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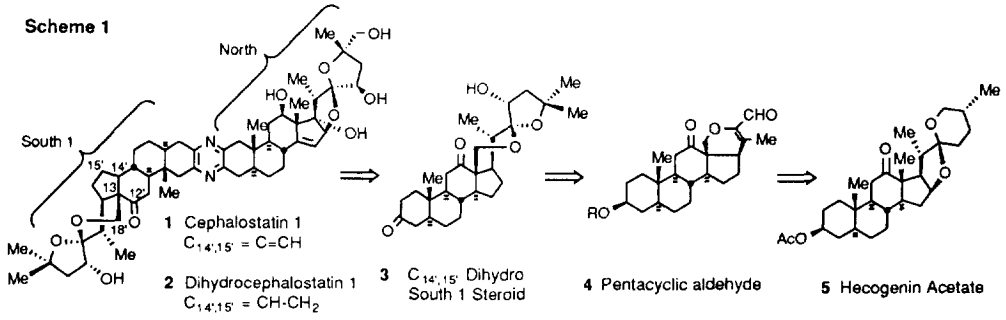
Synthesis of a $C_{14',15'}$ Dihydro Derivative of the South Hexacyclic Steroid Unit of Cephalostatin 1. Part I : Regiospecific Rh[II]-Mediated Intermolecular Oxygen Alkylation of a Primary Neopentyl Alcohol.[1]

Sudhakar Bhandaru and P. L. Fuchs*
Department of Chemistry, Purdue University
West Lafayette, Indiana 47907

Abstract: Hecogenin acetate **5** was converted to an intermediate suitable for the construction of a $C_{14',15'}$ dihydro derivative of the "South" hexacyclic spiroketal of cephalostatin 1 **1**. The key transformations include: (i) proximal functionalization of the C-18 methyl group in **17** via hypoiodite homolysis; (ii) Rhodium [II] catalyzed intermolecular oxygen alkylation of primary neopentyl hydroxyl group in **20** and (iii) intramolecular Wadsworth-Emmons reaction to provide **23**, the ester precursor of aldehyde **4**.

Cephalostatin 1 **1**[2] is the most potent member of a family of twenty eight trisdecacyclic pyrazines. This compound is active at sub-nanomolar concentrations in a substantial proportion of the 60 *in Vitro* anticancer screens of the NCI.[3] Recently we described the preparation of the North segment of cephalostatin 1 **1**.[1b] In conjunction with our synthetic program, we elected to initially prepare dihydrocephalostatin 1 **2**, the saturated "South" D-ring analog of **1**. The reasons for this were two-fold: To address the stereochemical issues of spiroketal synthesis and a desire to provide some insight into the anti-cancer mechanism of cephalostatins. This communication describes the transformation of hecogenin acetate **5** to pentacyclic aldehyde **4**, a precursor suitable for the construction of steroid **3** (Scheme 1).

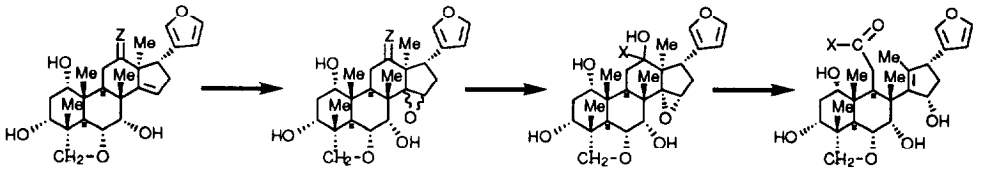
Scheme 1



The mechanism of antineoplastic activity of the cephalostatins is currently unknown. Cursory inspection of the structure of cephalostatin 1 **1** reveals no obvious functionality which might serve in the most common role of a DNA alkylating agent. While it may be possible that cephalostatins owe their potent biological activity to simply the fortuitous topological positioning of their collection of hydrogen-bond donors and acceptors, a more intriguing possibility is implied by considering a hypothetical biosynthesis of a series of

triterpenes of the azidirachta species. Trichilinin **6** and Nimbidinin **7** have the same C_{12} oxidation states as seen in the cephalostatin series.[4] Epoxidation of the C_{14} olefin could yield either **α-8,9** or **β-8,9**. Mechanistic considerations suggest that fragmentation of α-epoxides will occur,[5] while β-epoxides **β-8,9** should be inert. Nimbolidins-B,A (**12,13**) are compounds that could have arisen from such fragmentations,[6] while several "unreactive" C_{14} beta-epoxides related to **β-8,9** have also been isolated[6b,7] (Scheme 2).

