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Aluminum Triflate Catalyzed Tandem Reactions of D-Galactal: Toward Chiral Benzopyrans, Chromenes, and Chromans

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Supporting Information

ABSTRACT: 3,4,6-Tri-*O*-acetyl-D-galactal is selectively converted into 1-*O*-aryl-2-deoxy derivatives or chiral bridged benzopyrans under $Al(OTf)_3$ catalysis, depending on reaction conditions. The benzopyrans react with $Al(OTf)_3$/acetic anhydride in ring-opening reactions in the absence or presence of acetic acid to selectively produce chiral chromenes or chromans, respectively, in high yields.

Carbohydrates bearing an aromatic aglycon are attractive synthetic targets and are present in many complex chiral natural products with biological activity,[1] such as the antibiotics vancomycin and chromomycin. Since the first synthesis of aryl glycosides by Michael[1,2] a range of other synthesis procedures have been reported with a variety of promoters.[1] Donors for *O*-glycosylation reactions include glycosyl halides,[3] trichloroacetimidates,[4] thioglycosides,[5] and *p*-toluenesulfonyl hydrazides.[6] Although glycals have been extensively explored for the synthesis of 2-deoxyglycosides,[7] they are underrepresented as glycosyl donors for the synthesis of aryl 2-deoxy-*O*-glycosides. This may be due to the absence of a stereodirecting group at C-2 of the glycal and the tendency of phenols to form C-glycosides at elevated temperatures.[8] To improve the stereooutcome, Danishefsky et al. oxidized the double bond of the glycal to an epoxide which was reacted with potassium phenolate to give *β*-glucosides.[9] Direct use of glycals has been reported using triphenylphosphine hydrobromide as catalyst,[10] but the reaction was limited to glucals. In addition, glycosylations with galactals have been reported using *p*-toluenesulfonic acid as catalyst[11] and with $BF_3{\cdot}Et_2O$.[12]

We recently reported the aluminum triflate promoted preparation of 1-*O*-aryl-2-deoxy-D-glycosides from 3,4,6-tri-*O*-acetyl-D-glucal and 3,4,6-tri-*O*-acetyl-D-galactal.[13] At the time, we identified *C*-arylation products as minor species isolated from the reaction mixtures. We now detail a set of reactions of 3,4,6,-tri-*O*-acetyl-D-galactal with a range of phenols that produce, depending on the reaction conditions, the 1-*O*-aryl-2-deoxy derivative or a set of chiral, bridged benzopyrans in a tandem reaction. We discuss the use of the benzopyrans, also utilizing $Al(OTf)_3$ as catalyst, as precursors for the facile synthesis of chromenes and chromans. The 4*H*-chromene structural motif is important in the field of medicinal chemistry due to its wide range of biological activities. Chromenes have shown biological activity against prostate cancer (DU-145) and breast cancer (MCF-7)[14] and also antiviral[15] and antimicrobial[16] activity. Because of these diverse therapeutic applications, substituted 4*H*-chromene derivatives are valuable synthetic targets and have been prepared via multicomponent reactions involving an aryl aldehyde, malonitrile, and a phenol to yield 2-amino-3-cyano-4-aryl-4*H*-chromenes.[17] Alternative methods involve the use of ruthenium catalysts[18] and Grubbs' second-generation catalysts.[19] Chromans are structural motifs found in many natural products, including vitamin E[20] and others with potentially useful biological properties, such as calanolide A[21] and inophyllum B,[22] which were identified in screening assays as potent inhibitors of human immunodeficiency virus-1 reverse transcriptase (HIV-1 RT).

Treatment of various phenols with 3,4,6,-tri-*O*-acetyl-D-galactal in the presence of 5 mol % of $Al(OTf)_3$ in 1,2-dichloroethane (DCE) at 0 °C readily afforded the corresponding 1-*O*-aryl-2-deoxy-D-galactosides **3** (Scheme 1; see the Supporting Information). All of the products were isolated in good yield and good to excellent stereoselectivity, consistent with previous results.[13] Compounds **3** favor the *α* anomer. H-1 shows only small $^2J_{H1-H2}$ values of less than 3 Hz in each case, with doublet multiplicity. In addition, the $^1J_{H1-C1}$ values for this set of products is consistently in the order of 170 Hz. The $^2J_{H1-H2}$ value for the analogous *β* anomer of **3a**, which has been previously prepared,[23] is in the order of 9.5 Hz, while the $^1J_{H1-C1}$ values for a range of analogues is on the order of 160 Hz. When performing otherwise identical reactions at 40 °C, we quite unexpectedly obtained benzopyrans **4** in good yield as products of tandem reactions (Scheme 1). This provides a second example in our work of a temperature-

