A Useful Route to Optically Active 4-Oxygenated 4,5-Dihydroisoxazoles

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Summary: Optically active iodotosylates were prepared from carbohydrate precursors and were transformed by the action of excess sodium nitrite/propyl nitrite to bicyclic 4-oxygenated 4,5-dihydro-3-nitroisoxazoles.

4,5-Dihydroisoxazoles (DHIs; numbered below) possessing a 4-oxygen substituent are useful synthetic intermediates[1] which are, however, difficult to obtain in

DHI numbering scheme:

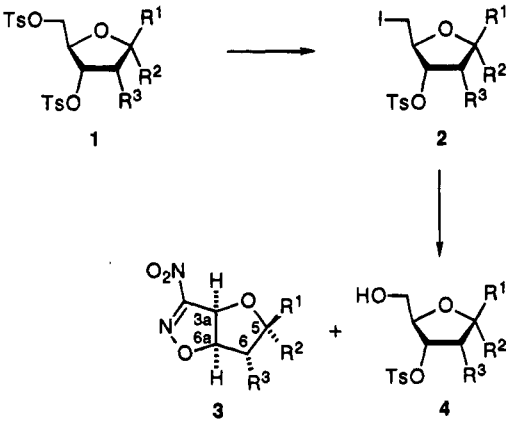
optically active form.[2] The usual method of DHI construction, nitrile oxide cycloaddition, typically affords 5-oxygenated rather than 4-oxygenated DHIs when vinyl ethers are employed. Cycloaddition to furans is an exception: bicyclic 4-oxygenated DHIs are produced but they are racemic.[1a] Here we describe a new route to optically active 4-oxygenated DHIs involving sequential nitrite displacement and nitrosative cyclization[3] of carbohydrate precursors possessing an iodo group located three carbon atoms from a tosylate group. In one synthetic step, these carbohydrates are converted to *cis*-fused bicyclic 4-oxygenated DHIs possessing a replaceable nitro group at the 3-position (Schemes 1 and 2).

The furanoside ditosylates **1a–c**[4] and the pyranosides **5a,b**[5] were prepared by published procedures. In order to provide the corresponding ditosylates, pyranoside **5a** was treated with excess tosyl chloride/pyridine and **5b** with butyllithium[6] followed by tosyl chloride. Subsequent treatment of the ditosylates with sodium iodide in refluxing 2-butanone provided iodotosylates **2a,b** and **6a,b** (93–97% yield) and **2c** (77% yield).

A DMSO solution of iodotosylate **2a**, excess sodium nitrite, and excess propyl nitrite was warmed at 50-55 °C to afford a mixture of the bicyclic DHI **3a**[7] (43% yield) and the known alcohol **4a**[4] (29% yield; Table 1). This reaction likely proceeded via initial nitrite displacement of iodide to afford a mixture of *N*-alkylate (nitro compound) and *O*-alkylate (nitrite ester). The nitro compound then underwent in situ nitrosative cyclization[3] to **3a** and the nitrite ester underwent propanolysis to **4a**. Presumably it should be possible to convert alcohol **4a** back to ditosylate **1a** and hence to more DHI **3a**. The ditosylate **1a** also underwent direct reaction to give DHI **3a**, but only in 27% yield. The ^{1}H-NMR spectrum of **3a**[7] closely resembled the spectrum of the known[8] racemic furanoside **11b** confirming the stereochemical assignment.

