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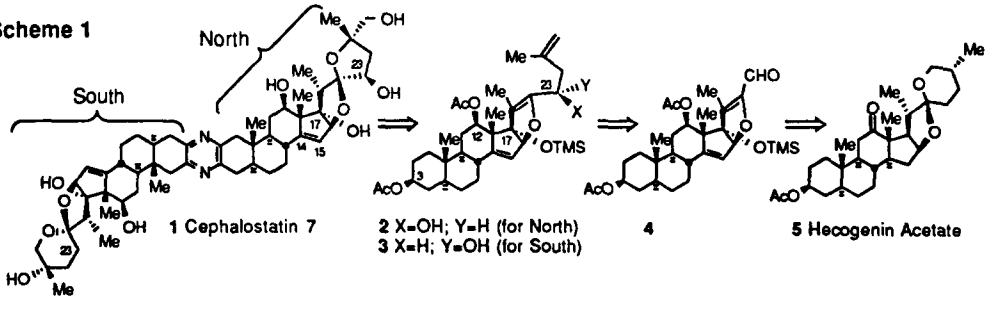
Chromium [II]-Mediated Reductive Cleavage of a Tertiary Halide Bearing Three β-alkoxy Groups. Synthesis of the North Hexacyclic Steroid Unit of the Cephalostatin Family.[1]

Seongkon Kim, Scott C. Sutton, and P. L. Fuchs*
Department of Chemistry, Purdue University
West Lafayette, Indiana 47907

Abstract:. Transformation of aldehyde **4** to **17nat**, a hexacyclic steroid bearing the requisite functionality and spiroketal stereochemistry of the North portion of the cephalostatin family is described. The key reaction involves $CrCl_2$ mediated reductive cleavage of a tertiary bromide which is beta to three alkoxy groups.

Cephalostatin 7 (**1**)[2] is a potent member of a family of sixteen trisdecacyclic pyrazines, principally characterized by the Pettit group at Arizona State. Many of these materials are highly active (10^{-9}-10^{-10} M) in a substantial proportion of the 60 *in Vitro* cancer screens of the NCI.[3] We have recently provided a multi-gram synthesis of aldehyde **4** from hecogenin acetate **5**.[1] Additionally, we have effected conversion of the "North" 5/5 ring spiroketal to the "South" 6/5 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 15 of the 16 cephalostatins, a logical approach to these targets involves aldehyde **4** as a common intermediate.

Scheme 1



Various procedures for addition of methallylstannane to aldehyde **4** are summarized in Table 1. The more polar major adduct **2** was hydrolyzed to the C3,12,17,23 tetraol **6** (not shown) and the C23 stereochemistry was secured by X-ray crystallography.[6] The best methallyl stannane reaction involved using 5.0 M $LiClO_4$ which provided a 1.3:1 mixture of **2** and **3** in near-quantitative yield. Since the unnatural epimer **3** serves as progenitor of the

South portion of Cephalostatin 7 via deoxygenation, the readily separable mixture of alcohols **2** and **3** is perfectly acceptable at this juncture.

