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Enantioselective Syntheses of Isoaltholactone, 3-*epi*-Altholactone, and 5-Hydroxygoniothalamin

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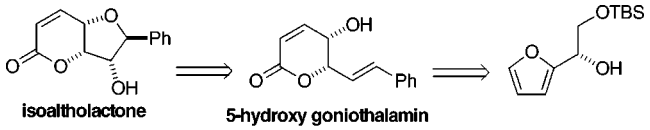
ABSTRACT



A flexible enantioselective route to highly functionalized α,β-unsaturated δ-lactones has allowed for the syntheses of the styryllactones: isoaltholactone, 3-*epi*-altholactone, and 5-hydroxygoniothalamin in 10%, 5%, and 13% overall yields from furfural, respectively. This approach derives its asymmetry by applying the Sharpless catalytic asymmetric dihydroxylation to vinylfuran. The resulting diols are produced in high enantioexcess and can be stereoselectively transformed into α,β-unsaturated δ-lactones via a short highly diastereoselective oxidation and reduction sequence.

Substituted α,β-unsaturated δ-lactones are an important class of natural products with a wide range of biological activity.[1] Many natural products from various plants and fungi share the common 5-oxygenated-5,6-dihydro-2*H*-pyran-2-one structural motif, such as goniodiol, acetylphomalactone, and altholactone.[1d] These natural products have biological activity including antitumor[1a] and antifungal properties,[1f] as well as antibiotic potential.[1f] Due to the wide distribution of 5,6-dihydro-2*H*-pyran-2-ones in plants and fungi, many synthetic methodologies have been employed to synthesize this core structure.[1,2]

As part of our synthetic efforts to enantioselectively synthesize biologically important *C*-arylglycoside natural products from achiral furans,[3] we chose to devise a route to the antitumor natural product altholactone **1b**. At the outset, we targeted a selective synthesis of the four possible C-2/C-3 diastereomers of altholactone **1a**−**d**. We opted for late installation of the arene ring, to allow for simple access to substituted arene analogues. Altholactone, a furanopyrone member of the styryllactone family, was first isolated by Loder and Nearn[4] from the bark of an unnamed *Polyathia* (Annonaceae) species and has subsequently been isolated from various *Goniothalamus* species.[1a] Previous syntheses of altholactone have been accomplished by Gesson,[5] Shing,[6] Ogawa,[7] Kang,[8] Honda,[9] Somfai,[10] and Mukai[11] and range from 11 steps from D-gluconolactone[6] to 16 steps from

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(5) (a) Gesson, J.-P.; Jacquesy, J.-C.; Mondon, M. *Tetrahedron Lett.* **1987**, *28*, 3945−3948. (b) Gesson, J.-P.; Jacquesy, J.-C.; Mondon, M. *Tetrahedron Lett.* **1987**, *28*, 3949−3952. (c) Gesson, J.-P.; Jacquesy, J.-C.; Mondon, M. *Tetrahedron* **1989**, *45*, 2627−2640.

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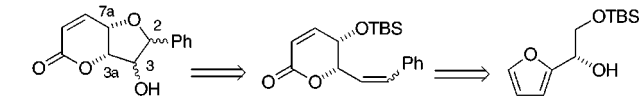
D-glycerldehyde acetonide.[9] Many of these syntheses derive their asymmetry from carbohydrate derivatives,[5−9] diethyl L-tartrate,[10] or a substituted benzaldehyde chromium(0) complex.[11]

Our approach to this class of natural products involves the diastereoselective synthesis of either double bond isomer of compound **2**, from furyl alcohol **3**, and subsequent conversion to **1a**−**d** through a diastereoselective epoxidation and acid-catalyzed cyclization sequence (Scheme 1).

