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Synthesis of model ring systems related to C10–C18 analogues of the mycalamides/theopederins ☆

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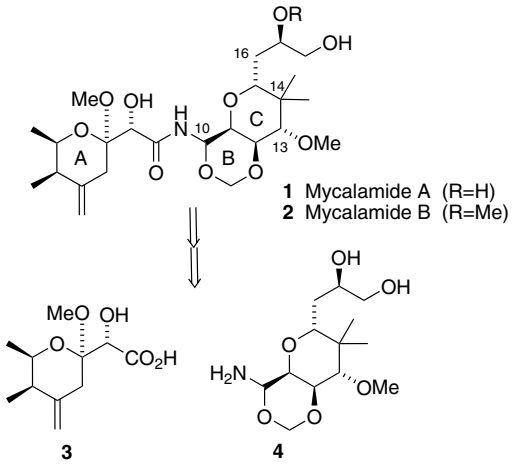
Abstract—Conjugate addition to D-galactose-derived pyranones **8** and **10**, with in situ enolate alkylation, or protonation, provides pyranones **11**–**13** or **16**–**19**. These are related to the C10–C18 fragment of the mycalamides and provide a short entry to C10, C11, C14 and C15 stereocentres. This approach is relevant to introduction of the side-chain and analogues thereof, and allows for variable C14 functionality. Two side-chain analogues, both C14 monomethylated diastereomers, the C14 unsubstituted system and the natural product-related C14 dimethyl functionality are prepared, and C13 epimeric functionality introduced.

Sponges of the genus *Mycale* and *Theonella*, have yielded a range of potently bioactive compounds sharing an unusual ring system, constituting the mycalamides (e.g., **1** and **2**),[1a] theopederins (extended and/or lactol/lactone containing side-chains)[1b] and Onnamide A (15-carbon guanidine-terminated side-chain).[1c] Their ring system is closely related to pederin[1d] (from the terrestrial blister beetle, *Paederus fuscipes*), which lacks the methylene acetal ring B and has a C13 hydroxyl group. The mycalamides show strong in vivo antiviral activity,[2a] potent inhibition of DNA and protein biosynthesis, promising antitumour activity (low nanomolar),[2b,c] and show powerful immunosuppressant activities, with comparable or better in vitro efficacy than cyclosporin A, rapamycin or FK506.[2d]

There have been several total or partial syntheses of the mycalamides, pederin and theopederin systems reported since 1990.[3] Poor diastereocontrol on dihydroxylation of C17,C18 alkene precursors (even using matched AD) has been a recurrent problem. Retrosynthetic disconnection provides components, **3** and **4** (Scheme 1). The aminal function at C10 has been introduced previously either through azidation of the C10 lactol (via the C10 carboxylate)[3b,c,d] and subsequent separation, or through



Scheme 1.

Curtius rearrangement from the C10 carboxylate.[3e,f,h] Carbamate protected variants of **4** have proven invaluable in completing assembly of the 'left' and 'right' hand fragments and analogues.[3e,h]

Targeting modified analogues is encouraged by natural product degradation studies showing various groups can be altered while retaining biological activity,[4] and by the structural diversity of bioactive natural products. Several ring C and side-chain-modified unnatural analogues have also been reported.[5]

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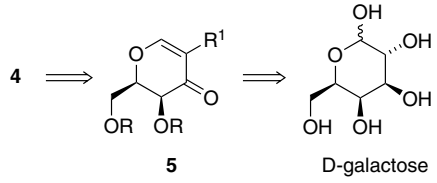
Our particular aims were to develop methodology applicable to new structural analogues at C13, C14 and the side-chain terminus of the mycalamide system.

We envisaged that the C15–C16 C–C bond could be introduced by stereoselective conjugate addition on a precursor pyranone with in situ trapping (at C14) of the intermediate enolate. This maps **4** back to a pyranone of type **5**, suggesting D-galactose as starting material (Scheme 2). This approach should allow entry to the natural *gem*-dimethyl system (using **5**, $R^1 = Me$, trapping with methyl electrophile) and also to various potential side chain *and* C14 analogues not readily available by other means, by simply changing one or more of the conjugate nucleophile, the nature of R^1 on the substrate, and on the enolate trapping employed. This would also avoid the use of AD on a terminal (allyl) C17,C18 alkene. (Late stage elaboration at C11 to intercept known intermediates is envisaged.)

We intended to use *non-acyl* protection of the hydroxyls of the conjugate acceptors **5**. Thus, 3,4,6-tri-*O*-acetyl-D-galactal **6** was directly converted to the tri-*O*-benzyl-D-galactal derivative **7** using NaOH and BnCl under phase transfer conditions (Scheme 3).[6] Treatment of **7** with iodobenzene diacetate provided (2*R*,3*S*)-3-(benzyloxy)-2-((benzyloxy)methyl)-2,3-dihydro-pyran-4-one **8** in good yield.[7] Pyranone **8** was converted into methylated analogue **10** by conversion to iodide **9** and then methyl insertion using tetramethyltin, CuI, $AsPh_3$ and $PdCl_2(PhCN)_2$ in NMP.[8] This methylated analogue provides a second conjugate addition substrate amenable to accessing the *gem*-dimethyl C14 functionality of the natural products. A range of side-chain variants and alternative substituents at C14 could be introduced via intermediates **8** and **10**.



Scheme 2. Retrosynthesis from **4**.

