Novel IBX-Mediated Processes for the Synthesis of Amino Sugars and Libraries Thereof[**]

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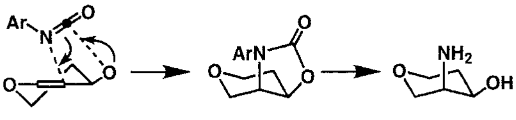
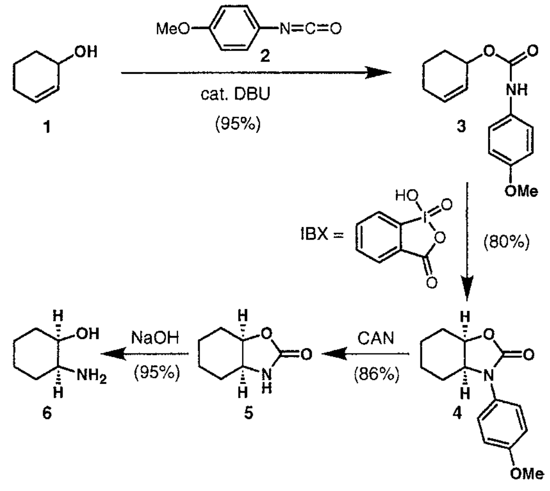
Dedicated to Professor David I. Schuster on the occasion of his 65th birthday

Novel molecular diversity is one of the most hotly pursued objectives[1] of modern organic synthesis,[2] medicinal chemistry,[3] and combinatorial synthesis.[4] Amino sugars constitute integral components of a plethora of natural products and medicinally relevant compounds.[5] Several refined methods for the construction of this class of compounds have been reported and extensively reviewed.[6] We have recently reported[1f] a fundamentally new protocol for the introduction of the *N*-phenyl amino functionality into allylic alcohols using IBX (*o*-iodoxybenzoic acid; 1-hydroxy-1,2-benziodoxol-3(1*H*)-one 1-oxide)[7] as a facile reaction mediator. By capitalizing on the convenient and readily available nature of IBX, in conjunction with cheap isocyanates as a nitrogen source, we realized that a tethered approach to amino sugars would provide a distinct advantage over current methods (Scheme 1). The concept of tethering a nitrogen source to an allylic alcohol has been employed to generate amino sugars;[8] however, these conventional methods leave behind additional functionality (such as iodide) which must be dealt with in subsequent steps. For the present method to be of widespread applicability, certain criteria have to be fulfilled: (a) the stereoselectivity of the reaction must be predictable;[9] (b) the *N*-phenyl substituent should be readily removable; and (c) the reaction conditions must be mild and reliable enough to operate on a variety of carbohydrate-based scaffolds. Herein we present (a) the realization of these goals; (b) application of the method to a concise synthesis of vancomycin's amino sugar, *l*-vancosamine (**35**, Scheme 4); (c) a revision of our previously proposed mechanism[1f] of the IBX reaction with unsaturated aryl amide carbamates and related systems; and d) the remarkable reactivity of glycals in this reaction.



Scheme 1. General concept for the IBX-mediated construction of amino sugars. Ar = aryl.

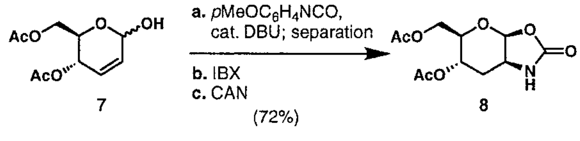
We first sought a method for the efficient removal of the extraneous, but enabling, aryl moiety.[10] Using 2-cyclohexen-1-ol (**1**) we probed whether adjustment of the phenyl moiety to *p*-methoxy phenyl (pMP) would be tolerated by the IBX reaction (Scheme 2). To our delight, reaction of **1** with *p*-methoxy isocyanate (**2**) in the presence of a catalytic amount of DBU followed by reaction with IBX furnished the bicyclic compound **4**, through urethane **3**, setting the stage for the investigation of the removal of the pMP group. In accord with literature precedent,[11] pMP cleavage using ceric ammonium nitrate (CAN), followed by treatment with 2 N NaOH led cleanly to the cis-1,2-amino alcohol **6** through the intermediacy of cyclic carbonate **5** (78 % overall yield from **4**, Scheme 2).



Scheme 2. IBX-Mediated synthesis of *cis*-1,2-amino alcohols (such as **6**) from allylic alcohols (like **1**) using *p*-methoxyphenyl isocyanates (such as **2**). CAN = cerium(IV) ammonium nitrate, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

Having established the viability of the pMP group in this reaction, we set out to explore its reactivity profile in the context of diverse carbohydrate-based scaffolds. Our first attempt (Scheme 3), which utilized the D-glucal-derived substrate **7**,[12] successfully led to protected amino sugar **8** in 72 % yield over three steps.

