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

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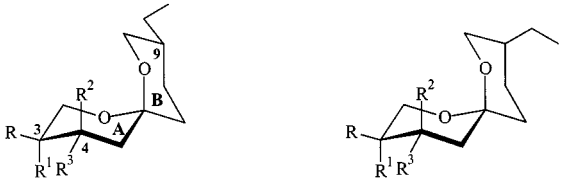
Diastereomeric enzymatic (Chirazyme® L-2, c.–f., C2) resolution of 3-*C*-acetoxymethyl-1,2,3,4,5-pentadeoxy-6,7:8,9-di-*O*-isopropylidene-β-D-*gluco*- and -D-*manno*-dec-6-ulo-6,10-pyranose (**6**), obtained from "diacetone D-fructose aldehyde" (**3**) and the corresponding phosphorane from (3-benzyloxy-2-ethylpropyl)triphenylphosphonium iodide (**2**), has enabled us to synthesize spiroketals (3*R*,4*S*,5*S*,6*R*,9*R*)- and (3*R*,4*S*,5*S*,6*R*,9*S*)-9-ethyl-3,4-isopropylidenedioxy-1,7-dioxaspiro[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.



A R = R^2 = H; R^1 = CH_2OH; R^3 = OH
B R = CH_2OH; R^1 = R^2 = H; R^3 = OH
C R = R^3 = H; R^1 = CH_2OH; R^2 = OH
E R CH_2OH; R^1 = R^3 = H; R^2 = OH
G R = R^2 = H; R^1 = CH_2OH; R^3 = OH
H R = CH_2OH; R^1 = R^2 = H; R^3 = OH
F R = R^3 = H; R^1 = CH_2OH; R^2 = OH
I R CH_2OH; R^1 = R^3 = H; R^2 = OH

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-ulose intermediate **5**, depending on the C-3 configuration (starred carbon atom).

A synthesis of the (3*R*) intermediate dec-6-ulose 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 (3*S*)-**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 (3*RS*)-**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-dioxaspiro[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 enantiomerically pure talaromycins C and E, which represent a novel and straightforward route to mycotoxin talaromycins.

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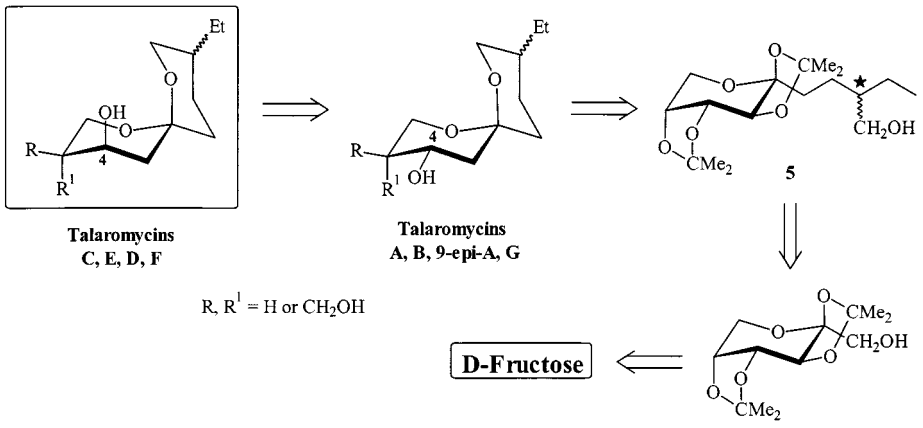
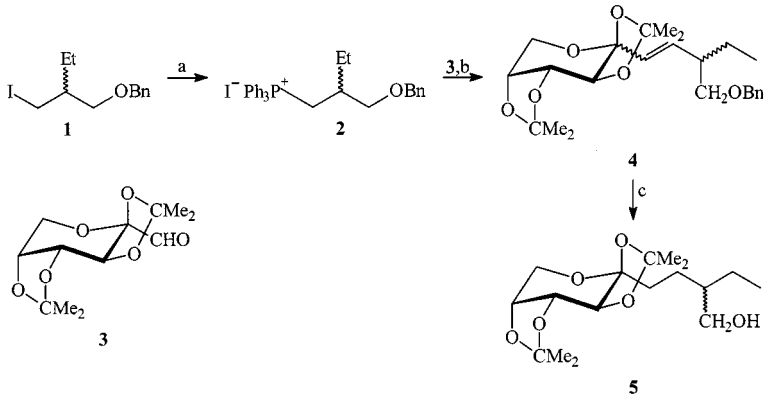


Scheme 2. Retrosynthesis of talaromycins

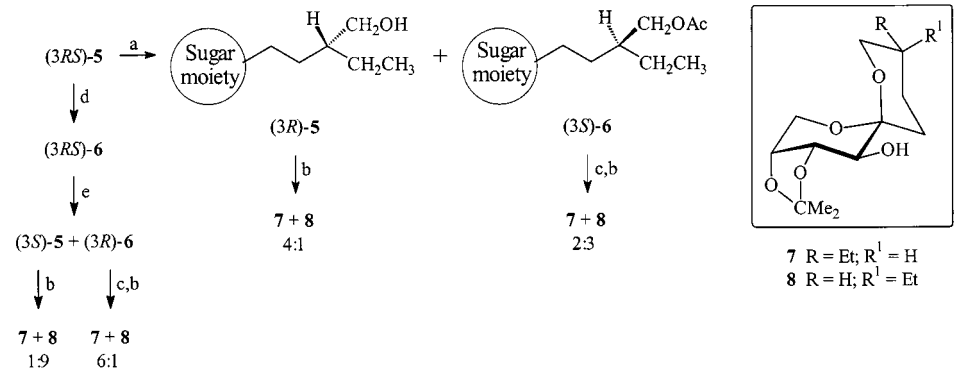
Results and Discussion

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 D-fructose aldehyde"[6] (**3**) in the presence of potassium *tert*-butoxide gave 3-*C*-(benzyloxymethyl)-1,2,3,4,5-pentadeoxy-6,7:8,9-di-*O*-isopropylidene-β-D-*gluco*- and -D-*manno*-dec-4-ene-6-ulo-6,10-pyranose (**4**) as a mixture of (*E*) and (*Z*) isomers, which was subsequently hydrogenated to give the related (3*RS*)-**5** (89% yield), the physical and spectroscopic data of which were as previously reported[6] (see Scheme 3).

Diastereomeric resolution of (3*RS*)-**5** was performed by partial esterification with an immobilized enzyme as catalyst. Thus, treatment of (3*RS*)-**5** in diethyl ether with vinyl acetate in the presence of Chirazyme® L-2, c.−f., C2 gave the corresponding acetate derivative (3*S*)-**6** together with unreacted (3*R*)-**5** (see Scheme 4 and Figure 1). It was not possible to determine the diastereomeric excess of either



Scheme 3. Synthesis of (3*RS*)-**5**: a: Ph_3P/toluene/Δ*T*; b: K^+tBuO^-/THF; c: 10% Pd-C/H_2/MeOH



Scheme 4. Diastereomeric resolution of (3*RS*)-**5**): a: Chirazyme® L-2, c.−f., C2/vinyl acetate/ether; b: Me_2CO/H^+; c: NaMeO/MeOH; d: $Ac_2O/Cl_2CH_2/Et_3N$/DMAP; e: Chirazyme® L-2, c.−f., C2/buffer (pH = 7)/room temp.

compound by GLC, even in a capillary β-DEX® 325 column, their transformation into the spiroketals (3*R*,4*S*,5*S*,6*R*,9*R*)- and (3*R*,4*S*,5*S*,6*R*,9*S*)-9-ethyl-3,4-isopropylidenedioxy-1,7-dioxaspiro[5.5]undecane (**7** and **8**),[12] as shown in Scheme 4, being necessary. This was achieved by treatment with acetone/sulfuric acid, which brought about concomitant isopropylidenation at the C-3,4 positions. Since the result was only a small diastereomeric excess, the partial enzymatic hydrolysis of (3*RS*)-**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,[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 ^{13}C chemical shift values for the spiro carbon atom − δ = 96.55 for **11** and 106.87 for **12** − suggested[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_3CD) 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,[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[15] with Ph_3P/3,5-dinitrobenzoic acid/DEAD to give **27** (quantitative) and **30** (45%). Finally, Zemplen deacylation of **27** and **30** gave the expected target molecules (−)-talaromycins E (72%) and C (86%), respectively.

