A Formal Synthesis of (±)-Cephalotaxine via Pauson–Khand Reaction

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Abstract: A concise route toward the formal synthesis of (±)-cephalotaxine has been developed. An intermolecular Pauson–Khand reaction was adopted to construct the cyclopentenone ring efficiently with high regioselectivity.

Key words: (±)-cephalotaxine, alkaloids, intermolecular Pauson–Khand reaction, cycloaddition, cyclopentenones, regioselectivity

Cephalotaxine is the parent structure of a class of complex natural products, *Cephalotaxus* alkaloids, which are isolated from the Asian plant *Cephalotaxus drupacea* or *Cephalotaxus fortunei*.[1] The unique spiro-annulated polycyclic structure was elucidated by X-ray analysis (Figure 1).[2] Several natural ester derivatives **2**–**5** of cephalotaxine have demonstrated potent anti-leukemic activity, exhibiting acute toxicity against P388 and L1210 leukemia cells with IC_{50} values in the ng/mL range.[3] The outstanding bioactivity of these derivatives has attracted great interest from the chemical community in the synthesis of cephalotaxine. Since the first total synthesis of (±)-cephalotaxine by Weinreb in 1972,[4] a number of innovative synthetic strategies have been developed.[5]

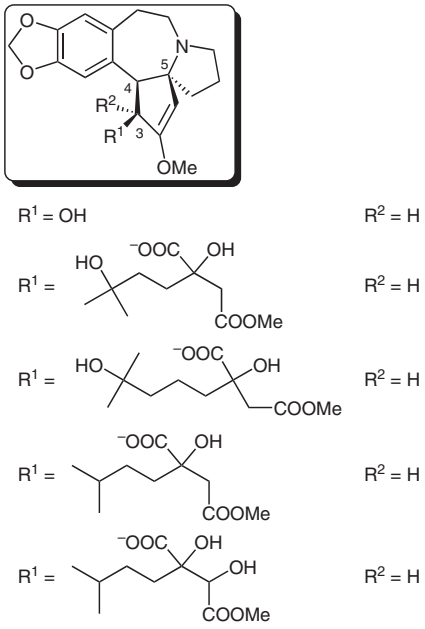
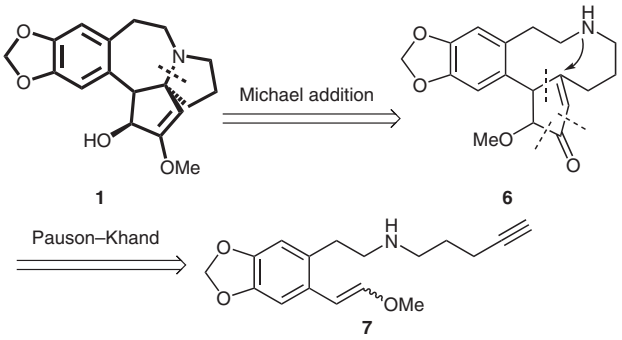


Figure 1 The structure of cephalotaxine and its derivatives

Construction of the unique spirocyclic amine moiety within cephalotaxine is the most challenging part of the reported synthetic work.[5d,g,6–8] The retrosynthetic analysis in Scheme 1 shows that the spirocyclic amine moiety might be constructed by an intramolecular Michael addition within **6**, and the cyclopentenone portion of **6** could be prepared by an intermolecular Pauson–Khand reaction from the 1,11-enyne **7**.[9] This appeared to be a straightforward and concise strategy, and employing the Pauson–Khand reaction for this purpose seemed to be worth attempting.[10]



Scheme 1 Retrosynthetic analysis of cephalotaxine

Piperonal and chloromethyl methyl ether were used to synthesize **8** and **9**, respectively, and coupling of these gave enolic ether **10** via a Wittig reaction. After lithium–halogen exchange and subsequent reaction with oxirane, two-carbon-atom-extended alcohol **11** was obtained. Reaction of **12** with pent-4-yn-1-amine gave the enyne precursor **7** for the Pauson–Khand reaction. However, although the reaction was attempted under a variety of different conditions, neither **7** nor **13** underwent the intramolecular Pauson–Khand reaction to form cyclopentenone **6** or **14**. Constructing the cyclopentenone moiety bearing a ten-membered ring via a Pauson–Khand reaction from our substrates seemed to be difficult (Scheme 2).

