Enantiodivergent synthesis of both enantiomers of the macrocyclic lactone lasiodiplodin

Franz Bracher * and Brigitte Schulte

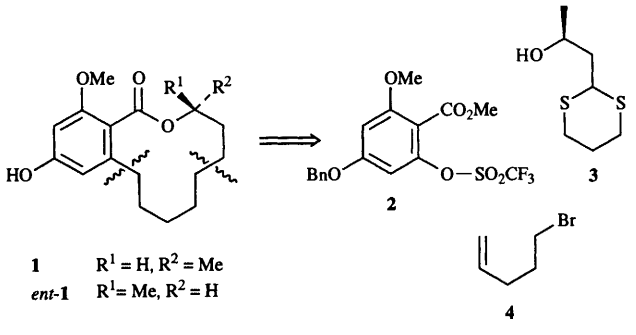
Institut für Pharmazeutische Chemie, Technische Universität Braunschweig, Beethovenstr. 55, 38106 Braunschweig, Germany

A straightforward approach to both enantiomers of lasiodiplodin 1 is described utilizing (*S*)-2-(2-hydroxypropyl)-1,3-dithiane 3 as a chiral building block. The key step is a Pd^0-catalysed cross coupling of an arene trifluoromethanesulfonate with a 9-alkyl-9-borabicyclo[3.3.1]nonane derivative. The two enantiomers 1 and *ent*-1 have been obtained in an enantiodivergent manner by macrolactonization of the hydroxy acid 10 with either Gerlach's modification of the Corey lactonization or a Mitsunobu lactonization.

The *R*-configurated 12-membered orsellinic acid type lactone lasiodiplodin **1** has been described as a constituent of the fungus *Lasiodiplodia theobromae*[1] and of the wood of *Euphorbia splendens*[2] and *Euphorbia fidjiana*.[3] In a first screening **1** showed significant antileukemic activity.[2] Racemic[4] and non-racemic[5] lasiodiplodin have been the subject of several synthetic investigations. Most of the multi-step syntheses[5b-d] of **1** utilized orsellinic acid (2,4-dihydroxy-6-methylbenzoic acid) derivatives as starting materials and attached an aliphatic chain by side-chain metallation/alkylation. All these procedures, however, gave lasiodiplodin methyl ether as an intermediate. The target compound was then prepared in poor yield by mono-demethylation. The alternative approaches involved *de novo* syntheses of the aromatic ring by cycloaddition[4b,4c,5a] or cyclocondensations.[4a] Related strategies have been used for the total syntheses of similar macrocyclic lactones like zearalenone.[6]

In order to provide sufficient amounts of both enantiomers for comprehensive screening and to investigate structure–activity relationships, we have worked out an efficient strategy for the syntheses of both **1** and *ent*-**1**.

The target compounds were to be built up from three components (Scheme 1): a benzoic acid derivative, an



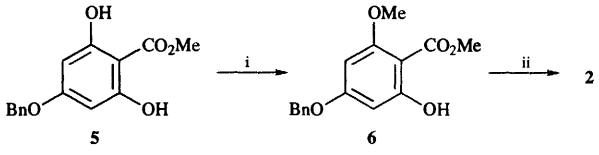
Scheme 1 Retrosynthetic analysis of lasiodiplodin **1** and *ent*-**1**

enantiomeric pure methyl-substituted methanol building block and an alkyl unit to complete the aliphatic part of the lactone.

For the introduction of the chiral centre we selected the *S*-configurated hydroxypropyldithiane **3**, the deprotonation of which followed by *C*-alkylation would, we thought, permit connection of **3** with an appropriate C_5-unit **4**. Subsequently, the dithiane functionality could be converted into a methylene group by reductive desulfurization. The olefinic group introduced by **4** would be suitable for conversion, by hydroboration, into a terminal organoborane which could then be coupled with an appropriately substituted arene trifluoromethanesulfonate (triflate) **2** under Pd catalysis. Finally, ring closure either with retention of configuration or inversion at the chiral centre could be accomplished by known macrolactonization methods.[7]

Results and discussion

The arene triflate **2** was prepared from known methyl 4-benzyloxy-2,6-dihydroxybenzoate **5**[8] in two steps. Reaction of **5** with diazomethane gave the monomethyl ether **6** (80%). Minor amounts of the corresponding dimethyl ether could easily be separated by column chromatography. Subsequent treatment with trifluoromethanesulfonic anhydride–pyridine yielded **2** (87%) (Scheme 2).