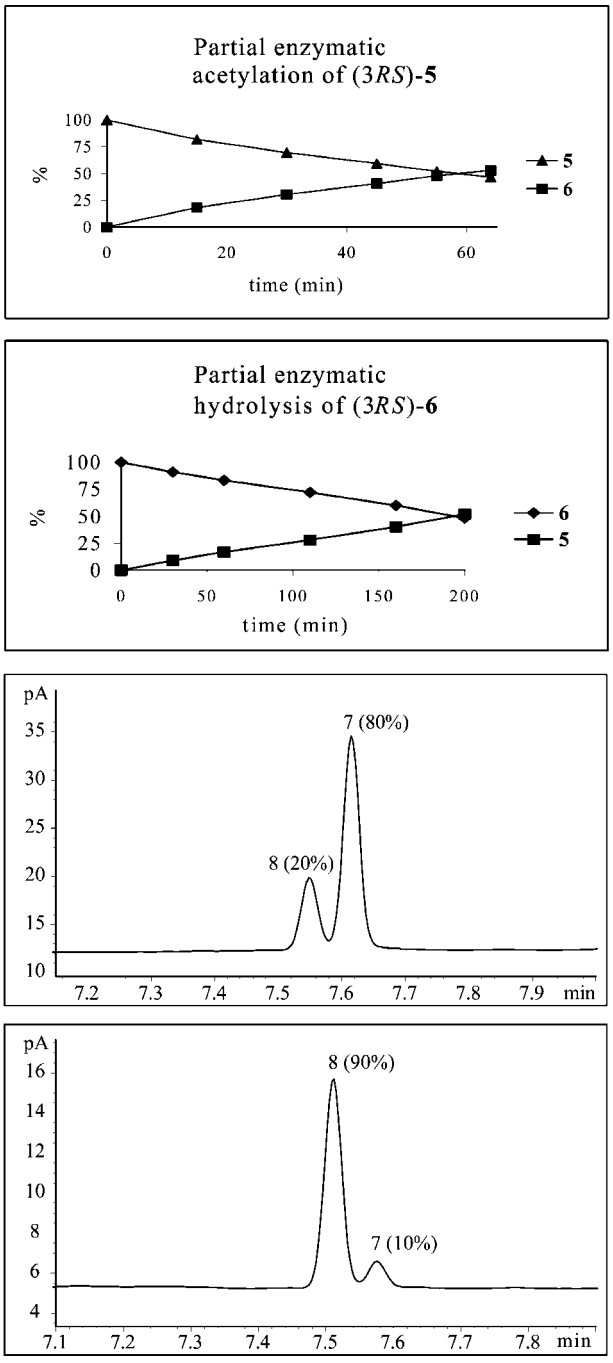
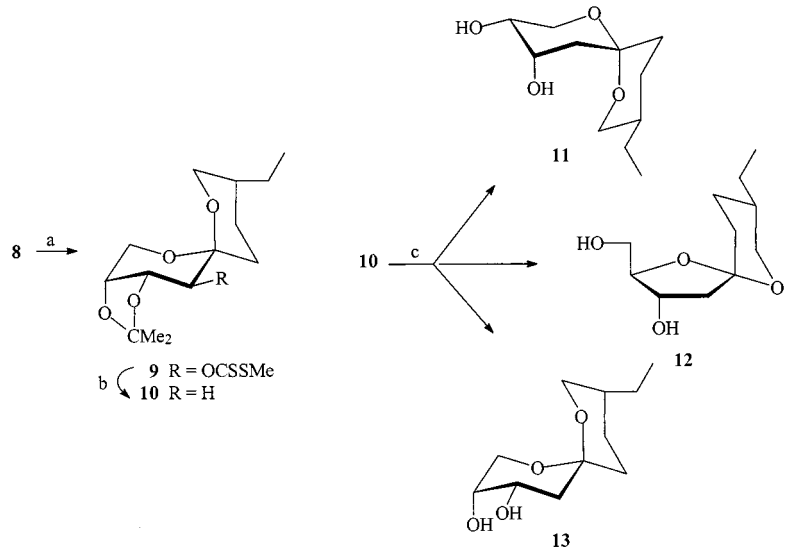
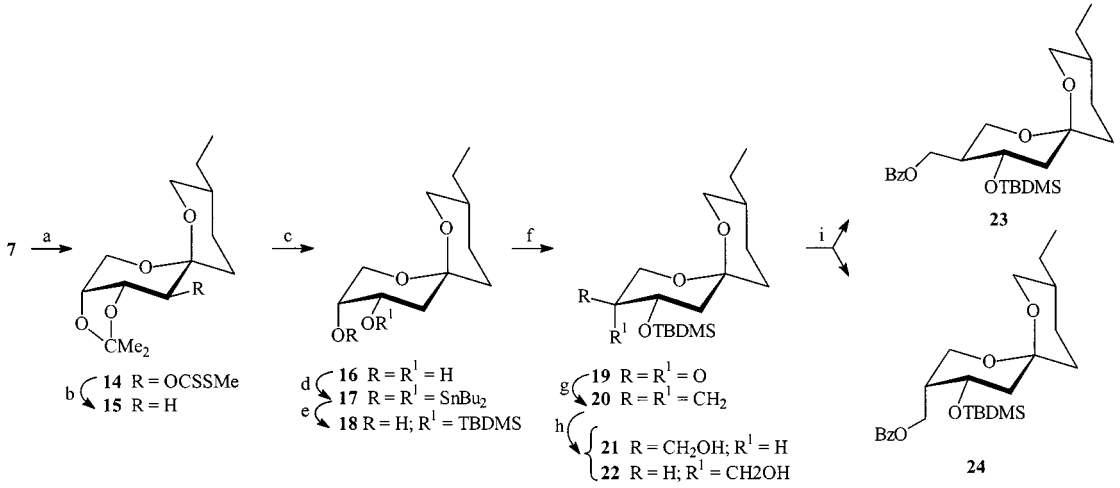


Figure 1. Kinetics of enzymatically catalysed acetylation of (3*RS*)-**5** and enzymatically catalysed hydrolysis of (3*RS*)-**6**; GLC analysis of compounds **7** and **8** produced by spiroketalization of **5** after enzymatic acetylation and enzymatic hydrolysis, respectively

The results described above indicate that the use of the chiral pool (carbohydrates) combined with chiral catalysts (lipases), both from natural sources, may be an excellent methodology by which to overcame many problems in the stereoselective synthesis of complex biologically active natural products.



