ORGANIC LETTERS

2003
Vol. 5, No. 13
2247−2250

New Oxidative Tools for the Functionalization of the Cephalostatin North 1 Hemisphere†

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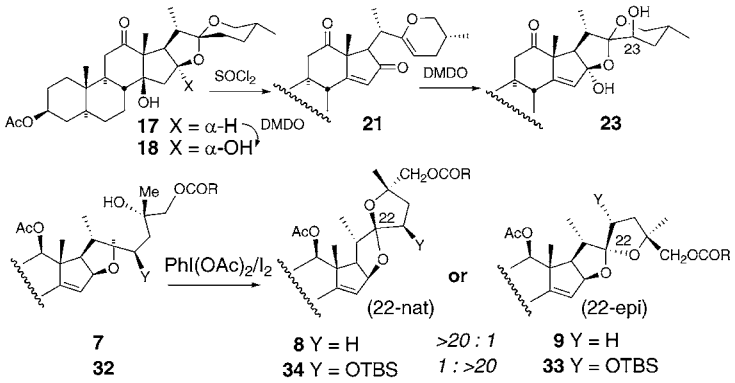
Received March 30, 2003

ABSTRACT



Dimethyldioxirane (DMDO) C−H oxidation of ketone 17 to hemiketal 18 (82%), bis-dehydration to vinyl ether 21 (77%), and DMDO again provides C-23 axial alcohol 23 (99%). Routine processing, including a double-stereoselective Sharpless AD reaction (de >98%), gives alcohols 7 and 32. C-23 deoxy substrate 7 undergoes Suarez hypoiodite oxidative cyclization to (natural) β spiroketal 34, but compound 32, bearing a C-23 silyl ether, generates unnatural spiroketal 33.

The cephalostatins[1] and ritterazines[2] comprise a family of 45 structurally unique marine natural products that display extreme cytotoxicity against human tumors (~1 nM mean GI_{50}'s in the 2-day NCI-60 screen and 10^{-14} M GI_{50}'s in 3-day tests in the Purdue minipanel).[3] The total syntheses of cephalostatin 1 **2** and cephalostatin 7 as well as many analogues have been reported by others[4] and us,[5] but chemical evidence for the site(s) of reactivity and the mechanism of action of the bissteroidal pyrazines remain unknown and *no scaleable synthesis for such testing has been achieved*. Our recent "second-generation" synthesis of the C-23′ deoxy South 1 hexacyclic spiroketal **Do-2** has substantially ameliorated the material supply problem with the South 1 hemisphere (12 operations, 23% overall yield from hecogenin acetate**1**),[6] but access to the North segment (and the South 7 hemisphere **3**) remained impractical, standing at ~34 operations.

As more extensively discussed in our previous publication,[6] we are now pursuing a strategy which retains all 27 carbon atoms of hecogenin acetate **1** and employs specific

† Cephalostatin Support Studies. 24. Oxidations. 2. For previous papers in these series, see ref 6 and: Lee, S. M.; Fuchs, P. L. *J. Am. Chem. Soc.* **2002**, *124*, 13978−13979.

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10.1021/ol034551g CCC: $25.00
Published on Web 06/06/2003

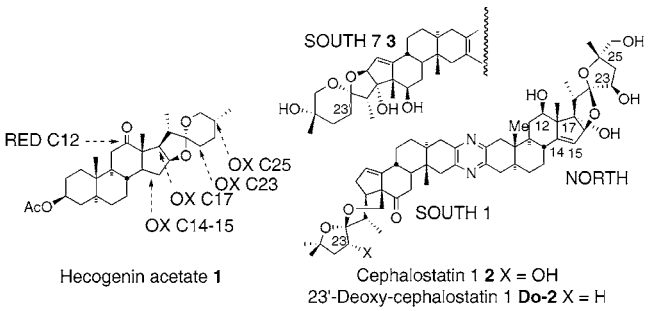


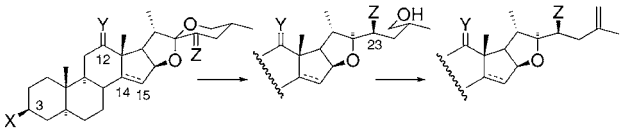
Figure 1.

oxidation reactions to introduce common features found in both cephalostatin hemispheres (Figure 1).

