Synthetic Studies on Spiroketal Natural Products. V.[1] Total Synthesis of (+)-Talaromycin A and (−)-Talaromycin B

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The total synthesis of (+)-talaromycin A and (−)-talaromycin B was accomplished by utilizing a common intermediate (3). The spiroketal (3) was converted to the olefin (4) *via* thermolysis of the sulfinyl group, C1-unit elongation at the C9-position, and isomerization at the spiro center. On the other hand, 3 was isomerized to 7 at the C9-position and then converted to the olefin (5) in a similar manner to that described for (+)-talaromycin A. These intermediates (4 and 5) were transformed into (+)-talaromycin A and (−)-talaromycin B *via* addition reaction of trifluoroacetic acid and oxymercuration, respectively.

Keywords (+)-talaromycin A; (−)-talaromycin B; stereodivergent synthesis; spiroketal; oxymercuration

Talaromycin A (**1**) and B (**2**) were isolated from the fungus *Talaromyces stipitatus* by Lynn and co-workers in 1982.[2] These compounds block outward potassium fluxes in smooth muscle, causing muscle dysfunction. Their unique spiroketal framework has attracted much attention as a challenging synthetic target.[3] In the preceding paper, we have reported asymmetric recognition of prochiral 1,3-diols and a diastereoselective preparation of the spiroketal (**3**).[1]

We herein report the stereodivergent synthesis of (+)-talaromycin A (**1**) and (−)-talaromycin B (**2**) starting from **3** (Chart 1).

Synthetic Strategy for Talaromycins First, for the transformation of **3** into (+)-talaromycin A (**1**) steric inversion at the spiro center is necessary. The hydroxymethyl group should be protected as the tosylate to prevent isomerization at the C9-position. Then, formation of the double bond at the C4- and C5-position *via* thermolysis of the sulfinyl group is considered to facilitate isomerization at the spiro center, owing to the $A^{(1,2)}$-strain between the benzyloxymethyl group and the olefinic proton. After C1-unit elongation at the C9-position, the resulting olefin (**6**) would be predominantly isomerized to **4**. The introduction of the hydroxy group should be achieved by addition reaction of trifluoroacetic acid to the olefin (**4**), leading to (+)-talaromycin A (**1**).

On the other hand, **3** could be converted to the more

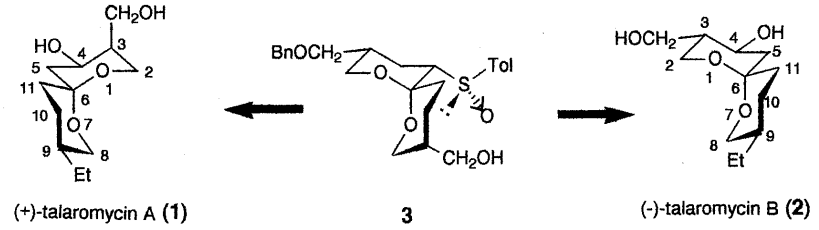


Chart 1

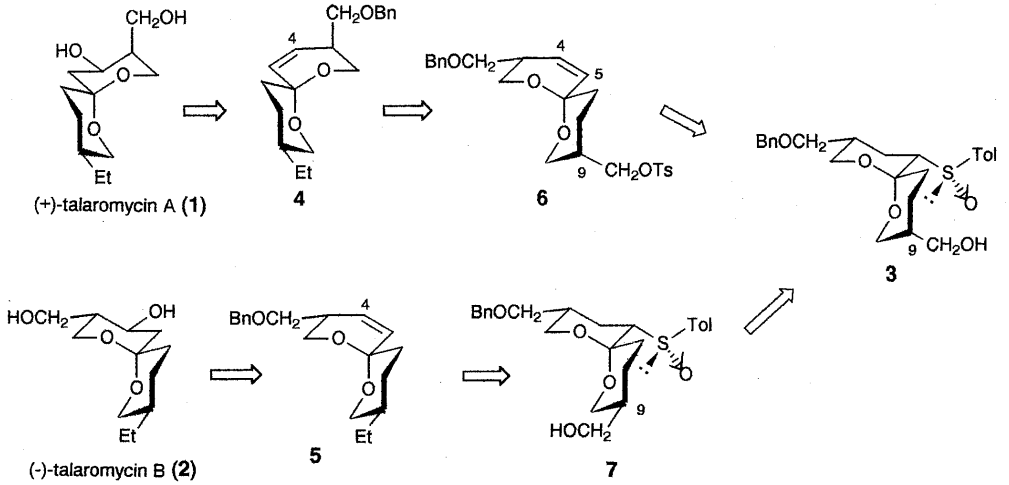


Chart 2

stable C9-epimer (**7**) by acid-catalyzed isomerization. As in the case of (+)-talaromycin A (**1**), **7** is transformed into the olefin (**5**) and then the remaining chirality at the C4-position would be introduced by oxymercuration and demercuration, leading to (−)-talaromycin B (**2**) after debenzylation (Chart 2).

