Site-Selective Oxidation and Metal-Induced 2-Propynylation of Pyranose Derivatives en route to Tetrodotoxins

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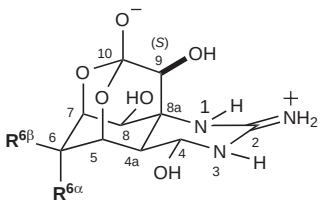
To the memory of Dr. Juan Carlos del Amo, victim of the vile terrorist attack of March 11th.

Abstract: The radical-based site-selective oxidation of 2-hydroxyethyl acetals and the metal(Zn,Ti)-induced 2-propynylation of aldehydes can both be carried out successfully on highly functionalized oxygenated substrates, as demonstrated in the context of a synthetic plan for tetrodotoxin and its analogues, for which promising synthetic intermediates were prepared from D-mannopyranoses.

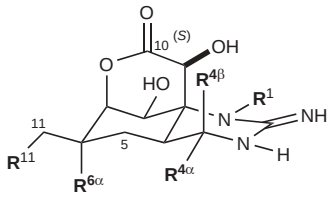
Key words: radical oxidation, acetal hydrolyses, aldehyde addition, 2-propynylation, tetrodotoxin

As aptly stated by Du Bois,[1] tetrodotoxin (TTX, **1a**, Figure 1) is one of the nature's great marvels. Its complex structure, featuring a highly heteroatomic core that contains unique *ortho*-acid and guanidine-aminal functionalities, continues to be a most attractive and challenging target offering clear opportunities for synthetic development.[2–4] In this context, as part of a project directed towards the development of a practical synthesis of tetrodotoxin and its natural analogues **1a**–**k** starting from D-mannopyranoses **I** (Scheme 1), we have explored the feasibility of several transformations which include the metal-mediated addition of three carbon unsaturated units to aldehydes of type **III** and the selective oxidation of the anomeric position, the precursor of C10 in the targets, to a spiro-orthoester.



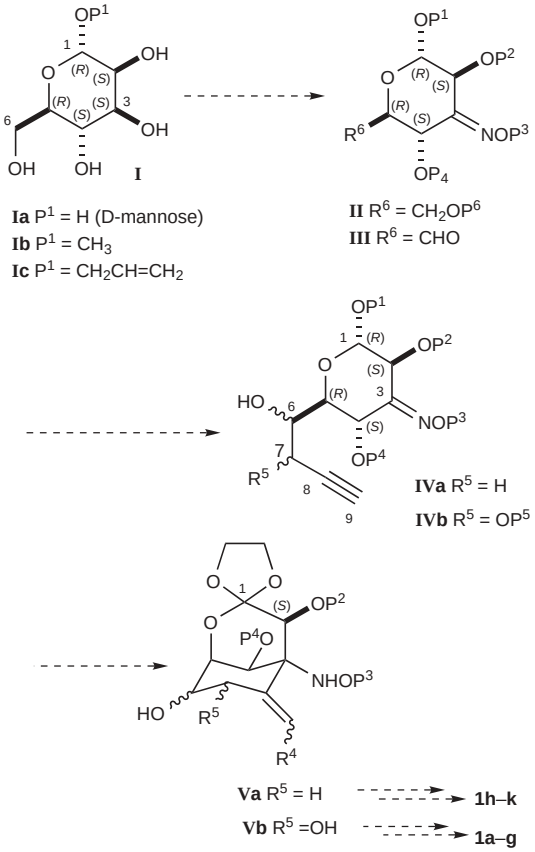
1a Tetrodotoxin (TTX): $R^{6\alpha}$ = OH, $R^{6\beta}$ = CH_2OH

1b–g $R^{6\alpha}$ and $R^{6\beta}$ = H, OH, CH_3, CH_2OH, CHO **or** $CH(OH)CH(NH_2)CO_2H$



1h–k 5-deoxy-TTX analogues:
R^1, $R^{4\alpha}$, $R^{4\beta}$, $R^{6\alpha}$ and R^{11} = H **or** OH

Figure 1 Structure of tetrodotoxin, and substitution variability observed to date among its natural analogues.



Ia P^1 = H (D-mannose)
Ib P^1 = CH_3
Ic P^1 = $CH_2CH{=}CH_2$

II R^6 = CH_2OP^6
III R^6 = CHO

IVa R^5 = H
IVb R^5 = OP^5

Va R^5 = H → **1h–k**
Vb R^5 = OH → **1a–g**

Scheme 1 Synthetic proposal for tetrodotoxin (**1a**) and its analogues **1b**–**k** starting from mannopyranoses **I**; sugar numbering is used.

