An Approach to the Tricyclic Lactone Core of Brasoside and Related Natural Products

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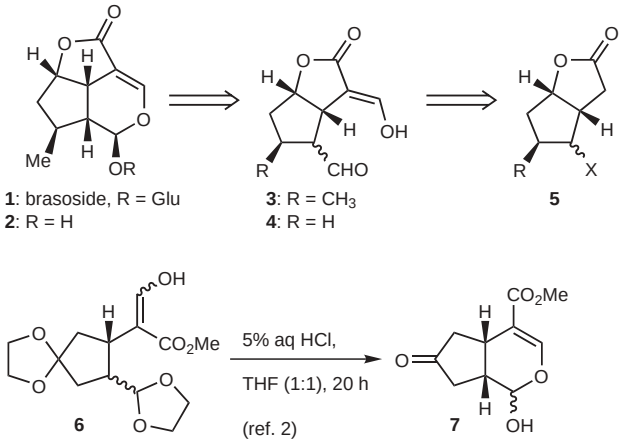
Abstract: A one-pot iodine atom transfer/cyclisation and intermolecular olefination is described for the efficient, stereoselective construction of bicyclic lactone intermediates en route to compound **21**, a potential precursor to the brasoside (**1**) skeleton.

Key words: cyclisations, domino reactions, natural products, radical reactions, stereoselective synthesis

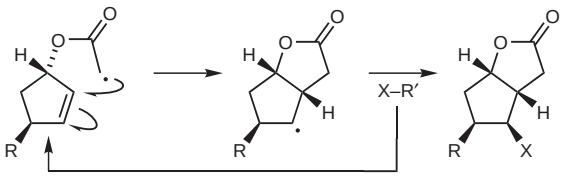
Littoralisone is a neuritogenic heptacyclic iridolactone that may be considered to be derived biosynthetically from brasoside (**1**) purely on the basis of their related structures and their co-occurrence in *Verbena littoralis*.[1] As part of our general interest in developing new synthetic methodology within the context of complex natural product synthesis, we initiated a programme of research to effect a total synthesis of brasoside as a prelude to littoralisone. This letter summarises our first approach to brasoside which was based, in part, on the conversion **6** → **7** in Vidari's formal synthesis of (±)-loganin (Scheme 1).[2]



Scheme 1

A key feature of the formation of hydroxydihydropyran **7** is that acetal hydrolysis under acidic conditions was accompanied by trapping of the epimerised aldehyde; in other words, in a projected synthesis of brasoside from an intermediate of the form **5** (R = CH_3), the stereochemistry at the X-bearing position should be of no consequence. Thus, synthesis of aldehyde **3**, by functional group interconversion and formylation, was expected to yield the aglucone of brasoside (**2**) by cyclisation[3] in situ.

Compounds of general structure **5** have featured in a variety of total synthesis endeavours and there is plenty of precedent from which to draw in planning their synthesis; however, in the light of separate results within our group,[4] an attractive possibility was a free-radical group transfer cyclisation of a suitable cyclopentyl ester (Scheme 2, X–R′ being the starting cyclopentenyl ester).



Scheme 2

Studies initiated with application to model iodoacetate **8** (Scheme 3) of the iodine atom transfer general method described by Curran.[5] In this process, it was expected that the slow cyclisation of the α-acetyl radical would proceed in synthetically useful yield because the more populated *s-trans* ester conformation cannot suffer direct reduction in the absence of a suitable H-atom source. In the event, exposure of a mixture of ester **8** and hexabutyldistannane in benzene to a 300 W tungsten filament lamp, at various concentrations (0.02–0.3 M), and in either Pyrex or quartz vessels, led to generally disappointing results, with a mixture of products, apparently deriving from trapping of the α-acetyl radical with either the stannane or the solvent, accompanying the desired product **9**, which was isolated in a maximum yield of 63% as a ca. 2:1 ratio of *exo*:*endo* iodo-diastereomers.