Scheme 5. Deisopropylidenation of **10**: a: NaH/THF/imidazole/CS_2/MeI; b: H_3PO_4/dioxane/H_2O/Et_3N/AIBN; c: AcOH/H_2O/40 °C/45 min

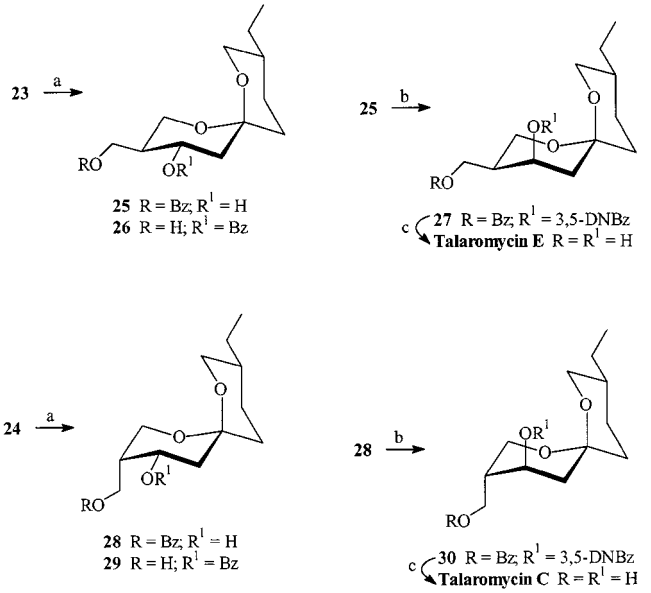


Scheme 6. Synthesis of protected (−)-talaromycins B (**23**) and A (**24**): a: NaH/THF/imidazole/CS_2/MeI; b: H_3PO_4/dioxane/H_2O/Et_3N/AIBN; c: AcOH/H_2O/50 °C/1 h; d: nBu$_2$SnO/MeOH; e: TBDMSCl/dioxane; f: PCC/CH_2Cl_2/NaAcO/MS (4 Å); g: $NaCH_2SOCH_3$/Ph_3PCH_3Br/DMSO; h: BH_3−SMe_2/THF, then NaOH/H_2O_2; i: BzCl/Et_3N/CH_2Cl_2

Experimental Section

General Remarks: Solutions were dried with $MgSO_4$ before concentration under reduced pressure. The ^1H and ^{13}C NMR spectra were recorded with Bruker AM 300, AXM 300, ARX 400, and AMX 500 spectrometers for solutions in $CDCl_3$ (internal Me_4Si). 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 $CHCl_3$ (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 F_{254} silica gel aluminium sheets and detection was by charring with H_2SO_4. Column chromatography was performed on silica gel (Merck, # 7734). Spectroscopic (^1H and ^{13}C NMR, MS) and/or analytical data were obtained with chromatographically homogeneous samples.

(3-Benzyloxy-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): $\tilde{\nu}$ = 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, PhCH_2), 3.97 (ddd, 1 H, $J_{1a,2}$ = 5.2, $J_{1a,1b}$ = 13.6, $J_{1a,P}$ = 16.0 Hz, 1a-H), 3.63 (t, 1 H, $J_{2,3a}$ = $J_{3a,3b}$ = 9 Hz, 3a-H), 3.58−3.49 (m, 2 H, 1b,3b-H), 2.02 (m, 1 H, 2-H), 1.49 and 1.20 (2 m, 2 H, CH_2CH$_3$), 0.78 (t, 3 H, J = 7.43 Hz, CH_2CH_3). ^{13}C NMR: δ = 137.70, 134.90, 133.81, 133.71, 130.44, 130.32, 128.21, 127.91,



Scheme 7. Synthesis of (−)-talaromycins E and C: a: nBu$_4$NF·3H$_2$O/THF; b: Ph$_3$P/3,5-dinitrobenzoic acid/DEAD/48 h/room temp.; c: NaMeO/MeOH

119.54 and 118.69 (Ph), 73.20 and 72.12 (C-3,Ph*C*H$_2$), 36.47 (C-2), 25.72 and 25.35 (C-1, *C*H$_2$CH$_3$), 11.62 (CH$_2$*C*H$_3$). C$_{30}$H$_{32}$IOP (566.44): calcd. C 63.61, H 5.69; found C 63.19, H 5.55.

3-*C*-(Benzyloxymethyl)-1,2,3,4,5-pentadeoxy-6,7:8,9-di-*O*-isopropylidene-β-D-*gluco*- and -D-*manno*-dec-4-ene-6-ulo-6,10-pyranose (4): A solution of *t*BuOK (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-*arabino*-hexos-2-ulopyranose[6] (**3**; 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 (t_R = 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**. ^{1}H NMR (inter alia): (*Z*)-**4**: δ = 5.61 and 5.60 (2 d, $J_{4,5}$ = 11.7 Hz, 5-H), 5.42 and 5.38 (2 dd, $J_{3,4}$ = 9.8 Hz, 4-H); (*E*)-**4**: δ = 5.90 and 5.89 (2 dd, $J_{4,5}$ = 15.4, $J_{3,4}$ = 8.7 Hz, 4-H), 5.66 and 5.63 (2 d, 5-H). HRMS (LSIMS): found 419.2435 [M$^+$ + 1]; calcd. 419.2434.

1,2,3,4,5-Pentadeoxy-3-*C*-hydroxymethyl-6,7:8,9-di-*O*-isopropylidene-β-D-*gluco*- and -D-*manno*-dec-6-ulo-6,10-pyranose (5): A solution of (*E*)-,(*Z*)-**4** (5.36 g, 12.4 mmol) in methanol (60 mL) was hydrogenated [75 psi (5.2 bar) H$_2$] over 10% Pd-C (125 mg) for 48 h. GLC then showed the absence of (*E*)-,(*Z*)-**4** and the presence of a new compound (t_R = 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.[6]

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 (3*S*)-**6** (4.32 g, 49%) first. $[\alpha]_D^{27}$ = −6.6 (*c* = 1). IR (film): $\tilde{\nu}$ = 1740 (OAc), 1382 and 1373 cm^{-1} (CMe$_2$). ^{1}H NMR: δ = 4.54 (dd, 1 H, $J_{7,8}$ = 2.4, $J_{8,9}$ = 8 Hz, 8-H), 4.20 (dd, 1 H, 9-H), 4.06 (d, 1 H, 7-H), 3.97 (m, 2 H, C*H*$_2$OAc), 3.82 (dd, 1 H, $J_{9,10ax}$ = 1.9, $J_{10ax,10eq}$ = 13 Hz, 10ax-H), 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 CMe$_2$), 1.39−1.32 (m, 2 H, 2,2-H), 0.88 (t, 3 H, $J_{1,2}$ 7.4 = Hz, 1,1,1-H). ^{13}C NMR: δ = 171.40 (Me*C*O), 108.94 and 107.44 (2 *C*Me$_2$), 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 C*Me*$_2$), 23.98 and 23.58 (C-2,4), 21.07 (*Me*CO), 10.89 (C-1). HRMS (LSIMS): found 395.2043 [M$^+$ + Na]; calcd. 395.2046. The second fraction was (3*R*)-**5** (3.8 g, 48.7%). $[\alpha]_D^{24}$ = −12.7 (*c* = 1). The physical and spectroscopic data of which matched those previously reported.[8] Zemplen deacetylation of (3*S*)-**6** with 0.5 M NaOMe in methanol afforded, after workup and column chromatography (diethyl ether), (3*S*)-**5** (quantitative); t_R = 9.16 min; $[\alpha]_D^{27}$ = −6.9 (*c* = 1).

Spiroketalization of (3*R*)- and (3*S*)-5: A solution of (3*R*)-**5** (3.8 g, 11.5 mmol) in a 20:1 acetone/conc. H$_2$SO$_4$ mixture (80 mL) was kept at room temperature for 8 h. GLC then revealed that (3*R*)-**5** had disappeared and that two new compounds were present in a 4:1 ratio. The reaction mixture was neutralised (NH$_3$), filtered, and concentrated. Column chromatography (diethyl ether/hexane, 1:3) first gave crystalline (3*R*,4*S*,5*S*,6*R*,9*R*)-9-ethyl-5-hydroxy-3,4-isopropylidenedioxy-1,7-dioxaspiro[5.5]undecane[6,8] (**7**; 820 mg), t_R = 7.61 min. Eluted second was a mixture of **7** and its 9-epimer **8** (1.25 g). Treatment of (3*S*)-**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**[6] (865 mg), t_R = 7.51 min.

Acetylation of (3*RS*)-5: DMAP (135 mg), Et$_3$N (8.6 mL, 61 mmol), and Ac$_2$O (5.9 mL, 61 mmol) were added to a solution of (3*RS*)-**5** (13.2 g, 40 mmol) in dry Cl$_2$CH$_2$ (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 (3*RS*)-**6** (14.3 g, 96%).

