SYNTHETIC APPROACHES TO 11-HYDROXY-CEPHALOTAXINE †

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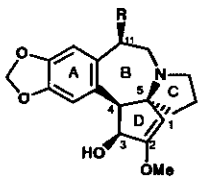
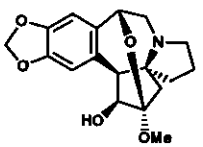
Abstract—Several approaches to functionalize the cephalotaxine skeleton based on the Pummerer reaction and Moriarty oxidation are described.

The genus *Cephalotaxus* produces, in addition to the major alkaloid cephalotaxine (**1**), several minor alkaloids having an oxygen function at the C-11 such as 11-hydroxycephalotaxine (**2**), drupacine (**3**), and demethylneodrupacine (**4**).[1,2] Recently we have succeeded in a total synthesis of (±)-**1**.[3] Our attention was then focused on the synthesis of **2**-**4** by utilizing the key intermediate (**5**).[3] To this end, we envisioned employing the Pummerer reaction for the introduction of the oxygen function at the C-11 and the Moriarty oxidation for the functionalization of the D-ring. Although we have not achieved the goal yet, we describe some results obtained so far during this study.



1, R=H; **2**, R=OH



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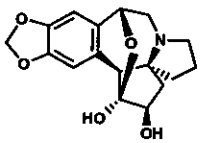

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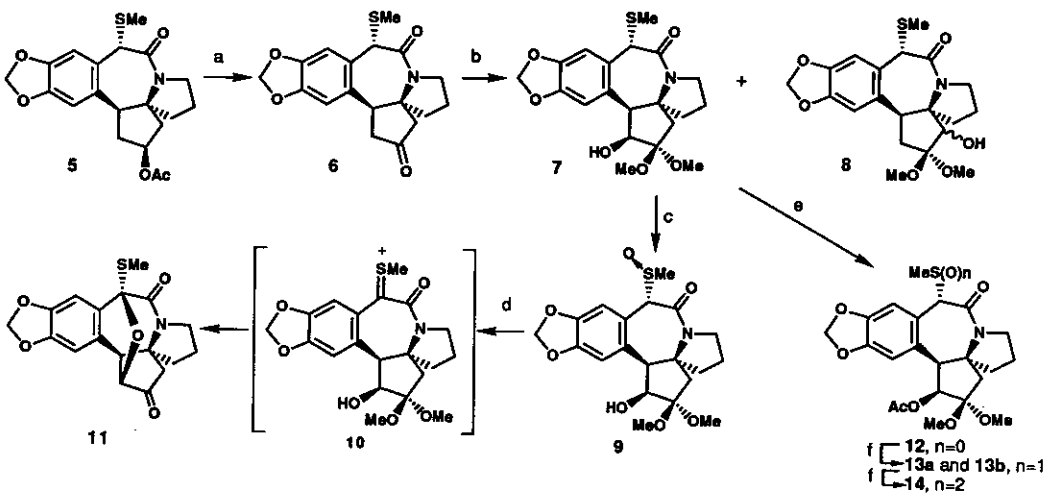
In order to make use of the Moriarty oxidation, **5** was converted into the cyclopentanone (**6**), mp 245-248°C (decomp.), by alkaline hydrolysis followed by pyridinium chlorochromate (PCC) oxidation of the resulting alcohol in 71% yield. Treatment of **6** with iodobenzene diacetate[4] gave the hydroxyacetal (**7**), mp 228-230°C (decomp.), and its regioisomer (**8**), mp 216-218°C (decomp.), in 84 and 6% yields, respectively. The two hydroxyacetals were readily differentiated by the ^{1}H-nmr spectroscopy: the major isomer (**7**) exhibited two

† This paper is dedicated to Professor Edward C. Taylor on the occasion of his seventieth birthday.

