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Published on Web 07/20/2006

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 IC_{50} 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 ($HONH_3Cl$, NaOH, 87%) and reductive Neber rearrangement ($LiAlH_4$, $HN(CHMe_2)_2$, 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 (Cs_2CO_3, 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**.

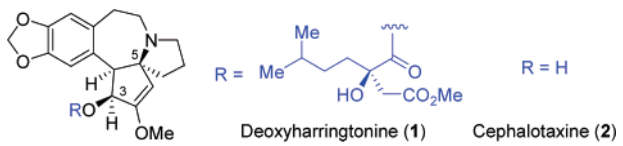
The establishment of this convergent approach to [3]benzazepine construction permitted its application to the synthesis of (−)-cephalotaxine (**2**, Scheme 2). Introduction of the β-chloro substituent on (*S*,*S*)-4,5-dihydroxycyclopent-2-enone isopropylidene acetal (**9**)[8] was accomplished in a four-step 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**.

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 Me_3SiCH_2I (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 $PhSO_2CH{=}CH_2$ 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]

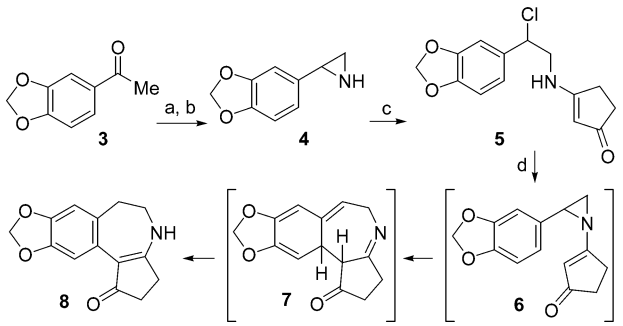
Further functional group interconversions in the synthesis of (−)-**2** involved SmI_2-mediated reductive desulfonylation (74%)[13] and exchange of the C3 enol ester in **15** to its enol benzyl carbonate counterpart **16** (85%, two steps). Manipulation of the C1−C2 oxidation states in **16** was then accomplished by isopropylidene removal followed by sequential $Yb(OTf)_3$-mediated selective C1-*O*-acylation (Boc_2O)[14] and C2 oxidation (IBX) to form the corresponding C2 ketone (50%, two steps). Subsequent C1 deoxygenation ($CrCl_2$) 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

Chart 1



Scheme 1 [a]



[a] Reagents and conditions: (a) $HONH_3Cl$, NaOH, EtOH, H_2O, 80 °C, 87%; (b) $LiAlH_4$, $HN(CHMe_2)_2$, 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%.

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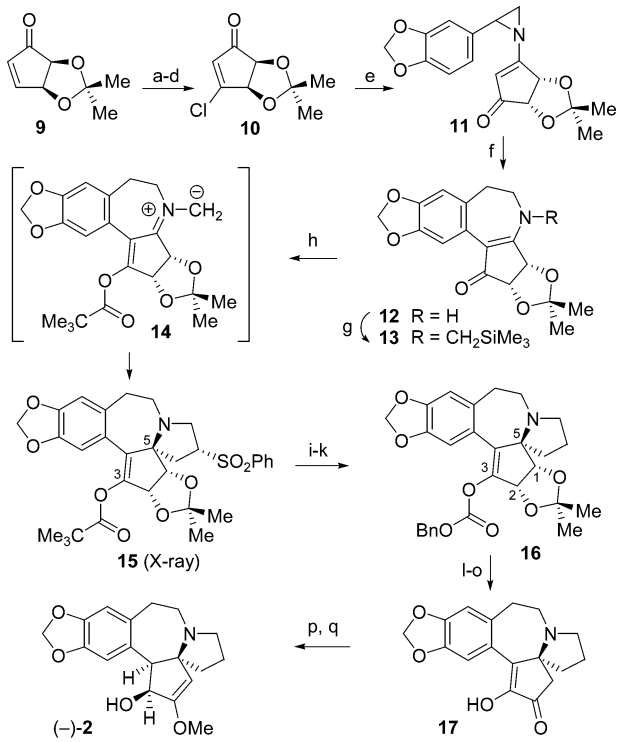
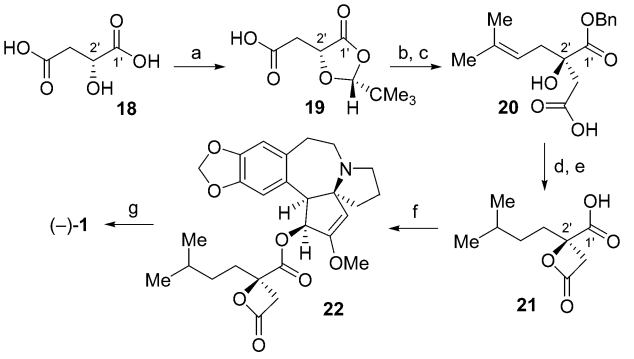
10.1021/ja063304f CCC: $33.50

Scheme 2 [a]



[a] Reagents and conditions: (a) $NaBH_4$, $CeCl_3$, MeOH, 23 °C; (b) PhSeCl, CH_2Cl_2, 23 °C, 73% (2 steps); (c) *m*-CPBA, CH_2Cl_2, 23 °C; Et_3N, 40 °C, 91%; (d) DMP, THF, 23 °C, 98%; (e) **4**, Et_3N, THF, 23 °C, 85%; (f) Cs_2CO_3, 1,4-dioxane, 100 °C, 76%; (g) Me_3SiCH_2I, Cs_2CO_3, MeCN, 23 °C, 75%; (h) PivCl, AgOTf, CH_2Cl_2; CH_2CHSO_2Ph, TBAT, −45 → 23 °C, 77%; (i) SmI_2, HMPA, *t*-BuOH, THF, −45 °C, 74%; (j) Cp_2ZrHCl, THF, 40 °C, 99%; (k) KHMDS, CbzCl, THF, 0 °C, 86%; (l) HCl, MeOH, 23 °C, 99%; (m) Boc_2O, $Yb(OTf)_3$·*x*H_2O, CH_2Cl_2, 0 °C; IBX, DMSO, 23 °C, 50%; (n) $CrCl_2$, acetone, H_2O, 25 °C; (o) H_2, Pd−C, EtOAc, 23 °C, 42% (2 steps); (p) $HC(OMe)_3$, *p*-TsOH, CH_2Cl_2, 23 °C, 55%; (q) $NaBH_4$, MeOH, −78 → 23 °C, 95%.

Scheme 3 [a]



[a] Reagents and conditions: (a) TMSCl, TMS_2NH, CH_2Cl_2, 23 °C; Me_3CCHO, Me_3SiOTf, CH_2Cl_2, −25 °C, 82%; (b) LHMDS, $Me_2C{=}CHCH_2Br$, THF, −78 °C, 66%; (c) NaH, BnOH, THF, 0 °C; 88%; (d) 2,4,6-$Cl_3C_6H_2COCl$, DMAP, CH_2Cl_2, 23 °C, 50%; (e) H_2, Pd−C, EtOAc, 23 °C, 99%; (f) 2,4,6-$Cl_3C_6H_2COCl$, DMAP, **2**, CH_2Cl_2, 23 °C, 81%; (g) NaOMe, MeOH, 23 °C, 76%.

with acetal derivatization of D-malic acid (**18**) with Me_3CHO 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′ alkylation[18] 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 anhydride[19] 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-$Cl_3C_6H_2COCl$[19] 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.

Acknowledgment. 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.

Supporting Information Available: Experimental details (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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JA063304F