Partial Enzymatic (Chirazyme® L-2, c.−f., C2) Hydrolysis of (3*RS*)-6: The title enzyme (3 g) was added to a gently stirred suspension of (3*RS*)-**6** (4 g, 10.7 mmol) in 50 mL of a buffered (pH = 7) aqueous 0.5 M phosphate solution (KH$_2$PO$_4$). 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 (3*R*)-**6** (1.77 g, 44%) and (3*S*)-**5** (1.35 g, 38%). Zemplen deacetylation of (3*R*)-**6** (1.77 g, 4.5 mmol) as above gave (3*R*)-**5** (1.57 g, quantitative).

Spiroketalization of (3*S*)- and (3*R*)-5 Produced from the Enzymatic Hydrolysis: Treatment of (3*S*)-**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, (3*R*)-**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).

(3*R*,4*R*,5*S*,6*R*,9*S*)-9-Ethyl-3,4-isopropylidenedioxy-5-[(methylthio)-thiocarbonyloxy]-1,7-dioxaspiro[5.5]undecane (9): A solution of **8** (2.18 g, 8. mmol) in anhydrous THF (10 mL) was added under argon at room temperature to a stirred suspension of NaH (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 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%); t_R = 12.8 min. $[\alpha]_D^{25} = -159$ (c = 1). IR (film): $\tilde{\nu}$ = 1383 and 1373 (CMe_2), and 1207 cm^{-1} (C=S). ^1H NMR: δ = 5.83 (d, 1 H, $J_{4,5}$ = 8 Hz, 5-H), 4.41 (dd, 1 H, $J_{3,4}$ = 5.4 Hz, 4-H), 4.25 (dd, 1 H, 3-H), 4.03 (d, 1 H, $J_{2ax,2eq}$ = 13.4 Hz, 2ax-H), 3.86 (dd, 1 H, $J_{2eq,3}$ = 2.8 Hz, 2eq-H), 3.71 (dd, 1 H, $J_{8ax,8eq}$ = 11.1, $J_{8ax,9}$ = 2.8 Hz, 8ax-H), 3.53 (br. d, 1 H, 8eq-H), 2.56 (s, 3 H, SMe), 1.92 (tt, 1 H, $J_{10ax,10eq} = J_{10ax,11ax}$ = 13.3, $J_{9,10ax} = J_{10ax,11eq}$ = 4.4 Hz, 10ax-H), 1.65 (dt, 1 H, $J_{11ax,11eq}$ = 13.7, $J_{11ax,10eq}$ = 4.6 Hz, 11ax-H), 1.51 and 1.31 (2 s, 6 H, CMe_2), 1.60−1.31 (m, 5 H, 9,10eq,11eq-H, CH_2CH_3), 0.88 (t, J = 7.4 Hz, 3 H, CH_2CH_3). ^{13}C NMR: δ = 217.22 (C=S), 109.62 (CMe_2), 97.77 (C-6), 82.93 (C-5), 74.35 and 74.32 (C-3,4), 64.01 (C-8), 59.22 (C-2), 34.03 (C-9), 27.81 and 26.54 (CMe_2), 25.15 (C-11), 22.14 and 21.59 (C-10, CH_2CH_3), 19.32 (MeS), 12.36 (CH_2CH_3). HRMS (LSIMS): found 363.1294 [M^+ + 1]; calcd. 363.1300.

(3*R*,4*S*,6*R*,9*S*)-9-Ethyl-3,4-isopropylidenedioxy-1,7-dioxaspiro-[5.5]undecane (10): Et_3N (6.7 mL, 47 mmol) and aqueous H_3PO_2 (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** (t_R = 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. $[\alpha]_D^{25} = -149$ (c = 1). IR (film): $\tilde{\nu}$ = 1382 and 1371 cm^{-1} (CMe_2). ^1H NMR: δ = 4.38 (dt, 1 H, $J_{4,5ax}$ = 8.2, $J_{3,4} = J_{4,5eq}$ = 6.1 Hz, 4-H), 4.06 (br. dd, 1 H, 3-H), 3.94 (br. d, 1 H, $J_{2ax,2eq}$ = 13.2 Hz, 2ax-H), 3.83 (dd, 1 H, $J_{2eq,3}$ = 2.5 Hz, 2eq-H), 3.76 (dd, 1 H, $J_{8ax,8eq}$ = 11.2, $J_{8ax,9}$ = 3 Hz, 8ax-H), 3.37 (dt, 1 H, $J_{8eq,9} = J_{8eq,10eq}$ = 2 Hz, 8eq-H), 1.98 (m, 1 H, 10ax-H), 1.89 (dd, 1 H, $J_{5ax,5eq}$ = 13.7 Hz, 5eq-H), 1.64 (dd, 1 H, 5ax-H), 1.49 and 1.33 (2 s, 6 H, CMe_2), 1.61−1.33 (m, 6 H, 9,10eq,11ax,11eq-H, CH_2CH_3), 0.90 (t, J = 7.3 Hz, 3 H, CH_2CH_3). ^{13}C NMR: δ = 108.49 (CMe_2), 96.78 (C-6), 71.77 (C-3), 70.06 (C-4), 63.86 (C-8), 60.21 (C-2), 37.98 (C-5), 34.48 (C-9), 31.08 (C-11), 28.05 and 26.18 (CMe_2), 22.73 and 22.45 (C-10,CH_2CH_3), 12.24 (CH_2CH_3). HRMS (LSIMS): found 279.1579 (M^+ + Na); calcd. 279.1572.

Deisopropylidenation of 10: A solution of **10** (1.92 g, 7.5 mmol) in aqueous acetic acid (60%, 15 mL), was heated at 40 °C for 45 min. TLC (ethyl acetate) then showed the presence of three new compounds of lower mobility. The mixture was concentrated and codistilled with toluene to remove the acetic acid, and the residue was submitted to chromatography (diethyl ether/hexane, 1:4) to yield (3*R*,4*S*,6*S*,9*S*)-9-ethyl-3,4-dihydroxy-1,7-dioxaspiro[5.5]undecane (**11**; 324 mg, 20%) first. $[\alpha]_D^{24} = +118$ (c = 1). IR (film): $\tilde{\nu}$ = 3471 cm^{-1} (OH). ^1H NMR: δ = 3.92 (m, 1 H, 4-H), 3.66−3.57 (m, 3 H, 2eq,3,8eq-H), 3.46 (t, 1 H, $J_{2ax,3eq} = J_{2ax,2eq}$ = 13.5 Hz, 2ax-H), 3.27 (t, 1 H, $J_{8ax,8eq} = J_{8ax,9}$ = 10.9 Hz, 8ax-H), 3.10 (br. s, 2 H, O3,4-H), 2.04 (dd, 1 H, $J_{5,5'}$ = 14.6, $J_{4,5}$ = 3.3 Hz, 5-H), 1.71 (dd, 1 H, $J_{4,5'}$ = 3.2 Hz, 5-H), 1.64−1.35 (m, 5 H, 9,10,10′,11,11′-H), 1.14 (m, 2 H, CH_2CH_3), 0.87 (t, J = 7.4 Hz, 3 H, CH_2CH_3). ^{13}C NMR: δ = 96.55 (C-6), 67.82 (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,CH_2CH_3), 11.13 (CH_2CH_3). HRMS (LSIMS): found 239.1259 [M^+ + Na]; calcd. 239.1259. Eluted second was (2*R*,3*S*,5*S*,8*S*)-8-ethyl-3-hydroxy-2-hydroxymethyl-1,6-dioxaspiro-[4.5]decane (**12**; 370 mg, 23%). $[\alpha]_D^{22} = +98$ (c = 1). IR (film): $\tilde{\nu}$ = 3467 cm^{-1} (OH). ^1H NMR: δ = 4.08 (m, 2 H, 2,3-H), 3.69 (dd, 1 H, $J_{2'a-2'b}$ = 11.7, $J_{2'a,2}$ = 3.7 Hz, 2′a-H), 3.59 (dd, 1 H, $J_{2'b,2}$ = 3.6 Hz, 2′b-H), 3.59 (m, 1 H, 7eq-H), 3.49 (t, 1 H, $J_{7ax,8} = J_{7ax,7eq}$ = 10.9 Hz, 7ax-H), 2.45 (m, 2 H, 2′,3-OH), 1.97 (dd, 1 H, $J_{3,4}$ = 1.2, $J_{4,4'}$ = 13.6 Hz, 4-H), 1.89 (dd, 1 H, $J_{3,4'}$ = 5.9 Hz, 4′-H), 1.79−1.37 (m, 5 H, 8,9,9′,10,10′-H), 1.16 (m, 1 H, CH_2CH_3), 0.86 (t, J = 7.4 Hz, 3 H, CH_2CH_3). ^{13}C 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,CH_2CH_3), 11.22 (CH_2CH_3). HRMS (LSIMS): found 239.1258 [M^+ + Na]; calcd. 239.1259. Finally, the third fraction was (3*R*,4*S*,6*R*,9*S*)-9-ethyl-3,4-dihydroxy-1,7-dioxaspiro[5.5]undecane (**13**; 850 mg, 52%). $[\alpha]_D^{26} = -104$ (c = 1). IR (film): $\tilde{\nu}$ = 3438 cm^{-1} (OH). ^{13}C 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,CH_2CH_3), 11.13 (CH_2CH_3). HRMS (LSIMS): found 239.1260 [M^+ + Na]; calcd. 239.1259.

