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A convenient synthesis of carbohydrate derived furo/pyrano[2,3-*b*] pyrans from 2-hydroxymethyl glycals

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ABSTRACT

An efficient method for the stereoselective synthesis of various linearly fused bicyclic acetals using 2-hydroxymethyl glycals, involving Ferrier type rearrangement and ring-closing metathesis as the key steps, is revealed. The methodology was shown to be very general by applying it to various sugar substrates which lead to the formation of various bicyclic furo/pyrano[2,3-*b*]pyran ring systems.

1. Introduction

Linearly fused bicyclic acetals are ubiquitously present as subunits in a number of bio-active natural products.[1] A major portion of these bicyclic acetals exists either as furo[2,3-*b*]pyrans or pyrano [2,3-*b*]pyrans. For instance, Benesudon (antibacterial and cytotoxic with IC_{90} values of 1–2 μg/mL),[2] Euplotin A, B, and C[3] (cytotoxic), Novaxenicin A and B (induces apoptosis),[4] (−)-Penifulvin A and B (potent insecticides),[5] Tetrahydroaplysulfurin-1,[6] Cadlinolides A, B and C,[7] and Neopeapyran[8] possess the furo[2,3-*b*]pyran framework. (Fig. 1). On the other hand, pyrano[2,3-*b*]pyran containing compound **1** is an important precursor in the total synthesis of ansamycins[9] whereas compound **2** is a natural product produced by a rare bacterial strain *Actinoalloteichus nanshanensis* sp. *Nov.*[10] The glycofused benzopyran **3** was recently identified as a novel ligand for amyloid β peptidase in the development of novel therapeutics for Alzheimer's disease[11] (Fig. 2).

Very often, the presence of the bicyclic acetal system in bio-active molecules is vital for acquiring the appropriate molecular conformation that helps in eliciting the biological response. In general, the formation of these bicyclic acetal motifs involves the halo etherification of cyclic vinyl ethers, using NBS or NIS and allyl or propargyl alcohol, followed by a radical cyclization to produce the corresponding bicyclic acetals.[12] Various radical initiators like Vitamin B_{12},[13] AIBN,[14] Et_3B,[15] Co(salen),[16] *etc*., have been studied for the radical cyclization reactions. Carbohydrate derived vinyl ethers, generally called as glycals, have been one of the highly studied precursors in radical cyclization reactions.[17] Apart from these, we previously reported the application of 2-*C*-branched sugars,[18] 3-*C*-branched glycals[19] and 1,2-cyclopropanated sugar derivatives[20] for the stereoselective preparation of a variety of furo/pyrano[2,3-*b*] furans/pyrans. Very recently, Vankar et al. reported a distinct method involving Grignard addition of allyl and vinyl magnesium halides on allyl-2-*oxo*-glycosides followed by ring-closing metathesis to produce pyrano[2,3-*b*]pyran/oxepines.[21a] A similar protocol was also described to synthesize 1,2-annulated sugars with β-mannose configuration.[21b] In addition to the above methods, very few approaches were available for the synthesis of furo/pyrano[2,3-*b*]pyran ring systems encompassing acid-catalyzed cyclization of hydroxyacetals,[22] cycloaddition reactions,[23] intramolecular dehydration reactions[24] and ketalization of acyclic dihydroxyaldehydes.[25]

In continuation of our efforts in the synthesis of fused bicyclic acetals,[26] herein we report the application of *C*-2-methylene glycosides in the synthesis of furo/pyrano[2,3-*b*]pyrans in two steps comprising Ferrier type rearrangement and ring closing metathesis.

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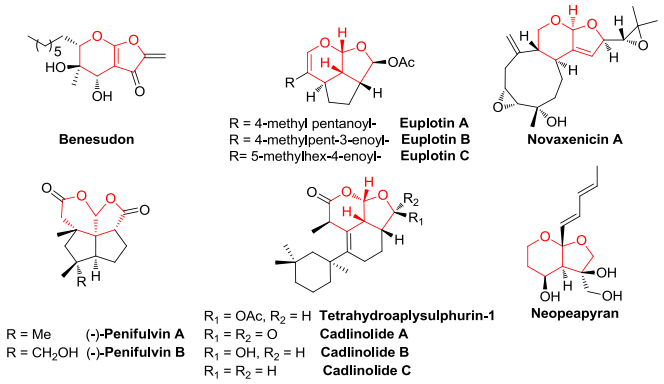


Fig. 1. Representative natural products possessing furo[2,3-*b*]pyran framework.

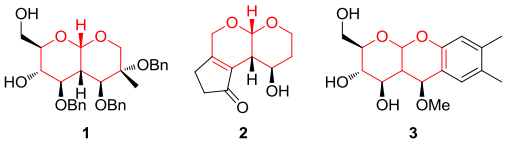
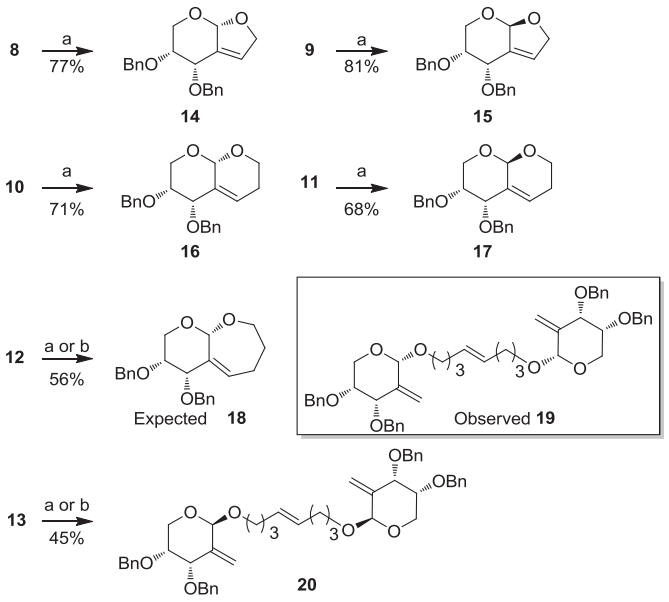


Fig. 2. Representative natural and synthetic products containing the pyrano[2,3-*b*] pyran structure.