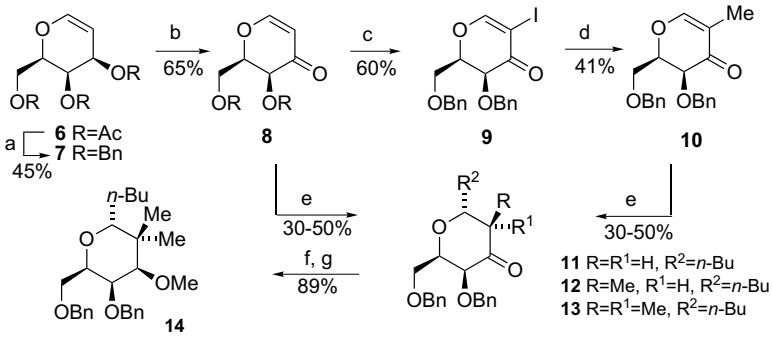
Conjugate additions to **8** and **10** were first evaluated using butyl cuprates. Treatment of pyranone **8** with the dibutyl cuprate $n\text{-}Bu_2Cu(CN)Li_2$ (or $n\text{-}Bu_2Cu(CN)(MgCl)_2$), with proton quench, gave **11**.

Trapping of the intermediate enolate with MeI gave **12**. The relative stereochemistry of **11** and **12** was established from coupling constants and NOED analyses. Conjugate addition to **10**, with concomitant enolate trapping using methyl iodide, afforded **13**. Reduction of **13** with sodium borohydride gave a single diastereoisomeric alcohol (89% yield), which was methylated (NaH, MeI) to yield **14**, a dideoxy homologue of the C ring functionality (C13 relative stereochemistry epimeric).

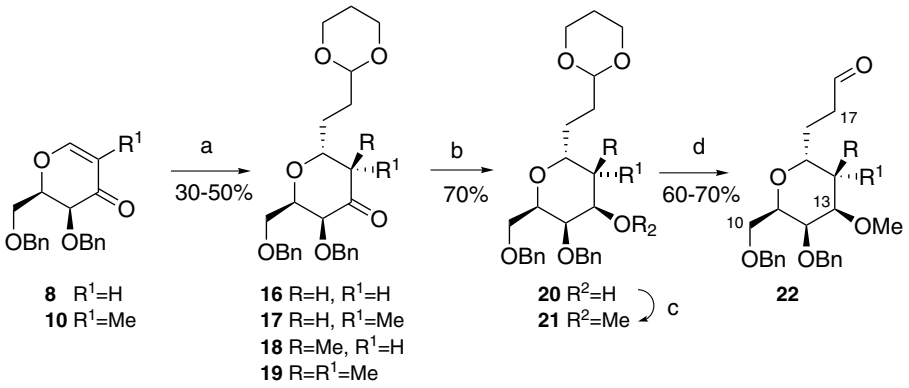
A quite direct entry to the mycalamide side-chain would be conjugate addition to **10** of a protected diol-containing nucleophile, or some precursor, which could avoid the AD of terminal unsubstituted alkene intermediates. Thus, copper-catalysed conjugate addition of 2-(1,3-dioxan-1-yl)ethylmagnesium bromide to **8** and **10** proceeded smoothly, and in both cases the reaction could be quenched by addition of a proton, or by trapping in situ with methyl iodide (Scheme 4), giving all C14 isomeric options, **16**–**19**. The acetal was envisaged as precursor to C17-deoxy analogues, and also to enol ether systems as better substrates for double diastereocontrol using AD methods. Reduction of **16**–**19** with sodium borohydride gave a single product alcohol, whose relative stereochemistry was established in the case of **20** and the derived methyl ether **21** by NMR.[9]

This establishes that C3 epimers of the natural product can be provided (alternative choice of reducing agent in directing analogous reductions to the natural product C3 configuration is also well known).[3b–d,g,h] Deprotection of the acetal provided aldehyde **22**. This intermediate is a precursor to reduction to a C17-deoxy analogue of the mycalamide 1,2-dihydroxy side-chain, or potentially to AD of the derived enol ether for introduction of C17,C18 hydroxylation, or elaboration to other side-chain analogue syntheses.

Elaboration of the C10 hydroxymethyl group to higher oxidation level would provide a route to intercept methods used by others[3] to provide the aminoacetal function of **4**. The current approach is also amenable to



Scheme 3. Reagents and conditions: (a) 50% aq NaOH, *t*-BuOH, $n\text{-}Bu_4NHSO_4$, BnCl, C_6H_6; (b) $PhI(OAc)_2$, *p*-TsOH, MeCN; (c) I_2, Py, CCl_4; (d) Me_4Sn, $PdCl_2(PhCN)_2$, CuI, $AsPh_3$, NMP; (e) $n\text{-}Bu_2Cu(CN)Li_2$ then NH_4Cl or MeI, HMPA; (f) $NaBH_4$, MeOH; (g) NaH, MeI.



Scheme 4. Reagents and conditions: (a) 2-(1,3-dioxan-1-yl)ethylmagnesium bromide, CuCN then NH_4Cl or MeI, HMPA; (b) $NaBH_4$, MeOH; (c) NaH, MeI, (d) CSA, H_2O.

elaborating the C15-branched side-chain towards further novel analogues.

In summary, the conjugate addition trapping is viable for a short entry to precursors to the right-hand side unit of the natural products and specifically to C14 variants, and the chemistry should be amenable to a further range of C13, C14 and side-chain analogues. The C15 stereochemistry can be introduced with high control, and with concurrent flexibility for structural and stereochemical variations at C14. This route provides access to either diastereomeric C14 monomethyl functionality, or to the nonmethylated system (as these are analogues unavailable by degradation/semi-synthesis or in most other syntheses, in such a divergent way), and affords the C13 epimer of the natural stereochemistry (already introduced by others).

Acknowledgements

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7. The structures of both **9** and **10** were unambiguously confirmed by X-ray structure analyses. CCDC22630 and CCDC226231 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).
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9. Through combination of COSY and GOESY (series of 1D-NOE experiments) at 500 MHz. Diagnostic interactions indicated in supplementary information.