γ-Alkoxylactones as Autounmasking Synthons for a One-step Construction of 1,3-Oxygenated Cyclopentanes. Synthesis of Fredericamycin A Core and Spirobenzylisoquinoline Alkaloids

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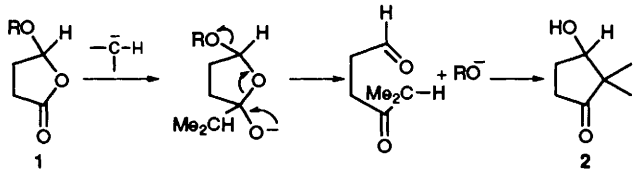
Reaction of γ-alkoxyphthalide **7a** with 3-indenyllithium leads to fredericamycin A core compound **5**, whereas condensation of methylenedioxyphthalide **7b** or **8** with lithiated *N*-methyltetrahydroisoquinoline–BF_3 complex **9** affords spirobenzylisoquinoline alkaloids raddeanine **12**, corydaine **13** and yenhusomidine **13**.

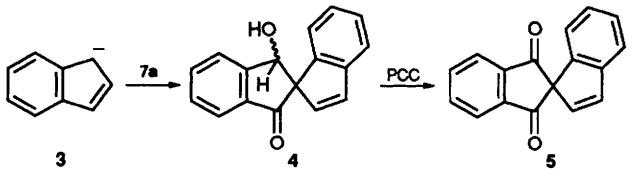
1,3-Oxygenated cyclopentane units are present in a variety of natural products of considerable pharmacological interest.[1] We envisaged a one step construction of such systems by condensation of a carbanion with a four-carbon synthon having appropriate carbonyl functionalities at each end. For sequential formation of two new carbon–carbon bonds in a single operation, it was necessary to use an autounmasking protective procedure. In other words, one carbonyl group of the synthon had to be protected in such a manner that its unmasking, for the subsequent step, is triggered by carbanion addition to the other. It seemed that readily accessible,[2] but little explored, γ-alkoxylactones might meet this requirement (**1** → **2**, Scheme 1). In the event, reaction† of 3-indenyllithium[3] with phthalide **7a** ($R^1 = R^2 = H$) gave a mixture of two isomeric alcohols, which on oxidation with PCC afforded fredericamycin A core compound **5**, mp 157–158°, in 55% yield (Scheme 2).[4]‡

The above approach was then combined with Lewis acid complexation methodology for generation of azacarbanions,[5] to synthesise spirobenzylisoquinoline alkaloids in which an additional nitrogen is appended to the dioxygenated cyclopentane ring.[6] The phthalide **8** (mp 141–142 °C) required for this purpose was secured by heating **6b** in ethanol containing a trace of sulfuric acid (Scheme 3). Its reaction with BF_3-complexed carbanion **9a**§ gave a mixture of hydroxyketones from which pure **10** (22%, mp 194–195 °C) and **11** (34%, mp 147–148 °C) were obtained by silica gel chromatography (Schme 4).[7]¶ *Trans* disposition of nitrogen and oxygen in **11** was assigned on the basis of the compounds tendency to convert to the more stable hydrogen bonded isomer **10**.[8] Reduction of **11** with sodium borohydride occured from the less hindered face of the molecule to afford (±)-raddeanine **12** (mp 223–224 °C, 90%, lit.[9] 219–220 °C), an alkaloid found in corydalis ledebouriana.

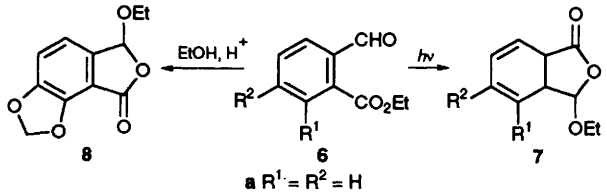
An additional advantage of the alkoxyphthalide approach is that oxidation levels at the two carbonyl carbons of the starting *o*-formylbenzoate can be transposed through a photorearrangement.[2a] Thus, irradiation of **6b** in benzene with Pyrex filtered light afforded lactone **7** (R^1, $R^2 = OCH_2O$, mp 129–130 °C). Treatment of **7** with carbanion **9b** yielded a mixture which was separated into (±)-corydaine (**13**, R^3, $R^4 = OCH_2O$, 45%, mp 140 °C, lit.[8] 142–143 °C) and its less stable isomer (±)-sibiricine (**14**, R^3, $R^4 = OCH_2O$, 20%, mp 220–221 °C, lit.[8] mp 220–221 °C). From a similar reaction of this phthalide with **9a** only the more stable isomer, (±)-yenhusomidine (**13**, $R^3 = R^4 = -OMe$, mp 240–241 °C, lit.[8] 240–241 °C), could be isolated in 65% yield.‖ Since the reaction of unprotected aldehyde **6** with **9** gives phthalideisoquinolines **15**,[5] it is interesting to note how changing the starting material leads to different alkaloids.