The generality and scope of this sequence is underscored by the considerable number of substrates (**9**–**19**) successfully employed so far to prepare useful building blocks (**20**–**30**), as shown in Table 1. The reactions consistently provide one



Scheme 3. IBX-Mediated synthesis of amino sugar derivative **8** from carbohydrate **7**. Reagents and conditions: a) pMeOC$_6$H$_4$NCO (**2**, 1.1 equiv), DBU (0.1 equiv), CH_2Cl_2, 25 °C, 1 h, 95 %; b) IBX (2.0 equiv), THF:DMSO (10:1), 90 °C (sealed tube), 8 h; then IBX (2.0 equiv), 8 h, 84 %; c) CAN (5.0 equiv), CH_3CN:H_2O (3:1), 25 °C, 30 min, 90 %.

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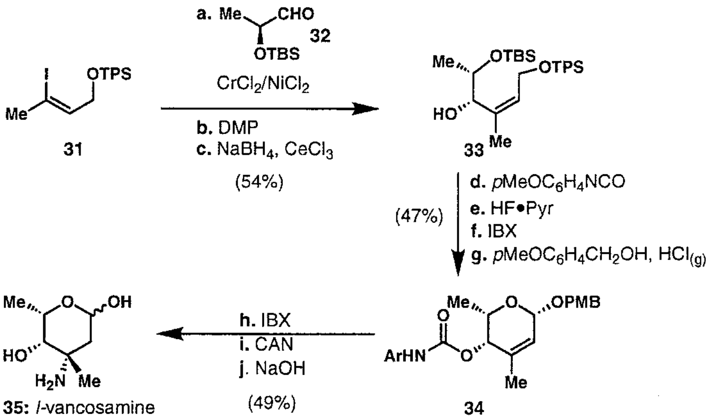
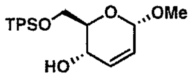
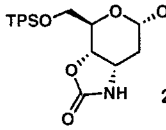
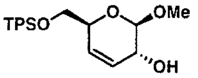
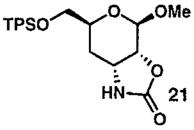
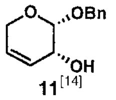
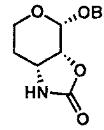
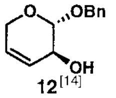
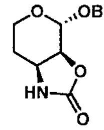
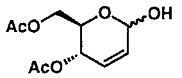
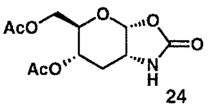
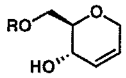
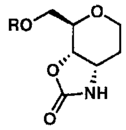
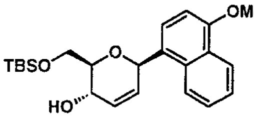
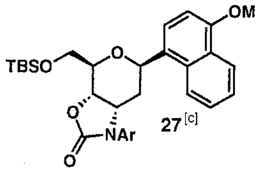
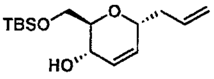
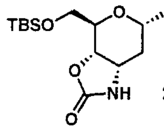
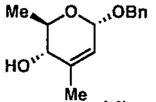
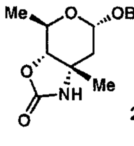
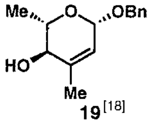
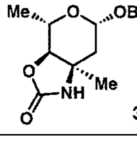
isomer (*cis*) of the protected cyclic urethane in excellent yield, and the ensuing deprotection occurs with similar efficiency to afford the parent urethanes. Base-labile (entries 5 and 6, Table 1), acid-sensitive (entries 7–11, Table 1), and sterically bulky (entry 8, Table 1) functionalities have no effect on the efficiency or stereoselectivity of the reaction. Despite the presence of an additional double bond in **17**[17] (entry 9, Table 1), the reaction proceeds with complete chemo- and stereoselectivity in high yield. In this process, rather than utilizing classical electrophiles (such as I^+, Br^+, $PhSe^+$) to invoke reactivity, the use of IBX selectively activates the nitrogen atom of anilides to react with a nearby olefin, thereby tolerating a wide range of functionalities. Enhanced substitution on the olefin does not deter the IBX-mediated cyclization, thus leading to quaternary centers with equal facility and efficiency (entries 10 and 11, Table 1).