Implementation of the proposed synthetic plan first required adequate differential manipulation of all hydroxyl groups in the starting d-mannopyranoses **I** to allow access to aldehydes of type **III**. This was initially attempted from **Ia** through bicyclic derivative **2b** (Scheme 2, *Route A*): protection of positions C1 and C6 in the form of a 1,6-anhydro bridge[5] allowed efficient functionalization of C3 by regioselective oxidation of an O2-O3 stannylene intermediate followed by ketoxime ether formation (**2b** → **3**).[6]

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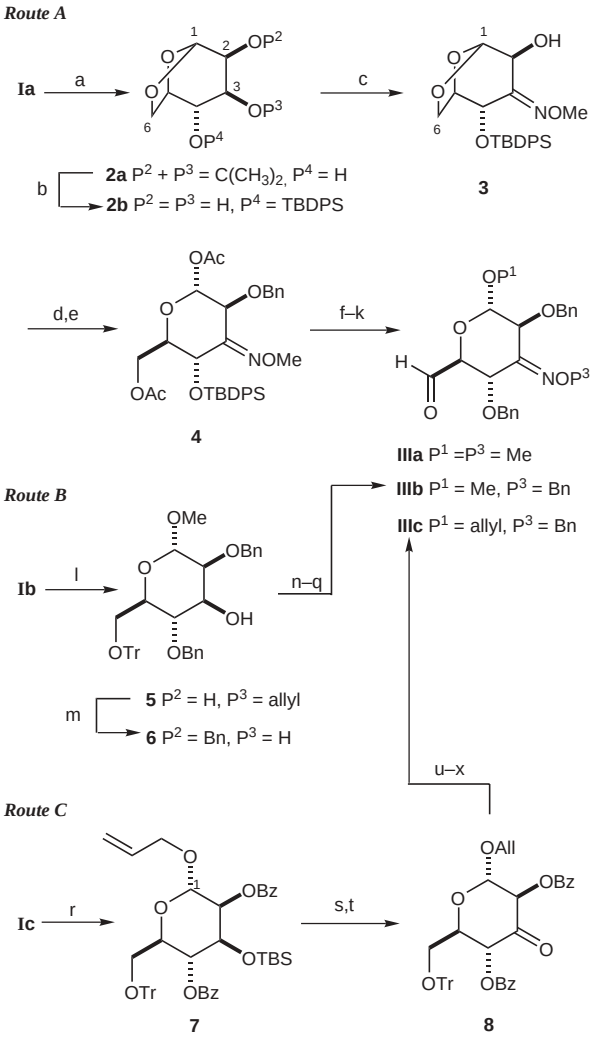
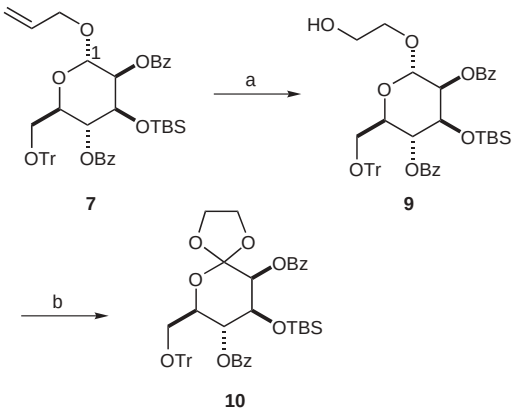
After considerable experimentation, appropriate differentiation of positions 1 and 6 of alcohol **3** was efficiently achieved via its benzyl ether derivative by acylium-ion-promoted opening of the ether bridge followed by selective hydrolysis of the resulting diacetate **4** at the anomeric position. Final access to the desired C6-aldehyde **IIIa** required five additional steps (g–k), a total of 14 from D-mannose **Ia**.



Scheme 2 Three routes for the preparation of intermediates of type **III** from mannopyranoses **I**. *Reagents and conditions:* ***Route A***: (a) 2 steps, 29% overall, ref.[5]; (b) and (c) 2 steps each, 71% overall, ref.[6]; (d) BnBr, NaH, TBAI, THF, r.t., 91%; (e) Et_3SiOTf, Ac_2O, 0 °C, 98%; (f) NH_3 (g), THF–MeOH, 89% (g) MeI, NaH, DMF, 0 °C, 90%; (h) K_2CO_3, MeOH, r.t., 69%; (i) BnBr, NaH, TBAI, THF, 0 ºC to r.t., 51%; (j) TBAF, THF, –78 ºC to r.t., 70%; (k) Dess–Martin periodinane, *t*-BuOH, MeCN, r.t., 97%. ***Route B***: (l) and (m) 2 steps each, 25% overall, ref.[7]; (n) PCC, sieves, r.t., 74%; (o) NH_2OBn, PPTS, $PhCH_3$, 80 ºC, 72%; (p) $FeCl_3{\cdot}6H_2O$, CH_2Cl_2, r.t., 82%; (q) Dess–Martin periodinane, *t*-BuOH, MeCN, r.t. ***Route C:*** (r) 3 steps one-pot reaction, 79% overall, ref.[8]; (s) 30% HF·pyridine, THF–pyridine (9:1), r.t., 50%; (t) PCC, sieves, CH_2Cl_2, r.t., 72%; (u) NH_2OBn, PPTS, $PhCH_3$, 70 ºC, 77%; (v) $FeCl_3{\cdot}6H_2O$, CH_2Cl_2, r.t., quant.; (x) Dess–Martin periodinane, *t*-BuOH, MeCN, r.t., 41%.

