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Synthesis of C14,15-Dihydro-C22,25-*epi* North Unit of Cephalostatin 1 via "Red-Ox" Modifications of Hecogenin Acetate

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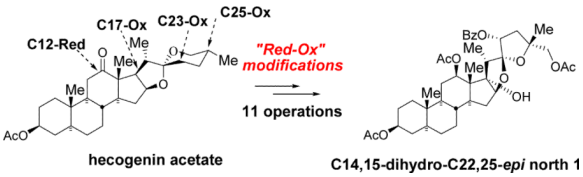
Abstract



C14,15-Dihydro-C22,25-*epi* north unit of cephalostatin 1 has been synthesized in eleven operations from a commercially available hecogenin acetate via multiple reductions and oxidations. The key transformations include: i) Cr^{VI}-catalyzed E-ring opening, ii) C17 hydroxylation, and iii) a base-triggered cyclization cascade.

The cephalostatins and ritterazines are structurally unique marine natural products that display extreme cytotoxicity against various human cancers.1 The natural targets cephalostatin 1, cephalostatin 7, cephalostatin 12, ritterazine M, and ritterazine K have been synthesized by us,2 while we and others3 have also been active in the synthesis and testing of analogs. The forty-five members of the cephalostatin and ritterazine family, along with the growing number of analogs and related monosteroidal glycosides afforded the basis for elucidating some of the structure activity relationships (SAR) and common pharmacophore of these potent cytotoxins:[4] (1) "polarity match" consisting of polar north domains and less polar south domains with a connecting pyrazine moiety; (2) bis-spiroketals as prooxocarbenium moieties; (3) C17 (north) and C23'(south) hydroxyl group; and (4) Δ^{14} olefin moiety.

Semiempirical calculations for rationalizing the SAR of the bis-steroidal pyrazines revealed a strong correlation between bioactivity and enthalpy of oxacarbenium ion formation.[5] Our efforts for calculation-guided design and synthesis of cephalostatin analogs led to the finding of the hyperactive C25-*epi*-ritterostatin G_N1_N (**2**), which is ~100 times more cytotoxic than ritterostatin G_N1_N (**1**) thereby being more potent than cephalostatin 1 (**3**, Figure 1), the most potent member of the cephalostatin family. Simply by comparing these three compounds (**1**, **2**, and **3**), most organic chemists would consider that C25-*epi*-cephalostatin 1 (**4**) would be a logical one to prepare. Calculations[5] also support that the C25-*epi*-cephalostatin 1 (**4**) should be in the hyperactive class.

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Supporting Information Available: General experimental procedure and NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

†Cephalostatin Support Studies. 35. For 34, see: Lee, J. S.; Cao, H.; Fuchs, P. L. *J. Org. Chem*. **2007**, 72, 5820.

In conjunction with our quest to achieve an efficient second generation synthesis of the north unit of cephalostatin analogs,[6] we have developed a "Red-Ox" strategy where multiple oxidations/reductions are employed as key transformations to deliver the target hemispheres. Herein, we report a progress toward the synthesis of C25-*epi* north 1 (**6**) from hecogenin acetate **5** via "Red-Ox" modifications (Scheme 1).

Our "Red-Ox" strategy synthesis of the C25-*epi* north 1 **6** started from commercially available plant-derived hecogenin acetate **5** (Scheme 2). Borohydride reduction of hecogenin acetate **5** at −78 °C followed by acetylation afforded rockogenin acetate **7** in a nearly quantitative yield. The action of *t*-$BuNO_2/BF_3\bullet OEt_2$[7] on 5/6 spiroketal **7** regioselectively delivered C23 oxime **8**, a masked ketone, which was then hydrolyzed in the presence of acid to unveil ketone **9**. Obtaining a workable stereoisomeric excess at C23 relied on (*S*)-CBS reduction[8] (C23*R* (axial OH) 78 % **10**; C23*S* (equatorial OH) 13 %). Regio- and stereoselective triethylsilane reduction of 5/6 spiroketal **10** resulted in the formation of F-ring opened diol **11** in 94 % yield. Selective tosylation of the primary alcohol in the presence of the secondary alcohol using catalytic 1,4-diazabicyclo[2,2,2]octane (DABCO) followed by C23 benzoylation furnished **12**, which was then subjected to a sequential iodination and DBU-mediated E2 elimination to give terminal olefin **13a**.

