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Natural (5′-oxoheptene-1′*E*,3′*E*-dienyl)-5,6-dihydro-2*H*-pyran-2-one: total synthesis and revision of its absolute configuration

Samir Bouzbouz,[a,*] Elsa de Lemos,[a] Janine Cossy,[a,*] Jairo Saez,[b] Xavier Franck[c] and Bruno Figadère[c,*]

[a]*Laboratoire de Chimie Organique associé au CNRS, ESPCI, 10 rue Vauquelin, 75231 Paris, Cedex 05, France*
[b]*Institute of Chemistry, Universidad de Antioquia, PO Box 1226, Medellin, Colombia*
[c]*Laboratoire de Pharmacognosie associé au CNRS (BioCIS), Université Paris-Sud, Faculté de Pharmacie, rue J-B. Clément, 92296 Châtenay-Malabry, France*

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Abstract—The synthesis of (5′-oxoheptene-1′*E*,3′*E*-dienyl)-5,6-dihydro-2*H*-pyran-2-one has been performed in seven steps using four key steps: a ring-closing metathesis reaction to build up the unsaturated lactone, a Wittig reaction to control the C6–C7 (*E*) double bond, a cross-metathesis reaction to control the (*E*) double bond at C8–C9, and an enantioselective allyltitanation to control the absolute configuration at C5. Spectroscopic data (IR, MS, ^{1}H, and ^{13}C NMR) were identical to those of the natural compound except for the optical rotation, which led us to re-assign the absolute configuration of the natural product.

Recently Saez and co-workers reported the isolation of a new 6-substituted 5,6-dihydro-α-pyranone from *Raimondia cf monoica* (Annonaceae), possessing leishmanicide activity, namely (*S*)-(5′-oxoheptene-1′*E*,3′*E*-dienyl)-5,6-dihydro-2*H*-pyran-2-one **A**.[1] In the same study a known compound was also isolated: the (*R*)-(5′-oxoheptene-1′*Z*,3′*E*-dienyl)-5,6-dihydro-2*H*-pyran-2-one **B** whose absolute configuration was determined to be (*R*) by analysis of its CD spectrum.[2]

Since compound **A** had the opposite sign for both its specific rotation ($[\alpha]_D$ +60.8°, *c* 9.2, EtOH)[1] and Cotton effect (λ_{max} 260 nm, $\Delta\varepsilon = +5.24$)[1] relative to those of **B** ($[\alpha]_D$ −48°, *c* 0.125, EtOH and Cotton effect: λ_{max} 260 nm, $\Delta\varepsilon = -4.7$),[1] the (*S*) absolute configuration was proposed for the natural compound **A** (Fig. 1).[1]

Previously, the C5 substituted unsaturated lactones present in fostriecin,[3] passifloricin,[4] and strictifolione[5] were synthesized by using enantioselective allyltitanium complexes to control the absolute configuration at C5. As a similar C5-substituted unsaturated lactone is present in compound **A**, we decided to synthesize this compound, based on the use of the highly enantioselective allyltitanium complex (*R,R*)-**I**[6] (Scheme 1), which produces homoallylic alcohols with the (*S*) configuration, to verify the absolute configuration in compound **A** at C5. The control of the (*Z*) double bond at C2–C3 would be achieved by using a ring-closing metathesis reaction (RCM), whereas the (*E*) double bond at C8–C9 would be controlled by using a cross-metathesis reaction (CM)[7] between acrolein and pent-1-en-3-ol **1**. The (*E*) double bond at C6–C7 would be controlled by applying a Wittig reaction to aldehyde **2** (Scheme 1).

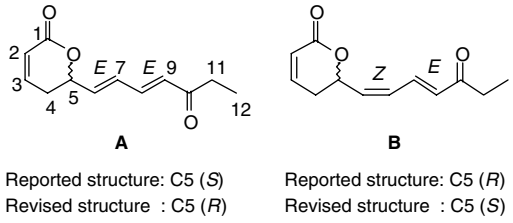

Figure 1.

Treatment of pent-1-en-3-ol **1** with 3 equiv of acrolein in the presence of Hoveyda's catalyst (3 mol%) at 25 °C in CH_2Cl_2 led to aldehyde **2** in 80% yield, and with an *E*/*Z* ratio superior to 30:1 (Scheme 2). To control the (*E*) double bond at C6–C7, aldehyde **2**[8] was treated with the

* Corresponding authors. Tel.: +33-01-46-83-55-92; fax: +33-01-46-83-53-99; e-mail addresses: samir.bouzbouz@espci.fr (S.B.); janine.cossy@espci.fr (J.C.); bruno.figadere@cep.u-psud.fr (B.F.)

