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ASYMMETRIC INDUCTION BY SULFINYL CHIRALITY. A TOTAL SYNTHESIS OF (+)-TALAROMYCIN A AND (-)-TALAROMYCIN B

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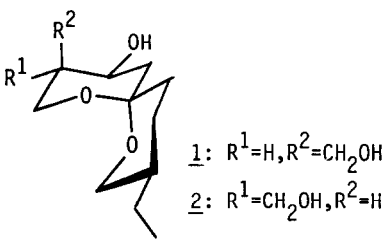
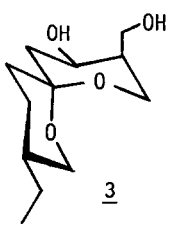
Summary: A total synthesis of (+)-talaromycin A and (-)-talaromycin B was accomplished by means of successive asymmetric induction of all chiral centers using a chiral sulfinyl group.

Talaromycin A and B were isolated as toxic metabolites of a fungus, Talaromyces stipitatus, which grows on chicken litter, and their structures (**1** and **2**, respectively) were determined on basis of 2D-COSY ^{1}H-NMR spectra.[1,2] There have been three reports concerning total synthesis of optically active talaromycin(s); two syntheses were achieved by use of readily available chiral carbon fragments,[1e,g] and the other utilized a crucial asymmetric reduction of β-keto esters with baker's yeast.[1h] In the foregoing paper we have described a novel method for asymmetric recognition of prochiral gem-bis(hydroxymethyl) groups by means of a sulfinyl chirality.[3] This communication deals with a novel enantioselective synthesis of (+)-talaromycin A (**3**; antipode of **1**) and (-)-talaromycin B (**2**) with successive creations of all asymmetric carbon centers, starting from the chiral dihydropyran **4**.



1: R^1=H,R^2=CH_2OH
2: R^1=CH_2OH,R^2=H



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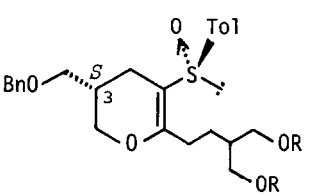
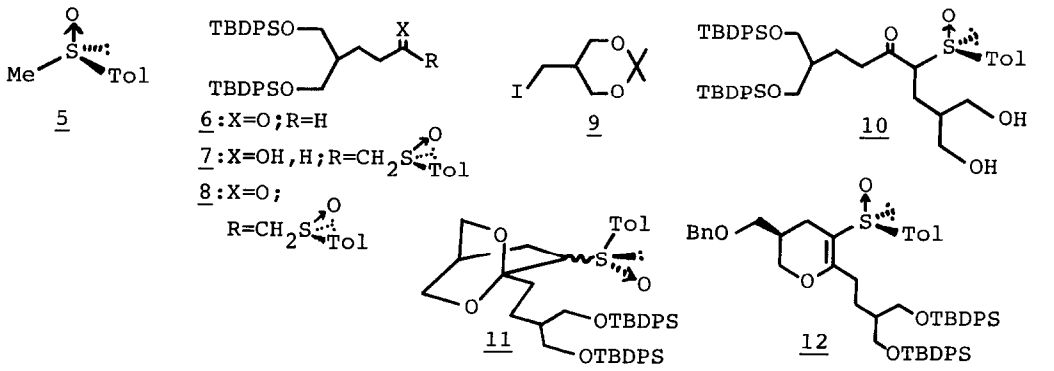
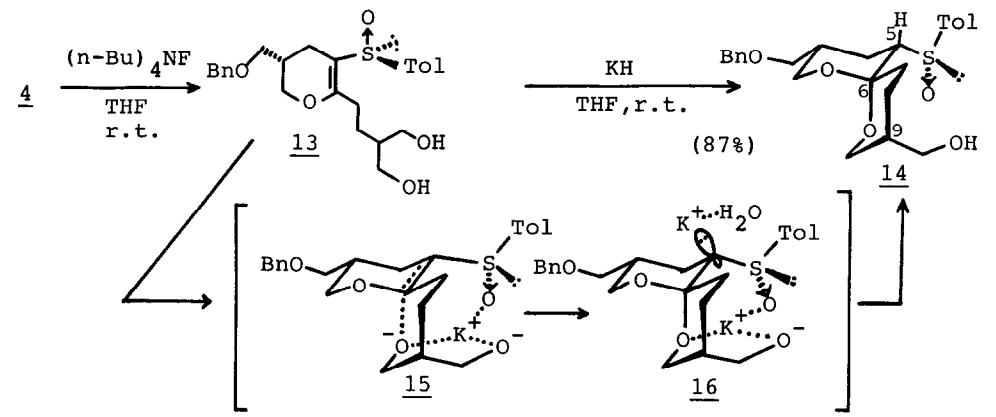