Scheme 1



1a: 2α, 3α **3-*epi*-altholactone**
1b: 2α, 3β **altholactone**
1c: 2β, 3α **isoaltholactone**
1d: 2β, 3β **2-*epi*-altholactone**

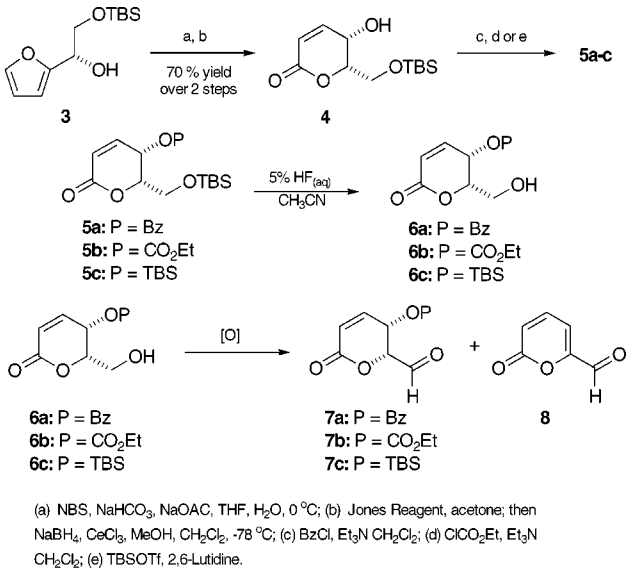
2a: cis
2b: trans

3

Recently, we developed an expeditious route to various D- or L-sugars and sugar lactones from furan diols using Sharpless's dihydroxylation to establish the absolute stereochemistry.[12] Continuing our investigations on the utility of this strategy, we turned our attention to the styryllactone class of natural products, especially the α,β-unsaturated δ-lactone motif. Herein, we describe our preliminary results in the synthesis of the altholactone diastereomers. This work led to a highly efficient enantioselective approach to 3 styryllactones: isoaltholactone (**1c**), 3-*epi*-altholactone (**1a**), and 5-hydroxy goniothalamin (**14**).

We envisioned synthesizing **2a** and **2b** from **4**, which we previously prepared enantioselectively from furyl alcohol **3** (Scheme 2).[13] Furyl alcohol **3** was synthesized from furfural via a Peterson olefination, dihydroxylation of the resulting vinylfuran using AD-mix-β,[14] and protection of the primary alcohol with TBSCl, in a 75% overall yield and >92% ee.[15] Treatment of furyl alcohol **3** with NBS[16] in aqueous THF produces a hemiacetal pyranone through an oxidative ring

Scheme 2



(a) NBS, $NaHCO_3$, NaOAC, THF, H_2O, 0 °C; (b) Jones Reagent, acetone; then $NaBH_4$, $CeCl_3$, MeOH, CH_2Cl_2, -78 °C; (c) BzCl, Et_3N CH_2Cl_2; (d) $ClCO_2Et$, Et_3N CH_2Cl_2; (e) TBSOTf, 2,6-Lutidine.

expansion (Achmatowicz reaction).[17] Treatment of the crude Achmatowicz product with excess Jones reagent gave a ketolactone intermediate, which was taken on without purification to a Luche reduction with $NaBH_4$ and $CeCl_3$ in MeOH, to give δ-lactone **4**[18] in 70% yield and >92% ee.

To gain access to a suitably protected aldehyde precursor necessary to install the olefin side chain, some protecting group manipulations were required (Scheme 2). Initial attempts included the use of a benzoyl or ethyl carbonate protecting group at C-4 (lactones **5a** and **5b**); however, C-4 carboxylate groups were incompatible with the ensuing oxidation step. The primary TBS groups of **5a** and **5b** were cleanly deprotected with 5% HF in CH_3CN to give primary alcohols **6a** and **6b**. Unfortunately, oxidation of either alcohol **6a** or **6b** under various conditions (Jones, PCC, TPAP, and Dess−Martin) failed to give the desired aldehydes **7a** and **7b**; only the elimination product **8** was formed.

A practical solution was found by using a bis-TBS group protection strategy (Scheme 2). Protection of the free hydroxy group of lactone **4** was accomplished with TBSOTf forming **5c** in 90% yield. Selective deprotection of the primary TBS group of **5c** was accomplished with 5% HF in CH_3CN to exclusively give the free primary alcohol **6c** in 90% yield. Dess−Martin oxidation of the primary alcohol gave the desired aldehyde **7c**, which was taken on without purification due to decomposition on silica gel. Although aldehyde **7c** was unstable, Wittig olefination of crude **7c** gave δ-lactone **2a** in a 60% yield and a diastereoselectivity of 7:1 in favor of the cis olefin at −78 °C (Scheme 3).[19]

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(9) (a) Tsubuki, M.; Kanai, K.; Honda, T. *Synlett* **1993**, 653−655. (b) Tsubuki, M.; Kanai, K.; Nagase, H.; Honda, T. *Tetrahedron* **1999**, *55*, 2493−2514.