(3*R*,4*S*,6*R*,9*R*)-9-Ethyl-3,4-isopropylidenedioxy-1,7-dioxaspiro-[5.5]undecane (15): Et_3N (6 mL, 42 mmol) and aqueous 50% H_3PO_2 (4.5 mL) were added to a solution of (3*R*,4*R*,5*S*,6*R*,9*R*)-9-ethyl-3,4-isopropylidenedioxy-5-[(methylthio)thiocarbonyloxy]-1,7-dioxaspiro[5.5]undecane[6] (**14**; 2.8 g, 7.73 mmol) in dioxane (50 mL), and the mixture was refluxed for 2 h. During this time, AIBN (200 mg) was added portionwise (25 mg each). The reaction was monitored by GLC, showing the presence of **15** (t_R = 5.31 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 **15** (1.74 g, 95%) as a syrup, which showed the same physical and spectroscopic data as previously reported.[6]

(3*R*,4*S*,6*R*,9*R*)-4-(*tert*-Butyldimethylsilyloxy)-9-ethyl-3-hydroxy-1,7-dioxaspiro[5.5]undecane (18): A solution of **15** (2.1 g, 8.2 mmol) in aqueous acetic acid (60%, 15 mL) was heated at 50 °C for 1 h. TLC (ethyl acetate) then revealed the presence of a slower-running compound. The reaction mixture was concentrated and repeatedly codistilled in order to remove acetic acid. Column chromatography (diethyl ether → diethyl ether/methanol, 10:1) then afforded the diol **16** (1.57 g, 88.6%) as a syrup. Di-*n*-butyltin oxide (1.56 g, 6.3 mmol) was added to a solution of **16** (1.36 g, 6.3 mmol) in anhydrous methanol (40 mL). The suspension was heated for 2 h under reflux, and then concentrated to afford the 3,4-dibutylstannylene derivative **17** as a syrup that was dried under vacuum over P_2O_5 overnight. A solution of **17** in dry dioxane (40 mL) was treated with *tert*-butyldimethylchlorosilane (1.04 g, 6.93 mmol),

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%); t_R = 8.9 min. $[\alpha]_D^{24}$ = −97 (*c* = 1). IR (film): $\tilde{\nu}$ = 3578 cm^{-1} (OH). ^{1}H NMR: δ = 4.11 (ddd, 1 H, $J_{3,4}$ = 5.5, $J_{4.5ax}$ = 11.1, $J_{4,5eq}$ = 3.4 Hz, 4-H), 3.80 (dd, 1 H, $J_{2ax,2eq}$ = 12.7, $J_{2ax,3}$ = 2 Hz, 2ax-H), 3.65 (d, 1 H, 2eq-H), 3.64 (dd, 1 H, 3-H), 3.52 (br. d, 1 H, 8eq-H), 3.20 (t, 1 H, $J_{8ax,8eq}$ = $J_{8ax,9}$ = 10.8 Hz, 8ax-H), 2.53 (d, 1 H, $J_{3,OH}$ = 1.8 Hz, OH), 1.75 (t, 1 H, $J_{5ax,5eq}$ = 11.1 Hz, 5ax-H), 1.81−1.41 (3 m, 6 H, 5eq,9,10ax,10eq,11ax,11eq-H), 1.14 (m, 2 H, CH_2CH$_3$), 0.88 (s, 9 H, CMe$_3$), 0.87 (t, *J* = 7.5 Hz, 3 H, CH$_2$CH_3), 0.08 (s, 6 H, SiMe$_2$). ^{13}C 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 (CMe_3), 25.32 and 24.86 (C-10, *C*H$_2$CH$_3$), 18.06 (*C*Me$_3$), 11.27 (CH$_2$*C*H$_3$), −4.42 and −4.68 (SiMe$_2$). HRMS (LSIMS): found 331.2307 [M$^+$ + 1]; calcd. 331.2305.

(4*S*,6*R*,9*R*)-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 CH_2Cl_2 (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, t_R = 8.6 min. IR (film): $\tilde{\nu}$ = 1744 cm^{-1} (C=O). This was used in the next step.

(4*S*,6*R*,9*R*)-4-(*tert*-Butyldimethylsilyloxy)-9-ethyl-3-methylene-1,7-dioxaspiro[5.5]undecane (20): Methyltriphenylphosphonium bromide (4.3 g, 12 mmol) was added under argon to a stirred solution of NaCH$_2$SOMe, produced from a dispersion of sodium hydride in oil (80%, 370 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; t_R = 7.8 min. $[\alpha]_D^{23}$ = −98 (*c* = 1). IR (film): $\tilde{\nu}$ = 1665 cm^{-1} (C=C). ^{1}H NMR: δ = 5.13 (t, 1 H, $J_{12,12'}$ = $J_{4,12}$ = 2.1 Hz, 12-H), 4.93 (br. s, 1 H, 12′-H), 4.57 (m, 1 H, 4-H), 4.15 (d, 1 H, $J_{2ax,2eq}$ = 12.1 Hz, 2ax-H), 3.96 (d, 1 H, 2eq-H), 3.59 (br. dd, 1 H, $J_{8eq,9}$ = 3.9 Hz, 8eq-H), 3.28 (t, 1 H, $J_{8ax,8eq}$ = $J_{8ax,9}$ = 10.9 Hz, 8ax-H), 2.00 (dd, 1 H, $J_{4,5eq}$ = 5.7, $J_{5ax,5eq}$ = 12.4 Hz, 5eq-H), 1.71−1.36 (m, 5 H, 9,10ax,10eq,11ax,11eq-H), 1.51 (t, 1 H, $J_{4,5ax}$ = 12.3 Hz, 5ax-H), 1.17 (m, 2 H, CH_2CH$_3$), 0.93 (s, 9 H, CMe_3), 0.90 (t, *J* = 7.3 Hz, 3 H, CH$_2$CH_3), and 0.10 (s, 6 H, SiMe$_2$). ^{13}C 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 (CMe_3), 25.37 and 25.05 (C-10, *C*H$_2$CH$_3$), 18.33 (*C*Me$_3$), 11.27 (CH$_2$*C*H$_3$), −4.69 and −4.84 (SiMe$_2$). HRMS (LSIMS): found 327.2350 [M$^+$ + 1]; calcd. 327.2356.

Hydroboration/Oxidation of 20: BH_3SMe_2 (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 H_2O_2 (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 irresolvable mixture (510 mg) of (3*R*,4*S*,6*R*,9*R*)-4-(*tert*-butyldimethylsilyloxy)-9-ethyl-3-hydroxymethyl-1,7-dioxaspiro-[5.5]undecane (**21**) and its (3*S*,4*S*,6*R*,9*R*)-epimer **22** in a 3:7 ratio, as a colourless syrup. GLC analysis: **22** (t_R = 9.99) and **21** (10.16 min).