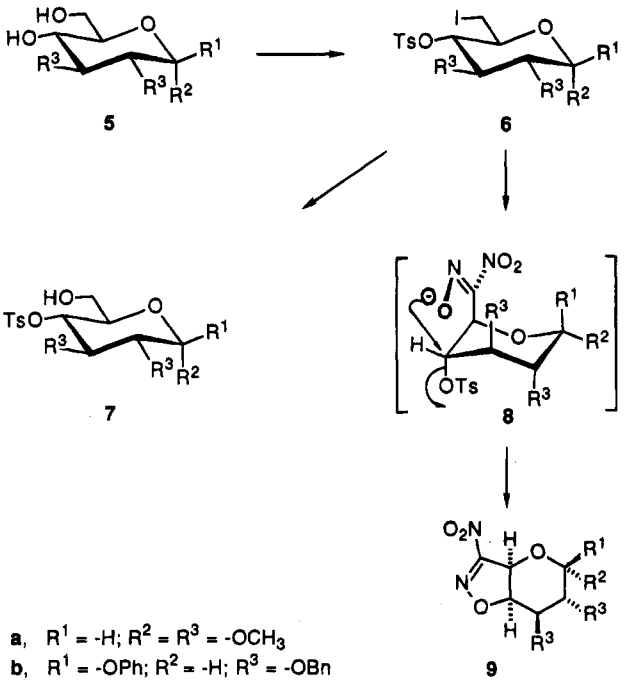
Iodotosylate **2b** reacted similarly with a mixture of excess sodium nitrite and excess propyl nitrite to give the bicyclic DHI **3b** (55% yield) and alcohol **4b** (30% yield). The isomeric iodotosylate **2c** cyclized less efficiently to afford bicyclic DHI **3c** (32% yield) accompa-

Scheme 1



a, R^1 = -H; R^2, R^3 = -OC(Me)$_2$O-
b, R^1 = R^3 = -H; R^2 = -OCH$_3$
c, R^1 = -OCH$_3$; R^2 = R^3 = -H

Scheme 2



a, R^1 = -H; R^2 = R^3 = -OCH$_3$
b, R^1 = -OPh; R^2 = -H; R^3 = -OBn

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(1) For reviews see: (a) Jäger, V.; Müller, I.; Schohe, R.; Frey, M.; Ehrler, R.; Häfele, B.; Schröter, D. *Lect. Heterocycl. Chem.* **1985**, *8*, 79. (b) Padwa, A. In *Comprehensive Organic Synthesis*; Trost, B. M., Flemming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 4, p 1069.

(2) Existing methods include (a) asymmetric oxidation of achiral DHIs: Davis, F. A.; Kumar, A.; Reddy, R. E.; Chen, B.-C.; Wade, P. A.; Shah, S. S. *J. Org. Chem.* **1993**, *58*, 7591. (b) oxidation of chiral DHIs: ref 1a and Panek, J. S.; Beresis, R. T. *J. Am. Chem. Soc.* **1993**, *115*, 7898.

(3) (a) Wade, P. A.; Price, D. T. *Tetrahedron Lett.* **1989**, *30*, 1185. (b) Wade, P. A. *J. Org. Chem.* **1978**, *43*, 2020. (c) Baum, K.; Tzeng, D. *J. Org. Chem.* **1985**, *50*, 2736.

(4) **1a**: Kiss, J.; D'Souza, R.; van Koeveringe, J. A.; Arnold, W. *Helv. Chim. Acta* **1982**, *65*, 1522. **1b,c**: Lumin, S.; Falck, J. R.; Schwartzman, M. L. *Tetrahedron Lett.* **1991**, *32*, 2315.

(5) **5a**: Nicoll-Grifith, D. A.; Weiler, L. *Tetrahedron* **1991**, *47*, 2733. Ditosylate of **5a** [60% yield]: mp 121–22 °C. **5b**: Micheel, F.; Klemer, A. *Chem. Ber.* **1958**, *91*, 663. Ditosylate of **5b** [58% yield]: mp 117–17.5 °C.

(6) Brown, H. C.; Bernheimer, R.; Kim, C. J.; Scheppele, S. E. *J. Am. Chem. Soc.* **1967**, *89*, 370.