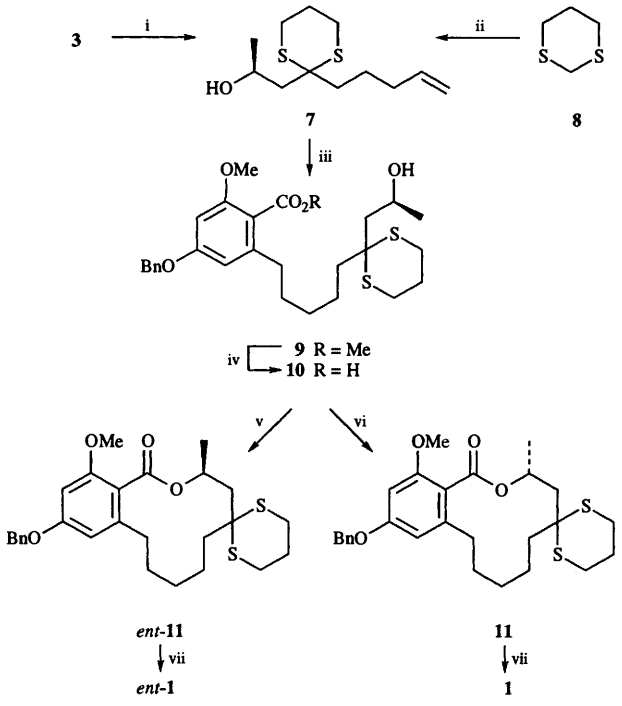


Scheme 2 *Reagents:* i, CH_2N_2, Et_2O; ii, $(CF_3SO_2)_2O$, pyridine

The chiral building block **3** is readily available in high yield and enantiomeric purity by microbial reduction of the corresponding oxopropyldithiane with baker's yeast (*Saccharomyces cerevisiae*)[9] and has already been used as a building block for the preparation of ketols.[10,11] Very recently, we reported on the application of **3** to the syntheses of the macrocyclic lactone (*S*)-curvularin[12] and the pheromone (*S*)-tridecanol acetate[13] by alkylation at C-2 of the dithiane ring and reductive desulfurization.

Dithiane **3** was converted into a dianion[10] with butyllithium (2.4 equiv.) and alkylated with 5-bromopent-1-ene **4** to give **7** (ee >95%; 85% yield). Later we found that **7** can also be prepared from commercially available starting materials. Thus, 1,3-dithiane **8** was deprotonated with butyllithium, alkylated with **4** and then treated with butyllithium again and allowed to react with (*S*)-propylene oxide. The overall yield of this one-pot procedure was 86%. Hydroboration of the olefin **7** with 9-borabicyclo[3.3.1]nonane (9-BBN) gave a terminal organoborane. Protection of the hydroxy group was not necessary in this step if 2 equiv. of 9-BBN were employed. The second equivalent of the borane was consumed by reaction with the hydroxy group. Pd^0-catalysed cross coupling[14] of the crude organoborane with the arene triflate **2** (1 equiv.) gave compound **9** (65%). Running the coupling reaction with an excess of the crude organoborane gave dramatically lower yields of **9**, because reductive removal of the trifluoromethylsulfonyloxy group from **2** became a severe side reaction. Alkaline hydrolysis of the methyl ester **9** gave the hydroxy acid **10** which

could be converted into the *S*-configurated lactone *ent*-**11** using Gerlach's modification[4a] of the Corey lactonization (2,2′-dipyridyl disulfide–Ph_3P–$AgClO_4$) in 61% yield (Scheme 3).