With olefin **13a** in hand, we investigated C25,26-oxyfunctionalization using Sharpless asymmetric dihydroxylation.[9] As expected from our previous studies,[10] stereoselective dihydroxylation of the olefin moiety was especially difficult. Reasonable excess of C25*R* stereoisomer was obtained only when using $(DHQ)_2PHAL$ ligand and C23 substituted substrate (Table 1). Stereochemistry at C25 was unambiguously determined by a single crystal X-ray crystallography. The diol **14a** was subjected to sequential protection of the primary alcohol with an acetyl group and the tertiary alcohol with the trifluoroacetyl group to provide **15** (Scheme 2).

Having established the requisite stereochemistry at C12, 23, and 25, we next turned to C17 hydroxylation (Scheme 3). For this transformation, opening of the E-ring was required. While there are a number of tetrahydrofuran ring opening methods,[11] steroidal E-ring of **15** was found inert to those conditions so that starting material was recovered in most cases. However, our recently developed Cr^{VI}-mediated C–H oxidation[12] protocol smoothly effected E-ring opening to deliver diketone **16** in 84 % yield. After extensive experimentations, formation of C17-OH **18** was finally achieved by TMSI/ hexamethyldisilazane-mediated[13] thermodynamic silylenol ether 17 formation followed by Rubottom oxidation by TFMDO[14] generated *in situ*. The C17-OH group was introduced in a stereoselective manner. The use of different bases other than hexamethyldisilazane or *in situ* generated TMSI resulted in no formation of the silylenolether **17**. Removal of trifluoroacetyl protecting group of **18** with 1,8-diazabicyclo[5,4,0]undec-7-ene triggered a cyclization cascade to form hemiacetal **19** as a single stereoisomer. Reduction of the hemiacetal **19** with excess triethylsilane and TMSOTf at −78 °C delivered C14,15-dihydro-C22,25-*epi* north 1 (**20**) in 89 % yield.[15]

In summary, we have developed an efficient synthetic route for C14,15-dihydro-C22,25-*epi* north 1 (**20**) wherein Cr^{VI}-catalyzed E-ring opening, stereoselective C17 hydroxylation, and a cyclization cascade are used as key reactions. Dihydro-22,25-*epi* north 1 (**20**) was prepared in 11 operations and 4 % overall yield from hecogenin acetate. The presented results illustrate that the "Red-Ox"-based synthesis provides a facile and efficient access to cephalostatin analogs from hecogenin acetate **5**. Further synthetic efforts to convert C17-hyroxy-C16,22-diketone **18** into C25-*epi* north 1 (**6**) and to make cephalostatin analogs containing C14,15-dihydro-C22,25-*epi* north 1 hemisphere **20** are in progress and results will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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15. The C22 stereochemistry was determined by comparing ^{1}H and ^{13}C NMR spectra of **20** with those of 14,15-dihydro-17-deoxy-22,25-*epi* north 1, of which structure was solved by a single crystal X-ray crystallography (see Supporting Information).

