Hexulose Derivatives and Lipase-Mediated Diastereomeric Resolution in the Enantiospecific Total Synthesis of (−)-Talaromycins C and E

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Diastereomeric enzymatic (Chirazyme® L-2, c.-f., C2) resolution of 3-C-acetoxymethyl-1,2,3,4,5-pentadeoxy-6:7:8:9-di-O-isopropylidene-β-D-gluc- and -D-manno-dec-6-ulo-6,10-pyranose (6), obtained from “diacetone d-fructose aldehyde” (3) and the corresponding phosphorane from (3-benzyloxy-2-ethylpropyl)triphenylphosphonium iodide (2), has enabled us to synthesize spiroketal (3R,4S,5S,6R,9R)- and (3R,4S,5S,6R,9S)-9-ethyl-3,4-isopropylidenedioxy-1,7-dioxaspiron[5.5]undecane (7 and 8). An attempt to transform 8 into (−)-talaromycins G and 9-epi-A was unsuccessful. However, (−)-talaromycins C and E could be enantiospecifically prepared from spiroketal 7 in twelve steps.

Introduction

Talaromycins (see Scheme 1), spiroketal mycotoxins, are produced by the fungus Talaromyces stipitatus. Talaromycins A and B were isolated and identified for the first time by Lynn et al.,[1] but in a reinvestigation, the same group[2] was also able to observe the presence of additional isomers such as talaromycins C, D, E, G, and F,[3] differing only in the configuration of the stereogenic centres in the A (C-3,4) and B (C-9) rings. Some of these compounds, as well as others with structures representing estrone-talaromycin hybrids, were shown to be active against neuroblastoma[2] and human lung cancer cells,[4] respectively.

Scheme 1. Talaromycins

Enantiospecific syntheses of talaromycins A and B based on various synthetic approaches can be found in the literature,[5] that reported by our own group,[6] in which d-fructose is used as a chiral starting material, among them. To the best of our knowledge, however, no enantiospecific syntheses of the rest of the talaromycins in Scheme 1 (C, D, E, etc.) have been reported to date. Retrosynthetic analysis (Scheme 2) indicates that transformation of talaromycins A, B, and 9-epi-A−G into the corresponding talaromycins C−E and D−F, would be feasible through inversion of the configuration at C-4, as has been previously proved to be the case in less highly elaborated analogues.[7] The four latter talaromycins would thus be prepared from the common 1,2,3,4,5-pentadeoxy-3-C-hydroxymethyldec-6-ulo-se intermediate 5, depending on the C-3 configuration (starred carbon atom).

A synthesis of the (3R) intermediate dec-6-ulo-se derivative 5, representing the formation of the spiroketal structure of talaromycins A, B, C, and E in a chiron with the required structure, functionalization, and stereochemistry, and obtained by enzymatic desymmetrization of 2-ethyl-1,3-propanediol, was recently reported by our group.[8] Unfortunately, a later attempt to obtain the corresponding (3S)-5 was unsuccessful, since the same chirality was obtained even after the use of different enzymes.[9] In order to generalize this synthetic approach, a similar, but racemic, synthon has now been used for the preparation of (3RS)-5, which was then submitted to a diastereomeric enzymatic resolution. In addition, the protected d-fructose derivative used in this paper may be viewed as an excellent chiral starting material for general synthesis of compounds with the 1,7-dioxaspiron[5.5]undecane skeleton, in accordance with results previously reported,[6,10] in terms not only of the partial transfer of the inherent chirality in the sugar to the target molecule, but also even of control over the stereochemistry of the spiroketalization process. In this context, we now report the first synthesis of enantiosymmetrically pure talaromycins C and E, which represent a novel and straightforward route to mycotoxin talaromycins.
Results and Discussion

Treatment of 1-O-benzyl-2-ethyl-3-iodopropanol[11] (1) with triphenylphosphane in dry toluene afforded the corresponding phosphonium salt 2. Subsequent treatment of 2 with “diacetone α-fructose aldehyde”[6] (3) in the presence of potassium tert-butoxide gave 3-C-(benzoxymethyl)-1,2,3,4,5-pentadeoxy-6,7,8,9-di-isopropylidene-β-d-gluc- and -d-manno-dec-4-ene-6-ul-6,10-pyranose (4) as a mixture of (E) and (Z) isomers, which was subsequently hydrogenated to give the related (3RS)-5 (89% yield), the physical and spectroscopic data of which were as previously reported[6] (see Scheme 3).