We then decided to adopt an intermolecular Pauson–Khand reaction strategy. As also reported by Mariano,[8] the spirocyclic amine moiety can be constructed by an intramolecular Michael addition reaction from **15** (Scheme

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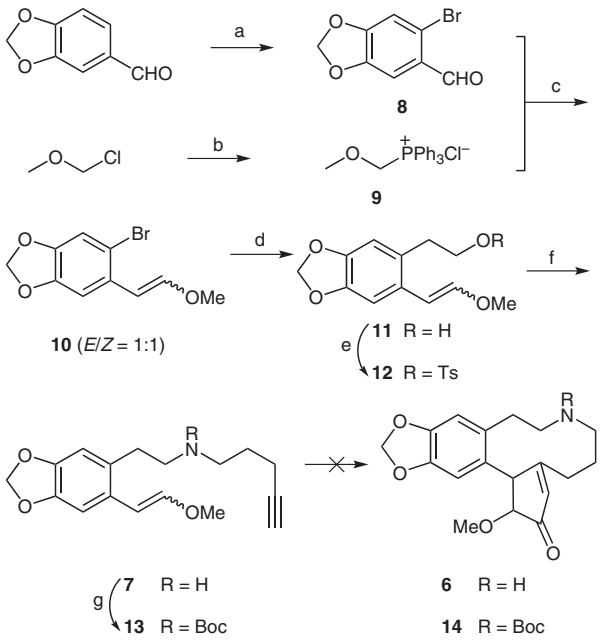
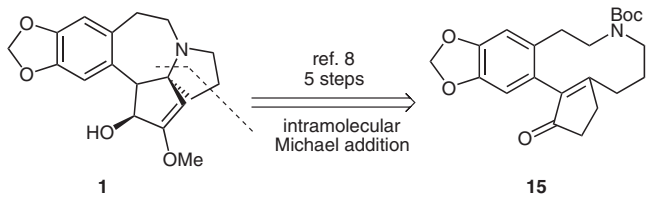


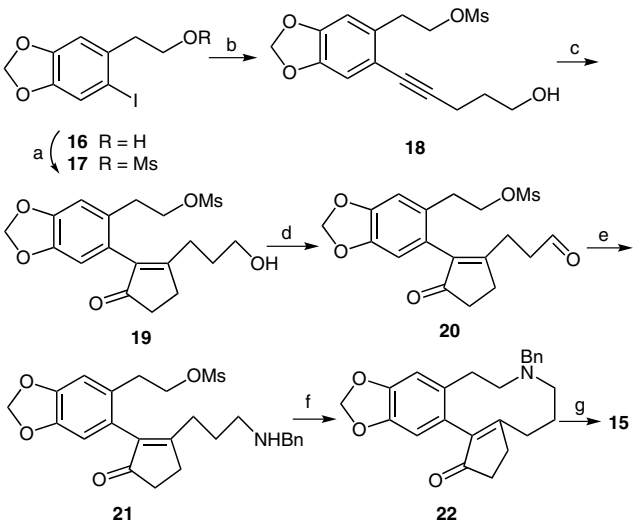
Scheme 2 Synthesis of **6** or **14**. *Reagents and conditions*: (a) Br_2, Fe, AcOH, r.t., 68%; (b) Ph_3P, CH_2Cl_2, quant.; (c) *t*-BuOK, THF, r.t., 1.5 h, 85%; (d) *t*-BuLi, oxirane, –78 °C to r.t., 70%; (e) TsCl, Et_3N, CH_2Cl_2, r.t., 95%; (f) pent-4-yn-1-amine, DIPEA, TBAI, THF, 74%; (g) Boc_2O, 5% NaOH, CH_2Cl_2, quant.

3). The cyclopentenone ring portion of **15** might be constructed via an intermolecular Pauson–Khand reaction with ethene.



Scheme 3 Mariano's work on cephalotaxine[8]

We synthesized **15** from **16** (Scheme 4). Firstly, we protected the hydroxyl group of **16** by reaction with mesyl chloride, to form **17**. We found that **17** tends to eliminate under traditional Sonogashira coupling reaction conditions; therefore, mild conditions at room temperature were applied, and the coupling product **18** could be obtained in 87% yield. Next, the intermolecular Pauson–Khand reaction of internal alkyne **18** was carried out. Although two isomeric products are possible, according to the direction of the carbonyl group,[11] we were delighted to find that only the desired isomer **19** was obtained. Under optimized conditions, a satisfactory yield of 58% was obtained when *n*-butyl methyl sulfide was used as a promoter with dimethyl sulfoxide as the oxidant. Subsequently, the hydroxyl group in **19** was converted into the benzylamine group in **21** by two steps consisting of pyridinium chlorochromate oxidation and reductive amination. Then **21** was cyclized to the ten-membered ring compound **22**, which was further converted into the critical intermediate **15**, which can be converted into cephalotaxine in five steps as described in the literature.[5g,8] This straightforward synthesis of **15** from **16** was achieved in an overall yield of 20% over eight steps.



Scheme 4 Synthesis of key intermediate **15**. *Reagents and conditions*: (a) MsCl, Et_3N, r.t., quant.; (b) $Pd(PPh_3)_4$, CuI, TBAI, pent-4-yn-1-ol, Et_3N, CH_2Cl_2, 87%; (c) $Co_2(CO)_8$, *n*-BuSMe, DMSO, ethene (50 atm), toluene, 100 °C, 58%; (d) PCC, CH_2Cl_2, r.t., 68%; (e) $BnNH_2$·HCl, THF–EtOH, then NaOAc, $NaBH_3CN$, r.t.; (f) DIPEA, MeCN, 75 °C, 72 h, 70% (2 steps); (g) 1. Pd/C, H_2; 2. Boc_2O, Et_3N, 83% (2 steps).

