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TOTAL SYNTHESIS OF (±)-TALAROMYCIN B

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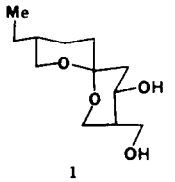
Abstract: The synthesis of (±)-talaromycin B is described which employs diastereotopic hydroxymethyl groups in a spiroketalization reaction as a means of controlling remote stereochemical relationships. The acyclic precursor is constructed in a lynchpin process from a single alkylating reagent.

The isolation and structure determination of the acute avian toxins talaromycin A 1 and talaromycin B 2 from the fungus Talaromyces stipitatus has recently been reported by D. Lynn and coworkers.[2] In this report, the quantitative acid catalyzed conversion of talaromycin A into talaromycin B suggests a method for controlling remote stereochemistry by the use of diastereo-



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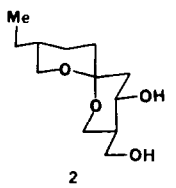

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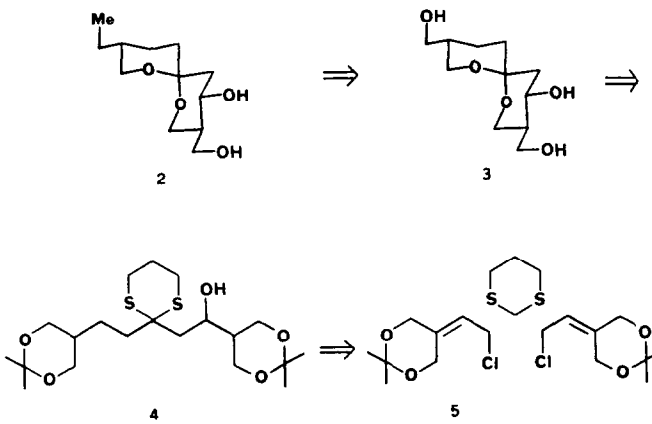
topic hydroxymethyl substituents in the spiroketalization reaction. We report a short synthesis of (±)-talaromycin B which applies this principle and further demonstrates the ability of the spiroketal to transmit remote stereochemical biases through the operation of the anomeric effect.[3,6]

In our synthetic planning, we noted that replacement of the single methyl substituent of talaromycin B with a hydroxyl would produce a spiroketal 3 which, in its open (hydrolyzed) form, contains a single chiral center (Scheme 1). Chirality should be induced from this secondary hydroxyl in the desired manner since thermodynamically controlled spiroketalization can provide a spiroketal which benefits from the anomeric effect[4] and has all substituents equatorially oriented.[5] A protected form of the acyclic precursor 4 should be derived from a single alkylating

reagent 5 and an acyl dianion equivalent.[6] The remaining problem of terminal hydroxyl differentiation should be solved by utilizing the single 1,3-diol relationship found in 3. For the synthesis of talaromycin A, the diastereotopic selectivity must be reversed in the pyran ring containing the 1,3-diol.

