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A NEW SHORT SYNTHESIS OF (±)-OLEAN THROUGH CROSS METATHESIS

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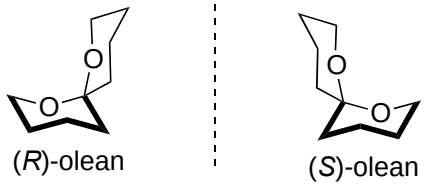
Abstract – A new synthesis of (±)-1,7-dioxaspiro[5.5]undecane (olean), the olive fruit fly pheromone, utilizing the cross-metathesis reaction as the key-step, is reported.

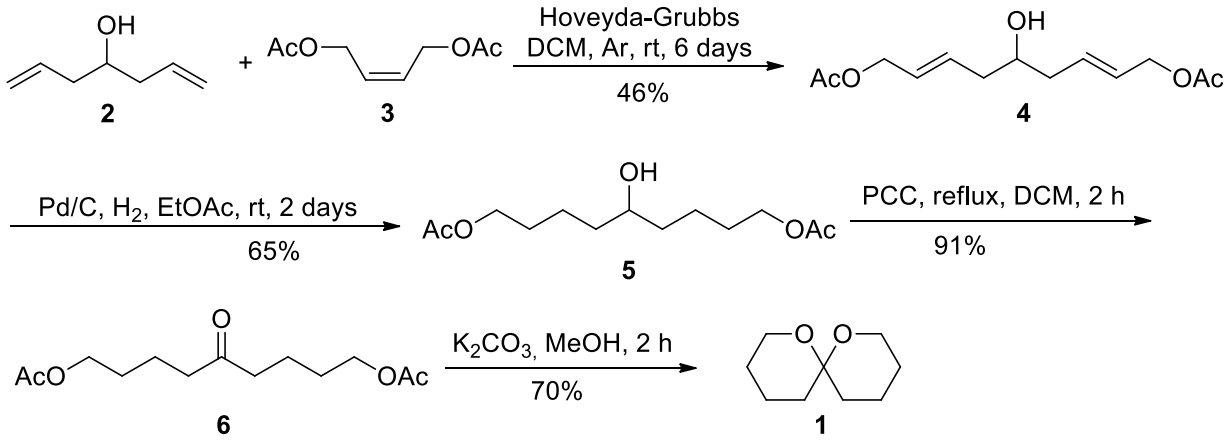
The two enantiomeric spiroacetal structures of (*R*)- and (*S*)-1,7-dioxaspiro[5.5]undecane (olean) are the main components of the male and female fruit fly (*Dacus oleae*) pheromone of olive tree (*Bactrocera oleae*), respectively. Given the great economic, nutritional and social importance of olive oil for the Mediterranean countries, and the need to combat the main pest in its production by effective and ecological methods, it is important to develop advanced technology in order to trap and control insects with the use of pheromones, as well as to develop new, economical and short methods of synthesis of olean.



From its isolation and structure assignment,[1] a considerable number of olean syntheses have been reported in literature,[2] including asymmetric syntheses,[3] a fact that highlights the wider interest for this molecule. Living in a country whose culture since ancient times is connected to the olive tree, and because the production of olive oil is a key element of its modern agricultural economy, we are participating in a program aimed at developing new ecological technology to combat the olive fruit fly, involving *inter alia* the development of new efficient methods of olean synthesis.

To this end, we considered the cross-metathesis as a useful reaction in order to construct the carbon skeleton of olean (**1**), properly functionalized from simpler commercial materials. Thus, a cross-metathesis of commercial hepta-1,6-dien-4-ol (**2**) with an 8-fold excess of the also commercial (*Z*)-but-2-ene-1,4-diyl

diacetate (**3**) was attempted, using the Grubbs II or Hoveyda-Grubbs catalysts. The second catalyst (*ca.* 1.5 mol%) was found to be more effective and the cross-metathesis product (**4**) was isolated in 46% yield, separated chromatographically from excess of reactants and side-products.



Scheme 1

Having prepared the carbon skeleton of olean, the following steps required conventional functional group transformations. Firstly, catalytic hydrogenation over Pd/C of **4** gave the desired saturated compound **5** in 65% yield, whereas the use of Raney Ni as a catalyst led to the formation mainly of allylic rearrangement/ elimination products. Oxidation of secondary alcohol in **5** proceeded efficiently and ketone **6** was obtained in high yield. Finally, deprotection of the primary hydroxyl groups by methanolysis liberated the respective dihydroxy ketone, which spontaneously acetalyzed intramolecularly to give olean (**1**) in 70% yield.

In conclusion, we have developed a new synthesis of olean (**1**) with 19% overall yield in four steps from commercial starting materials, utilizing the cross-metathesis reaction as the key-step. As the experimental methods reported here are operationally simple and no special care is needed, and since the expensive catalyst is used in very low catalyst/substrates ratio, this synthesis could be an interesting addition to the body of olean syntheses.

