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Spiroketal Equilibration: Interconversion of 1,6-Dioxaspiro[4.4]nonanes and 1,6-Dioxaspiro[4.5]decanes. Implications for the Synthesis of Cephalostatin 7.[1]

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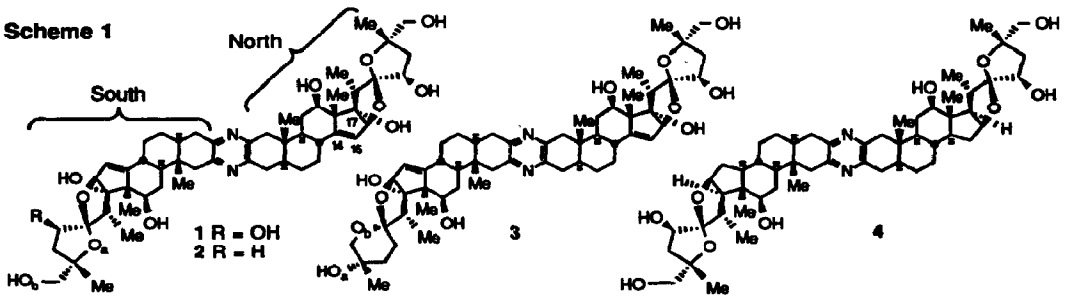
Abstract: Acid-catalyzed equilibration of spiroketals **55Hββ** and **55Hαβ** involves a two stage process whereby the 1,6-dioxaspiro[4.4]nonanes can be equilibrated under mild conditions to a pair of 1,6-dioxaspiro[4.5]decanes with preservation of the adjacent C-20 methyl stereocenter. Under more forcing conditions, both centers can be equilibrated in a reaction involving vinyl ether intermediate **10H**.

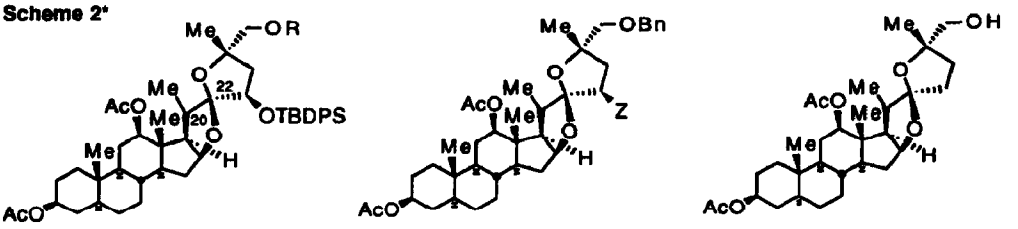
Cephalostatin 7 **3** is a potent member of a family of eleven trisdecacyclic pyrazines characterized by Pettit.[2] These materials are also highly active (10^{-9}-10^{-10} M) in a substantial proportion of the 60 *in Vitro* screens of the NCI.[3] While none of the cephalostatins isolated thus far possess a C_2 axis of symmetry (cf. the presently unknown "North dimer" **1**), cephalostatin 7 (**3**) is formally derived from **1** by dehydroxylation (to **2**) and transketalization (exchange of O_a and O_b). Since Heathcock and Smith have provided a method for synthesis of unsymmetrical pyrazines from 3-ketosteroids,[4] construction of **3** from a common intermediate can be envisaged, provided that interconversion of the "North" 55 ring spiroketal and "South" 65 ring spiroketal can be effected in a satisfactory manner.



Our recent synthesis of C_2 symmetric analog **4** has provided a set of intermediates appropriate for probing the interconversion of 5/5 and 6/5 spiroketals.[5,6] Reaction of $5\alpha\beta^{7,8}$ or $5\beta\beta^{7,8}$ with benzyl bromide and sodium hydride in DMF from -10 to 25°C for 1h provided benzyl ethers $6\alpha\beta^{8}$ or $6\beta\beta^{8}$ in 95-98% yield. These substrates were individually processed

by desilylation[9] using TBAF and HOAc (4:4.4 equiv) in THF at reflux for 8-16h to produce the crude alcohols. Treatment with sodium hydride in CS_2 for 1h at 0°C followed by addition of methyl iodide and TMEDA (0°- 25°C, 4h) afforded xanthates **7αβ**[8] or **7ββ**[8] in 91% and 82% overall yields, respectively. Deoxygenation[10] of a 0.01M solution of xanthates **7αβ** or **7ββ** using tributyltin hydride (4 equiv) and AIBN (10 mol%) in toluene at reflux for 40 min smoothly provided benzyl ethers **8αβ**[8] or **8ββ**[8] in 81% and 88% yield respectively. Debenzylation using Pd/C/H_2 in 100% EtOH for 1hr at 25°C quantitatively converted **8αβ** or **8ββ** to alcohols **55αβ**[8] and **55ββ**[8] (the double numbers in schemes 2,3 refer to the size of the spiroketal ring).