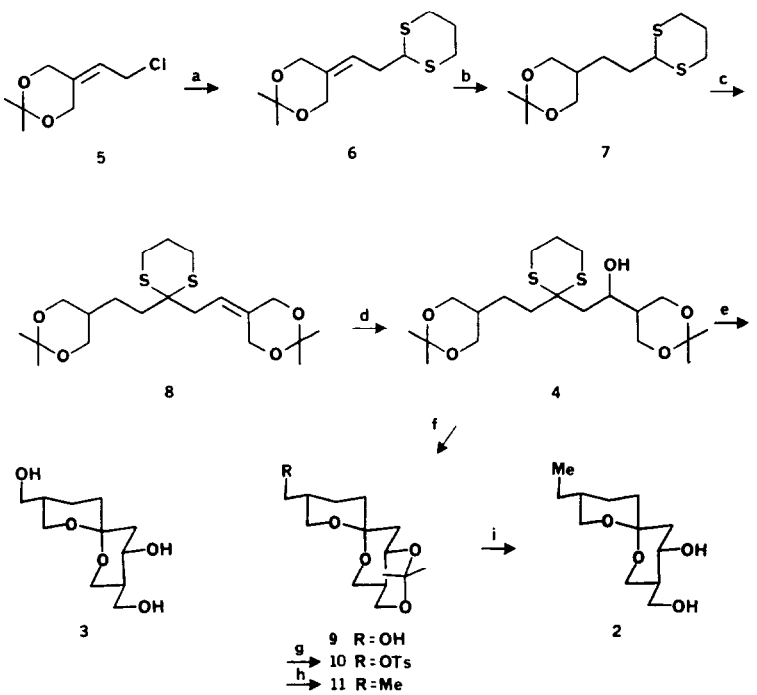
Scheme 1



2-Lithiodithiane was alkylated[7] with the chloride 5[8] to provide 6 in 81% yield (Scheme 2).[10] Hydrogenation of the olefin with the Crabtree catalyst[11] afforded 7 quantitatively. Metalation and alkylation with 5 furnished 8 in 71% yield (93% based on recovered 7). Hydroboration and Kabalka oxidation[12] produced the alcohol 4 and the corresponding regioisomeric tertiary alcohol in a 2:1 ratio in 93% yield (60% isolated yield of 4). The spiroketal 3 was obtained in 71% yield with a high degree of stereoselectivity ($\geq$10:1)[13] after treatment of 4 with mercuric chloride in freshly distilled acetonitrile. Attempts to form the acetonide of this triol with 2-methoxypropene or 2,2-dimethoxypropane resulted only in mono- and bis-mixed ketal formation. The requisite acetonide 9 could be prepared in a one-pot procedure from the acyclic precursor 4 by dithiane hydrolysis with mercuric chloride in 5% aqueous acetonitrile followed by direct treatment with excess 2,2-dimethoxypropane (65% yield). Tosylation and displacement with lithium dimethylcuprate[14] afforded 11 in 80% yield from 9. Quantitative removal of the acetonide with methanol and Dowex 50W-X8 provided (±)-talaromycin B. The spectral properties of this material agreed with the assigned structure and with the data supplied by Professor Lynn[2] for natural talaromycin B.

In conclusion, it should be noted that all four remote chiral centers of talaromycin B were controlled in a single step by the transformation of 4 into 3 and 4 into 9. The synthesis demonstrates the use of diastereotopic hydroxymethyl groups in the spiroketalization reaction as a means of controlling remote (1,6- and 1,7-) stereochemical relationships. We are studying the design of other systems which employ the thermodynamically controlled spiroketalization reaction as a means of controlling remote stereochemistry in acyclic systems.[15]

Scheme 2



a 2-lithiodithiane, THF, -78°; b H_2, 30 mol% $[Ir(cod)pyPCy_3]PF_6$, CH_2Cl_2; c BuLi, 5, -78°; d BH_3·THF, $Me_3\overset{+}{N}-\overset{-}{O}$; e $HgCl_2$, CH_3CN; f $HgCl_2$, 5% H_2O-CH_3CN; $(CH_3)_2C(OCH_3)_2$; g TsCl, Et_3N, DMAP, CH_2Cl_2, 25°; h Me_2CuLi, THF, 0°; i Dowex 50W-X8, MeOH

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References and Footnotes

1. Searle Scholar, 1982-1985.

2. D.G. Lynn, N.J. Phillips, W.C. Hutton, J. Shabanowitz, D.I. Fennell, and R. J. Cole, J. Am. Chem. Soc. (1982) 104, 7319.