Diastereomeric resolution of (3RS)-5 was performed by partial esterification with an immobilized enzyme as catalyst. Thus, treatment of (3RS)-5 in diethyl ether with vinyl acetate in the presence of Chirazyme® L-2, c.-f., C2 gave the corresponding acetate derivative (3S)-6 together with unreacted (3R)-5 (see Scheme 4 and Figure 1). It was not possible to determine the diastereomeric excess of either
compound by GLC, even in a capillary β-DEX® 325 column, their transformation into the spiroketsals (3R,4S,5S,6R,9R)- and (3R,4S,5S,6R,9S)-9-ethyl-3,4-isopropylidenedioxy-1,7-dioxaspiro[5.5]undecane (7 and 8)\textsuperscript{[12]} as shown in Scheme 4, being necessary. This was achieved by treatment with acetonitrile/sulfuric acid, which brought about concomitant isopropylidene ation at the C-3,4 positions. Since the result was only a small diastereomeric excess, the partial enzymatic hydrolysis of (3RS)-6 was also investigated (see Figure 1), and this gave a better diastereomeric excess. This may be attributable either to the larger size or the hydrophobicity of the substituent at the stereocentre.

An attempt to transform 8 into the related talaromycin G and 9-epi-talaromycin A was carried out as follows. Compound 8 was deoxygenated by a modified Barton procedure\textsuperscript{[13]} through its 5-O-xanthate (9) to afford 10 (in 89% yield from 8), which was submitted to acid hydrolysis in order to obtain the required free 3,4-diol (13). Unfortunately, however, a complex mixture was produced, from which it was possible to isolate and identify the expected spiroketal 13 (52%) together with 11 (20%) and 12 (23%). The structures of 11 and 12 were determined on the basis of the following results. A dramatic change in the values and signs of their optical rotations would indicate that inversion of the configuration at the spiroketal centre had occurred. On the other hand, the \textsuperscript{13}C chemical shift values for the spiro carbon atom – δ = 96.55 for 11 and 106.87 for 12 – suggested\textsuperscript{[14]} a 1,7-dioxaspiro[5.5]undecane and a 1,6-dioxaspiro[4.5]decane, respectively. In addition, 8a-H in 11 and 7a-H in 12 appeared as triplets (J = 10.9 Hz), indicating equatorial dispositions of the ethyl groups at C-9 and C-8, respectively. Compounds 11 and 12 could arise through acid-catalysed isomerization of 13, which would alleviate the steric strain produced by the axial ethyl group in 13; this could be demonstrated during the recording of its NMR spectrum, in which traces of acid in the solvent (Cl\textsubscript{3}CD) promoted its isomerization. These findings prompted the authors to give up this attempt.

Compound 7 was transformed into the known diol 16 by a previously reported procedure\textsuperscript{[6]} but including C-5 deoxygenation by the modified Barton procedure mentioned above (Scheme 6). Compound 16 was regioselectively O-silylated at C-4 by way of its n-dibutylstannylene derivative 17 to afford 18 (in 72% yield from 16), which was oxidised with PCC to afford the corresponding ketone 19, which was coupled with methylenetriphenylphosphorane to afford 20. Hydroboration/oxidation of 20 gave an unresolved mixture (3:7 ratio) of 4-O-silylated talaromycins B (21) and A (22), which were separated as their benzoyl derivatives 23 and 24, respectively.

Compounds 23 and 24 were O-desilylated to afford 25 (50%) and 28 (82%), together with minute quantities of their corresponding 12-O → 4-O benzoyl group migration compounds (26, 12.5% and 29, 8%, respectively, Scheme 7). Both 25 and 28 were submitted to a Mitsunobu reaction\textsuperscript{[15]} with Ph\textsubscript{3}P/3,5-dinitrobenzoic acid/DEAD to give 27 (quantitative) and 30 (45%). Finally, Zemplen deacetylation of 27 and 30 gave the expected target molecules (−)-talaromycins E (72%) and C (86%), respectively.

The results described above indicate that the use of the chiral pool (carbohydrates) combined with chiral catalysts (l一下子), both from natural sources, may be an excellent methodology by which to overcome many problems in the stereoselective synthesis of complex biologically active natural products.
Scheme 5. Deisopropylidenation of 10: a: NaH/THF/imidazole/CS₂/MeI; b: H₃PO₄/dioxane/H₂O/Et₃N/AIBN; c: AcOH/H₂O/40 °C/45 min

Scheme 6. Synthesis of protected (−)-talaromycins B (23) and A (24): a: NaH/THF/imidazole/CS₂/MeI; b: H₃PO₄/dioxane/H₂O/Et₃N/AIBN; c: AcOH/H₂O/50 °C/1 h; d: nBu₂SnO/MeOH; e: TBDMSCl/dioxane; f: PCC/CH₂Cl₂/NaAcO/MS (4 Å); g: NaCH₂SOCH₃/Ph₃PCH₃Br/DMSO; h: BH₃/THF, then NaOH/H₂O₂; i: BzCl/Et₃N/CH₂Cl₂