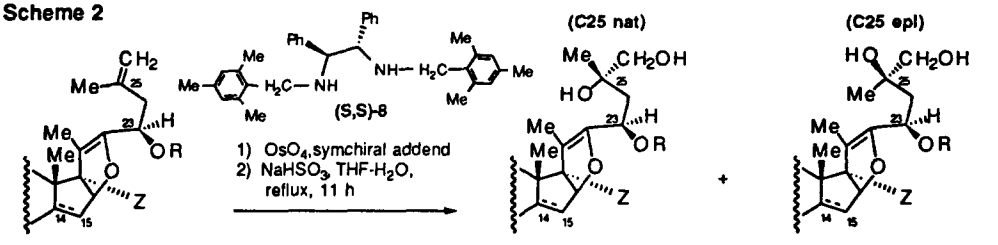
Table 1

Entry	Reagents	Conditions	Yield (ratio 2:3)
1	Methallyl Stannane	$BF_3{\cdot}Et_2O$[a], CH_2Cl_2, -78°C, 1h	80% (1.6:1.0)[a]
2	Methallyl Stannane	5.0 M $LiClO_4$,[7] Ether, 25°C, 1h	>95% (1.3:1.0)
3	(-)-IPc_2B-Methallyl[8]	THF, -78°, 1h	69% (1.7:1.0)[b]
4	Methallyl Stannane	(-)-Binapthol, $Ti(O\text{-}iPr)_4$, MS, CH_2Cl_2	No reaction[9,c]
5	Methallyl Stannane	(+)-Binapthol, $Ti(O\text{-}iPr)_4$, MS, CH_2Cl_2	No reaction[c]

(a) For large scale reactions the yields dropped below 50% due to the acid lability of the starting material; (b) The C3-acetate was also cleaved during the work-up; (c) Even at higher temperatures (25°C), no reaction was observed after 2 days.

Since an osmylation model study[4a] (Table 2, entry 1) with C17 deoxy, C14,15 dihydro olefin **7** required the use of symchiral Corey addend **8**[10] to provide reasonable diastereoselection, we first examined reaction of alcohol **2** using these conditions. While neither this reaction nor the Sharpless AD procedure[11] is acceptable for alcohol **2** (Table 2, entries 2-4), use of ligand **8** provides a usable 4:1 ratio of inseparable diols **12S/12R** when the reaction is conducted on t-butyldiphenylsilyl ether **11**.

Scheme 2



7 Z=H; R=TBDPS, 14,15 dihydro
2 Z=OTMS; R=H, Δ^{14}
11 Z=OTMS; R=TBDPS, Δ^{14}

9S Z=H; R=TBDPS, 14,15 dihydro
10S Z=OTMS; R=H, Δ^{14}
12S Z=OTMS; R=TBDPS, Δ^{14}

9R Z=H; R=TBDPS, 14,15 dihydro
10R Z=OTMS; R=H, Δ^{14}
12R Z=OTMS; R=TBDPS, Δ^{14}

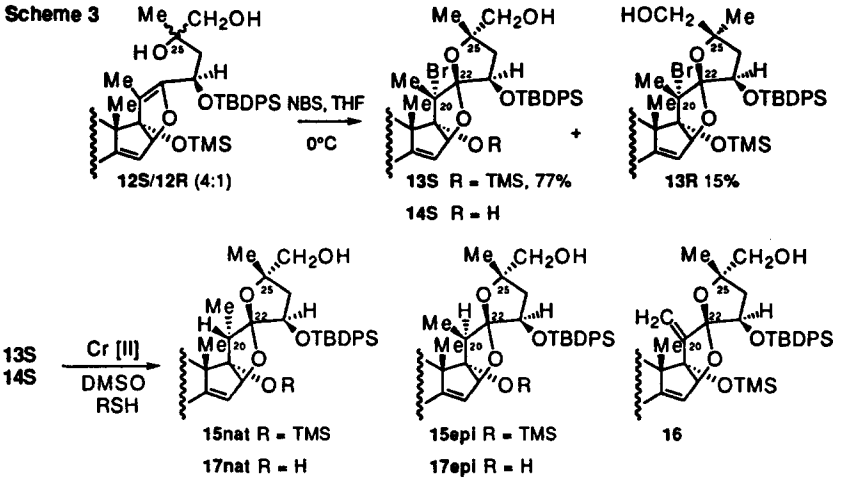
Table 2

Substrate	Conditions	Yield (%)	Ratio	C25 nat/epi
7	(S,S)-**8**, -100°C, 0.5h	98%	**9S/9R**	8:1
2	(S,S)-**8**, -95°C, 1h	95%	**10S/10R**	2:1
2	Sharpless AD-mix-α, 25°C, 24h	~25% conv.	**10S/10R**	2:1
2	Sharpless AD-mix-β, 25°C, 24h	~25% conv.	**10S/10R**	1:4
11	Sharpless AD-mix-α, 25°C, 24h	~30% conv.	**12S/12R**	1:2
11	(S,S)-**8**, -95°C, 1h	95%	**12S/12R**	4:1