Prompted by the obvious potential of this reaction in the construction of rare amino sugars, and in order to demonstrate its utility in natural product synthesis, we designed an expeditious synthesis of *l*-vancosamine (**35**, Scheme 4),[19] a prototypical natural amino sugar found on vancomycin's structure. Thus, intermolecular Kishi–Nozaki coupling[20] of building blocks vinyl iodide **31**[21] and **32**[22] led to a 1.3:1 mixture of alcohols which was immediately oxidized (with DMP) and subjected to Luche reduction[23] ($NaBH_4$/$CeCl_3$) to furnish, selectively, only the desired isomer (**33**, 54% overall from **31**). Reaction of alcohol **33** with *p*-methoxyphenyl isocyanate in the presence of catalytic amounts of DBU, followed by global deprotection (with HF · py), selective primary alcohol oxidation (by IBX), and protection of the anomeric hydroxyl group with a PMB protecting group afforded cyclization precursor **34** in 47% overall yield from **33**. IBX-induced cyclization and CAN-mediated removal of both the pMP and PMB groups, followed by basic hydrolysis, completed the stereocontrolled synthesis of *l*-vancosamine



Scheme 4. IBX-Mediated synthesis of *l*-vancosamine (**35**) from building blocks **31** and **32**. Reagents and conditions: a) $CrCl_2$ (4.0 equiv)/$NiCl_2$ (0.04 equiv), DMSO, 25 °C, 12 h, 61%; b) DMP (1.2 equiv), $NaHCO_3$ (5.0 equiv), CH_2Cl_2, 25 °C, 30 min, 98%; c) $NaBH_4$ (1.0 equiv), $CeCl_3$ (1.0 equiv), MeOH, −20 °C, 90%; d) pMeOC$_6$H$_4$NCO (**2**, 2.0 equiv), DBU (0.3 equiv), CH_2Cl_2, 25 °C, 5 h, 86%; e) HF · Pyr (5.0 equiv), THF, 25 °C, 5 h, 90%; f) IBX (1.2 equiv), THF/DMSO (10:1), 25 °C, 20 min, 79%; g) pMeOC$_6$H$_4$OH (**2**, 10.0 equiv), $HCl_{(g)}$, CH_2Cl_2, 0 °C, 30 min, 77%; h) IBX (4.0 equiv), $NaHCO_3$ (4.4 equiv), THF/DMSO (10:1), 90 °C (sealed tube), 24 h, 76%; i) CAN (3.0 equiv), CH_3CN/H_2O (5:1), 3 h, 92%; j) NaOH (3 N), 90 °C, 1 h, 70%. DMP = Dess–Martin periodinane, Pyr = pyridine.

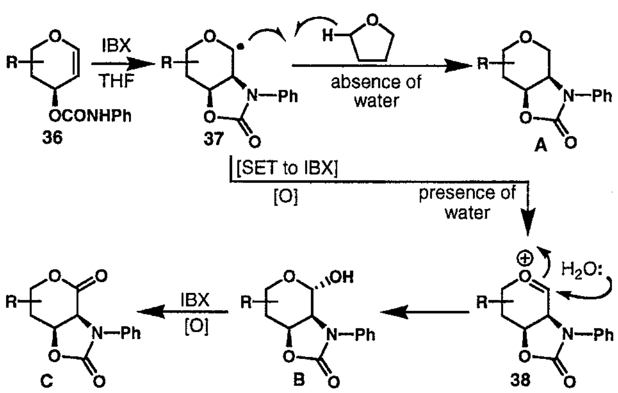
Table 1. IBX-Mediated synthesis of amino sugar derivatives from allylic alcohols and aryl isocyanates (ArNCO).

Entry	Allylic alcohol	Protected amino sugar	Yield [%, overall][a]
1	 **9**[13]	 **20**	79
2	 **10**[13]	 **21**	76
3	 **11**[14]	 **22**	74
4	 **12**[14]	 **23**	83
5	 **13**[12]	 **24**	60
6	 R = Bz **14**[15]	 **25**	80
7	R = TBS **15**[15]	**26**[b]	80
8	 **16**[16]	 **27**[c]	83[e]
9	 **17**[17]	 **28**	80
10	 **18**[18]	 **29**[d]	66
11	 **19**[18]	 **30**[d]	68

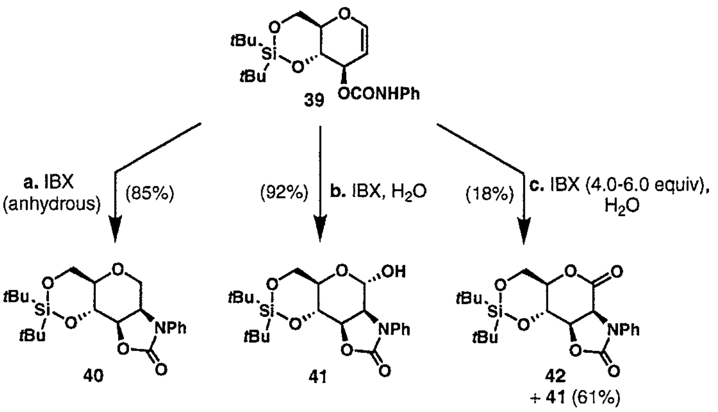
[a] Yields are for chromatographically and spectroscopically pure compounds. Reagents and conditions: a) pMeOC$_6$H$_4$NCO (1.1 equiv), DBU (0.1–0.3 equiv), CH_2Cl_2, 25 °C, 5 min–8 h; b) IBX (4.0 equiv), THF:DMSO (10:1), 90 °C (sealed tube), 3–12 h, then IBX (2.0–4.0 equiv), 3–12 h; c) CAN (3.0–5.0 equiv), CH_3CN:H_2O (3–5:1), 0–25 °C. Compounds **22**–**26** were also converted to the parent amino sugars upon treatment with 2–3 N NaOH (90 °C, 30 min) in 85–95% isolated yield. [b] $NaHCO_3$ (4.0 equiv) was added to prevent TBS cleavage (approximately 10%). [c] The CAN reaction was not performed due to the presence of the napthalene ring. [d] $NaHCO_3$ (4.0 equiv) was added as a buffer to prevent cleavage of the surprisingly labile benzyl functionality. [e] Yield over two steps (see footnote [c]).