In seeking a more practical alternative, attention then turned to Zard's elegant dithiocarbonate group transfer method[6] in which the intermediate α-acetyl radical could only suffer degenerate intermolecular group transfer, or group transfer following cyclisation. Thus, xanthate **12**, prepared in essentially quantitative yield (98%) from the iodide **8**, was heated in the presence of dilauroyl peroxide (DLP) to yield *exo*-xanthate derivative **13** in 66% yield (Scheme 4). This approach was operationally straight-

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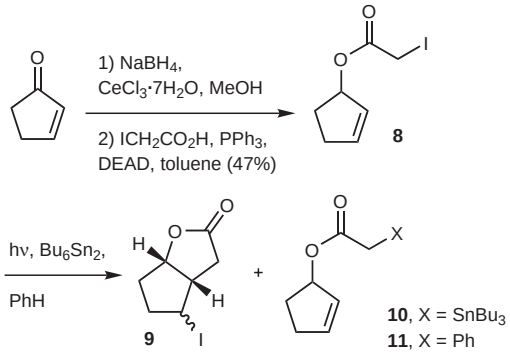
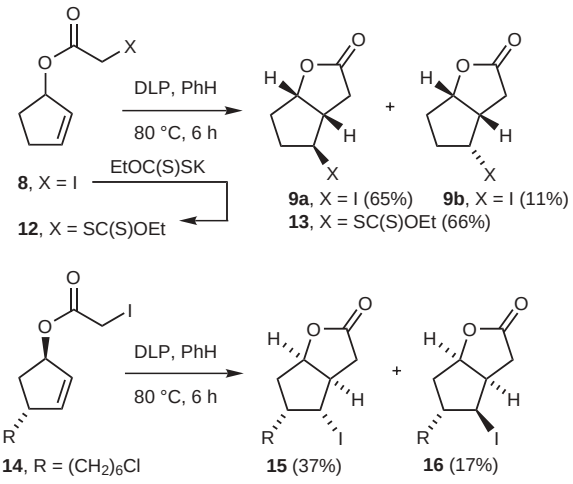


Scheme 3

forward and provided the bicyclic product in diastereomerically pure form.

Application of DLP-mediation to related iodine atom transfer reactions has been reported by Renaud et al.[7] and, pleasingly, heating iodide **8** in benzene in the presence of DLP led to clean cyclisation and atom transfer to give a 5.9:1 ratio of *exo*:*endo* iodo-diastereomers **9a** and **9b** that were separated for analytical purposes. Because this reaction was both practical and tin-free, it became our method of choice for the production of bicyclic products of general structure **5**. When the procedure was applied to an alkylated cyclopentenyl ester [(+)-**14**],[4] the reaction was less efficient and markedly less stereoselective (**15**:**16**, 2.2:1; Scheme 4).

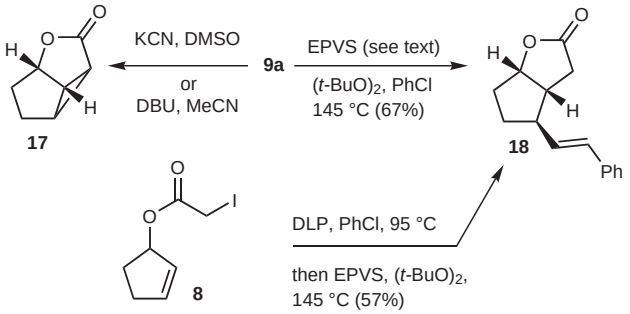


Scheme 4

Introduction of the two formyl groups present in compound **4** proved to be non-trivial. An initial attempt to displace iodide in an S_N2 manner, by treating compound **9a** with carbon-based nucleophiles, was not successful, presumably as a result of a hindered *endo*-approach to the bicyclic structure; in most cases (e.g. with KCN in DMSO at 80 °C) tricyclic lactone **17**[8] was obtained as a major product. More success was obtained under free-radical olefination conditions and, although xanthate **13** could be a useful precursor in this regard, the ease of access to iodide **9a** led us to adopt this compound for further study.

A convenient solution was found in another contribution by Zard.[9] Thus, heating iodide **9a** in chlorobenzene in the presence of ethyl 2-phenylvinyl sulfone (EPVS) and *tert*-butyl peroxide gave, in a slow reaction, the *exo*-β-styryl derivative **18** as a single diastereomer (67%) after recrystallisation from diethyl ether.

