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Synthesis of (+)-nocardione A — use of formal radical cyclization onto a benzene ring

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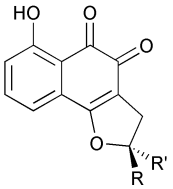
Received (in Cambridge, UK) 11th July 2003, Accepted 8th August 2003
First published as an Advance Article on the web 21st August 2003

Juglone (7) was converted into enone 13; this underwent radical cyclization to afford 15, which was aromatized to 16 and elaborated into (+)-nocardione A (1), the enantiomer of the naturally-occurring tyrosine phosphatase inhibitor (−)-nocardione A (2).

We report the synthesis of (+)-**1**, the enantiomer of the Cdc25B tyrosine phosphatase inhibitor (−)-nocardione A (**2**).[1,2] The latter was isolated from the fermentation broth of a soil microorganism tentatively identified as the Gram-positive bacterium *Nocardia* sp. TP-A0248, and is of interest because Cdc25B is a key enzyme in cell cycle regulation and is overexpressed in several types of human cancer cells.[3] Nocardione A (**2**) shows moderate antifungal and cytotoxic activity,[1] and causes cell death with characteristics of apoptosis in U937 human myeloid leukemia cell lines.[1]

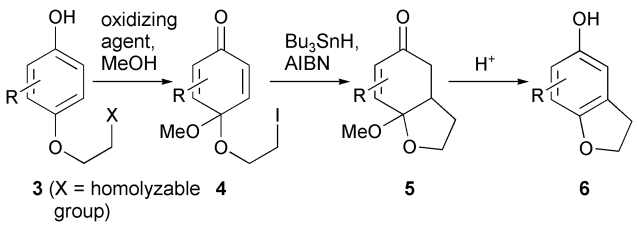


1 R = Me, R' = H
2 R = H, R' = Me

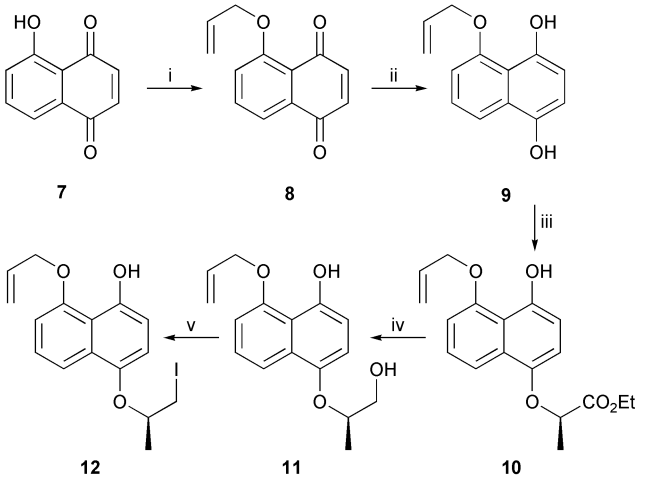
Our synthetic route is based on a method for achieving formal cyclization of a radical onto a benzene ring, along the lines summarized in Scheme 1. The overall sequence **3** → **6** is general;[4] our model studies[4] have shown that it is an efficient route to simple benzo-fused dihydrofurans, and its application to the synthesis of **1** or **2** promised to be a significantly more demanding test of the methodology. The prior synthesis[2,5] of nocardione A (**2**), revealed that the compound is rather sensitive and its construction challenging; deprotection of the corresponding *O*-methyl ether (a congener called nocardione B) was accompanied by racemization, and even hydrogenolysis of the corresponding *O*-benzyl ether was inefficient. Formation of the dihydrofuran segment, generated by Mitsunobu displacement, was also difficult. We chose to make the unnatural enantiomer **1** because ethyl (−)-lactate, a chiral building block used in our approach, is much cheaper than the *R*-enantiomer.

