JOC The Journal of Organic Chemistry

Note

Formal synthesis of ent-Cephalotaxine using a one-pot Parham–aldol sequence

Juha Henrik Siitonen, Lu Yu, Jakob Danielsson, Giovanni Di Gregorio, and Peter Somfai

J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.8b01540 • Publication Date (Web): 17 Jul 2018

ACS Publications

is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Formal Synthesis of *ent*-Cephalotaxine Using a One-pot Parham–aldol Sequence

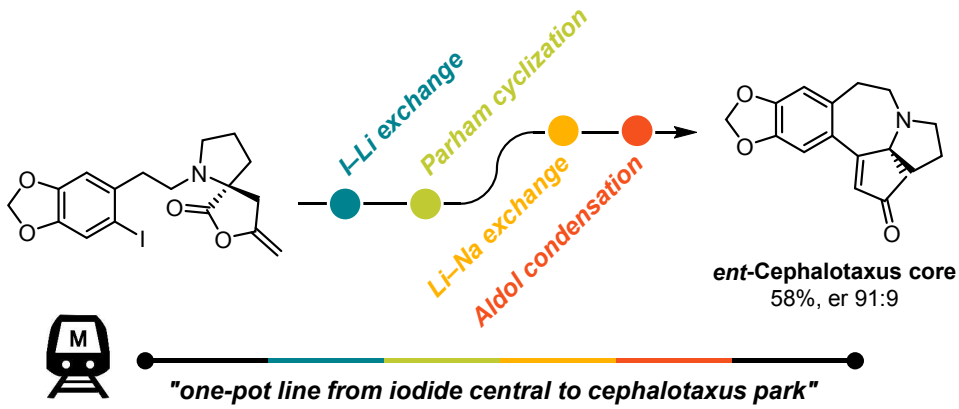
Juha H. Siitonen,[†,‡] Lu Yu,[†] Jakob Danielsson,[†] Giovanni Di Gregorio,[†,§] and Peter Somfai*[,†]

[†]Center for Analysis and Synthesis, Department of Chemistry, Lund University, Box 124, 221 00 Lund, Sweden

[‡]Present address: University of Jyvaskyla, Department of Chemistry, P.O. Box 35, FI-40014, University of Jyvaskyla, Finland

[§]Present address: Department of Biomolecular Sciences, University of Urbino "Carlo Bo", Piazza del Rinascimento 6, 61029 Urbino PU, Italy

*E-mail: peter.somfai@chem.lu.se



ABSTRACT. A short formal synthesis of *ent*-Cephalotaxine is achieved. The approach features a new Lewis acid mediated [2,3]-Stevens rearrangement of *N*-allylated prolineamide to generate a key quaternary stereogenic center. Additionally, a one-pot Parham–aldol sequence was developed to rapidly assembly two of the four rings in the cephalotaxine core.

Cephalotaxus alkaloids are a wide family of secondary metabolites isolated from Cephalotaxus genus trees and shrubs native to southern Asia (For representative members, see Figure 1).[1] Because of their intricate structure as well as the antileukemial activity of some members of the alkaloid family, especially the FDA

approved drug homoharringtonine (**2**), they have been of wide interest to the synthetic community.[1,2,3,4] Especially strategies relying on domino reactions forming several rings of the pentacyclic core in a single operation have proved highly successful. These strategies include an efficient radical domino reaction by the Ishibashi group, a stereospecific hydride reduction–iso-Nazarov domino reaction by the Li group as well as an amide acylation–cycloaddition domino reaction by the Gin group.[5a–c]

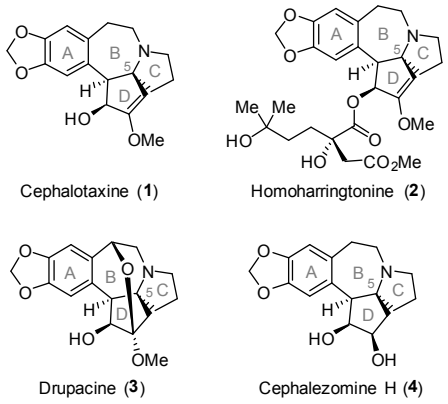


Figure 1: Examples of cephalotaxine-type alkaloids: Cephalotaxine (**1**), Homoharringtonine (**2**), Drupacine (**3**) and Cephalezomine H (**4**) all have a common ABCD ring system with a quaternary stereogenic center at the C5 spiro junction.

A retrosynthetic analysis of enone **5**, the racemate of which has previously been converted into (±)-cephalotaxine (*rac*-**1**), reveals an opportunity for an attractive domino sequence not yet explored (Figure 2, a).[6] Ring D of enone **5** is known to form in an intramolecular aldol condensation of an enolate intermediate **6**.[7] Instead of forming this enolate **6** from the parent diketone, we considered expelling the enolate from *exo*-butenolide **7** following a Parham cyclization to initially form the ring B.[8] Such a protocol would allow for forging both rings B and D in a single operation by lithiation of intermediate **7**. To construct the needed precursor **7** we considered iodolactonizing amide **8**, which can be derived from α-allylated prolineamide derivative **9**.