(**35**; ten steps; 13% overall yield from the readily available aldehyde **32**). To the best of our knowledge, this sequence constitutes one of the shortest syntheses reported for **35** to date[24] and attests to the efficiency of the present technology for amino sugar construction.

Intrigued by the possibility of engaging glycals in this reaction, and in order to extend the scope of the present reaction technology, we proceeded to explore their reactivity towards IBX. Based on a revised mechanistic proposal for the IBX reaction[1f] with unsaturated urethane substrates and related systems, we reasoned that a prototypical glycal would undergo single electron transfer (SET), loss of a proton, rearomatization, and 5-exo-trig cyclization, as depicted for the simple substrate[1f] in Scheme 5; a glycal such as **36** would, therefore, lead to **37** (Scheme 6). In the absence of water, we expected hydrogen abstraction to proceed as usual to give deoxy amino sugar **A** (Scheme 6). However, since radical species **37** is stabilized, we entertained the possibility that SET to IBX would lead to the oxonium species **38**. In the presence of water (the efficiency of IBX is only slightly decreased in the presence of excess water) such a species would be rapidly intercepted giving rise to the amino sugar **B**. Finally, further oxidation by excess IBX could be envisioned as a conceivable entry into amino sugar lactones such as **C**.

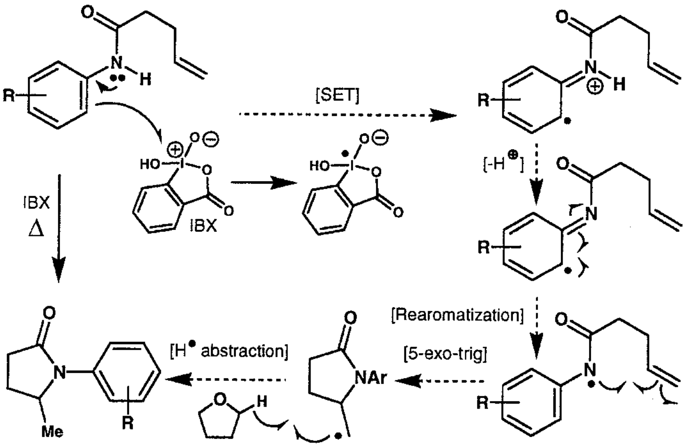


Scheme 6. Mechanistic blueprint for the reactions of IBX with glycals.



Scheme 7. Formation of three different products (**41**, **42**, **43**) at will from glucal urethanes (**40**) and IBX. Reagents and conditions: a) IBX (2.0 equiv), THF, 90°C (sealed tube), 8 h, then IBX (2.0 equiv), 8 h, 85%; b) IBX (2.0 equiv), THF:DMSO:H_2O (10:1:0.05), 12 h, 90°C, 92%; c) IBX (6.0 equiv), THF:H_2O (100:1), 8 h, 90°C (sealed tube), then IBX (6.0 equiv), 8 h, 73%.

Thus, utilizing D-glucal-derived **39**,[25] we investigated the plausibility of such a bold mechanistic hypothesis (Scheme 7).[26] As expected, the 1-deoxy amino sugar **40** was produced in excellent yield in the absence of water. Furthermore and much to our delight, reaction of **39** in the presence of water led to crystalline **41** with complete control of the two newly formed stereocenters and in 92% yield (see Figure 1 for X-ray structure of **41** and Table 2 for selected physical properties of **40** and **41**). Further reaction with excess IBX furnished the lactone **42** in 18% yield (accompanied by 61% of **41**). These key observations led us to probe the generality



Scheme 5. Revised mechanistic considerations for the IBX reaction. SET = single electron transfer.

