Application of a Dual Fries–Claisen Protocol to Access Pyranonaphthoquinone Natural Products

Liam J. Duffy,[a] Jason Garcia-Torres,[b] Raymond C. F. Jones,[b] Mark R. J. Elsegood,[b] Steven M. Allin*[c]

[a] Research Institute for the Environment, Physical Sciences and Mathematics, Keele University, Keele ST5 5BG, UK

[b] Chemistry Department, Loughborough University, Loughborough, Leics LE11 3TU, UK

[c] School of Science & Technology, Nottingham Trent University, Clifton, Nottingham NG11 8NS, UK
E-mail: steve.allin@ntu.ac.uk

Received: 23.11.2012; Accepted: 02.12.2012

Abstract: In this paper we describe the application of a recently developed dual Fries–Claisen protocol as a novel synthetic approach to the pyranonaphthoquinone natural products eleutherin and isoeleutherin.

Key words: annelation, pericyclic reaction, rearrangement, Fries, Claisen, cyclisation

The pyranonaphthoquinones (Figure 1) are an interesting class of naturally occurring antibiotic compound that also display a wide range of other biological activities, such as antifungal, antiviral and anticancer activity. In addition to the antibiotic activity shown by frenolicin A (**1**), and nanaomycin A, (**2**),[1] eleutherin (**3a**) has been shown to be a reversible inhibitor of the anticancer target topoisomerase II[2] and isoeleutherin (**3b**) has shown activity as a selective modulator of Th cell-mediated immune responses.[3] Isoeleutherin (**3b**) has also recently been shown to suppress nitric oxide synthase (NOS), responsible for the production of the important signalling molecule nitric oxide (NO).[4]

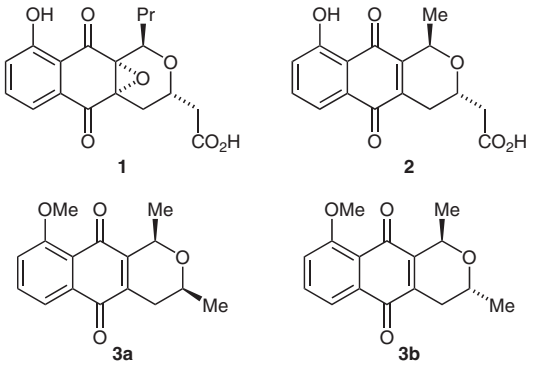
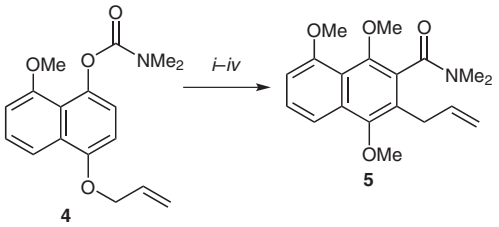


Figure 1 Pyranonaphthoquinone natural products

Previously reported annelation routes to compounds such as eleutherin have included application of Hauser–Kraus,[5] oxa-Pictet–Spengler,[6] Dötz,[7] Diels–Alder[8] and tandem enamine conjugate addition–cyclisation methodologies.[9] We have recently reported a novel protocol for benzannelation involving a dual Fries–Claisen rearrangement strategy[10] and we now wish to report the first application of this methodology in the synthesis of the pyranonaphthoquinone natural products eleutherin (**3a**) and isoeleutherin (**3b**).

The rearrangement precursor **4**, required for this study, was prepared following our reported route and subjected to the recently developed sequential anionic *ortho*-Fries–Claisen protocol, followed by O-methylation to yield advanced intermediate **5**.[10] The O-methylation [step (iv)] following the Claisen step [step (iii)] was carried out in order to prevent unwanted competitive cyclisation onto the pendant allyl substituent at a later stage of our synthesis (Scheme 1).

