5-*exo* Radical Cyclization onto 3-Alkoxyketimino-1,6-anhydromannopyranoses. Efficient Preparation of Synthetic Intermediates for (−)-Tetrodotoxin

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Ketoxime ethers at C3 of 1,6-anhydro-β-D-mannopyranose derivatives were found to be useful 5-*exo* radical traps of alkyl and vinyl radicals generated at a chain tethered to the C2 hydroxyl group, allowing advanced synthetic intermediates for (−)-tetrodotoxin to be prepared from D-mannose in good overall yield.

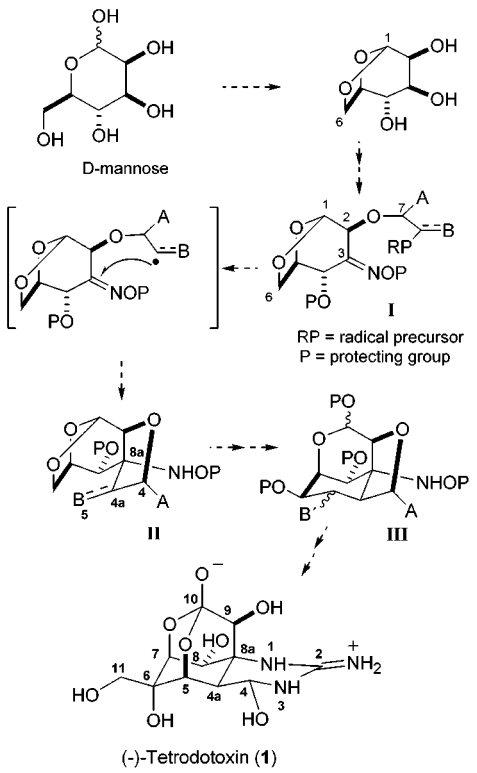
Tetrodotoxin (**1**) is a relatively small but biologically important and structurally fascinating molecule.[1] The unusual combination of a hemilactal and a guanidine unit is responsible for its zwitterionic form. Other structural features that make it a challenging synthetic target are its aminal at C4, its high heteroatom content (eight oxygens and three nitrogens, giving a total equal to the number of carbons), and the presence of eight stereogenic centers.[2,3]

We plan to prepare enantiomerically pure (−)-tetrodotoxin from D-mannose via intermediates **I**, **II**, and **III** as indicated in Scheme 1. We report here achievement of the radical addition **I** → **II**, which creates the key quaternary center at C8a and the C4−C4a−C5 chain. The intramolecular *5-exo* nature of this radical cyclization guarantees the approach of the radical chain to the concave face of the existing bicyclic structure and thus ensures that the new quaternary center has the stereochemistry as C8a in (−)-tetrodotoxin.[4]

Results and Discussion

Radical Cyclization of Model 5-Alkoxyketimino Alkyl Radical 5. We envisaged that, as Scheme 1 suggests, a mixed acetal at position C4 of intermediates **II** (i.e., A = OR) would be ideal for constructing the C4 aminal of tetrodotoxin. Consequently, the corresponding α-iodoacetals were chosen as radical precursors **I** (A = OR, RP = I). In particular, we decided to begin with simple alkyl iodoacetals (A = OR, RP = I, B = R′ + H), because alkyl haloacetals are easily obtained from alcohols and are known to behave well in *5-exo* radical cyclizations onto C=C double bonds.[5] It is important to note, however, that the transformation **I** → **II** involves

Scheme 1



* Fax: 34-981-547085.

(1) Kao, C. Y.; Levinson, S. R. Ann. N.Y. Acad. Sci. **1986**, *479*.

(2) To date, a single total synthesis of racemic tetrodotoxin has been accomplished: Kishi, Y.; Aratani, M.; Fukuyama, T.; Nakatsubo, F.; Goto, T.; Inoue, S.; Tanino, H.; Sugiura, S.; Kakoi, H. *J. Am. Chem. Soc.* **1972**, *94*, 9217−9219. Kishi, Y.; Fukuyama, T.; Aratani, M.; Nakatsubo, F.; Goto, T.; Inoue, S.; Tanino, H.; Sugiura, S.; Kakoi, H. *J. Am. Chem. Soc.* **1972**, *94*, 9219−9221.

(3) For the main attempts at total synthesis of enantiomerically pure toxin, see the following articles and the references therein: (a) Keana, J. F. W.; Kim, C. U. *J. Org. Chem.* **1971**, *36*, 118−127. (b) Keana, J. F. W.; Bland, J. S.; Boyle, P. J.; Erion, M.; Hartling, R.; Husman, J. R.; Roman, R. B.; Ferguson, G.; Parvez, M. *J. Org. Chem.* **1983**, *48*, 3627−3631. (c) Sato, K.; Kajihara, Y.; Nakamura, Y.; Yoshimura, J. *Chem. Lett.* **1991**, 1559−1562. (d) Alonso, R. A.; Burgey, C. S.; Rao, B. V.; Vite, G. D.; Vollerthun, R.; Zottola, M. A.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1993**, *115*, 6666−6672. (e) Burgey, C. S.; Vollerthun, R.; Fraser-Reid, B. *J. Org. Chem.* **1996**, *61*, 1609−1618. M. Isobe et al. recently succeeded in preparing a nonnatural dideoxygenated analogue of (−)-tetrodotoxin: (f) Nishikawa, T.; Asai, M.; Ohyabu, N.; Yamamoto, N.; Isobe, M. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 8, 3081−3084.

(4) Our first successful radical cyclization onto a sugar-based ketoxime ether was announced at the IASOC Advanced Research Workshop held in Ischia Porto (Naples, Italy) in September, 1992. A preliminary account of this work can be found in Noya, B.; Alonso, R. *Tetrahedron Lett.* **1997**, *38*, 2745−2748. For an approach to the (−)-tetrodotoxin C8a center based on 1,3-dipolar cycloaddition of a keto-nitrone, see: Torrente, S.; Noya, B.; Paredes, M. D.; Alonso, R. *J. Org. Chem.* **1997**, *62*, 6710−6711.

(5) Free radical cyclization of bromoacetals was first reported by Ueno and Stork: (a) Ueno, Y.; Chino, K.; Watanabe, M.; Moriya, O.; Okawara, M. *J. Am. Chem. Soc.* **1982**, *104*, 5564−5566. (b) Stork, G.; Mook, R. *J. Am. Chem. Soc.* **1983**, *105*, 3720−3722. Better results were subsequently obtained with iodoacetals in cyclization-trapping experiments using catalytic tin: (c) Stork, G.; Sher, P. M. *J. Am. Chem. Soc.* **1986**, *108*, 303−304.

