A Short Enantioselective Synthesis of the Topoisomerase II Inhibitor (+)-Eleutherin

Jennifer S. Gibson, Olivier Andrey, Margaret A. Brimble*

Department of Chemistry, University of Auckland, 23 Symonds St., Auckland, New Zealand
E-mail: m.brimble@auckland.ac.nz

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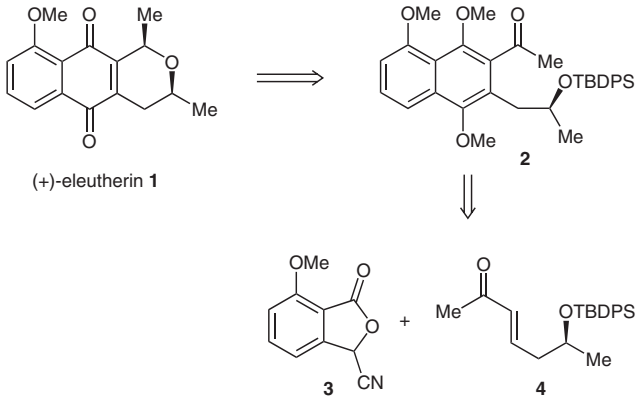
Abstract: A Hauser–Kraus annulation was used as a key step for the concise enantioselective synthesis of the topoisomerase II inhibitor (+)-eleutherin.

Key Words: Hauser–Kraus annulation, (+)-eleutherin, pyranonaphthoquinone

Eleutherin **1**, a member of the pyranonaphthoquinone family of antibiotics, was first isolated in 1950 from the bulb of *Eleutherine americana*.[1] The pyranonaphthoquinone family of antibiotics display a wide range of biological activities and have been proposed to act as bioactive alkylating agents.[2] Additionally, (+)-eleutherin (**1**) is a reversible inhibitor of topoisomerase II – a target for many clinically useful anticancer agents.[3]

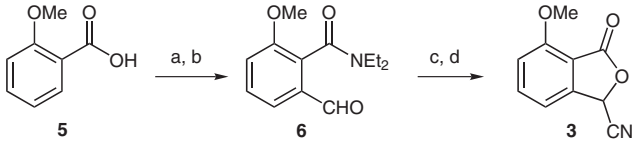


Scheme 1

Several syntheses of racemic eleutherin and analogues have been reported.[4] The first enantioselective synthesis of (+)-eleutherin **1** using (*S*)-mellein as a key intermediate was recently reported by Donner et al.[5] However, this synthesis requires several steps to prepare (*S*)-mellein[6] with a further five steps required to access (+)-eleutherin **1**.[5]

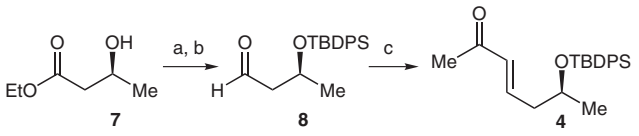
We therefore envisaged a more efficient, alternate route to (+)-eleutherin **1**, proceeding via the intermediate naphthalene **2**, which we planned to access via a Hauser–Kraus annulation[7] of known cyanophthalide **3**[8] with chiral α,β-unsaturated ketone **4**, followed by reductive methylation of the resulting naphthoquinone (Scheme 1).

Cyanophthalide **3** was readily prepared from 2-methoxybenzoic acid (**5**) by conversion to the corresponding *N*,*N*-diethylbenzamide, followed by *ortho*-lithiation and formylation, to afford *ortho*-formyl-*N*,*N*-diethylbenzamide **6**.[9] The latter benzamide **6** was then transformed into cyanophthalide **3** following the method reported by Yoshii et al.[8] (Scheme 2).



Scheme 2 *Reagents and conditions*: (a) $SOCl_2$ (2.2 equiv), toluene, reflux, 2 h then Et_2NH (3 equiv), Et_2O, 1 h, 71%; (b) *t*-BuLi (1.05 equiv), TMEDA (1.05 equiv), THF, –78 °C, 90 min then DMF (20 equiv), 70%; (c) Me_3SiCN (1.5 equiv), KCN (0.1 equiv), CH_2Cl_2, 0 °C, 90 min then r.t., 30 min; (d) AcOH, r.t., 18 h, 66% over 2 steps.