Total Synthesis of (+)-Talaromycin A (1) The spiroketal (**3**) was tosylated to **8**, followed by thermolysis to afford **9** by reaction with Me_2CuLi (67% from **3**). The product (**9**) was isomerized to the desired spiro compound (**4**) in 75% yield (**4**/**9**=3.2/1) on treatment with trifluoroacetic acid [**4**: 3.81 (1H, br d, J=11.5 Hz, 2-H_{eq})]. The isomerization was considered to occur due to the release of the 1,3-diaxial interaction between the ethyl group and the axial proton and the $A^{(1,2)}$-strain between the benzyloxymethyl group and the adjacent olefinic proton in **9**. Introduction of a hydroxy group at the C4-position of **4** was achieved by addition reaction of trifluoroacetic acid in chloroform and subsequent hydrolysis with potassium carbonate. The desired compound (**11**) was isolated in 37% yield from **4** accompanied with its isomer (**10**) (22% from **4**) (Chart 3).

The stereochemistry of compounds **10** and **11** was confirmed by the coupling constant of the C4-methine proton in the 500 MHz ^{1}H-NMR spectra; [**10**: δ 3.99 (ddd, J=4.9, 11.0, 11.0 Hz), **11**: δ 4.20—4.34 (m, $W_{1/2}$=20.0 Hz)]. Compounds **10** and **11** were assumed to be formed by acid-promoted S_N2' type C–O bond cleavage followed by thermodynamically favored reacetalization *via* pathways a and b, respectively as shown in Chart 4.[4] Protonation at the O1-position would be assisted by the benzyloxy group followed by the *syn* attack of trifluoroacetic acid to afford **11** as a major product.[5]

Then, **11** was converted to (+)-talaromycin A by means of the Birch reduction in 98% yield.

Total Synthesis of (−)-Talaromycin B (2) The spiroketal (**3**) was expected to be epimerized to the more stable **7**, by analogy with acid-catalyzed epimerization from (−)-talaromycin A to (−)-talaromycin B.[3] In fact, **3** was epimerized to **7** in the presence of *p*-toluenesulfonic acid, but the selectivity was not so high (61%, **3**/**7**=1/1.6). The abnormal stability of the C9-axial isomer (**3**) can be attributed to intramolecular hydrogen bonding between the hydroxy group and the sulfinyl oxygen (Chart 5).

