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Asymmetric synthesis of the C(6–18) bis(tetrahydropyran)spiroacetal fragment of the lituarines

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ABSTRACT

We describe efforts to achieve a multigram synthesis of the tricyclic spiroacetal core of the lituarines based on the addition of acyl anion equivalent to 4-(2-furyl)butan-2-one (**18**). We report the first cases of chemoselective Achmatowicz reaction in the presence of a second furan ring that lacks an α-hydroxyl group. The use of lithiated methoxyallene provides an efficient one-step conversion of ketone **18** into a tricyclic Diels–Alder adduct (**27**). In the final route, asymmetric cyanosilylation of ketone **29** achieved the construction of the stereogenic C(12) 3°-alcohol centre. Subsequent butenylation, diastereoselective reduction of keto-alcohol (+)-**33** and alkene cross metathesis set up an oxy-Michael reaction to close the C(8–12) tetrahydropyran ring. The second ring-closure, which completed the route, was achieved by oxidative spirocyclisation following our earlier work.

1. Introduction

The occurrence in nature of the spiro[furan-2,2′-pyrano[3,2-*b*]pyran] structural motif is limited to marine metabolites of the okadaic acid type[1] and the lituarines[2] (Fig. 1). The latter are a group of three macrolactones isolated from the New Caledonian sea pen *Lituaria australasiae*, with cytotoxicity towards KB cells (IC_{50}=1.0–6.0 ng mL^{-1}) and growth inhibitory effects against the fungi *Fusarium oxysporum*, *Helminthosporium turscicum*, *Penicillium italicum* and *Phytophtora parasitica*. Their structures were proposed on the basis of extensive NMR investigations as samples of the natural products suitable for X-ray crystallographic analysis were not available. However, Smith's group completed total syntheses of the structures proposed for lituarines B and C and found that the spectroscopic data for these compounds did not match those reported.[3] Thus, more recent synthetic efforts have been aimed at securing the correct structures for the lituarines.

In Smith's total synthesis, the C(8–12) tetrahydropyran (**2**, Scheme 1) was formed by acid-mediated O-cyclisation onto allylic epoxide **1** with inversion of stereochemistry at the newly-formed C(12) centre. The second tetrahydropyranyl ring, comprising carbons C(11–15), was then obtained by classical ketodiol spiroacetalisation (**3**→**4**) in a reaction that had to be run at high dilution with a short reaction time in order to minimise epimerisation at the C(15) and C(16) centres.

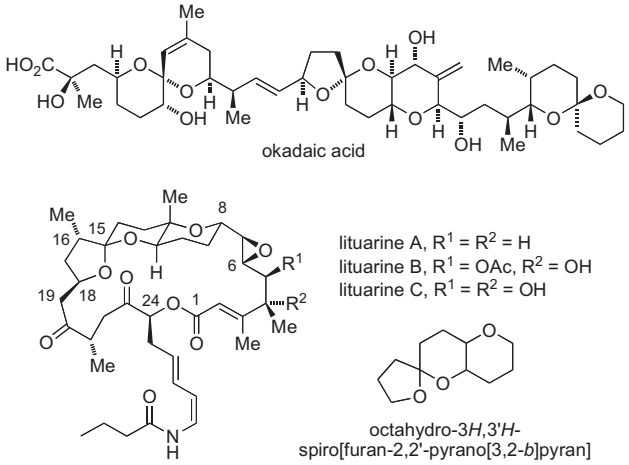

Fig. 1. Natural products containing the spiro[furan-2,2′-pyrano[3,2-*b*]pyran] structural motif.

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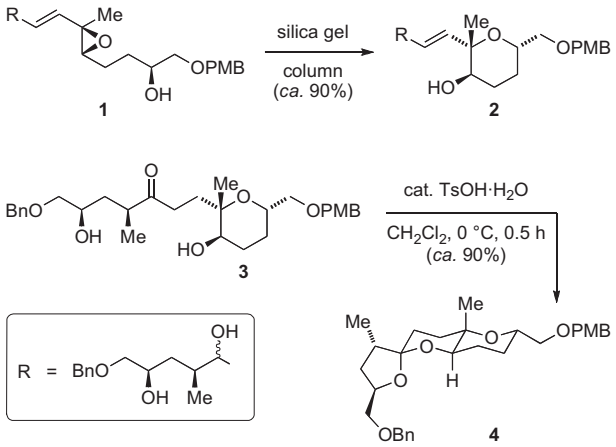
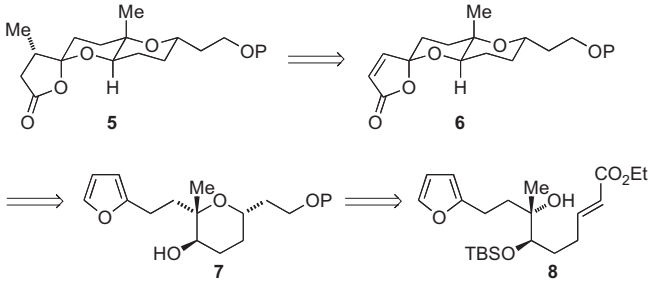


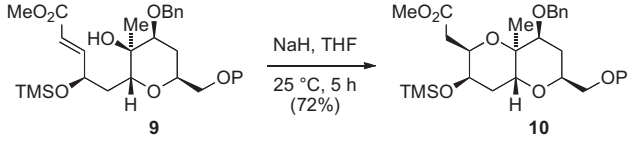
Scheme 1. Key steps in Smith's route to the lituarine tricyclic spiroacetal.