(10) Somfai, P. *Tetrahedron* **1994**, *50*, 11315−11320.

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(15) Enantiomeric excesses were determined by ^{1}H NMR and ^{19}F NMR of the Mosher ester derivative.

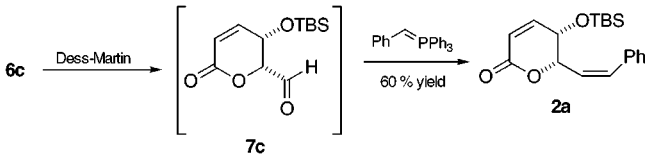
(16) (a) Grapsas, I.; Couladouros, E. A.; Georgiadis, M. P. *Pol. J. Chem.* **1990**, *64*, 823. (b) Georgiadis, M. P.; Couladoros, E. A. *J. Org. Chem.* **1986**, *51*, 2725−2727.

(17) Achmatowicz, O.; Bielski, R. *Carbohydr. Res.* **1977**, *55*, 165.

(18) All new compounds were identified and characterized by ^{1}H NMR, ^{13}C NMR, FTIR, HRMS, and EA analysis.

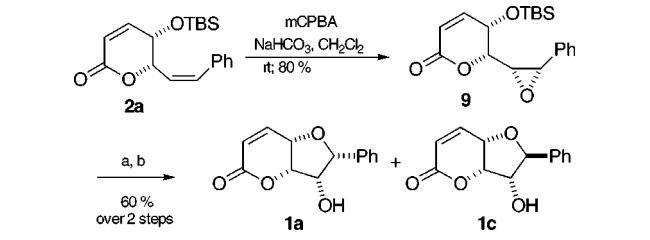
(19) The cis/trans selectivity of the Wittig reaction decreased to 4:1 at 0 °C and to 2:1 at room temperature.

Scheme 3



To introduce the remaining oxygenation for the altholactone ring system, we needed to epoxidize lactone **2a** both regioselectively and diastereoselectively. Treatment of **2a** with mCPBA yielded **9** in favor of the diastereomer shown (>10:1), in an 80% yield (Scheme 4). The stereochemistry

Scheme 4

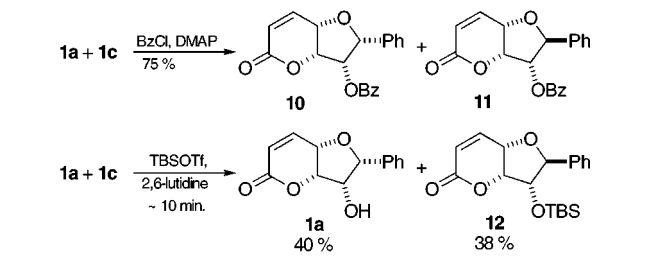


(a) TBAF, THF, rt; (b) CSA, CH_2Cl_2, rt.

of the epoxidation was assigned on the basis of the stereochemistry of the final cyclized product. Deprotection of the TBS group was accomplished with TBAF, followed by acid-promoted cyclization with camphor sulfonic acid to give an inseparable 1:1 mixture of 3-*epi*-altholactone **1a** and isoaltholactone[20] **1c** in 65% yield over the last two steps.

The inseparable mixture of 3-*epi*-altholactone **1a** and isoaltholactone **1c** was easily separated as benzoates **10** and **11**, which were prepared by treatment of a CH_2Cl_2 solution of **1a** and **1c** with BzCl and DMAP (Scheme 5). The relative