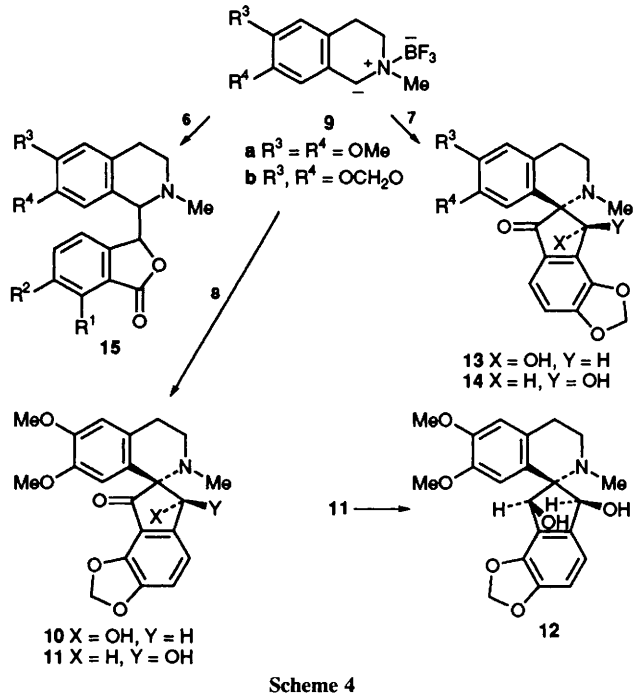
Scheme 1



Scheme 2



Scheme 3



Scheme 4

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Footnotes

† Conditions for reaction of **7** with carbanions; To a stirred solution of the carbanion (0.01 mol) in THF (10 ml) at −78 °C under a nitrogen atmosphere was added, through a syringe, a solution of **7** (0.01 mol) in THF (4 ml). After 45 min stirring at −78 °C, the reaction mixture was allowed to warm to −20 °C and quenched with water.

‡ This result may be compared with the recently reported conversion of **6a** to **5** through a sequence of six steps with less than 25% overall yield [ref. 4(*c*)].

§ Conditions for generation of carbanions from tertiary amines; $BF_3{\cdot}OEt_2$ (0.02 mol) was added to a stirred solution of the amine (0.01 mol) in THF (10 ml). After cooling to −78 °C, 0.025 mol of base (*sec*-butyllithium in pentane) was introduced and stirring continued for 30 min to complete the anion formation.

¶ NMR data of our compound is in accord with the reported values and its structure was further confirmed by reduction to raddeanine.

‖ The yields are calculated for pure compounds isolated through chromatography/crystallization and do not take into account starting materials recovered due to incomplete carbanion formation or subsequent protonation. Satisfactory spectral data and elemental analysis or HRMS (±3 a.m.u.) for compound **5**, **7**, **8**, **10–14** are in hand. Selected data for **10**: ^{1}H NMR ($CDCl_3$): δ 2.3 (s, 3H, NCH_3), 2.2–4.0 (m, 4H, $ArCH_2CH_2$), 3.7, 3.9 (2s, 6H, 2 × OCH_3), 5.03 (s, 1H, ArC*H*OH), 5.91 (br s, 1H, OH, D_2O exchangeable), 6.22 (s, 1H, Ar H), 6.25 (s, 2H, OCH_2O), 6.67 (s, 1H, Ar H) and 7.3 (s, 2H, Ar H); *m/z* (relative intensity): 384 (M^+ + 1, 20.6), 383 (95.6), 338 (26.5), 220 (30.5), 207 (18.3), 206 (100), 190 (23), 149 (29.7); Calc. for $C_{21}H_{21}NO_6$, 383.4000. Found: 383.3983. For **11**: ^{1}H NMR ($CDCl_3$): δ 2.47 (s, 3H, NCH_3), 2.75–3.9 (m, 4H, $ArCH_2CH_2$), 3.45, 3.8 (2s, 6H, 2 × OCH_3), 5.4 (s, 1H, ArC*H*OH), 5.87 (br s, 1H, OH, D_2O exchangeable), 5.97 (s, 1H, Ar H), 6.15 (s, 2H, OCH_2O), 6.7 (s, 1H, Ar H) and 7.2 (s, 2H, Ar H); *m/z* (relative intensity): 384 (M^+ + 1, 14), 383 (63.7), 368 (23), 340 (12), 338 (20), 324 (25.7), 220 (21.3), 207 (26), 206 (100), 190 (19), 177 (13.3), 147 (25.7); Calc. for $C_{21}H_{21}NO_6$, 383.4000. Found: 383.3978.

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