The electrophilic coupling partner for the Hauser–Kraus annulation, α,β-unsaturated ketone **4**, was synthesized from commercially available, chiral non-racemic ester **7**. The hydroxyl group of **7** was protected as a *tert*-butyldiphenylsilyl (TBDPS) ether, with diisobutylaluminum hydride (DIBAL-H) reduction of the ester and Horner–Wadsworth–Emmons reaction of the resulting known aldehyde **8**[10] with dimethyl 2-oxopropyl phosphonate, providing the desired enone **4** (Scheme 3).



Scheme 3 *Reagents and conditions*: (a) TBDPS-Cl (1.5 equiv), imidazole (1.5 equiv), CH_2Cl_2, r.t., 18 h, 97%; (b) DIBAL-H (1.1 equiv), toluene, –78 °C, 15 min, 79%; (c) dimethyl 2-oxopropyl phosphonate (1.3 equiv), NaH (1.3 equiv), THF, –10 °C, 30 min then aldehyde **8** (1 equiv), 1 h, 75%.

The key Hauser–Kraus annulation of cyanophthalide **3** with α,β-unsaturated ketone **4** was best carried out in dimethyl sulfoxide, using potassium *tert*-butoxide as the base. Reductive methylation of the crude naphthoquinone using sodium dithionite under phase transfer conditions, followed by addition of sodium hydroxide and dimethyl

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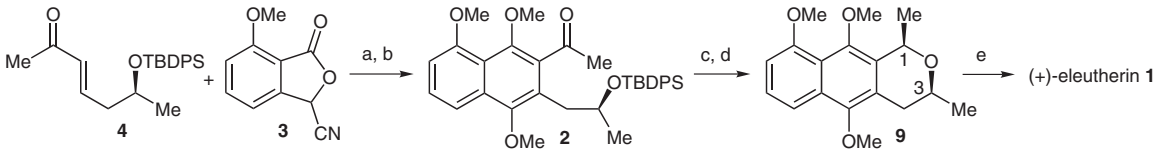

Scheme 4 *Reagents and conditions*: (a) *t*-BuOK (1.1 equiv) DMSO, 15 min; (b) TBABr (0.1 equiv), $Na_2S_2O_4$ (6 equiv), H_2O, THF, 30 min then NaOH (20 equiv), Me_2SO_4 (20 equiv), 2 h, 67% (2 steps); (c) TBAF (10 equiv), THF, r.t., 4 d; (d) TFA (3 equiv), $HSiEt_3$ (3 equiv), CH_2Cl_2, –78 °C → r.t., 56% (2 steps); (e) $(NH_4)_2Ce(NO_3)_6$ (3 equiv), MeCN, H_2O, 80%.

sulfate, gave the desired naphthalene **2** in good yield (Scheme 4). Silyl deprotection of naphthalene **2** using tetra-*n*-butylammonium fluoride and subsequent treatment of the resulting hemiacetal with trifluoroacetic acid and triethylsilane, afforded benzo[*g*]isochromene **9** as a single diastereoisomer, arising from pseudo-axial delivery of the hydride as reported by Kraus et al.[4g] (Scheme 4).

Finally, oxidation of (1*R*,3*S*)-dimethyl benzo[*g*]isochromene **9** with aqueous cerium(IV) ammonium nitrate, gave (+)-eleutherin **1** {$[\alpha]_D^{20}$ +335 (*c* 0.35, CH_2Cl_2); natural (+)-eleutherin[1] $[\alpha]_D^{20}$ +346 (*c* 1.01, $CHCl_3$)} (Scheme 4).

In conclusion, we have developed a concise, enantioselective synthesis of (+)-eleutherin **1** via a Hauser–Kraus annulation of cyanophthalide **3** with α,β-unsaturated ketone **4**.