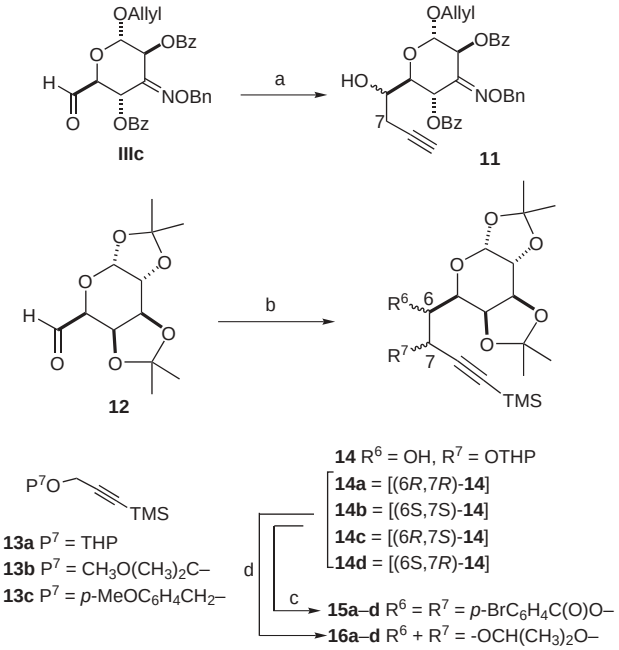
We consequently studied alternative syntheses. As a result, two new sequences were developed which allowed preparation of aldehydes **IIIb** and **IIIc** through intermediates **6**[7] and **7**[8] in just 8 steps from mannopyranosides **Ib** and **Ic** (Scheme 2, *Route B* and *Route C*). *Route C*[9] is particularly appealing because it features a most desirable tin-free three-step one-pot protection protocol **Ic** → **7**, and protection of the anomeric position by an allyl group; a structural element which proved to allow selective oxidation at C1 to form a precursor of the C10 lactone center of the final product. In the case of intermediate **7**, for example, conversion to **9** followed by Suarez's alkoxy radical forming conditions, furnished orthoester **10** (Scheme 3).[10a] Besides sustaining the proposed synthetic scheme for tetrodotoxin and its analogs, the conversion of **7** to **10** shows that mixed acetals in which one of the acetal R group is allyl and the other is cyclized as in **7** are potential synthetic precursors of spiroorthoesters – and hence of lactones – even in complex systems with multiple ether links.[10b,11]



Scheme 3 Site-selective radical-based anomeric oxidation. *Reagents and conditions:* (a) i. OsO_4, NMO, H_2O–acetone; ii. $NaIO_4$–H_2O, EtOH–H_2O, $NaBH_4$, 72% overall; (b) I_2, DAIB, cyclohexane, hν, 47%.

With access to aldehydes of type **III**, we next studied the extension of the C6 chain. Use of propargyl bromide and Zn[12] proved convenient and compatible with all the other functionalities present. In this way the desired type **IVa** derivative **11** was obtained from **IIIc** (Scheme 4). While this elongation directly opened the route to the 5-deoxy-TTX analogues **1h–k**, its application to TTX itself and to **1b–g** would require the presence of a hydroxyl group at C7 (sugar numbering) as well as that at C6, as in **IVb** (Scheme 1). Although this C7-hydroxyl could probably be introduced by oxidation at a later stage of the synthetic scheme, we decided to explore, as the final objective of this study, the direct construction of the C6-C7-diol system on a model sugar. For this we selected the known C6-aldehyde **12** and tested its reactivity against allenyltitanium species formed from a variety of TMS-protected propargylic alcohol precursors **13**; a type of reaction that is virtually unexplored in the case of heavily oxygenated substrates (Scheme 4).[13a] While in our hands **13b** [**13**,

P^7 = $CH_3O(CH_3)_2C$-] proved too acid-labile and **13c** (**13**, P^7 = *p*-$MeOC_6H_4CH_2$-) inappropriate for allenyltitanium formation, good results were obtained with **13a**, which afforded the tetrahydropyranyl-monoprotected diols **14** in 60% yield. The stereochemical outcome of the process favored the *threo* isomers **14a** and **14b** over their *erythro* analogues, in keeping with the accepted reaction model.[13b] Structural determination of **14a**–**d** was first attempted applying the CD exciton chirality method[14] to the *p*-bromobenzoates **15a**–**d**, with no success. The configuration of the monoprotected diols **14** at C6 and C7 was finally determined by conversion to their corresponding acetonides **16**: the major adduct was shown by X-ray crystallography to be the 6*R*,7*R*-diastereomer **16a**,[15] and comparative analysis of the ^{1}H NMR spectra then allowed the structural determination of **16b**–**d**, and hence of their precursors **14**.



Scheme 4 Metal-mediated 2-propargynylation of C6-sugar aldehydes (sugar numbering). *Reagents and conditions*: (a) $CHCCH_2Br$, Zn, THF–$NH_4Cl_{(aq)}$, 70 ºC, 64%; (b) i. **13a**, *t*-BuLi, THF, –78 ºC, 30 min; ii. $Ti(O\textit{i}\text{-}Pr)_4$, 10 min; iii. **12** in THF, 30 min at –78 ºC, then warm to r.t.; 60%; (c) i. camphorsulfonic acid (cat.), MeOH, 12 h, r.t.; ii. K_2CO_3, MeOH, r.t.; iii. *p*-BrC_6H_4COCl, DMAP, pyridine, 50 ºC; (d) 2,2-dimethoxypropane, *p*-TsOH (cat.), acetone.[16]