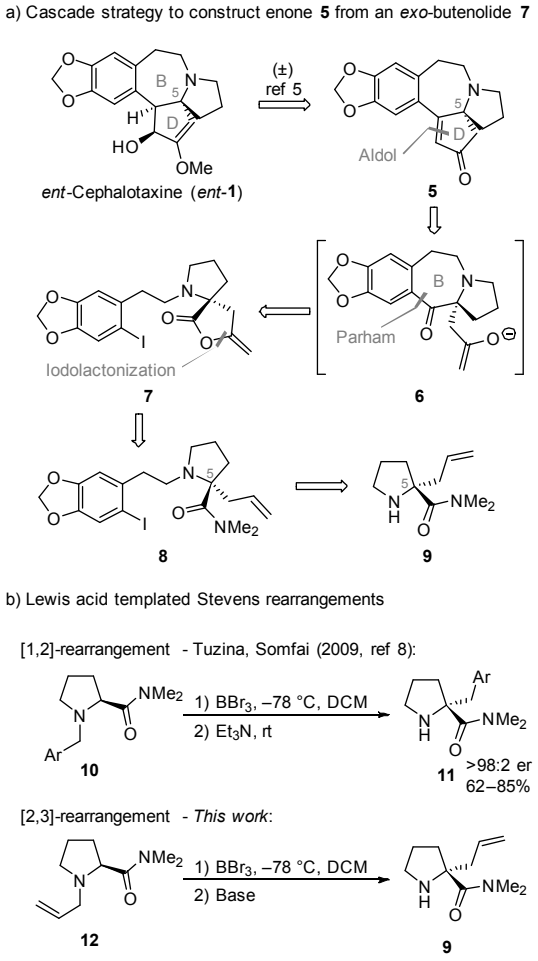
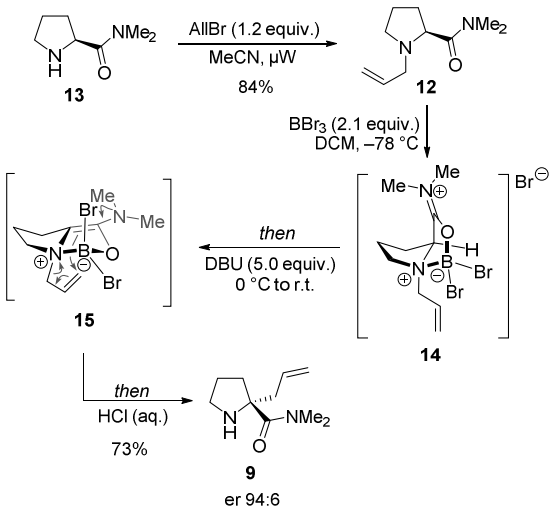


Figure 2: a) Proposed formal synthesis of *ent*-Cephalotaxine (*ent*-**1**) based on a Parham-aldol cascade of butanolide **7** b) Prior and current approaches to Lewis acid mediated rearrangements of *N*-substituted prolineamide derivatives.[9]

We recently disclosed an asymmetric Lewis acid mediated [1,2]-Stevens rearrangement of proline-derived benzyl derivatives of the type **10**, which afforded corresponding quaternary α-benzyl proline derivatives **11** in good to excellent yields (62–85%) and high enantiomeric purity (er >98:2) (Figure 2, b).[9] We speculated that *N*-allyl prolineamide **12** might also be a competent substrate for this reaction, and result in α-allyl prolineamide **9** (Figure 2, b).[10] This would be a powerful method for the installation of the challenging spirocyclic C5 stereogenic center in cephalotaxine (**1**) at an early stage in the synthesis. This choice of strategy was also backed up by a very informative formal synthesis of *rac*-cephalotaxine (*rac*-**1**) by the Liu group, applying a related [2,3]-Stevens rearrangement.[11]

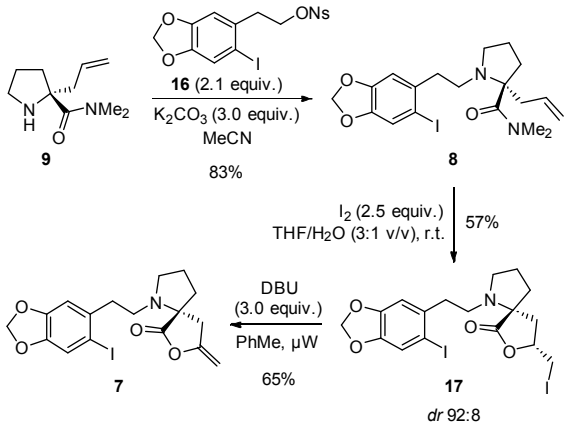
The campaign was started by optimizing the proposed [2,3]-Stevens rearrangement of *N*-allyl L-prolineamide **12**, readily available by allylating commercially available prolineamide **13** (Scheme 1). Conditions optimized for the *N*-benzyl rearrangement (BBr_3, then Et_3N) gave only traces of α-allylated product **9** in both dichloromethane and toluene as solvents.[9] Gratifyingly, replacing triethylamine with DBU improved the yield to 73% of α-allylated prolineamide **9** (er 94:6).[12] In contrast to the [1,2]-Stevens rearrangement, thought to proceed *via* a diradical intermediate, we presume the allyl transfer to be a formal [2,3]-rearrangement. Upon addition of DBU, oxazaborolidine **14** deprotonates to form the ammonium ylide **15**. Ylide **15** is primed for a [2,3]-rearrangement, transposing the allyl group with retention of configuration.[13] It is worth noting that this example is the first asymmetric Lewis acid mediated [2,3]-sigmatropic rearrangement of *N*-allyl proline derivatives and constitutes an attractive method for the synthesis of enantioenriched quaternary prolines.[14]



Scheme 1: Synthesis of enantioenriched α-allyl proline dimethylamide **9** from commercially available L-prolineamide **13**. Postulated mechanism proceeds *via* a [2,3]-Stevens rearrangement of ammonium ylide **15**.

