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# A short enantioselective synthesis of (+)-eleutherin, (+)-allo-eleutherin and a formal synthesis of (+)-nocardione B

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ABSTRACT

A short enantioselective synthesis of (+)-eleutherin, (+)-allo-eleutherin and the formal synthesis of (+)-nocardione B is described. The synthesis is completed in six steps in overall yields of 8% for eleutherin and 14% for allo-eleutherin. The synthetic strategy features an efficient combination of the Dötz annulation reaction with a chiral alkyne and an oxa-Pictet Spengler reaction as the keys steps in the stereodivergent synthesis of (+)-eleutherin and (+)-allo-eleutherin. The synthesis of (*S*)-(+)-2-(2′-hydroxypropyl)-5-methoxy-1,4-naphthoquinone entails the formal synthesis of (+)-nocardione B.



Eleutherin **1** was isolated from the bulbs of *Eleutherin bulbosa*[1] in 1950 and shortly after, the C-3 epimer, isoeleutherin **2**[2] was also isolated from the same bulb extracts (Fig. 1). Eleutherin **1** is shown to exhibit activity[3] against *Bacillus subtilis*. Extracts of *Eleutherin americana* of which eleutherin and isoeleutherin are the major constituents have been used to treat the heart disease angina pectoris.[4] Also, (+)-eleutherin is a reversible inhibitor of topoisomerase II—a target for anticancer agents.[5] (+)-Allo-eleutherin **3** (Fig. 1) is an enantiomer of isoeleutherin **2** and was produced when (+)-eleutherin **1** was treated with phosphoric acid.[2] In 2000, Otani et al. isolated (−)-nocardione A **4** and (−)-nocardione B *ent*-**5** as new tyrosine phosphate inhibitors.[6] These also possess moderate antifungal and cytotoxic activities.[6]

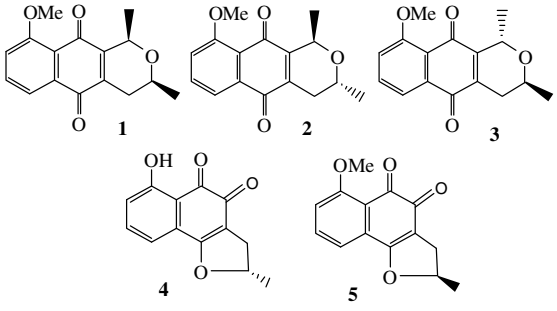


**Figure 1.** (+)-Eleutherin **1**, (−)-isoeleutherin **2**, (+)-allo-eleutherin **3**, (−)-nocardione A **4** and (+)-nocardione B **5**.

Eleutherin and isoeleutherin have been the targets of extensive synthetic studies; however, mostly in racemic form.[7] There are only two recent enantioselective syntheses[8] of (+)-eleutherin **1**, while (−)-isoeleutherin **2** or its enantiomer (+)-allo-eleutherin **3**[2] has not yet been synthesized in enantiopure form. The first enantioselective synthesis of **1** involved the synthesis of (*S*)-mellein[9] in several steps and then its conversion in a five-step sequence to eleutherin.[8a] The second synthesis by Brimble and co-workers[8b] based on the well-known Hauser–Kraus annulation[10] involves eight steps leading to a 5.5% overall yield.

Nocardiones **4** and **5** were first synthesized by Tanada and Mori,[11] and their absolute configuration was also determined. Racemic syntheses of nocardiones are also known.[12] A radical cyclization strategy has been used recently in the synthesis of (+)-norcardione A *ent*-**4**.[13]

In continuation of our efforts on the enantioselective synthesis of natural products,[14] we recently employed the Dötz annulation reaction and asymmetric dihydroxylation in the highly enantioselective synthesis of (−)-juglomycin A and its non-natural enantiomer.[14c] Herein, we report a short and stereodivergent synthesis of both (+)-eleutherin **1** and (+)-allo-eleutherin **3**. The synthetic strategy (Scheme 1) features a Dötz annulation reaction with the chiral alkyne **6** (to install the naphthalene **8**) and an oxa-Pictet Spengler reaction (to give the pyran ring compound **9**) as the key steps in the stereodivergent synthesis of both **1** and the first enantioselective synthesis of **3**. Compound **8** is an intermediate in the synthesis of (+)-nocardione B **5**.