In conclusion, from a general synthetic perspective we have demonstrated that, through radical-based selective oxidation of their hydroxyalkyl derivatives under Suarez's conditions, allyl glycosides can afford spiro-orthoesters, the anomeric carbon becoming the spiro atom; and that the zinc- and titanium-mediated 2-alkynylation of heavily oxygenated aldehydes can proceed smoothly in the presence of ester and alkoxyimino functionalities to afford either homoallylic alcohols, such as **11**,[16] or the corresponding diol derivatives, **14**–**16**.[17] The feasibility of these two transformations augurs well for the preparation of tetrodotoxin and its analogues from D-mannose in accordance with the proposed synthetic plan. In particular, the second implies that the three routes to compounds **III** investigated in this work all give access to intermediates of type **IV**, which possess all the carbon atoms of the final targets except the hydroxymethyl C11 and the imine carbon C2, and also feature structural functionalities promising further progress towards these targets. These include an allyl group at C1 that, in view of the present results, should allow its easy conversion into the lactone center C10 of tetrodotoxins **2h**–**k**; and at C6 and C3 a vinyl radical precursor (the extended alkynyl chain) and a good radical acceptor (the ketoxime ether), which should allow formation of the cyclohexane ring.[6]

Acknowledgment

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References

(1) Du Bois and Hinman recently completed a total synthesis of enantiomerically pure tetrodotoxin: Hinman, A.; Du Bois, J. *J. Am. Chem. Soc.* **2003**, *125*, 11510.

(2) Besides Du Bois (ref. [1]), Isobe and co-workers also completed (for the first time) a total synthesis of tetrodotoxin in enantiomeric pure form: (a) Ohyabu, N.; Nishikawa, T.; Isobe, M. *J. Am. Chem. Soc.* **2003**, *125*, 8798. (b) The same group has just published an improved synthesis: Nishikawa, T.; Urabe, D.; Isobe, M. *Angew. Chem. Int. Ed.* **2004**, *43*, 4782.

(3) Kishi first reported a racemic total synthesis of tetrodotoxin: (a) Kishi, Y.; Aratani, M.; Fukuyama, T.; Nakatsubo, F.; Goto, T. *J. Am. Chem. Soc.* **1972**, *94*, 9217. (b) Kishi, Y.; Fukuyama, T.; Aratani, M.; Nakatsubo, F.; Goto, T. *J. Am. Chem. Soc.* **1972**, *94*, 9219.

(4) Other synthetic efforts toward tetrodotoxin include: (a) Ohtani, Y.; Shinada, T.; Ohfune, Y. *Synlett* **2003**, 619. (b) Taber, D. F.; Storck, P. H. *J. Org. Chem.* **2003**, *68*, 7768. (c) Itoh, T.; Watanabe, M.; Fukuyama, T. *Synlett* **2002**, 1323. (d) Noya, B.; Paredes, M. D.; Ozores, L.; Alonso, R. *J. Org. Chem.* **2000**, *65*, 5960. (e) Fraser-Reid, B.; Burgey, C. S.; Vollerthun, R. *Pure Appl. Chem.* **1998**, *70*, 285; and references therein.

(5) Zottola, M. A.; Alonso, R.; Vite, G. D.; Fraser-Reid, B. *J. Org. Chem.* **1989**, *54*, 6123.

(6) Noya, B.; Alonso, R. *Tetrahedron Lett.* **1997**, *38*, 2745.

(7) (a) Ogawa, T.; Sasajima, K. *Carbohydr. Res.* **1981**, *93*, 53. (b) Koto, S.; Inada, S.; Yoshida, T.; Toyama, M.; Zen, S. *Can. J. Chem.* **1981**, *59*, 255.

(8) Du, Y.; Zhang, M.; Kong, F. *Org. Lett.* **2000**, *2*, 3797.

(9) **Preparation of C6-Sugar Aldehydes of Type III (Route *C*: 7 → 8 → IIIc). Selected Data of Allyl 2,4-Bis-*O*-Benzoyl-3-keto-6-*O*-trytil-β-D-mannopyranoside (8):** ^{1}H NMR (250 MHz, $CDCl_3$, TMS): δ = 8.22–8.18 (m, 2 H, Ar*H*), 7.87–7.84 (m, 2 H, Ar*H*), 7.69–7.12 (m, 21 H, ArH), 6.18 (d, *J* = 10.4 Hz, 1 H, CH), 6.00–5.85 (m, 1 H, OCH_2CHCH_2), 5.47 (d, *J* = 1.9 Hz, 1 H, CH), 5.40–5.23 (m, 3 H, OCH_2CHCH_2 + CH), 4.39–4.25 (m, 2 H, OCH_2CHCH_2), 4.19–4.13 (m, 1 H, CH), 3.60 (dd, *J* = 10.4 Hz, *J* = 1.6 Hz, 1 H, CH_2), 3.33 (dd, *J* = 10.4 Hz, *J* = 3.8 Hz, 1 H, CH_2). ^{13}C NMR and DEPT (63 MHz): δ = 195.2 (CO), 164.5 (2 × CO), 143.5 (Ar), 133.8 (CH), 133.3 (CH), 132.6

(CH), 130.1 (CH), 129.9 (CH), 128.8 (Ar), 128.73 (CH), 128.70 (Ar), 128.5 (CH), 128.2 (CH), 127.8 (CH), 126.9 (CH), 118.5 (OCH_2CHCH_2), 98.4 (CH), 86.6 (C), 76.6 (CH), 72.53 (CH), 72.47 (CH), 68.5 (CH_2), 61.8 (CH_2). $[\alpha]_D^{25}$ +12.0 (*c* 1.2, $CHCl_3$).

