

Short Note

## **(E)-2-((4R,5R)-5-((Benzyloxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)but-2-ene-1,4-diol**

**Carlos R. Carreras**<sup>1</sup>, **Celina E. García**<sup>2</sup>, **Víctor S. Martín**<sup>2</sup>, **Carlos E. Tonn**<sup>1</sup>, **David Díaz Díaz**<sup>3,4,\*</sup> and **Juan Pedro Ceñal**<sup>1,\*</sup>

<sup>1</sup> INTEQUI-CONICET-Facultad de Química, Bioquímica y Farmacia, Universidad Nacional de San Luis, Chacabuco y Pedernera, 5700 San Luis, Argentina

<sup>2</sup> Instituto Universitario de Bio-Organica “Antonio González”, Universidad de La Laguna, Avda. Astrofísico Francisco Sánchez, 2, 38206 La Laguna, Tenerife, Spain

<sup>3</sup> Institut für Organische Chemie, Universität Regensburg, Universitätsstr. 31, 93040 Regensburg, Germany

<sup>4</sup> ICMA, CSIC-Universidad de Zaragoza, Pedro Cerbuna 12, 50009 Zaragoza, Spain

\* Authors to whom correspondence should be addressed; E-Mails: jcenal@unsl.edu.ar (J.P.C.); David.Diaz@chemie.uni-regensburg.de (D.D.D.).

Received: 11 March 2010 / Accepted: 14 April 2010 / Published: 19 April 2010

---

**Abstract:** The synthesis of (E)-2-((4R,5R)-5-((benzyloxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)but-2-ene-1,4-diol by a one-step reduction of the appropriate 2-substituted butenolide is reported. Product characterization was carried out by IR, <sup>1</sup>H NMR, <sup>13</sup>C NMR, MS, elemental analysis and optical rotation.

**Keywords:** reduction; DIBAL-H; substituted butenolides; allylic diols

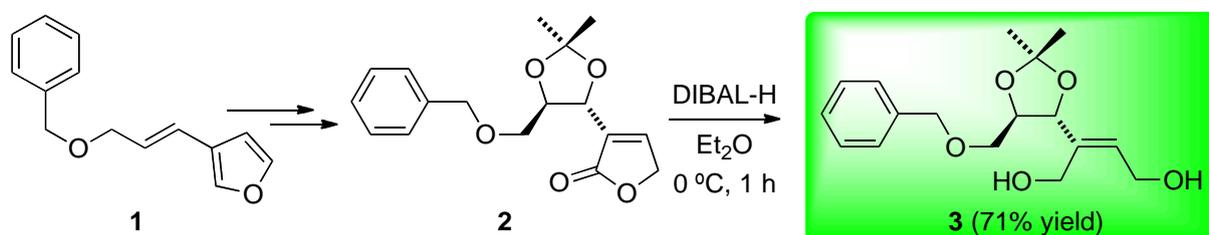
---

2-Alkylbut-2-ene-1,4-diols are present in a number of natural products and constitute highly versatile synthetic precursors [1–7]. For instance, biologically active 2-substituted 1,4-diacetoxybutadienes [8–10], acyclic sesquiterpenoids and acyclic diterpenoids [11–16] can be easily synthesized from the above building blocks. From a synthetic point of view, 2-alkylbut-2-ene-1,4-diols are typically prepared, among different methods [17,18], by hydrostannation [9] or addition of Grignard reagents to but-2-ynediols [19].

Herein, we report the facile synthesis of (E)-2-((4R,5R)-5-((benzyloxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)but-2-ene-1,4-diol (**3**) by treatment of the corresponding 2-substituted butenolide **2** at

0 °C under reductive conditions, employing DIBAL-H as reducing agent (Scheme 1). Chiral precursor **2** was prepared by acid-mediated regioselective oxidation of the appropriate 3-substituted furan **1** as previously described in the literature [20]. All stereochemical assignments were further confirmed by differential nOe experiments (see Supplementary Files). Compound **3** represents a practical polyoxygenated chiral synthon in which each hydroxy group could be independently functionalized.

**Scheme 1.** Synthesis of 2-alkylbut-2-ene-1,4-diol **3**.



## Experimental

### General

<sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded at 25 °C on a Bruker Avance 500 spectrometer in CDCl<sub>3</sub> as solvent, and chemical shifts are reported relative to Me<sub>4</sub>Si ( $\delta = 0$ ). Low- and high-resolution mass spectra were obtained by using a Micromass VG Autospec spectrometer. Elemental analysis was performed on a Fisons Instrument EA 1108 CHNS-O analyzer. Infrared spectra were recorded on a Bruker IFS 55 spectrophotometer for compounds dispersed on a NaCl disc. Optical rotations were determined for solutions in chloroform with a Perkin Elmer 343 polarimeter using a sodium lamp (589 nm). Thin-layer chromatography was carried out on Merck aluminium sheets coated with silica gel 60 F<sub>254</sub>. Compounds were visualized by use of 254 nm UV light and/or phosphomolybdic acid 20 wt.% solution in ethanol with heating. All solvents were purified by standard techniques [21]. Flash chromatography was performed on Merck silica gel 60 (0.040–0.063 mm, 230–400 mesh ASTM). Anhydrous magnesium sulfate was used for drying solutions.