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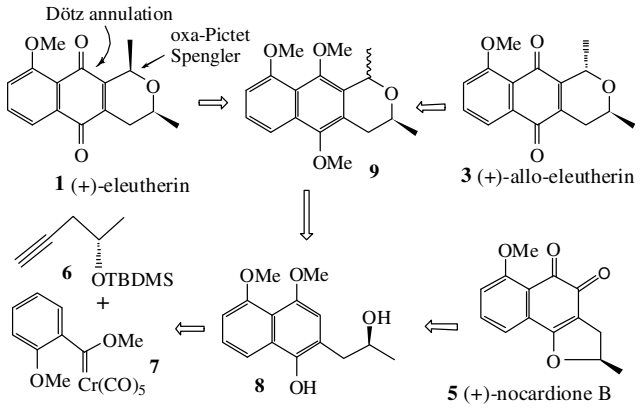
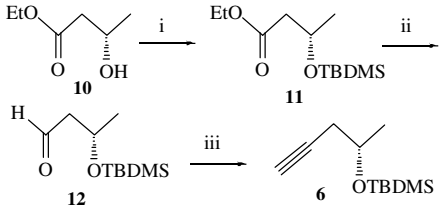



**Scheme 1.** Synthetic strategy to (+)-**1**, (+)-**3** and (+)-**5**.

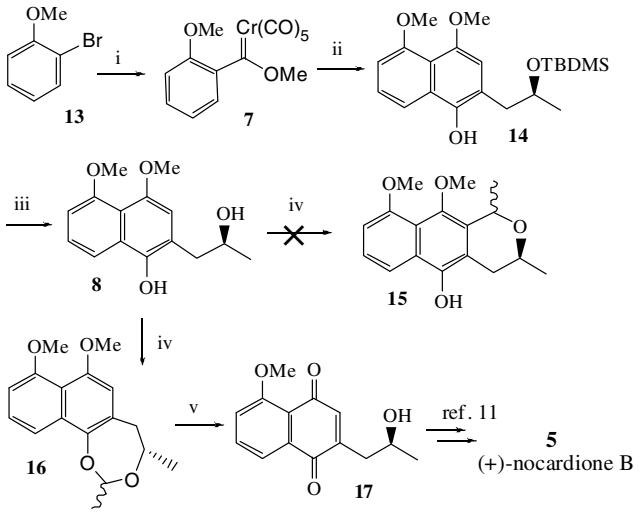



**Scheme 2.** Synthesis of chiral alkyne **6**. Reagents and conditions: (i) TBDMSCl (1.3 equiv), imidazole (2.5 equiv), $CH_2Cl_2$, rt, 12 h, quant.; (ii) DIBAL-H (1.1 equiv), $CH_2Cl_2$, −78 °C, 2 h; (iii) (a) $CBr_4$ (2.0 equiv), $PPh_3$ (4.0 equiv), $CH_2Cl_2$, 0 °C, 3.5 h; (b) *n*-BuLi (2.1 equiv), THF, −78 °C, 2 h, 82% over two steps.

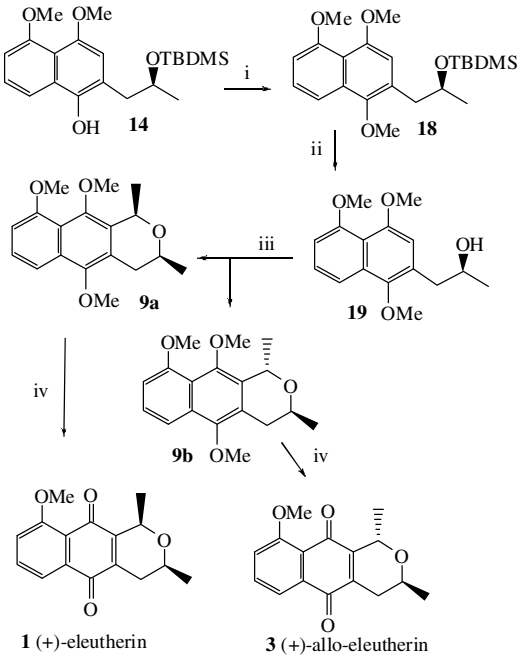
The chiral alkyne **6** required for the Dötz annulation reaction was easily prepared as shown in Scheme 2. Commercially available ethyl (*S*)-3-hydroxybutyrate **10** on hydroxyl protection as the TBDMS ether afforded **11** in quantitative yield. DIBAL-H reduction of the ester group gave aldehyde **12**, and Corey–Fuchs[15] alkyne formation gave the desired chiral alkyne **6** in 82% yield (over two steps).