Allyl 2,4-Bis-*O*-Benzoyl-3-benzyloximino-6-*O*-trytil-β-D-mannopyranoside: ^{1}H NMR (250 MHz, $CDCl_3$, TMS): δ = 8.16–8.12 (m, 2 H, Ar*H*), 7.86–7.83 (m, 2 H, ArH), 7.64–7.07 (m, 26 H, ArH), 6.49 (d, *J* = 1.4 Hz, 1 H, CH), 6.12 (d, *J* = 10.2 Hz, 1 H, CH), 6.00–5.87 (m, 1 H, OCH_2CHCH_2), 5.36–5.21 (m, 3 H, OCH_2CHCH_2 + CH), 5.03 (s, 2 H, $NOCH_2Ar$), 4.32–4.25 (m, 2 H, OCH_2CHCH_2), 4.16–4.08 (m, 1 H, CH), 3.46 (dd, *J* = 10.3 Hz, *J* = 1.9 Hz, 1 H, CH_2), 3.30 (dd, *J* = 10.3 Hz, *J* = 4.2 Hz, 1 H, CH_2). ^{13}C NMR and DEPT (63 MHz): δ = 165.1 (CO), 164.7 (CO), 146.9 (CNOBn), 143.6 (Ar), 137.3 (Ar), 133.4 (CH), 133.2 (CH), 132.9 (CH), 130.0 (CH), 129.8 (CH), 129.5 (Ar), 129.2 (Ar), 128.5 (CH), 128.1 (CH), 128.0 (CH), 127.7 (CH), 127.5 (CH), 126.8 (CH), 117.8 (OCH_2CHCH_2), 96.7 (CH), 86.4 (C), 76.5 ($NOCH_2Ar$), 71.5 (CH), 68.1 (CH_2), 66.1 (CH), 64.7 (CH), 62.0 (CH_2). $[\alpha]_D^{25}$ –11.2 (*c* 1.2, $CHCl_3$).

Allyl 2,4-Bis-*O*-Benzoyl-3-benzyloximino-β-D-mannopyranoside: ^{1}H NMR (250 MHz, $CDCl_3$, TMS): δ = 8.10–8.07 (m, 4 H, ArH), 7.66–7.26 (m, 11 H, ArH), 6.50 (d, *J* = 1.6 Hz, 1 H, CH), 6.05 (d, *J* = 10.0 Hz, 1 H, CH), 6.01–5.87 (m, 1 H, OCH_2CHCH_2), 5.38–5.24 (m, 2 H, OCH_2CHCH_2), 5.19 (d, *J* = 1.3 Hz, 1 H, CH), 5.11 (s, 2 H, $NOCH_2Ar$), 4.36–4.07 (m, 3 H, OCH_2CHCH_2 + CH), 3.93–3.80 (m, 2 H, CH_2). ^{13}C NMR and DEPT (63 MHz): δ = 165.4 (CO), 165.0 (CO), 146.6 (*C*NOBn), 137.2 (*Ar*), 133.5 (CH), 133.4 (CH), 133.0 (CH), 129.9 (CH), 129.3 (Ar), 129.0 (Ar), 128.5 (CH), 128.4 (CH), 128.2 (CH), 128.1 (CH), 127.6 (CH), 118.0 (OCH_2CHCH_2), 96.9 (CH), 76.6 ($NOCH_2Ar$), 72.1 (CH), 68.3 (CH_2), 65.6 (CH), 64.6 (CH), 61.6 (CH_2). MS (IQ^+ low resolution): *m/z* (%) = 532 (94) [M^+ + 1], 474 (100) [M^+ – OAllyl], 410 (71) [M^+ – Obz]. $[\alpha]_D^{25}$ –25.1 (*c* 1.2, $CHCl_3$).

1-*O*-Allyl-2,4-Bis-*O*-Benzoyl-3-deoxy-3-benzyloxyimino-6-aldehydo-β-D-arabino-hexopyranose (IIIc): ^{1}H NMR (250 MHz, $CDCl_3$, TMS): δ = 9.76 (d, *J* = 1.2 Hz, 1 H, CHO), 8.08–8.05 (m, 4 H, ArH), 7.64–7.44 (m, 6 H, ArH), 7.26–7.21 (m, 5 H, ArH), 6.46 (d, *J* = 1.4 Hz, 1 H, CH), 6.10 (d, *J* = 10.2 Hz, 1 H, CH), 5.88–6.04 (m, 1 H, OCH_2CHCH_2), 5.37–5.24 (m, 2 H, OCH_2CHCH_2), 5.09 (s, 2 H, $NOCH_2Ar$), 5.06–5.02 (m, 1 H, CH), 4.55 (d, *J* = 11.0 Hz, 1 H, CH), 4.33–4.15 (m, 2 H, OCH_2CHCH_2). ^{13}C NMR and DEPT (63 MHz): δ = 195.7 (CHO), 170.5 (CO), 164.9 (CO), 145.2 (*C*NOBn), 141.8 (CH), 136.9 (Ar), 133.3 (CH), 132.6 (CH), 131.8 (CH), 129.97 (Ar), 129.95 (CH), 129.91 (Ar), 128.5 (CH), 128.4 (CH), 128.2 (CH), 128.1 (CH), 127.9 (CH), 127.7 (CH), 118.4 (OCH_2CHCH_2), 97.0 (CH), 76.8 ($NOCH_2Ar$), 74.5 (CH), 68.8 (CH_2), 64.9 (CH), 64.2 (CH). $[\alpha]_D^{25}$ –17.5 (*c* 1.2, $CHCl_3$).