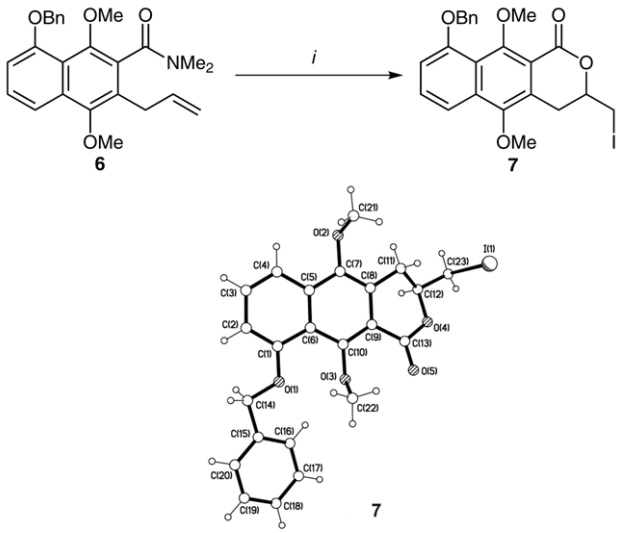


Scheme 1 *Reagents and conditions*: (i) *s*-BuLi, TMEDA, THF, –78 °C (92%); (ii) NaH, MeI, THF, 20 °C, 4 h (80%); (iii) mesitylene, reflux, 3 h (92%); (iv) K_2CO_3, MeI, acetone, reflux, 24 h, 83%.

In our recent paper highlighting the development of this methodology, compound **5** was subsequently subjected to acid-mediated lactonisation[10] to yield a pyranonaphthoquinone, with concomitant demethylation–oxidation of the aromatic ring to furnish quinone functionality. In this current paper we describe an alternative, and complementary, functionalisation of our rearrangement products.

Using the related rearrangement product **6** as a model substrate, cyclisation was investigated and achieved through iodolactonisation, affording the potentially useful iodolactone **7**, as outlined in Scheme 2, and an X-ray crystal structure was obtained to confirm the identity of the product.[11] It is noteworthy that this alternative sequence does not lead to formation of a quinone product as in our initial work,[10] but rather leaves the fused naphthalene unit intact. The ability to control the oxidation state of the product aromatic system in this manner will prove to be an impor-

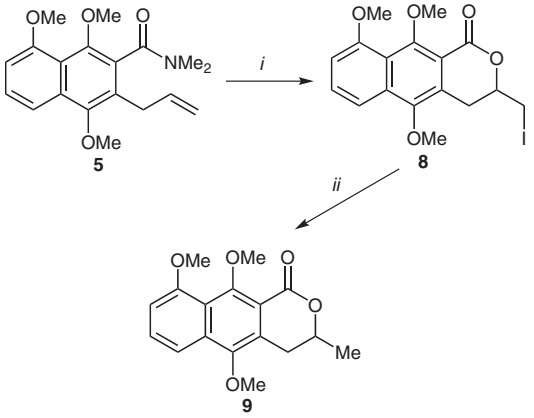
SYNLETT 2013, 24, 0185–0188
Advanced online publication: 18.12.2012
DOI: 10.1055/s-0032-1317943; Art ID: ST-2012-D1001-L



Scheme 2 *Reagents and conditions*: (i) I_2, $NaHCO_3$, THF–Et_2O, heat, 48 h, (77%).

tant asset as we seek to apply this chemistry to a range of targets.

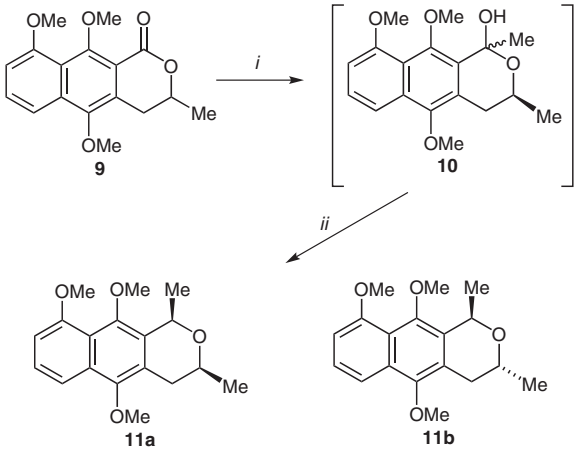
Our route to the target natural products in this study required the application of the Fries–Claisen rearrangement product, **5**, to this sequence. Thus, amide **5** was subjected to iodolactonisation to yield lactone **8** in 83% yield, followed by dehalogenation using tributyltin hydride to give the key eleutherin precursor, methyl lactone **9**, in 80% yield (Scheme 3).



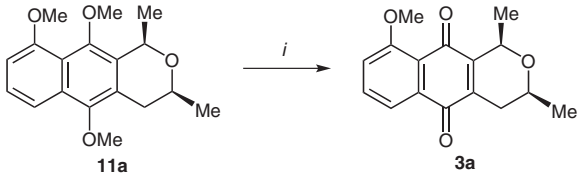
Scheme 3 *Reagents and conditions*: (i) I_2, $NaHCO_3$, THF–Et_2O, heat, 48 h, (83%); (ii) Bu_3SnH, AIBN, toluene, heat, 2 h, (80%).