PPTs-catalyzed spiroketal formation was investigated using the inseparable mixtures of diols **10S/10R** and **12S/12R**. Conditions which served to successfully cyclize **9S**[4] served to only return starting material, while forcing conditions generated a plethora of

undesired products, possibly via intervention of Ferrier-type processes.[12] While reaction of diols **12S/12R** with a variety of acids was totally unrewarding, NBS-mediated spirocyclization[4] afforded the C20 brominated 5/5 spiroketal **13S** (77%) along with diastereomer **13R** (15%) which resulted from cyclization of the minor diol **12R**. The structure of **13S** was confirmed by X-ray after hydrolysis of the C3 acetate (Scheme 3).

Scheme 3



Debromination of **13S** to **15** was initially attempted using the Ph_3SnH protocol employed in the C17 deoxy, C14,15 dihydro model series.[4] Unfortunately, only complex mixtures were isolated without any sign of the desired product. Presumably, the presence of the bulky TMS ether group at C17 hinders the quench of the radical formed as well as providing an additional site for radical fragmentation.[13] Inspired by the classic Chromium[II]-mediated halohydrin reductions described by Barton,[14] bromide **13S** was treated with excess $Cr(OAc)_2$ in the presence of a thiol (Table 3, entry 1). While the reaction was unacceptably slow, reduction product **15epi** was isolated in 30% yield in addition to recovered starting material (ca. 60%). The reactivity of $Cr(OAc)_2$ was greatly improved by adding ethylenediamine;[15] however the product was olefin **16** (entry 2). Attempts involving $CrCl_2$ were initially disappointing as no reaction occurred (entry 3). Finally, it was noted that reduction proceeded smoothly (80%) provided that a large excess of thiol was employed (entry 4). These observations indicated that the thiol might act not only as a hydrogen atom donor but also as a ligand, thereby enhancing the reducing power of chromium[II]. The ^1H NMR spectra of the products revealed a 7:1 ratio of **15epi** and **15nat** respectively. The stereochemistry of **15epi** was proven by X-ray after desilylation.[6] Repeating the reaction

using the more sterically-demanding hydrogen atom donors was not satisfactory (entries 5,6). The solution to obtaining the correct C20 stereochemistry was found to involve conducting the debromination on C17 alcohol **14S** (94% from **13S** via H_2SiF_6[16] cleavage); which provided a 3.6:1 ratio of **17nat** and **17epi** in 87% overall yield (entry 7).

Table 3

Entry	Reagents and H donor[a]	Temp	Time	Results
1	**13S** + 20 eq. $Cr(OAc)_2$; 80 eq. n-PrSH	50°C	48h	**15epi** (ca. 30%)
2	**13S** + 4 eq. $Cr(OAc)_2$; 40 eq. ED[b]	25°C	5 min.	**16** (99%)
3	**13S** + 4 eq. $CrCl_2$;10 eq. n-PrSH	25°C	24h	No reaction
4	**13S** + 4 eq. $CrCl_2$; 80 eq. n-PrSH	25°C	5h	**15epi** (70%) + **15nat** (10%)
5	**13S** + 4 eq. $CrCl_2$; 10 eq. Ph_3SnH	25°C	30 min.	**15epi** (20%) + **15nat** (10%)
6	**13S** + 5 eq. $CrCl_2$; 100 eq. t-BuSH	25°C	6h	**16** (50%) + **15epi** (5%)
7	**14S** + 5 eq. $CrCl_2$; 100 eq. n-PrSH	25°C	30 min.	**17epi** (19%) + **17nat** (68%)

(a) DMSO was degassed by Ar which was pretreated with basic pyrogallol solution; (b) ED = ethylenediamine.

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