4: R=TBDPS

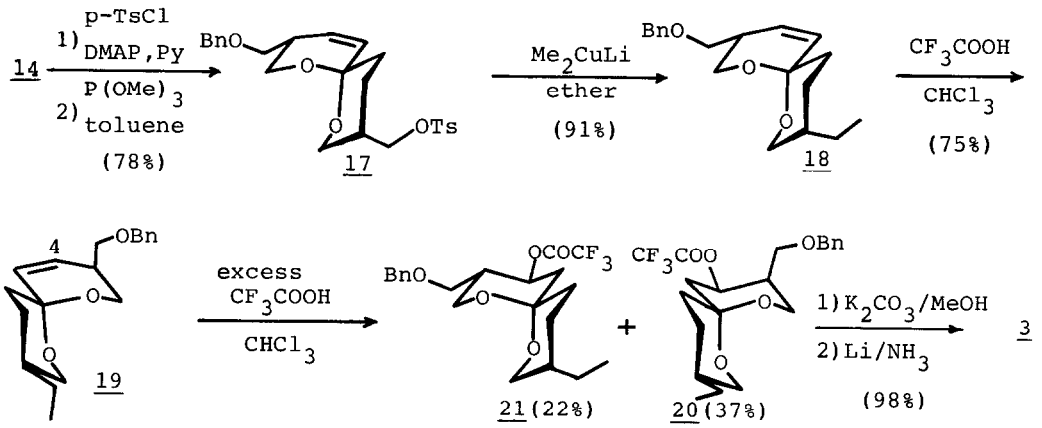
According to our previous knowledge,[3] the starting material **4** was prepared as follows. Lithium salt of the optically active sulfoxide **5**[4] was allowed to react with the aldehyde **6**[5] affording the alcohol **7** (84%), which was oxidized to **8** (87%). Alkylation of **8** with the iodide **9**[3] followed by a chemoselective hydrolysis provided the diol **10** (93%). The dioxabicyclic compound **11**, obtained in 91% yield by the reaction of **10** with zinc chloride, was treated with trifluoroacetic acid and subsequently with benzyl bromide to give **4** in 71% yield together with a small amount (17%) of its isomer **12** (**4**/**12** = 4.2).[6]



The contemporary asymmetric induction at three carbon centers (C_3, C_6, and C_9) was achieved by means of the intramolecular Michael addition of the hydroxyl group to chiral vinylic sulfoxide moiety.[7] The starting material **4** was converted into the diol **13**, which was subjected to the reaction with potassium hydride in THF at room temperature. The cyclized compound was isolated in 87% yield from **4** as a single stereoisomer and assigned as the represented structure **14** on the basis of its ^{1}H-NMR spectrum [δ 2.33 (1H, dd, J = 5.2, 12.5, C_5-H)] and a posturated mechanism. The reaction would proceed *via* chelated intermediates (**15** and **16**) and the final protonation occurs from the less-hindered side[8] to give **14**.[9]



For synthesis of talaromycin A from **14**, isomerization at the spiro center and the subsequent introduction of a hydroxyl group at C_4 with proper orientation are necessary. Thermolysis of the O-tosyl derivative of **14** afforded olefin **17** (89%), which was converted into **18** (91%) by reaction with lithium dimethyl cupurate. On treatment with a small amount of trifluoroacetic acid in dichloromethane, **18** underwent isomerization at the spirocenter smoothly and the more stable isomer **19** was obtained in 75% yield. After several unsuccessful attempts, introduction of the trifluoroacetoxyl group at desired C_4 position of **19** was achieved by the reaction with a large excess of trifluoroacetic acid in chloroform.[10] The desired compound **20** was isolated in 37% yield accompanied with its isomer **21** (22%). An alkaline