In conclusion, we have developed a concise route for the formal synthesis of cephalotaxine via an intermolecular Pauson–Khand reaction to form the cyclopentenone core structure conveniently. This formal synthetic route to the key intermediate **15** is the shortest reported so far. It demonstrates an efficient way to construct a cyclopentenone group in some natural products from alkyne precursors.

Chemicals and solvents were either purchased from commercial suppliers or purified by standard techniques. Analytical TLC was performed on Silicycle silica gel plates with F-254 as an indicator and compounds were visualized by irradiation with UV light. Flash column chromatography was carried out on silica gel H (40 μm). ^1H NMR and ^{13}C NMR spectra were recorded on a Varian Mercury-300 spectrometer (300 MHz, ^1H; 75 MHz, ^{13}C). The spectra were recorded of samples in $CDCl_3$ or acetone-d_6 as solvent at r.t., and ^1H and ^{13}C NMR chemical shifts are reported in ppm relative to either the residual solvent peak (^1H, ^{13}C), or TMS (^1H) as an internal standard. IR spectra were recorded by using a Bio-Rad FTS-185 instrument. MS was performed on an Agilent 5973N or HP 5989A mass instrument (EI). HRMS was performed on a Waters Micromass GCT (EI).

6-Bromobenzo[*d*][1,3]dioxole-5-carbaldehyde (8)

A suspension of Fe (11.72 g, 0.21 mol) in AcOH (140 mL) was treated dropwise with Br_2 (17 mL, 0.33 mol) and the mixture was then stirred for 20 min at 0 °C. Piperonal (30.00 g, 0.20 mol) in AcOH (100 mL) was added dropwise and the mixture was stirred for 5 min at 0 °C; then Br_2 (10 mL, 0.19 mol) was added dropwise at 0 °C. The dark brown soln was stirred at r.t. until no piperonal was detected by TLC. The soln was diluted with CH_2Cl_2 (to 1 L) and

neutralized with sat. aq $Na_2S_2O_3$ (500 mL). The organic layer was neutralized with 10% aq Na_2CO_3 and separated. The organic layer was washed with sat. aq NaCl (2 × 300 mL), dried (Na_2SO_4), and concentrated to dryness. The solid was recrystallized (EtOH); this gave **8**.

Yield: 31.40 g (68%); colorless crystals.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.17 (s, 1 H), 7.36 (s, 1 H), 7.26 (s, 1 H), 6.08 (s, 2 H).

(Methoxymethyl)triphenylphosphonium Chloride (9)
A soln of Ph_3P (10.00 g, 38.10 mmol) in CH_2Cl_2 (20 mL) was treated with MOMCl (3.20 mL, 42.60 mmol) and the mixture was stirred overnight under reflux until no Ph_3P was detected by TLC. The soln changed to a suspension after cooling to r.t., and benzene (10 mL) was added. CH_2Cl_2 and MOMCl were removed by vacuum distillation. Product **9** was collected by filtration and washed with petrol ether.

Yield: 14.50 g (100%); white solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.87–7.61 (m, 15 H), 5.89 (d, *J* = 4.0 Hz, 2 H), 3.69 (s, 3 H).

5-Bromo-6-(2-methoxyvinyl)benzo[*d*][1,3]dioxole (10)
A suspension of **9** (1.84 g, 5.38 mmol) in THF (20 mL) was treated with *t*-BuOK (0.57 g, 5.38 mmol) and the mixture was stirred for 20 min at r.t. under an argon atmosphere. The color of the suspension changed from white to brown. Then **8** (0.69 g, 3.00 mmol) was added and the mixture was stirred for 1.5 h at r.t. until no **8** was detected. The soln was quenched with sat. aq NH_4Cl soln (40 mL), the organic soln was separated, and the aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic layer was dried (Na_2SO_4), and concentrated to dryness; the residue was purified by flash chromatography (silica gel, PE–EtOAc, 100:1); this gave the products (*Z*)-**10** and (*E*)-**10**.

(*Z*)-**10**: yield: 330 mg (43%); light yellow liquid.

(*E*)-**10**: yield: 330 mg (42%); light gray solid.

IR (KBr): (*Z*)-**10**: 2937, 1648, 1477, 1090, 1040 cm^{-1}; (*E*)-**10**: 3001, 1639, 1481, 1135, 1038 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ (*Z*) = 7.63 (s, 1 H), 7.00 (s, 1 H), 6.13 (d, *J* = 7.2 Hz, 1 H), 5.92 (s, 2 H), 5.52 (d, *J* = 7.2 Hz, 1 H), 3.73 (s, 3 H); δ (*E*) = 6.98 (s, 1 H), 6.85 (d, *J* = 12.9 Hz, 1 H), 6.80 (s, 1 H), 6.01 (d, *J* = 12.9 Hz, 1 H), 5.93 (s, 2 H), 3.70 (s, 3 H).