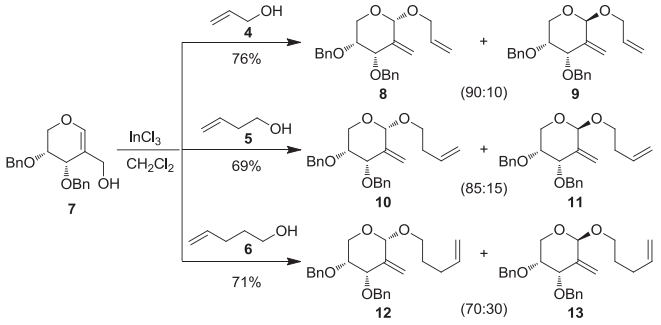


Scheme 2. Synthesis of D-arabinose derived furo/pyrano[2,3-*b*]pyran frameworks. Reagents and conditions: (a) G-II (20 mol%), toluene, 80 °C. (b) G-I (20 mol%), toluene, 80 °C.

2. Results and discussion

We intended the synthesis of furo/pyrano[2,3-*b*]pyran systems starting from *C*-2-methylene *O*-alkenyl glycosides of various length. Towards this, 2-hydroxymehtyl D-arabinal **7**[27] was treated with allyl alcohol **4** in the presence of catalytic $InCl_3$[28] to provide the *C*-2-methylene α- and β-glycosides **8** and **9**. In a similar way glycosides **10**, **11** and **12**, **13** were synthesized by the Ferrier type rearrangement of **7** with 3-butenyl alcohol **5** and 4-pentenyl alcohol **6**, respectively (Scheme 1).[29]

Having a series of D-arabinose derived glycoside dienes **8**–**13** in hand, we proceeded to synthesize various bicyclic acetals using ring closing metathesis reaction. Thus, allyl arabinopyranosides **8** and **9** upon treatment with Grubb's 2nd generation catalyst (G-II) provided the furo[2,3-*b*]pyran derivatives **14** and **15** as the only products respectively, in good yield (Scheme 2). Similarly, 3-butenyl alcohol derived arabinopyranoside derivatives **10** and **11** upon exposing to G-II provided the corresponding pyrano[2,3-*b*] pyran derivatives **16** and **17** respectively, again as the only products. However, subjecting the 4-pentenyl derived arabinopyranoside **12** to RCM reaction using G-II provided the dimerization product **19** and no detectable amount of the expected pyrano[2,3-*b*]oxepine **18** was observed. Carrying out the reaction using Grubbs 1st generation catalyst (G-I) also did not show any change in the product formation. Subjecting the β-isomer **13** to G-I or G-II mediated RCM reaction also lead to the formation of dimer **20** as the only isolable product (Scheme 2).



Scheme 1. Synthesis of D-arabinose derived *C*-2-methylene *O*-glycoside derivatives.

Encouraged by these observations, we extended the methodology to glucal and galactal derived 2-hydroxymethyl derivatives **21** and **22**[30] respectively. Thus, glucal derived *C*-2 methylene *O*-glycosides **23**,[28] **24** and **25**[31] were prepared from **21**, galactose derived *C*-2-methylene *O*-glycosides **26**,[28] **27** and **28**[31] were obtained from **22** by following the procedure for the preparation of compound **8**. (Table 1). Unlike in the case of 2- hydroxymethyl arabinal derivative **7**, the Ferrier type rearrangement of **21** and **22** with *O*-nucleophilic allyl alcohol **4**, 3-butenyl alcohol **5** and 4-pentenyl alcohol **6** provided the corresponding *C*-2-methylene-α-D-glycosides as the only products. No isolable amounts of the *C*-2-methylene-β-D-glycosides were obtained.

Subjecting *C*-2-methylene allyl α-D-glucopyranoside **23** to RCM provided the furo[2,3-*b*]pyran **29** along with the olefin migrated furo[2,3-*b*]pyran **30** in 1:1 ratio in 61% yield. On the other hand, *C*-2-methylene 3-butenyl α-D-glucopyranoside **24** upon RCM with G-II provided the expected pyrano[2,3-*b*]pyran derivative **31** in 34% yield along with a mixture of furo[2,3-*b*]pyran **30** and 2-*C*-branched glycal **32** in 34%. Whereas, RCM of compound **25** using G-I or G-II gave the dimer **33** (*cis*, *trans* (0.75:1) mixture) as the only isolable product (Scheme 3).

The formation of the unexpected products **30** and **32** from **24** could be explained by considering the following possible intermediates. It has been reported in the literature that terminal olefins undergo olefin migration under the influence of Ru catalysts.[32] Thus, **24** in the presence of Grubs II might undergo olefin migration producing the intermediates **24a** and **24b**. **24a** upon RCM would produce the furo[2,3-*b*]pyran **29** which could undergo further olefin migration leading to the formation of **30**. On the other hand, intermediate **24b** could result in the formation of 2-*C*-branched glycal **32** involving a 3,3-sigmatropic rearrangement (Scheme 4).

Unexpectedly, the *C*-2-methylene α-D-galactopyranoside derivatives **26** and **28** upon exposing to G-II provided only the