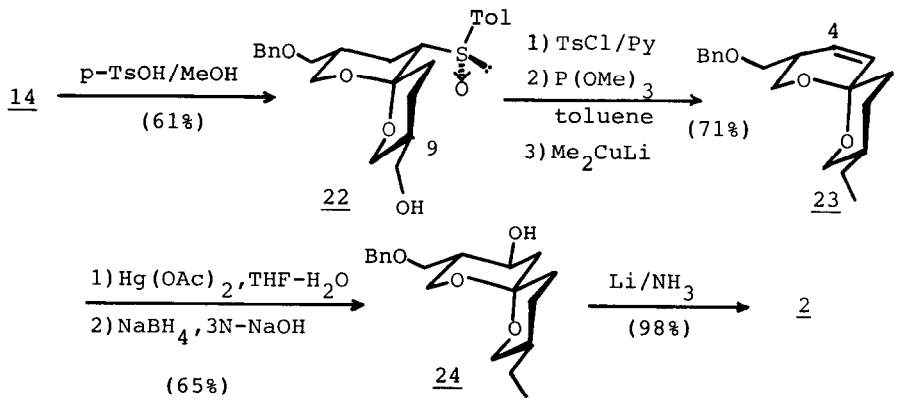


hydrolysis of the former followed by the Birch reduction produced (+)-talaromycin A[11] (**3**) in 98% yield.

On the other hand, transformation of **14** into (-)-talaromycin B requires initial epimerization at the C_9 position. Exposure of **14** to p-toluenesulfonic acid in methanol resulted in epimerization only at the C_9 to give **22** (61%), which was converted into **23** in the same manner as mentioned above in 71% overall yield. A typical oxymercuration-demercuration procedure[12] for **23** was found to result in a regio- and stereoselective hydration affording **24** (65%). Finally, the Birch reduction of **24** provided (-)-talaromycin B[13] (**2**) in 98% yield.

The synthetic talaromycins proved to be identical with corresponding natural talaromycins by means of ^{1}H-NMR spectral comparison.

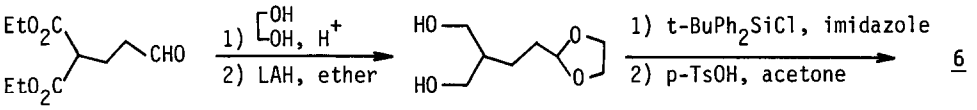
Thus, (+)-talaromycin A and (-)-talaromycin B were both stereoselectively synthesized from the same starting materials, two achiral segments and a chiral sulfoxide, through efficient creations of all four chiral centers in talaromycins. Since talaromycin A is known to isomerize easily to talaromycin B,[1,2] the present synthesis of (+)-talaromycin A means a formal synthesis of (+)-talaromycin B.



Acknowledgement. We are grateful to Prof. David G. Lynn, University of Chicago, for supplying the copies of spectra of natural talaromycin A and B, and also indebted to Takeda Science Foundation for financial support.

References and Notes

1. Isolation: Lynn, D.G.; Phillips, N.J.; Hutton, W.C.; Shabanowitz, J. J. Am. Chem. Soc. 1982, 104, 7319. Hutton, W.C., Phillips, N.J.; Graden, D.W.; Lynn, D.G. J. Chem. Soc., Chem. Commun. 1983, 864.
2. Synthesis: (a) Schreiber, S.L.; Sommer, T.J. Tetrahedron Lett. 1983, 24, 4781. (b) Kozikowski, A.P.; Scripko, J.G. J. Am. Chem. Soc. 1984, 106, 353. (c) Kocienski, P.; Yeates, C. J. Chem. Soc., Chem. Commun. 1984, 151. Idem J. Chem. Soc., Perkin Trans. I 1985, 1879. (d) Kay, I.T.; Bartholomew, D. Tetrahedron Lett. 1984, 25, 2035. (e) Smith, III, A.B.; Thompson, A.S. J. Org. Chem. 1984, 49, 1469. (f) Schreiber, S.L.; Sommer, T.J.; Satake, K. Tetrahedron Lett. 1985, 26, 17. (g) Midland, M.M.; Gabriel, J. J. Org. Chem. 1985, 50, 1143. (h) Mori, K.; Ikunaka, M. Tetrahedron. 1987, 43, 45.
3. Iwata, C.; Fujita, M.; Moritani, Y.; Sugiyama, K.; Hattori, K.; Imanishi, T. Tetrahedron Lett. submitted.
4. Solladie, G. Synthesis 1981, 185.
5. The aldehyde **6** was prepared from diethyl 3-oxopropylmalonate [Warner, D.T.; Moe, A.A. J. Am. Chem. Soc. 1948, 70, 3470] in the following manner.