Access to the natural product targets in this study from intermediate **9** was achieved by a two-step procedure involving addition of methyllithium to the lactone carbonyl group to form a diastereoisomeric mixture of lactols, **10**. This compound was not isolated but instead subjected to a Lewis acid mediated reduction using triethylsilane to yield a 5:1 mixture of racemic *cis*- and *trans*-pyrans, **11a**,**b** respectively, in a combined overall yield of 85% for the two steps (Scheme 4).

Isolation of the major isomer, *cis*-pyran **11a**,[12] could be achieved at this point by column chromatography, and this pure compound was subjected to CAN oxidation to access racemic eleutherin (**3a**) in 93% yield (Scheme 5).[13] Unfortunately separation of *trans*-isomer **11b** from the original **11a**,**b** mixture proved to be impossible by column chromatography, however an analytical sample of isoeleutherin (**3b**) was isolated following direct CAN oxidation of the **11a**,**b** mixture.[14]



Scheme 4 *Reagents and conditions*: (i) MeLi, THF–Et_2O (1:1), 0 °C, 12 h; (ii) TES, $BF_3{\cdot}OEt_2$, CH_2Cl_2, –78 °C, 8 h, (85% for both steps).



Scheme 5 *Reagents and conditions*: (i) CAN, MeCN–H_2O (2:1), 2 h, (93%).

In conclusion, we have successfully applied our recently reported dual Fries–Claisen protocol[10] to a racemic synthesis of the topoisomerase II inhibitor, eleutherin (**3a**) and its biologically active isomer isoeleutherin (**3b**). Further applications of the dual Fries–Claisen rearrangement strategy to the synthesis of more complex pyranonaphthoquinone natural product targets will be reported in due course.

Acknowledgment

We thank EPSRC for financial support of this project (EP/F026552/1), Keele and Loughborough Universities for facilities and financial support, and the EPSRC Mass Spectrometry Service Centre (Swansea) for some HRMS data.

References and Notes

(1) (a) Uno, H. *J. Org. Chem.* **1986**, *51*, 350. (b) Kraus, G. A.; Molina, M. T.; Walling, J. A. *J. Org. Chem.* **1987**, *52*, 1273. (c) Brimble, M. A.; Lynds, S. M. *J. Chem. Soc., Perkin Trans. 1* **1994**, 493. (d) Salaski, E. J.; Krishnamurthy, G.;

Ding, W.-D.; Yu, K.; Insaf, S. S.; Eid, C.; Shim, J.; Levin, J. I.; Tabei, K.; Toral-Barza, L.; Zhang, W.-G.; McDonald, L. A.; Honores, E.; Hanna, C.; Yamashita, A.; Johnson, B.; Li, Z.; Laakso, L.; Powell, D.; Mansour, T. S. *J. Med. Chem.* **2009**, *52*, 2181.

(2) Sperry, J.; Lorenzo-Castrillejo, I.; Brimble, M. A.; Machin, F. *Bioorg. Med. Chem.* **2009**, *17*, 7131.

(3) Hong, J.-H.; Yu, E. S.; Han, A.-R.; Nam, J.-W.; Seo, E.-K.; Hwang, E. S. *Biochem. Biophys. Res. Commun.* **2008**, *371*, 278.

(4) Song, S.-H.; Min, H.-Y.; Han, A.-R.; Nam, J.-W.; Seo, E.-K.; Park, S. W.; Lee, S. H.; Lee, S. K. *Int. Immunopharmacol.* **2009**, *9*, 298.

(5) Gibson, J.; Andrey, O.; Brimble, M. A. *Synthesis* **2007**, 2611.

(6) Sawant, R. T.; Jadhav, S. G.; Waghmode, S. B. *Eur. J. Org. Chem.* **2010**, 4442.

(7) Fernandes, R. A.; Chavan, V. P.; Ingle, A. B. *Tetrahedron Lett.* **2008**, *49*, 6341.

(8) Tewierik, L. M.; Dimitriadis, C.; Donner, C. D.; Gill, M.; Willems, B. *Org. Biomol. Chem.* **2006**, *4*, 3311.

(9) Kobatashi, K.; Uchida, M.; Uneda, T.; Tanmatsu, M.; Morikawa, O.; Konishi, H. *Tetrahedron Lett.* **1998**, *39*, 7725.

(10) Duffy, L. J.; Garcia-Torres, J.; Jones, R. C. F.; Allin, S. M. *Synlett* **2012**, *23*, 1821.

