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A Biomimetically Inspired, Efficient Synthesis of the South 7 Hemisphere of Cephalostatin 7

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Our quest to supply multigram quantities of cephalostatin analogues to the clinic has featured improved syntheses of several Southern hemispheres, including ritterazine G_N,[1] 23′-deoxy cephalostatin 1, and 17-hydroxy, 23-deoxy cephalostatin 1. Combining these segments with the North 1 segment has given a series of potent agents exhibiting promising cell-line specificity.[2]

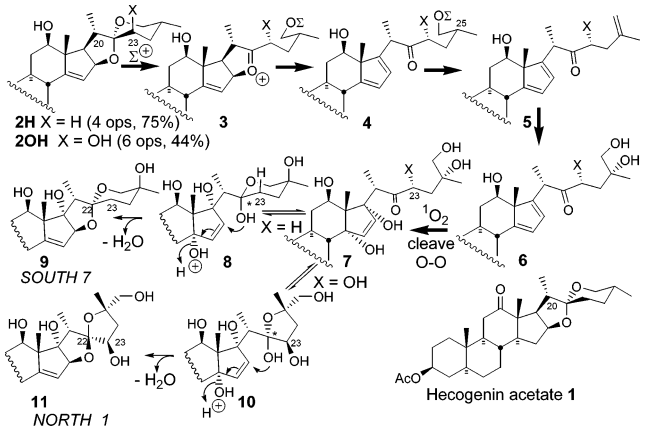
Completing the goal requires a vastly improved preparation of South 7 and several variants of the North 1 hemisphere. Our approach to these materials involves conversion of the plant-derived, hecogenin acetate **1** to spiroketals **2H** and **2OH**.[3] In concept, electrophilic opening of **2H** or **2OH** could give the corresponding oxonium ions **3H** or **3OH**. Furthermore, the enol from **3H** may serve as a precursor to **4OH**. Conversion of **4H** and **4OH** to key polyols **7H** and **7OH** requires elimination to **5** followed by dihydroxylation to D-ring dienes **6**. Cephalostatin-related steroidal D-ring dienes have previously been subjected to [4 + 2] reactions with singlet oxygen,[4] but this communication reports the first appropriately oxygenated, stereodefined substrates that deliver a synthetically relevant outcome.

Olefinic polyols **7H** and **7OH** each have the potential of being in equilibrium with four diastereomeric hemiketals, of which **8** and **10** appear preordained to suffer mild acid-catalyzed cyclization to **9** and **11**, respectively. Alternatively, ionization of the C-14 tertiary allylic alcohol of **7** may result in capture of the C-22 ketone followed by kinetic closure of the spiroketal, again potentially yielding **9** and **11** or their diastereomers (Scheme 1).

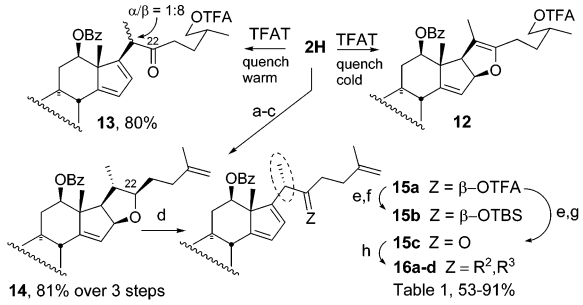
Acid-catalyzed ring-opening reactions of steroidal spiroketals are generally based upon the seminal 1939−1940 Marker protocol.[5] The reaction conditions are quite severe (Ac_2O, 200 °C, 10 h), and substrates such as **2** bearing a D-ring olefin decompose when subjected to these conditions. Our new procedure involves low temperature (−30 to −40 °C) treatment of spiroketals with trifluoroacetyltriflate (TFAT) for 2 h, followed by cold, aqueous workup.[6] Application of this protocol to steroid **2H** gave dihydrofuran **12**. If one allows the reaction to reach room temperature, the product is ring-opened diene **13**, which has unfortunately suffered equilibration of the doubly activated C-20 stereocenter (Scheme 2). The problem was avoided by reaction of **14**[3b,7] with TFAT to provide dienyl trifluoroacetate **15a** in high yield with no loss of C-20 stereochemistry. Mild hydrolysis and Swern oxidation (Hünig's base is essential to avoid C-20 isomerization) afforded the equilibration-sensitive ketone **15c** with only a trace epimerization at C-20 (Scheme 2).