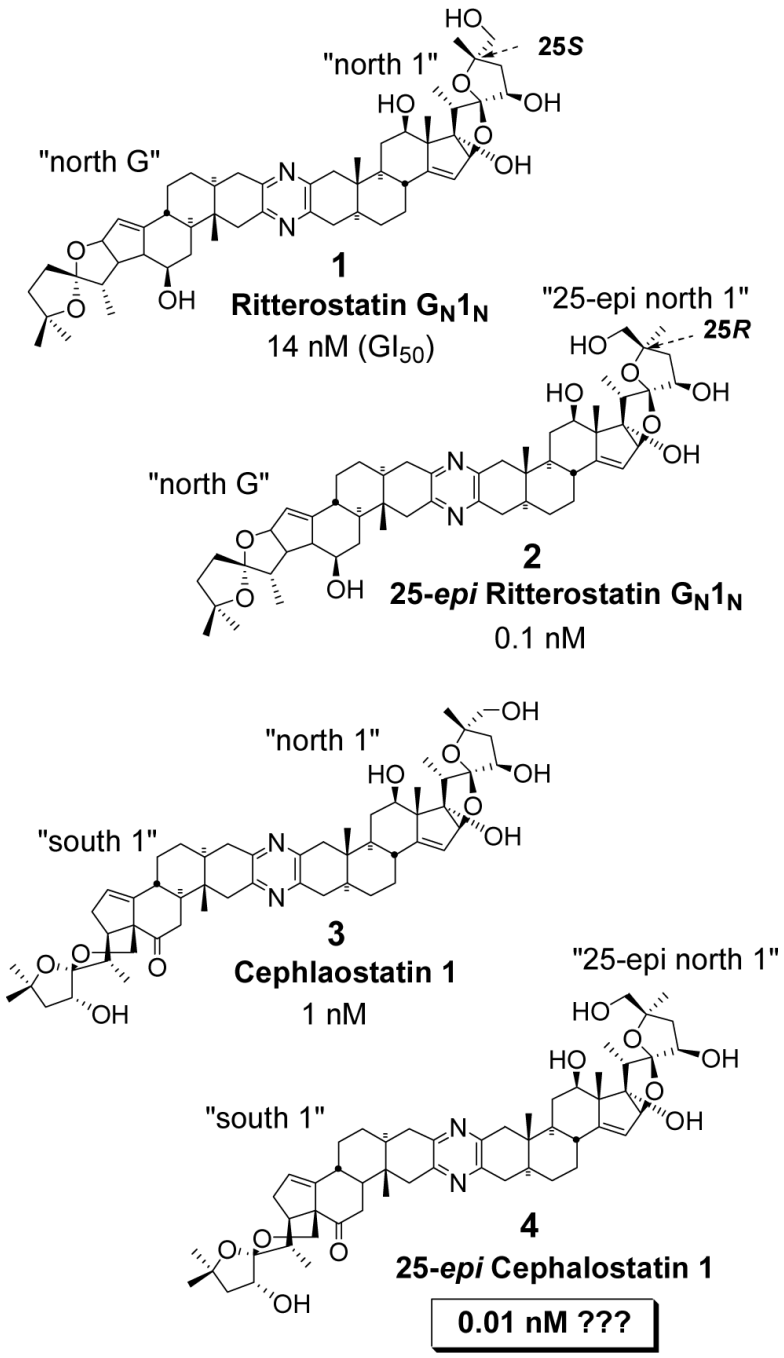
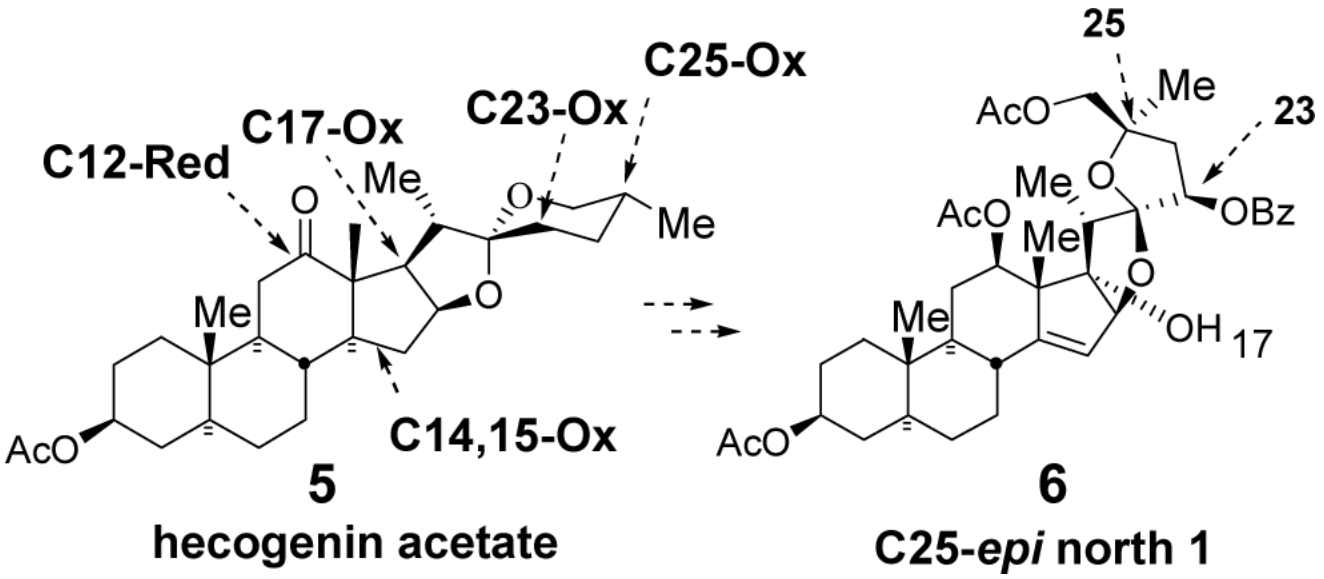
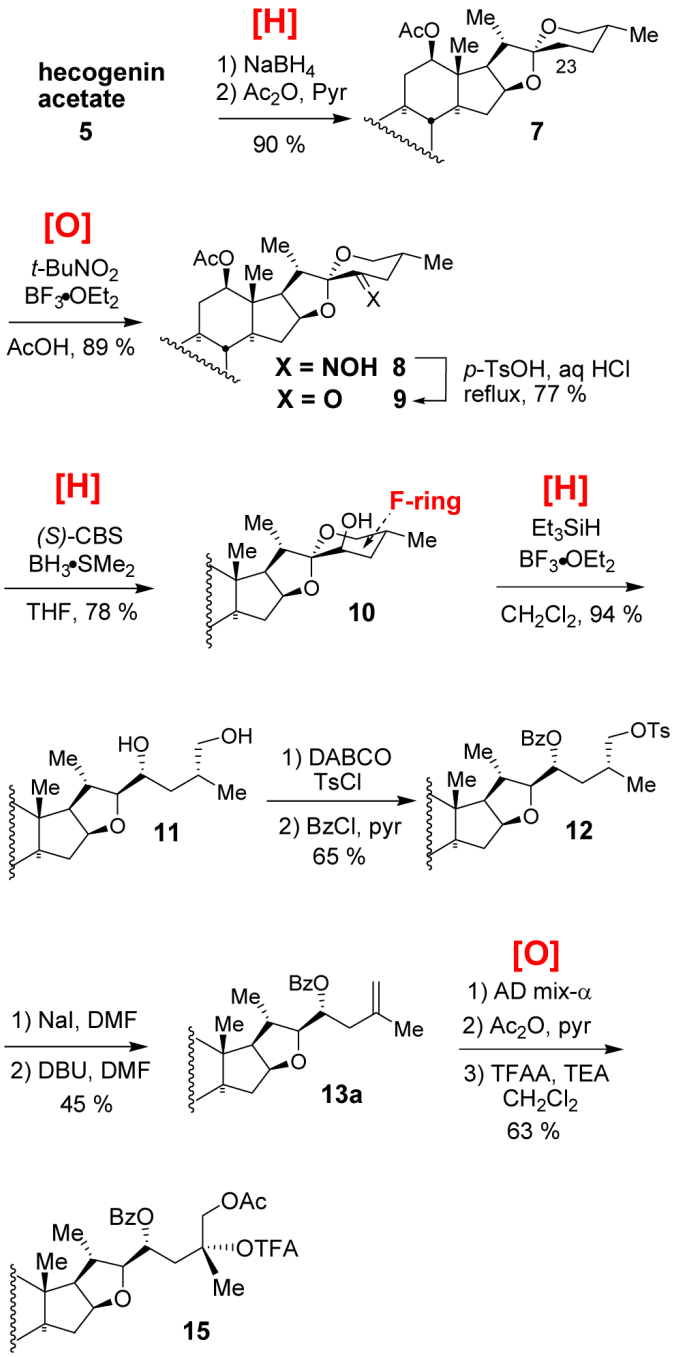