### Synthesis of (*E*)-2-((4*R*,5*R*)-5-((benzyloxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)but-2-ene-1,4-diol (**3**)

To a stirred solution of butenolide **2** (35 mg, 0.115 mmol) in dry Et<sub>2</sub>O (5 mL) was added dropwise diisobutylaluminium hydride (DIBAL-H) (0.5 mL of a 1M solution in cyclohexane, 0.5 mmol) under a nitrogen atmosphere at 0 °C. The reaction was allowed to continue at that temperature until no more starting material was detected by TLC analysis (1 h). Then H<sub>2</sub>O (0.2 mL) was added to the mixture under vigorous stirring to destroy excess DIBAL-H. MgSO<sub>4</sub> was directly added to the reaction mixture and filtered through a short pad of Celite. The filtrate was washed several times with Et<sub>2</sub>O until no more product could be detected by TLC analysis. The solution was concentrated and the crude material was purified by silica gel column chromatography, eluting with AcOEt:*n*-hexane 30:70. Product **3** (24.7 mg, 71% yield) was obtained as a colourless oil:  $[\alpha]_D^{25} = +0.99$  (*c* 1.60, CHCl<sub>3</sub>); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$ /ppm = 1.45 (s, 3H), 1.48 (s, 3H), 2.91 (brs, 2H), 3.61–3.66 (m, 2H), 4.03 (ddd, *J* = 4.4, 4.4, 8.8 Hz, 1H), 4.14–4.27 (m, 4H), 4.34 (d, *J* = 8.6 Hz, 1H), 4.57 (d, *J* = 12.0 Hz, 1H), 4.62

(d,  $J = 12.0$  Hz, 1 H), 5.88 (dd,  $J = 6.5, 6.5$  Hz, 1H), 7.29–7.38 (m, 5H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta/\text{ppm} = 26.9$  (q), 27.0 (q), 57.2 (t), 58.3 (t), 69.5 (t), 73.7 (t), 78.8 (d), 82.0 (d), 109.3 (s), 127.8 (d), 128.4 (d), 132.5 (d), 137.6 (s), 137.7 (d), 137.8 (s); FT-IR (thin film)  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ) 3400, 2986, 2930, 2870, 1374, 1219, 1086, 1020, 741; MS (EI+)  $m/z$  (relative intensity %) 293  $[\text{M}-\text{CH}_3]^+$  (5.8), 232 (3.6), 214 (2.8), 190 (3.0), 172 (8.6), 149 (6.9), 117 (53.4), 111 (21.9), 107 (38), 91.0 (100); HRMS (EI+) exact mass calculated for  $\text{C}_{16}\text{H}_{21}\text{O}_5$  ( $\text{M}-\text{CH}_3$ ) $^+$  293.1388, found 293.1389. Elemental analysis calculated for  $\text{C}_{17}\text{H}_{24}\text{O}_5$ : C, 66.21; H, 7.84; found: C, 65.78; H, 8.05.

## Acknowledgements

This research was supported by the Spanish MICINN co-financed by the European Regional Development Fund (CTQ2008-06806-C02-01/BQU) and the Canary Islands Government, and projects PROIPRO 2/0006 and 7301 of San Luis University (UNSL), PIP 628 CONICET, and PIT 352-ANPCyT. D.D.D. is an Experienced Research Fellow of the Alexander von Humboldt Foundation. C.G. thanks the Spanish MICINN-FSE for a Ramón y Cajal contract.