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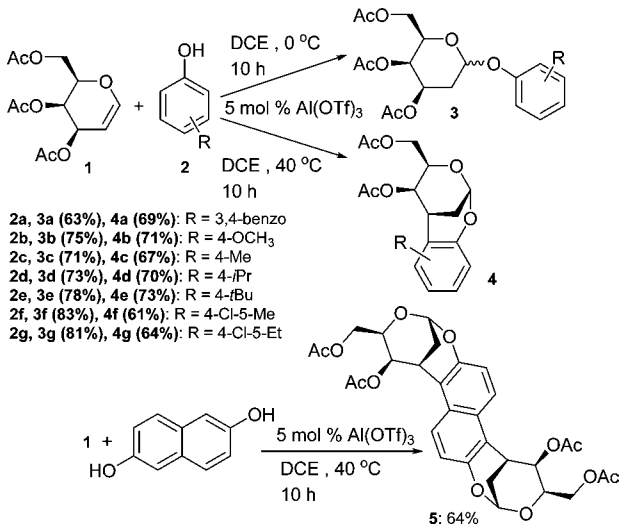
Scheme 1. Conversion of Galactal into Chiral Bridged Benzopyrans

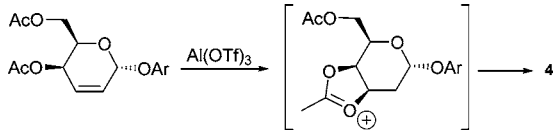


sensitive mechanism.[13] Either DCM or DCE can be used for the low temperature reaction (Scheme 1) with no difference in outcome. For consistency, though, the higher boiling DCE was selected for its use in the both reactions. The conversion of glycals into benzopyrans **4** appears to be unique to D-galactal: our previous work shows that D-glucal provides only the Ferrier rearranged product without benzopyran formation at low temperatures (−20 °C) while at elevated temperatures yields 1-*C*-arylation.[13]

With 3,4-substituted phenols, the reaction was selective for C−C bond formation at the less hindered C-6 position of the aryl ring (compared to C-2) of the aromatic ring, giving **4f** in C-6/C-2 (on the aryl ring) ratios of 9:1 and 4g in C-6/C-2 (on the aryl ring) ratios of 4:1. When using 2,6-dihydroxynaphthalene as the glycosyl acceptor and two equivalents of 3,4,6-tri-*O*-acetyl-D-galactal, a hexacyclic bridged chiral benzopyran **5** was formed. Single crystal X-ray crystallography[24] of **4c** confirmed the structural assignments for these products, while that of **5** demonstrated the hexacyclic structure and its C_{2h} symmetry which is also reflected in the NMR spectra of the compound. It is known that the glycosylation of phenols under acidic conditions at elevated temperatures affords *C*-glycosides.[8,12b] To the best of our knowledge, this tandem chemistry with $Al(OTf)_3$ is unprecedented, though, and presents a rapid access to these desirable chiral products.

A related intramolecular cyclization has been observed at the C-2 of the sugar ring when 2-*C*-acetoxymethyl galactal is used as a glycosyl donor.[25] Those authors indicated the reaction to be a tandem Ferrier rearrangement−exocyclic cyclization sequence, leading to pyrano[2,3-*b*][1]benzopyrans. In the previous work, the Friedel−Crafts step relied upon the presence of an allylic *O*-benzyl leaving group. In the present work, we isolated small amounts of the corresponding 1-*O*-aryl-2-deoxy glycoside **3** as a minor byproduct in most cases, along with the major products **4**. It was envisioned that the tandem sequence might proceed via this product as an intermediate, followed by a Friedel−Crafts step. To test this hypothesis, several of the 2-deoxy-D-galactosides **3** were subjected to heating in the presence of $Al(OTf)_3$ but failed to produce the bridged chiral benzopyrans **4**. This suggests that the 2-deoxy products **3** are byproducts of a competing reaction and unlikely to be intermediates leading to the benzopyran products. It is quite reasonable, then, to postulate that the first step in our sequence is a Ferrier rearrangement and that the second step, a Friedel−Crafts C−C bond-forming process, proceeds via the double bond. We propose that the second step ensues with anchimeric assistance from the acetate at C-4 of the glycoside (Scheme 2). It is quite likely that this transformation is