Experimental Section

General Remarks: Solutions were dried with MgSO₄ before concentration under reduced pressure. The ¹H and ¹³C NMR spectra were recorded with Bruker AM 300, AXM 300, ARX 400, and AMX 500 spectrometers for solutions in CDCl₃ (internal Me₄Si). IR spectra were recorded with a Perkin–Elmer 782 instrument and mass spectra with a Micromass Mod. Platform II and Autospec-Q mass spectrometers. Optical rotations were measured for solutions in CHCl₃ (1-dm tube) with a Jasco DIP-370 polarimeter. GLC was performed with a Hewlett Packard 6890 gas chromatograph equipped with a split/splitless injector, a flame-ionisation detector, and a capillary HP-5 column (30 m × 0.25 mm i.d. × 0.25 μm film thickness) at 3 min at 180 °C, program to 250 °C, 10 °C/min. The He flow rate was 1.1 mL/min, the injection port and the zone-detector temperatures were 275 °C. TLC was performed on precoated 60 F₂₅₄ silica gel aluminium sheets and detection was by charring with H₂SO₄. Column chromatography was performed on silica gel (Merck, # 7734). Spectroscopic (¹H and ¹³C NMR, MS) and/or analytical data were obtained with chromatographically homogeneous samples.

(3-Benzoyloxy-2-ethylpropyl)triphenylphosphonium Iodide (2): A solution of triphenylphosphane (2.67 g, 10.2 mmol) and 1-O-benzyl-2-ethyl-3-iodopropanol[11] (1; 3.1 g, 10.2 mmol) in dry toluene (50 mL) was heated under reflux for 3 d. During this time, 2 (8.2 g, 81%) precipitated as a white crystalline solid, which was collected by filtration, washed with diethyl ether and dried; m.p. 167–168 °C. IR (KBr): ν ~ 5305, 3051, 3025, 756, and 694 cm⁻¹ (aromatic). ¹H NMR: δ = 7.85–7.21 (3 m, 20 H, 4 Ph), 4.33 and 4.29 (2 d, 2 H, J = 11.3 Hz, PhCH₂), 3.97 (td, 1 H, J = 1a,2 = 5.2, J = 1a,1b = 13.6, J = 1a,1b = 13.6), 3.58–3.49 (m, 2 H, 1b,3b-H), 2.02 (m, 1 H, 2-H), 1.49 and 1.20 (2 m, 2H, CH₂CH₃), 0.78 (t, 3 H, J = 7.43 Hz, CH₂CH₃). ¹³C NMR: δ = 137.70, 134.90, 133.81, 133.71, 130.44, 130.32, 128.21, 127.91, 127.82
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Scheme 7. Synthesis of (−)-talaromycins E and C: a: nBu2NH·3H2O/THF; b: Ph3P/3,5-dinitrobenzoic acid/DEAD/48 h/ room temp.; c: NaMeO/MeOH

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119.54 and 118.69 (Ph), 73.20 and 72.12 (C-3,PhCH3), 36.47 (C-2), 25.72 and 25.35 (C-1, CH2CH3), 11.62 (CH2CH3), C30H32O2P (566.44): calc'd C 63.61, H 5.69; found C 63.19, H 5.55.

3-C-(Benzylxymethyl)-1,2,3,4,5-pentadecane-6,7,8,9-di-O-isopropylidene-β-d-glucopyranosyl-β-d-manno-dec-4-eno-6-ulo-6,10-pyranose (4): A solution of nBuOK (2.23 g, 19 mmol) in dry THF (15 mL) was added dropwise under argon to a stirred solution of 2,3,4,5-di-O-isopropylidene-β-d-arabinopyranose (3g) (4.8 g, 18.6 mmol) and compound 2 (9.8 g, 17.3 mmol) in the same solvent (70 mL). After 10 min, the resulting orange solution became brown and the reaction mixture was left at room temperature for 1 h. GLC then revealed the absence of 3 and the presence of two new compounds (tR = 15.36 and 15.60 min). The solvent was evaporated and the residue was partitioned between diethyl ether and water.

The organic phase was separated and the aqueous phase was extracted with diethyl ether (2 × 20 mL). The combined organic extracts were washed with brine and concentrated. Column chromatography (diethyl ether/hexane, 1:3) of the residue gave 4 (5.36 g, 74%), as a mixture of (E) and (Z) isomers. An aliquot was cautiously rechromatographed to afford first (Z)-4 and then (E)-4. 1H NMR (inter alia): (Z)-4: δ = 5.61 and 5.60 (2 d, J4,5 = 11.7 Hz, 5-H), 5.42 and 5.38 (2 dd, J3,4 = 9.8 Hz, 4-H); (E)-4: δ = 5.90 and 5.89 (2 dd, J4,5 = 15.4, J3,4 = 8.7 Hz, 4-H), 5.66 and 5.63 (2 d, 5-H). HRMS (LSIMS): found 419.2435 ([M + Na]+); calc'd 419.2434.