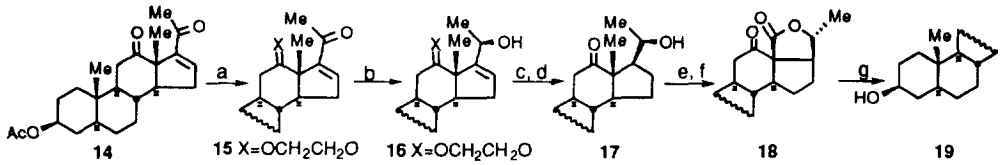
Scheme 2



Set in the context of the cephalostatin family, a related fragmentation might involve an electrophilic activation (protonation or β-epoxidation[8]) of the $C_{14'}$ olefin followed by a nucleophilic attack at the $C_{12'}$ ketone (c.f. **11**). Such a process generates up to five sites ($C_{12'}$, and the four carbons of the resulting ene-1,4-diol system: $C_{18'}$ and $C_{13',14',15'}$) for nucleophilic bond formation in compound **1** (Scheme 1). Since dihydrocephalostatin 1 **2** is incapable of forming an epoxide in the Southern hemisphere, it could potentially have diminished biological activity. It is noteworthy that Fusetani has postulated a somewhat related fragmentation to explain the biosynthesis of the recently identified cephalostatin, ritterazine A.[9]

Using a modified procedure of Dauben,[10] hecogenin acetate **5** was converted into enone **14** in 60% overall yield on an 80 gram scale. Efforts to convert **14** into saturated keto-alcohol **17** via reduction and/or hydrogenation were unsuccessful because of side reactions involving attack at the C_{12} carbonyl functionality. Therefore, **14** was converted to ketal **15** using standard protection procedures (89%).[11] Protected enone **15** was reduced stereospecifically to the allylic alcohol **16** with $NaBH_4$ in the presence of hydrated $CeCl_3$[12] in THF:MeOH (2:1) in 86% yield. Hydrogenation of **16** using platinum oxide in methylene chloride gave, after ketal deprotection, the saturated alcohol **17** in a two-step 77% yield. Proximal functionalization of the C_{18} methyl group in **17** was accomplished via the hypoiodite method of Meystre[13] which conveniently provided lactone **18** on a 7g scale after chromium trioxide oxidation. Hydrolysis of the C_3 acetate group of **18** gave alcohol **19** in 94% yield. Silylation of the hydroxyl group of **19** followed by LAH reduction of the lactone moiety gave triol **20** in 71% yield for the two steps (Scheme 3). The overall yield from hecogenin acetate **5** to triol **20** is 13%.