Scheme 3 *Reagents:* i, BuLi (2.4 equiv.), THF, 5-bomopent-1-ene; ii, BuLi, THF, 5-bromopent-1-ene; then BuLi, (*S*)-propylene oxide; iii, 9-BBN (2 equiv.), hexane; then **2**, K_3PO_4, $Pd(PPh_3)_4$, dioxane; then Me_3N–O; iv, KOH, EtOH, H_2O; v, $(PyS)_2$, PPh_3, MeCN; then $AgClO_4$; vi, DEAD, PPh_3, toluene, THF; vii, Raney nickel, THF

We also tried to build up the macrocyclic ring by a different sequence of the steps described above. Thus, we first formed the ester linkage betweeen **2** and **7** and then tried to perform an intramolecular Pd-catalysed coupling after 9-BBN-addition to the olefin. However, we were not able to detect any lactone *ent*-**11** in the reaction mixture.[15,16]

Treatment of *ent*-**11** with Raney nickel W7 resulted in reductive desulfurization of the dithiane moiety and concomitant removal of the *O*-benzyl protecting group[17] to give the target compound *ent*-**1** (72%).

Naturally occurring lasiodiplodin **1** was prepared from the (*S*)-hydroxy acid **10** with inversion at the chiral centre by lactonization under Mitsunobu conditions[18] and subsequent debenzylation/desulfurization with Raney nickel. Racemic lasiodiplodin was prepared in an analogous manner starting from *rac*-**3**.

In conclusion, we have elaborated a straightforward enantiodivergent strategy for the preparation of both enantiomers of lasiodiplodin. The arene triflate **2** should be an attractive alternative to orsellinic acid derivatives for the synthesis of related orsellinic acid type metabolites. Further, we could demonstrate another interesting application of (*S*)-2-(2-hydroxypropyl)-1,3-dithiane **3** as a building block for the preparation of enantiomerically pure methyl-substituted methanol derivatives. Work is in progress to apply this strategy to the synthesis of related natural products with different ring sizes.

Experimental

General

Elemental analyses were performed on a Carlo Erba CHNO Elemental Analyser. FTIR spectra were recorded on a Pye-Unicam PU-9800 spectrometer. NMR spectra were recorded in $CDCl_3$ with tetramethylsilane as internal standard on a Bruker AM-400 (400.1 MHz ^1H, 100.5 MHz ^{13}C) spectrometer. *J* Values are given in Hz. Mass spectra were recorded on a Finnigan MAT-8430 spectrometer. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter, and are given in units of 10^{-1} deg cm^2 g^{-1}. Flash column chromatography (FCC) was carried out on Merck Kieselgel 60 (230–400 mesh). Tetrahydrofuran (THF) was freshly distilled from sodium benzophenone ketyl prior to use. Raney nickel W7[19] was freshly prepared from nickel–aluminium alloy and used immediately for the reductions. The organic extracts were dried over anhydrous sodium sulfate which was later removed by filtration. The solvent used was concentrated using a rotary evaporator under reduced pressure. GLC was performed on a phenylmethylsilicon stationary phase AT-50 (Alltech) on a Shimadzu GC-14 A gas chromatograph equipped with FID.

Methyl 4-benzyloxy-6-hydroxy-2-methoxybenzoate 6

Methyl 4-benzyloxy-2,6-dihydroxybenzoate **5**[8] (4.23 g, 15.4 mmol) was added to a solution of diazomethane (*ca.* 30 mmol) in diethyl ether (200 cm^3). The mixture was stirred at room temperature for 12 h and then treated with acetic acid to destroy the excess of diazomethane. The mixture was evaporated and the residue purified by FCC. Crystallisation of the main fraction from dichloromethane–ethyl acetate gave *compound* **6** (3.56 g, 80%) as white needles, mp 106 °C (Found: C, 66.65; H, 5.66. $C_{16}H_{16}O_5$ requires C, 66.66; H, 5.59%); ν_{max}(KBr)/cm^{-1} 2950, 1640, 1570, 1440, 1325, 1265, 1165, 1100, 1040, 800 and 720; δ_H 3.81 (3 H, s, OCH_3), 3.91 (3 H, s, OCH_3), 5.04 (2 H, s, OCH_2), 6.05 (1 H, d, *J* 2.4, ArH), 6.19 (1 H, d, *J* 2.4, ArH), 7.32–7.42 (5 H, m, ArH) and 12.0 (1 H, s, OH); δ_C 52.2, 56.1, 70.2, 92.2, 94.4, 96.8, 127.7 (2 C), 128.3, 128.7 (2 C), 136.0, 162.2, 164.5, 165.9 and 171.7; *m/z* (EI) 288 (M^+, 39), 256 (41) and 91 (100).