(11) (a) X-ray crystal data for **7**: $C_{23}H_{21}IO_5$, M = 504.30, monoclinic, space group $P2_1/c$, a = 14.3715(5), *b* = 15.6087(5), *c* = 9.0761(3) Å, β = 94.3888(5), *V* = 2029.98(12) Å^3, *T* = 150 K, *Z* = 4, crystal dimensions 0.56 × 0.22 × 0.12 mm^3, Mo–Kα monchromated radiation (λ = 0.71073 Å), μ = 1.610 mm^{-1}, 23393 data measured using a Bruker APEX 2 CCD diffractometer. 6173 data were unique, R_{int} = 0.022; all unique data used in refinement against F^2 values to give final *wR* = 0.0622 (on F^2 for all data), *R* = 0.0236 {for 5369 data with $F^2 > 4\sigma(F^2)$}. Programs used were Bruker APEX 2 (see ref. 11b), SAINT (see ref. 11b), SHELXTL (see refs. 11c and 11d) and local programs. Crystallographic data (excluding structure factors) for the structure in this paper has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 854341. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [Fax: +44(1223)336033 or e-mail: deposit@ccdc.ac.uk]. (b) *APEX 2 and SAINT Software for CCD Diffractometers*; Bruker AXS Inc: Madison WI, **2008**. (c) Sheldrick, G. M. *SHELXTL User Manual, Version 5*; Bruker AXS Inc: Madison WI, **1994**. (d) Sheldrick, G. M. *Acta Crystallogr., Sect. A* **2008**, *64*, 112.

(12) **Synthesis of Eleutherin Precursor, 11a**:
Step (1): Methyllithium (2.01 mL, 3.23 mmol; 1.6 M solution in decane) was added dropwise to 5,9,10-trimethoxy-3-methyl-3,4-dihydro-1*H*-benzo[*g*]isochromen-1-one (**9**; 813 mg, 2.69 mmol) in anhyd THF–Et_2O (1:1; 50mL) at 0 °C. The reaction mixture was stirred vigorously and allowed to reach r.t. overnight. The reaction was stopped by careful addition of sat. aq NH_4Cl (50 mL) and the aqueous layer was extracted three times with EtOAc (3 × 30 mL). The combined organic phases were dried over anhyd $MgSO_4$ and concentrated under reduced pressure. The crude white foam recovered (**10**, 856 mg) was taken forward to the lactol reduction step without purification.
Step (2): Lactol **10** (856 mg, 2.69 mmol) was dissolved in anhyd CH_2Cl_2 (20 mL) and cooled to −78 °C before successive dropwise addition of $BF_3{\cdot}OEt_2$ (1.02 mL, 8.07 mmol) and TES (1.29 mL). The red solution was stirred vigorously for 1 h at −78 °C before being allowed to warm to r.t. over 2 h. The reaction was carefully quenched with the addition of H_2O (50 mL) and then partitioned between brine (50 mL) and CH_2Cl_2 (50 mL). The organic layer was separated and the aqueous phase was extracted twice more with CH_2Cl_2 (2 × 30 mL). The combined organics were dried over anhyd $MgSO_4$ and evaporated to dryness under reduced pressure. The crude ^{1}H NMR spectrum of this material showed a 5:1 *cis*/*trans* mixture of (±)-**11a** and (±)-**11b**, respectively. The mixture of naphthopyrans was chromatographed on silica using light petroleum (bp 40–60 °C)–EtOAc (6:1) as eluent to yield **11a** as a white solid (550 mg, 68% over 2 steps). It was not possible to separate the *trans*-naphthopyran **11b** from the *cis*-naphthopyran, (±)-**11a**, at this juncture, only 136 mg (17% over 2 steps) of a mixture (1:1 by ^{1}H NMR spectroscopy) was isolated (total combined yield 85%). Data for **11a**: mp 104–106 °C (Lit.[1a] mp 106–107 °C). IR (ATR): 1570, 1071, 1058 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.42 (d, *J* = 6.0 Hz, 3 H), 1.69 (d, *J* = 6.0 Hz, 3 H), 2.59 (dd, *J* = 11.1, 16.2 Hz, 1 H), 3.06 (dd, *J* = 1.8, 16.2 Hz, 1 H), 3.65–3.71 (m, 1 H), 3.77 (s, 3 H), 3.99 (s, 3 H), 4.01 (s, 3 H), 5.25 (q, *J* = 6.0 Hz, 1 H), 6.83 (d, *J* = 7.5 Hz, 1 H), 7.37 (t, *J* = 8.1 Hz, 1 H), 7.68 (dd, *J* = 0.6, 8.4 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.9, 23.2, 31.9, 56.1, 61.2, 61.6, 69.4, 71.3, 105.4, 114.5, 119.3, 125.9, 126.1, 129.8, 130.3, 148.5, 149.1, 156.1. MS (EI–CI): *m*/*z* [M + H$^+$] calcd for $C_{18}H_{22}O_4$: 303.1591; found: 303.1596.