(3*R*,4*S*,6*R*,9*R*)- and (3*S*,4*S*,6*R*,9*R*)-3-Benzoyloxymethyl-4-(*tert*-butyldimethylsilyloxy)-9-ethyl-1,7-dioxaspiro[5.5]undecane (23 and 24): Et_3N (0.4 mL, 2.9 mmol) and a solution of BzCl (0.2 mL, 1.66 mmol) in dry CH_2Cl_2 (5 mL) were added to a stirred and cooled (ice/water) solution of **21** and **22** (510 mg, 1.48 mmol) in the same solvent (15 mL). The reaction mixture was kept at room temperature for 24 h. TLC (diethyl ether/hexane, 1:1) then revealed the presence of two new products of higher mobility. Conventional workup and column chromatography (hexane → diethyl ether/hexane, 1:25) first gave **23** (190 mg, 29%) as a colourless syrup. $[\alpha]_D^{27}$ = −10 (*c* = 1). IR (film): $\tilde{\nu}$ = 3071 (aromatic), 1728 (C=O), 775 and 711 cm^{-1} (aromatic). ^{1}H NMR: δ = 8.06−7.43 (3 m, 5 H, Ph), 4.51 (dd, 1 H, $J_{3,12}$ = 3.1, $J_{12,12'}$ = 11.2 Hz, 12-H), 4.25 (dd, 1 H, $J_{3,12'}$ = 7.5 Hz, 12′-H), 4.06 (dt, 1 H, $J_{3,4}$ = $J_{4,5ax}$ = 10.5, $J_{4,5eq}$ = 5.0 Hz, 4-H), 3.82 (dd, 1 H, $J_{2eq,3}$ = 4.6 Hz, 2eq-H), 3.58 (t, 1 H, $J_{2ax,2eq}$ = $J_{2ax,3}$ = 11.6 Hz, 2ax-H), 3.60−3.52 (m, 1 H, 8eq-H), 3.23 (t, 1 H, $J_{8ax,8eq}$ = $J_{8ax,9}$ = 10.9 Hz, 8ax-H), 2.04 (m, 1 H, 3-H), 1.97 (dd, 1 H, $J_{5ax,5eq}$ = 12.8 Hz, 5eq-H), 1.50 (dd, 1 H, 5ax-H), 1.76−1.09 (m, 7 H, 9,10ax,10eq,11ax,11eq-H, CH_2CH$_3$), 0.90 (s, 9 H, CMe$_3$), 0.89 (t, *J* = 7.3 Hz, 3 H, CH$_2$CH_3), 0.09 and 0.07 (2 s, 6 H, SiMe$_2$). ^{13}C NMR: δ = 166.53 (CO), 133.01, 130.30, 129.62, and 128.47 (Ph), 97.36 (C-6), 65.89 (C-4), 65.27 (C-8), 63.23 and 61.26 (C-2,12), 45.19 (C-5), 44.22 (C-3), 36.78 (C-9), 35.40 (C-11), 25.87 (CMe_3), 25.36 and 25.01 (C-10,*C*H$_2$CH$_3$), 18.02 (*C*Me$_3$), 11.27 (CH$_2$*C*H$_3$), −4.82 and −3.93 (SiMe$_2$). HRMS (LSIMS): found 471.2549 [M$^+$ + Na]; calcd. 471.2543. Eluted second was **24** (390 mg, 59%). $[\alpha]_D^{25}$ = −110 (*c* = 1). IR (film): $\tilde{\nu}$ = 3066 (Ph), 1726 (C=O), 776 and 711 cm^{-1} (Ph). ^{1}H NMR: δ = 8.05−7.42 (3 m, 5 H, Ph), 4.49 (t, 2 H, 12,12′-H), 4.33 (dt, 1 H, $J_{3,4}$ = $J_{4,5eq}$ = 5.4, $J_{4,5ax}$ = 11.6 Hz, 4-H), 3.84 (dd, 1 H, $J_{2ax,2eq}$ = 11.2, $J_{2eq,3}$ = 1.2 Hz, 2eq-H), 3.71 (br. d, 1 H, 2ax-H), 3.54 (m, 1 H, 8eq-H), 3.23 (t, 1 H, $J_{8ax,9}$ = $J_{8ax,8eq}$ = 10.9 Hz, 8ax-H), 2.16 (m, 1 H, 3-H), 1.82−1.08 (m, 9 H, 5ax,5eq,9,10ax,10eq,11ax,11eq-H, CH_2CH$_3$), 0.90 (s, 9 H, CMe$_3$), 0.89 (t, *J* = 7.3 Hz, 3 H, CH$_2$CH_3), 0.09 and 0.07 (2 s, 6 H, SiMe$_2$). ^{13}C NMR: δ = 166.78 (CO), 132.85, 130.63, 129.63 and 128.35 (Ph), 97.17 (C-6), 65.67 (C-4), 65.38 (C-8), 61.06 and 59.05 (C-2,12), 41.31 (C-5), 40.63 (C-3), 36.74 (C-9), 35.29 (C-11), 25.87 (CMe_3), 25.36 and 25.02 (C-10,*C*H$_2$CH$_3$), 18.08 (*C*Me$_3$), 11.26 (CH$_2$*C*H$_3$), −4.60 and −4.69 (SiMe$_2$). HRMS (LSIMS): found 471.2544 [M$^+$ + Na]; calcd. 471.2543.

(3*R*,4*S*,6*R*,9*R*)-3-Benzoyloxymethyl-9-ethyl-4-hydroxy-1,7-dioxaspiro[5.5]undecane (25): A solution of $Bu_4NF{\cdot}3H_2O$ (135 mg, 0.43 mmol) in THF (5 mL) was added under argon to a solution of **23** (160 mg, 0.35 mmol) in the same solvent (5 mL). After 1 h, TLC (diethyl ether/hexane, 1:1) then revealed two new, slower-running compounds. The solvent was removed, water (5 mL) was added and extraction was performed with diethyl ether (2 × 15 mL). The combined extracts were concentrated and the residue was chromatographed (diethyl ether/hexane, 1:1), to afford first **25** (60 mg, 50%). $[\alpha]_D^{21}$ = −49 (*c* = 1). IR (film): $\tilde{\nu}$ = 3448 (OH), 3076 (Ph), 1723 (C=O), 758 and 711 cm^{-1} (Ph). ^{1}H NMR: δ = 8.03−7.41 (3 m, 5 H, Ph), 4.56 (dd, 1 H, $J_{12,12'}$ = 11.5, $J_{3,12}$ = 6.2 Hz, 12-H), 4.42 (dd, 1 H, $J_{3,12'}$ = 3.4 Hz, 12′-H), 3.95 (dt, 1 H, $J_{3,4}$ = $J_{4,5ax}$ =