Subsequent *N*-alkylation of **9** with iodonosylate **16** afforded **8** in 83% yield (Scheme 2).[15] The high stability of the amide group in α-quaternary dimethylamides such as **9** and **8** can pose problems due to the relatively forcing conditions required for their hydrolysis.[9] We were therefore pleased to find that the

unsaturated amide **8** can be directly iodolactonized under mild conditions (I_2, THF/H_2O, rt) to yield the iodolactone **17** (dr 92:8).[16] The relative stereochemistry is, however, inconsequential as the subsequent dehydrohalogenation of **17** with DBU under microwave conditions affords **7**.[17] These transformations set the stage for the Parham–aldol domino reaction.

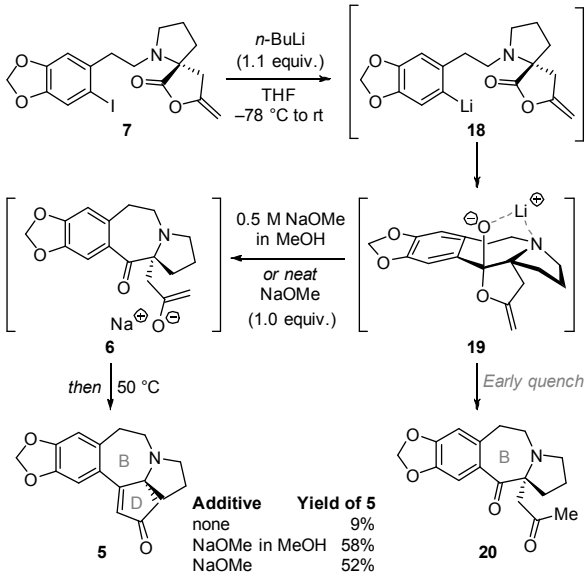


Scheme 2: Accessing the enantioenriched cyclization precursor *exo*-butenolide **7**.

Treatment of iodide **7** with variety of metalating agents (*t*-BuLi, *n*-BuLi, mesitylLi, *i*-PrMgCl·LiCl) at –100 °C in THF and allowing the reaction mixture to warm to room temperature resulted in near full consumption of **7** forming complex mixtures with varying amounts of diketone **20**, but only traces of desired enone **5** (Scheme 3). Attempts at chancing the solvent to heptane/THF led to no improvement, nor did additives such as TMEDA, *t*-BuOH or MeOH.[18,19] At best, the desired enone **5** was obtained in 9% isolated yield (*n*-BuLi, THF, –78 °C, 2 h, warmed to room temperature and heated to 50 °C for 20 min). Furthermore, screening addition rates, reverse addition and reaction temperatures led to no significant improvement.

These setbacks led us to analyze our proposed reaction mechanism in closer detail. The first step, lithium–halogen exchange to give **18** was clearly taking place as **7** was consumed. Also, indicative of the Parham cyclization, we could isolate varying amounts of the diketone **20** where the B-ring had been formed.[7] Yet conversion to enone **5** was only very low. The difficulty at forming ring D led us to speculate that the lithium alkoxide formed after the Parham cyclization does not collapse into enolate **6**, but rather chelates with the tertiary nitrogen to form the tentative intermediate **19**, which is too stable under the reaction

conditions to react further.[20] With this insight at hand, we repeated the most successful reaction sequence (*n*-BuLi, –78 °C, 2 h, warmed to room temperature) and then added sodium methoxide (1.0 equiv., 0.5 M in methanol) before heating to 50 °C to break the postulated chelate **19**, and to produce the more reactive sodium enolate **6**. Thankfully, with this modification enone **5** was isolated in a 58% yield (er 91:9).[21] The slight loss in enantiopurity in **5** (94:6 of **9** to 91:9 of **5**) can be assigned to partial scrambling at the C5 stereogenic center *via* a retro-Mannich-Mannich sequence.[22] Under the one-pot conditions, sodium enolate **6** can form *via* two pathways: 1) methanol quenching **19** into a transient ketone **20** which re-enolizes to **6** with NaOMe or 2) direct transmetallation of **19** to **6**. As a control experiment, adding solid anhydrous NaOMe instead of a methanolic solution, the yield of **5** remained the same (52%). In this case no protic solvent is available to quench enolate **19**, showing that direct metal exchange from **19** to **6** is also taking place. The pathway from **20** to **5** is also known in the literature, and with methanolic sodium methoxide the cascade from **19** to **5** likely proceeds *via* both pathways.[7,23]



Scheme 3: One-pot Parham–aldol reaction sequence forming both rings B and D of the cephalotaxine alkaloid core **5** proceeds *via* a postulated stable lithium chelate **19**.