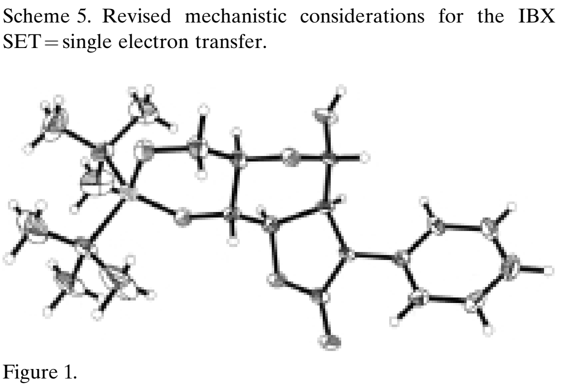


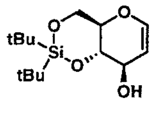
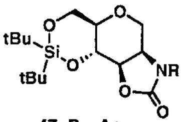
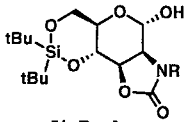
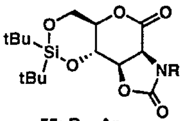
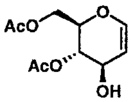
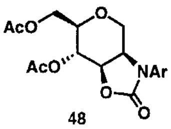
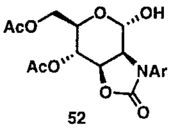
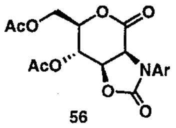
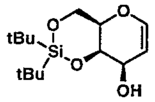
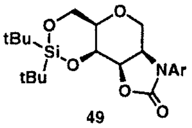
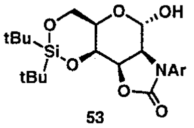
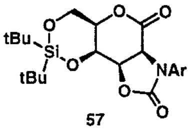
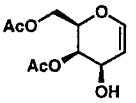
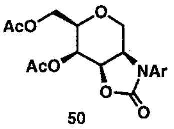
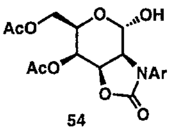
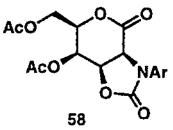
Figure 1.

Table 2. Selected physical properties of compounds **40** and **41**.

40: $R_f = 0.31$ (silica gel, diethyl ether: hexane 1:1); $[\alpha]_D = -96.0°$ (c = 0.30, MeOH); IR (film): $\tilde{\nu}_{max} = 2921$, 2851, 1680, 1651, 1453, 1394, 1132, 1103, 1016 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz): $\delta = 7.45-7.41$ (m, 2H), 7.29 (brt, $J = 7.9$ Hz, 1H), 7.20–7.17 (m, 2H), 4.61 (t, $J = 7.4$ Hz, 1H), 4.38 (dd, $J = 7.4, 2.6$ Hz, 1H), 4.18 (dd, $J = 10.5, 5.3$ Hz, 1H), 4.15–4.11 (m, 2H), 3.87 (t, $J = 10.5$ Hz, 1H), 3.65 (dd, $J = 13.6, 2.6$ Hz, 1H), 3.30–3.25 (m, 1H), 1.07 (s, 9H), 1.01 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 169.0$, 137.6, 128.0 (2C), 125.0 (2C), 124.6, 76.9, 76.0,73.6, 66.1,64.2, 57.7, 29.7, 27.4 (3C), 27.0 (3C), 22.7; HRMS (MALDI) m/z: calcd for $C_{21}H_{31}NO_5SiNa$ $[M + Na^+]$ 428.1864, found 428.1873.

41: Colorless needles; m.p. 118–119°C; $R_f = 0.31$ (silica gel, ethyl ether: hexane 1:1); $[\alpha]_D = -133.3°$ (c = 0.09, MeOH); IR (film) $\tilde{\nu}_{max} = 3400$, 2933, 2859, 1736, 1596, 1503, 1473, 1394, 1306, 1208, 1097, 1020, 971, 847, 826, 764, 694, 654 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): $\delta = 7.41$ (t, $J = 6.5$ Hz, 2H), 7.29–7.22 (m, 3H), 5.22 (s, 1H), 4.71 (t, $J = 6.4$ Hz, 1H), 4.52 (d, $J = 6.4$ Hz, 1H), 4.15–4.06 (m, 3H), 4.00 (m, 1H), 3.86–3.81 (m, 2H), 1.07 (s, 9H), 1.01 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta = 159.8$, 158.4, 156.2, 129.0, 125.5 (2C), 114.8 (2C), 90.2, 84.3, 80.4, 75.6, 66.8, 65.3, 55.8, 27.8, 27.1; HRMS (MALDI) m/z: calcd for $C_{21}H_{31}NO_6Si$ $[M + H^+]$ 422.2024, found 422.2023.

Table 3. IBX-Mediated synthesis of 1-deoxy amino sugars, amino sugars, and amino sugar lactones from glycals and aryl isocyanates (ArNCO).