1,2,3,4,5-Pentadecane-6,7,8,9-di-O-isopropylidene-β-d-glucopyranosyl-β-d-manno-dec-4-eno-6-ulo-6,10-pyranose (5): A solution of (E)-4 (5.36 g, 12.4 mmol) in methanol (60 mL) was hydrogenated [75 psi (5.2 bar) H2] over 10% Pd-C (125 mg) for 48 h. GLC then showed the absence of (E)-4 and the presence of a new compound (tR = 9.16 min). The catalyst was filtered off and washed with methanol, and the combined filtrate and washings were concentrated. Column chromatography (diethyl ether/hexane, 1:1) of the residue gave pure 5 (3.76 g, 89%) as a colourless syrup that showed the same spectroscopic data as previously reported.[9]

Partial Enzymatic (Chirazyme® L-2, c.-f., C2) Acetylation of 5: Chirazyme® L-2, c.-f., C2 (300 mg) was added to a gently stirred solution of 5 (7.8 g, 23.6 mmol) in diethyl ether (100 mL) and vinyl acetate (10 mL, 100 mmol) and the mixture was kept at room temperature and monitored by GLC. After 1 h, at least 50% conversion had occurred. The reaction was quenched by filtering off the enzyme and thoroughly washing with diethyl ether. The combined filtrate and washings were concentrated and the residue was chromatographed (diethyl ether/hexane, 1:2 → diethyl ether), to yield (3S)-6 (4.32 g, 49%) first. [α]D20 = −6.6 (c = 1). IR (film): ν = 1740 (OAc), 1382 and 1373 cm−1 (CMc2). 1H NMR: δ = 4.54 (dd, 1 H, J3,8 = 2.4, J5,6 = 8 Hz, 8-H), 4.20 (dd, 1 H, 9-H), 4.06 (d, 1 H, 7-H), 3.97 (m, 2 H, CH2OAc), 3.82 (dd, 1 H, J3,8 = 1.9), 3.69 (d, 1 H, 10eq-H), 2.02 (s, 3 H, Ac), 1.89−1.51 (m, 5 H, 3, 4, 4, 5, 5′-H), 1.50, 1.45, and 1.32 (3 s, 12 H, 2 CMc2), 1.39−1.32 (m, 2 H, 2,2-H), 0.88 (t, 3 H, J3,8 = 7.4 Hz, 1,1,1-H). 13C NMR: δ = 171.40 (MeCO), 108.94 and 107.42 (2 CMc2), 104.21 (C-6), 73.90 (C-7), 70.89 and 70.67 (C-8,9), 66.71 (C-1), 60.97 (C-10), 38.71 (C-3), 38.07 (C-5), 26.48, 25.85, 25.16, and 24.16 (2 CMc2), 23.98 and 23.58 (C-2,4), 21.07 (MeCO), 10.89 (C-1). HRMS (LSIMS): found 395.2043 ([M + Na]+); calc'd 395.2046. The second fraction was (3R)-5 (3.8 g, 48.7%). [α]D20 = −12.7 (c = 1). The physical and spectroscopic data of which matched those previously reported.[9] Zemplen deacylation of (3S)-6 with 0.5 M NaOMe in methanol afforded, after workup and column chromatography (diethyl ether), (3S)-5 (quantitative); tR = 9.16 min; [α]D20 = −6.9 (c = 1).

Spiroketalization of (3R)- and (3S)-5: A solution of (3R)-5 (3.8 g, 11.5 mmol) in a 20:1 acetone/conc. H2SO4 mixture (80 mL) was kept at room temperature for 8 h. GLC then revealed that (3R)-5 had disappeared and that two new compounds were present in a 4:1 ratio. The reaction mixture was neutralised (NH3), filtered, and concentrated. Column chromatography (diethyl ether/hexane, 1:3) first gave crystalline (3R,4S,5S,6S,9R,9′-ethyl-5-hydroxy-3,4-isopropylidenedioxy-1,7-dioxaspiro[5.5]undecane)[9] (7, 820 mg), tR = 7.61 min. Eluted second was a mixture of 7 and its 9-epimer 8 (1.25 g). Treatment of (3S)-5 (3.77 g, 11.4 mmol) as above gave 7 and 8 in a 2:3 ratio (GLC). Workup of the reaction mixture as above allowed the isolation of 7 (700 mg), a mixture of 7 and 8 (500 mg) and finally pure, crystalline 8 (865 mg) ([α]D20 = 865 mg), tR = 7.51 min.

Acetylation of (3RS)-5: DMAP (135 mg), Et3N (8.6 mL, 61 mmol), and Ac₂O (5.9 mL, 61 mmol) were added to a solution of (3RS)-5 (13.2 g, 40 mmol) in dry CH2Cl2 (50 mL), and the mixture was kept at room temperature for 6 h. TLC (diethyl ether/hexane, 1:2) then revealed the presence of a faster-running compound. Workup of the reaction mixture as usual, followed by column chromatography (diethyl ether/hexane, 1:3), afforded (3RS)-6 (14.3 g, 96%).