The Fischer carbene complex **7** was prepared as reported earlier[14c] (from 2-bromoanisole **13**) and condensed with the chiral alkyne **6** (1.5 equiv) via the Dötz annulation reaction[16] to afford the substituted naphthalene **14** in a good yield of 69% (Scheme 3). Deprotection of the TBDMS group gave the alcohol **8** in 91% yield. We planned to install the pyran ring through oxa-Pictet Spengler reaction[17] to prepare **15**. It is known in the literature that pyran ring formation on similar substrates with acetaldehyde under acidic conditions gives a variable mixture of cis- and trans-1,3-isomers depending on the reaction conditions.[7a,18] Towards this end, when we subjected the alcohol **8** to the oxa-Pictet Spengler reaction with acetaldehyde dimethylacetal and $BF_3{\cdot}OEt_2$, the seven-membered cyclic acetal **16** was obtained in 93% yield instead of **15**. This is different from the pyran ring formation of similar hydroquinone compounds when treated with acetaldehyde under acidic conditions.[18] Compound **16** gave four aryl-H signals in its $^1$H NMR spectrum including a singlet at $\delta$ 6.56 ppm corresponding to the naphthalene C-2 proton,[19] where the pyranylation could have occurred. We further confirmed the formation of **16** by treating it with cerium(IV) ammonium nitrate (CAN) to produce the quinone **17** in 83% yield. The quinone **17** is a useful intermediate in the synthesis of (+)-nocardione B as reported earlier.[11] Hence, this entails a formal synthesis of (+)-**5**.

Since pyranylation on **8** was not possible in the presence of the phenolic hydroxyl group, it became necessary to protect it before the pyranylation reaction. Phenol **14** was therefore converted into its methyl ether **18** in 85% yield (Scheme 4). Deprotection of the




**Scheme 3.** Dötz annulation and oxa-Pictet Spengler reactions. Reagents and conditions: (i) *n*-BuLi (1.04 equiv), THF, −78 °C, 5 min, $Cr(CO)_6$ (1.0 equiv), −78 °C to 0 °C, 3 h, then $Me_3OBF_4$ (1.5 equiv), $CH_2Cl_2$, 0 °C to rt, 3 h, 83%;[14c] (ii) **6** (1.5 equiv), THF, 45 °C, 12 h, 69%; (iii) TBAF (1.2 equiv), THF, rt, 2 h, 91%; (iv) $(CH_3O)_2CHCH_3$ (2.0 equiv), $BF_3{\cdot}OEt_2$ (3.0 equiv), $Et_2O$/THF (4:1), rt, 12 h, 93%; (v) $(NH_4)_2Ce(NO_3)_6$ (2.0 equiv), MeCN/$H_2O$ (1:1), rt, 1 h, 83%.




**Scheme 4.** Synthesis of **1** and **3**. Reagents and conditions: (i) NaH (3.0 equiv), MeI (3.1 equiv), DMF, 0 °C to rt, 2 h, 85%; (ii) TBAF (1.2 equiv), THF, rt, 2 h, 95%; (iii) see Table 1;[21] (iv) $(NH_4)_2Ce(NO_3)_6$ (2.0 equiv), MeCN/$H_2O$ (1:1), rt, 1 h, 86% for **1** and 89% for **3**.

TBDMS group gave the alcohol **19** in 95% yield. The oxa-Pictet Spengler reaction of **19** with acetaldehyde dimethylacetal and $BF_3{\cdot}OEt_2$ at room temperature for 14 h (Table 1, entry 1) gave a mixture of **9a**:**9b** in a 32:68 ratio and 92% yield.[20] We envisaged that the reaction over shorter time through kinetic control would produce the cis-isomer as the major product. However, when the reaction was carried out for 1 h at room temperature it resulted in only a marginal difference of the ratio of **9a**:**9b** = 36:64 (Table 1, entry 2) and an 84% yield. The reaction was also carried out at 0 °C which was rather slow and after 2 h gave **9a**:**9b** in a 43:57 ratio and 78% yield (Table 1, entry 3).