By means of the same procedure as described above, **7**

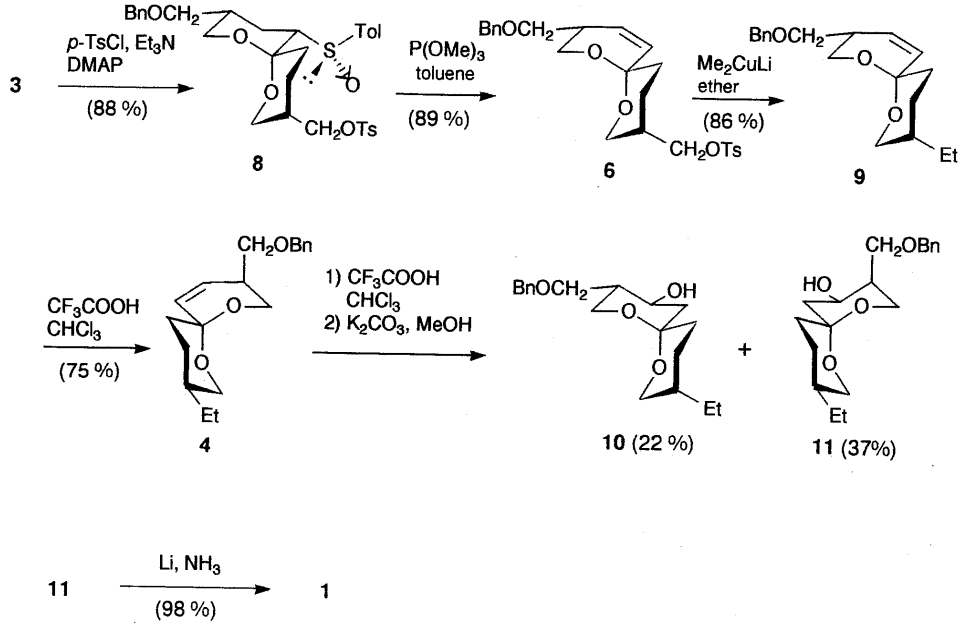


Chart 3

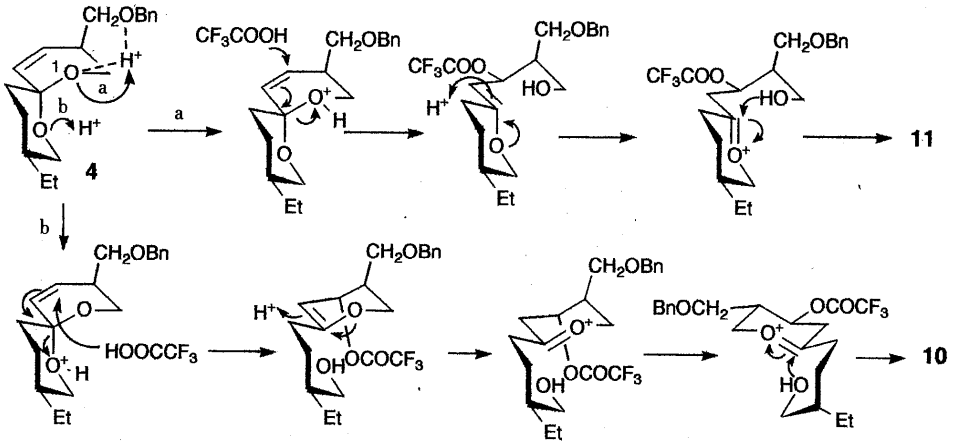
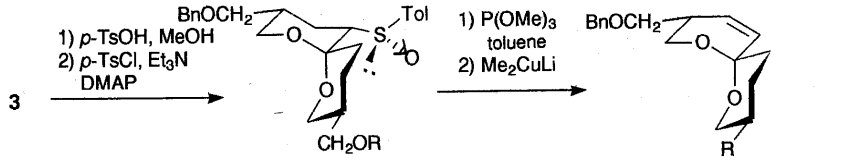


Chart 4



7: R=H (61 %)
12: R=Ts (quant.)

13: R=CH_2OTs (82 %)
5: R=Et (87 %)

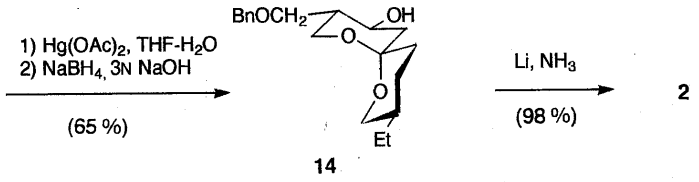


Chart 5

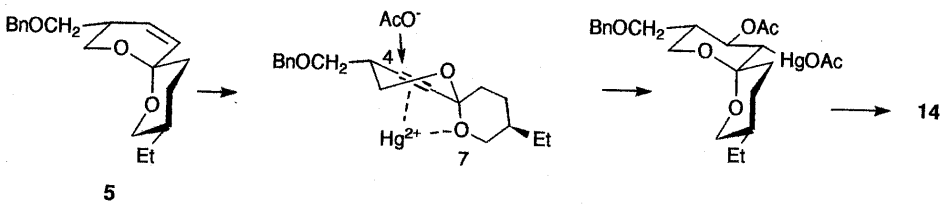


Chart 6

was transformed into **5** (71% in 3 steps). The final chiral induction at the C4-position was performed by oxymercuration and reductive demercuration[6] to give **14** regio- and diastereoselectively in 65% yield. The regio- and diastereoselectivities of this reaction can be explained as follows. The mercurium cation would approach the olefin from the same side as the benzyloxymethyl group owing to the coordination to C7-oxygen. The attack by the acetate anion would occur at the face opposite to that of mercurium cation addition. Since the double bond would be polarized toward the spiro center due to the inductive effect of the C1- and C7-oxygens, the acetate anion would attack regioselectively at the C4-position to afford **14** (Chart 6).[7]

Debenzylation by means of the Birch reduction of **14** provided (−)-talaromycin B (**2**) in 98% yield.

Both synthetic talaromycins exhibited ^{1}H-NMR spectroscopic properties in accordance with those of the corresponding natural talaromycins; [(+)-talaromycin A: $[\alpha]_D^{22}$ +115.00° (c=0.83, $CHCl_3$), *cf.* (−)-talaromycin A: lit.[3h] $[\alpha]_D^{20}$ −110.2° (c=0.83, $CHCl_3$), 91—93% ee, lit.[3j] $[\alpha]_D^{26}$ −124.9° (c=1.11, $CHCl_3$), (−)-talaromycin B: $[\alpha]_D^{23}$ −90.3° (c=0.78, $CHCl_3$), lit.[3h] $[\alpha]_D^{20}$ −84.1° (c=0.46, $CHCl_3$) for 91—93% ee]. Since talaromycin A is known to isomerize easily to talaromycin B, the synthesis of (+)-talaromycin A also represents a formal synthesis of (+)-talaromycin B.

Experimental

General Method Melting points were not corrected. Infrared (IR) spectra were recorded with a Hitachi 260-10 spectrometer. ^{1}H-NMR spectra were measured with a Hitachi R-22 (90 MHz), or a JEOL JNM-GX-500 (500 MHz) instrument. The chemical shifts are given as δ (ppm) values with tetramethylsilane (TMS) as an internal standard. Optical rotations were recorded with a Yanagimoto OR-20 or a JASCO DIP-360 polarimeter. Mass spectra (MS) and high-resolution MS (High-MS) were obtained with a Shimadzu QP-1000 or a JEOL JMS D-300 mass spectrometer. Analytical HPLC was performed by using a Shimadzu LC-5A equipped with a SOMA S-310A ultraviolet detector. A Sumipax OA-2000A optically active column was used for analysis. For column chromatography, Aluminiumoxid 90 or Kieselgel 60 (E. Merck) was used. For preparative TLC (PTLC), Kieselgel 60 PF_{254} (E. Merck) was used. All organic extracts were concentrated under reduced pressure.

