Stereoselective Thallium-induced Ring Contraction of Glycals†

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Various glycals, treated with $Tl(NO_3)_3 \cdot 3H_2O$ under mild conditions in an acetonitrile–methanol solvent mixture, underwent ring contraction in a stereoselective fashion, affording stable acetal products.

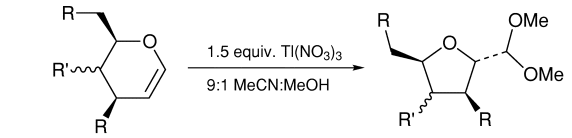
Chiral 2,5-disubstituted furanoids are found in a variety of natural products, including the many natural nucleosides (and their synthetic analogues). Important compounds bearing this moiety are nonactin[1] (an ionophoric antibiotic), furanomycin[2] (an α-amino acid) and showdomycin[3] (a *C*-glycosyl nucleoside antibiotic).

2,5-Disubstituted furanoids have been prepared *via* a number of routes. These include the introduction of a substituent at the anomeric position of a glycofuranoside,[4] furanoid ring synthesis from simple starting materials,[5] and the use of hexose carbohydrates.[6] Despite the elegance of many of these procedures, most are directed towards a single compound and are not general in their applicability. Herein, we describe the application of a ring contraction protocol[7] that is general in nature for the preparation of a variety of 2,5-disubstituted furanoid compounds, including a precursor to the antibiotic (+)-furanomycin. In addition, this study addressed the effects of stereochemistry on the ring contraction.

Oxythallation of olefins has been recognised as a powerful tool in synthesis, and has been used in the preparation of highly functionalised molecules.[7] The organothallium intermediate is subject to a variety of reactions due to the lability of the C–Tl^{III} bond and the reduction potential of the Tl^{III}–Tl^{I} couple.[8] The facility with which the reduction occurs allows the occurrence of Wagner–Meerwein-type rearrangements, which have been put to use in the synthesis of, for example, 11-desoxyprostaglandins.[9] The first results of the Tl^{III}-induced ring contraction of carbohydrate derivatives were reported a decade ago.[7] We set out to expand on this methodology and to gain an understanding of the roles that various chiral centres play in the ring-contraction step.

Our first attempts at a ring-contraction reaction of glucal **1a** employed the exact conditions as previously described.[7] It was found that slightly better results could be obtained when using methanol, at 0 °C followed by heating, as the solvent instead of acetonitrile. Subsequent experiments proved that a solvent comprising a 9:1 ratio of acetonitrile–methanol facilitated the reaction and allowed the isolation of an enantiomerically pure 2,5-*trans*-disubstituted acetal **2a** in a yield of 50% (Scheme 1). A similar reaction was carried out on galactal **1b**, affording the furanoid *C*-glycoside **2b** in a yield of 45%.

We were encouraged by these results and wished to expand the scope of this reaction to glycal esters since the further manipulation of esters is more readily accomplished than that of the corresponding ethers. Again it was established that a 9:1 acetonitrile–methanol solvent ratio provided the best results. Thus, tri-*O*-acetyl-D-glucal **1c** (Scheme 1) was treated with 1.5 equivalents of $Tl(NO_3)_3 \cdot 3H_2O$ under



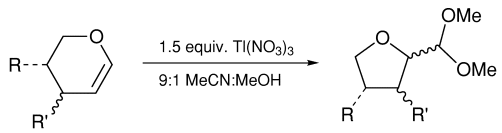
1a R = OBn, R' = α-OBn
1b R = OBn, R' = β-OBn
1c R = OAc, R' = α-OAc
1d R = OBz, R' = α-OBz
1e R = OBz, R' = β-OBz

2a R = OBn, R' = α-OBn
2b R = OBn, R' = β-OBn
2c R = OAc, R' = α-OAc
2d R = OBz, R' = α-OBz
2e R = OBz, R' = β-OBz

Scheme 1

identical conditions worked out for the ethers **1a** (see Experimental section) to yield acetal **2c** (55%). Similarly, glycals **1d** and **1e** afforded the corresponding furanoid products (**2d**, 47% and **2e**, 41%).

