Synthesis of Larreantin, a Novel, Cytotoxic Naphthoquinone from *Larrea tridentata*

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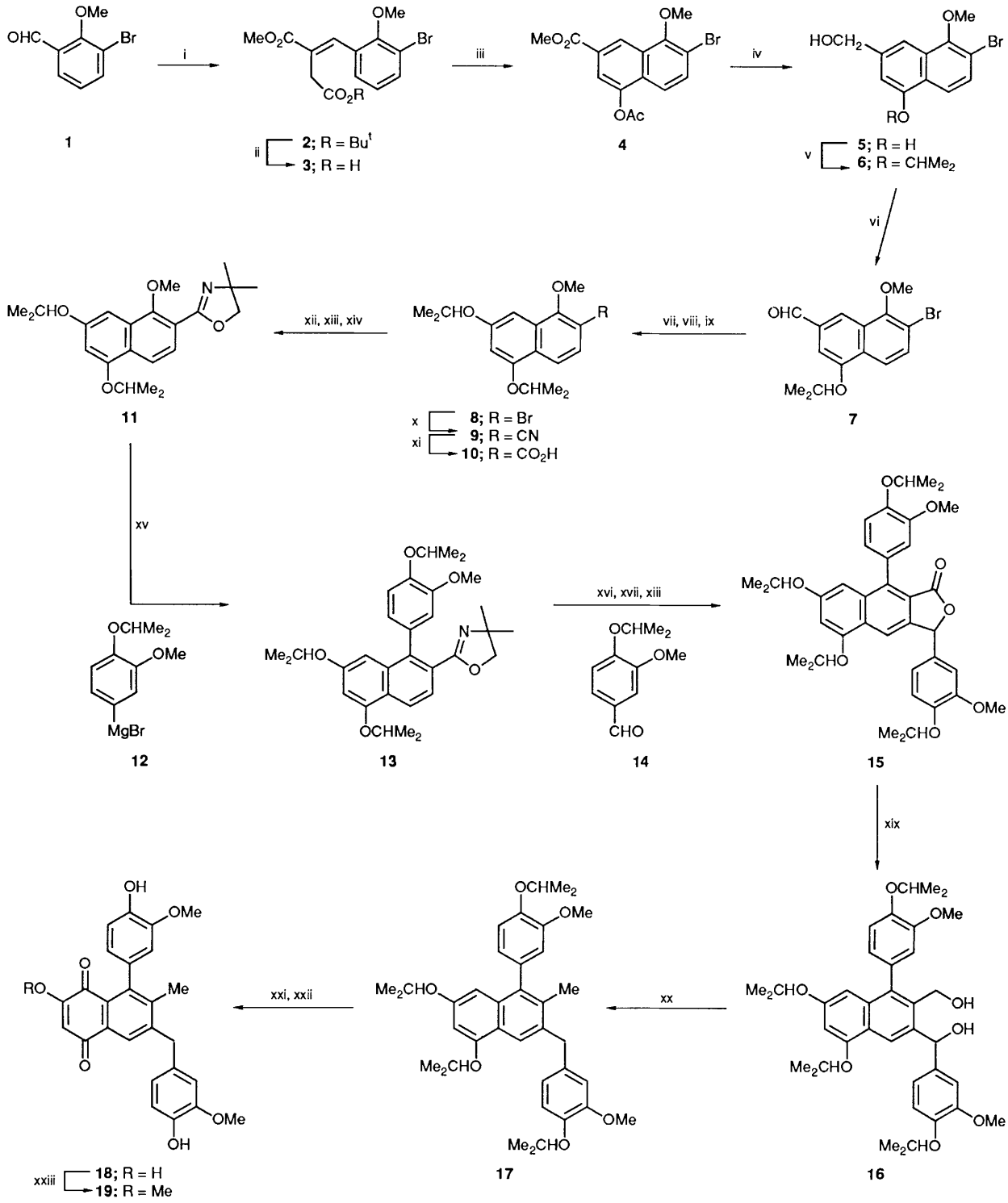
Larreantin, a biogenetically unique cytotoxic naphthoquinone, has been synthesized by a convergent route which depends upon the selective functionalization of a naphthyldihydro-oxazole.

Cordell and his co-workers[1] have recently isolated the highly cytotoxic naphthoquinone, larreantin **19**, from the roots of the creosote bush, *Larrea tridentata* (DC) Coville (Zygophyllaceae). The structure of larreantin, which represents an unprecedented class of naphthoquinone, and which appears to be derived biogenetically by the combination of two isomeric phenylpropene groups with a benzoquinone, was based on extensive application of high field NMR techniques.[1] We now confirm this structure by a convergent synthesis.