(3*S*,6*R*,9*S*)-3-Benzyloxymethyl-9-(*p*-tosyl)oxymethyl-1,7-dioxaspiro-[5.5]undec-4-ene (6) *p*-Toluenesulfonyl chloride (95.2 mg, 0.50 mmol) was added to a solution of **3** (148 mg, 0.33 mmol), triethylamine (0.09 ml, 0.65 mmol), and dimethylaminopyridine (DMAP) (20.5 mg, 0.17 mmol) in dry CH_2Cl_2 (15 ml) with stirring at 0 °C. The mixture was stirred at room temperature for 4 h. The mixture was washed with ice-saturated $NaHCO_3$ and the aqueous layer was extracted with $CHCl_3$. The combined organic layer was washed with brine, and dried over $MgSO_4$. The solvent was evaporated and the residue was purified by PTLC with hexane–AcOEt (1 : 1) to afford **8** (176 mg, 88%) as a colorless oil. $[\alpha]_D^{14}$ +47.0° (c=1.17, $CHCl_3$). IR ($CHCl_3$): 1600, 1500, 1365, 1175, 1095, 1085, 1040 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.10—2.50 (9H, m), 2.27 (3H, s, $S(O)C_6H_5C\underline{H}_3$), 2.37 (3H, s, $S(O)_2C_6H_5C\underline{H}_3$), 3.23 (2H, d, J=5.5 Hz, $C\underline{H}_2OBn$), 3.10—3.90 (4H, m), 4.17 (1H, dd, J=10.0, 6.0 Hz), 4.38 (1H, br d, J=10.0 Hz), 4.38 (2H, s, $OC\underline{H}_2Ph$), 7.00—7.50 (11H, m), 7.80 (2H, d, J=8.5 Hz). CI-MS m/z: 599 (M^++1).

A solution of **8** (32.2 mg, 0.05 mmol) and trimethyl phosphite (0.03 ml, 0.25 mmol) in dry toluene (3 ml) was heated at 150 °C for 8 h in a sealed tube. The mixture was washed with ice-saturated $NaHCO_3$ and the aqueous layer was extracted with ether. The combined organic layer was washed with brine, and dried over $MgSO_4$. The solvent was evaporated and the residue was purified by PTLC with hexane–AcOEt (3 : 1) to afford **6** (22.0 mg, 89%) as a colorless oil. $[\alpha]_D^{13}$ −62.8° (c=0.75, $CHCl_3$). IR ($CHCl_3$): 1655, 1600, 1500, 1400, 1363, 1174, 1095, 1075, 1033 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.20—2.20 (5H, m), 2.44 (3H, s, $ArCH_3$), 2.50—2.90 (1H, m, 3-H), 3.10—4.10 (6H, m), 4.18 (2H, d, J=7.5 Hz, $C\underline{H}_2OTs$), 4.27 (2H, s, $C\underline{H}_2OBn$), 5.52 (1H, dd, J=10.0, 3.0 Hz, 4-H), 5.80 (1H, dd, J=10.0, 1.0 Hz, 5-H), 7.25 (5H, s), 7.29 (2H, d, J=8.5 Hz), 7.76 (2H, d, J=8.5 Hz). MS m/z (%): 458 (M^+, 1.0), 91 ($C_7H_7^+$, 100). High MS Calcd for $C_{25}H_{30}O_6S$: 458.1763. Found: 458.1769.

(3*S*,6*R*,9*S*)-3-Benzyloxymethyl-9-ethyl-1,7-dioxaspiro[5.5]undec-4-ene (9) A 1.46 M MeLi ether solution (1.17 ml, 1.71 mmol) was added to a suspension of CuI (163 mg, 0.85 mmol) in dry ether (4 ml) with stirring at −20 °C over 10 min under N_2. The mixture was stirred for 10 min, then

a solution of **5** (85.8 mg, 0.19 mmol) in dry ether (4 ml) was added with stirring at −30°C and the whole was stirred for 2.5 h. The mixture was quenched with saturated NH_4Cl. The organic layer was separated and the aqueous layer was extracted with ether. The combined organic layer was washed with saturated $NaHCO_3$ and brine, and then dried over $MgSO_4$. The solvent was evaporated and the residue was chromatographed on silica gel with hexane–AcOEt (4 : 1) to afford **9** (48.5 mg, 86%) as a colorless oil along with **5** (4.9 mg, 5.7%). $[\alpha]_D^{13}$ −81.2° (c=0.48, $CHCl_3$). IR ($CHCl_3$): 1655, 1496, 1455, 1400, 1160, 1110, 1077, 1025 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.91 (3H, t, J=6.5 Hz, $CH_2C\underline{H}_3$), 1.00—2.30 (7H, m), 2.50—2.90 (1H, m, 3-H), 3.20—4.10 (6H, m), 4.49 (2H, s, $C\underline{H}_2OBn$), 5.68 (1H, dd, J=10.5, 2.0 Hz, 4-H), 5.84 (1H, br d, J=10.5 Hz, 4-H), 7.31 (5H, s-like, Ar–H). MS m/z (%): 302 (M^+). High MS Calcd for $C_{19}H_{26}O_3$: 302.1882. Found: 302.1905.

