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4-O-TfO-2,3-anhydro-β-L-ribopyranosides as Chiron : A Formal Synthesis of Canadensolide

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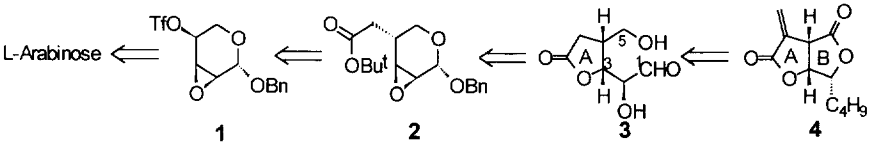
Abstract. *A methodology for the preparation of densely functionlized γ-Butyrolactones from 2,3-anhydro pentopyranosides is described.* Copyright © 1996 Elsevier Science Ltd

Carbohydrate-based syntheses generally revolve around the efficient preparation of branched chain monosaccharides. We have recently shown that 4-O-trifloxy-2,3-anhydro-pentopyranosides (**1**) are attractive chirons, since they may be obtained on multi-gram scale from common pentoses, and easily converted to 4-C-branched derivatives.[1] The latter appear to be especially appropriate precursors for the synthesis of highly oxygenated butyro-γ-lactone (scheme 1). Herein, we illustrate this methodology by application to the preparation of the densely functionlized, antibiotic, canadensolide (**4**).[2] Three syntheses of this target have been reported but are relatively lengthy and low yielding.[3-6]

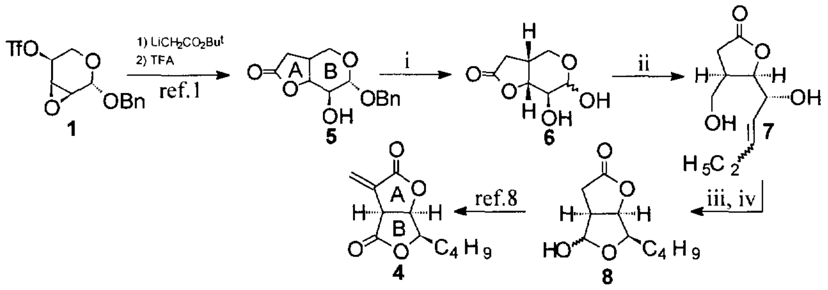


Scheme 1. Retrosynthetic analysis of canadensolide (**4**).

Retrosynthetically, canadensolide may be derived from the monocyclic butyro-γ-lactone **3** thence the 4-C-pentopyranoside **2**. This pivotal, branched chain sugar contains all the required stereogenic centers and is primed for elaboration to canadenosolide (scheme 1).

Thus, benzyl 4-O-trifloxy-2,3-anhydro-β-L-ribopyranoside (**1**) was transformed via reaction with the lithium salt of t-butylacetate to the 4-C-derivative **2**, which on treatment with trifluoroacetic acid gave the fused pyranobutyro-γ-lactone (**5**) in 87% overall yield from **1**.[1] Hydrogenolysis of **6** afforded the lactol **3**, the pyranose tautomer of the hydroxyaldehyde **3**.

Wittig reaction of **6** using propyl triphenylphosphoniumbromide and potassium *tert*.- butoxide in dry THF at room temperature for 30 min and then at 80°C for 20 min afforded an E/Z mixture of alkenes **7** in 58% yield.[7] Hydrogenation of **7** followed by Swern's oxidation of the reduced product afforded lactol **8**.[8,9] Since **8** has been previously transformed over three steps to canadenosolide, this constitutes a formal synthesis.



Scheme 2. Reagents and conditions: i) H_2/ $Pd(OH)_2$/ C (93%); ii) $C_2H_5CHPPh_3^+Br^-$/ K^tBuO (58%); iii) H_2/ Pd/ C (87%); iv) Ac_2O/ DMSO (63%).

The synthesis of **8** is considerably more practical than previous approaches. It involves a straightforward six step sequences in a good overall yield (26%) from benzyl 4-O-trifloxy-2,3-anhydro-β-L-ribopyranoside (**1**), a precursor which is available on 20 g scales. Moreover, the potential of the fused pyrano-γ-lactone **5** as a versatile intermediate for the preparation of the ubiquitous butyro-γ-lactone framework has been demonstrated.

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7. Isolated yield after chromatographic purification of the crude reaction mixture. The purification has not yet been optimized. The actual yield was much higher as indicated by a 90% yield of the diacetate derivative which was obtained through acetylation of the crude product.
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9. The spectroscopic data of compound **8** are identical with those reported in references 4 and 8.

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