10.8, $J_{4,5eq}$ 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, $J_{2ax,3}$ = 11.5 Hz, 2ax-H), 3.51 (m, 1 H, 8eq-H), 3.21 (t, 1 H, $J_{8ax,8eq}$ = $J_{8eq,9}$ = 10.9 Hz, 8ax-H), 2.05 (dd, 1 H, $J_{5ax,5eq}$ = 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, 9,10ax,10eq,11ax,11eq-H, CH_2CH$_3$), and 0.87 (t, J = 7.4 Hz, 3 H, CH$_2$CH_3). ^{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), 36.75 (C-9), 35.25 (C-11), 25.26 and 24.89 (C-10,*C*H$_2$CH$_3$), and 11.20 (CH$_2$*C*H$_3$). HRMS (LSIMS): found 357.1673 [M$^+$ + Na]; calcd. 357.1678. The second fraction was (3*S*,4*S*,6*R*,9*R*)-4-benzoyloxy-9-ethyl-3-hydroxymethyl-1,7-dioxaspiro[5.5]undecane (**26**, 20 mg, 12.5%). ^{1}H NMR: δ = 8.05−7.45 (3 m, 5 H, Ph), 5.51 (dt, 1 H, $J_{3,4}$ = $J_{4,5ax}$ = 11.2, $J_{4,5eq}$ = 5.1 Hz, 4-H), 3.85 (t, 1 H, $J_{2ax,2eq}$ = $J_{2ax,3}$ = 11.5 Hz, 2ax-H), 3.75 (dd, 1 H, $J_{2eq,3}$ = 5 Hz, 2eq-H), 3.62 (dd, 1 H, $J_{12,12'}$ = 12.3, $J_{3,12}$ = 4 Hz, 12-H), 3.61−3.51 (m, 1 H, 8eq-H), 3.54 (dd, 1 H, $J_{3,12'}$ = 2.3 Hz, 12′-H), 3.27 (t, 1 H, $J_{8ax,9}$ = $J_{8ax,8eq}$ = 10.9 Hz, 8ax-H), 2.14 (dd, 1 H, $J_{5ax,5eq}$ = 12.3 Hz, 5eq-H), 1.76 (t, 1 H, 5ax-H), 1.92−1.07 (m, 8 H, 3,9,10ax,10eq,11ax,11eq-H, CH_2CH$_3$), 0.89 (t, J = 7.5 Hz, 3 H, CH$_2$CH_3). ^{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-2,12), 44.53 (C-3), 41.11 (C-5), 36.73 (C-9), 35.20 (C-11), 25.28 and 24.93 (C-10,*C*H$_2$CH$_3$), 11.23 (CH$_2$*C*H$_3$).

(3*R*,4*R*,6*R*,9*R*)-3-Benzoyloxymethyl-4-(3,5-dinitrobenzoyloxy)-9-ethyl-1,7-dioxaspiro[5.5]undecane (27): Ph$_3$P (140 mg, 0.54 mmol), 3,5-dinitrobenzoic acid (114 mg, 0.54 mmol) and DEAD (0.1 mL, 0.54 mmol) were added to a solution of **25** (60 mg, 0.18 mmol) in anhydrous THF (5 mL), and the mixture was kept at room temperature for 48 h. TLC (diethyl ether/hexane, 1:1) then showed a new compound of higher mobility. Diethyl ether (5 mL) was added and the resulting solution was washed with saturated aqueous Na$_2$CO$_3$ solution and water. Concentration of the solvent gave a residue that was submitted to column chromatography (diethyl ether/hexane, 1:4) to afford **27** (95 mg, quantitative) as a pale yellow syrup. $[\alpha]_D^{28}$ = −75 (c = 1). IR (film): $\tilde{\nu}$ = 3074 (aromatic), 1730 and 1727 (C=O, benzoate and 3,5-dinitrobenzoate), 731 and 713 cm^{-1} (aromatic). ^{1}H NMR: δ = 9.16 (m, 3 H, 3,5-dinitrobenzoyl), 7.95−7.37 (3 m, 5 H, Ph), 5.62 (br. s, 1 H, 4-H), 4.32 (dd, 1 H, $J_{12,12'}$ = 11.3, $J_{3,12}$ = 7 Hz, 12-H), 4.24 (dd, 1 H, $J_{3,12'}$ = 7.1 Hz, 12′-H), 4.10 (t, 1 H, $J_{2ax,3}$ = $J_{2ax,2eq}$ = 11.5 Hz, 2ax-H), 3.83 (dd, 1 H, $J_{2eq,3}$ = 4.5 Hz, 2eq-H), 3.75 (m, 1 H, 8eq-H), 3.46 (t, 1 H, $J_{8ax,8eq}$ = $J_{8ax,9}$ = 10.9 Hz, 8ax-H), 2.53 (m, 1 H, 3-H), 2.12 (dd, 1 H, $J_{5ax,5eq}$ = 15.1, $J_{4,5eq}$ = 2.7 Hz, 5eq-H), 1.83 (dd, 1 H, $J_{4,5ax}$ = 1.8 Hz, 5ax-H), 1.72−1.11 (m, 7 H, 9,10ax,10eq,11ax,11eq-H, CH_2CH$_3$), 0.89 (t, J = 7.4 Hz, 3 H, CH$_2$CH_3). ^{13}C NMR: δ = 166.26 and 162.16 (2 CO), 148.64, 134.76, 133.31, 129.75, 129.68, 129.58, 128.50, 122.26 (Ph, DNBz), 95.14 (C-6), 69.51 (C-4), 65.69 (C-8), 62.31 (C-12), 57.40 (C-2), 38.70 (C-5), 38.09 (C-3), 36.49 (C-9), 35.39 (C-11), 25.36 and 24.86 (C-10,*C*H$_2$CH$_3$), 11.21 (CH$_2$*C*H$_3$). HRMS (LSIMS): found 551.1644 [M$^+$ + Na]; calcd. 551.1642.

(3*S*,4*R*,6*R*,9*R*)-9-Ethyl-4-hydroxy-3-hydroxymethyl-1,7-dioxaspiro[5.5]undecane [(−)-Talaromycin E]: NaOMe (0.5 M, 0.5 mL) was added to a solution of **27** (90 mg, 0.17 mmol) in anhydrous methanol (10 mL), and the reaction mixture was maintained at room temperature for 5 h. TLC (diethyl ether/hexane, 1:1) showed the presence of a slower-running compound. The reaction mixture was neutralized and concentrated. Column chromatography (methanol/ether, 1:5) of the residue gave (−)-talaromycin E (28 mg, 72%) as a viscous, colourless oil. $[\alpha]_D^{27}$ = −94 (c = 1). IR (film): $\tilde{\nu}$ = 3462 cm^{-1} (OH). ^{1}H NMR: δ = 4.14 (br. d, 1 H, 4-H), 3.91 (t, 1 H, $J_{2ax,2eq}$ = $J_{2ax,3}$ = 11.9 Hz, 2ax-H), 3.79 (dd, 1 H, $J_{12,12'}$ = 11.3, $J_{3,12}$ = 3.8 Hz, 12-H), 3.71 (dd, 1 H, $J_{3,12'}$ = 3.7 Hz, 12′-H), 3.64 (dd, 1 H, $J_{2eq,3}$ = 4.5 Hz, 2eq-H), 3.61 (m, 1 H, 8eq-H), 3.33 (t, 1 H, $J_{8ax,8eq}$ = $J_{8ax,9}$ = 10.9 Hz, 8ax-H), 2.82 (br. s, 1 H, OH), 1.90 (dd, 1 H, $J_{5ax,5eq}$ = 14.3, $J_{4,5eq}$ = 3 Hz, 5eq-H), 1.80 (m, 1 H, 3-H), 1.69−1.10 (m, 8 H, 5ax,9,10ax,10eq,11ax,11eq-H, CH_2CH$_3$), 0.88 (t, J = 7.5 Hz, 3 H, CH$_2$CH_3). ^{13}C NMR: δ = 96.98 (C-6), 68.16 (C-4), 65.67 (C-8), 63.30 (C-12), 57.57 (C-2), 40.80 (C-5), 40.73 (C-3), 36.56 (C-9), 35.08 (C-11), 25.20 (*C*H$_2$CH$_3$), 24.44 (C-10), 11.18 (CH$_2$*C*H$_3$). HRMS (LSIMS): found 253.1415 [M$^+$ + Na]; calcd. 253.1416.