Methyl 4-benzyloxy-6-methoxy-2-trifluoromethylsulfonyloxybenzoate 2

To a solution of **6** (3.21 g, 11.1 mmol) in anhydrous pyridine (30 cm^3) under nitrogen trifluoromethanesulfonic anhydride (3.68 g, 12.8 mmol) was added dropwise and the mixture was stirred for 5 h at room temperature. The mixture was then diluted with water (100 cm^3), acidified with hydrochloric acid (2 mol dm^{-3}) and extracted with ethyl acetate. The extract was washed with water and concentrated. Purification by FCC gave *compound* **2** (4.10 g, 88%) as white needles, mp 71 °C (from hexane–ethyl acetate) (Found: C, 48.86; H, 3.60. $C_{17}H_{15}F_3O_7S$ requires C, 48.57; H, 3.59%); ν_{max}(KBr)/cm^{-1} 3435, 2957, 1732, 1620, 1574, 1496, 1479, 1454, 1429, 1278, 1234, 1217, 1203, 1157, 1134, 1107, 1053 and 835; δ_H 3.89 (3 H, s, OCH_3), 3.90 (3 H, s, OCH_3), 5.08 (2 H, s, OCH_2), 6.50 (1 H, d, *J* 2.1, ArH), 6.55 (1 H, d, *J* 2.1, ArH) and 7.37–7.41 (5 H, m, ArH); δ_C 52.6, 56.5, 70.8, 99.3, 100.0, 110.1, 118.5 (*J* 320.5, CF_3), 127.7 (2 C), 128.6, 128.8 (2 C), 135.3, 148.2, 159.7, 161.6 and 163.4; *m/z* (EI) 420 (M^+, 20), 389 (16), 271 (8) and 91 (100).

(*S*)-2-(2-Hydroxypropyl)-2-(pent-4-enyl)-1,3-dithiane 7

Method A. A solution of (*S*)-2-(2-hydroxypropyl)-1,3-dithiane **3**[9] (3.14 g, 17.6 mmol) in anhydrous THF (40 cm^3) under nitrogen at −40 °C was treated dropwise with butyllithium solution (1.6 mol dm^{-3} in hexane; 26.4 cm^3, 42.2 mmol). The mixture was stirred for 30 min at −40 °C and then allowed to warm to 0 °C within 2 h after which it was again cooled to −40 °C. A solution of 5-bromopent-1-ene **4** (2.90 g, 19.5 mmol) in anhydrous THF (10 cm^3) was added dropwise to the mixture which was then stirred at −40 °C for 1 h and at 0 °C for 12 h. After dilution with water (50 cm^3) the mixture was brought to pH 5 with hydrochloric acid and extracted with ethyl acetate. Work-up and purification by FCC gave *compound* **7** (3.68 g, 85%) as a pale yellow oil.

Method B. A solution of 1,3-dithiane **8** (2.50 g, 20.8 mmol) in anhydrous THF (30 cm^3) under nitrogen was treated dropwise with butyllithium solution (1.6 mol dm^{-3} in hexane; 15.6 cm^3,

