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An expedient synthesis of 2,5-disubstituted-3-oxygenated tetrahydrofurans

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ABSTRACT

Single enantiomer 2,5-disubstituted-3-oxygenated tetrahydrofurans are synthesized in as little as four steps from a commercially available epoxide. The key steps are homoallylic alcohol epoxidation, palladium-catalysed alkoxy-carbonylation–lactonisation and Mitsunobu inversion. The protocol is applied to the formal total syntheses of (+)-kumausallene, (6*S*,7*S*,9*R*,10*R*)-6,9-epoxynonadec-18-ene-7,10-diol and the core of lytophilippine A.

The 2,5-disubstituted-3-oxygenated tetrahydrofuran unit is present in many marine natural products. Conspicuous examples include the C_{19} lipid diols **1** and **2** isolated from the southern Australian brown algae *Notheia anomala*, and (+)-*trans*-deacetylkumausyne (**3**) isolated from the Japanese red algae, *Laurenia nipponica* (Fig. 1).[1,2] This structural unit also appears as part of more complex ring systems such as the bicyclo[3.3.0]octane system of (−)-kumausallene (**4**), in which each ring constitutes a 2,5-disubstituted-3-oxygenated tetrahydrofuran.[3] It is noteworthy that natural products containing both the *syn* and *anti* stereochemical relationship across the ether linkage (cf. **1** and **2**) and both the *syn* and *anti* relationship between the C2 substituent and the C3 oxygen (vide infra), as well as members representing both enantiomeric series (cf. **2** and **3**) have been isolated.[4] The stereochemical variety around such a small core has stimulated much interest in the biosynthesis and the total synthesis of these natural products.[5]

Previous routes to stereochemically defined 2,5-disubstituted-3-oxygenated tetrahydrofurans have included a cascade Prins cyclisation–pinacol rearrangement–Baeyer–Villiger sequence,[6] intramolecular conjugate additions,[7] acyl radical cyclisations,[8] cyclodehydrations,[9] biotransformations[10] and ring contractions.[11] These approaches rely on chiral pool materials such as arabinose,[12] malic acid,[13] D-glucose,[14] diethyl tartrate[15] and L-galactono-1,4-lactone[16] for controlling the absolute stereochemistry. Whilst each of these routes gives access to at least one stereoisomer of the 2,5-disubstituted-3-oxygenated tetrahydrofuran unit, we wished to uncover a flexible, divergent route that would deliver all configurational isomers. The recent report by Britton and co-workers[17] of their aldol-based strategy to uncover such a general synthetic route has prompted us to disclose our own efforts in the area.

A concise route to single diastereomers of 2,5-disubstituted-3-oxygenated tetrahydrofurans involves the palladium-catalysed alkoxy-carbonylation of dihydroxy alkenes.[18,19] We envisaged that the requisite enediols could be generated from commercial benzyl glycidyl ether **9**, which is available in both enantiomeric forms (Scheme 1). The absolute stereochemistry of the C5 position of the products (using tetrahydrofuran numbering) would be dictated by the starting material, and the relative stereochemistry across the tetrahydrofuran ring could be controlled using either a directed reduction of an intermediate β-hydroxy ketone or an asymmetric epoxidation of an intermediate homoallylic alcohol.

Our initial efforts focused on the directed reduction route as Boukouvalas et al. successfully employed a similar strategy in their synthesis of (−)-*trans*-kumausyne.[13] The desired β-hydroxy ketone was envisaged to arise from the nucleophilic opening of **9** with a suitable acyl anion equivalent of acrolein. As such, the protected cyanohydrins **10** and **11** were synthesised in the standard fashion.[20] Despite exploring the use of several bases (KHMDS, LiHMDS), solvents (toluene, THF), Lewis acid additives and temperature combinations, the desired epoxide ring-opening could not be effected (Scheme 2). Given that **11** has been used to effect the ring-opening of epichlorohydrin,[21] we reasoned that the epoxide **9** was not suitably electrophilic enough to engage in a reaction with the

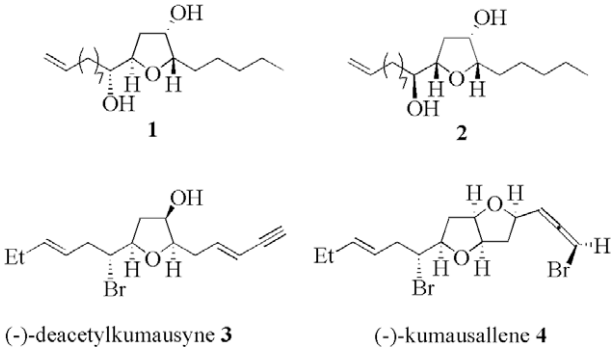

Figure 1. 2,5-Disubstituted-3-oxygenated tetrahydrofuran-containing natural products.