All reactions were conducted in flame-dried or oven-dried glassware under a dry nitrogen atmosphere unless otherwise noted. All solvents were purified according to standard procedures where necessary. Chemical reagents were used as purchased. Low-resolution mass spectra were recorded on a VG-70SE mass spectrometer at a nominal accelerating voltage of 70eV. Chemical ionisation (CI) mass spectra were obtained with ammonia as the reagent gas. Fast atom bombardment (FAB) mass spectra were obtained with 3-nitrobenzyl alcohol as the matrix. IR specta were obtained using a Perkin–Elmer spectrum 1000 Fourier Transform Infrared spectrometer as a thin film between NaCl plates. TLC was carried out on precoated silica plates (Merck Kieselgel 60F-254) and compounds were visualised by UV fluorescence or by staining with alkaline potassium permanganate solution or vanillin in methanolic sulfuric acid and heating. NMR spectra were obtained using a Bruker DRX-400 operating at either 400 MHz or 100 MHz or a Bruker Avance 300 spectrometer operating at either 300 MHz or 75 MHz. All chemical shifts are given in parts per million (ppm) downfield from TMS as internal standard (^{1}H) or relative to $CDCl_3$ (^{13}C).

(*S*,*E*)-6-(*tert*-Butyldiphenylsilyloxy)hept-3-en-2-one (4)

Dimethyl 2-oxopropylphosphonate (0.33 mL, 2.39 mmol) was added dropwise to a cooled (–10 °C) suspension of NaH (95 mg, 60% w/w) in THF (10 mL). After 30 min, a solution of aldehyde **5** (600 mg, 1.84 mmol) in THF (10 mL) was added. The reaction mixture was allowed to come to r.t., stirred for a further 1 h then quenched by addition of sat. aq NH_4Cl (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The resulting residue was purified by flash chromatography (hexane–EtOAc, 95:5) to afford α,β-unsaturated ketone **4**.

Yield: 505 mg, (75%); oil; $[\alpha]_D^{20}$ –40.3 (*c* 3.0, CH_2Cl_2).

IR (oil): 3071, 2961, 2930, 2857, 2894, 1698, 1675, 1630, 1427, 1389, 1361, 1253, 1111 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.09 [s, 9 H, $C(CH_3)_3$], 1.14 (d, *J* = 6.0 Hz, 3 H, $CHCH_3$), 2.21 (s, 3 H, $C{=}OCH_3$), 2.37 (m, 2 H, CH_2), 4.04 (sext, *J* = 6.0 Hz, 1 H, CH), 6.01 (dt, *J* = 16.0, 1.3 Hz, 1 H, =CH), 6.79 (dt, *J* = 16.0, 7.3 Hz, 1 H, =CH), 7.39–7.47 (m, 6 H, H-Ar), 7.69–7.71 (m, 4 H, H-Ar).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.2 (C-Si), 23.4 ($CHCH_3$), 26.6 ($C{=}OCH_3$), 26.9 [$C(CH_3)_3$], 42.3 (CH_2), 68.5 (CH), 127.5 (CH-Ar), 127.6 (CH-Ar), 129.6 (CH-Ar), 129.7 (CH-Ar), 133.4 (=CH), 133.9 (C-Ar), 134.1 (C-Ar), 138.8 (2 × CH-Ar), 144.8 (=CH), 198.5 (C=O).

MS (CI): *m*/*z* (%) = 384 (4) $[M + NH_4]^+$, 367 (6) $[M + H]^+$, 309 (72), 289 (41), 283 (52), 265 (100).

HRMS-CI: *m*/*z* $[M + H]^+$ calcd for $C_{23}H_{31}O_2Si$: 367.2093; found: 367.2096.

(*S*)-1-{3-[2-(*tert*-Butyldiphenylsilyloxy)propyl]-1,4,8-trimethoxynaphthalen-2-yl}ethanone (2)

To a solution of *t*-BuOK (83 mg, 0.70 mmol) in DMSO (1 mL) was added a solution of cyanophthalide **3** (120 mg, 0.63 mmol) in DMSO (1 mL) followed by a solution of α,β-unsaturated ketone **4** (255 mg, 0.70 mmol) in DMSO (1.5 mL). The reaction mixture was stirred for 15 min then diluted with Et_2O (30 mL) and quenched by addition of sat. NH_4Cl (5 mL). The aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, concentrated in vacuo and the resulting residue was taken up in THF (5 mL) and H_2O (2 mL). TBABr (0.1 equiv, 20 mg) was added, followed by a solution of sodium dithionate (662 mg, 6 equiv) in H_2O (2 mL). The reaction mixture was stirred for 30 min then a solution of NaOH (507 mg, 20 equiv) in H_2O (3 mL) was added followed by dimethyl sulfate (1.21 mL, 20 equiv). The reaction mixture was stirred for 2 h then H_2O (20 mL) was added and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, concentrated in vacuo and the resulting residue was purified by flash chromatography (hexane–EtOAc, 9:1) to afford naphthalene **2**.