25.0 mmol) at −40 °C with stirring. The mixture was kept at −40 °C for 30 min and then allowed to warm to 0 °C within 2 h after which it was again cooled to −40 °C. A solution of 5-bromopent-1-ene **4** (3.73 g, 25.0 mmol) in anhydrous THF (15 cm^3) was added to the mixture which was then kept at −40 °C for 1 h and at 0 °C for 12 h; it was then cooled to −40 °C again. A solution of butyllithium (1.6 mol dm^{-3} in hexane; 15.6 cm^3, 25.0 mmol) was added with stirring to the mixture which was then kept at −40 °C for 30 min and at 0 °C for 2 h; it was then again cooled to −40 °C. A solution of (*S*)-propylene oxide (1.52 g, 25.0 mmol) in anhydrous THF (5 cm^3) was added to the mixture after which it was stirred at 0 °C for 1 h and at room temperature for 12 h. After dilution with water, the reaction mixture was worked up as described above to give *compound* **7** (4.40 g, 86%) as a pale yellow oil (Found: C, 58.41; H, 9.18. $C_{12}H_{22}OS_2$ requires C, 58.59; H, 8.99%); ν_{max}(NaCl)/cm^{-1} 3441, 3074, 2934, 2909, 1639, 1415, 1130 and 908; δ_H 1.19 (3 H, d, *J* 6.3, CH_3), 1.49 (1 H, m), 1.66 (1 H, m), 1.85–2.14 (7 H, m), 2.32 (1 H, dd, *J* 15.2 and 9.4), 2.74–2.81 (2 H, m, SCH_2), 2.89–3.04 (2 H, m, SCH_2), 3.53 (1 H, br s, OH), 4.12 (1 H, m, OCH), 4.96–5.06 (2 H, m, $=CH_2$) and 5.79 (1 H, m, =CH); δ_C 23.2, 23.9, 25.0, 26.0, 26.4, 33.7, 39.2, 46.1, 52.0, 64.7, 115.2 and 138.0; *m*/*z* (EI) 246 (M^+, 22%), 187 (30), 177 (38), 171 (52), 145 (42), 133 (100), 107 (56) and 106 (98); $[\alpha]_D^{20}$ +21.9 (*c* 2.3, $CHCl_3$); ee >95% (GLC of the Mosher's acid derivative).

(*S*)-Methyl 4-benzyloxy-2-methoxy-6-{5-[2-(2-hydroxypropyl)-1,3-dithian-2-yl]pentyl}benzoate 9

Compound **7** (1.13 g, 4.59 mmol) was treated with a 9-BBN solution (0.5 mol dm^{-3} in hexane; 18.4 cm^3, 9.2 mmol) under nitrogen at 0 °C and the mixture then stirred for 12 h at room temperature. The resulting solution was transferred by a double-ended steel needle into a stirred mixture of triflate **2** (1.93 g, 4.59 mmol), potassium phosphate (2.90 g, 13.7 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.33 g, 0.29 mmol) in anhydrous dioxane under nitrogen. The mixture was refluxed for 5 h after which it was treated with trimethylamine *N*-oxide (1.00 g, 13.3 mmol) and refluxed for a further 1 h. After decantation the liquid layer was concentrated and purified by FCC to give *compound* **9** (1.54 g, 65%) as a yellow oil (Found: C, 64.79; H, 7.33. $C_{28}H_{38}O_5S_2$ requires C, 64.83; H, 7.38%); ν_{max}(NaCl)/cm^{-1} 3445, 2938, 2862, 1725, 1603, 1586, 1497, 1489, 1454, 1423, 1373, 1323, 1271, 1194, 1161, 1099, 1041, 1028, 738 and 700; δ_H 1.32 (3 H, d, *J* 7.4, CH_3), 1.28–2.04 (11 H, m), 2.32 (1 H, dd, *J* 15.2 and 9.4), 2.54 (2 H, t, *J* 7.7, $ArCH_2$), 2.75 (2 H, m, SCH_2), 2.95 (2 H, m, SCH_2), 3.5 (1 H, br s, OH), 3.75 (3 H, s, OCH_3), 3.87 (3 H, s, OCH_3), 4.11 (1 H, m, C*H*OH), 5.05 (2 H, s, OCH_2), 6.39 (1 H, d, *J* 2.3, ArH), 6.40 (1 H, d, *J* 2.3, ArH) and 7.26–7.43 (5 H, m, ArH); δ_C 23.7, 23.8, 24.9, 25.9, 26.4, 29.4, 30.8, 33.7, 39.7, 45.9, 52.0, 52.1, 55.8, 64.7, 70.0, 97.0, 106.7, 116.4, 127.5 (2 C), 128.1, 128.6 (2 C), 136.5, 142.6, 157.9, 160.7 and 168.8; *m*/*z* (EI) 518 (M^+, 0.4), 290 (36), 262 (100), 183 (52) and 91 (13); $[\alpha]_D^{20}$ +9.5 (*c* 1.45, $CHCl_3$).