Our revised approach to the North 1 and South 7 segments is based upon the Suarez cyclization we employed for the synthesis and structure correction of Ritterazine M.[7] A related model study has recently appeared from the Suarez group.[8] We have found that it is essential to define the "gestalt" effects of the entire steroid upon chemistry occurring at a supposedly remote site. In this light, comparison of the Suarez study[8] with our current investigation is particularly instructive.

Our study began with compound **4**,[9] having C12 and C14−15 in the *required oxidation state*. Reductive cleavage of the spiroketal gave alcohol **5**, which was converted to olefin **6** through the intermediate iodide (Scheme 1).

Scheme 1



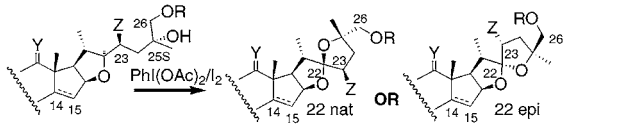
4 X = OAc; Y = β-OBz; Z = H,H, 14-15 olefin
5 Y = β-OBz; Z = H, 14-15 olefin
6 Y = β-OBz; Z = H, 14-15 olefin
10 X = OMe; Y = H,H; Z = O, 14-15 dihydro
11 Y = H,H; Z = OH, 14-15 dihydro
12 Y = H,H; Z = OTBS, 14-15 dihydro

The Suarez group started with compound **10** having C12 and C14 in the fully reduced state. This material was converted to the C23 ketone via the nitroimine.[10] Similar to previous cases, reduction of the spiroketal C-23 ketone was highly selective (5:95) for the (unnatural) equatorial alcohol, although a 63:37 ratio favoring the axial alcohol could be obtained using L-Selectride. Reductive cleavage to **11** followed by protecting group manipulation and elimination via the nitroselenoxide afforded silyl ether−olefin **12** (Scheme 1).

The parallel studies next examined osmylation of olefins **6** and **12**, respectively. The Purdue group employed double stereoselection via catalytic asymmetric dihydroxylation of **6**, which delivered a pair of spiroketals in ~6:1 selectivity *both bearing the 25S configuration*.[7,11] In comparison, stoichiometric osmylation of **12** gave a 1:2 mixture favoring the unnatural 25*R* stereochemistry.[8]

Application of the Suarez reaction to the C-23,26-diprotected diol mixture **13** generated a 28/72 mixture of the two 5/5 ring spiroketals **14/15** in 83% yield. In stark contrast, similar treatment of the C-26 protected substrate **7** generated a single diastereomeric spiroketal **8**, which was shown to have the desired 22-natural stereochemistry (Scheme 2).

Scheme 2



7 R = Bz; Y = β-OBz; Z = H, 14-15 olefin
8 R = Bz; Y = β-OBz; Z = H, 14-15 olefin
9 R = Bz; Y = β-OBz; Z = H, 14-15 olefin
13 R = Ac; Y = H,H; Z = OTBS, 14-15 dihydro
14 R = Ac; Y = H,H; Z = OTBS, 14-15 dihydro
15 R = Ac; Y = H,H; Z = OTBS, 14-15 dihydro

These and other experiments (vide infra) prove that a C14−15 olefin is required to achieve stereospecific asymmetric dihydroxylation at C25,26.

The new Purdue synthesis begins with our improved transformation of hecogenin acetate **16** to β-hydroxyketone **17** in a one-pot 94% yield.[9] Dimethyldioxirane has been effectively used for the oxidation of tertiary C−H bonds in steroids,[12] and application of this reagent to spiroketal **17** smoothly provides diol **18** in 82% yield (15.7 g).[14] Initial experiments to effect bis-dehydration of **18** were quite unrewarding. For example, treatment of hemiketal **18** with 2.1 equiv of $BF_3 \cdot OEt_2$ in CH_2Cl_2 from −10 to +25 °C for 18 h gave dienone **19** in 27% yield. Attempts to intercept

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(11) Originally this mixture was misassigned as a mixture of stereoisomers at C25,[7] but the minor isomer is actually the C22β spiroketal and can be equilibrated quantitatively to the natural C22α configuration under acidic conditions (Lee, S. M. Unpublished results).