Ring contractions of derivatives of D-arabinal, **3a** and **3b** (Scheme 2) did not display the stereoselectivity observed with the hexose glycals. Here, the ring contracted products were isolated as α/β mixtures (which could be separated). The isomer ratio was found to be substrate dependent. Similar results were obtained with derivatives of D-xylal, **3c** and **3d** (Scheme 2). These results indicated that the substituent on C-5 in the hexose sugar played a definitive role in determining the stereochemical outcome of the ring contraction reactions.



3a R = OAc, R' = α-OAc
3b R = OBz, R' = α-OBz
3c R = OAc, R' = β-OAc
3d R = OBz, R' = β-OBz

4a R = OAc, R' = α-OAc, 1.5:1 α:β acetal (60%)
4b R = OBz, R' = α-OBz, 1:1.5 α:β acetal (71%)
4c R = OAc, R' = β-OAc, 1:1 α:β acetal (54%)
4d R = OBz, R' = β-OBz, 1:1 α:β acetal (59%)

Scheme 2

Finally, this methodology was applied to the preparation of a late precursor in the synthesis of furanomycin. L-Rhamnal **6** (prepared from L-rhamnose by standard chemistry)[10] was treated with $Tl(NO_3)_3 \cdot 3H_2O$ under our optimal conditions to furnish (60%) the anticipated *trans*-furanoid acetal **7** (Scheme 3). This product was subsequently deprotected (quantitative) and deoxygenated[11] (78%) to afford the desired unsaturated acetal **9**. This compound has previously been employed to prepare (+)-furanomycin.[12]

The stereoselective outcome of the reactions described in Schemes 1 and 3 seems to rely exclusively on the stereochemistry of the substituent at C-5. This substituent has a preference for the equatorial position, rendering the $^4H_5$ conformation (**10**) the more stable (Scheme 4). It is through this conformation that reaction occurs. Attack of the Tl^{III} from the β-face would lead to intermediate **11a**, while attack from the α-face would lead to intermediate **11b**. The intramolecular S_N2-type reaction[13] of the ring oxygen atom

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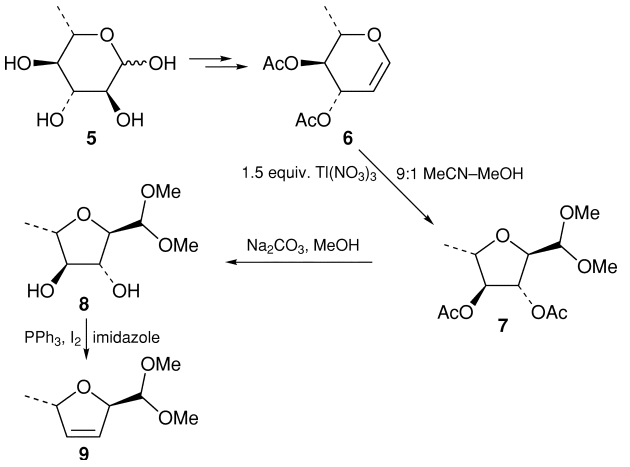
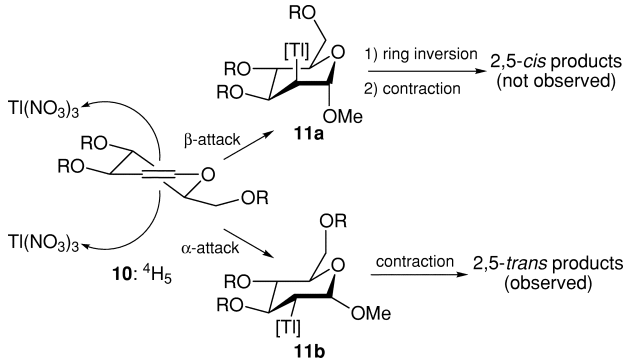


Scheme 3



Scheme 4

requires an equatorial placement of the thallium atom. While **11b** is set up for such a reaction (leading to the observed 2,5-*trans*-tetrahydrofuran product), **11a** requires a ring flip to the higher energy chair conformation (subsequent reaction would lead to the 2,5-*cis*-tetrahydrofuran product, which is not observed) before this reaction is theoretically possible. It is possible that intermediate **11a** is indeed formed but that this intermediate decomposes into other products.

