Synthesis of a 17-Deoxy, C-14,15-Dihydro Derivative of the North Spiroketal Moiety of the Cephalostatins. Conversion to a (+)-Trisdecacyclic C_2 Symmetrical Pyrazine

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Cephalostatin **1** (Chart 1) is the most potent member of a family of nine trisdecacyclic pyrazines characterized by Pettit.[1] These materials are also highly active (10^{-9}–10^{-10} M) in a substantial proportion of the 60 *in vitro* screens of the NCI.[1d] While none of the cephalostatins isolated thus far possesses a C_2 axis of symmetry (*cf.* unknown "north dimer" **2**), cephalostatin 7 (**4**) is formally derived from **2** by dehydroxylation (to **3**) and transketalization (Chart 1). All the known cephalostatins possess the "North" spiroketal moiety. In 1992, we published the syntheses of several simple, steroid-derived C_2 symmetric nonacyclic and trisdecacyclic cephalostatin analogs which possessed modest anti-cancer activity in animal trials (60% inhibition of tumor growth).[2] Shortly thereafter, Smith and Heathcock prepared additional symmetrical analogs and provided a specific protocol for the construction of unsymmetrical pyrazines.[3] This latter advance enables subsequent syntheses to target the north and south segments of cephalostatin with the expectation of unification late in the synthesis.

As a prelude to the synthesis of symmetrical dimer **2**, we report the synthesis of **31**, the 17-deoxy, C-14,15-dihydro derivative of **2**. Synthesis of the key 27-carbon pentacyclic superstructure **7**[4] for spirocyclization studies is shown in Scheme 1.[5]

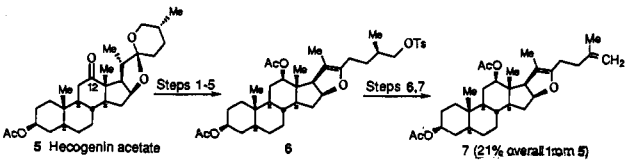
Reaction of **7** with TFAA-activated DMSO[6] or phenyl methyl sulfoxide provides the C-23 trifluoroacetates **9α/9β**,[4] which were hydrolyzed to **10α**[4] and **10β**[4] (C-23 stereochemistry assigned by X-ray).[7] MnO_2 oxidation of either **10α** or **10β** gave the C-23 ketone **12**[4] (not shown) in high yield. Further supplies of alcohol **10α** were secured through Mitsunobu inversion[8] of **10β** using $ClCH_2CO_2H$,[9] providing chloroacetate **13α**[4] (not shown), which was cleaved to alcohol **10α**[4] using the protocol of Cook and Maichuk.[10] Protection[11] of **10α** afforded the C-23 silyl ether **11α**[4] in 99% yield (Scheme 2).

Double stereoselection was required for meaningful specificity in the osmylation of olefin **11α**.[12] Reaction of **11α** with osmium tetroxide in the presence of (*S,S*)-**15**[13] afforded a 98% yield of **14S/14R** in a ratio of 7.7:1 (Scheme 3).

Cyclization of silyl ether diol **14S** under acidic conditions was not productive, but triol **16**[4] (95% from **14S**, 2.0 equiv TBAF, 25 °C, 3 h) underwent cyclization to provide spiroketals **17H**[4,7] and **19H**,[4,7] both bearing the "unnatural" β-methyl configuration at C-20.[7] Acid-catalyzed *C-20 equilibration* of the spiroketals was unsuccessful, but 6/5 spiroketal **19H** could be quantitatively isomerized to **17H**. NBS-mediated cyclizations exclusively afforded C-20 brominated 5/5 spiroketals **17Br**[4] and **18Br**[4] (Scheme 4).

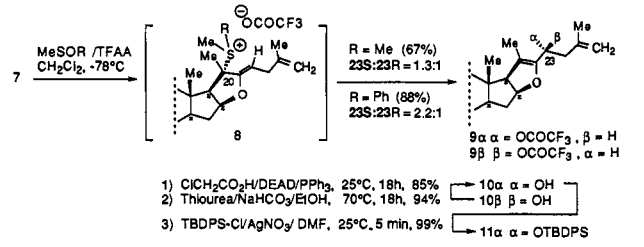
Reaction of **17Br** with *n*-Bu_3SnH only generated **17H**, but treatment of **18Br** with triphenyltin hydride provides a 4.2:1 mixture of **20α/20β** in essentially quantitative yield without a trace of olefin **21** (formed in 10% yield using *n*-Bu_3SnH at 80 °C) (Scheme 5).[12] The stereochemistry **20α** was proven by X-ray examination of derivative **22α**.[4,7]

Scheme 1[a]

