Published in final edited form as:

J Am Chem Soc. 2006 August 16; 128(32): 10370–10371. doi:10.1021/ja063304f.

Strain-Release Rearrangement of *N*-Vinyl-2-Arylaziridines. Total Synthesis of the Anti-Leukemia Alkaloid (–)-Deoxyharringtonine

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The cephalotaxus esters constitute a family of remarkably potent anti-leukemia alkaloids from the *Cephalotaxus* genus.¹ Several of these alkaloids, including deoxyharringtonine (**1**; Chart 1), exhibit acute toxicity toward P388 and L1210 leukemia cells with IC₅₀ values in the ng/mL range.¹ The bulk of the multistep synthetic efforts toward these targets have involved innovative routes to cephalotaxine (**2**),² the most abundant constituent of this family of alkaloids. However, **2**, itself, is biologically inactive, and the difficulties associated with acylation of its hindered C3-hydroxyl with sterically demanding carboxyl derivatives, such as that in **1**, have been noted.^{1,3} We report the total synthesis of (–)-deoxyharringtonine (**1**), employing novel synthetic strategies not only for the preparation of the [3]benzazepine and the spiro-fused pyrrolidine substructures present in cephalotaxine (**2**), but also for hindered acyl chain synthesis and attachment to **2** for efficient access to the biologically relevant and rare cephalotaxus esters.⁴

Strain-release [3,3]-rearrangements of *N*-aryl-2-vinylaziridines to generate [1]benzazepines are documented;⁵ however, to our knowledge, successful [3,3]-rearrangements of *N*-vinyl-2-arylaziridines to form [3]benzazepines, such as that present in **2**, have not been reported. The feasibility of this reaction was assessed in a model investigation (Scheme 1) commencing with the conversion of 3,4-methylenedioxyacetophenone (**3**) to aziridine **4** via the sequential steps of oxime formation (HONH₂Cl, NaOH, 87%) and reductive Neber rearrangement (LiAlH₄, HN(CHMe₂)₂, 88%).⁶ Treatment of aziridine **4** with 3-chloro-2-cyclopentenone under basic conditions afforded the benzylic chloride **5** (64%), likely the result of conjugate addition–elimination followed by chloride-mediated aziridine opening. The key *N*-aryl-2-vinylaziridine was regenerated in situ (Cs₂CO₃, 1,4-dioxane) and underwent sequential thermal rearrangement (100 °C, **6** → **7**)⁷ and tautomerization to provide **8** (67%), an achiral version of the tetracyclic fragment within **2**.

The establishment of this convergent approach to [3]benzazepine construction permitted its application to the synthesis of (–)-cephalotaxine (**2**, Scheme 2). Introduction of the β-chloro substituent on (*S,S*)-4,5-dihydroxycyclopent-2-enone isopropylidene acetal (**9**)⁸ was accomplished in a four-step sequence involving (1) Luche reduction of the enone to afford the (*R*)-allylic alcohol, (2) chloroselenenylation of the alkene (73%, two steps), (3) selenide oxidation–elimination to generate the corresponding vinyl chloride (91%), and (4) Dess–Martin periodinane (DMP) oxidation of the allylic alcohol to provide the β-chloroenone **10** (98%). Conjugate addition–elimination of **10** with racemic aziridine **4** provided *N*-vinyl-2-arylaziridine **11** (85%) as a 1:1 mixture of benzylic diastereomers. Smooth [3,3]-rearrangement of the epimeric aziridines **11** ensued upon thermal activation (100 °C) to provide [3]-benzazepine **12** (76%),⁹ the nonracemic tetracyclic core of (–)-**2**.

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The vinylogous amide group in **12** allowed for application of a variant of our recently disclosed approach to pyrrolidine construction from tertiary vinylogous amide precursors.¹⁰ Thus, [3] benzazepine **12** was *N*-alkylated with Me₃SiCH₂I (75%) to generate the tertiary vinylogous amide **13**, which permitted selective carbonyl *O*-acylation (pivaloyl triflate) followed by *C*-desilylation (TBAT)¹¹ to produce the transient nonstabilized azomethine ylide **14**. The presence of PhSO₂CH=CH₂ led to stereo- and regioselective dipolar cycloaddition to form the spiro-pyrrolidine **15** (77%). Notably, X-ray analysis of **15** confirmed that the cycloaddition proceeded via an apparent *contra-steric* face-selective approach of the dipolarophile onto ylide **14**, leading to the required C5 *R* configuration.¹²

Further functional group interconversions in the synthesis of (–)-**2** involved SmI₂-mediated reductive desulfonation (74%)¹³ and exchange of the C3 enol ester in **15** to its enol benzyl carbonate counterpart **16** (85%, two steps). Manipulation of the C1–C2 oxidation states in **16** was then accomplished by isopropylidene removal followed by sequential Yb(OTf)₃-mediated selective C1-*O*-acylation (Boc₂O)¹⁴ and C2 oxidation (IBX) to form the corresponding C2 ketone (50%, two steps). Subsequent C1 deoxygenation (CrCl₂) and benzyl carbonate hydrogenolysis provided the enol **17** (42%, two steps), which allowed for its two-step conversion to (–)-**2** via C2 enol ether formation (55%) and stereoselective C3 reduction (95%).^{2h}