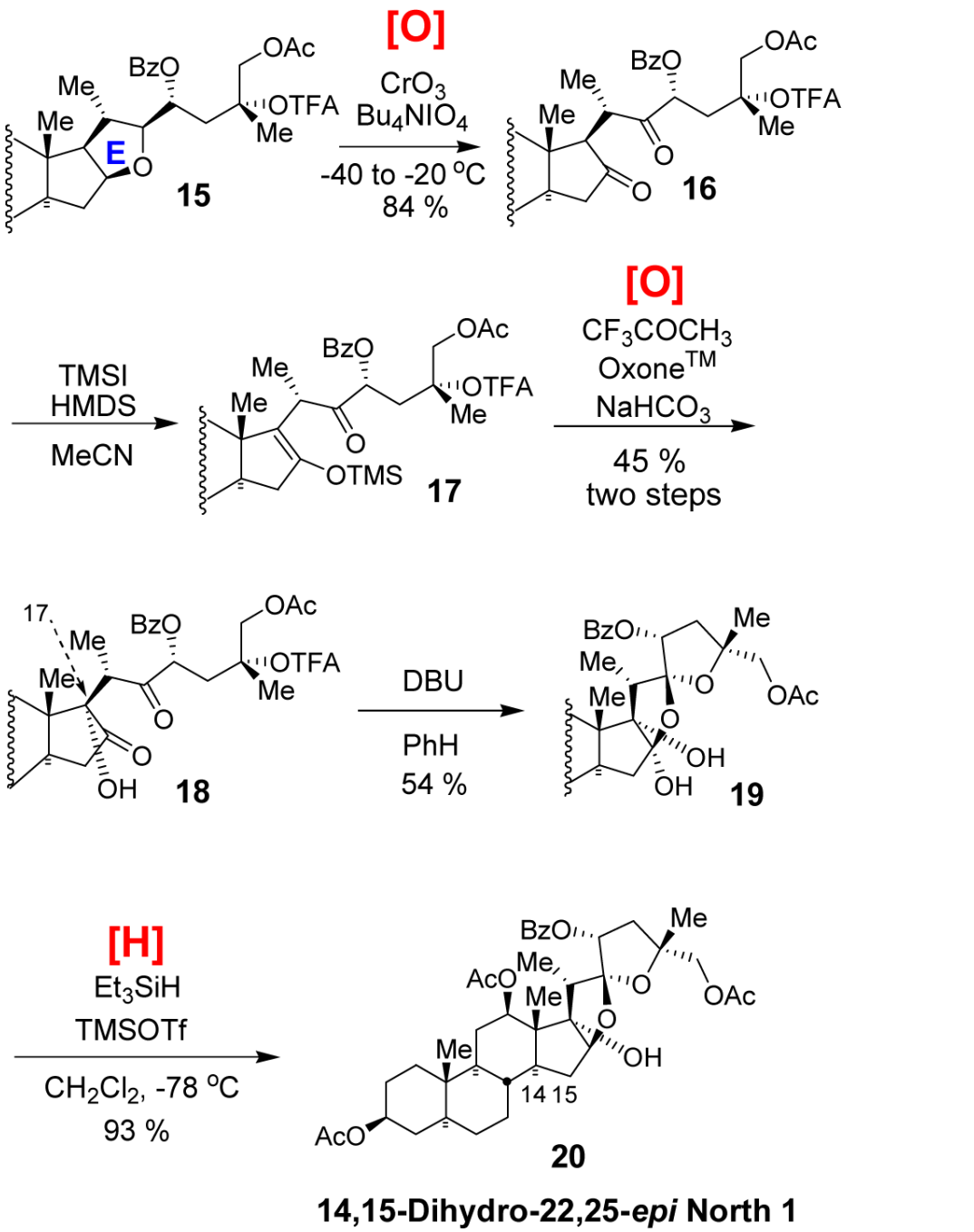
Figure 1.
Effect of C25 Stereochemistry on the Cytotoxicity of Cephalostatin Analogs