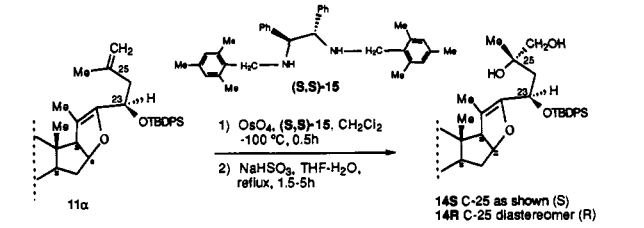


[a] DIBAH, THF, −78 °C, 0.2 h (β:α = 9:1; 80% β recovery); (2) Ac_2O, DMAP, Et_3N, CH_2Cl_2, 0 °C, 1.5 h (90%); (3) Py·HCl, $(Cl_2CHCO)_2O$, xylene, 150–155 °C, 0.5 h (70%); (4) acetone–H_2O, Na_2CO_3, 25 °C, 14 h; (5) TsCl, pyridine, 0 °C, 5 h (steps 4 and 5, 58%); (6) PhSeSePh, $NaBH_4$, EtOH, reflux, 1.5 h (89%); (7) mCPBA, THF, Na_2CO_3, 25 °C, 24 h (80%).

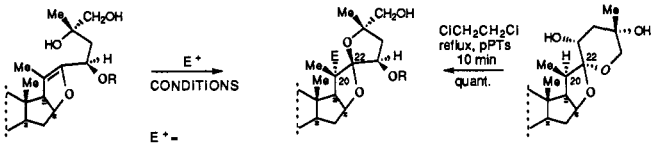
Scheme 2



Scheme 3



Scheme 4



	E+ =			
16 R = H	HCl/CDCl3 25°C	17H E = H, R = H 17%	19H E = H, R = H 68%
16 R = H	pPTs/CH2Cl2 0°C, 5h	17H E = H, R = H 80%	19H E = H, R = H 10%
16 R = H	pPTs/ClCH2CH2Cl,80°C, .2h	17H E = H, R = H 97%	19H E = H, R = H --
16 R = H	NBS/THF,-78°C, 5 min	17Br E = Br, R = H 89%	
14S R = TBDPS	NBS/THF, -78°C, 30 min	18Br E = Br, R = TBDPS 91%	

(1) (a) Pettit, G. R.; Inoue, M.; Kamano, Y.; Herald, D. L.; Arm, C.; Dufresne, C.; Christie, N. D.; Schmidt, J. M.; Doubek, D. L.; Krupa, T. S. *J. Am. Chem. Soc.* **1988**, *110*, 2006. (b) Pettit, G. R.; Inoue, M.; Kamano, Y.; Dufresne, C.; Christie, N.; Niven, M. L.; Herald, D. L. *Chem. Commun.* **1988**, 865. (c) Pettit, G. R.; Inoue, M.; Kamano, Y.; Dufresne, C.; Christie, N.; Niven, M. L.; Herald, D. L. *Chem. Commun.* **1988**, 1140. (d) 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.

(2) Pan, Y.; Merriman, R. L.; Tanzer, L. R.; Fuchs, P. L. *Biomol. Chem. Lett.* **1992**, 967.

(3) Smith, S. C.; Heathcock, C. H. *J. Org. Chem.* **1992**, *57*, 6379.

(4) All new materials were fully characterized. Copies of proton and carbon NMR spectra may be found in the supplementary information.

(5) Ring opening of spiroketal **5** is based upon the general method of Micovic and Piatak (see: *Synthesis* **1990**, 591).

(6) (a) Suryawanshi, S. N.; Fuchs, P. L. *J. Org. Chem.* **1986**, *51*, 902. (b) Jain, S.; Shukla, K.; Mukhopadhyay, A.; Suryawanshi, S. N.; Bhakuni, D. S. *Synth. Commun.* **1990**, *20*, 1315.

(7) Full X-ray data on compounds **10β**, **17H**, **19H**, and **22α** can be obtained from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK. Tel. 44-223-336408. Fax 44-223-336033.

(8) Review: Mitsunobu, O. *Synthesis* **1981**, 1.

(9) Safah, M.; Bessodes, M.; Antonakis, K. *Tetrahedron Lett.* **1992**, 4317.

(10) (a) Cook, A.; Maichuk, D. *J. Org. Chem.* **1970**, *35*, 1940. (b) Naruto, M.; Ohno, K.; Naruse, N.; Takeuchi, N. *Tetrahedron Lett.* **1979**, 251.

(11) Hardinger, S. A.; Wijaya, N. *Tetrahedron Lett.* **1993**, *34*, 3821.

(12) See the supplementary information for an extended discussion of this reaction, complete with an additional data table.

(13) (a) Corey, E. J.; Jardine, P. D.; Virgil, S.; Yuen, P.-W.; Connell, R. D. *J. Am. Chem. Soc.* **1989**, *111*, 9243. (b) Corey, E. J.; Lotto, G. I. *Tetrahedron Lett.* **1990**, 2665. (c) Wu, Y.; Wang, Y.; Houk, K. *J. Org. Chem.* **1992**, *57*, 1362.