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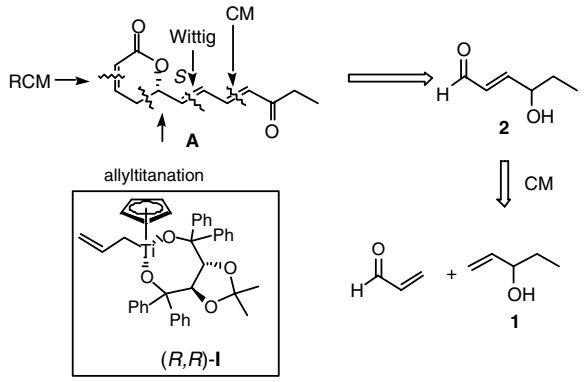
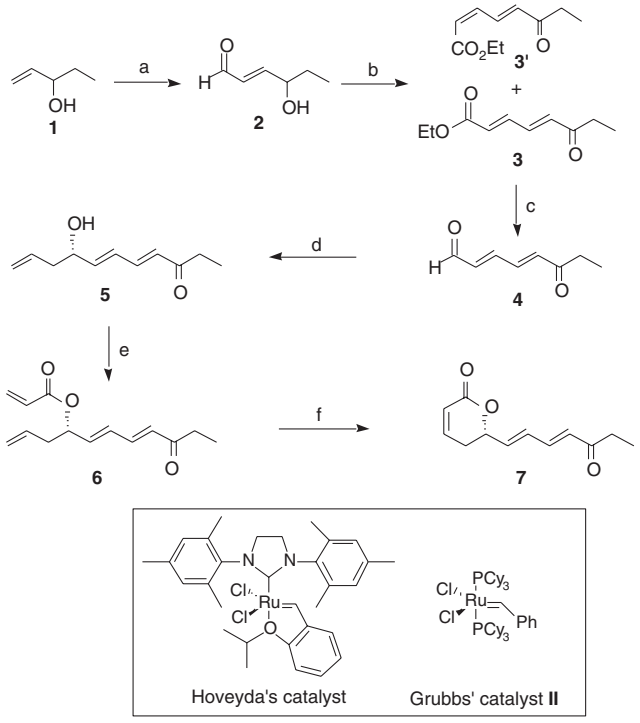


Scheme 1.



Scheme 2. Reagents and conditions: (a) acrolein, Hoveyda's catalyst (3 mol%), CH_2Cl_2, 25 °C, 80%; (b) Ph_3PCHCO_2Et, toluene, 110 °C; (c) (i) Dibal-H, CH_2Cl_2, −78 °C; (ii) MnO_2, CH_2Cl_2, rt, 15% from **2**; (d) (*R,R*)-**I**, ether, −78 °C, 4 h, 50%; (e) acryloyl chloride, *i*-Pr_2NEt, CH_2Cl_2, −78 °C, 96%; (f) Grubbs' catalyst **II**, (5 mol%), refluxing CH_2Cl_2, 12 h, 23%.

stabilized ylide ethyl (triphenylphosphoranylidene)acetate, in toluene at 110 °C. Under these conditions, the reaction was not stereoselective and the dienes **3** (*E*/*E*) and **3′** (*Z*/*E*) were obtained in a 4 to 1 ratio. These two dienes were separated by flash chromatography on silica gel. Aldehyde **4**, which will allow the control of the C5 stereogenic center present in **A**, was prepared in two steps from **3**. After reduction of **3** by Dibal-H (CH_2Cl_2, −78 °C), the resulting diol was directly oxidized by MnO_2 (CH_2Cl_2, 25 °C), and the (*E*)-aldehyde **4** was isolated in an overall yield of 15% from **2**. Aldehyde **4** was then transformed into the desired (*S*) homoallylic alcohol **5**[9] in 50% yield by using the chemoselective and enantioselective allyltitanium complex (*R,R*)-**I** (ether, −78 °C). Treatment of allylic alcohol **5** with acryloyl chloride (*i*-Pr_2NEt, CH_2Cl_2 −78 °C), produced the corresponding ester **6** in 96% yield, which after a ring-closing metathesis reaction, induced by Grubbs' catalyst **II**[10] (CH_2Cl_2, reflux 12 h), furnished lactone **7** in 23% yield. The spectroscopic data of **7** were identical to those of the natural product **A** except for the specific rotation ($[\alpha]_D$ − 32° *c* 0.10, EtOH), which has the opposite sign of the specific rotation reported for the extracted natural compound **A**. We were thus forced to re-examine the assignment of the absolute configuration of the natural lactone **A**.