^{13}C NMR (75MHz, $CDCl_3$): δ (*Z*) = 148.0, 146.9, 146.1, 128.5, 113.3, 112.3, 109.6, 103.8, 101.5, 60.7; δ (*E*) = 149.4, 147.4, 146.4, 129.4, 113.1, 112.5, 105.1, 104.4, 101.5, 56.4.

MS (EI): *m*/*z* (%) = 256 (100) [M$^+$].

HRMS (EI): *m*/*z* calcd for $C_{10}H_9O_3Br$: 255.9730; found: 255.9747.

2-{6-(2-Methoxyvinyl)benzo[*d*][1,3]dioxol-5-yl}ethanol (11)
A soln of **10** (514 mg, 2.00 mmol) in THF (10 mL) was treated with 1.5 M *t*-BuLi in pentane (3.6 mL, 4.00 mmol) and the mixture was stirred for 1 h at –78 °C under argon atmosphere. The color of the soln changed from colorless to orange. Oxirane (0.35 ml, 6.00 mmol) was added and the mixture was stirred for 2 h at –78 °C and 16 h at r.t. The soln was quenched with sat. aq NH_4Cl soln (1 mL) and filtered. The organic soln was concentrated to dryness, and the residue was purified by flash chromatography (silica gel, PE–EtOAc, 4:1); this gave the products (*Z*)-**11** and (*E*)-**11**.

(*Z*)-**11**: yield: 156 mg (35%); light yellow liquid.

(*E*)-**11**: yield: 156 mg (35%); light yellow liquid.

IR (KBr): (*Z*)-**11**: 3369, 2939, 2884, 1648, 1484, 1099, 1041 cm^{-1}; (*E*)-**11**: 3387, 2939, 2886, 1639, 1504, 1485 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ (*Z*) = 7.48 (s, 1 H), 6.67 (s, 1 H), 6.11 (d, *J* = 7.1 Hz, 1 H), 5.92 (s, 2 H), 5.32 (d, *J* = 7.1 Hz, 1 H), 3.84–3.66 (m, 5 H), 2.85 (t, *J* = 6.7 Hz, 2 H); δ (*E*) = 6.75 (s, 1 H), 6.73 (d, *J* = 13.4 Hz, 1 H), 6.65 (s, 1 H), 5.93 (d, *J* = 12.7 Hz, 1 H), 5.88 (s, 2 H), 3.75 (t, *J* = 6.6 Hz, 2 H), 3.65 (s, 3 H), 2.80 (t, *J* = 6.8 Hz, 2 H), 1.93 (br, 1 H).

^{13}C NMR (75MHz, $CDCl_3$): δ (*Z*) = 146.9, 145.7, 145.4, 128.7, 127.5, 109.8, 109.3, 101.9, 100.6, 62.8, 60.3, 36.5; δ (*E*) = 148.9, 146.3, 145.9, 128.4, 128.3, 110.1, 105.6, 102.7, 100.7, 62.8, 56.6, 36.3.

MS (EI): (*Z*)-**11**: *m*/*z* (%) = 222 (88.13) [M$^+$], 161 (100); (*E*)-**11**: *m*/*z* (%) = 222 (100) [M$^+$].

HRMS (EI) (*Z*)-**11**: calcd for $C_{12}H_{14}O_4Na$: 245.0784; found: 245.0788; (*E*)-**11**: calcd for $C_{12}H_{14}O_4Na$: 245.0784; found: 245.0782.

2-{6-(2-Methoxyvinyl)benzo[*d*][1,3]dioxol-5-yl}ethyl 4-Methylbenzenesulfonate (12)
A soln of **11** (27 mg, 0.12 mmol) in CH_2Cl_2 (1 mL) was treated with Et_3N (0.1 mL) and TsCl (30 mg, 0.16 mmol) and the mixture was stirred overnight at r.t. The soln was quenched with H_2O (1 mL), the organic soln was separated, and the aqueous layer was extracted by CH_2Cl_2 (3 × 3 mL). The combined organic layer was concentrated to dryness and the residue was purified by flash chromatography (silica gel, PE–EtOAc, 6:1); this gave products (*Z*)-**12** and (*E*)-**12**.

(*Z*)-**12**: yield: 22 mg (47%); light yellow liquid.

(*E*)-**12**: yield: 23 mg (48%); light yellow liquid.

IR (KBr): (*Z*)-**12**: 2900, 1486, 1358, 1176, 1098 cm^{-1}; (*E*)-**12**: 2900, 1639, 1487, 1357, 1176 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ (*Z*) = 7.71 (d, *J* = 8.2 Hz, 2 H), 7.37 (s, 1 H), 7.29 (d, *J* = 8.2 Hz, 2 H), 6.51 (s, 1 H), 6.07 (d, *J* = 7.2 Hz, 1 H), 5.90 (s, 2 H), 5.12 (d, *J* = 7.2 Hz, 1 H), 4.10 (t, *J* = 7.6 Hz, 2 H), 3.73 (s, 3 H), 2.91 (t, *J* = 7.6 Hz, 2 H), 2.44 (s, 3 H); δ (*E*) = 7.66 (d, *J* = 8.3 Hz, 2 H), 7.26 (d, *J* = 7.9 Hz, 2 H), 6.65 (s, 1 H), 6.64(d, *J* = 12.6 Hz, 1 H) 6.49 (s, 1 H), 5.85 (s, 1 H), 5.75 (d, *J* = 12.7 Hz, 1 H), 4.07 (t, *J* = 7.4 Hz, 1 H).

