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Dyotropic Rearrangement Facilitated Proximal Functionalization and Oxidative Removal of Angular Methyl Groups: Efficient Syntheses of 23′-Deoxy Cephalostatin 1 Analogues[1]

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We have reported the total syntheses of cephalostatin 1 (**1**) and designed interphylal analogue ritterostatin G_N1_N (**2**) (14 nM)[2a] via directed unsymmetrical pyrazine formation,[2b] but no scaleable synthesis for such testing has been achieved. We felt that advancement to clinical trials would demand a practical route to the South 1-type unit for **1** or a closer mimic such as **3**. The first-generation synthesis of South 1 subunit **7** (36 operations from **4**) employed traditional Marker spiroketal degradation[3] (**4** to **5**) and standard Pb-mediated hypoiodite proximal functionalization of the C18 angular methyl (**5** to **6**)[2a−c] (Scheme 1). This approach is unattractive on the strategic level, requiring excision of the entire F-ring and subsequent reintroduction of the same atoms (**6** to **7**).

We disclose herein a remedy to this shortcoming by retaining all 27 carbon atoms of **4** in a new *dyotropic rearrangement* to permit proximal functionalization of C18 and trans-spiroketalization. The route is especially attractive since we improved transformation of **4** to β-hydroxyketone **8** from 27% (three operations) to a one-pot 94% yield.[2a] As seen in Scheme 1, Baeyer−Villiger oxidation of **8** (mCPBA, Na_2HPO_4 buffer, 11 d, 25 °C) slowly afforded a 92% yield of lactone **9**.[4] Treatment of **9** with catalytic TMSOTf in toluene followed by addition of pyridine and $SOCl_2$ delivered exomethylene spirolactone **10** in 93% yield. Interruption of the sequence after rearrangement provided an equilibrium mixture (1:2) of the separable hydroxy spirolactones **11a** and **11b** (98%), whose structural assignments were confirmed by X-ray.[5] Compound **11b** features a strong internal H-bond (13OH···22βO) that renders the normally less-stable 22β spiroketal the thermodynamic product. Elimination of either of these alcohols as above gave **10** as a single isomer, confirming spiroketal reequilibration as noted during synthesis of North G.[2a]

Spirolactones **11a**/**11b** apparently arise via *stereospecific dyotropic rearrangement*[6] *of* **9** (Scheme 2). Although there have been many important synthetic studies featuring expansion of β-lactones,[7] dyotropic contraction of seven-membered lactones to their more stable 6-ring counterparts has apparently not been previously explored.[8]

Smooth S_N2' opening of the spirolactone moiety with HCOOH provided an equilibrium mixture (95:5) of allylic formate **12** and starting **10** (Scheme 3). Freidel−Crafts reaction employing PPSE[9] (from P_2O_5/$(TMS)_2O$ in base-treated dichloroethane) gave formate **15** in fair yield along with **14** (presumably formed via **13**) and traces of **10** and **16a**. Hydrolysis of **15** with greater than stoichiometric $KHCO_3$ at room temperature led to desmethyl enone **18** via retro-aldol cleavage of formaldehyde. Even catalytic carbonate also quantitatively provided **18**. However, deprotection of **15** with catalyticbicarbonate at 25 °C afforded alcohol **17** with no trace of retro-aldol product **18** or hydrolysis of the C3 acetate.

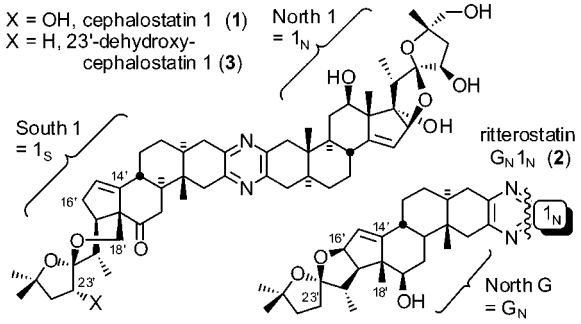
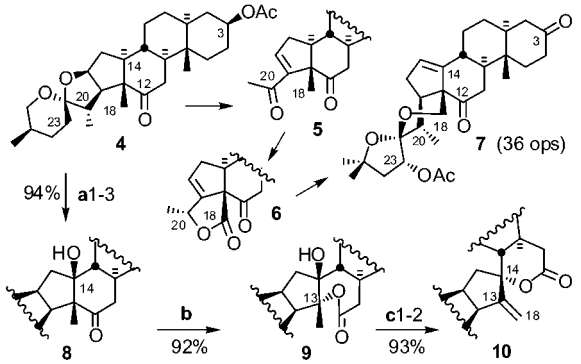


