Total Synthesis of *dl*-Cephalotaxine. The First Example of an Intramolecular 4 + 2 Cycloaddition Where the Dienophile Has Been Delivered from the Face Opposite to the Tethering Moiety[1]

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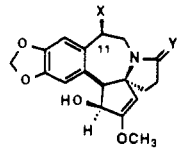
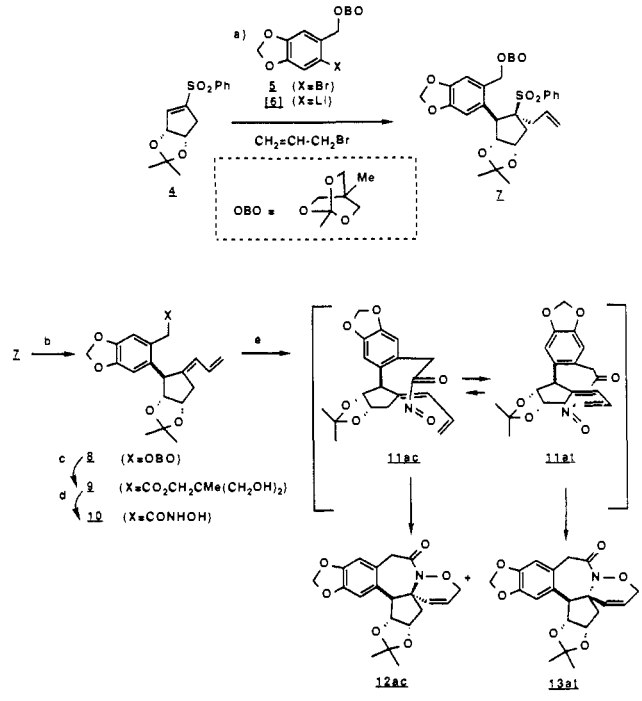
The *Cephalotaxus* alkaloid cephalotaxine (**1**) is the parent structure of a group of C-3 α-hydroxy succinate esters designated harringtonines which have recently been evaluated in phase II clinical trials as antileukemia agents.[2] While **1** has been synthesized several times,[3] the related alkaloids, 11-hydroxy cephalotaxine (**2**)[4a] and 8-oxocephalotaxine (**3**),[4b] have yet to be prepared.



1 (X=H, Y=H_2)
2 (X=OH, Y=H_2)
3 (X=H, Y=O)

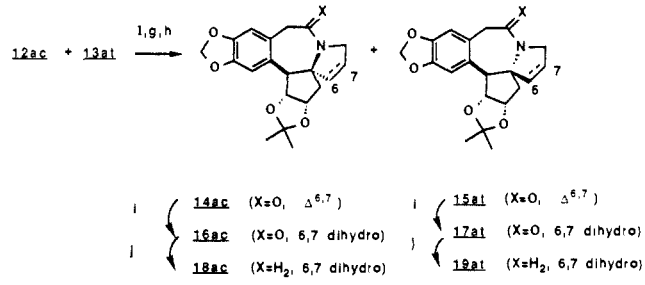
Our interest in this family of targets arose from the possibility of utilizing triply convergent vinyl sulfone methodology[5] for the introduction of the requisite carbon assemblage. Treatment of vinyl sulfone **4**[6] with aryllithium reagent **6** (derived from aryl bromide **5**[7] by transmetallation with *t*-BuLi) produces an α-sulfonyl anion which is further functionalized by cannula addition to a −78 °C solution of allyl bromide in HMPA to afford adduct **7** in 84% yield (11.5 mmol scale).[8] Self-immolative elimination[9] of homoallyl sulfone **7** with *t*-BuLi at −78 °C produces a 17:1 mixture of exocyclic dienes **8** (77%) favoring the stereochemistry shown, Hydrolysis of OBO ester[10] **8** provides ester **9** (99%) which

Scheme I[a]



[a](a) **5**, *t*-BuLi (2.2 equiv), THF, −78 °C; and **4**, THF, −78 °C; THF: HMPA (1:1); (b) *t*-BuLi, THF, −78 °C → room temperature; (c) *p*-TsOH (0.2 equiv), THF, H_2O, 0 °C; (d) NH_2OH, MeOH, 0 °C; (e) *n*-Bu_4NIO_4, CH_2Cl_2, −78 °C → room temperature.

Scheme II[a]



[a](f) 6% Na(Hg), EtOH, room temperature; (g) MsCl, Et_3N, CH_2Cl_2, 0 °C; (h) NaH, THF, room temperature; (i) H_2, 10% Pd/C, EtOH; (j) BH_3–THF, THF, reflux; MeOH, reflux.

is converted to hydroxamic acid **10** and then subjected to oxidation with tetrabutylammonium periodate as a dilute solution to generate acylnitroso intermediate **11**.[11]

The fate of intermediate **11** is especially informative. While any 4 + 2 process requires the exocyclic diene to adopt an unfavorable s-cis conformation, the intramolecularity of the trapping process is able to overcome this limitation.[12] Products resulting from intramolecular ene reactions[13] were not observed. The product from this reaction (71% from ester **9**) is an inseparable mixture of two isomeric components which are tentatively assigned to be tetracyclic lactams **12ac** and **13at**. When this mixture is subjected to 6% Na(Hg) in ethanol,[14] the two diastereomeric allylic

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(5) For a review of this strategy, see: Fuchs, P. L.; Braish, T. F. *Chem. Rev.* **1986**, *86*, 903. An earlier triply convergent approach was foiled due to the failure of a key amino spirocyclization reaction (Conrad, P. C.; Kwiatkowski, P. L.; Fuchs, P. L. *J. Org. Chem.* **1987**, *52*, 586.)

