Synthetic Access to Biologically Active Butenolides from *Streptomyces antibioticus*

Gilles Grossmann, Urs Séquin*

Institut für Organische Chemie der Universität Basel, St. Johanns-Ring 19, 4056 Basel, Switzerland
Tel. +41 61 267 11 10; Fax +41 61 267 11 03; E-mail: urs.sequin@unibas.ch

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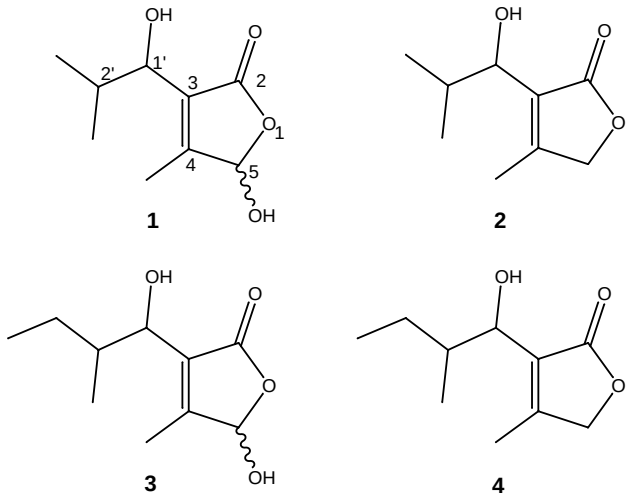
Abstract: A synthetic route to a class of substituted butenolides isolated from *Streptomyces antibioticus* has been elaborated. The process involves coupling of the readily available menthylated furanone **5** with aldehydes.

Key words: furanones, *Streptomyces antibioticus*, natural products, equilibrating hemiacetals, nucleophilic additions

The four lactones **1**-**4** (Scheme 1) were isolated a few years ago from *Streptomyces antibioticus* Tü99,[1] using a photoconductivity screening.[2] Since the compounds showed an antibiotic activity against *Pseudomonas* as well as a weak inhibition of the chitinase from *Serratia marcescens*, a synthetic access route to this class of compounds was sought.

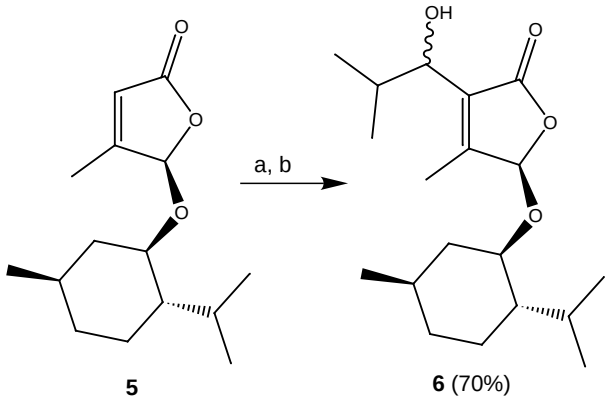


Scheme 1

A synthetic pathway was thus developed, which allows the introduction of different side chains. Deliberately, a non-stereoselective approach was used: Stereoisomers of biologically active natural products often allow interesting conclusions with respect to structure-activity relationships.[3]

The hemiacetalic compounds **1** and **3** equilibrate in solution to a mixture of epimers, which makes their isolation and characterization tedious. To alleviate this problem, we started with the menthyl ether **5** which is easily accessible in optically pure form[4,5] from the condensation product of propanal with glyoxylic acid and (-)-menthol. In compound **5** the hemiacetalic HO-group is blocked.

The key step of our synthesis is the nucleophilic addition of the furanone ring to an aldehyde to introduce the side chain (Scheme 2).[6] LDA was used as the base, which, together with the large protecting menthyl group, led to abstraction of H-C(3) rather than of the more activated H-C(5). The diastereomeric mixture **6** thus obtained from **5** and 2-methylpropanal was then separated into the two epimers **7** and **8** by flash chromatography (Scheme 3). The configurations at C(1') of these two compounds were assigned by esterification of HO-C(1') with *Mosher*'s reagent[7] and ^{1}H NMR spectroscopy.