(*S*)-4-Benzyloxy-2-methoxy-6-{5-[2-(2-hydroxypropyl)-1,3-dithian-2-yl]pentyl}benzoic acid 10

A solution of the ester **9** (1.50 g, 2.89 mmol) in a KOH solution [2 mol dm^{-3} in ethanol–water (1:1)] was refluxed for 2 h and then acidified to pH 5 with hydrochloric acid. The mixture was extracted with ethyl acetate and the extract dried and evaporated to give pure *compound* **10** (1.33 g, 91%) as a yellow oil (Found: C, 64.10; H, 7.28. $C_{27}H_{36}O_5S_2$ requires C, 64.25; H, 7.19%); ν_{max}(NaCl)/cm^{-1} 3420, 2934, 2858, 1720, 1603, 1585, 1454, 1423, 1161, 736 and 698; δ_H 1.20 (3 H, d, *J* 6.3, CH_3), 1.34–2.05 (11 H, m), 2.35 (1 H, dd, *J* 15.2 and 9.4), 2.72–2.80 (4 H, m, SCH_2 and $ArCH_2$), 2.88–3.05 (2 H, m, SCH_2), 3.85 (3 H, s, OCH_3), 4.13 (1 H, m, C*H*OH), 5.08 (2 H, s, OCH_2), 6.44 (1 H, d, *J* 2.1, ArH), 6.47 (1 H, d, *J* 2.1, ArH), 6.3–6.8 (2 H, br s, OH and COOH) and 7.32–7.44 (5 H, m, ArH); δ_C 23.5, 23.8, 25.0, 26.0, 26.4, 29.4, 30.9, 34.4, 39.6, 45.7, 52.0, 64.9, 70.1, 97.3, 108.2, 114.1, 127.6 (2 C), 128.2, 128.7 (2 C), 136.3, 145.8, 158.8, 161.0 and 169.7; *m*/*z* (EI) 504 (M^+, 4), 460 (7), 353 (12), 177 (20) and 91 (100); $[\alpha]_D^{20}$ +10.8 (*c* 0.51, $CHCl_3$).

(*R*)-3,4,5,6,7,8,9,10-Octahydro-12-benzyloxy-14-methoxy-3-methyl-5,5-(prop-1,3-ylenedithio)-1*H*-2-benzoxacyclododecin-1-one 11

Diethyl azodicarboxylate (2.00 g, 11.5 mmol) was added with stirring to a solution of triphenylphosphine (2.90 g, 11.1 mmol) in anhydrous toluene (1.3 dm^3) under nitrogen. After 20 min a solution of hydroxy acid **10** (1.10 g, 2.18 mmol) in a mixture of anhydrous toluene (15 cm^3) and THF (5 cm^3) was added very slowly (!) with a syringe pump to the reaction mixture. After 6 h about half of the solution had been added; at this point further diethyl azodicarboxylate (0.90 g, 5.17 mmol) and triphenylphosphine (1.40 g, 5.34 mmol) were added to the mixture followed by the remaining solution of **9**, added within 6 h. The mixture was stirred for a further 10 h at room temperature and then evaporated. Purification by FCC gave the lactone **11** (0.59 g, 56%) as a viscous colourless oil (Found: C, 66.27; H, 7.07. $C_{27}H_{34}O_4S_2$ requires C, 66.63; H, 7.04%); ν_{max}(NaCl)/cm^{-1} 2976, 2937, 2872, 2853, 1734, 1603, 1583, 1498, 1456, 1423, 1244, 1161, 1097, 738 and 700; δ_H 1.24–1.42 (12 H, m), 1.42 (3 H, d, *J* 6.4, CH_3), 2.50 (1 H, dd, *J* 15.9 and 7.4), 2.71–2.85 (4 H, m, 2 SCH_2), 3.00 (1 H, m), 3.75 (3 H, s, OCH_3), 5.03 (2 H, s, OCH_2), 5.47 (1 H, m, OCH), 6.37 (1 H, d, *J* 2.3, ArH), 6.38 (1 H, d, *J* 2.3, ArH) and 7.29–7.42 (5 H, m, ArH); δ_C 21.1, 22.5, 25.1, 25.8, 26.1, 26.3, 28.4, 31.2, 36.0, 43.8, 52.1, 55.9, 69.4, 70.0, 97.2, 107.0, 117.1, 127.5 (2 C), 128.1, 128.6 (2 C), 136.5, 142.7, 158.6, 160.5 and 167.5; *m*/*z* (EI) 486 (M^+, 8), 380 (25), 159 (9) and 91 (100); $[\alpha]_D^{20}$ +31.8 (*c* 0.87, $CHCl_3$).

