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DIASTEREOTOPIC SELECTIVITY AT PROCHIRAL CARBON CENTERS. A STEREODIVERGENT SYNTHESIS OF THE TALAROMYCINS.

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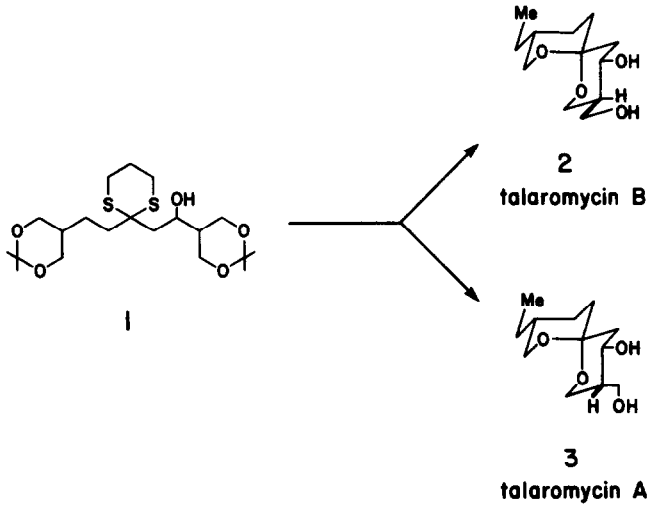
Abstract: The transformation of the acyclic precursor previously employed in the synthesis of talaromycin B to the stereoisomeric avian toxin talaromycin A is described. Diastereotopic selectivity at prochiral carbon centers in an acetonide migration and in a subsequent spiroketalization reaction provides the stereocontrol required for the synthesis.

Recently we described the preparation of dithiane 1 and its cyclization to spiroketal 4 which served as a progenitor to the avian toxin talaromycin B.[2,3,4] The single stereocenter in 1 is responsible for the remote internal asymmetric induction at the two prochiral carbon centers bearing diastereotopic hydroxymethyl groups. In this manner all four stereocenters are controlled in a single operation, providing the stereochemistry required for talaromycin B synthesis.



In this report, it was suggested that a method for reversing the diastereotopic selectivity in the tetrahydropyran containing the 1,3-diol would be required for talaromycin A synthesis.[3a] We now report two new reactions which proceed with diastereotopic selectivity at prochiral carbon centers and provide the reversal of selectivity which was sought. As a result, the acyclic spiroketal precursor 1 can be employed in the synthesis of talaromycin A as well as talaromycin B.

Differentiation of the pre-A and pre-B diastereotopic alkoxymethyl groups in 1 was achieved by way of an acetonide migration reaction (CSA, acetone,25°C, 30 min) which provided a 5.1:1.2:1.0 mixture of trans-disubstituted acetonide 5, the corresponding cis isomer, and unchanged starting material in 89% yield.[5] The three-component mixture could be separated by HPLC (10μ Porasil, 60% EtOAc/Hexane) and the two minor components could be re-equilibrated to establish the same three-