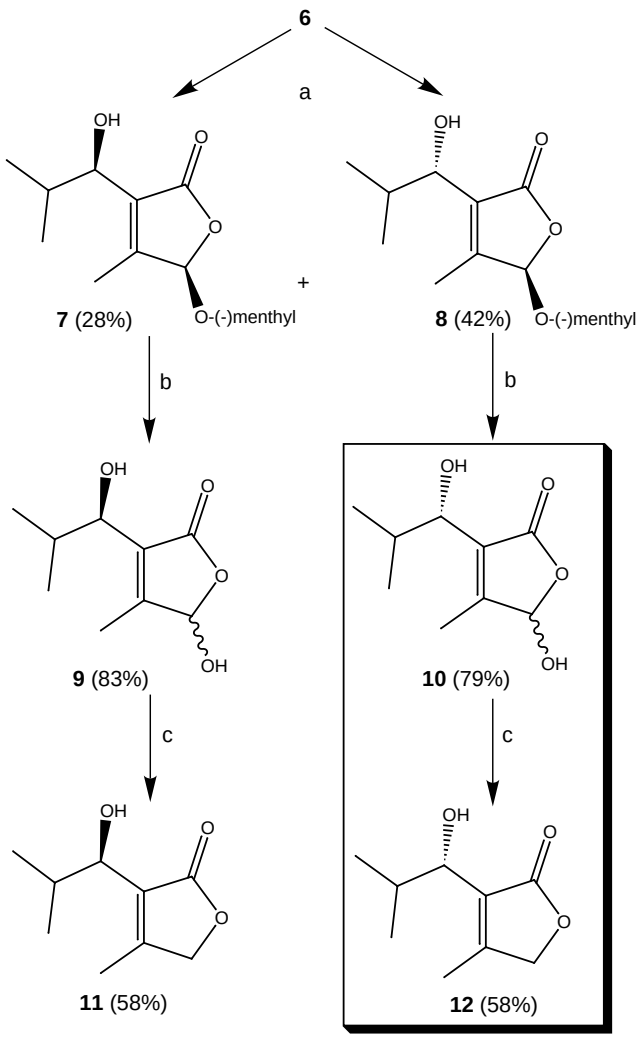


Reagents and conditions: (a) THF, LDA (1.1 eq), -78 °C, 30 min; (b) 2-methylpropanal, -78 °C, 30 min.

Scheme 2

After removal of the menthyl group with BBr_3,[8,9] **9** and **10** were obtained, respectively, the latter being identical to the natural product. The hemiacetalic furanones **9** and **10** were each reduced with $NaBH_4$ to give eventually **11** and **12**, respectively.[10] Again, the latter proved to be identical to the compound isolated from the *Streptomyces* fermentation broth.

When 2-methylbutanal was used instead of 2-methylpropanal in the reaction sequence described above, the natural products **3** and **4** could be obtained together with the respective 1'-epimers.



Reagents and conditions: (a) flash chromatography, SiO_2, AcOEt/hexane 1:5; (b) CH_2Cl_2, BBr_3, -78 °C, 4 h; (c) MeOH, $NaBH_4$, 0 °C, 2 h.