(*S*)-3,4,5,6,7,8,9,10-Octahydro-12-benzyloxy-14-methoxy-3-methyl-5,5-(prop-1,3-ylenedithio)-1*H*-2-benzoxacyclododecin-1-one *ent*-11

Hydroxy acid **10** (1.07 g, 2.12 mmol), di(2-pyridyl) disulfide (0.60 g, 2.72 mmol) and triphenylphosphine (0.71 g, 2.71 mmol) were dissolved in anhydrous acetonitrile (50 cm^3). This solution was stirred at room temperature for 1 h and then added dropwise (!) over 2 h to a refluxing solution of anhydrous[4a] silver perchlorate (2.0 g, 9.6 mmol) in anhydrous acetonitrile (300 cm^3). At the end of the addition the mixture was refluxed for a further 30 min and then cooled to room temperature and evaporated. The residue was partitioned between a solution of sodium cyanide (5 g) in water (150 cm^3) and ethyl acetate (3 × 100 cm^3). Evaporation of the combined organic layers followed by FCC gave *compound ent*-**11** (0.63 g, 61%) as a viscous colourless oil. The spectroscopic data for *ent*-**11** were in full accordance with those of **11**; $[\alpha]_D^{20}$ −31.5 (*c* 0.66, $CHCl_3$).

(*R*)-Lasiodiplodin 1

Freshly prepared Raney nickel W7 (20 g) was added to a solution of compound **11** (0.25 g, 0.51 mmol) in anhydrous THF (20 cm^3) and the mixture was refluxed until TLC monitoring showed the absence of starting material (*ca.* 3 h). Filtration and purification by FCC gave *compound* **1** (0.12 g, 71%) as a white solid, mp 182 °C (from hexane–dichloromethane) (lit.,[1] 183–184 °C) (Found: C, 69.62; H, 8.50. $C_{17}H_{24}O_4$ requires C, 69.83; H, 8.27%); ν_{max}(KBr)/cm^{-1} 3304, 2974, 2951, 2930, 1680, 1604, 1460, 1450, 1429, 1292, 1194, 1163, 846 and 829; δ_H 1.33 (3 H, d, *J* 6.5, CH_3), 1.20–2.00 (12 H, m), 2.43–2.77 (2 H, m, $ArCH_2$), 3.77 (3 H, s, OCH_3), 5.28 (1 H, m, OCH), 5.5–6.1 (1 H, br s, OH), 6.20 (1 H, d, *J* 2.2, ArH) and 6.22 (1 H, d, *J* 2.2, ArH); δ_C 19.5, 21.3, 24.2, 25.5, 26.4, 30.1, 30.4, 32.3, 55.8, 72.6, 97.0, 108.4, 117.1, 143.0, 157.8, 157.9 and 169.5; *m*/*z* (EI) 292 (M^+, 86), 182 (100), 177 (68) and 138 (68); $[\alpha]_D^{20}$ +7.3 (*c* 0.86, MeOH) [lit.,[5a] +7.4 (*c* 0.94, MeOH)].