Our own approach to the lituarine tricyclic spiroacetal (**5**, Scheme 2), initiated before Smith's first publications on the subject, was shaped by concerns that we would not be able to achieve spiroacetalisation in a sufficiently stereoselective manner. Thus, we opted to introduce the C(16) methyl substituent by kinetic 1,4-addition to butenolide spiroacetal **6**, which, in turn, was expected to exhibit an essentially complete preference for an axial disposition of the butenolide C–O acyl bond. Shown retrosynthetically, this butenolide would arise by furan oxidative spirocyclisation of tetrahydropyran **7**, a general transformation known since the late 1950s[4] and developed for application in natural product synthesis notably by Bohlmann,[5] Kociensky[6] and more recently by Vassilikogiannakis.[7]



Scheme 2. An approach to the lituarine tricyclic spiroacetal based on oxy-Michael cyclisation and furan oxidative spirocyclisation [P=*t*-BuPh$_2$Si].

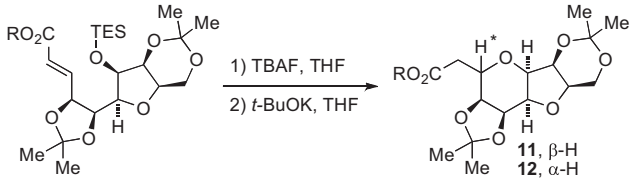
Of the various possibilities for producing the oxidative spirocyclisation substrate (**7**) we selected the oxy-Michael cyclisation of enoate **8**. When we initiated our work the only precedent that we could find for the stereoselective cyclisation of a 3°-alcohol onto an α,β-unsaturated ester was in Nicolaou's assembly of the J-ring of brevetoxin B by base-treatment of alcohol **9** to give bis(tetrahydropyran) **10** (Scheme 3). The stereochemical outcome in this transformation was assumed to be thermodynamically-controlled, leading to an equatorial CH_2CO_2Me substituent.[8]



Scheme 3. Oxy-Michael reaction in Nicolaou's synthesis of brevetoxin B intermediates [P=*t*-BuPh$_2$Si].

Although the oxy-Michael reaction with 3°-alcohols is scarcely precedented, the reaction with 2°-alcohols is a classic strategy for constructing tetrahydropyrans in natural product synthesis. Among over 90 publications referring to the transformation (with enoates), examples include applications to: ambructin,[9] aspergillides A and B,[10] bistramides A and D,[11] brevetoxin B,[12] ciguatoxin fragments,[13] clavosolides A and B,[14] decarestrictine L,[15] gambierol,[16] goniothalesdiol A,[17] halichondrins,[18] herboxidiene,[19] lasonolide A,[20] leucascandrolide A,[21] miyakolide,[22] montanacin,[23] mucocin,[24] neopeltolide,[25] phorboxazoles A and C,[26] polycavernoside A,[27] pyranicin,[28] spirastrellolide A,[29] spongistatin 1,[30] vermiculine[31] and zampanolide.[32]

In general, the geometry of the enoate double bond dictates the stereochemical outcome although the stereoselectivity may vary depending on the reaction conditions. Thus, the most common outcome is for *E*-enoates to cyclise kinetically to give the *trans*-2,6-disubstituted tetrahydropyrans, with the cis-diastereomers predominating under equilibrating conditions. A single example, taken from Yonemistu's PM3 study of the oxy-Michael cyclisation, shows kinetic cyclisation to *trans*-product **11** (Scheme 4), which then converts to the *cis*-product **12** following equilibration with *t*-BuOK.[33] The few reported examples of cyclisations of *Z*-enoates usually afford *cis*-2,6-disubstituted tetrahydropyrans. In both *E*- and *Z*-substrates, substituents in the allylic position can perturb these trends.



Scheme 4. Yonemitsu's results in the context of halichondrin B synthesis.

With this background we were confident that the cyclisation of hydroxy enoate **8** to tetrahydropyran **7** could be achieved and, indeed, this key step, the oxidative spirocyclisation and the stereoselective conjugate addition of methyl, giving tricycle **5**, all proceeded as planned.[34] This intermediate was taken forward to an advanced lituarine B and C precursor (**14**, Fig. 2) in readiness for macrocyclisation and introduction of the C(24) side-chain.[35]

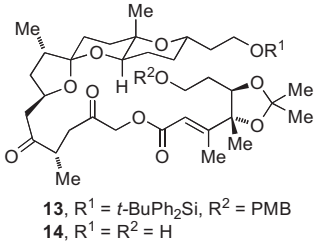


Fig. 2. Advanced intermediates towards lituarines B and C.

The later stages of our lituarine synthetic route (from **8** all the way through to diol **14**) were reliable but further progress was hampered because of difficulties in scaling up our published route to intermediate **8**. On a multigram scale the addition of organometallics of the form **16** to ketone **15** (Scheme 5) proved to be particularly problematic and the desired product was generated along with the other diastereomer (in variable ratio) and various cyclisation and degradation products, all close-running on TLC. In this paper we describe a more practically reproducible route that allowed us to prepare 1.5 g of tricycle **5** in the first run.[36]