In summary, we have achieved an enantioselective 6-step synthesis of **5**, the pentacyclic core of cephalotaxus alkaloids, starting from commercially available L-prolineamide **13**. In conjunction with a novel

Parham–aldol strategy to construct both rings B and D of **5** in a one-pot operation, we have disclosed the first example of an asymmetric Lewis acid mediated [2,3]-Stevens rearrangement of *N*-allyl proline amides to yield α-allyl proline amides with high enantiopurity (er 94:6). The two new reactions described herein are a testimony to the usefulness of total synthesis efforts in reaction discovery.

EXPERIMENTAL SECTION.

General experimental procedures. All reactions were carried out under an argon atmosphere in oven-dried glassware, unless otherwise noted. When needed, nonaqueous reagents were transferred under argon via syringe or cannula and dried prior to use. Dry solvents were obtained by passing deoxygenated solvents through activated alumina columns (MBraun SPS-800 Series solvent purification system). Other solvents and reagents were used as obtained from supplier, unless otherwise noted. Analytical TLC was performed using Merck silica gel F254 (230–400 mesh) plates and analyzed by UV light or by staining upon heating with $KMnO_4$ solution (1 g $KMnO_4$, 6.7 g K_2CO_3, 1.7 mL 1 M NaOH, 100 mL H_2O). For silica gel chromatography, the flash chromatography technique was used, with silica gel 60 (230–400 mesh) and p.a. grade solvents unless otherwise noted. The ^1H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ on Bruker Avance 400 spectrometer. The chemical shifts are reported in ppm relative to residual $CHCl_3$ (δ 7.26) for ^1H NMR. For the ^{13}C NMR spectra, $CDCl_3$ (δ 77.16) was used as the internal standards. The enantiomeric ratio of **5** was determined by HPLC in comparison to the corresponding racemic samples using Agilent 1260 Infinity HPLC. Melting points (mp) were determined in open capillaries using Stuart SMP3 melting point apparatus and are uncorrected. IR spectra were recorded on a Bruker Alpha Platinum FT-IR spectrometer with an ATR accessory. Optical rotations were obtained with a Perkin-Elmer 341 polarimeter. High resolution mass spectrometric data were measured using Waters QTOF XEVO-G2 spectrometer. Microwave reactions were carried out using Biotage Initiator EXP EU microwave reactor rated at maximum power output of 400 W with the magnetron running at 2450 MHz using an external surface sensor. Kugelrohr distillations were carried out using Büchi GKR-51 bulb-to-bulb distillation unit cooled with dry-ice.

(*S*)-1-Allyl-*N*,*N*-dimethylpyrrolidine-2-carboxamide (12). To a solution of *N*,*N*-dimethylprolineamide (**13**) (500 mg, 4.38 mmol, 1.0 equiv.) in acetonitrile (2 ml) allyl bromide (640 mg, 450 µL, 5.3 mmol, 1.2 equiv.) was added at 0 °C. The resulting solution was heated using a microwave reactor (100 W, 120 °C) for 5 min, allowed to cool to rt, and quenched with aqueous 2 M NaOH (10 ml). The resulting biphasic mixture was extracted with EtOAc (3 × 5 ml) and the combined organic layers washed with brine (10 ml), dried with Na_2SO_4, and concentrated *in vacuo*. The thus obtained crude **12** is NMR pure (540 mg, 84%). When scaling up, combined batches of **12** were further purified with Kugelrohr distillation (120 °C, 0.1 mbar) to yield the allyl amine as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.94 (dddd, *J* = 17.2, 10.1, 7.3, 6.1 Hz, 1H), 5.14 (ddd, *J* = 17.1, 3.2, 1.5 Hz, 1H), 5.05 (ddd, *J* = 10.1, 2.1, 1.1 Hz, 1H), 3.40–3.28 (m, 2H), 3.19 (td, *J* = 8.0 Hz, 2.8 Hz, ,1H), 3.06 (s, 3H), 3.00 (dd, J = 13.1, 7.3 Hz, 1H), 2.94 (s, 3H), 2.33 (dd, *J* = 16.5, 8.7 Hz, 1H), 2.15–2.04 (m, 1H), 2.01–1.89 (m, 1H), 1.87–1.74 (m, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ: 173.3, 136.1, 116.8, 63.9, 57.6, 53.3, 37.0, 36.1, 28.9, 23.0. IR (ATR, cm^{-1}) ν_{max}: 2945, 2799, 1638, 1418, 1261, 1115, 919. $[\alpha]_D^{20}$ –104.6° (*c* 1.0, DCM). HRMS (ESI$^+$) m/z: $[M+H]^+$ Calcd for $C_{10}H_{19}N_2O$ 183.1497; Found 182.1495; Δ = –1.1 mDa.