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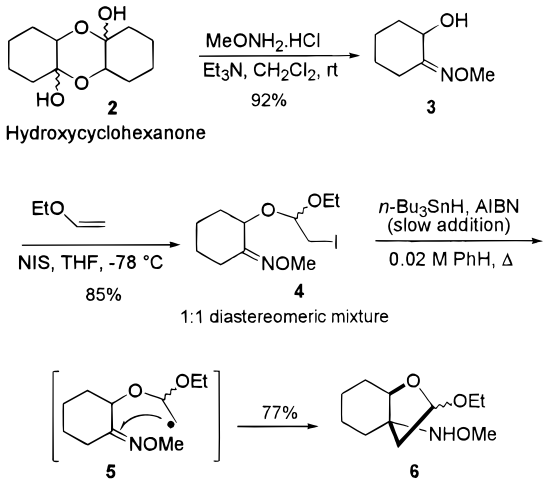
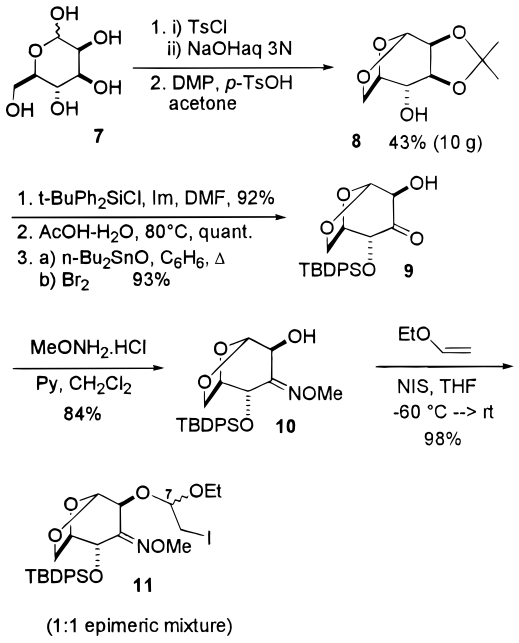
Scheme 2



the addition to a ketoxime ether, which in marked contrast with alkenes and aldoximes[6] have received scarce attention as radical trap. In fact at the outset of this work only one intramolecular addition of an alkyl radical onto a ketoxime ether had been reported.[7]

For a preliminary test of the key step **I** → **II**, we chose the easily accessible analogue **4**, which was efficiently obtained from commercial α-hydroxycyclohexanone dimer (**2**) as indicated in Scheme 2. Subjecting **4** to standard tributyltin radical conditions led to the desired bicyclic hydroxylamine ether **6** in good yield,[8] thus proving the feasibility and efficiency of cyclization for the formation of nitrogenated quaternary centers in simple 5-alkoxyketimino alkyl radicals such as **5**.

Scheme 3



Preparation of Alkyl Radical Precursors as Potential Intermediates I: Formation of Morpholine Derivatives upon Cyclization. Having found that the ketoxime ether group of model compound **4** efficiently trapped the alkyl radical in 1,5-*exo* fashion, we then studied the more complex case of 1,6-anhydro-β-D-mannopyranose C3-ketoxime ether derivatives (**I**, A = OR, RP = I, B = R′ + H). We began with iodoacetal **11**, which was prepared from D-mannose (**7**) via known intermediates **8**[9] and **9**[3d] (Scheme 3). The last step, treatment of α-hydroxyketoxime ether **10** with *N*-iodosuccinimide and ethyl vinyl ether in THF, afforded **11** as a 1:1 mixture of C7-epimers that was used without separation in the cyclization attempts described below.

Initial attempts to cyclize iodoacetal **11** under conditions similar to those successfully used for **4** gave the reduced acetal **13** as the main product; the desired cyclized compound **14** was not detected (Scheme 4). Thus the intermediate radical **12**, unlike **5**, abstracts a hydrogen atom from the stannane (path **a**) more readily than it undergoes the desired *5-exo* cyclization (path **b**). This difference between the behaviors of **12** and **5** may be due to the 1,5 methylene ether bridge of **12**; in the molecular conformation required for *5-exo* cyclization, this bridge holds the *endo* H atom of C6 in close proximity to one of the hydrogen atoms at the radical center C8, thus making *5-exo* cyclization too slow to compete successfully with alternative reaction pathways such as reduction to **13**.

Cyclization of iodoacetal **11** was also attempted under Stork's catalytic tin radical conditions,[5c] an approach where a low concentration of stannane is maintained throughout the reaction by reduction of a substoichiometric amount of a tin halide, which is initially added

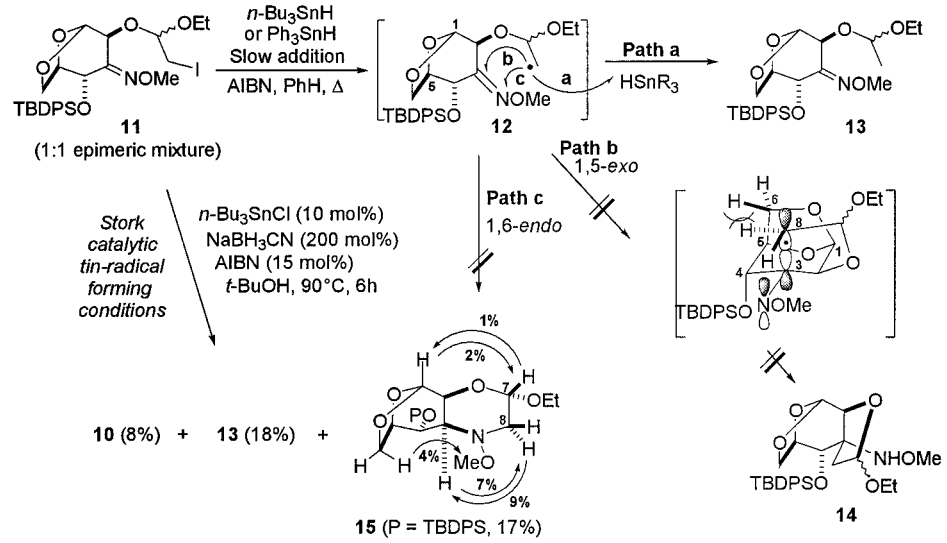
(6) The use of aldoxime ethers as radical traps was first reported by Corey in 1983: (a) Corey, E. J.; Pyne, S. G. *Tetrahedron Lett.* **1983**, *24*, 2821−2824. Subsequently, numerous reports from different groups have confirmed their excellent performance in radical cyclizations. For reviews see: (b) Martínez-Grau, A.; Marco-Contelles, J. *Chem. Soc. Rev.* **1998**, *27*, 155−162. (c) Fallis, A. G.; Brinza, I. M. *Tetrahedron* **1997**, *53*, 17543−17594. For selected cyclizations see, for example, (d) Barlett, P. A.; McLaren, K. L.; Ting, P. C. *J. Am. Chem. Soc.* **1988**, *110*, 1633−1634. (e) Hatem, J.; Henriet-Bernard, C.; Grimaldi, J.; Maurin, R. *Tetrahedron Lett.* **1992**, *33*, 1057−1058. (f) Parker, K. A.; Fokas, D. *J. Org. Chem.* **1994**, *59*, 3933−3938. (g) Santagostino, M.; Kilburn, J. D.; *Tetrahedron Lett.* **1995**, *36*, 1365−1368. (h) Miyabe, H.; Torieda, M.; Inoue, K.; Tajiri, K.; Kiguchi, T.; Naito, T. *J. Org. Chem.* **1998**, *63*, 4397−4407. (i) Keck, G. E.; Wager, T. W. *J. Org. Chem.* **1996**, *61*, 8366−8367. (j) Marco-Contelles, J.; Gallego, P.; Rodríguez-Fernández, M.; Khiar, N.; Destabel, C.; Bernabé, M.; Martínez-Grau, A.; Chiara, J. L. *J. Org. Chem.* **1997**, *62*, 7397. (k) Clive, D. L. J.; Zhang, J. *Chem. Commun.* **1997**, 549−550. (l) Boiron, A.; Zillig, P.; Faber, D.; Giese, B. *J. Org. Chem.* **1998**, *63*, 5877−5882. For the particular case of acylgermane oxime ethers see: (m) Iserloh, U.; Curran, D. P. *J. Org. Chem.* **1998**, *63*, 4711−4716. Intermolecular carbon radical addition to aldoxime ethers has received much less attention; see, for example: (n) Hart, D. J.; Seely, F. L. *J. Am. Chem. Soc.* **1988**, *110*, 1631−1633. (o) Hanamoto, T.; Inanaga, J. *Tetrahedron Lett.* **1991**, *32*, 3555−3556. (p) Bhat, B.; Swayze, E. E.; Wheeler, P.; Dimock, S.; Perbost, M.; Sanghvi, Y. S. *J. Org. Chem.* **1996**, *61*, 8186−8199. For more recent work in this field, see: (q) Kim, S.; Cheong, J. H. *J. Chem. Soc., Chem. Commun.* **1998**, 1143−1144 and (r) Miyabe, H.; Ushiro, C.; Ueda, M.; Yamakawa, K.; Naito, T. *J. Org. Chem.* **2000**, *65*, 176−185, and references therein. Plain aldoximes have also been shown to behave as radical traps in intermolecular reactions: Citterio, A.; Filippini, L. *Synthesis* **1986**, 473−474.

