Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters
Tetrahedron Letters 46 (2005) 5889–5892

The furan approach to oxacycles. Part 5: Synthesis of a chiral butenolide, building block towards biologically interesting natural products

Marta Teijeira, Pedro Lois Suárez, Generosa Gómez, Carmen Terán and Yagamare Fall*

Departamento de Química Orgánica, Facultad de Química, Universidad de Vigo, 36200 Vigo, Spain

Received 24 May 2005; revised 17 June 2005; accepted 22 June 2005
Available online 11 July 2005

Abstract—We describe an efficient new approach for the synthesis of a chiral butenolide that is based on the oxidation of a chiral furan ring with singlet oxygen in the presence of Hünig's base, followed by Luche reduction and in situ lactonization.

Butenolides and their corresponding saturated γ-lactones are found as structural subunits in a wide range of natural products with biological activities.[1] They are often used as intermediates for the synthesis of biologically and chemically significant natural products,[2] some of them are depicted in Figure 1.

We recently described a new methodology for the synthesis of oxacyclic compounds using either methoxyallene[3a,e] or furan.[3b–d] In order to further enlarge the scope of our methodology, we decided to use chiral furan **7** as starting material. Much to our surprise, we could not synthesize 4-methoxy butenolide **8** using the experimental conditions previously developed by us[3b–d] (Scheme 1). The reason for the non-formation of **8** could be explained by the steric hindrance of the two bulky protecting groups.

This setback steered us to look for an alternative to compound **8**. It was anticipated that the effect of the steric hindrance of the TBDPS groups would not prevent the formation of 4-hydroxybutenolide **9**. Indeed oxidation of **7** with singlet oxygen in methanol in the presence of diisopropylethylamine (Hünig's base)[4] cleanly afforded 4-hydroxybutenolide **9** (Scheme 1). Our initial aim was to synthesize butenolide **8** and transform it into the titled building block compound **14**. As shown in Scheme 2, 4-hydroxy butenolide **9** is even better than

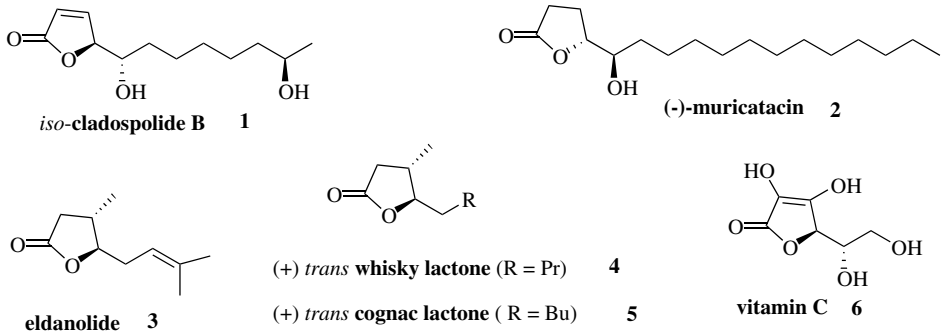
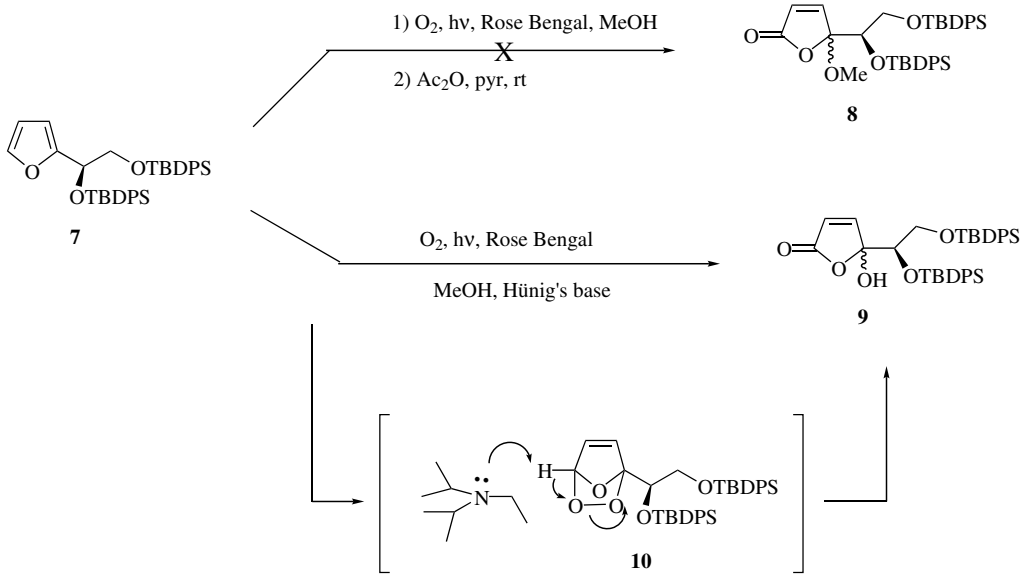