(3*S*,6*S*,9*S*)-3-Benzyloxymethyl-9-ethyl-1,7-dioxaspiro[5.5]undec-4-ene (4) Trifluoroacetic acid (0.005 ml, 0.06 mmol) was added to a solution of **9** (37.5 mg, 0.12 mmol) in $CHCl_3$ (1 ml) with stirring at 0 °C. The mixture was stirred at room temperature for 24 h, diluted with $CHCl_3$, washed with saturated $NaHCO_3$ and brine, and then dried over $MgSO_4$. The solvent was evaporated and the residue was purified by PTLC with hexane–AcOEt (10 : 1) to afford **4** (28.2 mg, 75%) as a colorless oil along with **9** (8.9 mg, 24%). $[\alpha]_D^{21}$ −39.76° (c=0.84, $CHCl_3$). IR ($CHCl_3$): 1655, 1175, 1125, 1080, 1010 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.89 (3H, t, J=5.5 Hz, $CH_2C\underline{H}_3$), 0.90—1.80 (10H, m), 2.00—2.40 (1H, m), 3.47 (2H, d, J=8.0 Hz, $C\underline{H}_2OBn$), 3.20—3.60 (2H, m), 3.81 (1H, br d, J=11.5 Hz), 4.00 (1H, dd, J=11.5, 3.5 Hz), 4.52 (1H, d, J=10.8 Hz, $C\underline{H}_2OPh$), 4.54 (1H, d, J=10.8 Hz, $C\underline{H}_2OPh$), 5.66 (1H, br d, J=10.0 Hz, 5-H), 5.89 (1H, br dd, J=10.0, 4.5 Hz, 4-H), 7.33 (5H, s-like, Ar–H). MS m/z (%): 302 (M^+, 4.2), 91 ($C_7H_7^+$, 100). High MS Calcd for $C_{19}H_{26}O_3$: 302.1879. Found: 302.1866.

(3*S*,4*S*,6*R*,9*R*)-9-Ethyl-3-hydroxymethyl-4-hydroxy-1,7-dioxaspiro-[5.5]undecane (10) and (3*S*,4*R*,6*S*,9*S*)-9-Ethyl-3-hydroxymethyl-4-hydroxy-1,7-dioxaspiro[5.5]undecane (11) Trifluoroacetic acid (0.08 ml, 1.00 mmol) was added to a solution of **4** (30.0 mg, 0.10 mmol) in dry $CHCl_3$ (1 ml) with stirring at 0 °C. The mixture was stirred at room temperature for 3 h, diluted with $CHCl_3$, washed with saturated $NaHCO_3$ and brine, and then dried over Na_2SO_4. The solvent was evaporated and the residue was roughly separated by PTLC with hexane–AcOEt (19 : 1) to afford the polar product (8.9 mg) as a colorless oil and the less polar product (15.1 mg) as a colorless oil, which were used in the next step without further purification.

To a solution of the polar product (8.9 mg) in dry MeOH (1 ml) was added K_2CO_3 (2.8 mg, 0.02 mmol) with stirring at 0 °C. Stirring was continued at room temperature for 5 min, then the mixture was partitioned between $CHCl_3$ and water, and the $CHCl_3$ layer was separated. The aqueous layer was extracted with $CHCl_3$. The combined organic layer was washed with brine and dried over Na_2SO_4. The solvent was evaporated and the residue was purified by PTLC with hexane–AcOEt (4 : 1) to afford **10** (6.8 mg, 22% from **4**) as a colorless oil. $[\alpha]_D^{14}$ −73.40° (c=0.30, $CHCl_3$). IR ($CHCl_3$): 3490, 1090, 1070, 1040 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.92 (3H, t, J=7.3 Hz, $CH_2C\underline{H}_3$), 1.35 (1H, dd, J=11.6, 11.6 Hz), 1.30—1.60 (3H, m), 1.57 (1H, ddd, J=12.9, 12.9, 5.3 Hz), 1.60—1.80 (1H, m), 1.67 (1H, ddd, J=13.5, 13.5, 4.3 Hz), 1.96 (1H, ddd, J=12.5, 4.9, 4.9 Hz), 1.90—2.05 (1H, m), 2.08 (1H, dd, J=12.8, 5.5 Hz), 3.36 (2H, dd, J=11.6, 11.6 Hz), 3.45—3.60 (2H, m), 3.60 (1H, dd, J=11.6, 4.9 Hz), 3.73 (1H, dd, J=11.6, 3.1 Hz), 3.99 (1H, ddd, J=11.0, 11.0, 4.9 Hz), 4.53 (2H, s, $C\underline{H}_2OPh$), 7.20—7.40 (5H, m, Ar–H). MS m/z (%): 320 (M^+, 0.8), 302 (M^+-H_2O, 1.9), 91 ($C_7H_7^+$, 100). High MS Calcd for $C_{19}H_{28}O_4$: 320.1985. Found: 320.1959.