## References and Notes

1. Gasparski, C.M.; Herrinton, P.M.; Overman, L.E.; Wolfe, J.P. Synthesis of 3-acyltetrahydrofurans from formaldehyde acetals of allylic diols. *Tetrahedron Lett.* **2000**, *41*, 9431–9435.
2. Commeiras, L.; Santelli, M.; Parrain, J.-L. First total synthesis of ( $\pm$ )-taxifolial a and ( $\pm$ )-isocaulerpenyne. *Org. Lett.* **2001**, *3*, 1713–1715.
3. Murakami, H.; Matsui, Y.; Ozawa, F.; Yoshifuji, M. Cyclodehydration of cis-2-butene-1,4-diol with active methylene compounds catalyzed by a diphosphinidene-cyclobutene-coordinated palladium complex. *J. Organomet. Chem.* **2006**, *691*, 3151–3156.
4. Miura, T.; Takahashi, Y.; Murakami, M. Rhodium-catalysed substitutive arylation of cis-allylic diols with arylboroxines. *Chem. Commun.* **2007**, 595–597.
5. Clarke, P.A.; Rolla, G.A.; Cridland, A.P.; Gill, A.A. An improved synthesis of (2*E*,4*Z*)-6-(benzyloxy)-4-bromohexa-2,4-dien-1-ol. *Tetrahedron* **2007**, *63*, 9124–9128.
6. Musolino, M.G.; Apa, G.; Donato, A.; Pietropaolo, R.; Frusteri, F. Supported palladium catalysts for the selective conversion of cis-2-butene-1,4-diol to 2-hydroxytetrahydrofuran: Effect of metal particle size and support. *Appl. Catal. A* **2007**, *325*, 112–120.
7. Aponick, A.; Biannic, B. Gold-catalyzed dehydrative cyclization of allylic diols. *Synthesis* **2008**, 3356–3359.
8. Commeiras, L.; Santelli, M.; Parrain, J.-L. total synthesis of (+) and (-)-furocaulerpin. *Synlett* **2002**, 743–746.
9. Commeiras, L.; Parrain, J.-L. Concise enantioselective synthesis of furocaulerpin. *Tetrahedron Asymmetry* **2004**, *15*, 509–517.
10. Commeiras, L.; Bourdrion, J.; Douillard, S.; Barbier, P.; Vanthuyne, N.; Peyrot, V. total synthesis of terpenoids isolated from caulerpale algae and their inhibition- of tubulin assembly. *Synthesis* **2006**, 166–181.

11. Commeiras, L.; Santelli, M.; Parrain, J.-L. On the construction of 2-substituted 1,4-diacetoxybutadiene moiety: Application to the synthesis of caulerpenyne. *Tetrahedron Lett.* **2003**, *44*, 2311–2314.
12. Commeiras, L.; Valls, R.; Santelli, M.; Parrain, J.-L. Efficient synthesis of (+/-)-dihydrorhipocephalin, a bioactive terpenoid from Caribbean marine algae of the Genera *Penicillus* and *Udotea*. *Synlett* **2003**, 1719–1721.
13. Gross, H.; König, G.M. Terpenoids from marine organisms: unique structures and their pharmacological potential. *Phytochem. Rev.* **2006**, *5*, 115–141.
14. Maimone, T.J.; Baran, P.S. Modern synthetic approaches to terpenes. *Nat. Chem. Biol.* **2007**, *3*, 396–407.
15. Gademann, K.; Portmann, C. Secondary metabolites from cyanobacteria: Complex structures and powerful bioactivities. *Curr. Org. Chem.* **2008**, *12*, 326–341.
16. Rezanka, T.; Siristova, L.; Sigler, K. Antiviral Sesqui-, Di- and Sesterterpenes. *Anti-Infect. Agents Med. Chem.* **2009**, *8*, 169–192.
17. Paul, M.; Domingo, R. Synthesis of 1H-Cyclopropa[b]naphthalenes via Trapping of o-benzoquinodimethanes. *Helv. Chim. Acta* **1985**, *68*, 975–980.
18. Myriam, S.; Narciso, C.; Manuel, R.-C.; Ester, I.; Tore, D.; Denis, T.; Albert, B.; Michel, R. Isoprenoid biosynthesis in *Escherichia coli* via the methylerythritol phosphate pathway: Enzymatic conversion of methylerythritol cyclodiphosphate into a phosphorylated derivative of (E)-2-methylbut-2-ene-1,4-diol. *Tetrahedron Lett.* **2002**, *43*, 1413–1415.
19. Yoshio, I.; Kohji, W.; Tsuneaki, H. A new synthesis of trans-2-Substituted-2-butene-1,4-diols from 2-Butyne-1,4-diol via nucleophilic addition of Grignard reagents. *Chem. Lett.* **1984**, *5*, 765–768.
20. Ceñal, J.P.; Carreras, C.R.; Tonn, C.E.; Padrón, J.I.; Ramírez, M.A.; Díaz, D.D.; García-Tellado, F.; Martín, V.S. Acid-mediated highly regioselective oxidation of substituted furans: A simple and direct entry to substituted butenolides. *Synlett* **2005**, 1575–1578.
21. Armarego, W.L.F.; Perrin, D.D. *Purification of Laboratory Chemicals*, 4<sup>th</sup> Ed.; Butterworth-Heinemann: Oxford, UK, 1996.

© 2010 by the authors; licensee MDPI, Basel, Switzerland. This article is an open-access article distributed under the terms and conditions of the Creative Commons Attribution license (<http://creativecommons.org/licenses/by/3.0/>).