3. a) D.A. Evans, C.E. Sacks, W.A. Kelschick, and T.R. Taber, J. Am. Chem. Soc., (1979), 101, 6789; b) D.P. Negri, Harvard P.D. Thesis, (1980) Am. Doct. Diss., (1980-81), 67; c) T. Fukuyama, K. Akasaka, D.S. Karanewsky, C.-L. J.Wang, G. Schmid, and Y. Kishi, J. Am. Chem. Soc., (1979), 101, 262; d) Y. Kishi, Lect. Heterocycl. Chem. (1980) 5, S95; e) D.B. Collum, J.H. McDonald, and W.C. Still, J. Am. Chem. Soc., (1980), 102, 2120; f) P. Deslongchamps, D.D. Rowan, N. Pothier, T. Sauve, and J.K. Saunders, Can. J. Chem., (1981), 59, 1105; g) T.R. Hoye, D.R. Peck, and P.K. Trumper, J. Am. Chem. Soc., (1981), 103, 5618; h) R. Baker, R.H. Herbert, and A. H.Parton, J.C.S. Chem. Commun., (1982), 601; i) G.R. Martinez, P.A. Grieco, E. Williams, K. Kanai, and C.V. Srinivasan, J. Am. Chem. Soc., (1982), 104, 1436 (1982); j) A.B. Smith, S.R. Schow, J.D. Bloom, A.S.Thompson, and K.N. Winzenberg, J. Am. Chem. Soc., (1982), 104, 4015; k) P.R. McGuirk and D.B. Collum, J. Am. Chem. Soc., (1982), 104, 4496; l) D.R. Williams, B.A. Barner, K.Nishitani, and J.G. Phillips, J. Am. Chem. Soc., (1982), 104, 4708; m) D.R. Williams and B.A. Barner, Tetrahedron Lett., (1983), 24, 427; n) R.E. Ireland and J.P. Daub, J. Org. Chem., (1983), 48, 1303, 1312.

4. A.J. Kirby, "The Anomeric Effect and Related Stereoelectronic Effects at Oxygen", Springer-Verlag, New York, 1983.

5. For example, a 20:1 equatorial/axial preference for a hydroxyl substituent has been reported in a related spiroketalization; see ref. 3h.

6. cf., D.A. Evans, C.E. Sacks, R.A. Whitney, and A.G. Mandel, Tetrahedron Lett., (1978), 727.

7. For a recent review, see: T.A. Hase and J.A. Koskimies, Aldrichimica Acta, (1982), 15, 35.

8. Multigram quantities can be readily prepared from dihydroxyacetone dimer by the following sequence: a) Ac_2O, py; b) CH_2=CHMgBr, THF; c) $SOCl_2$, Et_3N, DMAP, Et_2O; d) HCl, MeOH; e) $(Me)_2C(OMe)_2$, pTSOH.

9. E. Cereda, E. Bellora, and A. Donetti, Tetrahedron Lett., (1980), 21, 4977.

10. All yields refer to materials isolated by flash chromatography and all compounds were characterized by their NMR (500, 270 or 90 MHz), FT-IR, and mass spectral data.

11. Other catalysts suffered from poisoning by the sulfide. Attempts to decrease the mol% of the Crabtree catalyst resulted in diminished yields of 7 as well as competing olefin isomerization to afford the enol ether. a) R.H. Crabtree and G.E. Morris, J. Organometal. Chem., (1977), 135, 395; b) J.W. Suggs, S.D. Cox, R.H. Crabtree, and J.M. Quirk, Tetrahedron Lett., (1981), 22, 303.

12. G.W. Kabalka and H.C. Hedgecock, Jr., J. Org. Chem., (1975), 40, 1776.

13. The 500 MHz ^{1}H NMR spectrum of the spiroketalization reaction mixture indicated the presence of ca. 10% of an as yet unidentified material which may be an isomeric spiroketal.

14. C.R. Johnson and G.A. Dutra, J. Am. Chem. Soc., (1973), 95, 7777.

15. For despiroketalization methods to acyclic systems, see: a) D. Schomburg, P.B. Hopkins, W.N. Lipscomb, and E.J. Corey, J. Org. Chem., (1980), 45, 1544; b) R.E. Ireland and J.P. Daub, Tetrahedron Lett., (1982), 23. 3471; and reference 3g and 3n.

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