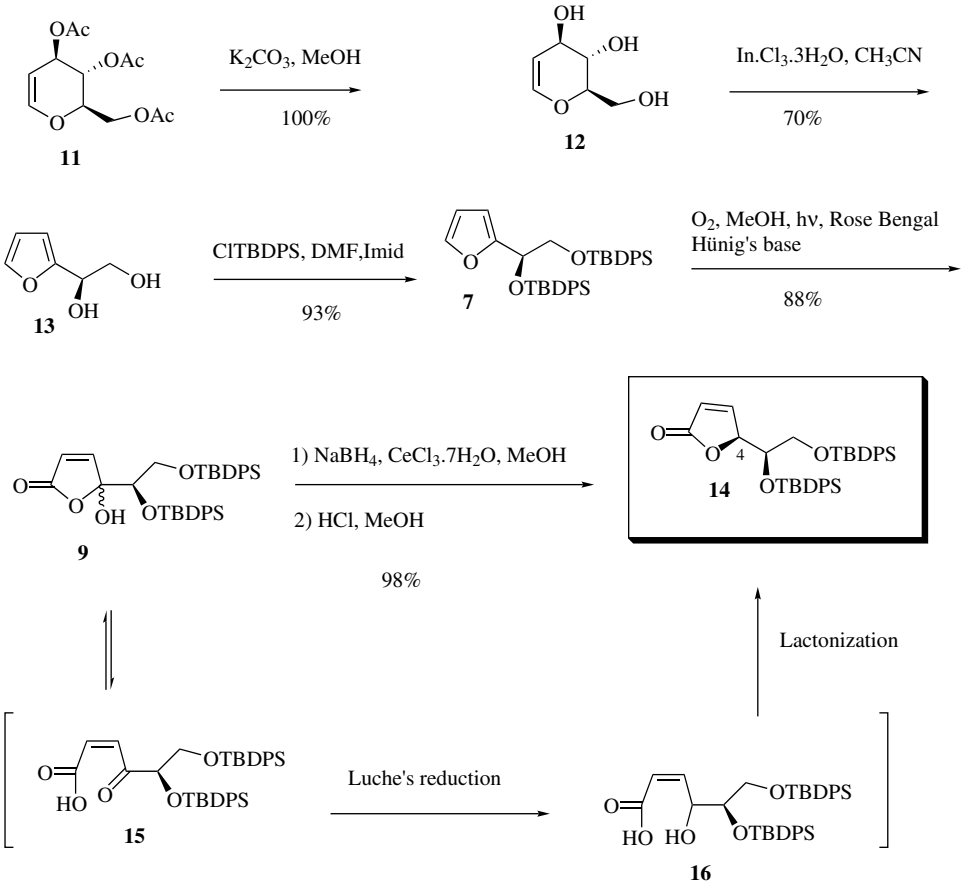
Figure 1. Some natural products containing the butenolide and the γ-lactone moiety.

Keywords: Butenolide; Singlet oxygen; Michael addition; Oxacycles; Natural products.
* Corresponding author. Fax: +34 986 81 22 62; e-mail: yagamare@uvigo.es