(7) (a) Barlett, P. A.; McLaren, K. L.; Ting, P. C. *J. Am. Chem. Soc.* **1988**, *110*, 1633−1634. During our work the use of this transformation for the formation of bicyclo[2.2.1]heptanes was also reported: (b) Della, E. W.; Knill, A. M. *Aust. J. Chem.* **1994**, *47*, 1833−1841. More recently, G. Fu and T. Naito have independently reported on the intramolecular addition of α-alkoxy alkyl radicals to form carbocycles and *N*-heterocycles, respectively: (c) Tormo, J.; Hays, D. S.; Fu, G. C. *J. Org. Chem.* **1998**, *63*, 201−202 and (d) Naito, T.; Nakagawa, K.; Nakamura, T.; Kasei, A.; Ninomiya, I.; Kiguchi, T. *J. Org. Chem.* **1999**, *64*, 2003−2009. For the intramolecular addition of vinyl and aryl radicals to ketoxime ethers see ref. 16.

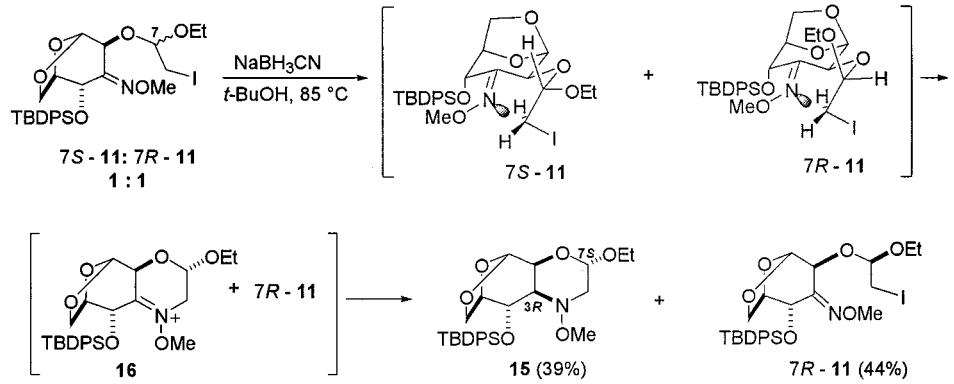
(8) Cis-fusion of the tetrahydrofuran ring in **6**, (also in **19**, **22a**, **22b**, **26**, and **30**) is assumed on the basis of numerous precedents in which exclusive formation of cis-fused bicyclic products in this type of radical cyclization has been reported. See for example Stork, G.; Mook, R.; Biller, S. A.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **1983**, *105*, 3741−3742. For **30**, indirect proof of this stereochemical outcome comes from its successful transformation into **32**.

(9) Zottola, M. A.; Alonso, R. A.; Vite, G. D.; Fraser-Reid, B. *J. Org. Chem.* **1989**, *54*, 6123−6125.

Scheme 4



Scheme 5



as tributyltin chloride and then continuously regenerated in situ by reaction between tin radicals and the starting haloderivative.[10] However, heating **11** with *n*-Bu_3SnCl, $NaBH_3CN$, and AIBN in deoxygenated *t*-BuOH produced acetal **13** (presumably via radical intermediate **12**), alcohol **10** (the result of acetal hydrolysis of **11** or **13**), and the unexpected morpholine derivative **15.** Structural determination of **15** follows from NMR data, which include COSY, HMQC, and one- and two-dimensional NOE experiments. Some of the most diagnostically informative nuclear Overhauser enhancements are shown in Scheme 4.[11]

The fact that no **15** had been formed on reaction of **11** with slowly added *n*-Bu_3SnH and AIBN, conditions which except for the solvent and the absence of the hydride reducing agent are very similar to the Stork's conditions, suggested that transformation of **11** into **15** had taken place not by 1,6-*endo* cyclization of the radical intermediate **12** (Scheme 4, path **c**)[12] but through a nonradical mechanism. Conclusive evidence for this came from the finding that reaction of **11** with $NaBH_3CN$ in *t*-BuOH, in the absence of *n*-Bu_3SnCl and AIBN also led to **15** (Scheme 5). The formation of **15** in this reaction is attributed to intramolecular N-alkylation of **11** followed by hydride reduction of the resulting iminium intermediate **16**. This mechanism also accounts for the observed stereochemical outcome. First, since proper alignment of the nitrogen lone pair and the carbon−iodine bond in **11** makes intramolecular nucleophilic displacement easier for 7*S*-**11** than for the 7*R* epimer, in which attack by the nucleophile is hindered by the ethoxy group, 7*R*-**11** is almost completely recovered and only 7*S*-**11** is transformed into the morpholine **15**, which consequently displays only *S* configuration at C7. Second, the exclusive formation of a product with *R* configuration at C3 is attributable to the hydride attacking the tricyclic alkoxyiminium ion **16** exclusively from its less hindered convex side.[13,14]

(10) This method (ref 5c) is a modification of the borohydride plus catalytic trialkyltin halide system (*n*-Bu_3SnCl or Me_3SnCl, $NaBH_4$, *hν*, EtOH), which was first used by Corey for dehalogenation of organic halides: Corey, E. J.; Suggs, J. W. *J. Org. Chem.* **1975**, *40*, 2554−2555, and was later applied by Giese to the addition of radicals derived from alkyl iodides to electrophilic olefins: Giese, B.; González-Gómez J. A.; Witzel, T. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 69−70 and Gerth, D. B.; Giese, B. *J. Org. Chem.* **1986**, *51*, 3726−3729.