^{13}C NMR (75MHz, $CDCl_3$): δ (*Z*) = 147.3, 146.1, 145.4, 144.4, 132.6, 129.5, 127.6, 127.5, 125.9, 109.7, 109.3, 101.2, 100.6, 69.8, 60.3, 32.9, 21.4; δ (*E*) = 149.3, 146.7, 145.8, 144.5, 132.7, 129.5, 128.5, 127.5, 125.6, 109.9, 105.6, 101.7, 100.7, 69.5, 56.4, 32.8, 21.4.

MS (EI): (*Z*)-**12**: *m*/*z* (%) = 376 (51.34) [M$^+$], 161 (100); (*E*)-**12**: *m*/*z* (%) = 376 (4.29) [M$^+$], 161 (100).

HRMS (MALDI): *m*/*z* calcd for $C_{19}H_{21}O_6S$: 377.1069; found: 377.1053.

***N*-(2-{6-(2-Methoxyvinyl)benzo[*d*][1,3]dioxol-5-yl}ethyl)pent-4-yn-1-amine (7)**
A soln of **12** (142 mg, 0.32 mmol), TBAI (117 mg, 0.32 mmol), and DIPEA (0.13 mL, 0.74 mmol) in THF (1.5 mL) was treated dropwise with pent-4-yn-1-amine (80 mg, 0.21 mmol) in THF (0.5 mL) and the mixture was stirred for 3 h under reflux. The soln was concentrated to dryness and the residue was purified by flash chromatography (silica gel, EtOAc–MeOH, 50:1); this gave **7**.

Yield: 45 mg (74%); red solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.75 (s, 1 H), 6.74 (d, *J* = 12.8 Hz, 1 H), 6.64 (s, 1 H), 5.94 (d, *J* = 12.8 Hz, 1 H), 5.88 (s, 2 H), 3.66 (s, 3 H), 2.83–2.67 (m, 6 H), 2.23 (dt, *J* = 2.7, 7.1 Hz, 2 H), 1.94 (t, *J* = 2.7 Hz, 1 H), 1.68 (5, *J* = 7.1 Hz, 2 H), 1.43 (br, 1 H).

ESI-MS: *m*/*z* = 288.1 [M + H]$^+$.

HRMS (EI): *m*/*z* calcd for $C_{17}H_{22}O_3N$: 288.1585; found: 288.1594.

***tert*-Butyl (2-{6-(2-Methoxyvinyl)benzo[*d*][1,3]dioxol-5-yl}ethyl)(pent-4-yn-1-yl)carbamate (13)**
An emulsion of **7** (29 mg, 0.10 mmol) in CH_2Cl_2 (1 mL) and H_2O (1 mL) was treated with NaOH (4.40 mg, 0.11 mmol) and Boc_2O (24 mg, 0.11 mmol) in CH_2Cl_2 (1.00 mL) and the mixture was stirred for 2 h at r.t. The emulsion was separated and the aqueous

layer was extracted by CH_2Cl_2 (3 × 3 mL). The combined organic layer was concentrated to dryness and the residue was purified by flash chromatography (silica gel, PE–EtOAc, 10:1); this gave **13**.

Yield: 39 mg (100%); brown solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.76 (s, 2 H), 6.60 (d, *J* = 14.4 Hz, 1 H), 6.08 (d, *J* = 12.5 Hz, 1 H), 5.89 (s, 2 H), 3.70 (br, 3 H), 3.29 (dd, *J* = 8.5, 6.8 Hz, 2 H), 3.21 (br, 2 H), 2.78 (br, 2 H), 2.17 (br, 2 H), 1.96 (t, *J* = 2.6 Hz, 1 H), 1.71 (br, 2 H), 1.45 (s, 9 H).

MS (EI): *m*/*z* (%) = 387 (57.23) [M$^+$], 57 (100).

HRMS (MALDI): *m*/*z* calcd for $C_{22}H_{29}NO_5Na$: 410.1938; found: 410.1937.

2-{6-Iodobenzo[*d*][1,3]dioxol-5-yl}ethyl Methanesulfonate (17)

A soln of **16** (190 mg, 0.65 mmol) in CH_2Cl_2 (10 mL) was treated with Et_3N (0.20 mL, 1.60 mmol) and MsCl (141 mg, 1.23 mmol) and the mixture was stirred for 1 h at r.t. until no **16** was detected. The soln was quenched with H_2O (10 mL) and separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layer was dried (Na_2SO_4) and concentrated to dryness; then the residue was purified by flash chromatography (silica gel, PE–EtOAc, 5:1); this gave **17**.

Yield: 241 mg (100%); light brown solid.