Partial Enzymatic (Chirazyme® L-2, c.-f., C2) Hydrolysis of (3RS)-6: The title enzyme (3 g) was added to a gently stirred suspension of (3RS)-6 (4 g, 10.7 mmol) in 50 mL of a buffered (pH = 7) aqueous 0.5 M phosphate solution (KH2PO4). Stirring was maintained for 3.5 h. GLC analysis of the mixture then showed 50% conversion. The enzyme was filtered off, and the filtrate was saturated with NaCl and repeatedly extracted with diethyl ether. Concentration of the extract and column chromatography (diethyl ether/hexane, 1:2) of the residue afforded (3R)-6 (1.77 g, 44%) and (3S)-5 (1.35 g, 38%). Zemplen decacylation of (3R)-6 (1.77 g, 4.5 mmol) as above gave (3R)-5 (1.57 g, quantitative).

Spiroketalization of (3S)- and (3R)-5 Produced from the Enzymatic Hydrolysis: Treatment of (3S)-5 (1.35 g, 4.1 mmol) with acetone/conc. sulfuric acid under the conditions described above afforded 7 and 8 in a 1:9 ratio (GLC). Workup of the reaction mixture as above first gave 7 (50 mg), then a mixture of 7 and 8 (125 mg), and

finally 8 (704 mg). In the same manner, (3R)-5 (1.57 g, 4.76 mmol) was transformed into a mixture of 7 and 8 in a 6:1 ratio (GLC). This was partially resolved, after workup and column chromatography, into 7 (675 mg), a mixture of 7 and 8 (145 mg) and, finally, 8 (135 mg).

(3R,4R,5S,6R,9S)-9-Ethyl-3,4-isopropylidenedioxy-5-[methylthiothiocarbonyloxy]-1,7-dioxaspiro[5.5]undecane (9): A solution of 8 (2.18 g, 8.8 mmol) in anhydrous THF (10 mL) was added under argon at room temperature to a stirred suspension of NaI (480 mg, 16 mmol, 80% oil dispersion) in the same solvent (20 mL) and imidazole (50 mg). After 30 min, carbon disulfide (1.13 mL, 18.8 mmol) was added, followed after an additional 30 min by methyl iodide (1.2 mL, 19 mmol). The mixture was stirred for 1 h. TLC (diethyl ether/hexane, 3:2) then showed the presence of a faster-running compound. The excess hydride was destroyed by a cautious addition of diethyl ether saturated with water (5 mL), and then water (5 mL). The organic phase was separated and the aqueous phase was extracted with diethyl ether (3 × 10 mL). The combined extracts were washed with brine and water, and concentrated, and the residue was chromatographed (diethyl ether/hexane, 1:3) to yield syrupy 9 (2.8 g, 97%); tR = 12.8 min. [α]D 32 +118 (c = 1). IR (film): ν = 3471 cm⁻¹ (OH). 1H NMR: δ = 3.92 (1H, 1H, 4-H), 3.66–3.57 (3H, 3 CH2, 3 eq-H). 13C NMR: δ = 95.45 (C-6), 76.82 (C-3), 66.32 (C-4), 65.74 (C-8), 59.35 (C-2), 36.69 (C-5), 36.41 (C-9), 34.43 (C-11), 25.15 and 24.49 (C-10, CH₃CH₂). HRMS (LSIMS): found 239.1259 [M⁺ + Na⁺]; calcd. 239.1259. Eluted second was (2R,3S,5S,8S)-8-ethyl-3-hydroxy-2-hydroxymethyl-1,6-dioxaspiro[5.5]decane (12) [370 mg, 23%]. [α]D 32 +98 (c = 1). IR (film): ν = 3467 cm⁻¹ (OH). 1H NMR: δ = 4.08 (2H, 2H, 3,4-H), 3.59 (1H, 1H, 3ax,8eq-H), 3.47 (1H, 1H, 4ax,8eq-H), 0.86 (1t, J = 7.4 Hz, 3H, CH₃CH₂). 13C NMR: δ = 106.87 (C-5), 88.06 (C-2), 73.81 (C-3), 66.30 (C-7), 63.30 (C-2'), 46.37 (C-4), 36.68 (C-8), 32.66 (C-10), 25.91 and 25.13 (C-9, CH₃CH₂), 11.22 (CH₃CH₂). HRMS (LSIMS): found 239.1258 [M⁺ + Na⁺]; calcd. 239.1259. Finally, the third fraction was (3R,4S,5R,9S)-9-ethyl-3,4-dihydroxy-1,7-dioxaspiro[5.5]undecane (13) [850 mg, 52%]. [α]D 32 −104 (c = 1). IR (film): ν = 3348 cm⁻¹ (OH). 13C NMR: δ = 96.58 (C-6), 67.84 (C-3), 66.34 (C-4), 65.77 (C-8), 59.35 (C-2), 39.72 (C-5), 36.44 (C-9), 34.45 (C-11), 25.16 and 24.51 (C-10, CH₃CH₂), 11.13 (CH₃CH₂). HRMS (LSIMS): found 239.1260 [M⁺ + Na⁺]; calcd. 239.1259.