Yield: 241 mg (67%); oil; $[\alpha]_D^{20}$ +12.1 (*c* 0.42, $CHCl_3$).

IR (oil): 3069, 2931, 2856, 1701, 1616, 1588, 1571, 1459, 1421, 1369, 1335, 1266, 1109 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.01 [s, 9 H, $C(CH_3)_3$], 1.02 (d, *J* = 5.8 Hz, 3 H, $CHCH_3$), 2.49 (s, 3 H, $C{=}OCH_3$), 2.84 (dd, *J* = 7.6, 13.0 Hz, 1 H, C*H*H), 3.56 (dd, *J* = 6.7, 13.0 Hz, 1 H, CH*H*), 3.73 (s, 3 H, OCH_3), 3.77 (s, 3 H, OCH_3), 4.05 (s, 3 H, OCH_3), 4.33 (m, 1 H, CH), 6.92 (d, *J* = 7.6 Hz, 1 H, H-Ar), 7.29–7.47 (m, 7 H, H-Ar), 7.58 (dd, *J* = 7.9, 1.3 Hz, 2 H, H-Ar), 7.64 (dd, *J* = 8.5, 0.1 Hz, 1 H, H-Ar), 7.71 (dd, *J* = 6.0, 1.5 Hz, 2 H, H-Ar).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.1 (C-Si), 23.4 ($CHCH_3$), 26.9 [$C(CH_3)_3$], 33.1 ($C{=}OCH_3$), 37.2 (CH_2), 56.0 (OCH_3), 61.3 (OCH_3), 63.7 (OCH_3), 69.4 (CH), 105.9 (CH-Ar), 115.1 (CH-Ar), 119.4 (C-Ar), 124.8 (C-Ar), 127.0 (CH-Ar),127.4 (2 × CH-Ar), 129.4 (2 × CH-Ar),131.4 (C-Ar), 134.3 (C-Ar), 134.7 (C-Ar), 135.2 (C-Ar), 135.8 (CH-Ar), 135.9 (CH-Ar), 148.9 (C-Ar), 151.3 (C-Ar), 156.3 (C-Ar), 205.8 (C=O).

MS (FAB): *m/z* (%) = 557 (12) $[M + H]^+$, 499 (50), 310 (87), 135 (100).

HRMS-FAB: *m/z* $[M + H]^+$ calcd for $C_{34}H_{41}O_5Si$: 557.2723; found: 557.2721.

(1*R*,3*S*)-5,9,10-Trimethoxy-1,3-dimethyl-3,4-dihydro-1*H*-benzo[*g*]isochromene (9)

Naphthalene **2** (90 mg, 0.16 mmol) was taken up in anhydrous THF (5 mL) and a solution of TBAF (10 equiv, 1.16 mmol, 422 mg) in THF (4 mL) was added. The reaction mixture stirred under N_2 at r.t. for 4 d, then the reaction mixture was concentrated in vacuo and the resulting residue flushed through a pad of silica (hexane–EtOAc, 1:1). The filtrate was concentrated in vacuo and the resulting oil was taken up in anhydrous CH_2Cl_2 (5 mL) and cooled to –78 °C. TFA (3 equiv, 0.48 mmol, 0.04 mL) was added and the reaction mixture was stirred for 15 min before addition of triethylsilane (3 equiv, 0.48 mmol, 0.08 mL). The reaction mixture was stirred at –78 °C for 30 min then allowed to reach r.t. and stirred overnight. H_2O (10 mL) was added and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, concentrated under vacuo and the resulting residue was purified by flash chromatography (hexane–EtOAc, 7:3) to afford isochromene **9**.

Yield: 27 mg (56%); oil; $[\alpha]_D^{20}$ +97.5 (*c* 1.1, CH_2Cl_2).