Entry	Glycal	1-deoxy amino sugar	Yield [%, overall][a]	Amino sugar	Yield [%, overall][a]	Amino sugar lactone	Yield [%, overall][a,c]
1	 **43**	 **47**: R = Ar **59**: R = H (85%)[b]	72	 **51**: R = Ar **60**: R = H (67%)[b]	81	 **55**: R = Ar **61**: R = H (72%)[b]	12
2	 **44**	 **48**	68	 **52**	73	 **56**	18
3	 **45**	 **49**	76	 **53**	78	 **57**	8
4	 **46**	 **50**	71	 **54**	81	 **58**	16

[a] Yields are for chromatographically and spectroscopically pure compounds. Reagents and conditions are as shown in Scheme 6 for **39**. [b] See Table 1 for reagents and conditions. [c] See text.

and scope of these controllable cascade reactions for the construction of diverse libraries of amino sugar derivatives from glycals.

As shown in Table 3 (Ar = pMP), the reaction is notably general for a range of glucal- and galactal-derived glycal substrates. Furthermore, by using pMP substitution (see above) the rapid and efficient removal of the aromatic residue is achievable (for example from **47** to **59**, **51** to **60**, and **55** to **61**; Table 3). These IBX-mediated routes to 1-deoxy amino sugar and amino sugar derivatives have been proven general and highly efficient. The direct, one-pot entry into the lactone series of compounds is, however, low yielding (Table 3); in such cases a stepwise approach is recommended. The success of this reaction, which was designed based on the mechanistic rationale shown in Schemes 6 and 7 lends credence to the proposed mechanism[1f, 26] and opens the door for further explorations.

To summarize, the cyclization of *N*-arylcarbamates onto olefins, orchestrated by IBX, exemplifies a new and general synthetic technology for the rapid and stereoselective preparation of a diverse array of amino sugar building blocks and compound libraries for biological screening. The unprecedented reactivity of IBX with glycals to allow programmable formation of three types of products from a single starting material, based merely on the presence or absence of water and the stoichiometry of the reagent, is a further demonstration of the unique and exciting potential of this reagent in organic synthesis. The amino sugar derivatives reported herein may prove interesting ligands for a variety of biological targets due to their higher lipophilicity than the naked amino sugars. Studies to elucidate the precise mechanism of these IBX-mediated processes, further exploration of DMP[1e] to generate novel carbohydrate-based polycycles, and investigations directed at the development of solid-phase versions of these new reactions suitable for high speed combinatorics (combinatorial synthesis) are in progress.

Experimental Section

CAUTION! IBX is explosive under impact or on heating to >200 °C. (See Ref. [7] and J. B. Plumb, D. J. Harper, *Chem. Eng. News* **1990**, *July 16*, 3.)

Substrates in Table 1 were prepared using the procedure reported in Ref. [7f]. Preparation of 1-deoxy amino sugar derivatives from glycals (Table 3): IBX (2.0 equiv) was added to a solution of **39** (0.1 mmol) in anhydrous THF (4 mL). The solution was placed in a sealed tube and heated for 6 h at 90 °C, followed by another addition of IBX (2.0 equiv) and heating for another 6–8 h at the same temperature. The reaction mixture was diluted with EtOAc, washed with 5% aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated. After purification by flash chromatography (silica, EtOAc: hexane 1:2), compound **40** was obtained in 85% yield. We prepared **41** in an identical manner to **40**, except THF:H_2O (50:1) was employed.

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[1] For some recent examples, see: a) K. C. Nicolaou, S. Snyder, A. Bigot, J. Pfefferkorn, *Angew. Chem.* **2000**, *112*, 1135–1138; *Angew. Chem. Int. Ed.* **2000**, *39*, 1093–1096; b) K. C. Nicolaou, H. J. Mitchell, K. C. Fylaktakidou, H. Suzuki, R. Rodriguez, *Angew. Chem.* **2000**, *112*, 1131–1135; *Angew. Chem. Int. Ed.* **2000**, *39*, 1089–1093; c) J. A. Pfefferkorn, G.-Q. Cao, *Angew. Chem.* **2000**, *112*, 750–755; *Angew. Chem. Int. Ed.* **2000**, *39*, 734–739; d) K. C. Nicolaou, J. A. Pfefferkorn, G.-Q. Cao, *Angew. Chem.* **2000**, *112*, 755–759; *Angew. Chem. Int. Ed.* **2000**, *39*, 739–743; e) K. C. Nicolaou, Y.-L. Zhong, P. S. Baran, *Angew. Chem.* **2000**, *112*, 636–639; *Angew. Chem. Int. Ed.* **2000**, *39*, 622–625; f) K. C. Nicolaou, Y.-L. Zhong, P. S. Baran, *Angew. Chem.* **2000**, *112*, 639–642; *Angew. Chem. Int. Ed.* **2000**, *39*, 625–628; g) D. S. Tan, M. A. Foley, B. R. Stockwell, M. D. Shair, S. L. Schreiber, *J. Am. Chem. Soc.* **1999**, *121*, 9073–9087; h) D. Lee, J. K. Sello, S. L. Schreiber, *J. Am. Chem. Soc.* **1999**, *121*, 10648–10649; i) D. S. Tan,