Scheme 3

Acknowledgement

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References and Notes

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(3) cf. Busch, J.; Grether, Y.; Ochs, D.; Séquin, U. *J. Nat. Prod.* **1998**, *61*, 591.
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(6) **Typical procedure:** In a dry apparatus 31.7 ml *n*-BuLi (1.5 M in hexane, 47.6 mmol) were added dropwise to a solution of 500 ml of dry THF and 6.77 ml (4.81 g, 47.6 mmol) of diisopropylamine at 0 °C. After 30 min of stirring at 0 °C, this solution was cooled to −78 °C and 10.0 g (40.0 mmol) of **5** were added dropwise. After 30 min of stirring at this temperature 4.00 ml (3.14 g, 43.7 mmol) of 2-methylpropanal were added dropwise and the solution was stirred for additional 30 min at −78 °C. Then, a saturated solution of NH_4Cl (100 ml) was added. The reaction mixture was extracted with CH_2Cl_2 (3 × 300 ml) and the combined organic layers were dried over $MgSO_4$. After evaporation of the solvent under reduced pressure, the residue was chromatographed on silica gel (AcOEt/hexane 1:5) to afford 3.60 g (11.1 mmol, 28%) of **7** and 5.40 g (16.7 mmol, 42%) of **8**.
7: Colorless plates, mp 82.0-83.5 °C. $[\alpha]_D^{20} = -130$ (*c* = 1.00 in $CHCl_3$, stab. 1% EtOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.75 (*s*, 1H, H-C(5)); 4.13 (*t*, 1H, H-C(1'), *J* = 8.4 Hz); 2.89 (*d*, 1H, HO-C(1'), *J* = 9.1 Hz); 2.05-1.97 (*m*, 1H, H-C(2')); 1.99 (*s*, 3H, CH_3-C(4)); 1.04 (*d*, 3H, CH_3-C(2'), *J* = 6.6 Hz); 0.84 (*d*, 3H, CH_3-C(2'), *J* = 6.9 Hz); menthyl resonances: 3.63 (*td*); 2.14 (*m*); 2.10 (*m*); 1.70 (*m*); 1.65 (*m*); 1.41 (*m*); 1.25 (*m*); 1.03 (*m*); 0.96 (*d*); 0.87 (*m*); 0.87 (*d*); 0.80 (*d*). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.6 (C(2)); 156.4 (C(4)); 129.9 (C(3)); 100.6 (C(5)); 72.4 (C(1')); 33.9 (C(2')); 18.8 and 18.3 ((*C*H$_3$)$_2$C(2')); 11.7 (*C*H$_3$C(4)); menthyl resonances: 79.4; 47.7; 40.4; 34.2; 31.4; 25.2; 23.1; 22.2; 20.8; 15.7. Anal. calcd. for $C_{19}H_{32}O_4$: C 70.33, H 9.94, O 19.72; found: C 70.54, H 10.04, O 19.48.
8: Colorless plates, mp 51.5-53.0 °C. $[\alpha]_D^{20} = -111$ (*c* = 1.00 in $CHCl_3$, stab. 1% EtOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.70 (*s*, 1H, H-C(5)); 4.09 (*dd*, 1H, H-C(1') *J* = 8.1 Hz and *J* = 9.7 Hz); 2.97 (*d*, 1H, HO-C(1'), *J* = 9.7 Hz); 2.05-1.98 (*m*, 1H, H-C(2')); 1.96 (*s*, 3H, CH_3-C(4)); 1.04 (*d*, 3H, CH_3-C(2'), *J* = 6.6 Hz); 0.84 (*d*, 3H, CH_3-C(2'), *J* = 6.9 Hz); menthyl resonances: 3.62 (*td*); 2.10 (*m*); 2.06 (*m*); 1.68 (*m*); 1.64 (*m*); 1.41 (*m*); 1.25 (*m*); 1.00 (*m*); 0.95 (*d*); 0.87 (*m*); 0.87 (*d*); 0.80 (*d*). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.7 (C(2)); 156.3 (C(4)); 129.7 (C(3)); 100.8 (C(5)); 72.6 (C(1')); 34.2 (C2')); 18.8 and 18.5 ((*C*H$_3$)$_2$C(2')); 11.8 (*C*H$_3$C(4)); menthyl resonances: 79.4; 47.7; 40.4; 34.2; 31.4; 25.5; 23.3; 22.2; 20.8; 16.0. Anal. calcd. for $C_{19}H_{32}O_4$: C 70.33, H 9.94, O 19.72; found: C 70.56, H 9.84, O 19.68.
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(9) **Typical procedure:** To a stirred solution of 400 mg (1.23 mmol) of **8** in 20 ml of dry dichloromethane was added at −78 °C a solution of 600 µl (1.54 g, 6.17 mmol) of BBr_3 in 1 ml of dichloromethane. After 4 h the mixture was warmed to −25 °C. The mixture was quenched with saturated sodium hydrogen carbonate solution and extracted with AcOEt (3 × 20 ml). The combined organic layers were dried over $MgSO_4$. After evaporation of the solvents under reduced pressure, the residue was chromatographed on silica gel (AcOEt/hexane 1:1) to afford 190 mg (1.02 mmol, 83%) of **10**.
10 (mixture of epimers): Colorless prisms, mp 103.5-105.0 °C. $[\alpha]_D^{20} = -16$ (*c* = 1.00 in $CHCl_3$, stab. 1% EtOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.88/5.87 (2*s*, 2 × 1H, H-C(5)); 5.25/5.05 (2*d*, 2 × 1H, HO-C(5), *J* = 9.3 Hz); 4.15-4.05 (*m*, 2 × 1H, H-C(1')); 3.33/3.09 (2*br s*, 2 × 1H, HO-C(1')); 2.08/2.06 (2*s*, 2 × 3H, CH_3-C(4)); 2.05-1.95 (*m*; 2 × 1H; H-C(2')); 1.04/1.03 (2*d*, 2 × 3H, (CH_3)-C(2'), *J* = 6.6 Hz); 0.85/0.83 (2*d*, 2 × 3H, (CH_3)-C(2'), *J* = 6.6 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.1/172.0 (C(2)); 158.54/158.52 (C(4)); 129.7/129.2 (C(3)); 98.9/98.8 (C(5)); 72.33/72.26 (C(1')); 33.9/33.5 (C(2')); 18.7/18.7/18.5/18.4 ((*C*H$_3$)$_2$-C(2')); 11.9/