(3*S*,4*S*,6*R*,9*R*)-3-Benzoyloxymethyl-9-ethyl-4-hydroxy-1,7-dioxaspiro[5.5]undecane (28): Compound **24** (360 mg, 1.04 mmol) was desilylated in THF (10 mL) as above, with Bu$_4$NF·3H$_2$O (395 mg, 1.25 mmol). Workup of the reaction mixture and chromatography first gave syrupy **28** (220 mg, 82%). $[\alpha]_D^{24}$ = −89 (c = 1.61). IR (film): $\tilde{\nu}$ = 3434 (OH), 3040 (aromatic), 1724 (C=O), 758 and 711 cm^{-1} (aromatic). ^{1}H NMR: δ = 8.08−7.42 (3 m, 5 H, Ph), 4.74 (dd, 1 H, $J_{12,12'}$ = 10.9, $J_{3,12}$ = 4.2 Hz, 12-H), 4.49 (dd, 1 H, $J_{3,12'}$ = 9.5 Hz, 12′-H), 4.40 (m, 1 H, 4-H), 3.85 (dd, 1 H, $J_{2,3}$ = 1.7, $J_{2,2'}$ = 11.7 Hz, 2-H), 3.75 (dd, 1 H, $J_{2',3}$ = 1.6 Hz, 2′-H), 3.55 (m, 1 H, 8eq-H), 3.25 (t, 1 H, $J_{8ax,8eq}$ = $J_{8eq,9}$ = 10.9 Hz, 8ax-H), 2.30 (m, 1 H, 3-H), 2.10 (d, 1 H, $J_{4,OH}$ = 3.2 Hz, OH), 1.89 (dd, 1 H, $J_{5ax,5eq}$ = 13, $J_{4,5eq}$ = 4.7 Hz, 5eq-H), 1.57 (t, 1 H, $J_{4,5ax}$ = 12.8 Hz, 5ax-H), 1.78−1.08 (3 m, 7 H, 9,10ax,10eq,11ax,11eq-H, CH_2CH$_3$), 0.89 (t, J = 7.4 Hz, 3 H, CH$_2$CH_3). ^{13}C NMR: δ = 166.87 (CO), 133.02, 130.37, 129.64, and 128.42 (Ph), 97.09 (C-6), 65.52 (C-8), 65.33 (C-4), 61.20 and 59.61 (C-2,12), 40.48 (C-5), 40.10 (C-3), 36.73 (C-9), 35.29 (C-11), 25.29 and 24.95 (C-10,*C*H$_2$CH$_3$), 11.20 (CH$_2$*C*H$_3$). HRMS (LSIMS): found 357.1680 [M$^+$ + Na]; calcd. 357.1680. The second fraction was (3*R*,4*S*,6*R*,9*R*)-4-benzoyloxy-9-ethyl-3-hydroxymethyl-1,7-dioxaspiro[5.5]undecane (**29**; 30 mg, 8%) as a colourless syrup. ^{1}H NMR: δ = 8.03−7.39 (3 m, 5 H, Ph), 5.64 (dt, 1 H, $J_{3,4}$ = $J_{4,5eq}$ = 5.4, $J_{4,5ax}$ = 11.9 Hz, 4-H), 3.96 (d, 2 H, $J_{12,3}$ = 6.5 Hz, 12,12-H), 3.88 (s, 2 H, 2,2-H), 3.58 (m, 1 H, 8eq-H), 3.24 (t, 1 H, $J_{8ax,8eq}$ = $J_{8ax,9}$ = 10.9 Hz, 8ax-H), 2.23 (m, 1 H, 3-H), 1.98 (dd, 1 H, $J_{5ax,5eq}$ = 12.8 Hz, 5eq-H), 1.78 (t, 1 H, 5ax-H), 1.76−1.04 (m, 7 H, 9,10ax, 10eq,11ax,11eq-H, CH_2CH$_3$), 0.87 (t, J = 7.5 Hz, 3 H, CH$_2$CH_3). ^{13}C NMR: δ = 165.59 (CO), 133.09, 130.36, 129.62, and 128.46 (Ph), 97.40 (C-6), 69.39 (C-4), 65.48 (C-8), 59.63 and 59.31 (C-2,12), 39.98 (C-3), 37.52 (C-5), 36.63 (C-9), 35.23 (C-11), 25.28 and 24.93 (C-10,*C*H$_2$CH$_3$), 11.20 (CH$_2$*C*H$_3$).

(3*S*,4*R*,6*R*,9*R*)-3-Benzoyloxymethyl-4-(3,5-dinitrobenzoyloxy)-9-ethyl-1,7-dioxaspiro[5.5]undecane (30): Compound **28** (200 mg, 0.58 mmol) was treated with Ph$_3$P (456 mg, 1.74 mmol), 3,5-dinitrobenzoic acid (368 mg, 1.74 mmol), and DEAD (0.27 mL, 1.74 mmol) in dry THF (5 mL) as above to afford syrupy **30** (143 mg, 45%). $[\alpha]_D^{28}$ = −89 (c = 1). IR (film): $\tilde{\nu}$ = 3035 (aromatic), 1739 and 1725 (C=O, benzoate and 3,5-dinitrobenzoate), 730 and 714 cm^{-1} (aromatic). ^{1}H NMR: δ = 9.21 (s, 3 H, 3,5-dinitrobenzoyl), 8.05−7.45 (3 m, 5 H, Ph), 5.48 (br. d, 1 H, 4-H), 4.54 (d, J = 7.7 Hz, 2 H, 12,12-H), 4.30 (dd, 1 H, $J_{2,2'}$ = 12, $J_{2,3}$ = 3 Hz, 2-H), 3.77 (m, 1 H, 8eq-H), 3.71 (br. d, 1 H, 2′-H), 3.42 (t, 1 H, $J_{8ax,8eq}$ = $J_{8ax,9}$ = 10.9 Hz, 8ax-H), 2.31 (m, 1 H, 3-H), 2.01 (dd, 1 H, $J_{5,5'}$ = 15.1, $J_{4,5}$ = 2.8 Hz, 5-H), 1.95 (dd, 1 H, $J_{4,5'}$ = 3.7 Hz, 5′-H), 1.78−1.10 (m, 7 H, 9,10ax,10eq,11ax,11eq-H, CH_2CH$_3$), 0.90 (t, J = 7.5 Hz, 3 H, CH$_2$CH_3). ^{13}C NMR: δ = 166.48 and 161.82 (2 CO), 148.73, 134.70, 133.36, 129.77, 129.72, 128.58 and 122.37 (Ph), 95.20 (C-6), 69.85 (C-4), 65.86 (C-8), 63.34 (C-12), 56.71 (C-2), 37.29 (C-3), 36.47 (C-9), 35.34 (C-5,11), 25.28 and 24.82 (C-10,*C*H$_2$CH$_3$), 11.22 (CH$_2$*C*H$_3$). HRMS (LSIMS): found 551.1647 [M$^+$ + Na]; calcd. 551.1642.

(3*R*,4*R*,6*R*,9*R*)-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. $[\alpha]_D^{27} = -122$ ($c = 1$). ^{1}H NMR (500 MHz; C_6D_6): δ = 4.08 (br. dd, 1 H, $J_{2,3}$ = 3.2, $J_{2,2'}$ 11.8 Hz, 2-H), 4.08 (br. s, 1 H, 4-H), 3.64 (d, 1 H, 2′-H), 3.56 (dd, 1 H, $J_{12,12'}$ = 10.6, $J_{3,12}$ = 7.8 Hz, 12-H), 3.46 (dd, 1 H, $J_{3,12'}$ = 6.9 Hz, 12′-H), 3.33 (ddd, 1 H, $J_{8eq,9}$ = 4.5, $J_{8eq,10eq}$ = 1.8 Hz, 8eq-H), 3.21 (t, 1 H, $J_{8ax,8eq} = J_{8ax,9}$ = 11 Hz, 8ax-H), 1.88 (m, 1 H, 3-H), 1.78 (br. dd, 1 H, $J_{5,5'}$ = 14.4, $J_{4,5}$ = 2.4 Hz, 5-H), 1.56 (dd, 1 H, $J_{4,5'}$ = 3.5 Hz, 5′-H), 1.55−0.90 (m, 7 H, 9,10ax,10-eq,11ax,11eq-H, CH_2CH_3), 0.77 (t, J = 7.5 Hz, 3 H, CH_2CH_3). ^{13}C 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 (CH_2CH_3), 24.79 (C-10), 11.16 (CH_2CH_3). HRMS (LSIMS): found 253.1416 [M^+ + Na]; calcd. 253.1416.

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