(10) (a) Suárez and co-workers recently reported on the synthesis of chiral spiroacetals from carbohydrates under similar conditions: Martín, A.; Salazar, J. A.; Suárez, E. *J. Org. Chem.* **1996**, *61*, 3999. (b) For the transformation of fully acetate-protected D-glucosyl halides into spiroorthoesters, see: Praly, J. P.; Descotes, G. *Tetrahedron Lett.* **1982**, *23*, 849.

(11) **Radical-Based Site-Selective Oxidation of Allyl Glycoside Derivatives into Anomeric Spiroorthoesters: 2-Hydroxyethyl 2,4-Bis-*O*-Benzoyl-3-*O*-(*tert*-butyldimethylsilyl)-6-*O*-trytil-β-D-mannopyranoside (9):** To a solution of the allyl mannopyranoside **7**[8] (369 mg, 0.47 mmol) in acetone–H_2O (8:2), *N*-methyl morpholine oxide (54 mg, 0.52 mmol) and OsO_4 (cat.), were added. After one day at r.t., the solvent was removed under reduced pressure, the residue was redissolved in EtOH–H_2O (95:5). $NaIO_4$ (113 mg, 0.52 mmol) as an aq solution (1.1 mL) and $NaBH_4$ (20 mg, 0.52 mmol) were added. After 4 h at r.t., the reaction mixture was quenched by addition of dilute aq HCl and extracted with Et_2O. Chromatographic purification (EtOAc–hexane 20:80) afforded **9** (267 mg, 72%). ^{1}H NMR (250 MHz, $CDCl_3$, TMS): δ = 8.18–8.14 (m, 2 H, ArH), 7.87–7.83 (m, 2 H, ArH), 7.60–7.05 (m, 21 H, ArH), 5.65 (t, *J* = 9.7 Hz, 1 H, CH), 5.42–5.41 (m, 1 H, CH), 5.10 (s, 1 H, CH), 4.34 (dd, *J* = 9.4 Hz, *J* = 3.4 Hz, 1 H, CH), 4.17–4.09 (m, 1 H, CH), 3.97–3.79 (m, 4 H, 2 × CH_2), 3.31–3.29 (m, 2 H, CH_2), 0.62 [s, 9 H, $SiC(CH_3)_3$], 0.04 (s, 3 H, $SiCH_3$), –0.16 (s, 3 H, $SiCH_3$). ^{13}C NMR and DEPT (63 MHz): δ = 166.1 (CO), 164.9 (CO), 143.6 (Ar), 133.2 (ArH), 132.8 (ArH), 129.9 (ArH), 129.71 (Ar), 129.69 (Ar), 129.6 (ArH), 128.5 (ArH), 128.4 (ArH), 128.1 (ArH), 127.6 (ArH), 126.7 (ArH), 98.3 (CH), 86.7 (C), 72.7 (CH), 70.8 (CH), 70.6 (CH_2), 69.7 (CH), 68.9 (CH), 62.6 (CH_2), 61.9 (CH_2), 25.2 [$SiC(CH_3)_3$], 17.5 [$SiC(CH_3)_3$], –4.8 ($SiCH_3$), –5.2 ($SiCH_3$). MS: *m/z* (%) = 485 (81) [M^+ – CH_2CH_2OH – $OCPh_3$], 243 (51) [CPh_3^+], 105 (100) [Bz^+]. $[\alpha]_D^{25}$ –6.9 (*c* 1.2, $CHCl_3$).