To a solution of the less polar product (15.1 mg) in dry MeOH (1 ml) was added K_2CO_3 (4.7 mg, 0.04 mmol) with stirring at 0°C. Stirring was continued at room temperature for 5 min, then the mixture was partitioned between $CHCl_3$ and water, and the $CHCl_3$ layer was separated. The aqueous layer was extracted with $CHCl_3$. The combined organic layer was washed with brine and dried over Na_2SO_4. The solvent was evaporated and the residue was purified by PTLC with hexane–AcOEt (4 : 1) to afford **11** (11.6 mg, 37% from **4**) as a colorless oil. $[\alpha]_D^{24}$ +71.60° (c=0.50, $CHCl_3$). IR ($CHCl_3$): 3480, 1185, 1165, 1070, 1040 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.87 (3H, t, J=7.3 Hz, $CH_2C\underline{H}_3$), 1.40—1.25 (2H, m). 1.37 (1H, dddd, J=12.8, 12.0, 12.0, 3.7 Hz), 1.40—1.50 (1H, m), 1.49 (1H, ddd, J=12.8, 12.8, 4.3 Hz), 1.55—1.65 (2H, m), 1.66 (1H, ddd, J=12.8, 3.7, 3.1 Hz), 1.89 (1H, dd, J=13.4, 4.9 Hz), 2.25—2.37 (1H, m), 3.19 (1H, dd, J=11.0, 11.0 Hz), 3.52 (1H, ddd, J=11.0, 4.3, 1.8 Hz), 3.56 (1H, dd, J=11.6, 1.8 Hz), 3.69 (1H, dd, J=9.2, 6.1 Hz), 3.73 (1H, dd, J=11.6, 2.7 Hz), 4.00 (1H, dd, J=9.2, 9.2 Hz), 4.20—4.34 (1H, m, $W_{1/2}$=20 Hz), 4.50 (2H, s, $C\underline{H}_2OPh$), 7.29—7.36 (5H, m, Ar–H). MS m/z (%): 320 (M^+, 0.6), 302 (M^+-H_2O, 2.9), 91 ($C_7H_7^+$, 100). High MS Calcd for $C_{19}H_{28}O_4$: 320.1988. Found: 320.2004.

(+)-Talaromycin A (1) A solution of **11** (6.8 mg, 0.02 mmol) in THF (1 ml) and Li (8 mg, 1.1 gram atom) was added to liquid NH_3 (5 ml) with stirring at −40 °C under N_2. Stirring was continued at room temperature for 1 h, then the mixture was quenched with NH_4Cl, and the NH_3 was evaporated. The residue was partitioned between ether and water. The ether layer was separated, and the aqueous layer was extracted with ether. The combined organic layer was washed with brine, and dried over Na_2SO_4. The solvent was evaporated and the residue was chromatographed on alumina with ether–MeOH (19 : 1) to afford **1** (4.8 mg, 98.0%) as a colorless oil. $[\alpha]_D^{22}$ +115.0° (c=0.16, $CHCl_3$). IR ($CHCl_3$): 3450, 1185, 1100, 1065, 1040 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, J=7.3 Hz, $CH_2C\underline{H}_3$), 1.07—1.23 (2H, m, $C\underline{H}_2CH_3$), 1.38 (1H, dddd, J=12.2, 12.2, 12.2, 4.3 Hz), 1.41—1.48 (1H, m), 1.51 (1H, ddd, J=12.2, 12.2, 4.3 Hz), 1.56—1.65 (1H, m), 1.72 (1H, dd, J=11.9, 12.8 Hz), 1.89 (1H, dd, J=12.8, 5.5 Hz), 2.11—2.17 (1H, m), 3.19 (1H, dd, J=11.0, 11.0 Hz), 3.52 (1H, ddd, J=11.0, 4.3, 1.8 Hz), 3.58 (1H, dd, J=11.6, 1.5 Hz), 3.75 (1H, dd, J=11.6, 3.1 Hz), 3.80 (1H, dd, J=11.0, 4.6 Hz), 4.21 (1H, dd, J=11.0, 8.5 Hz), 4.41 (1H, ddd, J=11.9, 5.5, 5.5 Hz). MS m/z (%): 230 (M^+, 3.6), 213 (M^+-OH, 6.3), 200 (M^+-CH_2O, 3.3), 126 (100). High MS Calcd for $C_{12}H_{22}O_4$: 230.1519. Found: 230.1534.

(3*S*,6*R*,9*S*)-3-Benzyloxymethyl-9-(*p*-tosyl)oxymethyl-1,7-dioxaspiro-[5.5]undec-4-ene (13) A solution of **3** (160 mg, 0.42 mmol) and *p*-toluenesulfonic acid monohydrate (80 mg, 0.42 mmol) in dry MeOH (16 ml) was refluxed for 8 h. After cooling, the mixture was neutralized with saturated $NaHCO_3$ and the solvent was evaporated. The residue was diluted with $CHCl_3$, washed with brine, and dried over Na_2SO_4. The solvent was evaporated and the residue was purified by PTLC with ether–MeOH (19 : 1) to afford **7** (98 mg, 61%) as a colorless oil along with **3** (62 mg, 39%). $[\alpha]_D^{14}$ +93.7° (c=0.98, $CHCl_3$). IR ($CHCl_3$): 3400, 1497, 1453, 1240, 1037 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.20—2.70 (9H, m), 2.36 (3H, s, $ArC\underline{H}_3$), 3.25 (2H, d, J=5.0 Hz, $C\underline{H}_2OH$), 3.43 (2H, d, J=6.0 Hz, $C\underline{H}_2OBn$), 3.30—3.70 (2H, m), 3.69 (1H, dd, J=11.0, 3.0 Hz), 3.93 (1H, dd, J=11.0, 4.0 Hz), 4.38 (2H, s, $OC\underline{H}_2Ph$), 7.00—7.50 (9H, m, Ar–H). MS m/z (%): 444 (M^+, 0.4), 426 (M^+-H_2O, 0.4).