(13) **Synthesis of Eleutherin (3a)**: A solution of cerium(IV) ammonium nitrate (1.99 g, 3.64 mmol) in H_2O (2 mL) was added to a solution of the *cis*-naphthopyran (±)-**11a** (550 mg, 1.82 mmol) in MeCN (4 mL) at r.t. After stirring for 2 h, the reaction was partitioned between CH_2Cl_2 (50 mL) and H_2O (50 mL). The organic phase was separated and the aqueous phase was re-extracted twice with CH_2Cl_2 (2 × 30 mL). The combined organic fractions were washed with brine, dried over anhyd $MgSO_4$ and concentrated under reduced pressure. The crude quinone was chromatographed on silica gel using light petroleum (bp 40–60 °C)–EtOAc (2:1) as eluent to give (±)-eleutherin (**3a**) as a yellow solid (462 mg, 93%). Data for **3a**: mp 156–157 °C (Lit.[1a] mp 155–156 °C). IR (ATR): 1651, 1584, 1276, 1059 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.37 (d, *J* = 6.0 Hz, 3 H), 1.54 (d, *J* = 6.0 Hz, 3 H), 2.20 (ddd, *J* = 3.6, 10.2, 18.3 Hz, 1 H), 2.75 (dt, *J* = 2.7, 18.3 Hz, 1 H), 3.56–3.62 (m, 1 H), 4.00 (s, 3 H), 4.83–4.89 (m, 1 H), 7.28 (d, *J* = 8.1 Hz, 1 H), 7.64 (t, *J* = 7.8 Hz, 1 H), 7.73 (dd, *J* = 0.9, 7.5 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.8, 21.3, 29.9, 56.5, 68.7, 70.3, 117.7, 119.0, 120.2, 133.9, 134.6, 139.9, 148.7, 159.4, 183.8, 184.1. MS (EI–CI): *m*/*z* [M + H$^+$] calcd for $C_{16}H_{16}O_4$: 273.1121; found: 273.1124.

(14) **Isolation of an Analytical Sample of Isoeleutherin (3b)**: A solution of cerium(IV) ammonium nitrate (493 mg, 0.90 mmol) in H_2O (1 mL) was added to a solution of 1:1 (±)-**11a**/**b** (136 mg, 0.90 mmol) in MeCN (2 mL) at r.t. After 2 h stirring the reaction was partitioned between CH_2Cl_2 (50 mL) and H_2O (50 mL). The organic phase was separated and the aqueous phase was extracted twice more with CH_2Cl_2 (2 × 30 mL). The combined organic fractions were washed with brine, dried over anhyd $MgSO_4$ and concentrated under reduced pressure. The crude quinone was chromatographed on silica gel using light petroleum (bp 40–60 °C)–EtOAc (4:1) as eluent to give a 1:1 mixture of (±)-eleutherin (**3a**) and (±)-isoeleutherin (**3b**) as a yellow solid (109 mg, 89%). It was only possible to isolate an analytical sample (7 mg) of (±)-isoeleutherin (**3b**) as a yellow solid for characterisation purposes; mp 151–152 °C (Lit.[1a] mp 154–155 °C). IR (ATR): 1651, 1584, 1276, 1058 cm^{-1}. ^{1}H NMR (300 MHz,

$CDCl_3$): δ = 1.35 (d, *J* = 6.0 Hz, 3 H), 1.54 (d, *J* = 6.9 Hz, 3 H), 2.24 (ddd, *J* = 2.1, 10.2, 19.2 Hz, 1 H), 2.70 (dd, *J* = 3.3, 18.9 Hz, 1 H), 3.96–4.01 (m, 1 H), 4.01 (s, 3 H), 5.02 (q, *J* = 6.6 Hz, 1 H), 7.29 (d, *J* = 8.7 Hz, 1 H), 7.66 (t, *J* = 7.8 Hz, 1 H), 7.76 (dd, *J* = 0.9, 7.5 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.8, 21.5, 29.5, 56.5, 62.4, 67.4, 117.8, 119.1, 119.3, 134.0, 134.8, 139.4, 148.0, 159.7, 182.8, 184.3. MS (EI–CI): *m*/*z* [M + H$^+$] calcd for $C_{16}H_{16}O_4$: 273.1121; found: 273.1127.