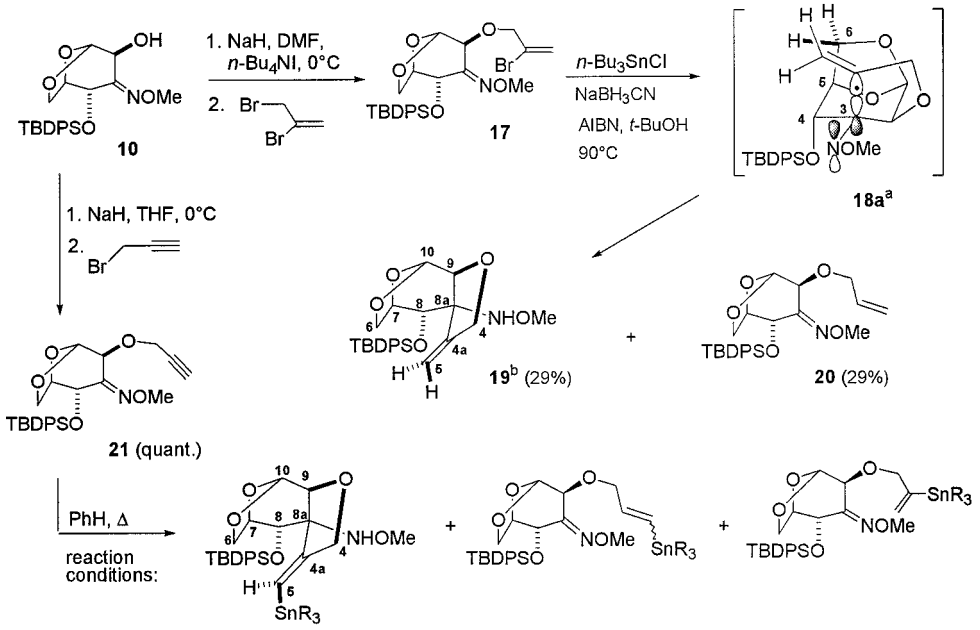
(11) See Supporting Information.

(12) Preferential 1,6-*endo* addition onto the nitrogen over the alternative 1,5-*exo* addition to the sp^2 carbon has been recently observed in the tosyl radical-mediated cyclization of *β*-allenyl ketoximebenzoates: Depature, M.; Siri, D.; Grimaldi, J.; Hatem, J. *Tetrahedron Lett.* **1999**, *40*, 4547−4550.

(13) The transformation of cyclic *N*-alkoxyketiminoiodoacetals derived from α-hydroxycyclohexanones into *cis*-fused morpholines on treatment with cyanoborohydride is possibly the rule. $NaBH_3CN$ transformed iodoacetal **4** (1:1 diastereomeric mixture) into the corresponding morpholine (unpublished results). The reaction was again highly stereoselective, one diastereomer of **4** being cleanly converted to the morpholine and the other recovered unchanged.

(14) α-Hydroxyketoxime ether **10** was obtained from ketone **9** as a single stereoisomer. Transformation of the iodoacetal **11** into morpholine **15** strongly supports the *Z* configuration for both **11** and its precursor **10**.

Scheme 6



[a] Sugar numbering
[b] Tetrodotoxin numbering
[c] Yields for **23a** and **24a** were not quantified under these conditions

Preparation of Vinyl Radical Precursors as Intermediates I and Cyclization to II. Having attributed the failure of **11** to cyclize to **14** to the presence of the 1,5 methylene ether bridge we decided to replace the π-radical **12** with the vinyl σ-radical **18a** (Scheme 6). We reasoned that the planar vinyl geometry would allow proper alignment of the orbitals for *5-exo* cyclization while minimizing interaction with the *endo* H6 atom of the ether bridge. Additionally, vinyl radicals are known to have comparatively higher *5-exo* cyclization/reduction rate ratios,[15] and since precursor vinyl halides would not attack the oxime nitrogen it would be possible to use Stork's radical-forming conditions.

All these expectations were fulfilled when treatment of substrate **17** with *n*-Bu_3SnCl, $NaBH_3CN$, and AIBN in refluxing *t*-BuOH gave the desired tetrahydrofuran derivative **19**. Similarly, generation of tin-substituted vinyl radicals from alkyne **21** under standard *n*-Bu_3SnH−AIBN conditions afforded **22a**.[16] Partial reduction of the intermediate vinyl radicals was observed in both cases, **19** being accompanied by allyl ether **20** and **22a** by vinyl stannanes **23a** and **24a**.

Optimization of the Radical Cyclization I → II. Intermediates **19** and **22a** contain all the carbon atoms of tetrodotoxin except two, C2 and C11, which belong to the guanidine and the hydroxymethyl units. They also have the quaternary C8a and three more of the eight tetrodotoxin stereocenters (C7, C8, and C9). Moreover, their precursors, **17** and **21**, can be prepared in only five steps, with excellent overall yields, from 2,3-isopropylidene-1,6-anhydro-β-D-mannopyranose **8**, which is readily obtained in multigram quantities from D-mannose. However, since the yield of the radical cyclization step was only about 30%, we next sought ways to increase the efficiency of this transformation.

Varying the tin reagent (*n*-Bu_3SnH, Ph_3SnH, (*n*-$Bu_3Sn)_2$), the radical initiator (AIBN, *hν*, Et_3B), the solvent and the temperature achieved only moderate improvement: **22b** was obtained in 41% yield when Ph_3SnH and Et_3B were slowly added to alkyne **21** in refluxing benzene (Scheme 6). Unexpectedly, removal of the silyl protecting group from alkyne **21** prior to the radical cyclization had a major impact: the free alcohol **25** gave the desired derivative **26** in 68% yield and only 3% yields of the hydrostannylated products **27** and **28** (Scheme 7). In view of this, we decided to check whether the same maneuver would allow *5-exo* cyclization of alkyl radical precursors. To our delight, when the α-iodoacetal **11** was desilylated at C4 and the resulting alcohol **29** was subjected to the same conditions as had completely failed to cyclize **11**, hydroxylamine ether **30** was obtained in a synthetically useful 58% yield (3 g scale).