0002-7863/94/1516-0773$04.50/0

Chart 1

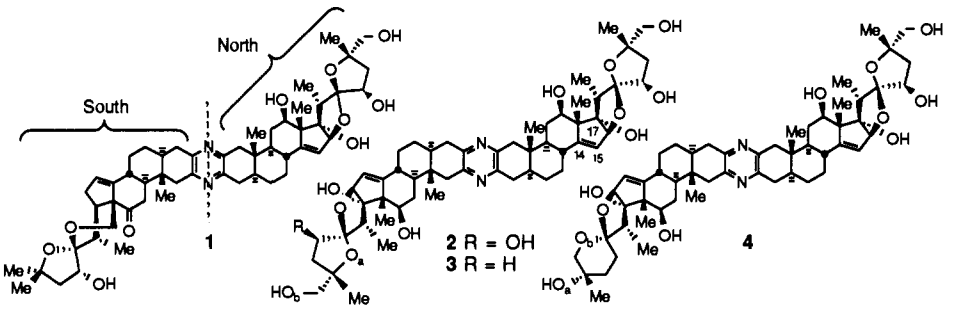
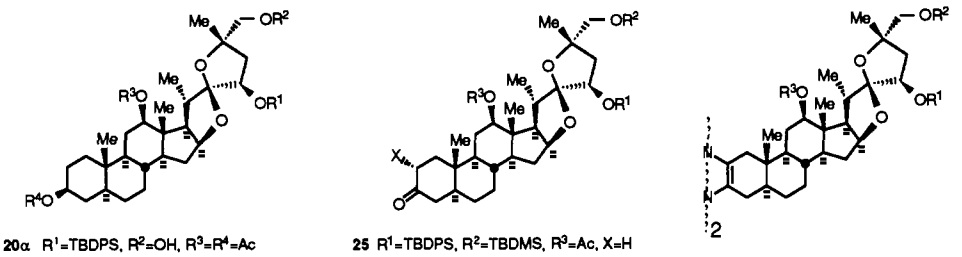
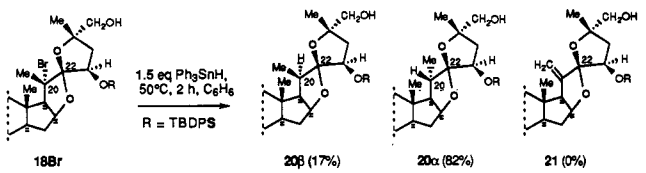


Chart 2



20α R¹=TBDPS, R²=OH, R³=R⁴=Ac
22α R¹= R²=OH, R³=R⁴=Ac
23 R¹=TBDPS, R²=TBDMS, R³=R⁴=Ac
24 R¹=TBDPS, R²=TBDMS, R³=Ac, R⁴=H
25 R¹=TBDPS, R²=TBDMS, R³=Ac, X=H
26 R¹=TBDPS, R²=TBDMS, R³=Ac, X=Br
27 R¹=TBDPS, R²=H, R³=Ac, X=Br
28 R¹=TBDPS, R²=TBDMS, R³=Ac, X=N_3
29 R¹=TBDPS, R²=TBDMS, R³= Ac
30 R¹= R²= H, R³= Ac
31 R¹= R²= R³= H

Scheme 5



Completion of the synthesis of **31** involved reaction of **20α** with (TBDMS-Cl, imidazole, DMF, 25 °C, 1 h)[14] to generate the C-26 silyl ether **23**,[4] which was hydrolyzed to C-3 alcohol **24**[4] using $KHCO_3$ in methanol–water at reflux for 3 h. Oxidation of crude **24** using the Brown–Jones oxidation[15] afforded ketone **25**[4] in 80% for the three steps. Subsequent reaction of **25** with PTAB in THF at 0 °C for 0.25 h provided bromide **26**[4] in 76% yield. This reaction also produced 14% of the C-26 desilylated monobromide **27**[4] accompanied by 7% of the 2,2-dibromoketone (not shown). Application of the existing methodology[2] to bromide **26** provided azide **28**[4] in 93% yield. Reduction of **28** with triphenyltin hydride (2.0 equiv) in benzene at reflux for 1.5 h followed by removal of the tin residues with KF[16] and cyclization of the resultant α-aminoketone using pPTs in chloroform[3] at 25 °C for 2 h produced fully-protected trisdecacyclic pyrazine **29**[4] in 79% yield along with 17% of deazidoketone **25**. Simultaneous cleavage of both the C-23 and the C-26 silyl moieties with TBAF in THF at 65 °C for 6 h gave diacetate **30**[4] (96%). Final hydrolysis of the C-12 ester groups delivered the target pyrazine **31**[5] {$[\alpha]^{25}$ = +5.4° (*c* = 0.003, CH_3OH), mp 306 °C dec.} in 98% yield, making the total overall yield 5% from hecogenin acetate **5** (Chart 2). Pharmacological evaluation of these materials is currently underway and will be reported in due course.

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Supplementary Material Available: Extended discussion of the chemistry of Schemes 3 and 5, copies of proton and carbon spectra for all new compounds, and tabulated spectral data (59 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(14) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.
(15) Brown, H. C.; Garg, C. P.; Liu, K.-T. *J. Org. Chem.* **1971**, *36*, 387.
(16) Ryu, I.; Kusano, K.; Yamazaki, H.; Sonda, N. *J. Org. Chem.* **1991**, *56*, 5003.