0040-4039/$ - see front matter
doi:10.1016/j.tetlet.2005.06.124

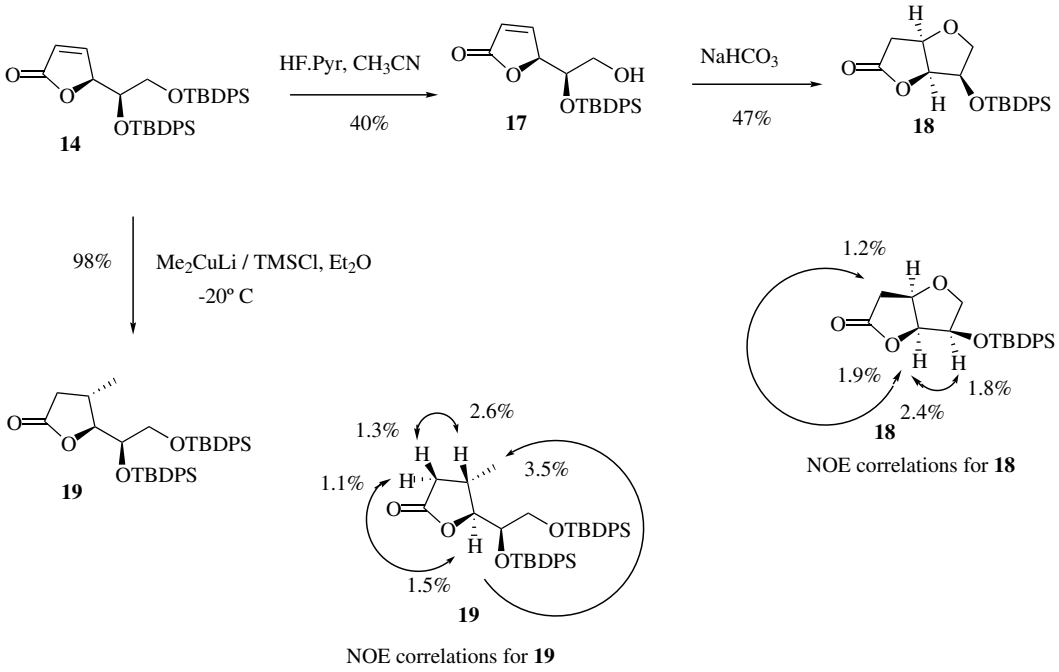


Scheme 1.



Scheme 2.

4-methoxybutenolide **8** as synthon for compound **14**. Accordingly, **9** being in equilibrium with its open form **15** could be reduced with sodium borohydride under Luche's conditions to give hydroxy acid **16** which underwent acid catalyzed in situ lactonization, affording butenolide **14** in excellent yield (98%).[5] 4-Hydroxybutenolide **9** can be synthesized as follows: commercially available tri-*O*-acetyl-D-glucal (**11**)[6] was deacetylated with methanolic K_2CO_3, in quantitative yield, giving D-glucal (**12**),[7] which on reaction with indium chloride



Scheme 3.

in acetonitrile afforded chiral furan diol **13**[8] in 70% yield. The hydroxy groups of the latter were protected as *tert*-butyldiphenylsilylethers affording **7** in 93% yield. Furan **7** was oxidized with singlet oxygen in the presence of Hünig's base giving the desired 4-hydroxybutenolide **9** in 88% yield.

Butenolide **14** was obtained enantiomerically pure but at this stage the stereochemistry of C-4 was unknown, so we decided to establish the stereochemistry by carrying out the following reaction sequence: the primary hydroxyl group of **14** was selectively deprotected and the resulting alcohol **17** on reaction with $NaHCO_3$ afforded bicyclic lactone **18**[9] through an intramolecular Michael addition (Scheme 3). From the NOE correlations of **18** it could be deduced that the stereochemistry of C-4 of butenolide **14** was the one depicted in Scheme 2. Butenolide **14** is a valuable building block for the synthesis of biologically and chemically significant natural products.[2,10] Reaction of **14** with dimethylcuprate[11] afforded **19**[12] in excellent yield (Scheme 3). The stereochemistry of **19** was established by NOE correlations. **19** is an advanced intermediate towards the synthesis of eldanolide (**3**), whisky lactone (**4**) and cognac lactone (**5**) (Fig. 1).

In conclusion, we demonstrated that from tri-*O*-acetyl-D-glucal (**11**) a commercially available chiral synthon, we could efficiently synthesize chiral butenolide **14** in excellent yield. The use of butenolide **14** as building block for the synthesis of various natural products is now under way in our laboratories.

Acknowledgements

This work was supported by a grant from the Xunta de Galicia (PGIDIT04BTF301031PR). We also thank the NMR service of the CACTI, University of Vigo, for NMR studies. M.T. thanks the Xunta de Galicia for a Parga Pondal contract.