Incorporation of preformed acyl chains of bioactive cephalotaxus esters onto **2** has proven to be challenging on two fronts. Typically, protracted synthetic routes to these chiral acyl fragments are required,¹⁵ and their direct attachment to the C3–OH of **2** is often inefficient, if not prohibitive.^{3,16} Thus, a short nonracemic synthesis of the acyl chain of (–)-**1** was developed (Scheme 3), commencing with acetal derivatization of *D*-malic acid (**18**) with Me₃CHO to afford [1,3]dioxolanone **19** (82%).¹⁷ The C2' stereocenter in the acyl chain was established via double deprotonation of **19** followed by diastereoselective C2' alkylation¹⁸ with prenyl bromide to provide the corresponding C2'-*R*-[1,3]dioxolanone (66%). Transesterification with acetal removal (BnOH) then provided the tertiary alcohol **20** (88%). The hydroxy acid **20** was cyclized via the Yamaguchi anhydride¹⁹ to provide the β-lactone, allowing for alkene hydrogenation and benzyl ester hydrogenolysis to yield the carboxylic acid **21** (99%). Activation of **21** with 2,4,6-Cl₃C₆H₂COCl¹⁹ proceeded without rupture of the β-lactone, allowing for acylation of **2** to afford ester **22** (81%). Methanolysis of the β-lactone in **22** concluded the synthesis of (–)-deoxyharringtonine (**1**, 76%).

The relative ease with which cephalotaxine (**2**) is acylated by the β-lactone **21** highlights this approach for the synthesis of the anti-leukemia cephalotaxus esters. This, in conjunction with novel strategies for *N*-heterocycle synthesis that include the rearrangement of an *N*-vinyl-2-arylaziridine and a vinylogous amide acylation–cycloaddition cascade, should allow rapid access to other related structures of potential therapeutic utility.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

This research was supported by the NIH-NIGMS (GM67659), Merck, Pfizer, Eli Lilly, and Abbott. A Procter & Gamble graduate fellowship to J.D.E. is acknowledged.

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Scheme 1 a.

^a Reagents and conditions: (a) HONH_3Cl , NaOH , EtOH , H_2O , 80°C , 87%; (b) LiAlH_4 , $\text{HN}(\text{CHMe}_2)_2$, THF , 60°C , 88%; (c) 3-chloro-2-cyclopentenone, Et_3N , THF , 60°C , 64%; (d) Cs_2CO_3 , 1,4-dioxane, 100°C , 67%.

Scheme 2 a.

^a Reagents and conditions: (a) NaBH₄, CeCl₃, MeOH, 23 °C; (b) PhSeCl, CH₂Cl₂, 23 °C, 73% (2 steps); (c) *m*-CPBA, CH₂Cl₂, 23 °C; Et₃N, 40 °C, 91%; (d) DMP, THF, 23 °C, 98%; (e) **4**, Et₃N, THF, 23 °C, 85%; (f) Cs₂CO₃, 1,4-dioxane, 100 °C, 76%; (g) Me₃SiCH₂I, Cs₂CO₃, MeCN, 23 °C, 75%; (h) PivCl, AgOTf, CH₂Cl₂; CH₂CHSO₂Ph, TBAT, -45 → 23 °C, 77%; (i) SmI₂, HMPA, *t*-BuOH, THF, -45 °C, 74%; (j) Cp₂ZrHCl, THF, 40 °C, 99%; (k) KHMDS, CbzCl, THF, 0 °C, 86%; (l) HCl, MeOH, 23 °C, 99%; (m) Boc₂O, Yb(OTf)₃·xH₂O, CH₂Cl₂, 0 °C; IBX, DMSO, 23 °C, 50%; (n) CrCl₂, acetone, H₂O, 25 °C; (o) H₂, Pd-C, EtOAc, 23 °C, 42% (2 steps); (p) HC(OMe)₃, *p*-TsOH, CH₂Cl₂, 23 °C, 55%; (q) NaBH₄, MeOH, -78 → 23 °C, 95%.

Scheme 3 a.

^a Reagents and conditions: (a) TMSCl, TMS₂NH, CH₂Cl₂, 23 °C; Me₃CCHO, Me₃SiOTf, CH₂Cl₂, -25 °C, 82%; (b) LHMDs, Me₂C=CHCH₂Br, THF, -78 °C, 66%; (c) NaH, BnOH, THF, 0 °C; 88%; (d) 2,4,6-Cl₃C₆H₂COCl, DMAP, CH₂Cl₂, 23 °C, 50%; (e) H₂, Pd-C, EtOAc, 23 °C, 99%; (f) 2,4,6-Cl₃C₆H₂COCl, DMAP, **2**, CH₂Cl₂, 23 °C, 81%; (g) NaOMe, MeOH, 23 °C, 76%.

Chart 1.