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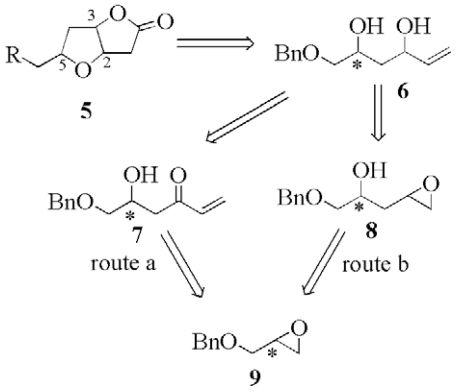
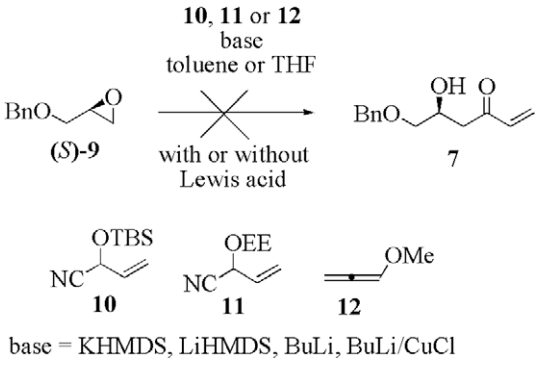
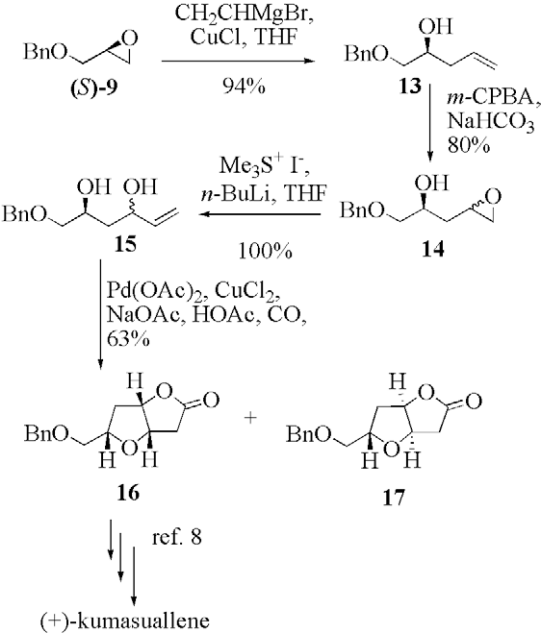


Scheme 1. Retrosynthetic analysis.



Scheme 2. Attempted reaction of acyl anions with epoxide **9**.



Scheme 3. Divergent synthesis of compounds **16** and **17**.

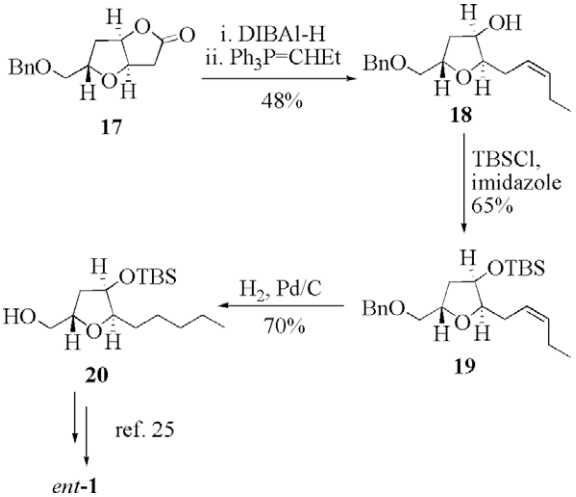
resonance stabilised anions of the deprotonated cyanohydrins. Therefore we prepared and investigated methoxyallene **12** as a more reactive acyl anion equivalent.[22] Disappointingly, the potassium, lithium and copper-based anions of this reagent also failed to undergo coupling to benzyl glycidyl ether **9**, even in the presence of a Lewis acid ($MgBr_2$, $BF_3{\cdot}OEt_2$, or $Sc(OTf)_3$). Our attention therefore turned to the epoxide-based approach.