It is at first sight surprising that the cyclization yield is so highly dependent on the presence or absence of a bulky silyl group on the reverse side of the face approached by the attacking radical and that the yields afforded by alkyl and vinyl radicals differ markedly when they are silylated at C4 (0% for **12** versus 29−41% for **18a**−**c**) but not if the C4 hydroxyl is unprotected (58% for **35**, 68% for **36**) (Chart 1). However, examination of

(15) See, for example Curran, D. P. *Synthesis* **1988**, 428−430 and references therein.

(16) Addition of vinyl radicals generated from alkynes to methyl ketoximes was first reported by Enholm: Enholm, E. J.; Burrof, J. A.; Jaramillo, L. M. *Tetrahedron Lett.* **1990**, *31*, 3727−3730. Use of aryl radicals was described by Jenkins: Booth, S. E.; Jenkins, P. R.; Swain, C. J.; Sweeney, J. B. *J. Chem. Soc., Perkin Trans. 1* **1994**, 3499−3508. For the special case of addition of vinyl radicals to ketoximes derived from cyclobutanone, see: Pattenden, G.; Schulz, D. *Tetrahedron Lett.* **1993**, *34*, 6787−6790 and Hollingworth, G. J.; Pattenden, G.; Schulz, D. J. *Aust. J. Chem.* **1995**, *48*, 8, 381. For a review of heteroatom radical addition-cyclization, see Naito, T. *Heterocycles* **1999**, 50, 505−541.

Scheme 7

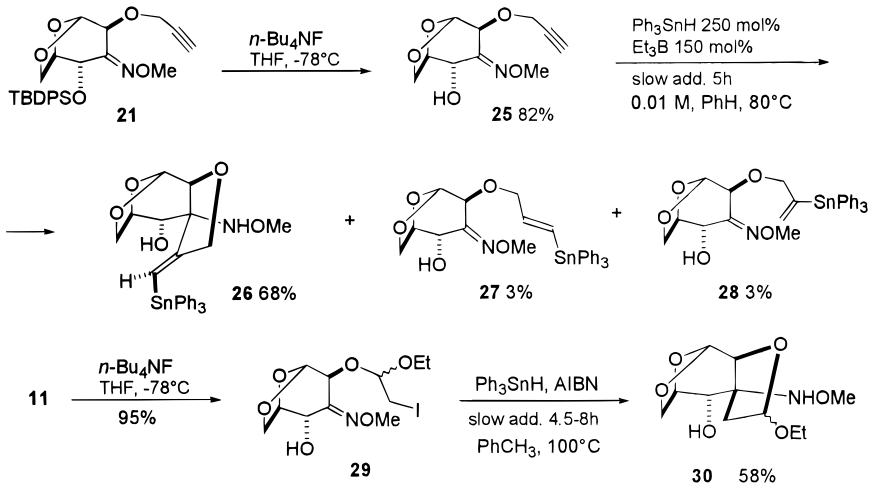
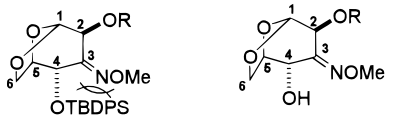


Chart 1

C3-KETOXIME ETHERS OF 1,6-ANHYDROMANNOPYRANOSES



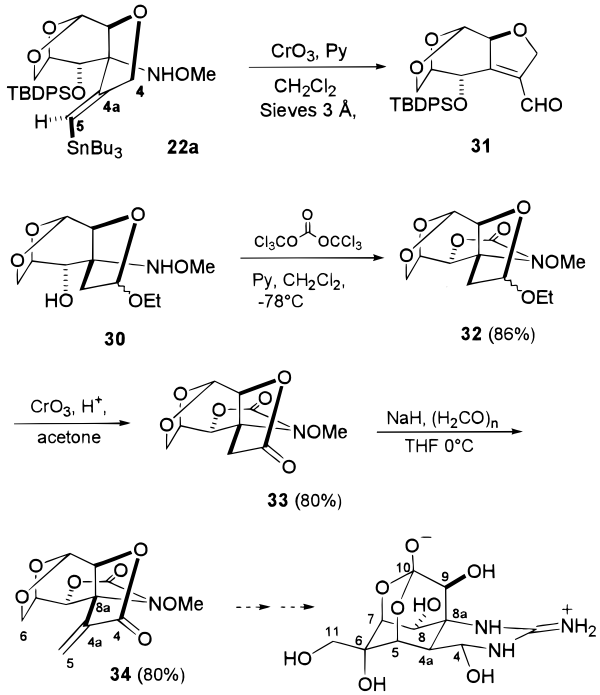
	C4-SILYLATED	C4-DESILYLATED
Radical Precursors:		
R = $CH(OEt)CH_2I$	**11**	**29**
R = $CH_2C(Br)=CH_2$	**17**	-
R = $CH_2C{\equiv}CH$	**21**	**25**
Radical Intermediates:		
alkyl:		
R = $CH(OEt)\dot{C}H_2$	**12** (0%)[a]	**35** (58%)[a]
vinyl:		
R = $CH_2\dot{C}{=}CHY$	**18a Y = H** (29%)[a]	**36** (68%)[a]
	18b Y = Sn*n*-Bu$_3$ (31%)[a]	
	18c Y = SnPh$_3$ (41%)[a]	

[a] Cyclization yields

models suggests a combined effect of the silyl ether at C4 and the C6−O−C1 bridge. It seems possible that the bulky *tert*-butyldiphenylsilyl group borne by C4 in intermediates **12** and **18** may force the C3 ketoxime ether group toward the C6−O−C1 ether bridge, as a consequence of which the C2-tethered radical-bearing chain, in attacking the C═NOMe group, has to approach this bridge more closely than in the C4-desilylated analogues **35** and **36**. This would explain the lower cyclization yields of **12** and **18**. Because of their geometry (see above), this effect must be greater for the alkyl radical **12** than for vinyl radicals **18**, to the extent that cyclization of **12** is completely prevented. By contrast, the cyclization yields of the C4-desilylated radicals **35** and **36** (generated from precursors **29** and **25**, respectively), should be more similar, because in the absence of the bulky silyl group interaction between the attacking radical and the ether bridge must be slight regardless of which radical is used.

Completion of Intermediates II. Vinyl derivatives **19**, **22**, and **26** possess a carbon corresponding to C5 in tetrodotoxin but are unsubstituted at C4, while alkylacetal derivative **30** has the C4 oxygen of tetrodotoxin but lacks C5. We first attempted to remedy the deficiency of

Scheme 8



vinyl derivative **22a**, but treatment with CrO_3−pyridine gave a complex mixture from which it was possible to isolate only unsaturated aldehyde **31**, the result of oxidation followed by elimination. Gratifyingly, however, addition of an extra carbon to acetal **30** was completely successful, compound **30** being efficiently transformed into the desired methylenelactone **34** in three high yielding steps, via **32** and **33** (Scheme 8).