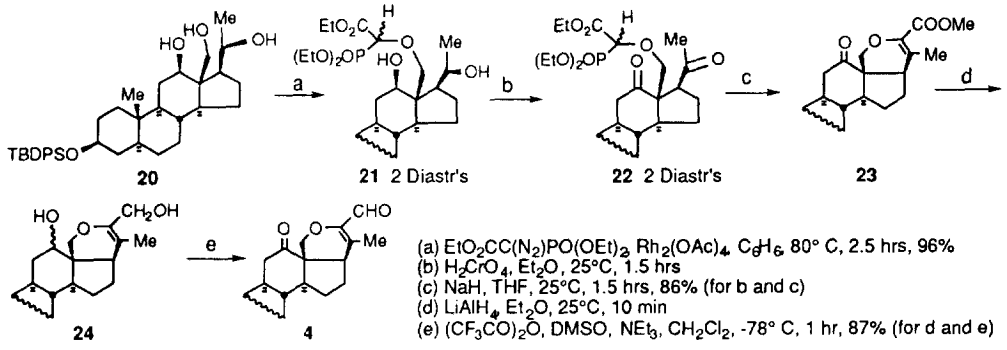
Scheme 3



(a) $HOCH_2CH_2OH$, PPTs, C_6H_6, 80°C, 4.5 hrs, 89%
(b) $NaBH_4$, $CeCl_3.7H_2O$, THF: MeOH (2: 1), 25°C, 10 min, 86%
(c) PtO_2 (5 mol%), H_2 (1 atm), CH_2Cl_2, 25°C, 45 min, 99%
(d) PPTs, Acetone - H_2O, 80°C, 6 hrs, 78%
(e) $Pb(OAc)_4$ (4.5 eq), I_2 (1.2 eq) , C_6H_{12}, 80°C, 2 hrs
(f) H_2CrO_4, Acetone, 0°C, 1 hr, 56% (for e and f)
(g) $KHCO_3$, MeOH - H_2O (9:1), 80 - 90°C, 4 hrs, 94%
(h) TBDPS-Cl, $AgNO_3$, DMF, 25°C, 10 min
(i) $LiAlH_4$, Et_2O, 40°C, 15 min, 71% (for h and i).

The use of diazophosphonates in the synthesis of cyclic ethers was extensively studied[14] by Moody et al. and has been effectively applied in our laboratories.[15] We therefore decided to construct the pyran ring in **3** using this protocol which required insertion of a diazophosphonate regioselectively into the primary neopentyl hydroxyl group of **20**. A review of literature revealed no examples of regioselective insertion reactions of diazophosphonates into polyhydroxylated substrates. Initial treatment of **20** in benzene with ethyldiazophosphonate using 3 mole% of $Rh_2(OAc)_4$ as a catalyst gave, among other products, ~60% of the desired ether **21** (Scheme 4). However, syringe-drive addition of ethyldiazophosphonate to a 0.01M solution of triol **20** in benzene, with 3 mole% of $Rh_2(OAc)_4$ regiospecifically provided a 1:1 diastereomeric mixture of neopentyl α-alkoxyphosphonoacetates **21** in a superb 96% yield.

Scheme 4



(a) $EtO_2CC(N_2)PO(OEt)_2$, $Rh_2(OAc)_4$, C_6H_6, 80° C, 2.5 hrs, 96%
(b) H_2CrO_4, Et_2O, 25°C, 1.5 hrs
(c) NaH, THF, 25°C, 1.5 hrs, 86% (for b and c)
(d) $LiAlH_4$, Et_2O, 25°C, 10 min
(e) $(CF_3CO)_2O$, DMSO, NEt_3, CH_2Cl_2, -78° C, 1 hr, 87% (for d and e)

This is the first example of a rhodium-carbenoid mediated O-H insertion reaction into a primary neopentyl alcohol system. Bis-oxidation using the Brown-Jones procedure[16] provided **22** as another 1:1 mixture of phosphonate esters. Treatment of the diastereomeric mixture of **22** with sodium hydride in THF effected the intramolecular Wadsworth-Emmons

reaction exclusively affording the dihydropyran ester **23** in 86% yield for the two step procedure. Selective reduction of the ester functionality in **23** to aldehyde using DIBAL proved unsuccessful because of attack at the C-12 keto group. Therefore **23** was reduced by LAH to diol mixture **24** which was then directly subjected to Swern oxidation[17] generating the key pentacyclic keto-aldehyde **4** in a two-step 87% yield (Scheme 4).

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[8] Cephalostatin 4 bears a beta-epoxide which has the appropriate stereochemistry to possibly undergo such a fragmentation (See Pettit. G. R.; Inoue, M.; Kamano, Y.; Dufrensne, C.; Christie, N.; Niven, M.L.; Herald, D. L. *J. Chem. Soc. Chem. Commun.* **1988**, 865.)

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[11] Reaction of **14** with ethylene glycol and PPTs in benzene at 80°C for 4.5 hrs produced a thermodynamic mixture of two ketals (70% of C-12 monoketal and 27% of the C-12, C-20 bisketal). After column separation, overnight stirring (at room temperature) of the bisketal in benzene along with magnesium sulfate and a catalytic amount of water re-established another 2.6:1 ratio of mono to bisketals, for a total yield of 89% of the mono C-12 ketal.

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