(*S*)-Benzyl glycidyl ether **9** was reacted with vinylmagnesium bromide to give the corresponding homoallylic alcohol **13** in excellent yield (Scheme 3). Whilst this compound could be subjected to a vanadium-catalysed asymmetric epoxidation,[23] we chose to use it as a point of divergence. As such, compound **13** was subjected to a non-selective *meta*-chloroperbenzoic acid epoxidation to give **14** as a ca. 1:1 mixture of diastereomers. The diastereomeric mixture of epoxides was reacted with dimethylsulfonium methylide to give the corresponding enediols **15** in quantitative yield.[24] Compound **15** was then subjected to the palladium-catalysed alkoxycarbonylation conditions described by Semmelhack[18] to give the known bicyclic-γ-lactones **16** and **17**, which were readily separated by flash chromatography.[8,19] Compound **16** contains a (2*S*,3*S*,5*S*) and compound **17** contains a (2*R*,3*R*,5*S*)-2,5-disubstituted-3-oxygenated tetrahydrofuran moiety in a protected form. Performing the same sequence on the enantiomeric (*R*)-benzyl glycidyl ether would give the enantiomeric (2*R*,3*R*,5*R*) and (2*S*,3*S*,5*R*)-2,5-disubstituted-3-oxygenated tetrahydrofurans. As compound **16** corresponds to an advanced intermediate in Evan's synthesis of kumausallene,[8] the current work constitutes a concise formal synthesis of (+)-kumausallene.

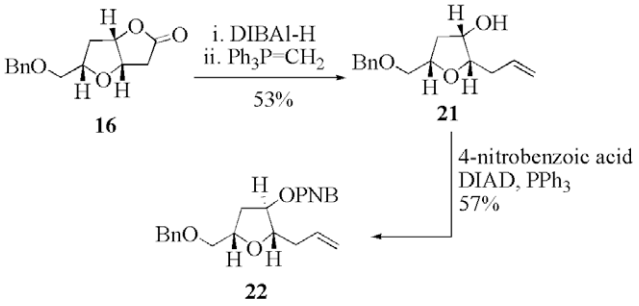
Compound **17** has the same relative stereochemical arrangement (but opposite absolute stereochemistry) found in the marine algal metabolite **1**. As such, **17** was reduced to the lactol and subjected to Wittig olefination to give **18** as a mixture of geometric isomers (Scheme 4). The secondary alcohol was protected to give silyl ether **19**. Hydrogenation of the alkene with concomitant hydrogenolysis of the benzyl group gave the diol **20**, which is an advanced intermediate in Wang's synthesis of **1**.[25] This work, therefore, constitutes a formal synthesis of *ent*-**1**.

The remaining (2*S*,3*R*,5*S*), (2*R*,3*S*,5*S*), (2*R*,3*S*,5*R*) and (2*S*,3*R*,5*R*) isomers are available through inversion of the C3 alcohol. As an illustration, **16** was reduced to the corresponding lactol and subjected to Wittig olefination to give the known alcohol **21**[9] (Scheme 5). Alcohol **21** was then converted into the C3 epimer **22** under standard Mitsunobu conditions. The (2*S*,3*R*,5*S*)-2,5-disubstituted-3-oxygenated tetrahydrofuran moiety in **22** contains an *anti* relationship between the C2 substituent and C3 oxygen and corresponds to the core of the marine natural product lytophilippine A.[26]

In summary, we have disclosed an expedient route to all possible stereoisomers of the 2,5-disubstituted-3-oxygenated tetrahydrofuran ring system from commercially available (*R*)- and



Scheme 4. Formal synthesis of *ent*-**1**.



Scheme 5. Inversion of the C3 alcohol.

(*S*)-benzyl glycidyl ether. The methodology has been illustrated by the formal total synthesis of the marine natural products (+)-kumausallene, *ent*-**1** and the core of lytophilippine A.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.08.114.

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