26.29, 24.77, 19.30, 14.17 ppm.

(S)-6-((4S,5R)-2,2-dimethyl-5-propyl-1,3-dioxolan-4-yl)-5,6-dihydro-2H-pyran-2-one, 12.

To a solution of the previously prepared phenylselenated compound (0.096 g, 0.24 mmol) in 10 mL of CH_2Cl_2 at 0 °C, was added H_2O_2 (0.5 mL, 50%) dropwise. After stirring for 20 min, the solution became colorless, the reaction was quenched with water and was extracted with

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AcOEt (3x5 mL). The organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure.

The crude product was purified by FCC with a 4: 1 hexane-AcOEt to obtain 0.058 g of lactone α,β- unsaturated in quantitative yield.

*Analytical data of **12**:*

Colorless syrup, $[\alpha]_D^{20}$= +19.72 (0.1, $CHCl_3$)

HRMS-FAB (m/z): $[M+1]^+$ Calculated for $C_{13}H_{21}O_4$ 241.1440, found 241.1458

^{1}H NMR ($CDCl_3$, 500 MHz) δ: 6.93 (ddd, J = 9.8, 6.1, 2.4 Hz, 1H), 6.04 (ddd, J = 9.8, 2.8, 1.0 Hz, 1H), 4.46 (ddd, J = 12.0, 4.0, 2.6 Hz, 1H), 4.27 – 4.23 (m, 1H), 3.70 (dd, J = 8.2, 2.5 Hz, 1H), 2.71 (ddt, J = 18.4, 12.0, 2.6 Hz, 1H), 2.35 (dddd, J = 18.5, 6.0, 4.1, 1.0 Hz, 1H), 1.60 – 1.52 (m, 3H), 1.46 – 1.40 (m, 7H), 0.96 (t, J = 7.1 Hz, 4H) ppm.

^{13}C NMR ($CDCl_3$, 125 MHz) δ: 163.71, 145.02, 121.28, 109.24, 81.36, 75.48, 75.06, 35.19, 27.50, 26.60, 26.49, 19.30, 14.15 ppm.

(S)-6-((1S,2R)-1,2-dihydroxypentyl)-5,6-dihydro-2H-pyran-2-one, 13.

In a flask was weighted the α,β-unsaturated lactone **12** (0.02 g, 0.08 mmol) and was cooled at -10°C, then was added an acid mixture of H_2O: AcOH: H_2SO_4 (38:46:16 % v/v/v), and stirred for 30 min to -10°C. After that, the reaction mixture was neutralized with a $NaHCO_3$ solution and extracted with AcOEt (3x5mL). The organic phase was dried with Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by FCC with Hexanes: AcOEt (1:1, 5 mL) followed by hexanes: AcOEt (3:7, 10mL), to obtain the truncated Tetradenolide 0.013g with 76% of yield.

*Analytical data of **13**:*

Colorless syrup, $[\alpha]_D^{20}$= -50.9 (0.08, $CHCl_3$)

HRMS-FAB (m/z): $[M]^+$ Calculated for $C_{10}H_{15}O_4$ 199.097, found 199.0977

^{1}H NMR ($CDCl_3$, 500 MHz) δ: 6.96 (ddd, J = 9.7, 6.4, 2.1 Hz, 1H), 6.03 (ddd, J = 9.8, 2.9, 0.9 Hz, 1H), 4.58 (dt, J = 12.6, 4.1 Hz, 1H), 3.80 (d, J = 4.2 Hz, 1H), 3.52 (t, J = 6.4 Hz, 1H), 3.02 (d, J = 5.7 Hz, 1H), 2.74 – 2.67 (m, 1H), 2.53 (d, J = 8.0 Hz, 1H), 2.37 (dddd, J = 18.5, 6.4, 3.8, 0.9 Hz, 1H), 1.80 – 1.34 (m, 4H), 0.95 (t, J = 7.2 Hz, 3H) ppm.

^{13}C NMR ($CDCl_3$, 125 MHz) δ: 163.61, 145.83, 120.75, 80.04, 74.01, 70.95, 35.99, 25.76, 18.83, 13.99 ppm.

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[11] X-ray structure for **8**, $C_{12}H_{16}O_6$: *a* = 6.7295(5), *b* = 9.4123(8), *c* = 20.942(2) Å, *V* = 1326.5(2) Å^3, space group $P2_12_12_1$, 35626 reflections collected at *T* = 295 K (Stoe Stadivari diffractometer, Ag *K*α radiation), 2886 independent reflections (R_{int} = 5.77%) for 166 refined parameters. R_1 = 3.56% (obs. data), wR_2 = 8.81% (all data), *S* = 0.891. CCDC deposition reference: CCDC-1961831.

[12] X-ray structure for **10**, $C_{15}H_{24}O_6$: *a* = 5.5171(3), *b* = 10.1365(5), *c* = 29.066(2) Å, *V* = 1625.49(17) Å^3, space group $P2_12_12_1$, 24180 reflections collected at *T* = 295 K (Stoe Stadivari diffractometer, Ag *K*α radiation), 3063 independent reflections (R_{int} = 8.88%) for 194 refined parameters. R_1 = 4.08% (obs. data), wR_2 = 10.21% (all data), *S* = 0.828. CCDC deposition reference: CCDC-1961830.

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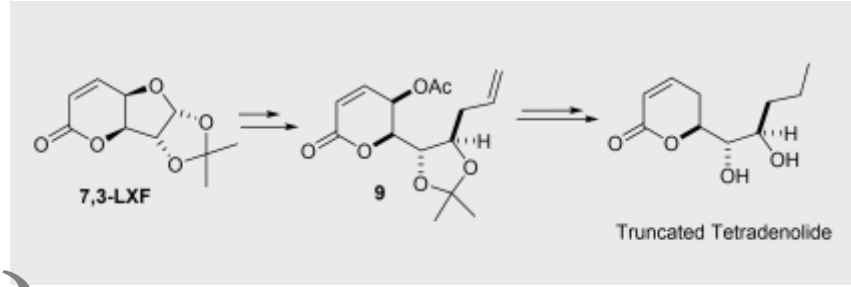

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Synthesis of a Truncated Tetradenolide

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