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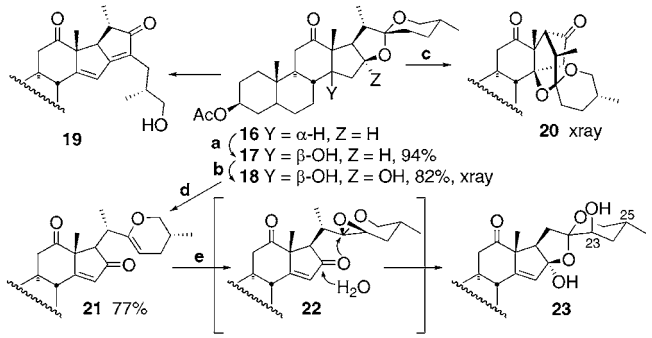
(14) X-ray structural information relating to compounds **18**, **20**, and **26** can be obtained from the Cambridge Crystallographic Data Centre.

the putative D-ring enone by adding triethylsilane to the above conditions provided a 75:11 mixture of **19** and isomeric spiroketal **20** in 86% yield.[14] Under many conditions (see the Supporting Information), **20** is the exclusive product and yields in excess of 95% may be obtained.

After much experimentation, it was discovered that reaction of diol **18** with 4 equiv of thionyl chloride and 20 equiv of pyridine in toluene at −50 °C afforded the long-sought crystalline vinyl ether **21** in 77% yield. This labile material was immediately subjected to DMDO oxidation and underwent quantitative oxidative cyclization to the requisite C-23 axial alcohol **23**, presumably via the intermediacy of nonobserved epoxide **22** (Scheme 3).

Scheme 3[a]

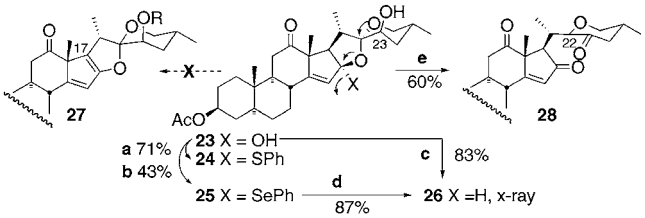


[a] Key: (a) (i) *hν*, CH_2Cl_2, (ii) evap, add 3:1 HOAc/H_2O, (iii) add H_2CrO_4; (b) DMDO (750 mL), CH_2Cl_2 (50 mL), 25 °C, 7 days; (c) TMSCl (1 equiv), NaI (1 equiv), CH_3CN, 30 min, 25 °C, or DMF, 85 °C, or AcOH/CH_2Cl_2 (1:3), 25 °C, 8 h, 99%; (d) 4 equiv of $SOCl_2$, 20 equiv of pyridine, toluene, −50 °C, 40 min; (e) DMDO, −50 °C, 30 min, >99%.

The synthetic plan envisaged dehydration of **23** to dienyl ether **27** in preparation for introduction of the C-17 hydroxyl group via hydroboration. The first try involved conversion of hemiacetal **23** to sulfide **24** in 71% yield using standard conditions for this transformation.[13] We next examined introduction of the selenide moiety in hopes of generating a selenoxide leaving group which might eliminate to **27** under milder conditions. Treatment of lactol **23** with 1.1 equiv of phenylselenol in the presence of boron trifluoride etherate gave the expected selenide **25** in 43% yield along with ever-increasing amounts of **26**, the product of reductive cleavage, in addition to an equivalent amount of diphenyl diselenide. Compound **26** and diphenyl diselenide could be obtained in 83% yield by running the reaction of **23** with 2.5 equiv of selenol with irradiation by a sun lamp. Compound **26** has been verified by X-ray,[14] thereby also securing the structure of alcohol **23**.