Spiroorthoester 10: (Diacetoxy)iodobenzene (146 mg, 0.43 mmol) and I_2 (99 mg, 0.39 mmol) were added to a solution of the 2-hydroxyethyl mannopyranoside **9** (309 mg, 0.39 mmol) in cyclohexane (30 mL, 0.01 M) under argon. After irradiating with a 100 W sunlamp for 7 h, the reaction mixture was washed with a sat. aq solution of $Na_2S_2O_3$ and extracted with Et_2O. Column chromatography (EtOAc–hexane 10:90) afforded **10** (145 mg, 47%). ^{1}H NMR (250 MHz, $CDCl_3$, TMS): δ = 8.20–8.17 (m, 2 H, ArH), 7.87–7.84 (m, 2 H, ArH), 7.60–7.06 (m, 21 H, ArH), 5.74 (t, *J* = 10.0 Hz, 1 H, CH), 5.57 (d, *J* = 3.1 Hz, 1 H, CH), 4.35 (dd, *J* = 9.4 Hz, *J* = 3.1 Hz, 1 H, CH), 4.29–3.98 (m, 5 H, 2 × CH_2 + CH), 3.33–3.30 (m, 2 H, CH_2), 0.64 [s, 9 H, $SiC(CH_3)_3$], 0.09 (s, 3 H, $SiCH_3$), –0.14 (s, 3 H, $SiCH_3$). ^{13}C NMR and DEPT (63 MHz): δ = 165.8 (CO), 164.8 (CO), 143.8 (Ar), 133.0 (ArH), 132.8 (ArH), 130.0 (ArH), 129.9 (Ar), 129.8 (Ar), 129.6 (ArH), 128.6 (ArH), 128.4 (ArH), 128.1 (ArH), 127.6 (ArH), 126.7 (ArH), 117.4 (OCO), 86.5 (C), 72.7 (CH), 72.5 (CH), 70.9 (CH), 69.5 (CH), 65.2 (CH_2), 64.7 (CH_2), 62.7 (CH_2), 25.2 [$SiC(CH_3)_3$], 17.5 [$SiC(CH_3)_3$], –4.8 ($SiCH_3$), –5.2 ($SiCH_3$). MS (electron impact): *m/z* (%) = 730 (0.1) [M^+ – $C(CH_3)_3$], 243 (100) [$C(Ph)_3^+$], 165 (24), 105 (100) [Bz^+]. MS (chemical ionization, CH_4): *m/z* (%) = 545 (11) [M^+ – $C(Ph)_3$], 243 (100) [$C(Ph)_3^+$]. $[\alpha]_D^{25}$ –19.3 (*c* 1.1, $CHCl_3$).

(12) Alcaide, B.; Almendros, P.; Aragoncillo, C. *Org. Lett.* **2000**, *2*, 1411.

(13) (a) Anies, C.; Lallemamd, J.-Y.; Pancrazi, A. *Tetrahedron Lett.* **1996**, *37*, 5519. (b) Hiraoka, H.; Furuta, K.; Ikeda, N.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 2768.

(14) Harada, N.; Saito, A.; Ono, H.; Murai, S.; Li, H.-Y.; Gawronski, J.; Gawronska, K.; Sugioka, T.; Uda, H. *Enantiomer* **1996**, *1*, 119.

(15) CCDC 244334 contains the supplementary crystallographic data for **16a**. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 (1223)336033.

(16) **Zn-Promoted 2-Propynylation of C6-Sugar Aldehydes: IIIc → 11:**
Zn dust (80 mg, 1.21 mmol) and propargylic bromide (68 μL, 0.60 mmol) were added in two portions to aldehyde **IIIc** (54 mg, 0.10 mmol) in a mixture of THF and aq sat. NH_4Cl (1:5, 5 mL) at r.t. After 6 h at r.t. and 2 h at 70 °C, the reaction mixture was diluted with brine and extracted with

EtOAc. Chromatography afforded **11** (37 mg, 64%). ^{1}H NMR (250 MHz, $CDCl_3$, TMS): δ = 8.09–8.05 (m, 4 H, ArH), 7.62–7.44 (m, 6 H, ArH), 7.26–7.21 (m, 5 H, ArH), 6.45 (d, *J* = 12.2 Hz, 1 H, CH), 6.10–6.06 (m, 1 H, CH), 6.05–5.90 (m, 1 H, OCH_2CHCH_2), 5.37–5.04 (m, 5 H, OCH_2CHCH_2 + $NOCH_2Ar$ + CH), 4.39–4.31 (m, 2 H, OCH_2CHCH_2), 4.14–4.09 (m, 2 H, 2 × CH), 2.62–2.60 (m, 2 H, CH_2), 2.05–2.04 (m, 1 H, CH). ^{13}C NMR + DEPT (63 MHz): δ = 165.1 (CO), 165.0 (CO), 146.9 (CN), 146.3 (CN), 137.2 (Ar), 133.6 (ArH), 133.5 (ArH), 133.3 (ArH), 133.0 (ArH), 130.1 (ArH), 130.0 (ArH), 129.0 (Ar), 128.6 (Ar), 128.4 (ArH), 128.3 (ArH), 128.28 (ArH), 128.25 (ArH), 128.11 (ArH), 127.7 (ArH), 118.11 (OCH_2CHCH_2), 96.9 (CH), 96.7 (CH), 80.0 (C), 76.5 (CH_2), 73.0 (CH), 72.4 (CH), 71.4 (C), 70.6 (CH), 68.4 (CH_2), 67.8 (CH), 66.6 (CH), 65.9 (CH), 65.6 (CH_2), 64.6 (CH), 64.5 (CH), 22.7 (CH_2).