The biomimetic hypothesis was initially tested with dienes **15a**−**c**, which added singlet oxygen in high yield, but gave no facial preference (Table 1, entries 1−3). Molecular modeling of C-22 propylene glycol ketals prefigured the singlet oxygen reaction as a function of the conformational bias of the C-21 methyl moiety. Specifically, it appears that the natural C-21α methyl ketal exists as a group of three low-energy conformers, which shield the top face of the D-ring diene, while the corresponding five conformers of the *β*-methyl isomer block the bottom face (Figure 1).

Scheme 1. Biomimetic Strategy of North 1 and South 7



Scheme 2. Synthesis of Dienes **15a**−**c** and **16a**−**d**



a. $BF_3.OEt_2$, Et_3SiH, CH_2Cl_2; b. imidazole, Ph_3P, I_2, Et_2O/CH_3CN; c. DBU, DMF, 90 °C, 1 h; d. 1.5 eq. TFAT, 1.2 eq. 2,6-di-*tert*-butyl-4-methylpyridine, CH_2Cl_2, -30 °C, 1h; e. 2 eq. Na_2CO_3, $THF/H_2O/MeOH$, rt, 9 h, 92% over 2 steps; f. 1.5 eq. TBSOTf, 5 eq. 2,6-lutidine, CH_2Cl_2, 0 °C, 3 h, 95%; g) 2.5 eq. DMSO, 3 eq. TFAA, 3 eq. DIPEA, CH_2Cl_2, -78 °C to rt, 94%; h. 10 mol% $Sc(OTf)_3$, 10 eq 1,3-diol, 10 eq. $(MeO)_3CH$, CH_3CN, rt, 17 h.

In the event, C-22 ketals **16a**−**c** (from **15c** in 91, 53, and 91% yield, respectively)[8,9] smoothly underwent [4 + 2] cycloaddition of singlet oxygen in 80−98% yield (entries 4−6), stereospecifically providing α-face adducts. In striking contrast, but consistent with the model in Figure 1, unnatural C-21 methyl ketal **16d** gave only the expected *β*-adduct **20d-*β*** (entry 7).

With selective cycloaddition achieved, biomimetic synthesis of the South 7 hemisphere was next addressed. Conversion of terminal olefin **14** to differentially protected C-25,26 diol **21a-α** (not shown) was accomplished in three operations with 93% yield and >4.3:1 de with either C-25 selectivity as a function of catalyst in the Sharpless AD reaction (see Supporting Information).

Cleavage of the isolable and characterized peroxide **22a-α** (see Supporting Information) with Zn/HOAc provided diol **23a-α** in 86% yield (Scheme 3). The stage was now set to deprotect ketal **23a-α**

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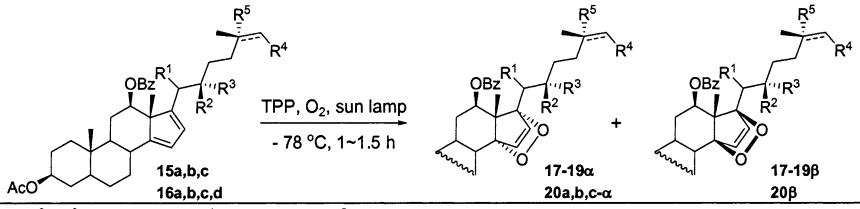
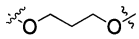
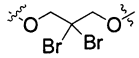
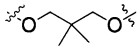
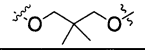
Table 1. [4 + 2] Cycloaddition of Steroidal D-ring Dienes with Singlet Oxygen