(*R*)-2-Allyl-*N*,*N*-dimethylpyrrolidine-2-carboxamide (9). To a solution of *N*-allylproline amide **12** (1.0 g, 5.5 mmol, 1.0 equiv.) in DCM (60 ml) at –78 °C BBr_3 (12.0 ml, 2.89 g, 11.5 mmol, 2.10 equiv., 1.0 M solution in DCM) was added dropwise. The resulting solution was allowed to warm to rt and stirred for 1 h, then cooled to 0 °C followed by dropwise addition of DBU (4.1 ml, 4.2 g, 27 mmol, 5.0 equiv.). The mixture was allowed to warm to rt and stirred for 1 h. The resulting deep orange reaction mixture was quenched with 1 M HCl (10 ml), biphasic mixture separated, and the organic layer washed with 1 M NaOH (20 ml). The basified aqueous layer was further extracted with DCM (3 × 30 ml), and the combined organic layers washed with brine (50 ml), dried with Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by flash column chromatography (50% acetone/pentane, 1% *i*-$PrNH_2$) to afford amine **9** as a pale-yellow oil (729 mg, 73%, er = 94:6, Mosher derivative, see SI). R_f = 0.13 (50% Acetone/heptane, $KMnO_4$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.79 (ddd, *J* = 17.4, 10.4, 7.1 Hz, 1H), 5.05–5.03 (m, 1H), 5.02–4.99 (m, 1H), 3.09–2.88 (m, 7H), 2.78 (td, *J* = 9.2, 6.4 Hz), 2.50 (dd, *J* = 13.9, 7.1 Hz), 2.38 (dd, *J* = 13.9, 7.1 Hz, 1H), 2.07 (d, *J* = 12.4, 8.3 Hz, 1H), 1.91–1.84 (m, 1H), 1.82–1.69 (m, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ: 175.5, 134.3, 117.5, 68.5,

46.6, 44.7, 35.3, 26.5. IR (ATR, cm^{-1}) ν_{max}: 3074, 2942, 2869, 1624, 1434, 1254, 1162, 992, 731. $[\alpha]_D^{20}$ –104.6° (*c* 1.0, DCM). HRMS (ESI^+) m/z: $[M+H]^+$ Calcd for $C_{10}H_{19}N_2O$ 183.1497; Found 183.1499; Δ = 0.2 mDa.

Mosher derivatization: To a stirred solution of amine **9** (30 mg, 0.21 mmol, 1.0 equiv.) in dichloromethane (1 ml), DIPEA (25 µL, 18.3 mg, 181 µmol, 2.2 equiv.) followed by (*R*)-(–)-MTPA-Cl (11 µL, 12.7 mg, 1.1 equiv.) was added at 0 °C. The resulting solution was warmed to 40 °C for 16 h and after full consumption of starting material allowed to cool to room temperature. The reaction was quenched with aqueous saturated $NaHCO_3$ (1 ml) and extracted with dichloromethane (3 × 1 ml). The combined organic layers were dried with anhydrous Na_2SO_4 and concentrated in vacuo. The crude was analyzed using ^1H NMR for a dr of 94(*RR*):6(*RS*).

(*R*)-2-Allyl-1-(2-(6-iodobenzo[*d*][1,3]dioxol-5-yl)ethyl)-*N*,*N*-dimethylpyrrolidine-2-carboxamide (8). A beige suspension of amine **9** (294 mg, 1.90 mmol, 1.00 equiv.), nosylate **16** (1.0 g, 2.1 mmol, 1.2 equiv.)[22] and K_2CO_3 (790 mg, 5.70 mmol, 3.00 equiv.) in acetonitrile (10 ml) was refluxed for 13 h. The resulting mixture was cooled to rt, filtered through a fritted funnel and the filter cake washed with thoroughly with EtOAc (3 × 3 ml). The combined filtrates were concentrated under reduced pressure. The crude product was purified by flash column chromatography (35% EtOAc/heptane) to afford iodide **8** as a yellow oil (724 mg, 83%). R_f = 0.31 (30% EtOAc/heptane, UV, $KMnO_4$). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.20 (s, 1H), 6.69 (s, 1H), 6.02–5.90 (m, 3H), 5.93 (s, 2H), 5.02 (app. d, *J* = 12.6 Hz, 2H), 3.31 (td, *J* = 8.6, 3.6 Hz, 1H), 3.00 (br. s, 6H, NCH_3), 2.89–2.68 (m, 5H), 2.65 (dd, *J* = 16.8, 8.9 Hz, 1H), 2.61–2.53 (m, 1H), 2.08 (dd, *J* = 16.1, 11.2 Hz, 1H), 2.06–1.99 (m, 2H), 1.97–1.80 (m, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ: 174.3, 148.5, 147.0, 137.4, 136.6, 118.6, 117.1, 109.6, 101.6, 88.0, 71.9, 50.2, 49.6, 40.3, 38.1, 36.6, 31.4, 22.1. IR (ATR, cm^{-1}) ν_{max}: 2904, 2811, 1623, 1474, 1384, 1225, 1110, 1006, 931. $[\alpha]_D^{20}$ –21.4° (*c* 0.5, CH_2Cl_2). HRMS (ESI^+) m/z: $[M+H]^+$ Calcd for $C_{19}H_{26}IN_2O_3$ 457.0988; Found: 457.0989; Δ = 0.1 mDa.

