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Synthesis and absolute configuration of lactone II isolated from *Streptomyces* sp. Go 40/10

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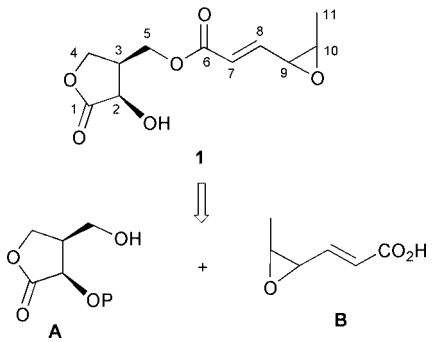
All four possible stereoisomers of lactone II isolated from *Streptomyces* sp. Go 40/10, an autoregulator, have been efficiently synthesized in a stereoselective manner starting from (*S*)-malic acid and sorbic acid, and the absolute configuration was determined to be 2*S*, 3*S*, 9*R*, 10*S*.

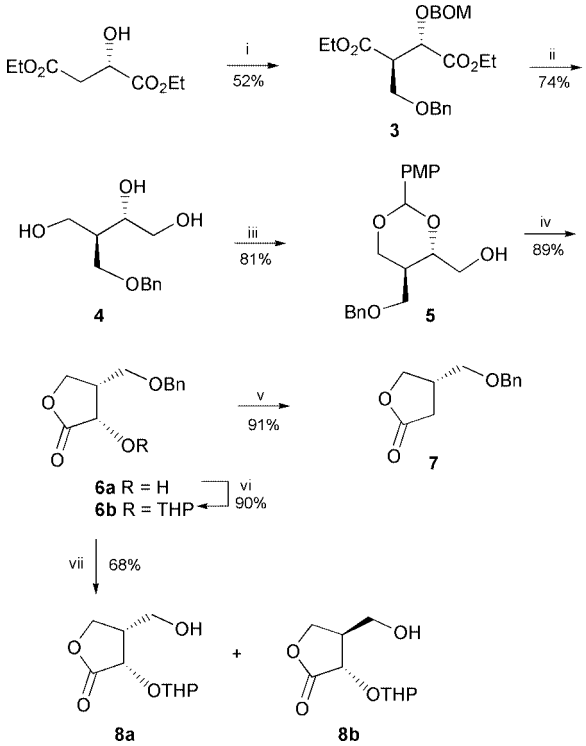
Lactone II **1**, which contains a highly oxidized γ-butyrolactone including a conjugated epoxy enone, was isolated[1] from *Streptomyces* sp. Go 40/10 in 1999 (Scheme 1). The stereochemistry of the epoxide was proposed to be *cis* by spectroscopic analysis; however, the relative, as well as the absolute configurations of the four stereocenters remain unknown. The synthesis of all four possible stereoisomers (**1a**, **1b**, **2a** and **2b**) of lactone II was therefore undertaken to determine the absolute configuration and to provide samples for further biological assay. Our synthetic plan is illustrated in Scheme 1. Lactone part **A** and epoxy acid part **B** were derived from commercially available (*S*)-malic acid and sorbic acid, respectively.

The synthesis of parts **A** and **B** are outlined in Schemes 2 and 3. (*S*)-Malic acid was converted into **3** according to the known procedure.[2] Reduction of the ester group with $LiAlH_4$, followed by acid hydrolysis and protection of the hydroxy group with *p*-anisaldehyde gave an alcohol **5**, which was submitted to the Dess–Martin and sodium chlorite oxidation and subsequent acid-catalyzed deprotection to afford the *cis*-γ-butyrolactone **6a** (mp 85–86 °C; $[\alpha]_D^{29}$ +44.1 (*c* 1.0, $CHCl_3$). By reductive deoxygenation (*via* mesylate) of the hydroxy group, lactone **6a** was converted to the known compound **7** [overall 22.6% yield from (*S*)-diethyl malate].[3] THP protection[4] of the hydroxy group of (2*S*, 3*S*)-**6a** gave separable diastereomeric isomers **6b** (6:5). After separation an isomer was transformed into the mixture of lactone alcohols **8a** and **8b**.[5] The epoxy acid part was efficiently prepared from methyl sorbate with AD-mix-α according to the Sharpless method,[6] the diol ester **9** was converted by the usual procedure into **10b** (Scheme 3). Deprotection of the hydroxy groups with tetrabutylammonium fluoride yield the epoxy ester **11**. Successful hydrolysis of **11** with potassium trimethylsilanolate afforded (4*R*, 5*S*)-**12a**[7] without complication.