Application of the general method of Scheme 1 to the particular case of (+)-nocardione A requires the substituted naphthalenol **12** (see Scheme 2) as a key intermediate, and this compound was prepared as shown. Juglone (**7**) was converted (allyl bromide, Ag_2O, 79%) into allyl ether **8** (Scheme 2), and reduction with aqueous $Na_2S_2O_4$ (100%) then gave bis-phenol **9**. At this point, introduction of the chiral two-carbon chain needed for the radical cyclization could be achieved under the following conditions. First, ethyl (−)-lactate[6] was converted into its trifluoromethanesulfonate by the literature method,[7] and a solution of this derivative (4 equiv.) was added to a stirred and cooled (−78 °C) solution of **9** in the presence of Cs_2CO_3.[8] After an 18-hour reaction period, **10** could be isolated in 50% yield (88% after correction for recovered **9**). Under these conditions, stereochemical inversion of the trifluoromethanesulfonate occurs and the alkylation is regioselective (**9** → **10**). Ester reduction ($LiAlH_4$, 100%) gave alcohol **11** (ee > 95% by ^{19}F NMR on the derived Mosher ester) and replacement of the hydroxyl by iodine (Ph_3P, imidazole, I_2, 89%) took the route as far as phenolic ether **12**. When this was oxidized with DDQ (Scheme 3) in the presence of MeOH and K_2CO_3, the required enone **13** was formed in good yield (87%) as a 1.1 : 1 mixture of diastereoisomers. Radical cyclization under standard conditions[4] (Bu_3SnH, AIBN, PhMe, 85 °C) led to the diastereoisomeric furans **15** (82%) by way of the intermediate radicals **14**. We found no evidence for cyclization of **14** through oxygen onto the allyl pendant. Aromatization (**15** → **16**) was easily achieved, either by storage in $CDCl_3$ (12 h, 97%) or by treatment with AcOH in $CHCl_3$ (88%); under these conditions 7-*exo* cyclization of the phenolic hydroxyl onto the allyl group was not observed. With the phenolic dihydrofuran **16** in hand, the *o*-quinone system was readily generated (96%, 82% after crystallization from $CHCl_3$–hexane) by the action of $[PhSe(O)]_2O$[9] and, finally, palladium-mediated removal of the allyl protecting group afforded (+)-nocardione A, which crystallized from EtOAc–hexane as bright red needles (74% yield from **17**, 22% overall from juglone), mp 168–169 °C,[10] [Lit. 115–120 °C;[1] 172.5–173.5 °C[2]]. Examination of the compound by HPLC on a chiral column[11] showed the material to have an ee of 98.5%[12]

We thank the Natural Sciences and Engineering Research Council of Canada for financial support, and Dr X. Lu and H.

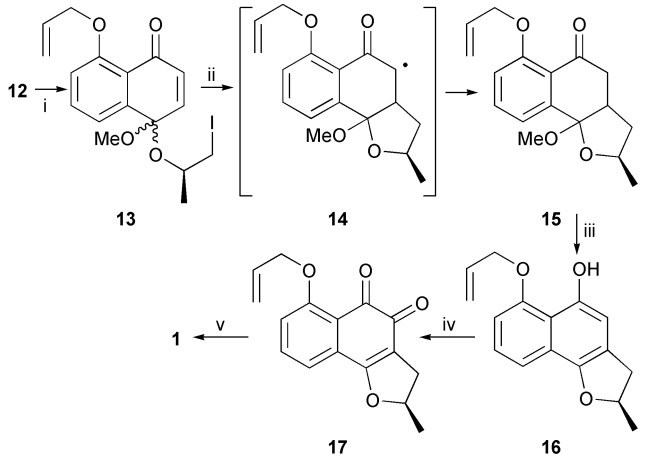


Scheme 1



Scheme 2 *Reagents and conditions*: (i) allyl bromide, Ag_2O, CH_2Cl_2, reflux, 11 h, 79% ; (ii) $Na_2S_2O_4$, ether–water, 40 min, 100%; (iii) triflate of ethyl (−)-lactate, Cs_2CO_3, CH_2Cl_2, −78 °C, 18 h, 50%, 88% corrected for recovered **9**; (iv) $LiAlH_4$, THF, 10 min, 100%; (v) Ph_3P, imidazole, I_2, THF, 12 h, 89%.

DOI: 10.1039/b307937f



Scheme 3 *Reagents and conditions*: (i) DDQ, MeOH, K_2CO_3, 4 min, 87%; (ii) Bu_3SnH and AIBN (addition over 9 h), heat 6 h more, PhMe, 85 °C, 82%; (iii) AcOH, $CHCl_3$, 2 h, 88%; (iv) $[PhSe(O)]_2O$, THF, 12 min, 96%, 82% after recrystallization; (v) 10 mol% $Pd(PPh_3)_4$, dimedone, THF, 4 min, 74%.

Lachance for HPLC measurements. SPF holds an NSERC Postgraduate Scholarship.

Notes and references

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10 There is a form change to needles at, or below, 158 °C if the original material is a powder, as obtained by evaporation of a solution.

11 Chiralcel AD-RH column (0.46 cm × 15 cm); eluant 2 : 1 water–MeCN; flow rate 0.6 mL min^{-1}; detection at 230 nm, temperature 25 °C; sample concentration and injection value 1 mL mg^{-1} in MeCN × 0.5 μL. Under these conditions there is baseline separation between the nocardione A enantiomers.

12 Our $[\alpha]_D$ values are unreliable; the high extinction coefficient of the compound prevents adequate light transmission in our instrument: found for **1**, $[\alpha]_D^{24}$ +36.8, *c* = 1.0 $CHCl_3$, 10 cm cell; $[\alpha]_D^{24}$ +49.5, *c* = 0.97 $CHCl_3$, 1 cm cell. Lit. for **2**, $[\alpha]_D^{21}$ −56.0, *c* = 0.97 $CHCl_3$ (ref. 2) $[\alpha]_D^{26}$ −85.4, c = 1.0 $CHCl_3$ (ref. 1).