(5S,8R)-1-(2-(6-iodobenzo[d][1,3]dioxol-5-yl)ethyl)-8-(iodomethyl)-7-oxa-1-azaspiro[4.4]nonan-6-one (17). To a solution of amide **8** (1.70 g, 3.73 mmol, 1.0 equiv.) in THF (38 ml) and DI H_2O (12 ml) at 0 °C and protected from light was added iodine (2.36 g, 9.31 mmol, 2.5 equiv.). The reaction mixture was allowed to

warm to rt and after 16 h quenched with aq. sat. Na_2SO_3 (7 ml) and basified with 2 M NaOH (5 ml). The resulting biphasic solution was extracted with EtOAc (4 × 20 ml). The combined organic layers were washed with brine (50 ml), dried with Na_2SO_4 and concentrated *in vacuo* (bath temperature 30 °C). The resulting black residue (dr 92:8 based on ^{1}H NMR of reaction mixture) was purified using flash column chromatography (20% EtOAc/heptane to 30% EtOAc/heptane) to give *cis*-butyrolactone **17** as a clear oil (1.17 g, 57%).[23] R_f = 0.44 (50% EtOAc/heptane, $KMnO_4$, decomposes under UV). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.21 (s, 1H), 6.74 (s, 1H), 5.94 (s, 2H), 4.31 (ddt, *J* = 10.3, 6.8, 5.3 Hz, 1H), 3.40 (dd, *J* = 10.3, 4.6 Hz, 1H), 3.26 (dd, *J* = 10.3, 7.2 Hz, 1H), 3.14 (dt, *J* = 15.7, 7.8 Hz, 2H), 2.88–2.79 (m, 2H), 2.79–2.72 (m, 2H), 2.27–2.15 (m, 2H), 2.09–1.88 (m, 4H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ: 177.8, 148.6, 147.1, 136.1, 118.7, 110.0, 101.7, 88.0, 75.1, 70.8, 51.7, 50.2, 40.8, 39.5, 36.8, 22.3, 7.1. IR (ATR, cm^{-1}) ν_{max}: 2937 (br), 1768, 1475, 1248, 1153, 1039. $[\alpha]_D^{20}$ 16.1° (*c* 1.0, DCM). HRMS (ESI$^+$) m/z: $[M+H]^+$ Calcd for $C_{17}H_{20}I_2NO_4$ 555.9482; Found: 555.9485; Δ = 0.3 mDa.

(*S*)-1-(2-(6-iodobenzo[*d*][1,3]dioxol-5-yl)ethyl)-8-methylene-7-oxa-1-azaspiro[4.4]nonan-6-one (7). A solution of iodide **17** (100 mg, 0.180 mmol, 1.0 equiv.) and DBU (81 µL, 82 mg, 0.54 mmol, 3.0 equiv.) in toluene (3 ml) was heated in a microwave reactor (100 W, 120 °C) for 45 min. The resulting dark tar was taken up in DCM (4 × 2 ml), concentrated *in vacuo* and purified using flash column chromatography (50% Et_2O/pentane) to give the product **7** as a white solid (65 mg, 84%). mp: 81.2 – 83.3 °C. R_f = 0.66 (50% EtOAc/heptane, UV, $KMnO_4$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.21 (s, 1H), 6.72 (s, 1H), 5.95 (app. d, *J* = 1.4 Hz, 1H), 5.94 (d, *J* = 1.4 Hz, 1H), 4.70 (dd, *J* = 4.3, 2.2 Hz, 1H), 4.30 (dd, *J* = 4.3, 1.8 Hz, 1H), 3.23 (td, *J* = 8.6, 4.5 Hz, 1H), 3.04–2.96 (m, 1H), 2.91–2.71 (m, 3H), 2.58 (ddd, *J* = 11.3, 10.0, 5.0 Hz, 1H), 2.28–2.19 (m, 1H), 2.03–2.13 (m, 1H), 1.89–2.01 (m, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ: 176.4, 153.3, 148.6, 147.1, 135.9, 118.7, 109.8, 101.7, 89.4, 88.0, 69.2, 51.6, 50.1, 40.6, 36.5, 36.4, 21.8. IR (ATR, cm^{-1}) ν_{max}: 2940 (br), 1790, 1672, 1502, 1251, 1227, 1084, 999, 844. $[\alpha]_D^{20}$ +34.2° (*c* 0.5, DCM). HRMS (ESI$^+$) m/z: $[M+H]^+$ Calcd for $C_{17}H_{19}INO_4$ 428.0359; Found: 428.0360; Δ = 0.1 mDa.