(3R,4S,5R,9S)-9-Ethyl-3,4-isopropylidenedioxy-1,7-dioxaspiro[5.5]undecane (10): Et₃N (6.7 mL, 47 mmol) and aqueous 50% H₂PO₃ (50%, 5 mL) were added to a solution of 9 (2.95 g, 8.15 mmol) in dioxane (50 mL), and the mixture was refluxed for 90 min. During this time, AIBN (200 mg) was added portionwise (25 mg each). The reaction was monitored by GLC, showing the presence of 10 (tR = 5.38 min). The solvent was evaporated, water (30 mL) was added, and the resulting suspension was extracted with diethyl ether (3 × 10 mL). The combined extracts were concentrated and the residue was submitted to column chromatography (diethyl ether/hexane, 1:3) to yield pure 10 (1.92 g, 92%) as a syrup. [α]D 22 +149 (c = 1). IR (film): ν = 1382 and 1371 cm⁻¹ (C=O). 1H NMR: δ = 4.38 (1t, 1H, 4ax,8eq-H), 3.21 (1H, 1H, 3ax,8eq-H), 1.95 (s, 6H, CMe₂). 13C NMR: δ = 65.74 (C-8), 65.71 (C-9), 32.66 (C-10), 16.60 (21.59 (C-10, CH₃CH₂), 19.32 (MeS), 12.36 (CH₃CH₂). HRMS (LSIMS): found 363.1294 [M⁺ + Na⁺]; calcd. 363.1300.
and heated at 40 °C for 3 d. TLC (diethyl ether/hexane, 1:2) then revealed a faster-running compound. Methanol (1 mL) was added and the reaction mixture was stirred for 15 min and then concentrated. Column chromatography (diethyl ether/hexane, 1:6) of the residue gave 18 (1.74 g, 72%); tN = 8.9 min. [α]bD 25 = −97 (c = 1). IR (film): ν = 3578 cm−1 (OH). 1H NMR: δ = 4.11 (ddd, 1 H, J9,11ax = 5.5, J9,11eq = 11.1, J9ax,9eq = 3.4 Hz, 4-H), 3.80 (dd, 1 H, J9ax,9eq = 12.7, J9ax-3 = 2 Hz, 2ax-H), 3.65 (dd, 1 H, 2eq-H), 3.64 (dd, 1 H, 3-H), 3.52 (br. d, 1 H, 1eq-H), 3.20 (t, 1 H, J9ax,9eq = J9ax-3 = 10.8 Hz, 8ax-H), 2.53 (d, 1 H, J11ax-1 = 18.8 Hz, OH), 1.75 (t, 1 H, J9ax,9eq = 11.1 Hz, 5ax-H), 1.81−1.41 (3 m, 6 H, 5eq,9ax,10ax,10eq,11ax,11eq-H), 1.14 (m, 2 H, CH2(CH3)), 0.88 (s, 9 H, CMe3), 0.87 (t, J = 7.5 Hz, 3 H, CH3(CH2)5), 0.08 (s, 6 H, SiMe2). 13C NMR: δ = 97.08 (C-6), 68.17 (C-3), 66.53 (C-4), 65.63 (C-8), 62.11 (C-2), 38.84 (C-5), 36.81 (C-9), 35.15 (C-11), 25.84 (C-Me), 25.32 and 24.86 (C-10, CH2(CH3)5), 18.06 (C-Me), 11.27 (CH3(CH2)5), −4.42 and −4.68 (SiMe2). HRMS (LISMS): found 331.2307 [M+ + 1]; calcd. 331.2305.

(4S,6R,9R)-4-(tert-Butyldimethylsilyloxy)-9-ethyl-3-oxo-1,7-dioxaspiro[5.5]undecane (19): Sodium acetate (180 mg, 2.2 mmol), molecular sieves (4 Å, powder; 2.5 g), and pyridinium chlorochromate (2.4 g, 11 mmol) were added to a stirred and cooled (ice/water) solution of 18 (1.9 g, 5.75 mmol) in anhydrous CH2Cl2 (25 mL). Stirring was maintained at room temperature for 30 min. TLC (diethyl ether/hexane, 1:2) then revealed a new compound of higher mobility. The mixture was diluted with diethyl ether (50 mL) and stirred for 1 h, filtered through silica gel G and concentrated to a residue that was percolated (diethyl ether) through silica gel to give 19 (1.55 g, 82%) as a colourless syrup, tN = 8.6 min. IR (film): ν = 1744 cm−1 (C=O). This was used in the next step.

