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Application of the Reich Iodoso syn-Elimination for the Preparation of an Intermediate Appropriate for the Synthesis of both Hexacyclic Steroidal Units of Cephalostatin 7.[1]

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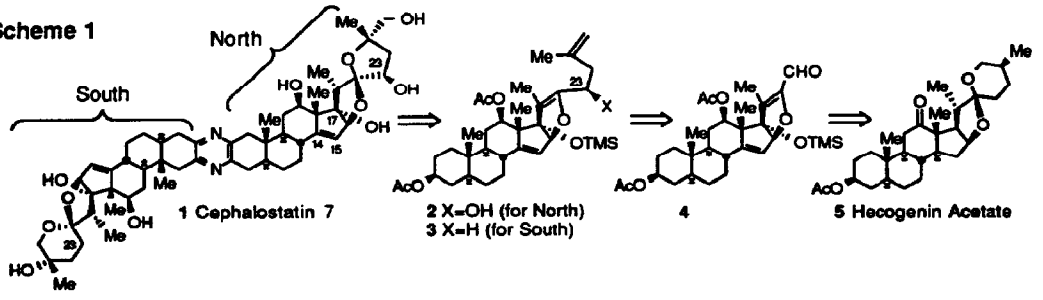
Abstract: Hecogenin acetate **5** was converted to an intermediate suitable for construction of both "North" and "South" hexacyclic spiroketals present in cephalostatin **7**. The key chemical transformations involved are: (1) the Reich iodoso syn-elimination of iodide **18**; (2) Rhodium [II] catalyzed intermolecular oxygen alkylation of secondary neopentyl alcohol **21**; and (3) Intramolecular Wadsworth-Emmons reaction to provide the ester precursor of aldehyde **4**.

Cephalostatin 7 **1** is a potent member of a family of eleven trisdecacyclic pyrazines characterized by Pettit.[2] These materials are also highly active (10^{-9}-10^{-10} M) in a substantial proportion of the 60 *in Vitro* screens of the NCI.[3] We have recently effected conversion of the "North" 55 ring spiroketal to the "South" 65 ring spiroketal in model systems.[4] Since Heathcock and Smith.[5] have provided a method for synthesis of unsymmetrical pyrazines from 3-ketosteroids construction of **1** from intermediates **2** and **3** can be envisaged. As the "North" spiroketal moiety is present in ten of the eleven currently known cephalostatins a logical approach to these targets was felt to involve aldehyde **4** as a common intermediate. The construction of **4** from commercially available (Austin Chemical) hecogenin acetate **5** constitutes the subject of this letter.

Scheme 1

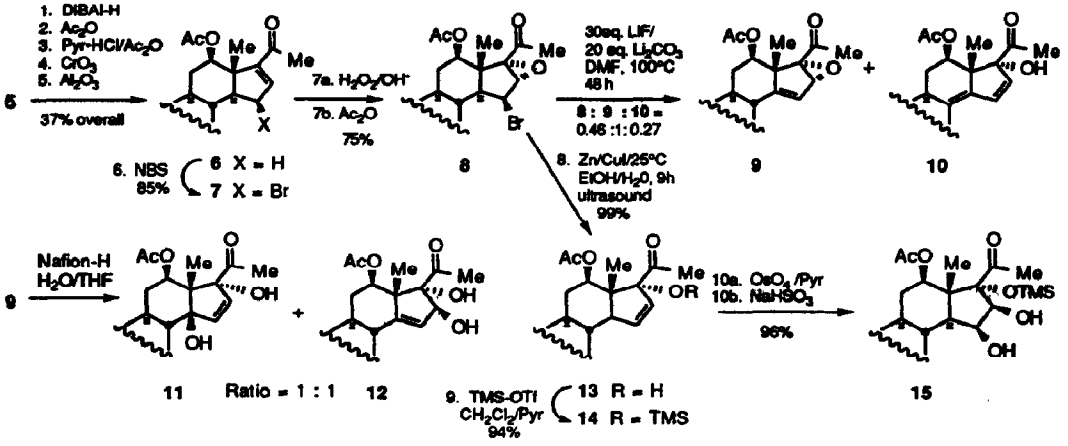


Conversion of hecogenin acetate **5** to enone **6** was easily accomplished using standard technologies.[6] Allylic bromination of **6** yielded **7** which was stereospecifically converted to epoxide **8**. Completion of the D-ring oxidation pattern proved extremely challenging. Elimination of bromoepoxide **8** to vinyl epoxide **9** was only marginally

successful, yielding a mixture of starting material **8**, desired product **9**, and dienylic alcohol **10** (via further consumption of **9**). This route was abandoned after finding that hydrolysis of vinyl epoxide **9** yielded a 1:1 mixture of 1,4-diol **11** along with diol **12**.

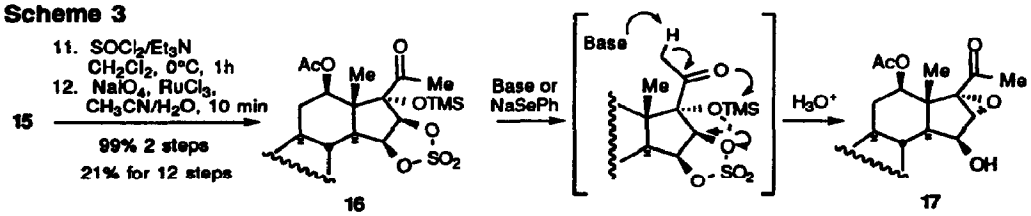
In contrast, reductive cleavage of bromoepoxide **8** using ultrasonicated Zinc/Copper couple[7] provided allylic alcohol **13** which was protected as TMS ether **14**. Osmylation of **14** stereospecifically generated diol **15** in near-quantitative yield (Scheme 2).