IR (KBr): 2903, 1478, 1354, 1174 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.43 (s, 1 H), 7.00 (s, 1 H), 6.16 (s, 2 H), 4.55 (t, *J* = 7.0 Hz, 2 H), 3.30 (t, *J* = 7.0 Hz, 2 H), 3.14 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 148.5, 147.6, 131.8, 118.6, 110.2, 101.7, 87.8, 68.6, 39.9, 37.2.

MS (EI): *m*/*z* (%) = 370 (27.68) [M$^+$], 274 (100).

HRMS (MALDI): *m*/*z* calcd for $C_{10}H_{11}NO_5IS$: 369.9372; found: 369.9379.

2-{6-(5-Hydroxypent-1-yn-1-yl)benzo[*d*][1,3]dioxol-5-yl}ethyl Methanesulfonate (18)

A soln of **17** (629 mg, 1.70 mmol), TBAI (940 mg, 2.54 mmol), $Pd(PPh_3)_4$ (196 mg, 0.17 mmol), CuI (34 mg, 0.18 mmol) and pent-4-yl-1-ol (275 g, 3.27 mmol) in CH_2Cl_2 (8 mL) and Et_3N (1 mL) was stirred overnight at r.t. under an argon atmosphere. The soln was filtered and concentrated to dryness and the residue was purified by flash chromatography (silica gel, PE–EtOAc, 1:1); this gave **18**.

Yield: 483 mg (87%); light yellow liquid.

IR (KBr): 3380, 2940, 1486, 1352, 1174 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.81 (s, 1 H), 6.66 (s, 1 H), 5.91 (s, 2 H), 4.37 (t, *J* = 7.2 Hz, 2 H), 3.76 (t, *J* = 6.1 Hz, 2 H), 3.10 (t, *J* = 7.2 Hz, 2 H), 2.90 (s, 1 H), 2.52 (t, *J* = 6.9 Hz, 2 H), 2.21 (br, 1 H), 1.82 (p, *J* = 6.6 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 147.4, 146.4, 132.1, 116.5, 111.8, 109.8, 101.3, 92.4, 78.6, 69.3, 61.2, 37.2, 34.4, 31.2, 15.8.

ESI-MS: *m*/*z* = 349.1 [M + Na]$^+$.

HRMS (MALDI): *m*/*z* calcd for $C_{15}H_{18}O_6SNa$: 349.0716; found: 349.0711.

2-{6-[2-(3-Hydroxypropyl)-5-oxocyclopent-1-en-1-yl]benzo[*d*][1,3]dioxol-5-yl}ethyl Methanesulfonate (19)

A soln of **18** (258 mg, 0.79 mmol) and $Co_2(CO)_8$ (297 mg, 0.87 mmol) in toluene (10 mL) was stirred at r.t. under an argon atmosphere until no **18** was detected. *n*-BuSMe (82 mg, 0.79 mmol) and DMSO (450 mg, 5.76 mmol) were added and the soln was transferred to a high-pressure reactor. The soln was stirred overnight at 100 °C under an ethene atmosphere (50 atm). The soln was concentrated to dryness and the residue was purified by flash chromatography (silica gel, PE–EtOAc, 1:4); this gave **19**.

Yield: 175 mg (58%); colorless liquid.

IR (KBr): 3384, 2938, 1486, 1353, 1174 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.76 (s, 1 H), 6.44 (s, 1 H), 5.96 (d, *J* = 12.1 Hz, 2 H), 4.20 (t, *J* = 7.3 Hz, 2 H), 3.61 (br, 1 H), 2.91 (s, 3 H), 2.80–2.69 (m, 4 H), 2.60–2.53 (m, 2 H), 2.53–2.32 (m, 2 H), 1.83–1.70 (m, 2 H), 1.55 (br, 1 H).

ESI-MS: *m*/*z* = 383.1 [M + Na]$^+$.

HRMS (MALDI): *m*/*z* calcd for $C_{18}H_{22}O_7SNa$: 405.0978; found: 405.0999.

2-{6-[5-Oxo-2-(3-oxopropyl)cyclopent-1-en-1-yl]benzo[*d*][1,3]dioxol-5-yl}ethyl Methanesulfonate (20)

A suspension of **19** (46 mg, 0.12 mmol) and silica gel (50 mg, 200–300) in CH_2Cl_2 (2.0 mL) was treated with PCC (52 mg, 0.24 mmol) at 0 °C and the mixture was stirred for 2 h at r.t. until no **19** was detected. The black suspension was filtered though Celite and the filtrate was concentrated to dryness; the residue was purified by flash chromatography (silica gel, PE–EtOAc, 1:2); this gave **20**.

Yield: 31 mg (68%); colorless liquid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.75 (s, 1 H), 6.78 (s, 1 H), 6.46 (s, 1 H), 5.97 (dd, *J* = 10.4, 1.1 Hz, 2 H), 4.20 (br, 2 H), 2.91 (s, 3 H), 2.82–2.52 (m, 10 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 208.1, 199.9, 175.1, 147.9, 141.8, 128.5, 125.0, 110.0, 101.3, 70.0, 40.6, 37.1, 34.5, 33.3, 29.6, 29.3, 24.0.