For this purpose we adopted as the key intermediate the naphthyldihydro-oxazole **11**. The intention was to take advantage of the directing power of the dihydro-oxazole moiety to introduce an aryl group by displacement of the *o*-methoxy group by an aryl Grignard reagent, and to introduce a benzyl group into the other *ortho*-position by lithiation and subsequent reaction with an electrophile.[2] The protected 1,3-oxygenation in the above intermediate would also serve as a precursor to the quinonoid system.[3]

The known aldehyde **1**[4] was caused to react with 2-*tert*-butoxycarbonyl-1-methoxycarbonylethylidenetriphenylphosphorane[5] and hydrolysis of the resultant ester **2**† gave the acid **3**,† which on ring-closure provided the acetate **4**.† Reduction of this intermediate afforded the diol **5**,† which was selectively converted into the isopropyl ether **6**.† Manganese dioxide oxidation furnished the aldehyde **7**† which on Baeyer–Villiger

† New compounds gave satisfactory elemental analyses and spectra in accord with the assigned structures.



Scheme 1 *Reagents and conditions*: i, $Ph_3P:C(CO_2Me)CH_2CO_2Bu^t$, PhH, reflux, 20 h, 91%; ii, 90% aq. CF_3CO_2H, 25 °C, 15 min, 95%; iii, Ac_2O, KOAc, reflux, 5 min, 84%; iv, DIBAL, THF, −10 °C, 94%; v, Me_2CHBr, DMF, K_2CO_3, Ar, 25 °C, 96 h, 82%; vi, MnO_2, CH_2Cl_2, 25 °C, 12 h, 90%; vii, *m*-$ClC_6H_4CO_3H$, CH_2Cl_2, reflux, 72 h; viii, NaOMe, MeOH, Ar, 5 min; ix, Me_2CHBr, DMF, K_2CO_3, Ar, 50 °C, 72 h, 26% overall; x, CuCN, DMF, reflux, N_2, 12 h, 95%; xi, NaOH, aq. MeOH, reflux, 96 h, 85%; xii, $(COCl)_2$, CH_2Cl_2, 25 °C, 2.5 h; xiii, $HOCH_2CMe_2NH_2$, CH_2Cl_2, 25 °C, 2 h; xiv, $SOCl_2$, CH_2Cl_2, 25 °C, 2 h, 81% overall; xv, **12**, THF, 25 °C, Ar, 45 min, 88%; xvi, Bu^sLi, THF, TMEDA, −78 °C, Ar, 1 h; xvii, **14**, −78–25 °C, 1 h; xviii, conc. HCl, dioxane, reflux, 0.5 h, 59% overall; xix, $LiAlH_4$, THF, Ar, 25 °C, 2 h, 99%; xx, THF, Et_3N, $(CF_3CO)_2O$, 10% Pd/C, H_2, 18 h, 80%; xxi, BCl_3, CH_2Cl_2, Ar, −10 °C, 8 h; xxii, KOH, EtOH, EtOAc, air, 30 s; xxiii, MeI, $KHCO_3$, DMF, Ar, 8 h, 13% overall. (DIBAL = diisobutylaluminium hydride; THF = tetrahydrofuran; DMF = dimethylformamide; TMEDA = tetramethylethylenediamine.)

oxidation, hydrolysis of the intermediate formate, and subsequent isopropylation afforded the intermediate **8**.† Displacement of the bromine with copper(I) cyanide now supplied the nitrile **9**† and then hydrolysis gave the acid **10**,† which was converted into the required dihydro-oxazole **11**† by the standard method.[6]

The dihydro-oxazole **11** was now caused to react with the Grignard reagent **12** and the arylated product **13**† was lithiated with *sec*-butyl lithium. The resultant lithio-derivative underwent smooth reaction with the known aldehyde **14**[7] and anchimerically assisted hydrolysis of the intermediate hindered dihydro-oxazole provided the phthalide **15**.† Reduction

of this intermediate with lithium aluminium hydride yielded the diol **16**.† In order to prevent cyclization to the derived 1,3-dihydronaphtho[2,3-*c*]furan the diol was catalytically hydrogenated in the presence of trifluoroacetic anhydride and an excess of triethylamine, which smoothly afforded the deoxygenated product **17**.† Deprotection of this intermediate and brief aerial oxidation of the anion of the resultant tetrol gave the quinone **18**, which was immediately selectively methylated thereby providing larreantin **19**† in an overall yield of 0.5% for 23 steps. The physical properties of the synthetic material were identical to those of the natural product.[1]

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