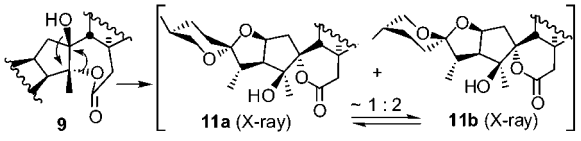
Figure 1.

Scheme 1 [a]



[a] **a**1. *hν*, CH_2Cl_2; **a**2. evap; add 3:1 HOAc/H_2O; **a**3. add H_2CrO_4; **b**. 2 equiv mCPBA, 4 equiv Na_2HPO_4, CH_2Cl_2, 11 d; **c**1. 2% TMSOTf, PhMe, 3 h; **c**2. add 5 equiv pyridine, 1.5 equiv $SOCl_2$, 50−55 °C, 50 min.

Scheme 2



Elimination of allylic O16 accompanied transketalization of **17** with strong Lewis or protic acid to give D-ring diene **21**[5] in high yield via internal ketal **19**; however, the action of warm aqueous acetic acid readily established a **17**/**19** equilibrium mixture (1:2.2) without further advancement to **21**. Conversion of **19** to tosylate **20** proceeded in excellent yield. By contrast, direct access to the 26-iodide from either **17** or **21** proved inferior using any variation of our $Ph_3P{\cdot}I_2$ method.

Tosylate **20** was eliminated via the iodide[10] to olefin **22** (Scheme 4), setting the stage for a remarkable TMSOTf-mediated rearrange-

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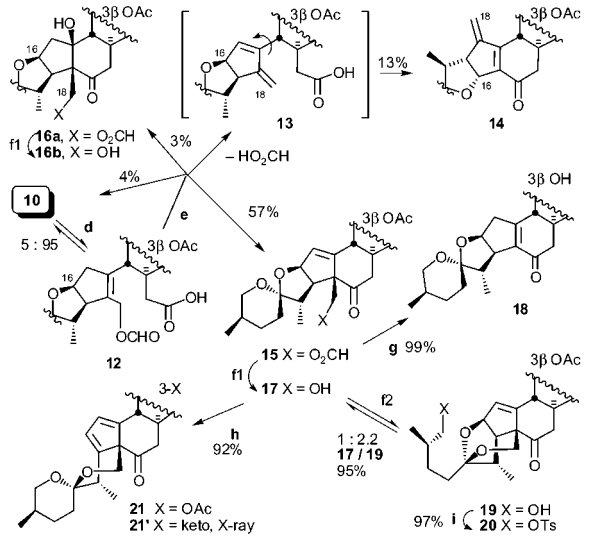
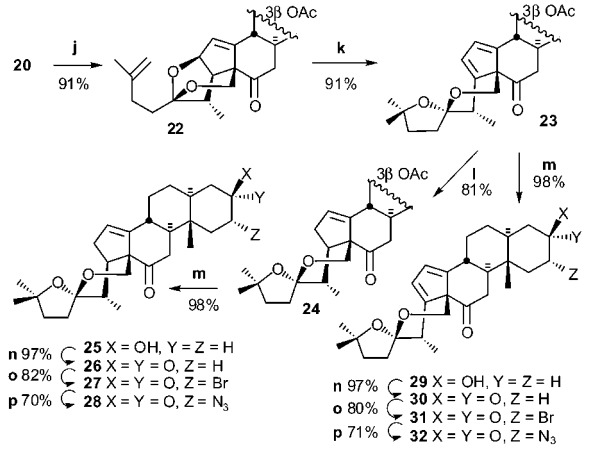
Scheme 3 [a]