Oxidation of **24** or **25** with 1 equiv of *m*-CPBA provided neither the expected sulfoxide, selenoxide, nor diene **27**. Presumably, the putative allylic sulf- (selen-) oxide suffered spiroketal-assisted ionization to the enone−oxonium ion followed by pinacol rearrangement of the C-23 hydride to the C-22 position, thereby yielding ketone **28** in ∼60% yield (Scheme 4).

Scheme 4[a]

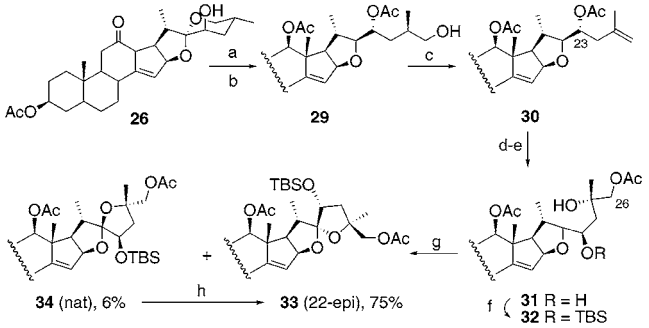


[a] Key: cat. $BF_3{\cdot}OEt_2$ (5 mol %), PhSH (1.5 equiv), CH_2Cl_2, −40 °C, 30 min; (b) dark, 1.1 equiv of PhSeH, cat. $BF_3{\cdot}OEt_2$ (10 mol %), CH_2Cl_2, −30 to −10 °C, 20 min; (c) 2.5 equiv of PhSeH, cat. $BF_3{\cdot}OEt_2$ (10 mol %), CH_2Cl_2, −30 °C, 2 h, sun lamp; (d) 1.1 equiv of PhSeH, sun lamp, 2 h, −30 to −20 °C; (e) 70% *m*-CPBA (1.0 equiv), CH_2Cl_2, 25 °C, 10 min.

After an unsuccessful survey of methods designed to use the axial C-23 alcohol to axially oxygenate the C-25 position (see the Supporting Information), we returned to the strategy we had previously applied in the ritterazine M synthesis.[7]

Conversion of the diol (not shown) from the Sharpless AD reaction of olefin **30** gives a high yield of C-26 acetate **31**(Scheme 5). Presumably, this interesting transformation

Scheme 5[a]



[a] Key: (i) 1.2 equiv of $NaBH_4$, MeOH, CH_2Cl_2, −78 °C, 9 h, α/β = 1:20, (ii) 3 equiv of Ac_2O, 12 equiv of pyridine, cat. DMAP, CH_2Cl_2, rt, 8 h, 99%; (b) 9 equiv of $BF_3{\cdot}OEt_2$, 9 equiv of Et_3SiH, CH_2Cl_2, 0 °C to rt, 36 h; (c) (i) 2.5 equiv of PPh_3, 3 equiv of I_2, 5 equiv of imidazole, Et_2O, CH_3CN, 0 °C to rt, 2.5 h, (ii) DBU, CH_3CN, reflux, 3 h, 83% in two steps; (d) 3 equiv of $K_3Fe(CN)_6$, 3 equiv of K_2CO_3, 0.1 equiv of $(DHQ)_2{\cdot}PHAL$, 0.014 equiv of $K_2OsO_4{\cdot}2H_2O$, tBuOH, H_2O, 0 °C, 17 h; (e) K_2CO_3, THF, H_2O, rt, 3 h, 72% in two steps, C25-*S*/-*R* = 7.8:1; (f) 1.7 equiv of TBDMSOTf, 3 equiv of TEA, CH_2Cl_2, 0 °C, 4 h, 78%; (g) 2.6 equiv of $PhI(OAc)_2$, 2.2 equiv of I_2, UV lamp (300 nm), cyclohexane, 40 °C, 2 h; (h) HCl gas, CH_2Cl_2, rt, 8 h, 99%.

involves sequential double transacylation from C-23. Substrate **32** suffers kinetic Suarez cyclization conditions; now the unnatural isomer **33** is favored over **34** *by a 12.5:1 ratio.* Thermodynamic equilibration of these two isomers demonstrates that the minor isomer ***34*** *can be completely converted to the unnatural spiroketal* ***33***.