References and notes

1. (a) Alali, F. Q.; Liu, X. X.; McLaughlin, J. L. *J. Nat. Prod* **1999**, *62*, 504–540; (b) Zafra-polo, M. C.; Figadere, B.; Gallardo, T.; Tormo, J. R.; Cortes, D. *Phytochemistry* **1998**, *48*, 1087–1117; (c) Koch, S. S. C.; Chamberlin, A. R. In *Enantiomerically Pure γ-Butyrolactones in Natural Products Synthesis*; Atta-ur-Rahman, Ed.; Elsevier Science: Amsterdam, 1995, pp 687–725.
2. (a) Yoshimitsu, T.; Makino, T.; Nagaoka, H. *J. Org. Chem.* **2004**, *69*, 1993–1998; (b) Ma, S. *Acc. Chem. Res.* **2003**, *36*, 701–712; (c) de March, P.; Figueredo, M.; Font, J.; Raya, J.; Alvarez-Larena, A.; Piniella, J. F. *J. Org. Chem.* **2003**, *68*, 2437–2447; (d) Kang, K. H.; Cha, M. Y.; Pae, A. N.; Choi, K. I.; Cho, Y. S.; Koh, H. Y.; Chung, B. Y. *Tetrahedron Lett.* **2000**, *41*, 8137–8140; (e) Ha, J. D.; Cha, J. K. *J. Am. Chem. Soc.* **1999**, *121*, 10012–10020; (f) Sinha, S. C.; Keinan, E. *J. Org. Chem.* **1999**, *64*, 7067–7073; (g) Kabeya, M.; Hamada, Y.; Shioiri, T. *Tetrahedron* **1997**, *53*, 9769–9776; (h) Pearson, W. H.; Hembre, E. J. *J. Org. Chem.* **1996**, *61*, 7217–7221.
3. (a) Fall, Y.; Gómez, G.; Fernández, C. *Tetrahedron Lett.* **1999**, *40*, 8307–8308; (b) Fall, Y.; Vidal, B.; Alonso, D.; Gómez, G. *Tetrahedron Lett.* **2003**, *44*, 4467–4469; (c) Pérez, M.; Canoa, P.; Gómez, G.; Terán, C.; Fall, Y. *Tetrahedron Lett.* **2004**, *45*, 5207–5209; (d) Alonso, D.; Pérez, M.; Gómez, G.; Covelo, B.; Fall, Y. *Tetrahedron* **2005**, *61*, 2021–2026; (e) Pérez, M.; Canoa, P.; Gómez, G.; Teijeira, M.; Fall, Y. *Synthesis* **2005**, 411–414.
4. Kernan, M. R.; Faulkner, D. J. *J. Org. Chem.* **1988**, *53*, 2773–2776.
5. Obtention of **14** from **9**: To a solution of 4-hydroxybutenolide **9** (200 mg, 0.31 mmol) in MeOH (6 mL) were added $CeCl_3{\cdot}7H_2O$ (6 mg) and $NaBH_4$ (48 mg, 1.27 mmol) at 0 °C. After being stirred for 1 h, the reaction mixture

was acidified by adding concd HCl (pH = 3) and extracted with CH_2Cl_2. The organic phase was washed with H_2O, dried with Na_2SO_4 and concentrated under reduced pressure giving a residue which was chromatographed on silica gel using 20% EtOAc/hexane as eluent affording 0.19 g of butenolide **14** [98%; solid mp: 83–85 °C; $[\alpha]_D^{25}$ −2.18 (*c* 0.55, MeOH); R_f: 0.33 (20% EtOAc/hexane)]. ^{1}H NMR ($CDCl_3$): δ 7.28–7.55 (20H, m, –Ph), 6.97 (1H, dd, *J* = 5.72, 1.58 Hz, H4), 5.99 (1H, dd, *J* = 5.72, 2.08 Hz, H3), 5.26 (1H, m, H5), 3.89 (1H, m, H1′), 3.80 (1H, m, CH_2), 3.63 (1H, m, CH_2), 0.98 (9H, s, ^{t}Bu) 0.95 (9H, s, ^{t}Bu); ^{13}C NMR ($CDCl_3$): δ 173.14 (CO), 154.17 (C4), 135.93 (CH–Ph), 135.76 (CH–Ph), 135.49 (CH–Ph), 135.36 (CH–Ph), 133.10 (C–Ph), 133.06 (C–Ph), 132.78 (C–Ph), 132.67 (C–Ph), 130.02 (CH–Ph), 129.85 (CH–Ph), 129.78 (CH–Ph), 129.74 (CH–Ph), 127.75 (CH–Ph), 127.72 (CH–Ph), 127.57 (CH–Ph), 122.37 (C3), 83.05 (C5), 72.62 (C1′), 64.04 (C2′), 26.82 ($6CH_3$–^{t}Bu), 19.26 (C–^{t}Bu), 19.15 (C–^{t}Bu); HRMS (FAB+) calcd for $C_{38}H_{44}O_4Si_2$ [M−^{t}Bu] 564.2200. Found 563.2065.