**Table 1**
Oxa-Pictet Spengler reaction on **19** to give **9a** and **9b**

| Entry | Reaction conditions | % Yield | **9a**:**9b** |
|---|---|---|---|
| 1 | $(CH_3O)_2CHCH_3$ (2.0 equiv), $BF_3{\cdot}OEt_2$ (3.0 equiv), THF/$Et_2O$ (1:4), rt, 14 h | 92 | 32:68 |
| 2 | $(CH_3O)_2CHCH_3$ (2.0 equiv), $BF_3{\cdot}OEt_2$ (3.0 equiv), THF/$Et_2O$ (1:4), rt, 1 h | 84 | 36:64 |
| 3 | $(CH_3O)_2CHCH_3$ (2.0 equiv), $BF_3{\cdot}OEt_2$ (3.0 equiv), THF/$Et_2O$ (1:4), 0 °C, 2 h | 78 | 43:57 |

The mixture of **9a**:**9b** was easily separated by preparative TLC[21] to give **9a**[22] (30%) and **9b**[23] (51%) from **19**. Oxidation of **9a** with CAN produced (+)-eleutherin **1** {$[\alpha]_D^{25}$ +338 (*c* 0.25, $CHCl_3$); natural (+)-eleutherin **1** $[\alpha]_D^{25}$ +346 (*c* 1.01, $CHCl_3$)[1]} in 86% yield. Similarly, oxidation of **9b** with CAN gave (+)-allo-eleutherin **3** {$[\alpha]_D^{25}$ +65.6 (*c* 0.3, $CHCl_3$), lit.[2a] $[\alpha]_D^{25}$ +45 (*c* 1.075, $CHCl_3$)} in 89% yield. The spectroscopic and analytical data of **1** were in full agreement with those reported.[8] (+)-Allo-eleutherin **3** was fully characterized by spectroscopic and analytical methods.[24]

In summary, a short enantioselective synthesis of both (+)-eleutherin (8% overall yield) and (+)-allo-eleutherin (14% overall yield) has been achieved in six steps (for both). The synthetic strategy features an efficient combination of a Dötz annulation reaction with a chiral alkyne and the oxa-Pictet Spengler reaction as the key steps in the stereodivergent synthesis of both (+)-eleutherin and the first enantioselective synthesis of (+)-allo-eleutherin. Since (+)-allo-eleutherin is an enantiomer of (−)-(1*R*,3*R*)-isoeleutherin **2**,[8] it should have the (1*S*,3*S*) configuration. The synthesis of (*S*)-(+)-2-(2′-hydroxypropyl)-5-methoxy-1,4-naphthoquinone **17** entails the formal synthesis of (+)-nocardione B **5**.[11] Application of this strategy to the synthesis of other related pyranonaphthoquinone natural products is in progress.