(S)-5,6,8,9-tetrahydro-4H-[1,3]dioxolo[4',5':4,5]benzo[1,2-d]cyclopenta[b]pyrrolo[1,2-a]azepin-2(3H)-one (5). To a solution of **7** (20 mg, 0.05 mmol, 1.0 equiv.) in THF (1 ml) at –78 °C *n*-BuLi (2.5 M in hexanes, 21 µL, 0.05 mmol, 1.1 equiv.) was added dropwise. The reaction mixture was stirred at –78 °C for 2 h and then allowed to slowly warm to room temperature. After stirring at room temperature for 30 minutes, NaOMe (0.5 M in MeOH, 94 µL, 1.0 equiv.) was added and the reaction was stirred for an additional 2 h at room temperature and then heated to 50 °C for 20 minutes and then cooled to rt. The mixture was diluted with EtOAc (20 ml) and brine (10 ml). The layers were separated and the aqueous layer was extracted with EtOAc (3 × 10 ml). The combined organic layers were dried with anhydrous Na_2SO_4, filtered and concentrated. The residue was purified using flash chromatography (EtOAc) to afford **5** as an off-white amorphous solid (7.7 mg, 58%). R_f = 0.31 (EtOAc, UV, $KMnO_4$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.70 (1H, app. s), 6.67 (1H, app. s), 6.08 (s, 1H), 6.00 (2H, dd^{AB}, $|J_{AB}|$ = 1.4 Hz, Δν = 23.8 HZ.), 3.43 (1H, ddd, *J* = 4.8 Hz, 12.1 Hz, 16.4 Hz), 3.32 (1H, ddd, *J* = 2.9, 12.1, 15.0 Hz), 3.10 (app. dt, *J* = 3.6, 15.0 Hz), 2.97–2.92 (m, 3H), 2.64 (2H, distorted dd^{AB}, $|J_{AB}|$ = 18.0 Hz, Δν = 6.0 Hz), 1.95–1.81 (3H, m), 1.79–1.74 (1H, m). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ: 205.9, 149.2, 146.4, 132.1, 131.7, 126.7, 110.1, 109.5, 101.6, 74.9, 54.2, 49.4, 44.4, 39.5, 32.8, 24.7. $[\alpha]_D^{20}$ –72.8° (*c* 0.006, DCM). HRMS (ESI$^+$) m/z: $[M+H]^+$ Calcd for $C_{17}H_{18}NO_3$ 283.1287; Found: 283.1286; Δ = 0.1 mDa. HPLC: Chiralcel IA, 15% 2-propanol/hexane, 0.5 mL·min^{-1}, rt, λ=254 nm, t_R(*R*) = 10.9 min, t_R(*S*) = 12.7 min.

SUPPORTING INFORMATION

Chromatograms for **5** and ^{1}H and ^{13}C NMR spectra for all new compounds.

ACKNOWLEDGMENTS

This research was supported by Lund University, the Swedish Research Council, the Royal Physiographic Society of Lund, University of Jyväskylä (J. H. S) and Jenny and Artturi Wihuri Foundation (J. H. S).

REFERENCES

1. Abdelkafi, H.; Nay, B. Natural Products from *Cephalotaxus* sp.: Chemical Diversity and Synthetic Aspects. *Nat. Prod. Rep.* **2012**, *29*, 845–869.
2. Powell, R. G.; Weisleder, D.; Smith, Jr., C. R.; Rohwedder, W. K. Structures of Harringtonine, Isoharringtonine, and Homoharringtonine. *Tetrahedron Lett.* **1970**, *11*, 815–818.
3. Chen, Y.; Li, S. Omacetaxine Mepesuccinate in the Treatment of Intractable Chronic Myeloid Leukemia. *Onco Targets Ther.* **2014**, *7*, 177–186.
4. For recent syntheses of Cephalotaxus alkaloids, see: (a) Liu, H.; Jing, Y.; Li, X.; Yan, R.; Xiao, J.-C., Hong, R. Stereoselectivity in *N*-Iminium Ion Cyclization: Development of an Efficient Synthesis of (±)-Cephalotaxine. *Org. Lett.* **2015**, *17*, 4444–4447. (b) Gouthami, P.; Chegondi, R.; Chandrasekhar, S. Formal Total Synthesis of (±)-Cephalotaxine and Congeners via Aryne Insertion Reaction. Org. Lett. **2016**, *18*, 2044–2046. (c) Ma, X.-Y.; An, X.-T.; Zhao, X.-H.; Du, J.-Y.; Deng, Y.-H.; Zhang, X.-Z.; Fan, C.-A. Au-Catalyzed [2 + 3] Annulation of Enamides with Propargyl Esters: Total Synthesis of Cephalotaxine and Cephalezomine H. *Org. Lett.* **2017**, *19*, 2965–2968.
5. (a) Taniguchi T.; Ishibashi, H. Short Synthesis of (−)-Cephalotaxine Using a Radical Cascade. *Org. Lett.* **2008**, *10*, 4129–4131. (b) Li, W. D. Z.; Duo, W. G.; Zhuang, C. H. Concise Total Synthesis of (±)-Cephalotaxine via a Transannulation Strategy: Development of a Facile Reductive oxy-Nazarov Cyclization. *Org. Lett.* **2011**, *13*, 3538–3541. (c) Eckelbarger, J. D.; Wilmot, J. T.; Gin, D. Y. Strain-Release Rearrangement of *N*-Vinyl-2-Arylaziridines. Total Synthesis of the Anti-Leukemia Alkaloid (−)-Deoxyharringtonine. *J. Am. Chem. Soc.* **2006**, *128*, 10370–10371.
6. Li, W.-D. Z.; Wang, Y.-Q. A Novel and Efficient Total Synthesis of Cephalotaxine. *Org. Lett.* **2003**, *5*, 2931–2934.
7. Zhang, Z. W.; Zhang, X. F.; Feng, J.; Yang, Y. H.; Wang, C. C.; Feng, J. C.; Liu, S. X. Formal Synthesis of Cephalotaxine. *J. Org. Chem.* **2013**, *78*, 786–790.
8. Ahmed, M.; Naseer, M. M. Organolithium-mediated Cyclization Reactions: a Practical Way to Access Hetero- and Carbocycles. *New J. Chem.* **2017**, *41*, 7824–7835.