In conclusion, we have described an efficient application of $Tl(NO_3)_3 \cdot 3H_2O$ to the ring contraction of various hexose and pentose glycals. The modest yields (41–71%) obtained are the result of competing reactions (*e.g.* ring opening and/or ring ketone formation), but were acceptable in the light of the easy access to the starting materials. This work indicated that the ring contraction remains more or less independent of changes in stereochemistry at C-3 or C-4 of both hexose and pentose sugars, and is more directly influenced by stereochemistry at C-5. The methodology is amenable to the use of readily removable protecting groups and, under the correct conditions, affords stable, enantiomerically pure products. Our protocol shows significant potential for the rapid elucidation of glycals into natural products, as confirmed by the preparation of an advanced synthetic precursor of (+)-furanomycin.

Experimental

General procedure for ring contraction reactions: The glycal was dissolved in a 9:1 mixture of acetonitrile and methanol (250 mg in 10 ml) and the solution was cooled to 0 °C. $Tl(NO_3)_3 \cdot 3H_2O$ (1.5 equivalents) in the acetonitrile–methanol mixture (half of the volume used above) was added and the mixture was stirred at 0 °C until the brown colour disappeared. The solution was then heated under reflux until precipitation of the thallium salts occurred (usually *ca.* 12 h). The mixture was filtered through Celite and concentrated *in vacuo* to approximately one third of the original volume. An equal volume of chloroform was added and the crude product was adsorbed onto silica gel and subjected to column chromatography.

Selected Data. *Acetal* **2c**.—55% yield; $[\alpha]_D + 32.3$ (*c* 1.03, $CHCl_3$); IR ($CHCl_3$) 1747 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 5.36 (dd, 1H, $J = 3.8$ and 2.9 Hz), 5.09 (dd, 1H, $J = 4.0$ and 2.9 Hz), 4.41 (d, 1H, $J = 5.8$ Hz), 4.21 (m, 3H), 4.10 (dd, 1H, $J = 5.8$ and 3.8 Hz), 3.41 (s, 3H), 3.40 (s, 3H), 2.07 (br s, 9H); δ_C 170.6, 169.9, 169.7, 103.3, 82.1, 81.1, 78.3, 77.9, 63.1, 55.4, 54.1, 20.8; HRMS for M – OMe, found *m/z* 303.1076, calc. for $C_{14}H_{19}O_8$ 303.1080.

Acetal **4a**-α.—36% yield; $[\alpha]_D - 22.9$ (*c* 1.15, $CHCl_3$); IR ($CHCl_3$) 1750 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 5.51 (dd, 1H, $J = 5.0$ and 4.2 Hz), 5.34 (ddd, 1H, $J = 7.1$, 6.8 and 5.0 Hz), 4.53 (d, 1H, $J = 7.7$ Hz), 4.08 (dd, 1H, $J = 9.3$ and 7.1 Hz), 4.00 (dd, 1H, $J = 7.7$ and 4.2 Hz), 3.82 (dd, 1H, $J = 9.3$ and 6.8 Hz), 3.40 (s, 3H), 3.33 (s, 3H), 2.10 (s, 3H), 3.01 (s, 3H); δ_C 169.9, 169.4, 101.7, 77.9, 71.7, 71.3, 69.2, 54.7, 53.2, 21.5; HRMS for M – OMe, found *m/z* 231.0868, calc. for $C_{10}H_{15}O_6$ 231.0869.

Acetal **7**.—60% yield; $[\alpha]_D + 21.4$ (*c* 0.95, $CHCl_3$); IR ($CHCl_3$) 1746 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 5.29 (dd, 1H, $J = 4.2$ and 3.5 Hz), 4.86 (dd, 1H, $J = 4.2$ and 2.9 Hz), 4.42 (d, 1H, $J = 6.1$ Hz), 4.06 (dd, 1H, $J = 6.1$ and 3.5 Hz), 3.97 (qd, 1H, $J = 6.1$ and 2.9 Hz), 3.40 (s, 6H), 2.06 (br s, 6H), 1.30 (d, 3H, $J = 6.1$ Hz); δ_C 170.3, 170.0, 103.4, 82.3, 81.1, 79.4, 78.4, 55.3, 54.0, 20.9, 18.2; HRMS for M – OMe, found *m/z* 245.1025, calc. for $C_{11}H_{17}O_6$ 245.1025.

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