Summary. 1,6-Anhydro-β-D-mannopyranose derivatives with both a ketoxime ether at position C3 and an alkyl or vinyl radical precursor tethered to C2 were efficiently prepared from D-mannose. When the C4 oxygen was protected by a *tert*-butyldiphenylsilyl group and the radical precursor was an alkyl iodide, hydride-based catalytic tin radical generation led to the stereoselective formation of a *cis*-fused morpholine by a two-step nonradical cyclization process; when a TBDPS-protected vinyl radical precursor was used, the same conditions achieved the desired cyclization in modest yield. Removal of the TBDPS group from O4 allowed *5-exo* cyclization of alkyl radicals in fair yield and

improved the efficiency of the vinyl radical cyclization. The resulting products are expected to be susceptible of transformation into tetrodotoxin.

From a more general perspective, this work shows that ketoxime ethers derived from sugars, which have not previously been used in radical transformations, are in fact useful radical traps allowing the preparation of compounds with nitrogen-bearing quaternary centers by intramolecular cyclization. Tethering the chain containing the radical center to a sugar hydroxyl group adjacent to the ketoxime group allows stereocontrolled formation of a fused heterocycle on the sugar skeleton.

Experimental Section

General. All reactions were carried out under argon with the exclusion of moisture. The reagents were purchased from Sigma-Aldrich Chemical Co. and Fluka Chemical Co. and were used without further purification. THF, Et_2O, benzene and toluene were distilled from sodium/benzophenone ketyl; CH_2Cl_2, pyridine and Et_3N from calcium hydride. Anhydrous Na_2SO_4 was used to dry the organic solutions during workups. Flash column chromatography was performed using 230−400 mesh silica gel (Merck). Analytical thin-layer chromatography was done on precoated silica gel aluminum plates containing a fluorescent indicator (GF-254 Merck). ^{1}H NMR spectra were recorded at 250, 300, or 500 MHz; ^{13}C NMR spectra at 63, 75, or 125 MHz; $CDCl_3$ and CD_3CN were used as solvents.

2-Hydroxy-1-methoxyimine-cyclohexane 3. A suspension of dimer **2** (2 g, 8.76 mmol), *O*-methylhydroxylamine hydrochloride (1.8 g, 21.02 mmol, 240 mol %) and Et_3N (2.9 mL, 21.02 mmol, 240 mol %), in 80 mL of CH_2Cl_2 was stirred at room temperature overnight. The reaction mixture was washed with brine, and the organic layer was dried, filtered and concentrated in vacuo. Purification through silica gel (EtOAc−hexane, 30:70) afforded oxime **3** (essentially one isomer, 2.3 g, 92%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.11 (m, 1H), 3.84 (s, 3H), 3.34 (d, J = 3.2 Hz, 1H), 3.03 (m, 1H), 2.15 (m, 1H), 1.90−1.70 (m, 3H), 1.51−1.39 (m, 3H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 159.6, 70.1, 61.6, 36.0, 25.4, 23.6, 22.6; LRMS *m*/*z* (%) 143 [0.3, M^+].

Iodoacetals 4. To a solution of **3** (300 mg, 2.09 mmol) in dry THF (22 mL) kept under Ar at −78 °C in a light protected vessel, were added NIS (613 mg, 2.72 mmol, 130 mol %) and ethyl vinyl ether (0.3 mL, 3.14 mmol, 150 mol %). The cold bath was removed and the reaction was allowed to warm. Additional NIS (30 mol %) and ethyl vinyl ether (50 mol %) were needed to consume completely the starting material. A saturated aqueous solution of $Na_2S_2O_3$ was then added and the aqueous phase was extracted with Et_2O. The organic extracts were dried, filtered and concentrated. Purification of the oily residue (EtOAc−hexane, 5:95) gave iodoacetals **4** (609 mg, 85%, approximately 1:1 diastereomeric mixture) as a colorless oil which turned to brown-yellow on standing: ^{1}H NMR ($CDCl_3$, 250 MHz) δ 4.59 and 4.56 (t each, J = 5.4 Hz, 1H), 4.17 and 4.05 (m each, 1H), 3.84 and 3.82 (s each, 3H), 3.71−3.41 (m, 2H), 3.20 (d, J = 5.4 Hz, 1H), 3.16 (d, J = 5.4 Hz, 1H), 3.03−2.96 (m, 1H), 2.16−1.99 (m, 2H), 1.90−1.75 (m, 2H), 1.67−1.50 (m, 2H), 1.46−1.25 (m, 1H), 1.18 (m, 6H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 158.8 and 157.8, 101.0 and 99.4, 74.1 and 73.0, 62.9 and 62.3, 61.4 and 61.2, 33.0 and 32.8, 25.2 (for both diastereomers), 22.12 and 22.07, 20.15 and 20.12, 15.2 and 14.9, 6.3 and 5.9.

***O*-Methylhydroxylamines 6.** A solution of iodoacetals **4** (1:1 diastereomeric mixture, 186 mg, 0.55 mmol) in dry benzene (27 mL) was deoxygenated (Ar bubbling for 30 min) and brought to reflux in an oil bath. A solution of *n*-Bu_3SnH (0.5 mL, 1.8 mmol, 340 mol %) and AIBN (54 mg, 0.32 mmol, 59 mol %) in dry deoxygenated benzene (2 mL) was added dropwise for 3 h. After 30 min the oil bath was removed. Because of the volatility of the cyclized products benzene was carefully removed in the rotavapor. The oily residue was treated with Et_2O and an aqueous solution of KF (10%), and vigorously stirred for 12 h. After filtering through a pad of Celite, the organic phase was washed with brine and water, dried with Na_2SO_4 and evaporated. Flash column chromatography (AcOEt−hexane, 17:83) afforded **6** (91 mg, 77%, 44:56 diastereomeric mixture). **Fast moving diastereomer**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.81 (s, broad, 1H; NH), 5.08 (dd, J = 5,8 and 2.9, 1H), 3.9 (dd, J = 4,9, 1H), 3.82−3.74 (m, 1H), 3.52 (s, 3H), 3.46−3.41 (m, 1H), 2.07 (dd, J' = 13.6 and 5.8, 1H), 1.94 (dd, J = 13.6 and 2.9, 1H), 1.71−1.32 (m, 8H), 1.2 (t, J = 7.1, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 103.6, 76.8, 65.8, 63.8, 63.3, 42.3, 29.8, 28.3, 21.6, 20.8, 15.19; LRMS *m*/*z* (%) 170 [10.58, $(M - OEt)^+$], 169 [100, $(M - NHOCH_3)^+$]; HRMS calcd for $C_{11}H_{21}NO_3$ ($M^+ + H$) 216.159969, found 216.159414. **Slow moving diastereomer**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.41 (s, broad, 1H; NH), 5.17 (dd, J = 6.3 and 4.3, 1H), 3.86 (dd, J = 9.2 and 6.0, 1H), 3.81−3.73 (m, 1H), 3.52 (s, 3H), 3.49−3.39 (m, 1H), 2.13 (dd, J' = 14.0 and 6.3, 1H), 1.91 (dd, J' = 14.0 and 4.3, 1H), 2,0−1.2 (m, 8H), 1.19 (t, J = 7.11, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 103.7, 78.6, 67.1, 63.6, 63.1, 39.4, 30.01, 29,8, 22,5, 21.9, 15.32; LRMS *m*/*z* (%) 186 [18, $(M - Et)^+$], 169 [18, $(M - NHOCH_3)^+$], 81 [100, $(C_6H_9)^+$]; HRMS calcd for $C_{11}H_{21}NO_3$ ($M^+ + H$) 216.159969, found 216.159583.