EXPERIMENTAL

All reagents are commercially available and were used without further purification. Solvents were dried by standard methods. The progress of reactions was checked by thin layer chromatography (TLC) on Merck silica gel 60F254 glass plates (0.25 mm). The spots were visualised by heat staining with anisaldehyde in $EtOH/H_2SO_4$. Column chromatography was performed with Merck silica gel 60 (0.063-0.200 mm). ^1H and ^{13}C NMR spectra were recorded at 300 or 500 MHz and 75 or 126 MHz, respectively. ^1H NMR chemical shifts (δ) are reported in ppm relative to tetramethylsilane (δ = 0.0 ppm), using the residual solvent signal as

an internal standard (δ = 7.26, singlet, for $CDCl_3$), or using tetramethylsilane itself. The proton resonances are annotated as: chemical shift, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br., broad), coupling constant (J [Hz]), and integration. ^{13}C NMR chemical shifts are reported in ppm, and spectra were calibrated using the central line of the triplet at δ = 77.0 ppm for $CDCl_3$. High-resolution mass spectra (HRMS) were obtained using the electrospray technique, positive mode.

(2*E*,7*E*)-5-Hydroxynona-2,7-diene-1,9-diyl diacetate (4). To a solution of hepta-1,6-dien-4-ol (**2**) (0.88 g, 7.84 mmol) and (*Z*)-but-2-ene-1,4-diyl diacetate (**3**) (10.8 g, 62.72 mmol) in dry DCM (75 mL), Hoveyda-Grubbs catalyst (73 mg, 1.5 mol%) was added and the mixture was stirred at ambient temperature under argon atmosphere for 6 days. Solids were then removed by filtration and the solvent was evaporated off under reduce pressure. The residue was chromatographed on a silica gel column (EtOAc/hexane 1:10) to give firstly the excess of reactants and undesired side-products, followed by (2*E*,7*E*)-5-hydroxynona-2,7-diene-1,9-diyl diacetate (**4**) (0.95 g, 46%) as a colorless oil. ^1H NMR δ 2.06 (s, 6H), 2.16-2.25 (m, 2H), 2.25-2.34 (m, 2H), 3.73 (tt, J = 7.4, 4.7 Hz, 1H), 4.54 (d, J = 6.1 Hz, 4H), 5.68 (dt, J = 15.0, 6.1 Hz, 2H), 5.78 (dt, J = 15.0, 7.3 Hz, 2H); ^{13}C NMR δ 20.77, 39.77, 64.75, 70.16, 127.21, 131.20, 170.67; HRMS (ESI) Calcd for $C_{13}H_{21}O_5$ $[M+H]^+$ 257.1389. Found 257.1385.

5-Hydroxynonane-1,9-diyl diacetate (5). To a degassed solution of (2*E*,7*E*)-5-hydroxynona-2,7-diene-1,9-diyl diacetate (**4**) (0.92 g, 3.59 mmol) in EtOAc (75 mL) was added Pd/C 5% (55 mg) and the resulting mixture was stirred at ambient temperature under hydrogen atmosphere for 2 days. Solids were then removed by filtration and the solvent was evaporated off under reduce pressure. The residue was chromatographed on a silica gel column (EtOAc/hexane 1:6) to give 5-hydroxynonane-1,9-diyl diacetate (**5**) (0.61 g, 65%) as a colorless oil. ^1H NMR δ 1.36-1.52 (m, 8H), 1.60-1.68 (m, 4H), 2.05 (s, 6H), 3.61 (m, 1H), 4.07 (t, J = 6.6 Hz, 2H) ^{13}C NMR δ 20.99, 22.07, 28.62, 37.03, 64.36, 71.55, 171.38; HRMS (ESI) Calcd for $C_{13}H_{25}O_5$ $[M+H]^+$ 261.1702. Found 261.1699.

5-Oxononane-1,9-diyl diacetate (6). A solution of 5-hydroxynonane-1,9-diyl diacetate (**5**) (0.57 g, 2.19 mmol) and PCC (0.95 g, 4.36 mmol) in dry DCM (15 mL) was refluxed for 2 h. Solvent was then evaporated off and the residue was chromatographed on a silica gel column (EtOAc/hexane 1:8) to give 5-oxononane-1,9-diyl diacetate (**6**) (0.52 g, 91%) as a colorless oil. ^1H NMR δ 1.63 (m, 8H), 2.04 (s, 6H), 2.43 (t, J = 6.8 Hz, 2H), 4.06 (t, J = 6.1 Hz, 2H); ^{13}C NMR δ 20.12, 28.09, 30.85, 42.07, 63.97, 170.93, 206.62; HRMS (ESI) Calcd for $C_{13}H_{23}O_5$ $[M+H]^+$ 259.1545. Found 259.11542.

1,7-Dioxaspiro[5.5]undecane (olean, 1). To a solution of 5-oxononane-1,9-diyl diacetate (**6**) (0.46 g, 1.79 mmol) in MeOH (20 mL), solid K_2CO_3 (1.48 g, 10.74 mmol) was added and the resulting mixture was refluxed for 2 h. Saturated aq. NH_4Cl (20 mL) and water (20 mL) were then added and the mixture was extracted with EtOAc (12x20 mL). The combined organic layers were dried over $MgSO_4$, solvent was evaporated off and the residue was chromatographed on a silica gel column (EtOAc/hexane 1:7) to give

1,7-dioxaspiro[5.5]undecane (**1**) (0.22 g, 70%) as a colorless liquid with spectra identical to those reported in the literature.[2a] ^{1}H NMR δ 1.43-1.63 (m, 10H), 1.82 (m, 2H), 3.61 (m, 2H), 3.70 (m, 2H); ^{13}C NMR δ 18.51, 25.29, 35.72, 60.18, 94.95.

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