(4S,6R,9R)-4-(tert-Butyldimethylsilyloxy)-9-ethyl-3-methylen-1,7-dioxaspiro[5.5]undecane (20): Methyltriphenylphosphonium bromide (4.3 g, 12 mmol) was added under argon to a stirred solution of NaCH2SOMe produced from a dispersion of sodium hydride in oil (80%, 376 mg, 12.4 mmol) and imidazole (62 mg) in anhydrous methyl sulfoxide (20 mL). The mixture was stirred for 15 min and a solution of 19 (1.55 g, 4.73 mmol) in anhydrous diethyl ether (10 mL) was added dropwise. After 30 min, TLC (diethyl ether/hexane, 1:1) then revealed a new compound of higher mobility. The reaction mixture was diluted with water (20 mL) and extracted with diethyl ether (3 × 15 mL). The combined extracts were concentrated and the residue was chromatographed (diethyl ether/hexane, 1:10) to yield 20 (1 g, 64% from 18) as a colourless syrup, tN = 7.8 min. [α]bD 25 = −98 (c = 1). IR (film): ν = 1665 cm−1 (C=C). 1H NMR: δ = 5.13 (t, 1 H, J9,11ax = 12.1, 2ax-H), 4.93 (br, s, 1 H, J12-12′, 4-H), 4.57 (m, 1 H, 1-H), 4.15 (d, 1 H, J9ax,9eq = 12.1, 2ax-H), 3.96 (d, 1 H, 2eq-H), 3.59 (br. dd, 1 H, J9ax,9eq = 9.3 Hz, 3eq-H), 3.02 (t, 1 H, J9ax,9eq = J9ax,9eq = 10.9 Hz, 8ax-H), 2.00 (dd, 1 H, J9ax,9eq = 5.7, J9ax,9eq = 12.4 Hz, 7eq-H), 1.71−1.36 (5 m, 5 H, 9,10ax,10eq,11ax,11eq-H), 1.51 (t, 1 H, J9ax,9eq = 12.5 Hz, 5ax-H), 1.17 (m, 2 H, CH2(CH3)5), 0.93 (s, 9 H, CMe3), 0.90 (t, J = 7.3 Hz, 3 H, CH3(CH2)5), and 0.10 (s, 6 H, SiMe2). 13C NMR: δ = 146.93 (C-3), 107.17 (C-12), 97.72 (C-6), 67.10 (C-4), 65.55 and 64.34 (C-2,8), 47.32 (C-5), 36.82 (C-9), 35.11 (C-11), 25.94 (C-Me), 25.37 and 25.05 (C-10, CH2(CH3)5), 18.33 (C-Me), 11.27 (CH3(CH2)5), −4.69 and −4.84 (SiMe2). HRMS (LISMS): found 327.2350 [M+ + 1]; calcd. 327.2356.

Hydroboration/Oxidation of 20: BH3·SiMe2 (10 m, 0.4 mL, 4 mmol) was added, dropwise under argon, to an ice-cooled and stirred solution of 20 (660 mg, 2.02 mmol) in anhydrous THF (10 mL). After 2 h, aqueous NaOH (3 m, 5 mL), and aqueous H2O2 (30%, 5 mL) were added dropwise and the mixture was stirred for 30 min at room temperature. The reaction mixture was extracted with diethyl ether (3 × 10 mL) and the combined extracts were concentrated. Column chromatography (diethyl ether/hexane, 1:5) of the residue gave an inseparable mixture (510 mg) of (3R,4S,6R,9R)-4-(tert-butyldimethylsilyloxy)-9-ethyl-3-hydroxy-1,7-dioxaspiro[5.5]undecane (21) and its (3S,4S,6S,9R)-epimer 22 in a 3:7 ratio, as a colourless syrup. GLC analysis: 22 (tN = 9.99) and 21 (10.16 min).
10.8, J$_{2ax,2eq}$ = 5.0 Hz, 4-H), 3.84 (dd, 1 H, J$_{2eq,3}$ = 4.7, J$_{2ax,2eq}$ = 11.5 Hz, 2eq-H), 3.56 (t, 1 H, J$_{3ax,3}$ = 11.5 Hz, 2ax-H), 3.51 (m, 1 H, 8eq-H), 3.21 (t, 1 H, J$_{3ax,3}$ = J$_{3ax,3}$ = 10.9 Hz, 8ax-H), 2.05 (dd, 1 H, J$_{1ax,12}$ = 12.7 Hz, 5eq-H), 1.97 (m, 1 H, 3-H), 1.48 (dd, 1 H, 5ax-H), 1.75–1.06 (2 m, 7 H, 9ax,10ax,11eq,11ax,11eq-H, CH$_2$CH$_3$), and 0.87 (t, J = 7.4 Hz, 3 H, CH$_3$CH$_2$). $^{13}$C NMR: δ = 167.02 (CO), 133.25, 129.73, and 128.52 (Ph), 97.34 (C-6), 65.37 (C-8), 65.10 (C-4), 63.14 and 61.13 (C-2,12), 44.37 (C-3), 44.16 (C-5), 35.25 (C-9), 25.26 and 24.89 (C-10,CH$_3$), and 11.20 (CH$_3$CH$_2$). HRMS (LSIMS): found 357.1673 [M$^+$ + Na$^+$]; calcld. 357.1678.