(3*Z*)-1,6-Anhydro-4-*O*-(*tert*-butyldiphenylsilyl)-3-deoxy-3-methoxyimine-*β*-D-arabino-hexopyranose (10). A solution of hydroxyketone **9**[2d] (2000 mg, 5.02 mmol) *O*-methylhydroxylamine hydrochloride (629 mg, 7.53 mmol, 150 mol %) and pyridine (0.6 mL, 7.53 mmol, 150 mol %) in CH_2Cl_2 (7 mL) was refluxed for 3 h. The solvent was rotary-evaporated and the residue was redisolved in EtOAc, washed with brine, dried and evaporated. Chromatography (EtOAc−hexane, 20:80) afforded ketoxime ether **10** (1912 mg, 89%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.74 (m, 2H), 7.63 (m, 2H), 7.41 (m, 6H), 5.51 (d, $J_{1,2}$ = 1.9, 1H), 4.84 (d, $J_{4,5}$ = 2.1, 1H), 4.61 (dd, $J_{2,OH}$ = 6.8, $J_{2,1}$ = 1.9,), 4.32 (m, 1H), 3.66 (s, 3H), 3.62 (dd, J = 8.0 and 5.8, 1H), 3.32 (dd, J = 8.0 and 0.9, 1H), 3.03 (d, J = 6.8, 1H), 1.07 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 152.9, 135.8, 135.7, 133.2, 132.5, 129.97, 129.90, 127.7, 127.5, 102.4, 77.3, 69.8, 65.3, 65.1, 61.9, 26.7, 19.3; LRMS *m*/*z* (%) 370 [$(M - t$Bu$)^+$, 0.6], 350 [$(M - Ph)^+$, 0.1], 339 [$(M - t$Bu $- NOCH_3)^+$, 1], 91 (100), 77 (Ph^+, 35), 57 (tBu$^+$, 34). Anal. Calcd for $C_{23}H_{29}NO_5Si$: C, 64.61; H, 6.84; N 3.28. Found: C, 64.67; H, 7.14; N, 3.37.

(3*Z*)-1,6-Anhydro-4-*O*-(*tert*-butyldiphenylsilyl)-2-*O*-(1′-ethoxy-2′-iodoethyl)-3-deoxy-3-methoxyimine-*β*-D-arabino-hexopyranose (11). Iodoacetals **11** were prepared from alcohol **10** (400 mg, 0.93 mmol), NIS (274 mg, 1.22 mmol, 130 mol %) and ethyl vinyl ether (136 μL, 1.40 mmol, 150 mol %) in dry THF (12.5 mL) at −60 °C, following the procedure reported for **4**. Purification by chromatography (EtOAc−hexane, 25:75) rendered **11** as a 1:1 mixture of epimers (572 mg, 98%). Enough quantities of pure samples of each epimer for characterization purposes were obtained by careful chromatography. **7*R*-11**: ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.72 (m, 2H), 7.63 (m, 2H), 7.43 (m, 6H), 5.52 (d, J = 1.9 Hz, 1H), 4.87 (m, 2H), 4.65 (d, J = 1.9 Hz, 1H), 4.32 (m, 1H), 3.77 (m, 1H), 3.62 (s, 3H), 3.66−3.57 (m, 2H), 3.45−3.39 (m, 2H), 3.30 (dd, J = 10.6 Hz, J = 7.6 Hz, 1H), 1.28 (t, J = 7.0 Hz, 3H), 1.07 (s, 9H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 152.1, 135.8 (4C), 133.3, 132.8, 130.0 (2C), 127.8 (2C), 127.5 (2C), 101.9, 101.8, 77.2, 71.1, 65.5, 65.3, 61.5, 62.9, 26.7 (3C), 19.3, 14.8, 4.9; IR (neat) 1587 (sharp, weak, C=N) cm^{-1}; LRMS *m*/*z* (%) 568 [0.02, $(M - t$Bu$)^+$], 426 [3, $(M - t$BuPh$_2$SiOH$)^+$]; HRMS calcd for $C_{27}H_{36}NO_6SiI$ (M^+) 625.131198, found 625.131482; $[\alpha]_D$ −10.5° (*c* 0.86, CH_2Cl_2). **7*S*-11**: ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.72 (m, 2H), 7.62 (m, 2H), 7.41 (m, 6H), 5.50 (d, J = 1.5 Hz, 1H), 4.94 (dd, J = 7.7 Hz, J = 3.6 Hz, 1H), 4.89 (d, J = 1.8 Hz, 1H), 4.64 (d, J = 1.5 Hz, 1H), 4.34 (m, 1H), 3.65 (dd, J = 8.0 Hz, J = 6.0 Hz, 1H), 3.59 (s, 3H), 3.41 (d, J = 8.0 Hz, 1H), 3.90−3.70 (m, 2H), 3.35 (dd, J = 10.4 Hz, J = 3.6 Hz, 1H), 3.21 (dd, J = 10.4 Hz, J = 7.7 Hz, 1H), 1.25 (t, J = 7.0 Hz, 3H), 1.07 (s, 9H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 152.1, 135.9 (2C), 135.8 (2C), 133.4, 132.7, 130.0 (2C), 127.8 (2C), 127.6 (2C), 102.3, 101.9, 77.3, 73.4, 65.5, 65.4, 61.7, 62.1, 26.7 (3C), 19.3, 15.0, 5.2.