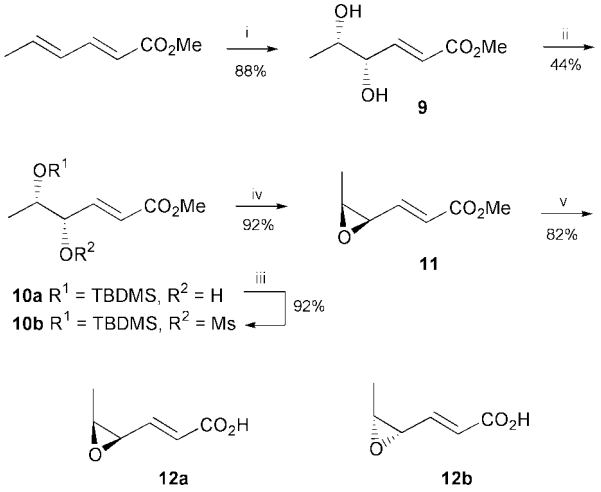
Esterification of **12a** with the mixture of **8a** and **8b** was achieved by the DCC method to provide **13** (67%) and **14** (13%)



Scheme 1



Scheme 2 *Reagents and conditions*: i, LDA, $ClCH_2OCH_2Ph$, HMPA, THF, −78 °C to RT; ii, (a) $LiAlH_4$, Et_2O; (b) HCl, MeOH–H_2O; iii, $ZnCl_2$, $MeOC_6H_4CHO$, Et_2O, MS 4Å; iv, (a) Dess–Martin periodinane, CH_2Cl_2; (b) $NaClO_2$, NaH_2PO_4, *t*-BuOH–H_2O; (c) HCl, dioxane; v, (a) MsCl, Et_3N, CH_2Cl_2; (b) Zn, NaI, DME, 85 °C; vi, dihydropyran, CSA; vii, H_2, Pd–C, EtOH.



Scheme 3 *Reagents and conditions*: i, AD-mix-α; ii, TBDMSCl, DMAP, CH_2Cl_2, RT, 12 h; iii, MsCl, Et_3N, CH_2Cl_2, RT, 17 h; iv, TBAF, THF, RT, 3 h; v, TMSOK, THF, RT 3 h.

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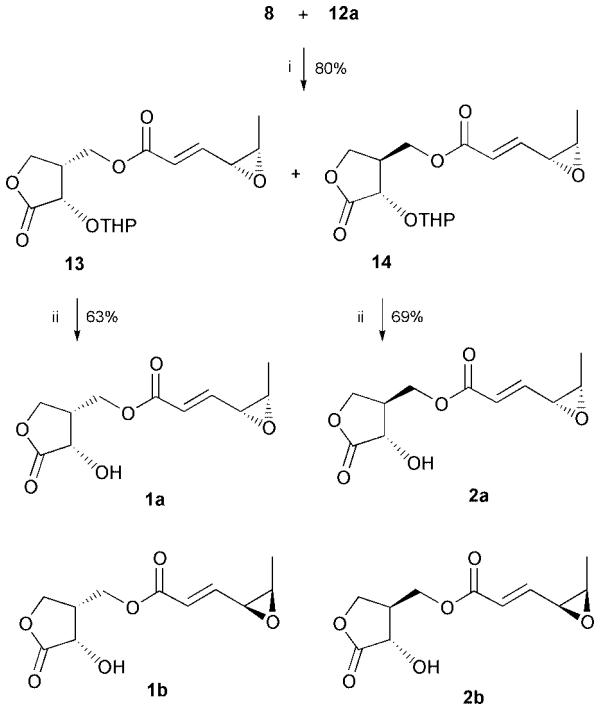

Scheme 4 *Reagents and conditions*: i, DCC, DMAP, CH_2Cl_2, RT, 24 h; ii, AcOH, THF, H_2O, 50 °C, 3 h.