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Table 1. Cyclization[a] of Iodotosylates

entry	iodotosylate	reaction time, h	DHI	yield,[b] %	alcohol	yield,[b] %
1	**2a**	2	**3a**	43	**4a**	29
2	ditosylate **1a**	2	**3a**	27	**4a**	36
3	**2b**	5	**3b**	55	**4b**	30
4	**2c**	5	**3c**	32	**4c**	36
5	**6a**	6	**9a**	60	**7a**	23
6	**6b**	6	**9b**	14	**7b**	37

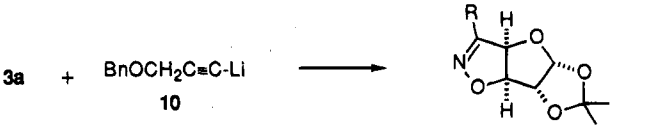
[a] Using iodotosylate (1 mmol), $NaNO_2$ (8 mmol), PrONO (5 mmol), and DMSO (15 mL). [b] After preparative TLC.

nied by alcohol **4c** (36% yield). Reaction of the **2b,c** isomeric mixture reflected a similar bias for formation of **3b** which could be separated from **3c**. The stereochemical assignment for bicyclic DHIs **3b,c** is based on ^{1}H-NMR spectra: notably the lack of observable vicinal coupling[8] ($J_{5,6} \approx J_{6a,6} \approx 0$) for one of the C-6 protons in only one isomer is consistent with structure **3c**.

The preference for formation of **3b** over **3c** is attributed mainly to the ease of nitrite *N*-alkylation by iodotosylate **2b** relative to **2c**.[9] Backside attack by iodide on **1c** was considerably slower[10] than on **1b** and proceeded in lower yield; presumably, nitrite attack on **2c** was also slower than on **2b**. Reproducibly more of the *O*-alkylate-derived alcohol **4c** (36% yield) than **4b** (30% yield) was formed. Corey et al.[11] have noted a correlation between sluggish backside attack and disfavored *N*-alkylation of nitrite in the case of a 6-iodogalactopyranoside.

Pyranosides as well as furanosides could be converted to optically active bicyclic 4-oxygenated DHIs. Thus, reaction of iodotosylate **6a** with a mixture of excess sodium nitrite and excess propyl nitrite afforded bicyclic DHI **9a**[7] (60% yield) accompanied by alcohol **7a** (23% yield). The iodotosylate **6b** also gave the reaction but the DHI **9b** was obtained in only 14% yield. The low yield for **9b** is attributed mainly to inefficient nitrosative cyclization. Molecular models clearly show that for backside displacement of the tosylate leaving group, the diaxial conformation of oxime anions **8a,b** is required. For **8b** the anomeric phenoxy group would have a severe 1,3-diaxial interaction with C-6 lowering the population of the conformation necessary for cyclization. Increased *O*-alkylation of nitrite ion by iodotosylate **6b** also probably contributed to the low yield of **8b**: the *O*-alkylate-derived alcohol **7b** was formed in 37% yield.

Nucleophilic displacement of the nitro group from the 3-position of DHIs has been reported.[3ab,12] Thus, **3a–c** and **9a,b** should be transformable to other 3-substituted DHIs in straightforward fashion. This has been confirmed by reaction of **3a** with the acetylide **10**[13] to produce alkynyl DHI **11a**[7], isolated in 46% yield (not optimized).



11 a, R = $BnOCH_2C{\equiv}C$-
b, R = *t*-$BuOCH_2$-

Alkynyl DHI **11a** represents a synthetic intermediate with all of the carbon atoms and three of the five stereogenic centers present in the tetrahydroxylated indolizidine castanospermine:[14] its transformation to castanospermine is under further investigation.