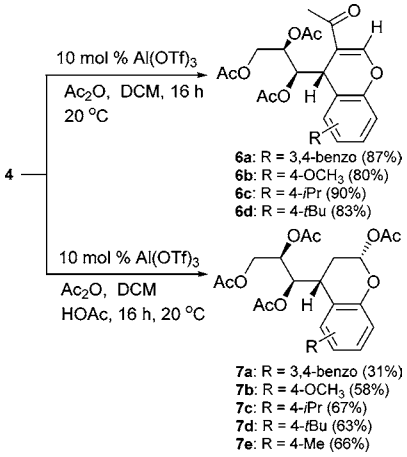
Scheme 2. Proposed Intermediate en Route to Bridged Structures 4



facilitated by Lewis acid-assisted Brønsted acidity, which we have shown several times with $Al(OTf)_3$.[26] This is in contrast to earlier work in which the 1-*O*-aryl-2-deoxy intermediates **3b** and **3c** formed the corresponding benzopyrans **4** in a two-step approach with $BF_3{\cdot}Et_2O$ as catalyst.[27]

Very usefully, the bridged chiral benzopyrans could be ring-opened via acetolysis using $Al(OTf)_3$ and acetic anhydride in dichloromethane to afford the corresponding chiral galactose derived 4*H*-chromenes in high yield (Scheme 3). Again,

Scheme 3. Conversion of Bridged Benzopyrans into Chiral Chromenes or Chromans



confirmation of the structure was obtained by single-crystal X-ray crystallography of **6a**.[24] The current protocol supplements existing methods to stereoselectively prepare the privileged chromenes.

To our surprise and delight, acetolysis of the benzopyran substrates in the presence of a mixture of acetic acid and acetic anhydride (2:1 v/v) and 10 mol % of $Al(OTf)_3$ yielded chiral chromans in acceptable yields (Scheme 3). The corresponding 4*H*-chromene is a minor byproduct in most cases. The presence of both acetic acid and acetic anhydride was critical for the success of this transformation: use of acetic acid and $Al(OTf)_3$ alone in dichloromethane failed to produce any reaction at all, while the acetic anhydride/$Al(OTf)_3$ set of reagents afforded the chromene instead. The *syn* arrangement of the pendant C-3 arm and the anomeric OAc group was readily demonstrated by single-crystal X-ray crystallography of **7a**.[23]

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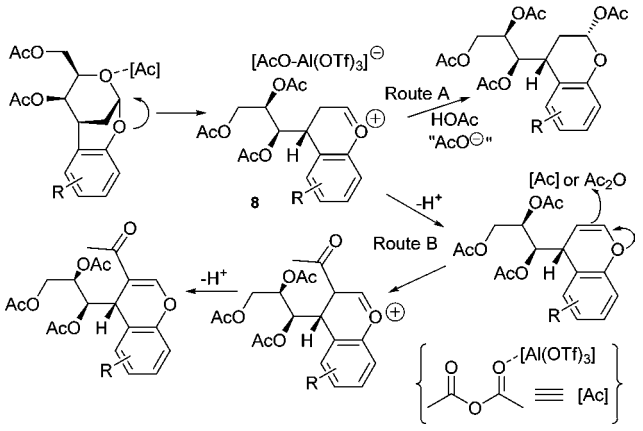
We proffer the mechanistic rationale in Scheme 4 by which to account for the different outcomes in the presence/absence

Scheme 4. Proposed Mechanistic Rationale for Experimental outcomes



of acetic acid. We propose that the initially formed oxocarbenium intermediate **8** can be captured by acetate (or acetic acid) to produce the chiral substituted chroman (Route A). It is possible that Al-activated acetic anhydride is causative in the initial ring-opening step (hence the need for both $Al(OTf)_3$ and acetic anhydride before activity is seen), which would generate an acetylated oxocarbenium intermediate. It is also quite probable that close ion-pairing in the nonpolar DCM solvent retains the aluminate in the immediate proximity of the oxocarbenium cation, facilitating stereoselective transfer of the acetate on the Al center. Conversely, chromenes are produced via Route B, in which a chromene intermediate is acylated under the reaction conditions to produce the ketone product.

In summary, we have described the use of $Al(OTf)_3$ to catalyze several interesting and useful transformations of galactal and its derivative bridged chiral benzopyrans, which are produced in a tandem fashion. The protocols highlight a rapid entry to a range of highly sought after chiral scaffolds from which various other products bearing the chromene and chroman motifs may be synthesized. The reactions are stereoselective, high yielding, and tolerant of various functional groups on the aromatic rings. The overall protocol results in a highly efficient two-pot approach from galactal to produce chiral chromenes and chromans.

■ ASSOCIATED CONTENT

Supporting Information

ORTEP diagrams for **4c**, **5**, **6b**, and **7a**; experimental and analytical details; copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org. Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre as CCDC 1010940, CCDC 1010942, CCDC 1010941, and CCDC 1010943 for **4c**, **5**, **6b** and **7a**, respectively. Copies of data can be obtained, free of charge, upon application to CCDC, 12 Union Road, Cambridge CB2 1EZ, U.K. (deposit@CCDC.com.ac.uk).

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Notes

The authors declare no competing financial interest.

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