Scheme 1.
"Red-Ox" Strategy



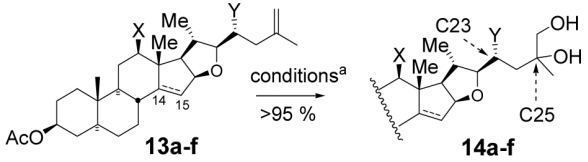
Scheme 2.



Scheme 3.

Table 1

Asymmetric Dihydroxylation of the C25-olefin



13a-f **14a-f**

substrate	X	Y	C14-15	ligand	product	25*R*:25*S*
13a	OAc	OBz	14α-H	$(DHQ)_2PHAL$	**14a**	5:1
13b	OAc	OBz	14α-H	$(DHQD)_2PHAL$	**14b**	1:3
13c	OBz	H	14α-H	$(DHQ)_2PHAL$	**14c**	1:1
13d	OBz	H	14α-H	$(DHQD)_2PHAL$	**14d**	1:1
13e	OBz	H	Δ^{14}	$(DHQ)_2PHAL$	**14e**	1:5
13f	OBz	H	Δ^{14}	$(DHQD)_2PHAL$	**14f**	2:1

[a]OsO_4 (2 mol %), ligand (10 mol %), $K_3Fe(CN)_6$ (3 equiv), K_2CO_3 (3 equiv), t-BuOH/H_2O (1:1), 0 °C.

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