7-Benzyl-2,3,4,5,6,7,8,9-octahydro-1*H*-[1,3]dioxolo[4′,5′:4,5]benzo[1,2-*d*]cyclopenta[*f*]azecin-1-one (22)

A soln of **20** (76 mg, 0.20 mmol) in anhyd THF (4.5 mL) and anhyd EtOH (2 mL) was treated with $BnNH_2$·HCl (117 mg, 0.81 mmol) and the mixture was stirred for 1 h at r.t. The soln was sequentially treated with NaOAc (67 mg, 0.40 mmol) and $NaBH_3CN$ (26 mg, 0.40 mmol) and then stirred overnight at r.t. until no imine was detected. The soln was quenched with H_2O (20 mL) and NaCl (to saturate the soln), and then separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layer was dried (Na_2SO_4), and concentrated to dryness to give **21**. A soln of **21** and DIPEA (0.15 mL) in MeCN (50 mL) was stirred for 72 h at 75 °C under an argon atmosphere in a sealed tube. The soln was concentrated to dryness and the residue was purified by flash chromatography (silica gel, PE–EtOAc, 8:1); this gave **22**.

Yield: 52 mg (70%); white solid.

IR (KBr): 2953, 2789, 1697, 1500, 1484, 1030 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.20–7.05 (m, 3 H), 6.79–6.72 (m, 2 H), 6.42 (s, 1 H), 6.30 (s, 1 H), 6.02 (d, *J* = 1.4 Hz, 1 H), 5.92 (d, *J* = 1.4 Hz, 1 H), 3.70 (d, *J* = 14.2 Hz, 1 H), 3.13 (dt, *J* = 12.8, 4.2 Hz, 1 H), 3.04 (d, *J* = 14.3 Hz, 1 H), 2.86–2.73 (m, 1 H), 2.62–2.55 (m, 3 H), 2.55–2.06 (m, 7 H), 1.85 (dt, *J* = 13.9, 3.8 Hz, 1 H), 1.69 (br, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 208.7, 177.1, 147.2, 145.4, 144.3, 139.4, 134.0, 128.2, 127.7, 126.4, 125.8, 109.4, 108.5, 100.7, 58.4, 54.6, 48.8, 34.6, 30.8, 28.3, 27.9, 23.4.

ESI-MS: *m*/*z* = 376.2 [M + H]$^+$.

HRMS (MALDI): *m*/*z* calcd for $C_{24}H_{26}NO_3$: 376.1907; found: 376.1922.

***tert*-Butyl 1-Oxo-2,3,5,6,8,9-hexahydro-1*H*-[1,3]dioxolo[4′,5′:4,5]benzo[1,2-*d*]cyclopenta[*f*]azecine-7(4*H*)-carboxylate (15)**

A suspension of **22** (36 mg, 0.10 mmol) and Pd/C (4 mg) in *i*-PrOH (5 mL) was stirred overnight at 50 °C under a H_2 atmosphere (1 atm) until no **22** was detected. The suspension was filtered and concentrated to give **23**. A soln of **23** (0.05 mmol), Et_3N (0.1 mL), and Boc_2O (0.1 mL, 0.40 mmol) in CH_2Cl_2 (5 mL) was stirred at r.t. for 2 h until no **23** was detected; then the soln was concentrated to dryness and the residue was purified by flash chromatography (silica gel, PE–EtOAc, 2:1); this gave **15**.

Yield: 16 mg (83%); white solid.

IR (KBr): 2921, 1695, 1484, 1160 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 6.76 (s, 1 H), 6.37 (s, 1 H), 5.92 (d, *J* = 6.0 Hz, 1 H), 3.44 (br, 2 H), 3.02 (br, 2 H), 2.93–2.76 (m, 1 H), 2.64–2.37 (m, 7 H), 2.14 (br, 2 H), 1.72 (br, 2 H), 1.34 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 208.0, 178.1, 156.0, 147.6, 146.1, 142.4, 132.7, 125.9, 109.8, 108.6, 100.9, 79.4, 51.4, 47.6, 34.7, 32.1, 29.6, 29.0, 28.2, 23.9.

MS (EI): *m*/*z* (%) = 385 (6.04) [M^+], 57 (100).

HRMS (EI): *m*/*z* calcd for $C_{24}H_{27}NO_5$: 385.1889; found: 385.1894.