(17) **Ti-Promoted 2-Propynylation of C6-Sugar Aldehydes: 12 → 14 → 16:**

t-BuLi (1.7 M, 1.5 mL, 2.67 mmol) was added to a solution of 3-(tetrahydro-2-pyranoxyl)-1-(trimethylsilyl)propyne (**13a**, 0.566 g, 2.67 mmol) in THF (3 mL) at –78 °C. Stirring for 0.5 h was followed by the addition of Ti(O*i*-Pr)$_4$ (0.8 mL, 2.67 mmol), further stirring for 10 min, addition of a solution of 1,2:3,4-di-*O*-isopropyliden-α-D-galacto-hexodialdo-1,5-piranose (**12**, 355 mg, 1.37 mmol) in the same solvent and final stirring for 0.5 h at –78 °C. One hour after the reaction mixture reached r.t., aq HCl (0.1 M, 25 mL) was added. Extraction with Et_2O (3 × 50 mL) and final chromatography (20% EtOAc–hexane) rendered **14** (60%) in two fractions (fraction A: R_f = 0.39, **14a** + **14c**, 248 mg, 38% and fraction B: R_f = 0.58, **14b** + **14d**, 143 mg, 22%), which were subsequently seperately dissolved in acetone and treated with 2,2-dimethoxypropane (2 equiv) and *p*-TsOH (cat.) at r.t. for 0.5 h. Addition of Et_3N to reach a pH = 8 and final chromatography gave the acetonides **16a**:**16b**:**16c**:**16d** (27:20:10:4). Compound **16a [(6*R*,7*R*)-16]**: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.16 (s, 9 H, Si-CH_3) 1.32 (s, CH_3), 1.38 (s, CH_3), 1.38 (s, CH_3), 1.45 (s, CH_3), 1.54 (s, CH_3), 1.61 (s, CH_3), 4.06 (dd, J_1 = 1.6 Hz, J_2 = 9.3 Hz, 1 H, CH-5), 4.18 (dd, J_1 = 4.8 Hz, J_2 = 9.3 Hz, 1 H, CH-6), 4.30 (dd, J_1 = 2.3 Hz, J_2 = 4.9 Hz, 1 H, CH-2), 4.40 (dd, J_1 = 1.7 Hz, J_2 = 7.9 Hz, 1 H, CH-4), 4.63 (dd, J_1 = 2.3 Hz, J_2 = 7.9 Hz, 1 H, CH-3), 4.85 (d, *J* = 4.8 Hz, 1 H, C*H*-7-C≡C-TMS), 5.50 (d, *J* = 4.8 Hz, 1 H, CH-1). ^{13}C NMR and DEPT (75 MHz, $CDCl_3$): δ = 0.37 ($SiCH_3$), 25.02 (CH_3), 25.41 (CH_3), 26.48 (CH_3), 26.69 (CH_3), 27.19 (CH_3), 28.06 (CH_3), 67.13 (CH), 69.39 (CH), 70.89 (CH), 71.08 (CH), 71.55 (CH), 76.18 (CH), 94.13 (C), 96.37 (CH), 101.92 (C), 109.07 (C), 109.58 (C), 110.33 (C). For the X-ray data of **16a** see ref.[15]; $[\alpha]_D^{20}$ –20.1 (*c* 1.6, $CHCl_3$); mp 132 °C. Compound **16b [(6*S*,7*S*)-16]**: ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.17 (s, 9 H, Si-CH_3) 1.33 (s, 9 H, 2 CH_3), 1.39 (s, 2 CH_3), 1.46 (s, CH_3), 1.58 (s, 9 H, CH_3), 4.12 (dd, J_1 = 1.5 Hz, J_2 = 8.6 Hz, 1 H, CH), 4.28 (dd, J_1 = 5.3 Hz, J_2 = 8.5 Hz, 1 H, CH), 4.35 (dd, J_1 = 2.6 Hz, J_2 = 5.0 Hz, 1 H, CH), 4.44 (dd, J_1 = 1.6 Hz, J_2 = 7.9 Hz, 1 H, CH), 4.60 (dd, J_1 = 2.3 Hz, J_2 = 7.9 Hz, 1 H, CH), 4.85 (d, *J* = 4.8 Hz, 1 H, OCH), 5.50 (d, *J* = 4.8 Hz, 1 H, OCH-C≡C-TMS). ^{13}C NMR and DEPT (63 MHz, $CDCl_3$): δ = 0.38 ($SiCH_3$), 25.12 (CH_3), 25.48 (CH_3), 26.43 (CH_3), 26.63 (CH_3), 26.93 (CH_3), 28.25 (CH_3), 67.42 (CH), 69.36 (CH), 70.64 (CH), 71.25 (CH), 71.28 (CH), 77.59 (C), 92.81 (C), 96.73 (CH), 96.82 (C), 102.81 (C), 109.27 (C), 110.18 (C), 111.49 (C). Compound **16c [(6*R*,7*S*)-16]**: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.15 (s, 9 H, Si-CH_3), 1.32 (s, CH_3), 1.38 (s, CH_3), 1.41 (s, CH_3), 1.48 (s, CH_3), 1.50 (s, CH_3), 1.60 (s, CH_3), 3.59 (d, *J* = 9.1 Hz, 1 H, CH), 4.30–4.37 (m, 3 H, CH), 4.63 (dd, J_1 = 2.3 Hz, J_2 = 7.9 Hz, 1 H, CH), 4.79 (d, *J* = 2.4 Hz, 1 H, OCH-C≡C-TMS), 5.51 (d, *J* = 4.9 Hz, 1 H, CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 0.38 ($SiCH_3$), 24.87 (CH_3), 25.41 (CH_3), 26.31 (CH_3), 26.47 (CH_3), 27.36 (CH_3), 28.70 (CH_3), 68.75 (CH), 69.62 (CH), 69.67 (CH), 70.93 (CH), 71.14 (CH), 80.47 (CH), 91 (C), 96.77 (CH), 105 (C), 109.19 (C), 109.99 (C), 113 (C). $[\alpha]_D^{20}$ –110.24 (*c* 0.26, $CHCl_3$).