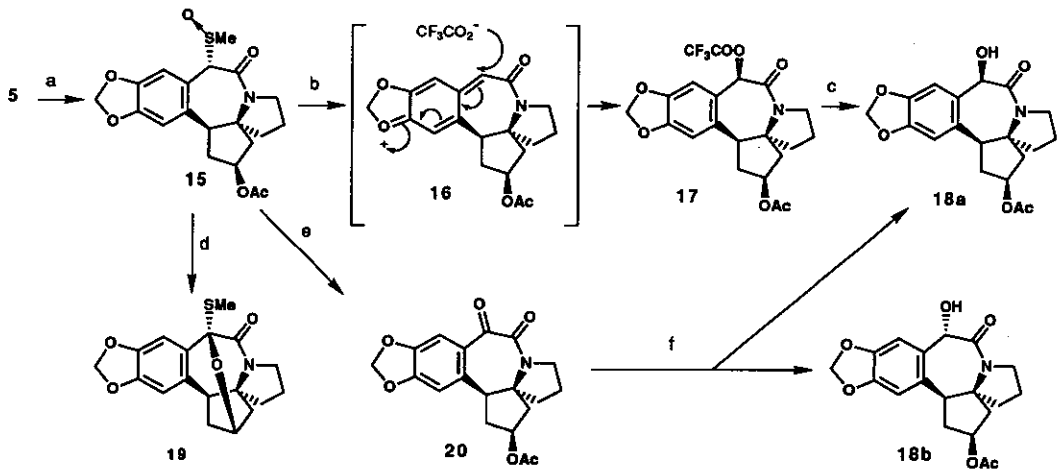
doublets at δ 4.17 (H-3) and δ 3.44 (H-4) with J=5.9 Hz, while the minor one (**8**) showed a singlet at δ 3.70 (H-1).

Since the functionalization of the D-ring was achieved, we next attempted the conversion of the methylthio group of **7** into an oxygen function. Thus, the Pummerer reaction of the sulfoxide (**9**) derived from **7** with trifluoroacetic anhydride (TFAA) in dichloromethane gave the thioacetal (**11**), mp 272-274°C (decomp.), in 82% yield. The ir spectrum (KBr) showed two carbonyl absorption bands at 1760 cm^{-1} (a five-membered ketone) and 1630 cm^{-1} (a lactam) with no hydroxyl absorption band. In the ^{1}H-nmr spectrum of **11**, a singlet at δ 6.06 (H-11) observed in that of **7** disappeared. This compound appears to arise *via* the Pummerer intermediate (**10**) which is trapped by the internal 3β-hydroxyl group. Therefore, the hydroxyl group was protected by an acetyl group. Acetylation of **7** followed by oxidation of the resulting acetoxy derivative (**12**) with *m*-chloroperbenzoic acid (MCPBA) gave two diastereomeric sulfoxides, which could be separated by silica gel chromatography to the polar sulfoxide (**13a**) (83%), mp 191-193°C, and the less polar sulfoxide (**13b**) (1.5%), mp 119-122°C, along with a small amount of the sulfone (**14**).[5] Surprisingly, treatment of the major sulfoxide (**13a**) with TFAA in dichloromethane at room temperature resulted in only epimerization on the sulfur atom to give the isomeric sulfoxide (**13b**). On the other hand, the sulfoxide (**13b**) was stable and recovered unchanged under the same conditions and even after refluxing in benzene in the presence of TFAA. Although the exact mechanism for the epimerization is not clear, the bulky 3β-acetoxy group may be responsible for the failure of the normal Pummerer reaction. At this stage we abandoned this approach.



Scheme 1. *Reagents and conditions*: (a) 1) K_2CO_3, MeOH; 2) PCC; (b) $PhI(OAc)_2$, KOH, MeOH; (c) $NaIO_4$, MeOH-H_2O; (d) $(CF_3CO)_2O$, CH_2Cl_2; (e) Ac_2O, DMAP, pyridine; (f) MCPBA, CH_2Cl_2

We then examined the Pummerer reaction of the sulfoxide (**15**), which was prepared by oxidation of the sulfide (**5**) with MCPBA as an inseparable diastereomeric mixture. Treatment of **15** with TFAA in dichloromethane at 0°C followed by silica gel chromatography of the resulting trifluoroacetate (**17**) [ir 1780 cm^{-1}] furnished the 11β-alcohol (**18a**), mp 197-199°C,[6] in 83% yield, along with the ketone(**20**)(12%), mp 208-210°C. Refluxing **15** in 1,2-dichloroethane containing 2.5 equiv. of *p*-toluenesulfonic acid (TsOH) monohydrate afforded only the thioacetal (**19**) (93%), mp 251-253°C, while use of anhydrous TsOH gave the ketone (**20**) (58%). Sodium borohydride reduction of the ketone (**20**) in ethanol at -20°C gave the 11α-alcohol (**18b**) (72%), mp 287-289°C (decomp.),[6] and **18a** (27%). The unusual formation of the alcohol (**18a**) from **15** can be rationalized by assuming the intermediate **16** which arises by elimination of sulfenic acid from **15**. Attack of trifluoroacetate ion on **16** from the β-side gives the trifluoroacetate (**17**) which undergoes hydrolysis during silica gel chromatography leading to **18a**. The preferential β-attack of the nucleophiles seems to be general in this system.[2] Alternatively, it may be formed by direct SN2 type attack of trifluoroacetate ion on a sulfonium salt derived from **15**.