9. Tuzina, P.; Somfai, P. Asymmetric Lewis Acid Mediated [1,2]-Rearrangement of Proline-Derived Ammonium Ylides. *Org. Lett.* **2009**, *11*, 919–921.
10. We have previously developed similar [2,3]-rearrangements on acyclic systems: (a) Bild, J.; Panknin, O.; Somfai, P. Asymmetric [2,3]-Sigmatropic Rearrangement of Allylic Ammonium Ylides. *J. Am. Chem. Soc.* **2005**, *127*, 9352–9353. (b) Bild, J.; Panknin, O.; Tuzina, P.; Somfai, P. Lewis Acid Mediated Asymmetric [2,3]-Sigmatropic Rearrangement of Allylic Amines. Scope and Mechanistic Investigation. *J. Org. Chem.* **2007**, *72*, 1294–1300.
11. Sun, M.; Lu, H.; Wang, Y.; Yang, H.; Liu, H. Highly Efficient Formal Synthesis of Cephalotaxine, Using the Stevens Rearrangement−Acid Lactonization Sequence as A Key Transformation. *J. Org. Chem.* **2009**, *74*, 2213–2216.
12. The absolute configuration of **9** was assigned in analogy to our previous results from the rearrangement of a benzyl group. See reference 9 for details. The er of **9** was determined by converting it into the corresponding Mosher amide and integrating the peaks from the two diastereomers in the crude ^{1}H NMR spectrum. See Supporting Information.
13. This is in line with our previous observations of the [2,3]-Stevens rearrangements in acyclic systems. See reference 9.
14. Alternative methods for preparing α-allylated quaternary proline derivatives: (a) Seebach, D.; Boes, M.; Naef, R.; Schweizer, W. B. Alkylation of Amino Acids Without Loss of the Optical Activity: Preparation of α-substituted Proline Derivatives. A case of Self-reproduction of Chirality. *J. Am. Chem. Soc.* **1983**, *105*, 5390–5398. (b) Wang, H.; Germanas, J. P. 4-Alkyl-2-trichloromethyloxazolidin-5-ones: Valuable Precursors to Enantiomerically Pure *C*- and *N*-Protected α-Alkyl Prolines. *Synlett* **1999**, *1*, 33–36.
15. Tietze, L. F.; Schirok, H.; Wöhrmann, M.; Schrader, K. Efficient Synthesis of Six-Membered Ring D Analogues of the Pentacyclic Alkaloid Cephalotaxine by Two Palladium-Catalyzed Reactions. *Eur. J. Org. Chem.* **2000**, *13*, 2433–2444.

16. For recent applications of similar iodolactonizations, see (a) Blot, V.; Reboul, V.; Metzner, P. Studies Directed Towards the Enantioselective Synthesis of Ethisolide and Isoavenaciolide. *Eur. J. Org. Chem.* **2006**, *8*, 1934–1939. (b) Blot, V.; Reboul, V.; Metzner, P. J. Asymmetric Induction of the Iodolactonization Reaction of α-Sulfurated γ-Unsaturated Amides. *Org. Chem.* **2004**, *69*, 1196–1201. For a review on electrophilic cyclizations of unsaturated amides (c) Robin, S.; Rousseau, G. Electrophilic Cyclization of Unsaturated Amides. *Tetrahedron*, **1998**, *54*, 13681–13736.
17. Using an oil-bath instead of microwave reactor took several days to fully consume all **17** and gave lower yields (14–20%).
18. Wang, Z.; Li, Z.; Wang, K.; Wang, Q. Efficient and Chirally Specific Synthesis of Phenanthro-Indolizidine Alkaloids by Parham-Type Cycloacylation. *Eur. J. Org. Chem.* **2010**, *2*, 292–299.
19. Parham reactions can be very condition dependent, see reference 8 and Moreau, A.; Lorion M.; Couture, A.; Deniau, E.; Grandclaudon, P. A New Total Synthesis of Porritoxin. *J. Org. Chem.* **2006**, *71*, 3303–3305.
20. Ruiz, J.; Sotomayor, N.; Lete, E. Parham-Type Cycliacylation with Weinreb Amides. Application to the Synthesis of Fused Indolizinone Systems. *Org. Lett.* **2003**, *5*, 1115–1117.
21. The er was determined by HPLC analysis, comparing with racemic material that was prepared by an identical route starting from *rac*-**13**. See Supporting Information.
22. Isono, N.; Mori, M. Total Synthesis of (–)-Cephalotaxine. *J. Org. Chem.* **1995**, *60*, 115–119.
23. Zhang, Z.-W.; Wang, C.-C.; Xue, H.; Dong, Y.; Yang, J.-H.; Liu, S.; Liu, W.-Q.; Li, W.-D. Z. Asymmetric Formal Synthesis of (−)-Cephalotaxine via Palladium-Catalyzed Enantioselective Tsuji Allylation. *Org. Lett.*, **2018**, *20*, 1050–1053.
24. Prepared according to ref 15.
25. Minor diastereomer of **17** co-elutes with impurities and was not characterized further.