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19. *Data for* **16**: Pale yellow solid; mp 143–144 °C; $[\alpha]_D^{25}$ −71.5 (*c* 0.34, $CHCl_3$); IR ($CHCl_3$): $\nu$ = 3138, 2968, 2928, 2835, 1627, 1603, 1509, 1463, 1388, 1333, 1284, 1250, 1115, 1072, 1045, 977, 927, 894, 863, 842, 761 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$/TMS): $\delta$ 1.40 (d, 3H, *J* = 6.0 Hz, $CHCH_3$), 1.69 (d, 3H, *J* = 5.2 Hz, $CHCH_3$), 3.33 (m, 2H, $CH_2$-Ar), 3.76 (m, 1H, $CH_2CHCH_3$), 3.94 (s, 3H, $OCH_3$), 3.97 (s, 3H, $OCH_3$), 4.84 (q, 1H, *J* = 5.2 Hz, $CHCH_3$), 6.56 (s, 1H, H-Ar), 6.85 (d, 1H, *J* = 7.7 Hz, H-Ar), 7.40 (dd, 1H, *J* = 8.4, 8.0 Hz, H-Ar), 7.74 (d, 1H, *J* = 8.0 Hz, H-Ar); $^{13}C$ NMR (100 MHz, $CDCl_3/CHCl_3$): $\delta$ 22.51 ($CHCH_3$), 22.76 ($CHCH_3$), 44.36 ($CH_2$), 56.59 ($OCH_3$), 57.22 ($OCH_3$), 74.68 (CH), 103.50 ($OOCHCH_3$), 106.34 (Ar), 109.32 (Ar), 114.88 (Ar), 116.2 (Ar), 126.61 (Ar), 127.15 (Ar), 131.43 (Ar), 148.15 (Ar), 152.83 (Ar), 157.09 (Ar); MS (I): *m*/*e* = 288 [$M^+$] (100); Calcd for $C_{17}H_{20}O_4$ (288.34): C, 70.81, H, 6.99. Found: C, 70.77; H, 7.28.
20. The diastereomer ratio was determined by $^1H$ NMR.
21. All the mixtures in entries 1–3, Table 1, were mixed to give an average **9a**:**9b** = 37:63 mixture and 85% yield. This on separation by preparative thin layer chromatography (PTLC) gave **9a** in 30% yield and **9b** in 51% yield from **19**. These yields were taken into account while calculating the overall yield.
22. The spectroscopic and analytical data of **9a** were in full agreement with those reported.[8b]
23. *Data for* **9b**: Pale yellow oil; $[\alpha]_D^{25}$ +37.5 (*c* 1.2, $CHCl_3$); IR ($CHCl_3$): $\nu$ = 3022, 2934, 2835, 1715, 1654, 1594, 1497, 1462, 1374, 1262, 1213, 1108, 1067, 1012, 988, 757, 669 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$/TMS): $\delta$ 1.40 (d, 3H, *J* = 6.1 Hz, $CHCH_3$), 1.64 (d, 3H, *J* = 6.7 Hz, $CHCH_3$), 2.61 (dd, 1H, *J* = 16.8, 10.9 Hz, $CH_{ax}H$), 3.08 (dd, 1H, *J* = 16.8, 3.4 Hz, $CH_{eq}H$), 3.81 (s, 3H, $OCH_3$), 3.85 (s, 3H, $OCH_3$), 4.01 (s, 3H, $OCH_3$), 4.15 (m, 1H, $CH_2CHCH_3$), 5.34 (q, 1H, *J* = 6.7 Hz, $CHCH_3$), 6.84 (d, 1H, *J* = 7.2 Hz, H-Ar), 7.38 (dd, 1H, *J* = 8.0, 7.6 Hz, H-Ar), 7.66 (dd, 1H, *J* = 8.1, 1 Hz, H-Ar); $^{13}C$ NMR (100 MHz, $CDCl_3/CHCl_3$): $\delta$ 20.89 ($CHCH_3$), 22.26 ($CHCH_3$), 30.75 ($CH_2$), 56.15 ($OCH_3$), 60.74 ($OCH_3$), 62.03 ($OCH_3$), 62.40 (CH), 69.00 (CH), 105.45 (Ar), 114.64 (Ar), 119.26 (Ar), 124.44 (Ar), 125.82 (Ar), 129.97 (Ar), 130.12 (Ar), 148.12 (Ar), 149.05 (Ar), 156.12 (Ar); MS (I): *m*/*e* = 303 [$M^+$+1] (100), 288 (5), 229 (2); Calcd for $C_{18}H_{22}O_4$ (302.37): C, 71.50; H, 7.33. Found: C, 71.41; H, 7.44.
24. *Data for* **3**: Yellow needles; mp 168–170 °C; $[\alpha]_D^{25}$ +65.6 (*c* 0.3, $CHCl_3$); IR ($CHCl_3$): $\nu$ = 3016, 2923, 2852, 1717, 1657, 1586, 1470, 1375, 1256, 1216, 1054, 927, 760, 669 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$/TMS): $\delta$ 1.36 (d, 3H, *J* = 6.1 Hz, $CHCH_3$), 1.55 (d, 3H, *J* = 6.7 Hz, $CHCH_3$), 2.27 (ddd, 1H, *J* = 18.9, 10.2, 2.1 Hz, $CH_{ax}H$), 2.72 (dd, 1H, *J* = 19.1, 3.5 Hz, $CH_{eq}H$), 3.98 (m, 1H, $CH_2CHCH_3$), 4.01 (s, 3H, $OCH_3$), 5.03 (q, 1H, *J* = 6.7 Hz, $CHCH_3$), 7.29 (d, 1H, *J* = 8.5 Hz, H-Ar), 7.66 (dd, 1H, *J* = 8.1, 7.6 Hz, H-Ar), 7.76 (dd, 1H, *J* = 7.6, 1 Hz, H-Ar); $^{13}C$ NMR (100 MHz, $CDCl_3/CHCl_3$): $\delta$ 19.87 ($CHCH_3$), 21.62 ($CHCH_3$), 29.62 ($CH_2$), 56.56 ($OCH_3$), 62.57 (CH), 67.52 (CH), 117.93 (Ar), 119.20 (Ar), 119.8 (Ar), 134.17 (Ar), 134.83 (Ar), 139.47 (Ar), 148.13 (Ar), 159.83 (Ar), 182.84 (C=O), 184.34 (C=O); MS (I): *m*/*e* = 273 [$M^+$+1] (6), 243 (2), 229 (100), 201 (1.5); Calcd for $C_{16}H_{16}O_4$ (272.3): C, 70.57; H, 5.92. Found: C, 70.25; H, 5.86.