The route for completing the cephalostatin North 1 hemisphere is now becoming fairly well defined after integrating

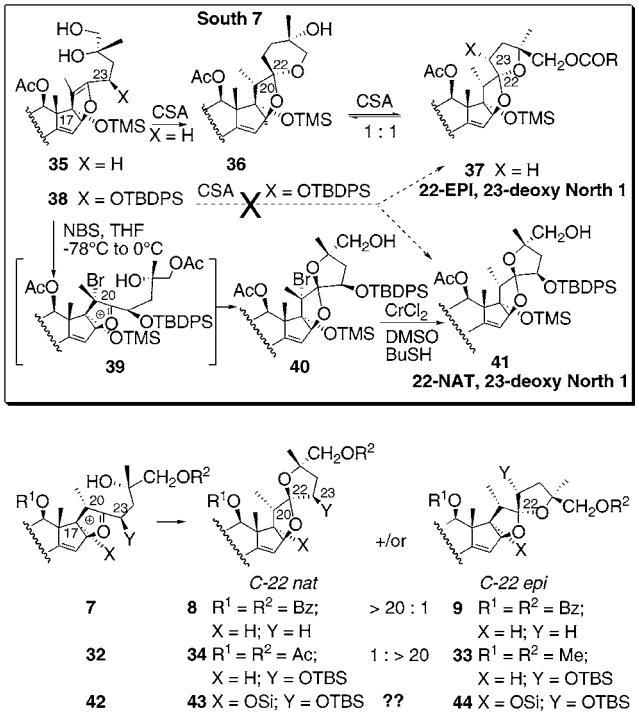


Figure 2.

the current work with our earlier efforts. We have previously demonstrated that C-23 deoxy diol **35** thermodynamically cyclizes to a ~1:1 mixture of the natural South 7 spiroacetal **36** and the 22-epi, 23-deoxy North 1 spiroacetal **37** when treated with catalytic camphor sulfonic acid, a result predicted by molecular mechanics modeling calculations.[15] However, the "real", oxygenated substrate **38** is very unreactive because of the combined steric and electronic deactivation of the enol ether moiety imparted by the C-23 silyl ether. Application of forcing conditions on **38** only serves to generate a plethora of products, probably via the Ferrier pathway. This problem was solved in our (lengthy) first-generation synthesis via a two-step bromocyclization/reduction strategy.[16] Kinetic bromination from the α-face yields oxonium ion **39**, which suffers stereospecific cyclization to **40**. Subsequent chromium(II)-mediated reductive cleavage then provides a ~10:1 separable mixture from which C-20 methyl compound **41** can be obtained in 70% yield (Figure 2).

The results previously discussed above can now be contrasted with the findings of this paper. While C-17, C23 bis-deoxy compound **7** smoothly affords spiroacetal **8** bearing the C-22 natural configuration via the Suarez hypoiodite reaction, it is clear that *the C-23 silyl ether is a dominant negative control element*, since alcohol **32** completely favors the unnaturally configured spiroacetal **33** under thermodynamic conditions. Thus, the key question remaining to be tested is whether **42**, bearing the requisite C-17 oxygen functionality *and* a C-20 α-methyl will be cyclize to natural spiroketal **43** or its unwanted isomer **44**. Put another way, is geminal substitution required at C-20 (intermediate **39)** to ensure formation of *β*-face spiroketal **40**, or can oxonium intermediate **42** bearing a C-17 silyl ether and an α-face C-20 methyl moiety overcome the deleterious effect of the C-23 silyl ether (Figure 7)?

Acknowledgment. We thank the National Institutes of Health (CA 60548) for funding. Arlene Rothwell provided the MS data.

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

OL034551G

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