Synthesis of (±)-Eleutherin, (±)-Isoeleutherin, and their Demethoxy Analogues. A Novel Synthetic Approach

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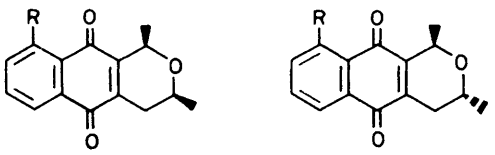
Summary (±)-Eleutherin (**1**) and (±)-isoeleutherin (**3**) are prepared by intramolecular cyclization to the naphthopyrans of 2-acetyl-3-allyl-8-methoxy-1,4-naphthoquinone, which is itself obtained by the Lewis acid-mediated allylation of 2-acetyl-8-methoxy-1,4-naphthoquinone (**5**) with allyltrimethylstannane (**7**).

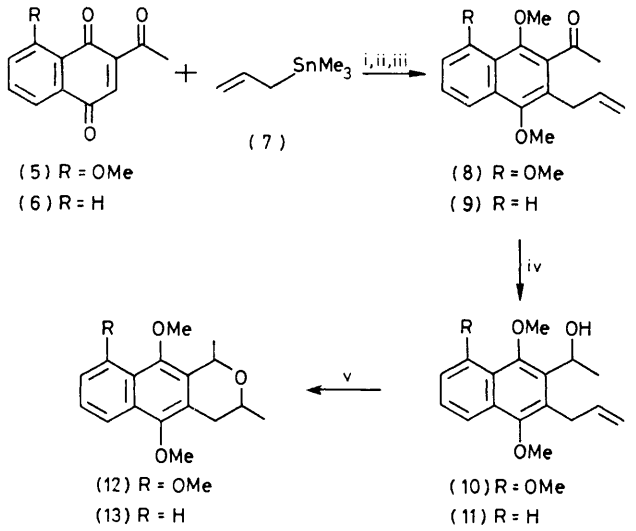
ELEUTHERIN (**1**) and isoeleutherin (**3**) are the simplest examples of naturally occurring naphtho[2,3-*c*]pyran-5,10-quinones and are found in *Eleutherin bulbosa*.[1] Development of new methods for synthesis of the above ring system[2–7] is also relevant to the study of the naphthoquinone antibiotics (frenolicin,[8] nanaomycins,[9] and kalafungin[10]). An alkanoylallylnaphthoquinone[11] is a promising precursor for this purpose. However, direct allylation of quinones substituted by an alkanoyl group is difficult using conventional methods. We have developed a method for the regioselective allylation of quinones using allylstannanes.[12,13] In this paper, we describe the efficient synthesis of the title compounds by sequential reactions including such an allylation.

In our synthetic approach, we needed 2-acetyl-8-methoxy-1,4-naphthoquinone (**5**) in quantity. The reported method[14] for its synthesis, however, is not efficient, so we developed a new route. Fries rearrangement of 1-acetoxy-4,8-dimethoxy-naphthalene, which was obtained by acetylation of 4,8-dimethoxy-1-naphthol,[15] with 1·1 equiv. of $BF_3{\cdot}OEt_2$ (*ca.* 120 °C; 5 min) afforded 2-acetyl-4,8-dimethoxy-1-naphthol† (87% yield, yellow crystals, m.p. 133—135 °C), oxidative demethylation of which with cerium(IV) ammonium nitrate (CAN) in aqueous acetonitrile solution gave (**5**)† (77%).



(**1**) R = OMe
(**2**) R = H

(**3**) R = OMe
(**4**) R = H

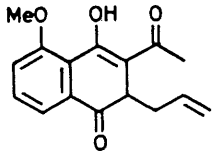


(**5**) R = OMe
(**6**) R = H
(**8**) R = OMe
(**9**) R = H
(**12**) R = OMe
(**13**) R = H
(**10**) R = OMe
(**11**) R = H

SCHEME. *Reagents and conditions:* i, $BF_3{\cdot}OEt_2$, −78 °C; ii, H_2O; iii, MeI, K_2CO_3; iv, $LiAlH_4$; v, $Hg(OAc)_2$ then $NaBH_4$, or PhSeBr then Raney Ni.

† All new compounds gave satisfactory elemental analyses and their spectroscopic data were in accord with the assigned structure.

Nucleophilic addition of allyltrimethylstannane (**7**) (1·2 equiv.) to (**5**) with $BF_3{\cdot}OEt_2$ (1·0 equiv.) (at −78 °C for 1 h followed by warming to room temperature in CH_2Cl_2) selectively afforded the conjugate adduct (**14**) [pale yellow



(**14**)

oil; δ ($CDCl_3$) 2·25 (s, 3H), 2·39 (m, 2H), 2·59 (dd, 1H, *J* 6 and 8 Hz), 4·00 (s, 3H), 4·8—5·1 (m, 2H), 5·67 (ddt, 1H, *J* 7, 11, and 17 Hz), 7·2—7·4 (m, 1H), 7·4—7·7 (m, 2H), and 16·92 (s, 1H)] quantitatively after hydrolysis. The allylated product (**14**) was converted into the corresponding hydroquinone dimethyl ether (**8**)† [92% from (**5**)] using MeI and K_2CO_3 in acetone. Reduction of the ketone (**8**) with lithium aluminium hydride provided the benzylic alcohol (**10**)† (98%). Intramolecular acetoxymercuration[16] and successive reduction using sodium borohydride gave a mixture (*ca.* 1 : 1) of the two isomeric naphthopyrans (**12**) (total yield 93%). After separation of the isomers by column chromatography on silica gel (10—20% ether–hexane as eluant), oxidative demethylation using CAN of *cis*-(**12**)† (colourless crystals, m.p. 95·5—96·5 °C) and *trans*-(**12**)† (colourless crystals, m.p. 106—107 °C) provided eleutherin† (**1**)‡ (90% yield; m.p. 154—155 °C) and isoeleutherin† (**3**)‡ (89% yield; m.p. 147—149 °C), respectively.

A further example of the synthesis of demethoxy-analogues displays the general applicability of this pathway. Allylation of 2-acetyl-1,4-naphthoquinone (**6**) followed by methylation gave the dimethyl ether (**9**)† (91%). Reduction of (**9**) provided (**11**) (68%), phenylselenoetherification[17] (PhSeBr in dichloromethane at −78 °C then water at 20 °C; Raney Ni in tetrahydrofuran) instead of acetoxymercuration of which gave the corresponding naphthopyrans (**13**) (*cis* : *trans ca.* 2 : 1; total yield 56%). Interestingly this cyclization reaction preferentially afforded the *cis*-isomer. Oxidation of (**13**) with CAN gave a mixture (*cis* : *trans ca.* 2 : 1) of (**2**) and (**4**) (total yield 98%), which were chromatographed on silica gel using CH_2Cl_2–hexane (1 : 1) as eluant to afford pure demethoxyeleutherin† (**2**)‡ (m.p. 143—144 °C) and demethoxyisoeleutherin† (**4**)‡ (m.p. 150·5—151·5 °C).

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‡ Compounds depicted as single enantiomers represent racemates.

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