Scheme 2



Conversion of diol **15** to cyclic sulfate **16** occurred without incident via the Sharpless protocol.[8] Attempts to introduce the requisite olefin functionality using base-catalized elimination of sulfate **16** were completely unrewarding. The only product isolated from these reactions was epoxysulfate **17** which may have arisen via intramolecular oxygen silylation of the ketone enolate. No attempts were made to detect the putative silyl enol ether since an acidic workup was necessary to neutralize sulfate monoester. Compound **17** also resulted from the reaction of sodium phenyl selenide with sulfate **16** (Scheme 3).

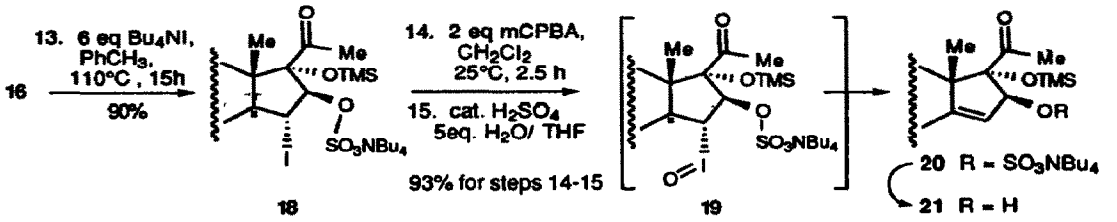
Scheme 3



In order to avoid the base lability problem, we elected to investigate the S_N2 chemistry of substrate **16** with iodide ion. Treatment of sulfate **16** with excess tetrabutylammonium

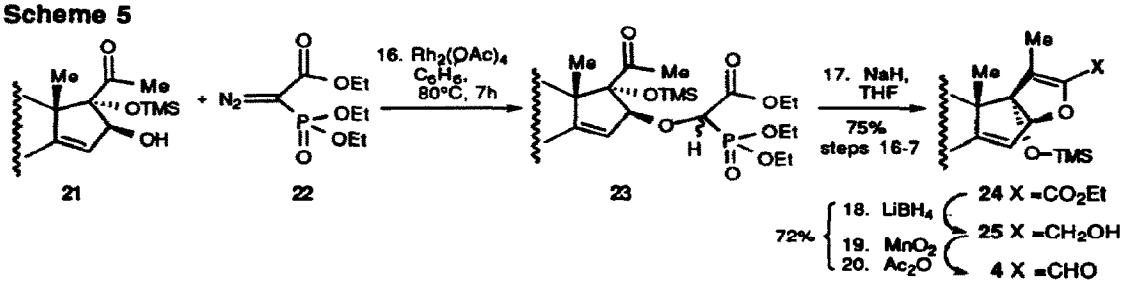
iodide in toluene at reflux affords iodo ammonium sulfate **18** in 90% yield. Oxidation of **18** with mCPBA in methylene chloride provides key alcohol **21** after protonolysis of ammonium sulfate **20**. Lability of the C-17 TMS ether is not observed. It should be noted that this reaction likely proceeds via syn-elimination of hypoiodous acid from iodoso intermediate **19**, a reaction originally developed by Reich[9] which is vastly under-exploited in complex synthesis[10] relative to the standard sulfoxide and selenoxide protocols (Scheme 4).

Scheme 4



Completion of the synthesis of target aldehyde **4** proceeded via the reaction of alcohol **21** with diazophosphonate **22** in the presence of dirhodium tetraacetate as prescribed by Moody[11] for oxygen alkylations. Although this substrate represents the most highly functionalized alcohol which has been transformed to an α-alkoxy phosphonate thus far, the reaction is highly satisfactory for synthesis of compound **23** as a diastereomeric mixture. Addition of sodium hydride to **23** effects rapid and quantitative conversion to dihydrofuran-ester **24**. Lithium borohydride reduction of **24** provides alcohol **25** which is re-oxidized to aldehyde **4**. A final acetylation step is employed on the crude aldehyde to reacetylate the C-3 alcohol which suffers partial cleavage during the initial borohydride step. The overall yield of **4** from hecogenin acetate 8% in twenty steps.[12] Further efforts directed at utilizing compounds **2-4** for the synthesis of cephalostatin 7 **1** will be described in due course.

Scheme 5



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[6]Ring opening of spiroketal **5** followed by oxidation of the intermediate dihydrofuran and elimination of the resultant β-keto ester provided desired enone **6** in 37% overall yield. (see: *Synthesis* **1990**, 591 and/or Dauben, W. G.; Fonken, G. J. *J. Am. Chem. Soc.* **1954**, *76*, 4618).

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[10]For a recent example of the synthetic potential of this strategy see: Knapp, S.; Naughton, A. B. J.; Dhar, T. G. M. *Tetrahedron Lett.* **1992**, *33*, 1025.

[11]For review, see: Cox, G. G.; Miller, D. J.; Moody, C. J.; Sie, E.-R. H. B. *Tetrahedron* **1994**, *50*, 3195. For applications in synthesis, see: Wood, H. B.; Buser, H. P.; Ganem, B. *J. Org. Chem.* **1992**, *57*, 178.

[12]The structure of this material was secured by X-ray analysis of a derivative.

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