Re-examination of Snatzke's rules,[11] modified by Beecham,[12] led us to re-attribute the (*R*) absolute configuration at C5 for the natural compound **A**. In fact, unsaturated six-membered lactones substituted at C5, which show a positive Cotton effect in their CD spectrum, (due to the carbonyl n–π^* transition) have (*R*) absolute configurations.[11–13] The chromophoric enone side chain (weak n–π^* at λ_{max} around 310–330 nm) can adopt different conformations but the energy difference between these conformations is small and their contributions to the Cotton effect are substantially compensated.[11]

In conclusion, the synthesis of (*S*)-(5′-oxoheptene-1′*E*,3′*E*-dienyl)-5,6-dihydro-2*H*-pyran-2-one **7** was accomplished in seven steps and with good enantiomeric excess, from pent-1-en-3-ol. We also conclude that the natural compound **A** has the (*R*) absolute configuration at C5, implying that the natural compound **B** has the (*S*) absolute configuration at C5.

Acknowledgements

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References and notes

1. Carmona, D.; Saez, J.; Granados, H.; Perez, E.; Angulo, A.; Blair, S.; Figadère, B. *Nat. Prod. Res.* **2003**, *17*, 275.
2. Matsuda, M.; Endo, Y.; Fushiya, S.; Endo, T.; Nozoe, S. *Heterocycles* **1994**, *38*, 1229.
3. Cossy, J.; Pradaux, F.; BouzBouz, S. *Org. Lett.* **2001**, *3*, 2233.
4. BouzBouz, S.; Cossy, J. *Tetrahedron Lett.* **2003**, *44*, 4471.
5. BouzBouz, S.; Cossy, J. *Org. Lett.* **2003**, *5*, 1995; *Additions Corrections Org. Lett*. **2003**, *5*, 3365.
6. Hafner, A.; Duthaler, R. O.; Marti, R.; Rihs, J.; Rothe-Streit, P.; Schwarzenbach, F. *J. Am. Chem. Soc.* **1992**, *114*, 2321.
7. Cossy, J.; Bouzbouz, S.; Hoveyda, A. H. *J. Organomet. Chem.* **2001**, *624*, 327.
8. Spectroscopic data for compound **2**:
^1H NMR ($CDCl_3$,) δ: 9.38 (d, $J = 8.1$ Hz, 1H); 6.60 (dd, $J = 15.8$ and 4.4 Hz, 1H); 6.02 (ddd, $J = 16.2$, 8.1, and 1.5 Hz, 1H); 4.06 (q apparent, $J = 5.5$ Hz, 1H); 3.46 (s large, OH); 1.46–1.21 (m, 2H); 0.73 (t, $J = 7.4$ Hz, 3H) ^{13}C

NMR ($CDCl_3$, 75 MHz) δ: 194.2 (d); 160.1 (d); 130.3 (d); 71.7 (d); 29.0 (t); 9.3 (q).
MS (IE) *m/z* (70 eV): 114 (M+,0.01); 85 (80); 57 (100).

9. Spectroscopic data for compound **5**:
$[\alpha]_D^{20} - 11°$ (*c*, 0.21, $CHCl_3$).
IR (neat): 3400, 1650; 1600, 1205, 1000 cm^{-1}.
^1H NMR ($CDCl_3$,) δ: 7.08 (dd, $J = 15.4$ and 10.3 Hz, 1H); 6.30 (dd, $J = 14.7$ and 10.7 Hz, 1H); 6.10 (m, 2H); 5.70 (ddd, $J = 17.6$, 13.6, and 2.6 Hz, 1H); 5.08 (m, 2H); 4.25 (m, 1H+OH); 2.55 (q, $J = 7.4$ Hz, 2H); 2.30 (m, 2H); 1.05 (t, $J = 7.3$ Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 201.2 (s); 144.8 (d); 141.4 (d); 133.4 (d); 129.3 (d); 127.8 (d); 118.6 (t); 70.5 (d); 41.4 (t); 33.5 (t); 8.0 (q).
MS (IE) *m/z* (70 eV): 180 ($M^{+\cdot}$, 0.2); 139 ($M-C_3H_5$, 89); 81 (22); 57 (100).
10. Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413.
11. Snatzke, G. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 14.
12. Beecham, A. F. *Tetrahedron* **1972**, *28*, 5543.
13. (a) Davis-Coleman, M. T.; Rivett, D. E. A. In *Progresss in the Chemistry of Organic Natural Products*; Herz, W., Grisebach, H., Kirby, G. W., Tamm, Ch., Eds.; Spinger: New York, 1989; Vol. 55, pp 1–55; (b) Pereda-Miranda, R.; Fragoso-Serrano, M.; Cerda-Garcia-Rojas, C. *Tetrahedron* **2001**, *57*, 47; (c) Juliawaty, L. D.; Kitajima, M.; Takayama, H.; Achmad, S. A.; Aimi, N. *Phytochemistry* **2000**, *54*, 989.