Scheme 1

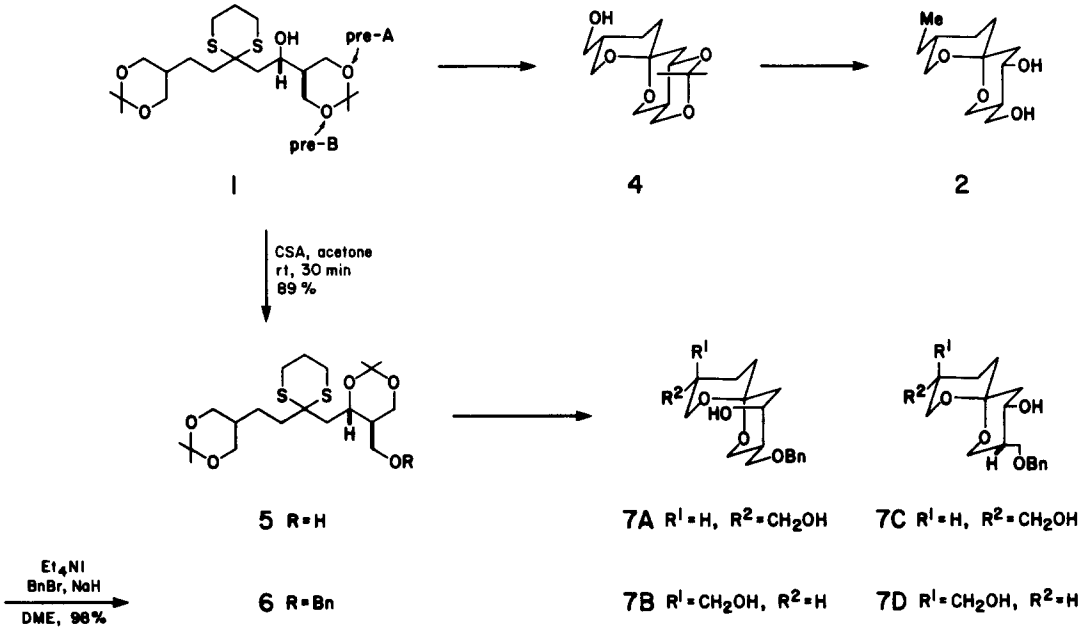


TABLE 1 SPIROKETAL STEREOCHEMISTRY

		Percentage of ketal isomer (relative ratio)[a]			
entry	conditions	7A	7B	7C	7D
1.	a. Amberlyst-15/MeOH b. $Hg(OAc)_2/CH_3CN/H_2O$ c. 10% aq AcOH/Et_2O	17(1.1)	16(1.0)	38(2.4)	29(1.8)
2.	CSA, CH_2Cl_2	69(17.4)	16(4.0)	11(2.8)	4(1.0)
3.	$ZnCl_2$, CH_2Cl_2	66(66.0)	29(29.0)	4(4.0)	1(1.0)
4.	2N HCl(aq)THF(1:5)	37(4.6)	8(1.0)	45(5.5)	10(1.2)
5.	CSA, MeOH	34(4.7)	7(1.0)	47(6.6)	12(1.6)
6.	CSA, DMSO	17(4.6)	4(1.0)	66(17.2)	13(3.4)

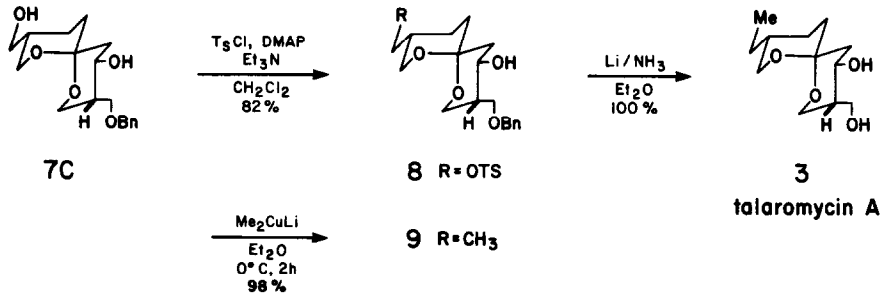
(a) ratios determined by HPLC integration

component mixture. In compound 5 we have liberated the hydroxymethyl group which is required for spiroketalization to talaromycin B. Benzylation of the hydroxyl provided assurance that a subsequent ketalization would not afford this avian toxin already available by the previous route.[3a]