Scheme 2*



5αβ R = H
5ββ R = H

6αβ R = Bn
6ββ R = Bn

7αβ Z = OCS_2Me
7ββ Z = OCS_2Me

8αβ Z = H
8ββ Z = H

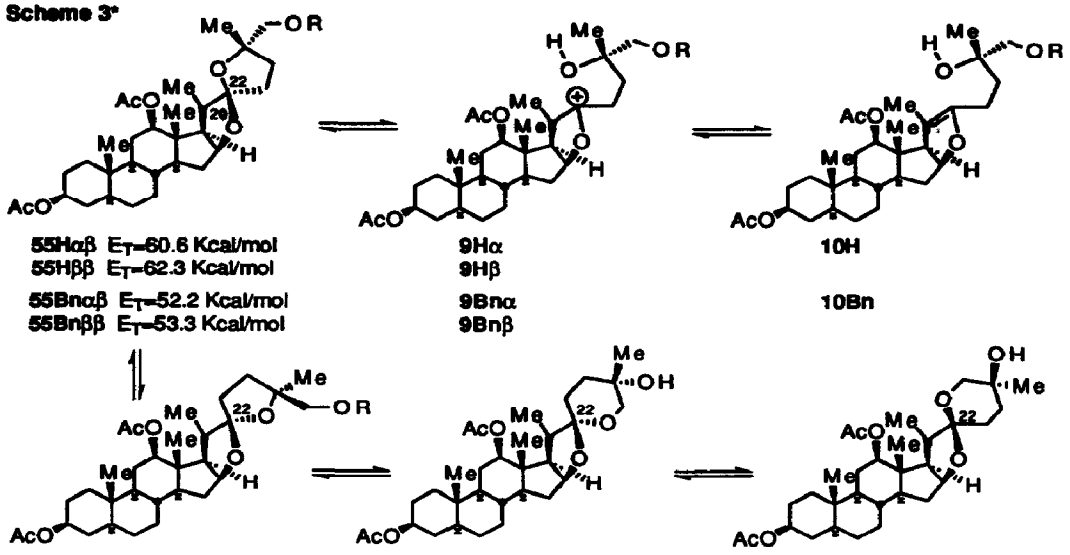
55αβ
55ββ

*Scheme legend: Greek letters designate the C-20 methyl and C-22 oxygen stereochemistry, respectively.

As shown in Scheme 3, molecular mechanics calculations[11] predict **55Hαα**[8,12] and **65Hαα**[8] to be of similar energy, substantially preferred over the other six diastereomeric **H** series possibilities. As can be deduced from the data in the table, the transformation involves two separate acid-catalyzed equilibria. At 25°C compounds **55Hββ** and **55Hαβ** bearing different C-20 methyl configurations undergo facile interconversion with C-22 a spiroketals **65Hβα**[8,13] and **65Hαα**,[8] respectively via intermediates **9Hα,β** (entries 1,5), but retain their C-20 stereochemistry. Control studies (entries 3,4,7) with products **65Hβα** and **65Hαα** establish approximately the same ratios. At higher temperature (entries 2,6), complete equilibration of both stereocenters occurs, presumably via enol ether **10H**.

In order to further investigate the energetics of the 55 spiroketal, benzyl ethers **55Bnββ**[8] and **55Bnαβ**[8] were also subjected to the same conditions (entries 8-11). As was seen in the alcohol series, equilibration of the spiroketal could be effected independently of the C-20 center, but at full equilibrium the **55Bnαα**[8] is formed exclusively, as expected from the molecular mechanics calculations.

Scheme 3*



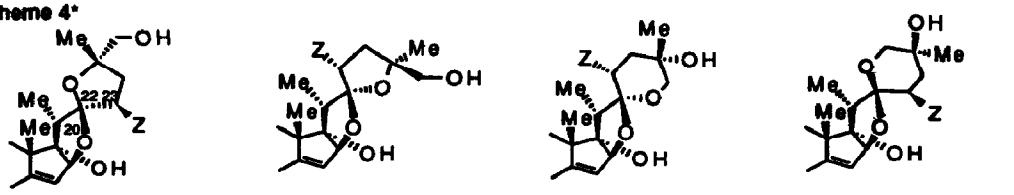
*Scheme legend: Greek letters designate the C-20 methyl and C-22 oxygen stereochemistry, respectively. "H" series: R = H; "Bn" series: R = Bn.