6. The ratio of **4/12** was found to be almost constant on changing the ration of two diastereomers in **11**.
7. Iwata, C.; Hattori, K.; Uchida, S.; Imanishi, T. Tetrahedron Lett. 1984, 25, 2995. Iwata, C.; Fujita, M.; Hattori, K.; Uchida, S.; Imanishi, T. ibid. 1985, 26, 2221.
8. Tsuchihashi, G.; Mitamura, S.; Inoue, S.; Ogura, K. Tetrahedron Lett. 1973, 323. Tsuchihashi, G.; Mitamura, S.; Ogura, K. ibid. 1976, 855.
9. An abnormal stability of the C_9-axial isomer **7** would be attributable to its intramolecular hydrogen bonding.
10. Similar reactions appeared in reference 2e.
11. An oil. $[\alpha]_D^{22}$ +115.0°(c = 0.160, $CHCl_3$). IR ($CHCl_3$): 3450, 1185, 1100, 1065, 1040 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 0.88 (3H, t, J = 7.3 Hz), 1.07-1.23 (2H, m), 1.38 (1H, dddd, J = 4.3, 12.2, 12.2, 12.2 Hz), 1.41-1.48 (1H, m), 1.51 (1H, ddd, J = 4.3, 12.2, 12.2 Hz), 1.56-1.65 (1H, m), 1.66-1.73 (1H, m), 1.72 (1H, dd, J = 11.9, 12.8 Hz), 1.89 (1H, dd, J = 5.5, 12.8 Hz), 2.11-2.17 (1H, m), 2.50 (2H, br s), 3.19 (1H, dd, J = 11.0, 11.0 Hz), 3.52 (1H, ddd, J = 1.8, 4.3, 11.0 Hz), 3.58 (1H, dd, J = 1.5, 11.6 Hz), 3.75 (1H, dd, J = 3.1, 11.6 Hz), 3.80 (1H, dd, J = 4.6, 11.0 Hz), 4.21 (1H, dd, J = 8.5, 11.0 Hz), 4.41 (1H, ddd, J = 5.5, 5.5, 11.9 Hz). MS m/z: 230 (M^+, 3.6%), 213 (6.3%), 200 (3.3%), 126 (100%). High Ms m/z 230.1534 (Calcd for $C_{12}H_{22}O_4$ m/z 230.1519.
12. cf. Isobe, M.; Ichikawa, Y.; Goto, T. Tetrahedron Lett. 1985, 26, 5199.
13. Mp. 136-138°C. $[\alpha]_D^{23}$ -90.3° (c = 0.775, $CHCl_3$). IR (KBr): 3350, 1380, 1186, 1084, 1074, 1058, 1045, 1035 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 0.88 (3H, t, J = 7.3 Hz), 1.00-1.20 (2H, m), 1.39 (1H, dddd, J = 3.6, 12.5, 12.5, 12.5 Hz), 1.44 (1H, dd, J = 11.0, 12.5 Hz), 1.38-1.64 (1H, m), 1.53 (1H, ddd, J = 4.3, 12.8, 13.4 Hz), 1.57-1.64 (1H, m), 1.70 (1H, ddd, J = 2.4, 3.6, 13.4 Hz), 1.77-1.87 (1H, m), 1.98 (1H, dd, J = 4.9, 12.5 Hz), 2.40 (2H, br s), 3.19 (1H, dd, J = 11.0, 11.0 Hz), 3.31 (1H, dd, J = 11.6, 11.6 Hz), 3.51 (1H, ddd, J = 1.8, 4.3, 11.0 Hz), 3.59 (1H, dd, J = 4.9, 11.6 Hz), 3.70 (2H, d, J = 6.7 Hz), 4.05 (1H, ddd, J = 4.9, 11.0, 11.0 Hz). MS m/z: 230 (M^+, 1.9%), 212 (0.7%), 200 (2.5%), 147 (100%). High-MS m/z 230.1513 (Calcd for $C_{12}H_{22}O_4$ m/z: 230.1516.

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