entry	R^1	R^2, R^3	R^4	R^5	diene	product	facial selectivity[a]	yield (%)
1	α–Me	$OCOCF_3$, H	H	Δ^{25}	**15a**	**17α/17β**	$\alpha/\beta = 1.3{:}1$	ns[a]
2	α–Me	OTBS, H	H	Δ^{25}	**15b**	**18α/18β**	$\alpha/\beta = 1{:}1$	ns[a]
3	α–Me	O	H	Δ^{25}	**15c**	**19α/19β**	$\alpha/\beta = 1{:}1$	ns[a]
4	α–Me		H	Δ^{25}	**16a**	**20a-α**[c]	α–adduct only	98[b]
5	α–Me		H	Δ^{25}	**16b**	**20b-α**	α–adduct only	80[b]
6	α–Me		H	Δ^{25}	**16c**	**20c-α**	α–adduct only	94[b]
7	β–Me		$OCOCF_3$	H	**16d**	**20d-β**	β–adduct only	81[b]

[a] Calculated by crude ^{1}H NMR spectrum; ns = not separated. [b] Isolated yields. [c] Structure confirmed by X-ray crystallography. See Supporting Information.

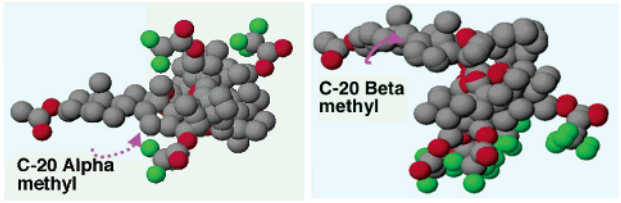
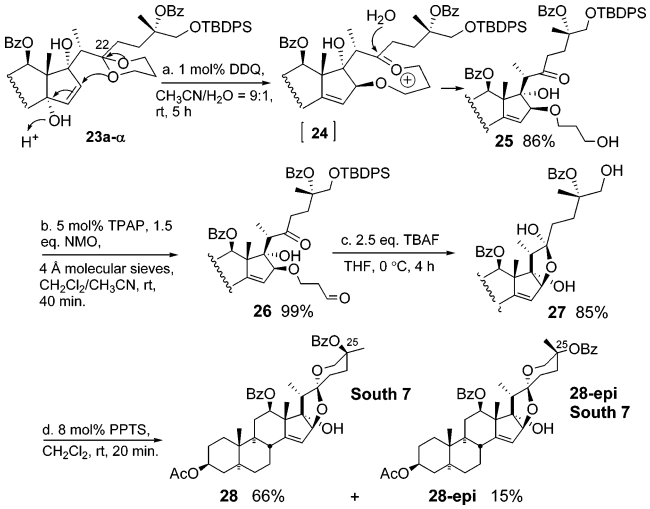


Figure 1. Molecular models of C-22 propylene glycol ketals.

Scheme 3. Completion of Synthesis of South 7 (**28**)



to ketone **7** and test the plan for formation of spiroketal **9** (Scheme 1) by selective monodeprotection at C-25,26.

After many unsuccessful attempts at ketal deprotection, treatment of **23a-α** via HCN catalysis (controlled release from aqueous DDQ)[10] afforded the unexpected, but welcome, hydroxypropyl ether **25**, presumably via ketal participation followed by hydrolysis of intermediate oxonium ion **24**. Oxidation to **26**, concurrent cleavage of silyl ether and acrolein gives **27**, which, upon a finishing acidification, directly gave the South 7 spiroketal **28** in 66% yield accompanied by the C-25 diastereomer **28-epi**, resulting from parallel processing of the inseparable C-25 diol carried forward from the stage of the Sharpless AD reaction (Supporting Information).

In conclusion, the above synthesis affords a new, practical route to the South 7 hemisphere **28** in 20% overall yield over 16 operations from hecogenin acetate **1**. This compares with our first-generation synthesis that required 25 operations with an overall yield of 2%.[11] In addition, this communication provides a biomimetic strategy potentially appropriate for a vastly improved synthesis of the crucial North 1 hemisphere and its analogues.

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Supporting Information Available: Extended discussion, experimental procedures, and ^{1}H, ^{13}C spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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