Entry	Starting material	Conditions	Products	(Ratio)*
1	55Hββ	CH_2Cl_2, PPTs, 25°C, 18h	55Hββ: 65Hβα	(1.0:4.8)
2	55Hββ	$ClCH_2CH_2Cl$, PPTs, 83°C, 18h	55Haa: 65Haα	(1.5:1.0)
3	65Hβα	CH_2Cl_2, PPTs, 25°C, 18h	55Hbb: 65Hβα	(1.0:4.0)
4	65Hβα	$ClCH_2CH_2Cl$, PPTs, 83°C, 18h	55Haα: 65Haα	(1.4:1.0)
5	55Haβ	CH_2Cl_2, PPTs, 25°C, 1h	55Haβ:55Haα:65Haα	(2.0:1.0:1.3)
6	55Haβ	$ClCH_2CH_2Cl$, PPTs, 83°C, 18h	55Haα: 65Haα	(1.5:1.0)
7	65Haα	$ClCH_2CH_2Cl$, PPTs, 83°C, 1h	55Haα: 65Haα	(1.5:1.0)
8	55Bnββ	CH_2Cl_2, PPTs, 25°C, 24h	55Bnββ: 55Bnβα	(1.3:1.0)
9	55Bnββ	$ClCH_2CH_2Cl$, PPTs, 83°C, 40min	55Bnαα	only
10	55Bnαβ	CH_2Cl_2, PPTs, 25°C, 24h	55Bnαβ: 55Bnαα	(1.0:5.0)
11	55Bnαβ	$ClCH_2CH_2Cl$, PPTs, 83°C, 40min	55Bnαα	only

*The yield in all reactions is >90%.

The above results, in conjunction with molecular mechanics calculations, have implications for the synthesis of cephalostatin 7 3. Namely, any synthesis which seeks to employ the "North" spiroketal as a starting material for preparation of the "South" spiroketal should delay the deoxygenation of the C-23 alcohol until after the spiroketal equilibration has been achieved (see calculations Scheme 4).

Scheme 4*



A55β E_T=59.8 Kcal/mol
B55β E_T=64.4 Kcal/mol

A55α E_T=55.2 Kcal/mol – A65α E_T=54.6 Kcal/mol
B55α E_T=59.6 Kcal/mol > B65α E_T=57.1 Kcal/mol

A65β E_T=59.6 Kcal/mol
B65β E_T=62.1 Kcal/mol

*Scheme legend: C-20 α-methyl C-23 (R) spiroketals; "A" series: Z=H; "B" series: Z=OH.

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[1]Cephalostatin Chemistry 3. For paper 1 see Pan, Y.; Merriman, R. L.; Tanzer, L. R.; Fuchs, P. L. *Biomolecular Chem. Lett.*, **1992**, 967; for paper 2 see reference 5.
[2] Pettit, G. R.; Xu, J.-P.; Williams, M. D.; Christie, N. D.; Doubek, D. L.; Schmidt, J. M.; Boyd, M. R. *J. Nat. Prod.*, **1994**, *57*, 52; and references cited therein.
[3] Pettit, G. R.; Kamano, Y.; Inoue, M.; Dufresne, C.; Boyd, M. R.; Herald, C. L.; Schmidt, J. M.; Doubek, D. L.; Christie, N. D. *J. Org. Chem.* **1992**, *57*, 429.
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[5]Jeong, J. U.; Fuchs, P. L. *J. Am. Chem. Soc.* **1994**, *116*, 773.
[6]For other synthetic efforts in the cephalostatin area see: a) ref 4; and b) Kramer, A.; Ullmann, U.; Winterfeldt, E. *J. Chem. Soc. Perkin Trans. I* **1993**, 2865.
[7]The structure of this material has been secured by X-ray (see reference 5).
[8]Proton NMR, Carbon NMR, and exact mass spectra are in accord with this structure.
[9]cf. Newton, R. F.; Reynolds, D. P.; Finch, M. A. W.; Kelly, D. R.; Roberts, S. M. *Tetrahedron Lett.* **1979**, *79*, 3981.
[10]Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc. Perkin Trans. I* **1975**, 1574.
[11]CAChe v3.5.
[12]Structure confirmed by X-ray.
[13]An independent sample of this material has been prepared by radical deoxygenation of the C-23 alcohol which has been shown by X-ray to bear the 65βα configuration (see ref 5).

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