(Scheme 4).[5] The stereochemistries of these compounds were confirmed by ^{1}H NMR analysis and NOE experiments. The signals of H-2 appeared at δ 4.63 (J = 7.7 Hz) in **13** and δ 4.43 (J = 9.3 Hz) in **14**, respectively. In **13**, a NOE was observed between H-2 and H-3, whereas a NOE was not observed in **14**. From these results, **13** and **14** are presumed to be 2,3-*cis*- and 2,3-*trans*-isomers, respectively. On treatment of **13** or **14** with acetic acid in THF–H_2O at 50 °C to remove THP protection, the final products **1a** and **2a** were obtained in satisfactory yield, respectively. Isomers **1b** and **2b** were synthesized from **8** and (4*S*, 5*R*)-**12b** in the same manner.

By comparison[8] of the ^{1}H and ^{13}C NMR results,† there was little difference among natural, **1a** and **1b**, and also between **2a** and **2b**. However, an obvious difference was observed between **1a** and **2a**, and also between **1b** and **2b**. Smaller coupling constants of **1a** (J = 8.0 Hz) and **1b** (J = 7.7 Hz) than those of **2a** (J = 9.8 Hz) and **2b** (J = 10.3 Hz) and the observation of NOE in **1a** (no NOE in **2a**) show that the stereochemistries of **1a** (and **1b**) and **2a** (and **2b**) are presumed to be 2,3-*cis* and 2,3-*trans* configurations, respectively. The value of specific rotation [natural: $[\alpha]_D^{20}$ +32 (*c*, 0.1, MeOH); synthetic **1a**: $[\alpha]_D^{21}$ +38.8 (*c*, 0.1, MeOH); synthetic **1b**: $[\alpha]_D^{20}$ +121.0 (*c*, 0.12, MeOH)] showed that **1a** must be the natural product, *i.e.* lactone II has the absolute configuration 2*S*, 3*S*, 9*R*, 10*S*.

In conclusion, we have completed the first synthesis of lactone II (and its stereoisomers) from (*S*)-malic acid and sorbic acid, and determined the absolute configuration of lactone II to be 2*S*, 3*S*, 9*R*, 10*S*. Submitting these isomers to further biological assay and total synthesis of analogous butalactin are currently under investigation and will be reported in due course.

Notes and references

† *Data for synthetic* **1a**: mp 75 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.22 (d, 3H, J = 5.5 Hz, H-11), 2.86 (m, 1H, H-3), 3.33 (dq, 1H, J = 4.4, 5.5 Hz, H-10), 3.61 (ddd, 1H, J = 0.7, 4.4, 7.1 Hz, H-9), 4.10–4.36 (m, 4H, H-4 and H-5), 4.56 (dd, 1H, J = 6.0, 8.0 Hz, H-2), 6.12 (dd, 1H, J = 0.7, 15.5 Hz, H-7), 6.13 (d, 1H, J = 5.9 Hz, 2-OH), 6.66 (dd, 1H, J = 7.1, 15.5 Hz, H-8); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.1, 38.9, 55.2, 55.5, 61.0, 67.6, 67.8, 124.2, 143.5, 165.2, 176.5.