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Supplementary Material Available: Preparations and characterization data for iodotosylates and DHIs (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(7) ^{1}H-NMR spectra of DHIs: **3a** (C_6D_6) δ 5.08 (d, 1 H, J = 3.5 Hz), 4.94 (d, 1 H, J = 6.6 Hz), 4.43 (d, 1 H, J = 6.6 Hz), 4.04 (d, 1 H, J = 3.5 Hz), 1.18 (s, 3 H), and 1.0 (s, 3 H); **3b** (C_6D_6) δ 4.82 (d, 1 H, J = 7.2 Hz), 4.6 (apparent td, 1 H, J = 3.7, 7.3 Hz), 4.39 (dd, 1 H, J = 2.4, 4.8 Hz), 2.88 (s, 3 H), 1.75 (ddd, 1 H, J = 2.4, 7.5, 14.4 Hz), and 1.61 (apparent dt, 1 H, J = 4.3, 14.4 Hz); **3c** ($CDCl_3$) δ 5.86 (d, 1 H, J = 7.6 Hz), 5.62 (apparent t, 1 H, J = 7.2 Hz), 5.28 (d, 1 H, J = 4.9 Hz), 3.28 (s, 3 H), 2.62 (apparent d, 1 H, J = 15 Hz), and 2.34 (ddd, 1 H, J = 4.9, 6.8, 15 Hz); **9a** ($CDCl_3$) δ 5.15 (d, 1 H, J = 4.8 Hz), 5.06 (apparent t, 1 H, J = 4.8 Hz), 4.92 (d, 1 H, J = 2.8 Hz), 4.07 (dd, 1 H, J = 4.8, 9.9 Hz), 3.62 (s, 3 H), and 3.57, 3.54 (2s, 6 H) on 3.5–3.6 (m, 1 H); **9b** ($CDCl_3$) δ 7.2–7.5 (m, 12 H), 7.05 (t, 1 H, J = 6.3 Hz), 6.92 (d, 2 H, J = 7.7 Hz), 5.66 (d, 1 H, J = 10.2 Hz), 5.61 (d, 1 H J = 3.5 Hz), 5.22 (dd, 1 H, J = 3.2, 10.2 Hz), 4.94 (d, 1 H, J = 12 Hz), 4.81, 4.79 (2d, 2 H, J = 12, 11.4 Hz), 4.68 (d, 1 H, J = 11.4 Hz), 4.05 (dd, 1 H, J = 3.5, 10 Hz), 3.93 (dd, 1 H, J = 3.2, 10 Hz); **11a** ($CDCl_3$) δ 7.3–7.4 (m, 5 H), 5.87 (d, 1 H, J = 3.4 Hz), 5.55 (d, 1 H, J = 6.6 Hz), 5.07 (d, 1 H, J = 6.6 Hz), 4.81 (d, 1 H, J = 3.4 Hz), 4.64 (s, 2 H), 4.38 (s, 2 H), 1.52 (s, 3 H), and 1.39 (s, 3 H).

(8) Jäger, V.; Müller, I. *Tetrahedron* **1985**, *41*, 3519 and references cited therein.

(9) It is also possible that the yield difference may arise at least in part from conformationally disfavored cyclization of the oxime anion intermediate formed from **2c**. The necessary 1,3-pseudodiaxial interaction between the anomeric methoxy group and C-5 would not be severe, however.

(10) Indeed, ditosylates **1b,c** could be conveniently separated by partial conversion to the iodotosylates: **1b** was completely converted to **2b** while much **1c** remained and could be isolated pure.

(11) Corey, E. J.; Samuelsson, B.; Luzzio, F. A. *J. Am. Chem. Soc.* **1984**, *106*, 3682.

(12) (a) Wade, P. A.; Rao, J. A.; Bereznak, J. F.; Yuan, C.-K. *Tetrahedron Lett.* **1989**, *30*, 5969. (b) Wade, P. A.; Cole, D. T.; D'Ambrosio, S. G. *Tetrahedron Lett.* **1994**, *35*, 53.

(13) Shiklev, I. A.; Karaev, S. F.; Alieva, Ş. Z.; Yur'eva, G. A. *Zhurn. Organ. Khim.* ***1975***, *11*, 2134 (*J. Org. Chem. SSSR*, **1975**, *11*, 2168).

(14) For a recent synthesis of castanospermine and references to the literature, see: Kim, N.-S.; Choi, J.-R.; Cha, J. K. *J. Org. Chem.* **1993**, *58*, 7096.