[a] **d**. 0.5 M HCOOH, 25 °C, 10 h; **e**. 30 equiv P_2O_5, 45 equiv $(TMS)_2O$, DCE, 83 °C, 3.5 h; **f**1. 0.2 equiv $KHCO_3$, MeOH, 2 h; **f**2. 75% AcOH, 50−55 °C, 1 h, 2.2:1 **19**/**17**; **g**. 0.1 equiv K_2CO_3, MeOH, 25 °C, 10 h; **h**. 0.1 equiv TMSOTf, MC, 0 °C, 2 h; **i**. 3 equiv TsCl, 12 equiv pyr, MC, 0 °C, 16 h.

Scheme 4 [a]



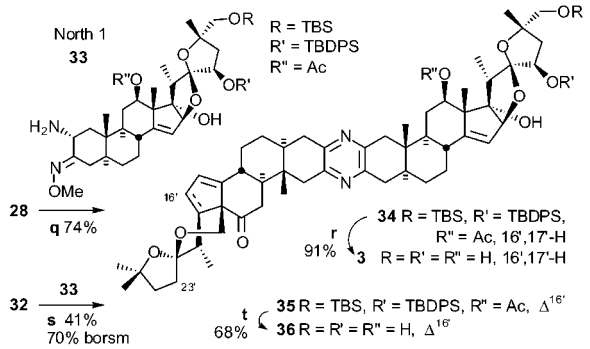
[a] **j**. 2.5 eq NaI, DMF, 50−58 °C, 10 h, then 1.5 equiv DBU, 80−85 °C, 3h; **k**. 0.1 equiv TMSOTf, MC, 0 °C, 2 h; **l**. H_2, 0.1 equiv Pd/C (5%), EtOAc, −5 → 10 °C, 7 h; **m**. 1.0 equiv K_2CO_3, MeOH, 8 h; **n**. Jones, 0 °C, 15 min; **o**. 1.0 equiv PTAB, THF, 0 °C, 0.5 h; **p**. 4 equiv TMGA, nitromethane (freshly distilled), 10 h.

ment to transketalized diene **23**, whose structure was verified by X-ray of a derivative (see Supporting Information).[5] Significantly, hydrogenation of diene **23** was rendered quite regio- and stereoselective after much experimentation, affording 17αH olefin **24** with modest overreduction. Heightened reactivity toward nucleophiles imparted by the D-ring cyclopentadiene moiety was noted, and we therefore chose to elaborate **23** in parallel to **24**.

Mild hydrolysis (25 °C) of acetate **24** followed by oxidation gave 3-keto **26** in near quantitative yield, and diene **23** similarly afforded 3-keto **30**. Our standard two-operation method[2] gave azidoketone coupling candidates **28** and **32** in good yield. Unions of **28** and **32** (Scheme 5) with protected North 1 partner **33**[2] using the Guo unsymmetrical pyrazine synthesis[2b] provided **34** (74% yield) and **35** (41% yield, 70% based on recovered **33**), respectively. Finally, deprotection of **34** and **35** completed the synthesis of **3** (91% yield) and **36** (68% yield).

In conclusion, this work provides a superior new method for oxidative functionalization (or removal) of the C18 methyl group

Scheme 5 [a]



[a] **q**. 0.7 equiv **33**, PVP, 10% Bu_2SnCl_2, PhH, 80 °C, 3 h; **r**. 3 equiv TBAF, THF, 65 °C, 2 h, then 5 equiv K_2CO_3, aq MeOH, reflux, 0.5 h; **s**. 1.0 equiv **33**, PVP, 10% Bu_2SnCl_2, PhH, 80 °C, 3 h; **t**. 10 equiv TBAF, THF, 25 °C, 3 h.

featuring a previously unknown dyotropic rearrangement of a seven-membered fused C-ring lactone to a 6-ring spiro lactone. Spiroketal equilibration studies led to the 23-deoxy South 1 subunit **26** in only 12 steps (23% overall yield) from hecogenin acetate **4**, and to strained diene South 1 analogue **30** in 11 steps (28% overall). Total synthesis of 23′-deoxy cephalostatin 1 (**3**) was accomplished in 16 operations from **4** (9% overall; average 86% yield per operation), and that of 16′,17′-dehydro-23′-deoxy cephalostatin 1 (**36**) in 15 operations from **4** (8% overall; av 84%/op). Biological evaluation of these materials is currently underway and will be reported elsewhere.