We have examined the spiroketalization of 6 and found the stereochemical outcome is critically dependent on the conditions of the reaction.[6] Since the four spiroketals produced in these reactions undergo equilibration at an appreciable rate, we sought thermodynamically controlled

conditions which would maximize the equilibrium constant in favor of 7C, which has all stereocenters properly disposed for talaromycin A synthesis. Thermodynamically controlled conditions would insure reproducibility of product ratios and allow for re-equilibration (and thus recycling) of undesired ketal isomers. Complete hydrolysis of 6 and spiroketalization with 10% aq AcOH-Et_2O quantitatively provided a non-equilibrium mixture of spiroketals 7A,B,C,D in a 1.1:1.0:2.4:1.8 ratio.[7] Thermodynamic equilibration was established under the conditions indicated in the Table. Whereas the use of methylene chloride as solvent favored formation of 7A, a compound which could be converted to 4-epi-talaromycin B in analogy to our previous work,[3a] methanol or dimethylsulfoxide provided an equilibrium mixture enriched in the pre-talaromycin A isomer 7C. These results indicate an intramolecular hydrogen bond between the axial C-4 hydroxyl and ketal oxygen results in stabilization of isomers 7A and 7B relative to 7C and 7D in the non-polar solvent.[6a,c] The more polar solvents stabilize 7C and 7D relative to 7A and 7B since the equatorial hydroxyl can hydrogen bond to solvent. Optimal conditions employed CSA as catalyst and DMSO as solvent[8] and provided a 4.6:1.0:17.2:3.4 equilibrium ratio of 7A:7B:7C:7D. After HPLC separation, isomer 7C could be isolated in 54% yield from 6 with $\geq$ 97% purity. Each minor isomer was isolated and provided the same equilibrium ratio upon resubjection to the reaction conditions.[9]

Scheme 2



Conversion of 7C to talaromycin A proceeded in analogy to the talaromycin B synthesis.[3a] Mono-tosylation provided the tosyloxymethyl compound 8 which underwent displacement with excess lithium dimethylcuprate to afford 9. Debenzylation produced (±)-talaromycin A which exhibited spectroscopic properties in accord with the structure and 500 MHz ^1H NMR and mass spectra identical to that of natural talaromycin A.

Further studies in diastereotopic selectivity at prochiral carbon centers are in progress and will be presented in due course.

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References and Footnotes

1. Searle Scholar, 1982-1985.

2. Isolation and structure determination: (a) Lynn, D.G.; Phillips, N.J.; Hutton, W.C.; Shabonowitz, J.: Fennell, D.I.; Cole, R.J. J. Am. Chem. Soc. 1982, 104, 7319. (b) Hutton, W.C. Phillips, N.J.; Graden, D.W.; Lynn, D.G. J. Chem. Soc. Chem. Commun. 1983, 864.

3. (±)-Talaromycin B 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. (d) Kay, I.T.; Bartholomew, D. Tetrahedron Lett. 1984, 25, 2035.

4. (-)-Talaromycins A and B: (a) Smith, A.B.; Thompson, A.S. J. Org. Chem. 1984, 49, 1469. (b) Professor Mark Midland (U.C. Riverside) has completed a synthesis of (-)-talaromycin A; personal communication from Professor Midland.

5. For other examples of acetonide equilibration studies, see: (a) McCarthy, P.A. Tetrahedron Lett. 1982, 23, 4199. (b) Meyers, A.I.; Lawson, J.P. Tetrahedron Lett. 1982, 23, 4883. (c) Williams, D.R.; Sit, S.Y. J. Am. Chem. Soc. 1984, 106, 2949.

6. For other examples of spiroketalization equilibration studies, see: (a) Fukuyama, T.; Akasaka, K.; Karanewsky, D.S.; Wang, C.-L.J.; Schmid, G; Kishi, Y. J. Am. Chem. Soc. 1979, 101, 262. (b) McGuirk, P.R.; Collum, D.B. J. Am. Chem. Soc. 1982, 104, 4496. (c) McGuirk, P.R.; Collum, D.B. J. Org. Chem. 1984, 49, 843. (d) See also references 2a, 3b,d, 4a, and 5c.