Given the experimental similarity of the two homolytic steps leading to lactone **18**, it was an attractive possibility to run the two processes – atom transfer cyclisation and olefination – as a single step. In practice, this worked very well: iodide **8** was heated with DLP in chlorobenzene at 95 °C until formation of lactone **9** was complete then EPVS and *tert*-butyl peroxide were added and the temperature raised to 145 °C to complete the reaction; lactone **18** was then isolated in 57% yield as a single diastereomer (Scheme 5).[10]



Scheme 5

From this point (**18**), completion of the route to the brasoside core structure appeared to be readily achievable merely by oxidative cleavage of the styryl group, formylation of the lactone, and cyclisation (following the Vidari precedent). The first two of these objectives were reduced to practice without complication; thus, ozonolysis of alkene **18** afforded aldehyde **19** that was immediately protected as its ethylene acetal **20** and formylated (→ **21**). Interestingly, the formyl lactone **21** existed almost entirely in the enol form (according to ^{1}H NMR analysis) and NOE experiments confirmed the *E*-geometry of the hydroxymethylene group, suggesting the presence of a hydrogen bond between the enolic hydrogen and an acetal oxygen (Scheme 6).[11]

All of our attempts to effect hydrolysis, epimerisation and cyclisation of functionalised lactone **21** have, to date, proven unsuccessful. Application of Vidari's conditions as well as a range of alternative acidic reagents showed that acetal hydrolysis proceeded quickly but the so-formed dialdehyde showed no propensity to cyclise, decomposing instead to intractable materials. On the assumption that the lactone present in **21** could be responsible for problems with this reaction, substrates **22**–**24** were prepared and subjected to a similar investigation. In no case were we able to observe formation of a hydroxy- or alkoxy-dihydropyran.[12]

Whilst it remains disappointing that we have been unable to complete this first-generation route to the brasoside

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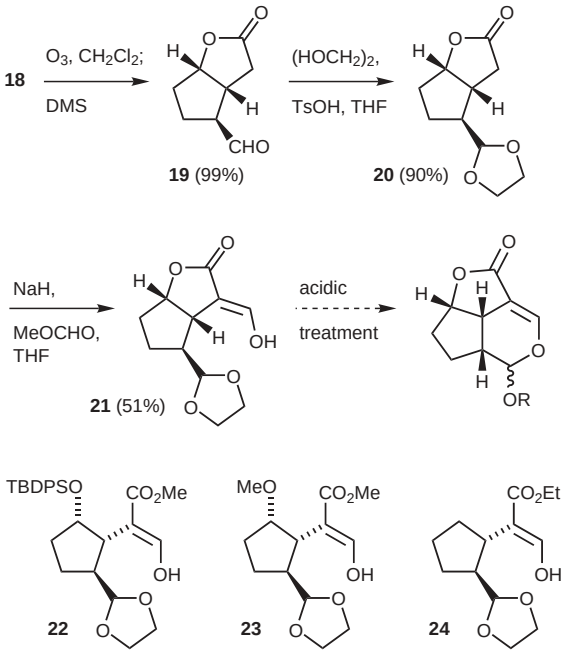

Scheme 6

core structure, this investigation generated an efficient synthesis of bicyclic compounds of general structure **5** [R = H, $(CH_2)_6Cl$; X = I, SC(S)OEt, CH=CHPh, CHO, $CH(OCH_2CH_2O)$]. This chemistry, represented by the retrosynthetic disconnection shown in Scheme 7 is a practical and efficient alternative to, for example, Stork's radical cyclisation and trapping with *tert*-butylisocyanide,[13] and tandem organometallic approaches.[14]