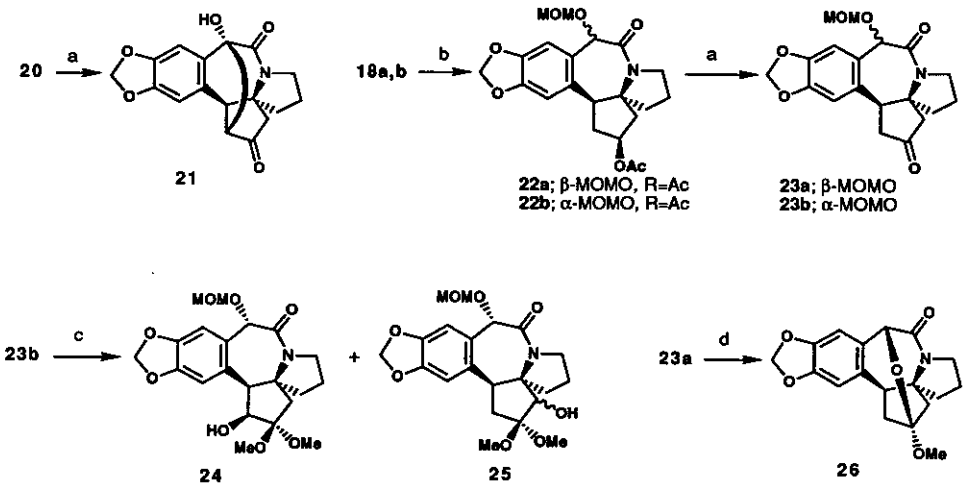


Scheme 2. *Reagents and conditions*: (a) MCPBA, CH_2Cl_2; (b) $(CF_3CO)_2O$, CH_2Cl_2; (c) silica gel; (d) TsOH H_2O, $(CH_2Cl)_2$, reflux; (e) TsOH, $(CH_2Cl)_2$, reflux; (f) $NaBH_4$, EtOH at -20°C

Since we succeeded in the introduction of the oxygen function at the C-11, we proceeded to study the functionalization of the D-ring. An initial attempt to obtain the 2,11-diketo lactam was unsuccessful: alkaline hydrolysis of **20** followed by the Swern oxidation of the resulting alcohol gave only the intramolecular aldol product (**21**), mp 233-236°C, in 69% yield. However, repetition of the same sequence of the reactions on **22a,b** produced the corresponding cyclopentanones (**23a**), mp 176-179°C, and (**23b**), mp 136-138°C, in 86

and 73% overall yields, respectively. Unfortunately, all attempts to oxidize the stereochemically correct ketone (**23a**) with iodobenzene diacetate were disappointing; only a complex mixture was obtained, although the oxidation of the isomeric ketone (**23b**) readily afforded the hydroxyacetal (**24**) (54%), mp 181-183°C, and its regioisomer (**25**).(18%), mp 174-177°C.

The reactions described herein would offer novel means for the synthesis of the cephalotaxine analogues.



Scheme 3. *Reagents and conditions*: (a) 1) K_2CO_3, MeOH; 2) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; (b) $CH_2(OMe)_2$, P_2O_5, $CHCl_3$; (c) $PhI(OAc)_2$, KOH, MeOH; (d) 1) $Ph_3C^+ BF_4^-$, CH_2Cl_2; 2) TsOH, $CH(OMe)_3$, MeOH

REFERENCES AND NOTES

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2. The first total synthesis of (±)-**2** has recently been reported ; T. P. Burkholder and P. L. Fuchs, *J. Am. Chem. Soc.*, 1990, **112**, 9601.
3. H. Ishibashi, M. Okano, H. Tamaki, K. Maruyama, T. Yakura, and M. Ikeda, *J. Chem. Soc., Chem. Commun.*, **1990**, 1436; M. Ikeda, M. Okano, K. Kosaka, M. Kido, and H. Ishibashi, *Chem. Pharm. Bull.*, 1993, **41**, 276.
4. R. M. Moriarty, H. Hu, and S. C. Gupta, *Tetrahedron Lett.*, 1981, **22**, 1283.
5. Oxidation of the sulfoxides (**13a,b**) with MCPBA gave the same sulfone (**14**), mp 235-238°C (decomp.).
6. Stereochemistry of the alcohols (**18a,b**) was assigned by conversion of **18a** into the acetal (**26**), mp 226-228°C, *via* **23a**.

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