6. Mori, Y.; Hayashi, H. *J. Org. Chem.* **2001**, *66*, 8666–8668.
7. Although D-glucal is commercially available, tri-*O*-acetyl-D-glucal is much cheaper and should be used for large scale synthesis.
8. Sobhana Babu, B.; Balasubramanian, K. K. *J. Org. Chem.* **2000**, *65*, 4198–4199.
9. Compound **18**: $[\alpha]_D^{25}$ −40.65 (*c* 0.46, MeOH); ^{1}H NMR ($CDCl_3$): δ 7.62 (4H, m, H_o–Ph), 7.47–7.38 (6H, m, $H_{m,p}$–Ph), 4.90 (1H, m, H5), 4.76 (1H, m, H1), 4.49 (1H, m, H8), 3.78 (2H, m, 2 × H7), 2.65 (2H, m, 2 × H4), 1.07 (1H, s, ^{t}Bu); ^{13}C NMR ($CDCl_3$): δ 175.00 (CO), 135.58 (CH–Ph), 132.68 (C–Ph), 130.22 (CH–Ph), 130.17 (CH–Ph), 128.01 (CH–Ph), 127.94 (CH–Ph), 88.42 (C1), 77.17 (C5), 76.25 (C8), 74.13 (C7), 35.93 (C4), 26.81 ($3CH_3$–^{t}Bu), 19.11 (C–^{t}Bu); HRMS (FAB+) calcd for $C_{22}H_{24}O_4Si$ [M+1] 383.1600. Found 583.1676.
10. For some chemistry related to the preparation of compounds of type **14** using ADH or vinylogous aldol reaction, see: (a) Wang, Z.-M.; Kolb, H. C.; Sharpless, K. B. *J. Org. Chem.* **1994**, *59*, 5104–5105; (b) Casiraghi, G.; Zanardi, F.; Appendino, G.; Rassu, G. *Chem. Rev.* **2000**, *100*, 1929–1972; Evans, P.; Leffray, M. *Tetrahedron* **2003**, *59*, 7973–7981.
11. Mandville, G.; Ahmar, M.; Bloch, R. *J. Org. Chem.* **1996**, *61*, 1122–1124.
12. Compound **19**: $[\alpha]_D^{25}$ −30.71 (*c* 0.28, MeOH); ^{1}H NMR ($CDCl_3$): δ 7.24–7.54 (20H, m, –Ph), 4.31 (1H, m, H5), 3.78 (1H, m, H2′), 3.72 (1H, m, H1′), 3.60 (1H, m, H2′), 2.65 (1H, dd, *J* = 17.33, 8.88 Hz, H3), 2.44 (1H, m, H4), 2.10 (1H, dd, *J* = 17.33, 8.10 Hz H3), 0.94 (9H, s, ^{t}Bu), 0.84 (3H, d, *J* = 6.78, Hz, CH_3); ^{13}C NMR ($CDCl_3$): δ 176.79 (CO), 135.74 (CH–Ph), 135.44 (CH–Ph), 135.35 (CH–Ph), 133.27 (C–Ph), 133.11 (C–Ph), 132.86 (C–Ph), 129.88 (CH–Ph), 129.81 (CH–Ph), 129.67 (CH–Ph), 129.63 (CH–Ph), 127.80 (CH–Ph), 127.67 (CH–Ph), 127.64 (CH–Ph), 127.58 (CH–Ph), 85.53 (C5), 72.54 (C1′), 63.79 (C2′), 37.03 (C3), 30.65 (C4), 26.88 ($3CH_3$–^{t}Bu), 26.80 ($3CH_3$–^{t}Bu), 19.38 (C–^{t}Bu), 19.13 (C–^{t}Bu), 18.07 (CH_3).