The second fraction was (3S,4S,6R,9R)-4-benzoxyloxy-9-ethyl-3-hydroxyethyl-1,7-dioxaspiro[5.5]undecane (26): 100 mg (0.17 mmol) was treated with Bu$_3$NF-3H$_2$O (355 mg, 1.25 mmol). Workup of the reaction mixture and chromatography first gave syrup 28 (220 mg, 82%). $^{13}$C NMR: δ = 8.05–7.45 (3 m, 5 H, Ph), 5.51 (dt, 1 H, J$_{4ax,5}$ = J$_{4ax,5}$ = 11.2, J$_{4ax,5}$ = 5.1 Hz, 4-H), 3.85 (t, 1 H, J$_{2ax,2eq}$ = J$_{2ax,2eq}$ = 11.5 Hz, 2ax-H), 3.87 (dd, 1 H, J$_{1ax,12}$ = 12.3, J$_{1ax,12}$ = 4 Hz, 12-H), 3.61–3.51 (m, 1 H, 8eq, 3-H), 2.41 (dd, 1 H, J$_{1ax,9}$ = J$_{1ax,9}$ = 12.3 Hz, 5eq-H), 1.76 (t, 1 H, 5ax-H), 1.08–1.07 (m, 8 H, 3,9ax,10ax,10eq,11eq,11ax,11eq-H, CH$_2$CH$_3$), 0.89 (t, J = 7.5 Hz, 3 H, CH$_3$CH$_2$). $^{13}$C NMR: δ = 167.31 (CO), 133.38, 129.85, 129.69, 128.51 (Ph), 97.16 (C-6), 68.66 (C-4), 65.36 (C-8), 61.47, 59.78 (C-2), 44.53 (C-3), 41.11 (C-5), 36.73 (C-9), 35.20 (C-11), 25.28 and 24.93 (C-10,CH$_3$), 11.23 (CH$_3$CH$_2$).
Enantiospecific Total Synthesis of (−)-Talaromycins C and E

FULL PAPER

Enantiospecific Total Synthesis of (−)-Talaromycins C and E

(3R,4R,6R,9R)-9-Ethyl-4-hydroxy-3-hydroxymethyl-1,7-dioxaspiro-[5.5]undecane [(−)-Talaromycin C]: Zemplen deacylation of 30 (120 mg, 0.23 mmol) with 0.5 m NaOMe in anhydrous methanol (10 mL), followed by the same workup as above, gave (−)-talaromycin C (45 mg, 86%) as a viscous, colourless oil. [α]D27 = 52.122 (c = 1). 1H NMR (500 MHz; C6D6): δ 4.08 (br. dd, 1 H, J2,3 = 3.2, J2,2 = 11.8 Hz, 2-H), 4.08 (br. s, 1 H, 4-H), 3.64 (d, 1 H, 29-H), 3.56 (dd, 1 H, J12,12 = 10.6, J3,12 = 7.8 Hz, 12-H), 3.46 (dd, 1 H, J12,12 = 6.9 Hz, 12-H), 3.33 (ddd, 1 H, J8eq,9,1 = 4.5, J8eq,10eq = 1.8 Hz, 8eq-H), 3.21 (t, 1 H, J8ax,8eq = 11 Hz, 8ax-H), 1.88 (m, 1 H, 3-H), 1.78 (br. dd, 1 H, J8,8 = 14.4, J4,5 = 2.4 Hz, 5-H), 1.56 (dd, 1 H, J4,5 = 3.5 Hz, 5'-H), 1.55–0.90 (m, 7 H, 9,10ax,10eq,11ax,11eq-H, CH2C2H3), 0.77 (t, J7 = 7.5 Hz, 3 H, CH2CH3). 13C NMR: δ 97.01 (C-6), 65.88 (C-4), 65.47 (C-8), 62.45 (C-12), 56.54 (C-2), 43.93 (C-3), 37.80 (C-5), 36.71 (C-9), 35.46 (C-11), 25.38 (CH2CH3), 24.79 (C-10), 11.16 (CH2C2H3). HRMS (LSIMS): found 253.1416 [M+Na]; calcd. 253.1416.

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[3] In Scheme 1 we have represented the enantiomers of the structures of talaromycins D, F, and G reported in ref.[2] since those authors could not establish their absolute configurations.


[12] Corrigendum: The (4R) configuration for compound 7 and 8 that appeared in refs.[6,8], should read (4S).


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