For **1b**: mp 95 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.23 (d, 3H, J = 5.4 Hz), 2.87 (m, 1H), 3.33 (dq, 1H, J = 4.4, 5.5 Hz), 3.61 (dd, 1H, J = 4.4, 7.1 Hz), 4.13-4.37 (m, 4H), 4.56 (dd, 1H, J = 5.7, 7.7 Hz), 6.12 (dd, 1H, J = 0.7, 15.5 Hz), 6.13 (d, 1H, J = 5.7 Hz, OH), 6.66 (dd, 1H, J = 7.2, 15.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.1, 38.9, 55.2, 55.5, 61.1, 67.5, 67.8, 124.3, 143.5, 165.1, 176.6.

For **2a**: oil; $[\alpha]_D^{21}$ −78.5 (*c*, 0.11, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.30 (d, 3H, J = 5.5 Hz), 2.90 (m, 1H), 3.35 (dq, 1H, J = 4.4, 5.5 Hz), 3.55 (ddd, 1H, J = 0.9, 4.6, 5.5 Hz), 4.07 (t, 1H, J = 9.8 Hz), 4.32–4.50 (m, 4H), 6.15 (dd, 1H, J = 0.9, 15.7 Hz), 6.87 (dd, 1H, J = 6.3, 15.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.0, 43.1, 55.1, 55.5, 61.9, 66.9, 68.8, 124.0, 143.4, 165.2, 176.7.

For **2b**: oil; $[\alpha]_D^{21}$ −23.6 (*c*, 0.19, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.30 (d, 3H, J = 5.4 Hz), 2.89 (m, 1H), 3.35 (dq, 1H, J = 4.6, 5.5 Hz), 3.54 (ddd, 1H, J = 0.9, 4.4, 5.3 Hz), 4.33 (d, 1H, J = 10.3 Hz), 4.32–4.50 (m, 4H), 6.15 (dd, 1H, J = 1.1, 15.6 Hz), 6.88 (dd, 1H, J = 6.2, 15.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.1, 43.2, 55.1, 55.5, 61.8, 66.8, 68.9, 124.0, 143.6, 165.2, 173.6.

1 H.-J. Schiewe and A. Zeeck, *J. Antibiotics*, 1999, **52**, 635.

2 D. Seebach, J. Aebi and D. Wasmuth, *Org. Synth. Coll. Vol. VII*, 1990, 153.

3 Synthetic **7**: $[\alpha]_D^{26}$ +34.6 (*c* 0.9, $CHCl_3$). *Cf.* (*a*) $[\alpha]_D^{23}$ +32.5 (*c* 0.9, $CHCl_3$), 95% ee: K. Takabe, M. Tanaka, M. Sugimoto, T. Yamada and H. Yoda, *Tetrahedron: Asymmetry*, 1992, **3**, 1385; (*b*) $[\alpha]_D^{19}$ −36.8 (*c* 1.4, $CHCl_3$) for *R*-form: C. Mazzini, J. Lebreton, V. Alphand and R. Furstoss, *J. Org. Chem.*, 1997, **62**, 5215.

4 THP protection was more successfully removed under mild conditions than MOM (methoxymethyl) protection in the final step.

5 Hydrogenation with palladium on carbon yielded the inseparable mixture 2,3-*cis* **8a** and 2,3-*trans* **8b**; the ratio was approximately 6:1 by NMR. The mixture arose solely from hydrogenolytic cleavage of the benzyl group from **6b**. It is probably that the *cis* **8a** partly yielded the *trans* **8b** by intramolecular translactonization.

6 D. Xu, G. A. Crispino and K. B. Sharpless, *J. Am. Chem. Soc.*, 1992, **114**, 7570.

7 (4*R*, 5*S*)-**12a**: mp 94 °C (hygroscopic), $[\alpha]_D^{21}$ −70.0 (*c* 0.5, $CHCl_3$). By a similar oxidation of methyl sorbate with AD-mix-β and a subsequent series of reactions, the other isomer (4*S*, 5*R*)-**12b** was also obtained: mp 95 °C, $[\alpha]_D^{23}$ +77.8 (*c* 0.9, $CHCl_3$).