11.6 (CH_3-C(4)). Anal. calcd. for $C_9H_{14}O_4$: C 58.05, H 7.58, O 34.37; found: C 58.06, H 7.58, O 34.40.

(10) **Typical procedure:** A solution of 750 mg (4.03 mmol) of **10** in MeOH (20 ml) was cooled to 0 °C. $NaBH_4$ (620 mg, 16.1 mmol) was added in portions within 10 min and the solution was stirred for 2 h at 0 °C. Then the reaction mixture was quenched with water (5 ml) and extracted with CH_2Cl_2 (3 × 20 ml) and with AcOEt (3 × 20 ml). The combined organic layers were dried over $MgSO_4$. After evaporation of the solvents under reduced pressure, the residue was chromatographed on silica gel (*tert*-butyl methyl ether) to afford 397 mg (2.34 mmol, 58%) of **12**.

12: Colorless, amorphous solid. $[\alpha]_D^{20} = -16.5$ (*c* = 1.00 in $CHCl_3$, stab. 1% EtOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.71 (*d*, 1H, H_a-C(5), *J* = 17.3 Hz); 4.66 (*s*, 1H, H_b-C(5), *J* = 17.3 Hz); 4.14 (*d*, 1H, H-C(1'), *J* = 7.9 Hz); 3.13 (*br. s*, 1H, HO-C(1')); 2.09 (*s*, 3H, CH_3-C(4)); 2.08-1.98 (*m*, 1H, H-C(2')); 1.04 (*d*, 3H, CH_3-C(2'), *J* = 6.7 Hz); 0.84 (*d*, 3H, CH_3-C(2'), *J* = 6.7 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.2 (C(2)); 158.5 (C(4)); 127.3 (C(3)); 72.7 (C(5)); 72.3 (C(1')); 33.8 (C(2')); 18.7 and 18.3 ((CH_3)$_2$C(2')); 12.4 (CH_3C(4)). Anal. calcd. for $C_9H_{14}O_3$: C 63.51, H 8.29, O 28.20; found: C 63.22, H 8.33, O 28.27.

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