IR (oil): 3444, 2970, 2934, 2840, 1781, 1738, 1618, 1595, 1571, 1447, 1372, 1335 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.43 (d, *J* = 6.2 Hz, 3 H, CHCH_3), 1.70 (d, *J* = 6.3 Hz, 3 H, CHCH_3), 2.62 (dd, *J* = 16.0, 10.9 Hz, 1 H, C*H*H), 3.09 (ddd, *J* = 16.0, 1.9, 0.7 Hz, 1 H, CH*H*), 3.69 (m, 1 H, C*H*CH_3), 3.80 (s, 3 H, OCH_3), 3.91 (s, 3 H, OCH_3), 4.03 (s, 3 H, OCH_3), 5.28 (q, ^3J = 6.3 Hz, 1 H, C*H*CH_3), 6.86 (d, *J* = 8.0 Hz, 1 H, H-Ar), 7.43 (t, *J* = 8.0 Hz, 1 H, H-Ar), 7.74 (dd, *J* = 8.0, 0.7 Hz, 1 H, H-Ar).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.6 (CH*C*H_3), 23.2 (CH*C*H_3), 31.7 (CH_2), 56.0 (OCH_3), 61.3 (OCH_3), 61.7 (OCH_3), 69.9 (CH), 71.4 (CH), 105.6 (CH-Ar), 114.5 (CH-Ar), 119.3 (C-Ar), 125.7 (C-Ar), 126.1 (CH-Ar), 129.7 (C-Ar), 129.8 (C-Ar), 148.6 (C-Ar), 148.8 (C-Ar), 155.9 (C-Ar).

MS (EI): *m/z* (%) = 302 (91) $[M]^+$, 287 (100) $[M - Me]^+$, 272 (24) $[M - 2 \times Me]^+$), 257 (27) $[M - 3 \times Me]^+$.

HRMS-EI: *m/z* $[M]^+$ calcd for $C_{18}H_{22}O_4$: 302.1518; found: 302.1517.

(+)-Eleutherin (1)

(1*R*,3*S*)-5,9,10-Trimethoxy-1,3-dimethyl-3,4-dihydro-1*H*-benzo[*g*]isochromene (**9**; 90 mg, 0.30 mmol) was taken up in MeCN (7 mL) and a solution of cerium(IV) ammonium nitrate (490 mg, 0.90 mmol) in H_2O (4 mL) was added. The reaction mixture was stirred at r.t. for 1 h then H_2O (10 mL) was added and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, concentrated in vacuo and the resulting residue was purified by flash chromatography (hexane–EtOAc, 3:2) and then recrystallized from Et_2O–EtOAc to afford (+)-eleutherin **1**.

Yield: 65 mg (80%); yellow needles; $[\alpha]_D^{20}$ +335 (*c* 0.35, CH_2Cl_2).

^1H NMR (300 MHz, $CDCl_3$): δ = 1.36 (d, *J* = 6.2 Hz, 3 H, CHCH_3), 1.53 (d, *J* = 6.6 Hz, 3 H, CHCH_3), 2.21 (ddd, *J* = 18.3, 10.2, 3.8 Hz, 1 H, CH_{ax}H), 2.75 (dt, *J* = 18.3, 2.6 Hz, 1 H, CHH_{eq}), 3.56 (ddq, *J* = 10.2, 6.2, 2.5 Hz, 1 H, CH_2C*H*CH_3), 3.99 (s, 3 H, OCH_3), 4.85 (m, 1 H, C*H*CH_3), 7.27 (dd, *J* = 8.3, 1.0 Hz, 1 H, H-Ar), 7.63 (dd, *J* = 8.3, 7.0 Hz, 1 H, H-Ar), 7.73 (dd, *J* = 7.0, 1.0 Hz, 1 H, H-Ar).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.8 (CH*C*H_3), 21.3 (CH*C*H_3), 29.9 (CH_2), 56.5 (OCH_3), 68.7 (CH), 70.3 (CH), 117.7 (CH-Ar), 119.0 (CH-Ar), 120.3 (C-Ar), 133.9 (C-Ar), 134.6 (CH-Ar), 139.9 (C-Ar), 148.7 (C-Ar), 159.4 (C-Ar), 183.8 (C=O), 184.1 (C=O).

MS (EI): *m/z* (%) = 272 (100) $[M]^+$, 257 (78) $[M - Me]^+$, 243 (52).

HRMS-EI: *m/z* $[M]^+$ calcd for $C_{16}H_{16}O_4$: 272.1048; found: 272.1050.

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