Scheme 7

Acknowledgement

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(10) DLP (100 mg, 0.25 mmol) was added every 2 h (3×) to a solution of iodide **8** (750 mg, 2.98 mmol) in dry chlorobenzene (40 mL) at 95 °C. After 7 h in total, a solution of ethyl 2-phenylvinyl sulfone[15] (1.75 g, 8.93 mmol) in chlorobenzene (5 mL) was added and the reaction mixture was heated at 145 °C. *tert*-Butyl peroxide was added every 2 h (3 × 100 μL) and the solution was heated at 145 °C for 16 h. The cooled solution was poured directly onto the top of a silica gel column, and the column was flushed with petroleum ether to remove chlorobenzene. Elution was then continued with a 4:1 mixture of petroleum ether–EtOAc to afford lactone **18** (390 mg, 57%) as colourless crystals after recrystallisation from Et_2O. R_f = 0.42 (3:1 petroleum ether–EtOAc); mp 76–81 °C. IR (KBr disc): ν_{max} = 2971 (m), 1779 (s), 1493 (w), 1448 (w), 1421 (w), 1357 (w), 1299 (w), 1248 (w), 1176 (s), 1042 (s), 974 (s), 898 (w), 752 (m), 696 (m) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.57–1.66 (1 H, m), 1.93–2.01 (1 H, m), 2.04–2.11 (1 H, m), 2.23–2.31 (1 H, m), 2.42–2.50 (1 H, m), 2.44 (1 H, dd, *J* = 18.8, 1.4 Hz), 2.57 (1 H, br q, apparent *J* = 8.0 Hz), 2.76 (1 H, dd, *J* = 18.8, 8.8 Hz), 4.99–5.08 (1 H, m), 6.08 (1 H, dd, *J* = 15.6, 7.6 Hz), 6.44 (1 H, d, *J* = 15.6), 7.21–7.36 (5 H, m, Ph). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 32.0, 34.1, 45.7, 49.6, 77.2, 85.8, 126.1, 127.5, 128.6, 130.6, 130.8, 136.8, 176.9. MS (CI, NH_3): *m/z* (%) = 246 (100) [MNH_4^+], 229 (25) [MH^+], 169 (10), 87 (20), 70 (20). HRMS (CI): *m/z* calcd for $C_{15}H_{20}NO_2$ [MNH_4^+]: 246.1494; found: 246.1491.
(11) Compounds analogous to lactone **21** that lack oxygen-containing functionality in the cyclopentane ring (cf. the dioxolane in **21**) exist, in general, as tautomeric mixtures. Spectroscopic data for **21**: R_f = 0.35 (EtOAc); mp 81–84 °C. IR (KBr disc): ν_{max} = 2967 (s), 2883 (m), 2740 (s), 1718 (s), 1682 (s), 1618 (s), 1420 (s), 1373 (m), 1198 (s), 1128 (s), 1074 (s), 1014 (s), 966 (m), 943 (m) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.51–1.63 (1 H, m), 1.68–1.80 (1 H, m), 2.01–2.10 (1 H, m), 2.24–2.39 (2 H, m), 3.27 (1 H, ddd, *J* = 9.1, 6.8, 2.3 Hz), 3.95–4.03 and 4.09–4.16 (4 H, m), 4.86–4.93 (1 H, m) overlaying 4.89 (1 H, d, *J* = 5.2 Hz), 7.44 (1 H, dd, *J* = 14.1, 2.3 Hz), 9.13 (1 H, d, *J* = 14.1 Hz). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 27.0, 33.5, 39.1, 49.0, 65.0, 65.1, 82.3, 105.6, 105.9, 154.6, 172.8. HRMS (ES): *m/z* calcd for $C_{11}H_{13}O_5$ [M – H]: 225.0763; found: 225.0754. NOE experiment: Irradiation of the enolic hydroxyl proton at δ = 9.13 ppm led to enhancement of the resonances at δ = 3.27 (-CHC=), 3.95–4.03 and 4.09–4.16 ($-OC_2H_4O-$), 4.89 [$-CH(OR)_2$], and 7.44 (=C*H*OH) ppm; irradiation of the olefinic proton at δ = 7.44 ppm led only to an enhancement at δ = 9.13 (=CHO*H*) ppm.
(12) Conditions attempted: CSA, THF; HCl, THF; HCl, acetone; TsOH, MeOH; $BF_3{\cdot}OEt_2$, CD_2Cl_2; Dowex, MeOH; CSA, CD_3OD. For further details, see ref. 4.
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