(6) Radisson, X.; Nantz, M. H.; Fuchs, P. L. *Synth. Commun.* **1987**, *17*, 592.

(7) OBO ester **5** is prepared from piperonyl alcohol in 42% overall yield as described in the Supplementary Material.

(8) The triply convergent process was investigated with a number of other aryllithium reagents in the course of this research; these results will be subsequently reported in a full paper.

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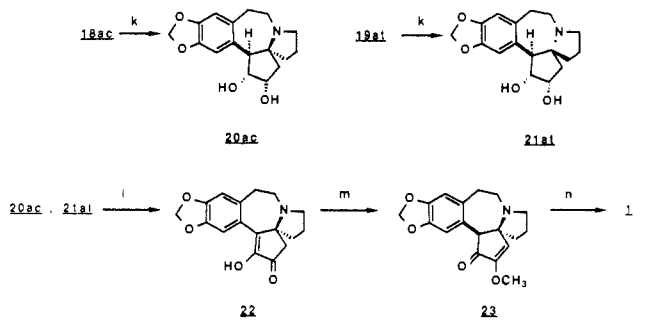
Scheme III[a]



[a](k) 1 N HCl:THF (1:1), room temperature; (l) DMSO, TFAA, Et_3N, CH_2Cl_2, -78 °C; (m) dimethoxypropane, dioxane, *p*-TsOH, reflux; (n) $NaBH_4$, MeOH, -78 °C → room temperature.

alcohols can be separated.[15] It is more expedient to simply carry the mixture through the three steps of NO bond cleavage, mesylation, and intramolecular nitrogen alkylation of the resultant lactam-mesylate. This procedure affords 46% of **14ac** and 23% of **15at** which are easily separable by plug filtration on silica. The major product from this sequence is assigned the expected anti-cis stereochemistry **14ac**,[15] The minor product was proposed to be the anti-trans adduct **15at**.[15] The formation of **13at** is *formally* the result of an intramolecular Diels-Alder reaction which requires the acyl nitroso moiety to approach the diene moiety from the opposite face of the tethering arene group. Although several examples of unusual regiochemical arrangements have been observed in the macrocyclic version of the IDA reaction[16] and other examples of simultaneous formation of fused 7/6 ring systems are known,[17] this observation is unprecedented in the intramolecular Diels-Alder literature.[18,19] This finding would seem to necessitate critical evaluation of the implicit assumption of "syn-tether specificity" in all intramolecular reactions where a ring size of seven or greater is being formed.

Both adduct **14ac** and **15at** have been converted to *dl*-cephalotaxine (**1**). Hydrogenation of the $C_{6,7}$ double bond followed by lactam reduction with BH_3-THF[20] provided the saturated pentacyclic amines **18ac** (81%) and **19at** (87%), respectively. At this stage it was possible to verify by X-ray crystallography[21,22] that **19** (and by implication **13**, **15**, and **17**) bore the assigned anti-trans stereochemistry (see Supplementary Material).

Culmination of the synthesis involved individual deprotection of the acetonide moieties of **18ac** and **19at** and to afford amino diols **20ac** (91%) and **21at** (99%), respectively. Swern oxidation[23] of both of these diols afforded demethylcephalotaxinone **22** (75-88%)[24,25] which was converted to cephalotaxinone **23** (70-84%) followed by borohydride reduction to afford *dl*-cephalotaxine (**1**) (97%).[25,26] The overall yield of **1** from **4** is 14-17% considering that both isomers **12ac** and **13at** were utilized.

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Supplementary Material Available: Experimental data for the preparation of OBO ester **5** from piperonyl alcohol, structures, carbon, proton, spectral data for ABD allylic alcohols and acetates, 2D NMR and spectral data for **14ac** and **15at**, stereoscopic and ORTEP drawings of **19at**, and tables of crystal data, bond angles and distances, torsion angles, and positional parameters (32 pages). Ordering information is given on any current masthead page.

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(15) Additonal chemical and spectral evidence in support of **14ac** and **15at**, and their derivatives may be found in the Supplementary Material.

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(19) Speculations on the relative importance of various conformational and electronic effects (including the possibility of nonsynchronous bond formation) pertaining to the generation of **13** will have to await future computational modeling. These results will be subsequentially published in a full paper.

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(21) We wish to thank Dr. P. Fanwick of the Purdue chemistry department X-ray crystallography center for these results. The MICROVAX computer and diffractometer were provided by NSF Grant CHE-8615556.

(22) Tables of bond angles and distances can be found in the Supplementary Material.

(23) For references on the 1,2-diol to α-diketone oxidations, see: Govindan, S. V.; Fuchs, P. L. *J. Org. Chem.* **1988**, *53*, 0000 and references cited therein.

(24) As can be seen in Scheme III, the oxidation of **20ac** and **21at** afford the same racemic enolized α-diketone **22**. It should be noted that an alternative structure (**13sc**, see Supplementary Material) for the minor Diels-Alder adduct would also have given **22** after the oxidation step, underscoring the need for the X-ray determination for **19at**.

(25) We wish to thank Professor Steve Weinreb of Penn State for an authentic sample of **22** and R. G. Powell of the USDA, Peoria, IL, for an authentic sample of **1**.

(26) Conversion of **22** to **23** was carried out by a Merck modification of the original Weinreb procedure (literature yields: 99×86%).[3b] We thank Professor Weinreb for this information.

Poly(*n*-hexylsilyne): Synthesis and Properties of the First Alkyl Silicon $[RSi]_n$ Network Polymer

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Linear silicon-silicon bonded polymers $[R_1R_2Si]_n$ are presently the focus of intense investigation[1] and have already found applications as SiC precursors,[2] photoresists,[3] and photoinitiators.[4] However, little progress has been made toward the synthesis of

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