p-Toluenesulfonyl chloride (63.1 mg, 0.33 mmol) was added to a solution of **7** (98 mg, 0.22 mmol), triethylamine (0.06 ml, 0.43 mmol), and DMAP (13.6 mg, 0.11 mmol) in dry CH_2Cl_2 (10 ml) with stirring at 0 °C. The mixture was stirred at room temperature for 4 h, then washed with ice-saturated $NaHCO_3$, and the aqueous layer was extracted with $CHCl_3$. The combined organic layer was washed with brine, and dried over $MgSO_4$. The solvent was evaporated and the residue was purified by PTLC with hexane–AcOEt (1 : 3) to afford **12** (132 mg, quant.) as a colorless oil. $[\alpha]_D^{14}$ +59.7° (c=1.32, $CHCl_3$). IR ($CHCl_3$): 1600, 1495, 1458, 1361, 1174, 1095, 1038 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.10—2.70 (9H, m), 2.38 (3H, s, $S(O)C_6H_5C\underline{H}_3$), 2.43 (3H, s, $S(O)_2C_6H_5C\underline{H}_3$), 3.26 (2H, d, J=6.0 Hz, $C\underline{H}_2OBn$), 3.20—3.90 (4H, m), 3.88 (2H, d, J=6.5 Hz, $C\underline{H}_2OTs$), 4.40 (2H, s, $OC\underline{H}_2Ph$), 7.00—7.50 (11H, m), 7.74 (2H, d, J=8.5 Hz). MS m/z (%): 583 (M^+-Me, 1.4).

A solution of **12** (131 mg, 0.22 mmol) and trimethyl phosphite (0.13 ml, 1.10 mmol) in dry toluene (13 ml) was heated at 150 °C for 10 h in a sealed tube. The mixture was washed with ice-saturated $NaHCO_3$ and the aqueous layer was extracted with ether. The combined organic layer was washed with brine, and dried over $MgSO_4$. The solvent was evaporated and the residue was chromatographed on silica gel with hexane–AcOEt (3 : 1) to afford **13** (82.0 mg, 82%) as a colorless oil. $[\alpha]_D^{13}$ −46.1° (c=0.82, $CHCl_3$). IR ($CHCl_3$): 1655, 1600, 1498, 1459, 1400, 1361, 1180, 1100, 1090, 1030 cm^{-1}. ^{1}H-NNR ($CDCl_3$) δ: 1.40—2.20 (5H, m), 2.43 (3H, s, $ArCH_3$), 2.50—2.90 (1H, m, allylic-H), 3.10—4.10 (6H, m), 3.84 (2H, d, J=6.0 Hz, $C\underline{H}_2OTs$), 4.47 (2H, s, $OC\underline{H}_2Ph$), 5.57 (1H, dd, J=10.0, 2.0 Hz, 4-H), 5.82 (1H, br d, J=10.0 Hz, 5-H), 7.20—7.40 (7H, m), 7.74 (2H, d, J=8.0 Hz). MS m/z (%): 458 (M^+, 0.7), 91 ($C_7H_7^+$, 100). High MS Calcd for $C_{25}H_{30}O_6S$: 458.1760. Found: 458.1740.

(3*S*,6*R*,9*R*)-3-Benzyloxymethyl-9-ethyl-1,7-dioxaspiro[5.5]undec-4-ene (5) A 1.46 M MeLi ether solution (1.12 ml, 1.64 mmol) was added to a suspension of CuI (156 mg, 0.82 mmol) in dry ether (4 ml) with stirring at −20 °C over 20 min under N_2. Stirring was continued for 10 min, then a solution of **13** (82.0 mg, 0.18 mmol) in dry ether (4 ml) was added to the mixture with stirring at −30 °C, and the whole was stirred for 40 min. The mixture was quenched with saturated NH_4Cl. The organic layer was separated and the aqueous layer was extracted with ether. The combined organic layer was washed with saturated $NaHCO_3$ and brine, and then dried over $MgSO_4$. The solvent was evaporated and the residue was

chromatographed on silica gel with hexane–AcOEt (3 : 1) to afford **5** (46.9 mg, 87%) as a colrless oil. $[\alpha]_D^{13}$ −77.6° (c=0.47, $CHCl_3$). IR ($CHCl_3$): 1660, 1658, 1498, 1455, 1402, 1365, 1162, 1085, 1025 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.87 (3H, t, J=6.0 Hz, $CH_2C\underline{H}_3$), 1.00—1.90 (7H, m), 2.50—2.90 (1H, m, allylic-H), 3.20—3.70 (4H, m), 3.67, (1H, d, J=10.0 Hz), 3.84 (1H, dd, J=5.0, 10.0 Hz), 4.46 (2H, s, $OC\underline{H}_2Ph$), 5.58 (1H, dd, J=10.0, 2.5 Hz, 4-H), 5.79 (1H, br d, J=10 Hz, 5-H), 7.26 (5H, s-like, Ar-H). MS m/z (%): 302 (M^+, 0.7), 91 ($C_7H_7^+$, 100). High MS Calcd for $C_{19}H_{26}O_3$: 302.1879. Found: 302.1869.