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References

(1) For reviews on the *Cephalotaxus* alkaloids, see: (a) Miah, M. A. J.; Hudlicky, T.; Reed, J. W. *Cephalotaxus alkaloids*, In *The Alkaloids*; Vol. 51; Academic Press: New York, **1998**, 199–269. (b) Huang, L.; Xue, Z. *Cephalotaxus alkaloids*, In *The Alkaloids*; Vol. 23; Academic Press: New York, **1984**, 157–226.
(2) Abraham, D. J.; Rosenstein, R. D.; McGandy, E. L. *Tetrahedron Lett.* **1969**, *10*, 4085.
(3) Morita, H.; Arisaka, M.; Yoshida, N.; Kobayashi, J. *Tetrahedron* **2000**, *56*, 2929.
(4) Auerbach, J.; Weinreb, S. M. *J. Am. Chem. Soc.* **1972**, *94*, 7172.
(5) (a) Yasuda, S.; Yamada, T.; Hanaoka, M. *Tetrahedron Lett.* **1986**, *27*, 2023. (b) Kuehne, M. E.; Bornmann, W. G.; Parsons, W. H.; Spitzer, T. D.; Blount, J. F.; Zubieta, J. *J. Org. Chem.* **1988**, *53*, 3439. (c) Burkholder, T. P.; Fuchs, P. L. *J. Am. Chem. Soc.* **1988**, *110*, 2341. (d) Burkholder, T. P.; Fuchs, P. L. *J. Am. Chem. Soc.* **1990**, *112*, 9601. (e) Ikeda, M.; Okano, M.; Kosaka, K.; Kido, M.; Ishibashi, H. *Chem. Pharm. Bull.* **1993**, *41*, 276. (f) Isono, N.; Mori, M. *J. Org. Chem.* **1995**, *60*, 115. (g) Lin, X.; Kavash, R. W.; Mariano, P. S. *J. Org. Chem.* **1996**, *61*, 7335. (h) Tietze, L. F.; Schirok, H. *Angew. Chem. Int. Ed.* **1997**, *36*, 1124. (i) Nagasaka, T.; Sato, H.; Saeki, S. I. *Tetrahedron: Asymmetry* **1997**, *8*, 191. (j) Tietze, L. F.; Schirok, H. *J. Am. Chem. Soc.* **1999**, *121*, 10264. (k) Suga, S.; Watanabe, M.; Yoshida, J. *J. Am. Chem. Soc.* **2002**, *124*, 14824. (l) Koseki, Y.; Sato, H.; Watanabe, Y.; Nagasaka, T. *Org. Lett.* **2002**, *4*, 885. (m) Li, W.-D. Z.; Wang, Y.-Q. *Org. Lett.* **2003**, *5*, 293. (n) Eckelbarger, J. D.; Wilmot, J. T.; Gin, D. Y. *J. Am. Chem. Soc.* **2006**, *128*, 10370. (o) Li, W.-D. Z.; Wang, X.-W. *Org. Lett.* **2007**, *9*, 1211. (p) Liu, Q.; Ferreira, E. M.; Stoltz, B. M. *J. Org. Chem.* **2007**, *72*, 7352. (q) Hameed, A.; Blake, A. J.; Hayes, C. J. *J. Org. Chem.* **2008**, *73*, 8045. (r) Esmieu, W. R.; Worden, S. M.; Catterick, D.; Wilson, C.; Hayes, C. J. *Org. Lett.* **2008**, *10*, 3045. (s) Taniguchi, T.; Ishibashi, H. *Org. Lett.* **2008**, *10*, 4129. (t) Sun, M.-R.; Lu, Y.-Z.; Yang, H.; Liu, H.-M. *J. Org. Chem.* **2009**, *74*, 2213. (u) Li, W.-D. Z.; Duo, W.-G.; Zhuang, C.-H. *Org. Lett.* **2011**, *13*, 3538.
(6) Parry, R. J.; Schwab, J. M. *J. Am. Chem. Soc.* **1975**, *97*, 2555.
(7) Schwab, J. M.; Parry, R. J.; Foxman, B. M. *J. Chem. Soc., Chem. Commun.* **1975**, 906.
(8) Lin, X.; Kavash, R. W.; Mariano, P. S. *J. Am. Chem. Soc.* **1994**, *116*, 9791.
(9) Shore, N. E. In *Comprehensive Organic Synthesis*; Vol. 5; Trost, B. M.; Fleming, I., Eds.; Pergamon: Oxford, **1991**, 1037–1064.
(10) For some examples, see: (a) Ahmar, M.; Locatelli, C.; Colombier, D.; Cazes, B. *Tetrahedron Lett.* **1997**, *38*, 5281. (b) Perez-Serrano, L.; Casarrubios, L.; Dominguez, G.; Perez-Castells, J. *Chem. Commun.* **2001**, 2602. (c) Perez-Serrano, L.; Dominguez, G.; Perez-Castells, J. *J. Org. Chem.* **2004**, *69*, 5413. (d) Mukai, C.; Nomura, I.; Yamanishi, K.; Hanaoka, M. *Org. Lett.* **2002**, *4*, 1755. (e) Mukai, C.; Nomura, I.; Kitagaki, S. *J. Org. Chem.* **2003**, *68*, 1376. (f) Mukai, C.; Inagaki, F.; Yoshida, T.; Kitagaki, S. *Tetrahedron Lett.* **2004**, *45*, 4117. (g) Krafft, M. E.; Fu, Z.; Bonaga, L. V. R. *Tetrahedron Lett.* **2001**, *42*, 1427.
(11) For a review, see: Laschat, S.; Becheanu, A.; Bell, T.; Baro, A. *Synlett* **2005**, 2547.