M. A. Foley, M. D. Shair, S. L. Schreiber, *J. Am. Chem. Soc.* **1998**, *120*, 8565 – 8566; for reviews of molecular diversity, see: j) *Comb. Chem. Mol. Diversity Drug Discovery* (Eds.: E. M. Gordon, J. F. Kerwin, Jr.), Wiley, New York, **1998**, p. 516; R. E. Dolle, *Mol. Diversity* **1998**, *3*, 199 – 233; R. E. Dolle, K. H. Nelson, Jr., *J. Comb. Chem.* **1999**, *1*, 235 – 282; H. Fenniri, *Curr. Med. Chem.* **1996**, *3*, 343 – 378.

[2] For a recent review, see: K. C. Nicolaou, D. Vourloumis, N. Winssinger, P. S. Baran, *Angew. Chem.* **2000**, *112*, 46 – 126; *Angew. Chem. Int. Ed.* **2000**, *39*, 44 – 122.

[3] For a comprehensive discussion, see: *The Practice of Medicinal Chemistry* (Ed.: C. G. Wermuth), Academic Press, London, **1996**, p. 968.

[4] For selected reviews, see: a) M. S. Lee, H. Nakanishi, M. Kahn, *Curr. Opin. Drug Discovery Dev.* **1999**, *2*, 332 – 341; b) P. J. Edwards, M. Gardner, W. Klute, G. F. Smith, N. K. Terrett, *Curr. Opin. Drug Discovery Dev.* **1999**, *2*, 321 – 331; c) C. D. Floyd, C. Leblanc, M. Whittaker, *Prog. Med. Chem.* **1999**, *36*, 91 – 168; d) S. Wilson, A. W. Czarnik, *Combinatorial Chemistry: Synthesis and Application*, Wiley, New York, **1997**, p. 314.

[5] For some recent examples, see: G. W. Plant, S. Woerly, A. R. Harvey, *Exp. Neurol.* **1997**, *143*, 287 – 299; M. Chatterjee, P. J. Smith, C. A. Townsend, *J. Am. Chem. Soc.* **1996**, *118*, 1938 – 1948; G. S. Jacob, *Front. Biomed. Biotechnol.* **1993**, *1*, 74 – 86.

[6] Anonymous in *Carbohydr. Chem. Vol. 30,* Royal Society of Chemistry, London, **1998**, pp. 123 – 140; J. Jurczak, *Prep. Carbohydr. Chem.* **1997**, 595 – 614.

[7] For the first preparation of IBX, see: C. Hartman, V. Meyer, *Chem. Ber.* **1893**, *26*, 1727; for a superior route to IBX, see: M. Frigerio, M. Santagostino, S. Sputore *J. Org. Chem.* **1999**, *64*, 4537 – 4538; for the introduction of the acronym "IBX", see: A. R. Katritzky, B. L. Duell, J. K. Gallos, *Org. Magn. Reson.* **1989**, *27*, 1007 – 1011; for use as a selective oxidant for alcohols, see: M. Frigerio, M. Santagostino, *Tetrahedron Lett.* **1994**, *35*, 8019 – 8022; E. J. Corey, A. Palani, *Tetrahedron Lett.* **1995**, *36*, 7945 – 7948.

[8] For an insightful review of this approach, see: S. Knapp, *Chem. Soc. Rev.* **1999**, *28*, 61 – 72.

[9] Although, with such a mode of reaction as that shown in Scheme 1, one might expect *cis* delivery to the olefin, *trans* addition is also conceivable in certain cases. In the absence of a definitive mechanistic trend for this IBX-mediated reaction at the outset of this work, it was left to empirical observation to provide the answer as to the stereochemical outcome.

[10] The aryl moiety and nitrogen atom of the carbamate group are intimately involved in this IBX reaction, see Ref. [1f] for more details.[26]

[11] D. R. Kronenthal, C. Y. Han, M. K. Taylor, *J. Org. Chem.* **1982**, *47*, 2765 – 2768; S. Knapp, P. J. Kukkola , S. Sharma, *J. Org. Chem.* **1990**, *55*, 5700 – 5710.

[12] H. H. Baer, L. Siemsen, J. DaFaye, K. Burak, *Carbohydr Res.* **1984**, *134*, 49 – 61. The α- and β-isomers of this pyranose were separated after reaction with DBU and p-methoxyphenyl isocyanate (α-anomer used in Scheme 3; β-anomer used in entry 5, Table 1).

[13] Compounds **9** and **10** were derived from methyl-α-D-mannose pyranoside and methyl-β-D-galactose pyranoside, unpublished results.