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Supporting Information Available: Representative experimental procedures, and ^1H, ^{13}C NMR of all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Cephalostatin Support Studies 22. For articles 20−21, see: Lee, S. M.; LaCour, T. G.; Lantrip, D. A.; Fuchs, P. L. *Org. Lett.* **2002**, *4*, 313−317.
(2) (a) LaCour, T. G.; Guo, C.; Bhandaru, S.; Boyd, M. R.; Fuchs, P. L. *J. Am. Chem. Soc.* **1998**, *120*, 692. (b) Guo, C.; Bhandaru, S.; Fuchs, P. L.; Boyd, M. R. *J. Am. Chem. Soc.* **1996**, *118*, 10672. (c) Bhandaru, S.; Fuchs, P. L. *Tetrahedron Lett.* **1995**, *36*, 8351. (d) Jeong, J. U.; Sutton, S.; Kim, S.; Fuchs, P. L. *J. Am. Chem. Soc.* **1995**, *117*, 10157. (e) Kim, S.; Sutton, S.; Guo, C.; LaCour, T. G.; Fuchs, P. L. *J. Am. Chem. Soc.* **1999**, *121*, 2056.
(3) For an excellent historical perspective on the chemistry of Russell Marker, see: *Chem. Eng. News* **1999**, October 25, 78.
(4) Oxidation of **4** (12 d) affords the expected 7-ring lactone (Rothman, E. S.; Wall, M. E. *J. Am. Chem. Soc.* **1955**, *77*, 2229−2233; Rothman, E. S.; Wall, M. E.; Eddy, C. R. *J. Am. Chem. Soc.* **1954**, *76*, 527−532). Oxidation of systems such as **8** have not previously appeared.
(5) X-ray data for compounds **11a, 11b,** 3-keto-**21′**, and a singlet oxygen adduct of **23** have been submitted to the Cambridge Crystallographic database.
(6) A *dyotropic* (from the Greek *dyo*, meaning two) rearrangement can be defined as a process in which two σ-bonds simultaneously migrate intramolecularly. For a review of the dyotropic rearrangement by Reetz, who coined the term, see: M. Reetz, *Tetrahedron* **1973**, *29*, 2189.
(7) (a) J.; Hoyer, K.; Müller-Fahrnow, A. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1476. (b) Black, T. H.; DuBay, W. J., III; Tully, P. S. *J. Org. Chem.* **1988**, *53*, 5922−5927.
(8) For apparent examples of 6- to 5-ring lactone dyotropic rearrangements, see: Evans, R. H., Jr.; Ellestad, G. A.; Kunstmann, M. P. *Tetrahedron Lett.* **1969**, 1791−1794 and Cambie, R. C.; McNally, H. M.; Robertson, J. D.; Rutledge, P. S.; Woodgate, P. D. *Aust. J. Chem.* **1984**, *37*, 409−416. For 5- to 6-ring lactone rearrangement: Marson, C. M.; Grabowska, U.; Walsgrove, T.; Eggleston, D. S.; Baures, P. W. *J. Org. Chem.* **1994**, *59*, 284.
(9) (a) Berman, E. M.; Showalter, H. D. H. *J. Org. Chem.* **1989**, *54*, 5642. (b) Imamoto, T.; Yokoyama, H.; Yokoyama, M. *Tetrahedron Lett.* **1981**, *22*, 1803.
(10) Wolff, S.; Huecas, M. E.; Agosta, W. C. *J. Org. Chem.* **1982**, *47*, 4358.

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