(3*S*,4*S*,6*R*,9*R*)-3-Benzyloxymethyl-9-ethyl-4-hydroxy-1,7-dioxaspiro-[5.5]undecane (14) A solution of **5** (46.9 mg, 0.16 mmol) in THF (1 ml) was added to a solution of $Hg(OAc)_2$ (247 mg, 0.78 mmol) in water (4 ml) with stirring at 0 °C. Stirring was continued at room temperature for 30 min, then 3 N NaOH (0.78 ml) was added to the mixture followed by the addition of a solution of $NaBH_4$ (14.7 mg, 0.39 mmol) in 3 N NaOH (0.78 ml). The mixture was saturated with NaCl, extracted with THF, washed with brine, and dried over $MgSO_4$. The solvent was evaporated and the residue was purified by PTLC with hexane–AcOEt (3 : 1) to afford **14** (32.2 mg, 65%) as a colorless oil. $[\alpha]_D^{14}$ −69.7° (c=0.29, $CHCl_3$). IR ($CHCl_3$): 3500, 1162, 1090, 1030, 985 cm^{-1}. ^{1}H-NMR ($CDCl_2$) δ: 0.88 (3H, t, J=7.6 Hz, $CH_2C\underline{H}_3$), 1.09—1.20 (2H, m, $C\underline{H}_2CH_3$), 1.41 (1H, dd, J=11.0, 12.8 Hz), 1.20—1.70 (5H, m), 1.90—2.20 (1H, m, 3-H), 2.00 (1H, dd, J=5.2, 13.1 Hz), 3.18 (1H, t, J=11.0 Hz), 3.31 (1H, t, J=11.3 Hz), 3.47—3.55 (3H, m), 3.57 (1H, dd, J=11.3, 4.6 Hz), 4.00 (1H, dt, J=10.3, 5.2 Hz, 4-H), 4.53 (2H, s, $OC\underline{H}_2Ph$), 7.20—7.40 (5H, m, Ar-H). MS m/z (%): 320 (M^+, 0.5), 302 (M^+-H_2O, 1.3), 291 (M^+−Et, 0.1), 91 ($C_7H_7^+$, 100). High MS Calcd for $C_{19}H_{28}O_4$: 320.1987. Found: 320.1987.

(−)-Talaromycin B (2) A solution of **14** (29.0 mg, 0.09 mmol) in THF (1 ml) and Li (12 mg, 1.7 gram atom) was added to liquid NH_3 (*ca.* 60 ml) with stirring at −40 °C under N_2. Stirring was continued at room temperature for 5 h, then the mixture was quenched with NH_4Cl, and the NH_3 was evaporated. The residue was partitioned between ether and water. The organic layer was separated, and the aqueous layer was extracted with $CHCl_3$. The combined organic layer was washed with brine, and dried over $MgSO_4$. The solvent was evaporated and the residue was purified by PTLC with ether–MeOH (20 : 1) to afford **2** (20.4 mg, 98%) as colorless scales. mp 136—138 °C from n-hexane : benzene = 2 : 1. $[\alpha]_D^{23}$ −90.3° (c=0.78, $CHCl_3$). IR (KBr): 3350, 1380, 1186, 1084, 1074, 1058, 1045, 1035 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, J=7.3 Hz, $CH_2C\underline{H}_3$), 1.10—1.20 (2H, m, $C\underline{H}_2CH_3$), 1.45 (1H, dd, J=12.2, 11.6 Hz), 1.20—1.80 (5H, m), 1.80—1.90 (1H, m, 3-H), 2.00 (1H, dd, J=12.5, 5.3 Hz), 3.19 (1H, t, J=11.0 Hz), 3.31 (1H, t, J=11.6 Hz), 3.51 (1H, dd, J=11.0, 2.4 Hz), 3.59 (1H, dd, J=11.6, 4.9 Hz), 3.72 (2H, d, J=6.1 Hz, $C\underline{H}_2OH$), 4.07 (1H, dt, J=10.7, 5.2 Hz). MS m/z (%): 230 (M^+, 1.9), 212 (M^+-H_2O, 0.7), 200 (M^+-CH_2O, 2.5), 147 (100). High MS Calcd for $C_{12}H_{22}O_4$: 230.1516. Found: 230.1513.

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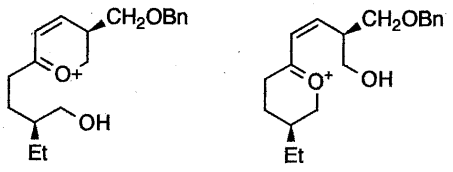

15 **16**

Fig. 1

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