(*S*)-Lasiodiplodin *ent*-1

Compound *ent*-**1** was prepared in an analogous manner from *ent*-**11**. The spectroscopic data are in full accordance with those of **1**; $[\alpha]_D^{20}$ −7.1 (*c* 0.62, MeOH).

Acknowledgements

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References

1 D. C. Aldridge, S. Galt, D. Giles and W. B. Turner, *J. Chem. Soc. C*, 1971, 1623.
2 K. H. Lee, N. Hayashi, M. Okano, I. Hall and R. Y. Wu, *Phytochemistry*, 1982, **21**, 1119.
3 R. Cambie, A. Lat, P. Rutledge and P. Woodgate, *Phytochemistry*, 1991, **30**, 287.
4 (*a*) H. Gerlach and A. Thalmann, *Helv. Chim. Acta*, 1977, **60**, 2866; (*b*) S. Danishefsky and S. J. Etheredge, *J. Org. Chem.*, 1979, **44**, 4716; (*c*) A. J. Birch, N. S. Mani and G. S. R. Subba Rao, *J. Chem. Soc., Perkin Trans. 1*, 1990, 1423.
5 (*a*) M. Fink, H. Gaier and H. Gerlach, *Helv. Chim. Acta*, 1982, **65**, 2563; (*b*) M. Braun, U. Mahler and S. Houben, *Liebigs Ann. Chem.*, 1990, 513; (*c*) G. Solladié, A. Rubio, M. C. Carreno and J. L. Garcia Ruano, *Tetrahedron: Asymmetry*, 1990, **1**, 187; (*d*) G. B. Jones and R. S. Huber, *Synlett*, 1993, 367.
6 For an overview, see: E. Keinan, S. C. Sinha and A. Sinha-Bagchi, *J. Chem. Soc., Perkin Trans. 1*, 1991, 3333.
7 Q. Meng and M. Hesse, *Top. Curr. Chem.*, 1991, **161**, 107.
8 R. Bass, B. J. Banks, M. R. G. Leeming and M. Snarey, *J. Chem. Soc., Perkin Trans. 1*, 1981, 124.
9 D. Ghiringhelli, *Tetrahedron Lett.*, 1983, **24**, 287.
10 (*a*) R. Bernardi and D. Ghiringhelli, *J. Org. Chem.*, 1987, **52**, 5021; (*b*) H. Chikashita, E. Kittaka, Y. Kimura and K. Itoh, *Bull. Chem. Soc. Jpn.*, 1989, **62**, 833.
11 P. F. Deschenaux, T. Kallimopoulos and A. Jacot-Guillarmod, *Helv. Chim. Acta*, 1989, **72**, 1259.
12 F. Bracher and B. Schulte, *Nat. Prod. Lett.*, 1995, **7**, 65.
13 F. Bracher and B. Schulte, *Org. Prep. Proced. Int.*, 1995, **27**, 682.
14 T. Oh-e, N. Miyaura and A. Suzuki, *Synlett*, 1990, 221.
15 A related intramolecular hydroboration/cross coupling sequence starting from bromophenylalkenes was described to give benzo-fused cyclopentenes and cyclohexenes, but failed to give seven-membered rings: N. Miyaura, T. Ishiyama, H. Sasaki, M. Ishikawa, M. Satoh and A. Suzuki, *J. Am. Chem. Soc.*, 1989, **111**, 314.
16 For the preparation of macrocyclic lactones (*e.g.* zearalenone) by intramolecular Pd-catalysed coupling of an aryl iodide with a vinyl stannane, see, A. Kalivretenos, J. K. Stille and L. S. Hegedus, *J. Org. Chem.*, 1991, **65**, 2883.
17 For an example of reductive desulfurization without affecting a benzyl ether, see, D. Dobson, A. Todd and J. Gilmore, *Synth. Commun.*, 1991, **21**, 611.
18 O. Mitsunobu, *Synthesis*, 1981, 1.
19 H. Adkins and H. R. Billica, *J. Am. Chem. Soc.*, 1948, **70**, 655.

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