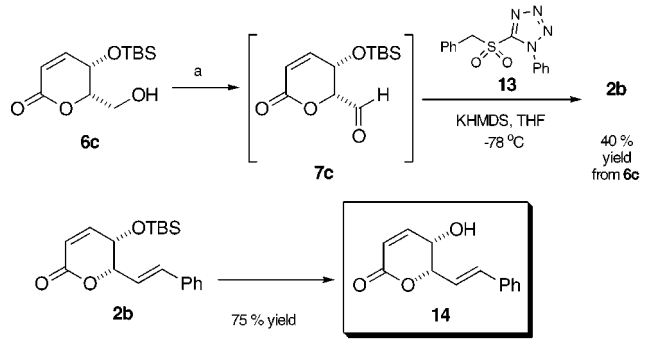
Scheme 5



stereochemistries of benzoates **10** and **11** were confirmed by a detailed NOE study. Particularly indicative for **10** were the enhancements between the hydrogen at C-2 to the bridgehead hydrogens at C-3a and C-7a, whereas for **11** no NOE enhancements were detected between the hydrogen at C-2 to the bridgehead hydrogens at C-3a and C-7a. A pure sample of **1a** was obtained upon treatment with TBSOTf for 10 min to give a 40% yield of unprotected **1a** and a 38% yield of the TBS-protected isoaltholactone **12**.

Having established the ability to prepare the connectivity of the altholactone skeleton, we turned our attention to selectively synthesizing the trans olefin side chain lactone **2b** (Scheme 6). Treatment of the aldehyde **7c** generated from

Scheme 6



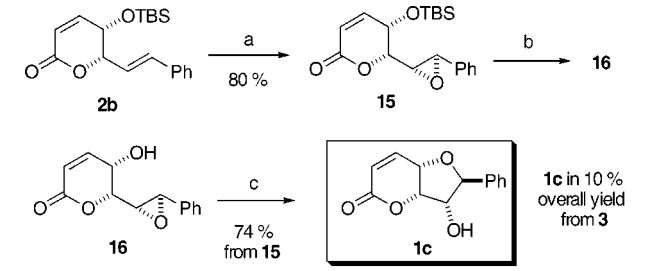
(a) Dess Martin periodinane, CH_2Cl_2, $NaHCO_3$, rt

Dess−Martin oxidation of lactone **6c** with the anion of sulfone **13**[21] in THF at −78 °C gave the desired 1,2-trans alkene **2b** in 40% yield from **6c** and a diastereoselectivity of >13:1 in favor of the trans alkene.

Deprotection of the TBS group with TBAF gave the styrylpyrone natural product 5-hydroxy goniothalamin **14** in 10 steps from furfural and 13% overall yield.

Using the same reaction sequence as before on lactone **2b**, we were able to selectively synthesize isoaltholactone **1c** (Scheme 7). Treatment of **2b** with mCPBA gave epoxide

Scheme 7



(a) mCPBA, $NaHCO_3$, CH_2Cl_2, rt; (b) TBAF, THF, rt; (c) CSA, CH_2Cl_2, rt.

15 as the major diastereomer (>10:1) in 80% yield. Deprotection of the TBS group was easily achieved with TBAF, providing **16** in 80% yield. Treating epoxide **16** to the same

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acid-promoted cyclization with CSA as before yielded isoaltholactone **1c** exclusively in 93% yield. The excellent stereoselectivity of this acid-catalyzed epoxide opening of **16** is in contrast to that of the opening of **9** which unfortunately gives a 1:1 mixture of diastereoisomers **1a** and **1c**. Isoaltholactone **1c** was synthesized in 10% overall yield and 12 steps from furfural with an enantiomeric excess determined to be >91% ee by Mosher ester analysis.

In conclusion, this highly enantio- and diastereocontrolled route to α,β-unsaturated δ-lactones **2a** and **2b** allows access to a variety of styryllactone natural products including 5-hydroxygoniothalamin, 3-*epi*-altholactone, and isoaltholactone in 13%, 5%, and 10% overall yields from furfural, respectively.[22] This methodology illustrates the utility of the enantioselective dihydroxylation reaction of vinylfuran, eliminating the need for kinetic resolution of 2-furylcarbinols. The route provides rapid and enantioselective access to α,β-unsaturated δ-lactones that are useful synthons for natural product synthesis from a commercially available, inexpensive starting material. Further biological evaluation of these diastereomers as well as the synthesis of other styryllactone natural products will be reported in due course.

(22) Our spectral data for synthetic **1a**, **11**, and **1c** (^{1}H NMR, ^{13}C NMR, FTIR, HRMS, and optical rotation) matched the data for the isolated material.

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Supporting Information Available: Spectroscopic and analytical data for all new compounds as well as experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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