7. Satisfactory ^{1}H NMR, ^{13}C NMR, IR, and mass spectral data were obtained for all new compounds. Stereochemical assignments for compounds 7A-D were made on the basis of D_2O exchange and extensive decoupling experiments. 500 MHz ^{1}H NMR data of compounds 7A-D are as follows: 7A ($CDCl_3$); 7.40-7.25 (m,5H), 4.55 (d,J=12Hz, 1H), 4.47 (d,J=12Hz, 1H), 4.01 (br.d*,J=2.8 Hz, 1H) 3.77 (dd,J=11,4.1 Hz, 1H), 3.73 (m,1H), 3.64 (t,J=12 Hz, 1H), 3.58 (dd,J=9.4,6.2 Hz, 1H), 3.52 (dd,J=11,5.4 Hz, 1H), 3.46 (t,J=11 Hz, 1H), 3.48-3.40 (m, 2H), 2.09 (m, 1H), 1.95 (dd,J=14 2.8 Hz), 1.85 (m, 1H), 1.76-1.45 (m, 5H) *after addition of D_2O 7B; 7.40-7.25 (m,5H), 4.55 (d,J=12 Hz, 1H) 4.48 (d,J=12 Hz, 1H), 4.00 (br.d*,J=2.9 Hz, 1H), 3.89-3.85 (m, 2H), 3.76 (dd,J=12,5.2 Hz, 1H), 3.73-3.65 (m, 2H), 3.66 (t,J=12 Hz, 1H), 3.58 (dd,J=9.4, 6.2 Hz, 1H), 3.42 (dd,J=9.4,7.7 Hz,1H), 2.12-2.02 (m, 2H), 1.94 (dd,J=14, 2.9 Hz, 1H), 1.71 (m, 1H), 1.68-1.40 (m, 4H) 7C; 7.40-7.25 (m, 5H), 4.57 (d,J=12 Hz, 1H), 4.53 (d,J=12 Hz, 1H), 4.29 (dt*,J=12,4.9 Hz, 1H) 4.01 (t,J=9 Hz, 1H), 3.74 (dd,J=12,2.7 Hz, 1H), 3.70 (dd,J=9,5.9 Hz, 1H), 3.70-3.67 (m, 1H), 3.58 (dd,J=12,1.4 Hz, 1H), 3.55-3.42 (m, 2H), 3.34 (t,J=11 Hz, 1H), 2.30 (m, 1H), 1.92 (dd, J=13,4.9 Hz, 1H), 1.83 (m, 1H), 1.70 (m, 1H), 1.61-1.48 (m, 4H) 7D; 7.40-7.23 (m, 5H), 4.56 (d,J=12 Hz, 1H), 4.52 (d,J=12 Hz, 1H), 4.26 (dt*,J=12,4.9 Hz, 1H), 3.85 (dd,J=8.1,11 Hz, 1H), 3.77 (dd,J=2.8,12 Hz, 1H), 3.76 (dd,J=2.8,12 Hz, 1H), 3.72-3.68 (m, 2H) 3.60 (dd,J=1.5,12 Hz, 2H), 2.30 (m, 1H), 2.00 (m, 1H), 1.92 (dd,J=4.9,13 Hz, 1H), 1.69 (m, 1H), 1.65-1.40 (m, 4H), 4.00 (t, J=9 Hz, 1H).

8. DMSO is known to form strong hydrogen bonds to hydroxylic protons as evidenced by the downfield shift of hydroxyl resonances in this solvent ($\geq$ 4.0 ppm), see: Chapman, O.L.; King, R.W. J. Am. Chem. Soc. 1964, 86, 1256.

9. Kozikowski and Scripko have reported an attempt to prepare talaromycin A by a route which, by virtue of its design, would have been nonstereoselective.[3b] However, a spiroketalization reaction similar to those described in this report provided a compound identified as having the structure of 7A, leading to the abandonment of their efforts.

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