[14] Compounds **11** and **12** were derived from *l*-arabinose, unpublished results..

[15] K. C. Nicolaou, C. K. Hwang, B. E. Marrow, S. A. DeFrees, E. A. Couladouros, Y. Abe, P. J. Carrol, J. Snyder, *J. Am. Chem. Soc.* **1990**, *112*, 3040 – 3054.

[16] M. Brakta, G. Massiot, G. D. Sinou, G. Daves, *J. Org. Chem.* **1993**, *58*, 2992 – 2998.

[17] G. F. Bordwell, S. R. Mrozack, *J. Org. Chem.* **1982**, *47*, 3802 – 3803.

[18] Compounds **18** and **19** were derived from ethyl *l*-lactate, unpublished results.

[19] A. W. Johnson, R. M. Smith, R. D. Guthrie, *J. Chem. Soc. Perkin Trans. 1* **1972**, *17*, 2153 – 2159; W. D. Weringa, D. H. Williams, J. Feeny, J. P. Brown, R. W. King, *J. Chem. Soc. Perkin Trans. 1* **1972**, *3*, 443 – 446.

[20] a) K. Takai, K. Kimura, T. Kuroda, T. Hiyama, H. Nozaki, *Tetrahedron Lett.* **1983**, *24*, 5281 – 5284; b) H. Jin, J. Uenishi, W. J. Christ, Y. Kishi, *J. Am. Chem. Soc.* **1986**, *108*, 5644 – 5646.

[21] X. Lu, G. Zhu, S. Ma, *Chin. J. Chem.* **1993**, *11*, 267 – 271.

[22] Prepared in two steps from ethyl *l*-lactate by TBS protection (TBSCl, imidazole) and DIBAL reduction (toluene, – 78 °C).

[23] J.-L. Luche, *J. Am. Chem. Soc.* **1978**, *100*, 2226 – 2227.

[24] For selected syntheses of *l*-vancosamine and derivatives thereof, see: a) T. T. Thang, F. Winternitz, *J. Chem. Soc. Chem. Commun.* **1979**, 153 – 154; b) I. Dyong, H. Friege, *Chem. Ber.* **1979**, *112*, 3273 – 3281; c) T. T. Thang, F. Winternitz, *Tetrahedron Lett.* **1980**, *21*, 4495 – 4498; d) H. I. Ahmad, J. S. Brimacombe, A. S. Mengech, L. C. N. Tucker, *Carbohydr. Res.* **1981**, *93*, 288 – 293; e) I. Dyong, H. Friege, H. Luftmann, H. Merten, *Chem. Ber.* **1981**, *114*, 2669 – 2680; f) G. Fronza, C. Fuganti, P. Grasselli, G. Pedrocchi-Fantoni, *Tetrahedron Lett.* **1981**, *22*, 5073 – 5076; g) J. S. Brimacombe, A. S. Mengech, K. M. M. Rahman, L. C. N. Tucker, *Carbohydr. Res.* **1982**, *110*, 207 – 215; h) G. Fronza, C. Fuganti, P. Grasselli, G. Pedrocchi-Fantoni, *J. Carbohydr. Chem.* **1983**, *2*, 225 – 248; i) Y. Hamada, A. Kawai, T. Shioiri, *Tetrahedron Lett.* **1984**, *25*, 5413 – 5414; j) F. M. Hauser, S. R. Ellenberger, *J. Org. Chem.* **1986**, *51*, 50 – 57; k) I. Dyong, J. Weigand, J. Thiem, *Liebigs Ann. Chem.* **1986**, 577 – 599; l) A. Klemer, H. Wilbers, *Liebigs Ann. Chem.* **1987**, 815 – 823; m) Y. Hamada, A. Kawai, T. Matsui, O. Hara, T. Shioiri, *Tetrahedron* **1990**, *46*, 4823 – 4846; n) R. Greven, P. Jutten, H.-D. Scharf, *Carbohydr. Res.* **1995**, *275*, 83 – 93; o) K. C. Nicolaou, H. J. Mitchell, F. L. van Delft, F. Rübsam, R. M. Rodríguez, *Angew. Chem.* **1998**, *110*, 1972 – 1974; *Angew. Chem. Int. Ed.* **1998**, *37*, 1871 – 1874.

[25] J. O. Hoberg, *Carbohydr. Res.* **1997**, *300*, 365 – 367.

[26] Extensive mechanistic studies dealing with the interactions of periodinanes with anilides will be reported in due course.

[27] Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-142005. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

Novel Reactions Initiated by Titanocene Methylidenes: Deoxygenation of Sulfoxides, *N*-Oxides, and Selenoxides[**]

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Scott A. Snyder, and Klaus B. Simonsen

Over the course of the past several years, sulfoxides have become an increasingly important functional group in organic synthesis, particularly as chirons in asymmetric synthesis.[1] As

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