Morpholine 15. (a) From 11 by treatment with $NaBH_3CN$. A mixture of iodoacetals **11** (1:1 mixture of epimers, 90 mg,

0.14 mmol) and $NaBH_3CN$ (19 mg, 0.28 mmol, 200 mol %) in dry and deoxygenated *t*-BuOH (9.3 mL) was refluxed for 13 h. The solvent was removed, CH_2Cl_2 was added and the resulting mixture was washed with saturated NH_4Cl. The aqueous layer was extracted with CH_2Cl_2 (3×) and the combined organic extracts were washed with brine. After drying and filtering, evaporation of the solvent gave a residue which was purified by p-TLC (EtOAc−cyclohexane, 22:78) affording morpholine **15** (28 mg, 39%) and unaltered starting iodoacetal **7R-11** (40 mg, 44%). **(b) From 11 under Stork radical forming conditions.** A solution of **11** (1:1 mixture of epimers, 90 mg, 0.14 mmol), $NaBH_3CN$ (19 mg, 0.28 mmol, 200 mol %), *n*-Bu_3SnCl (4 μL, 0.014 mmol, 10 mol %) and AIBN (4 mg, 0.02 mmol, 15 mol %) in degassed *t*-BuOH (9.3 mL) was heated for 9 h at 90 °C. Additional *n*-Bu_3SnCl (10 mol %) and AIBN (15 mol %) were then added. After refluxing for an additional 3 h, the mixture was concentrated, redisolved in CH_2Cl_2 and washed with a saturated aqueous solution of NH_4Cl. The aqueous phase was extracted with CH_2Cl_2 and the combined organic extracts were washed with brine, dried, filtered and concentrated in vacuo. Purification by p-TLC (EtOAc−hexane, 22:78), afforded morpholine **15** (12 mg, 17%), reduced acetal **13** (13 mg, 18% of the fast moving epimer −15% EtOAc in hexane-; ≈2 mg of the slow moving epimer), and α-hydroxy-ketoxime-ether **10** (5 mg, 8%). **Morpholine 15:**[14] ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.75 (m, 2H, ArH_o), 7.69 (m, 2H, ArH_o), 7.40 (m, 6H, ArH_m, ArH_{para}), 5.45 (s, 1H, H1), 5.12 (d, J_{7-8} = 8.9 Hz, 1H, H7), 4.26 (d, J_{2-3} = 6.2 Hz, 1H, H2), 4.21 (m, 1H, H5), 4.13 (d, $J_{6endo-6exo}$ = 6.9 Hz, 1H, H6endo), 4.00 (s, 1H, H4), 3.91 (m, 1H, H9), 3.59 (m, 1H, H9′), 3.49 (dd, $J_{6exo-6endo}$ − J_{6exo-5} = 6.9 Hz, 1H, H6exo), 3.35 (d, $J_{8'-8}$ = 9.7 Hz, 1H, H8′), 3.24 (s, 3H, OCH_3), 3.02 (d, J_{3-2} = 6.2 Hz, 1H, H3), 2.22 (m, 1H, H8), 1.22 (t, J_{10-9} = 7.0 Hz, 3H, H10), 1.07 (s, 9H, *t*-Bu); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 135.9 (Ar, 2C, C_{ortho}), 135.8 (Ar, 2C, C_{ortho}), 133.8 (Ar, C_{ipso}), 132.8 (Ar, C_{ipso}), 129.9 (Ar, C_{para}), 129.8 (Ar, C_{para}), 127.7 (Ar, 4C, C_{meta}), 102.3 (C1), 95.9 (C7), 76.5 (C5), 72.2 (C2), 69.4 (C4), 66.6 (C3), 64.9, 64.8 (C6, C9), 59.2 (OCH_3), 58.0 (C8), 26.8 ($C(CH_3)_3$), 19.2 ($C(CH_3)_3$), 15.2 (C10); LRMS *m*/*z* (%) 500 [10, $(M + 1)^+$], 499 [28, $(M)^+$]. Anal. Calcd for $C_{27}H_{37}O_6NSi$: C, 64.90; H, 7.46; N, 2.80. Found: C, 64.93; H, 7.44; N, 3.17. **Acetal 13:** fast moving epimer; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.74 (m, 2H), 7.64 (m, 2H), 7.41 (m, 6H), 5.51 (d, J = 1.7 Hz, 1H), 4.95 (c, J = 5.4 Hz, 1H), 4.89 (d, J = 1.9 Hz, 1H), 4.69 (d, J = 1.7 Hz, 1H), 4.30 (m, 1H), 3.80−3.50 (m, 3H), 3.62 (s, 3H), 3.42 (d, J = 8.0 Hz, 1H), 1.42 (d, J = 5.4 Hz, 3H), 1.24 (t, J = 7.1 Hz, 3H), 1.07 (s, 9H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 152.3, 135.8 (2C), 135.7 (2C), 133.4, 132.7, 129.9, 129.8, 127.7 (2C), 127.4 (2C), 102.3, 100.2, 77.2, 72.4, 65.5, 65.3, 61.5, 60.1, 26.7 (3C), 20.0, 19.3, 15.3; LRMS *m*/*z* (%) 442 [0.3, $(M - t\text{Bu})^+$], 427 [1, $(M - t\text{Bu} - \text{Me})^+$]. Anal. Calcd for $C_{27}H_{37}O_6NSi$: C, 64.90; H, 7.46; N, 2.80. Found: C, 64.64; H, 7.42; N, 3.12. **Acetal 13:** slow moving epimer; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.73 (m, 2H), 7.63 (m, 2H), 7.46−7.33 (m, 6H), 5.47 (br s, 1H), 4.99 (m, 1H), 4.89 (br s, 1H), 4.71 (br s, 1H), 4.32 (m, 1H), 3.85 (dd, J = 8.7 Hz, J = 7.3 Hz, 1H), 3.78−3.55 (m, 2H), 3.61 (s, 3H), 3.41 (d, J = 8.7 Hz, 1H), 1.42 (d, J = 5.5 Hz, 3H), 1.22 (t, J = 7.1 Hz, 3H), 1.07 (s, 9H, *t*-Bu); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 152.4, 135.8 (2C), 135.7 (2C), 133.3, 132.6, 129.9, 129.8, 127.7 (2C), 127.4 (2C), 102.1, 99.2, 77.1, 70.2, 65.5, 65.3, 61.7, 61.4, 26.7 (3C), 19.6, 19.3, 15.1; LRMS *m*/*z* (%) 454 [0.3, $(M - \text{EtO})^+$], 442 [1, $(M - t\text{Bu})^+$].

(*Z*)-1,6-Anhydro-4-*O*-(*tert*-butyldiphenylsilyl)-3-deoxy-3-methoxyimine-2-*O*-(2′-bromo-prop-2′-enyl)-*β*-D-*arabino*-hexopyranose 17. NaH (60% in parafine, 18 mg, 0.44 mmol, 150 mol %) was added to a solution of alcohol **10** (125 mg, 0.29 mol) in dry DMF (2 mL) kept at 0 °C. After evolution of hydrogen ceased, *n*-Bu_4NI (27 mg, 0.07 mmol, 25 mol %) and 2,3-dibromopropene (71 μL, 0.58 mmol, 200 mol %) were added. The reaction mixture was left to reach room temperature and diluted with Et_2O. Washing with saturated aqueous solutions of NH_4Cl and NaCl and drying, followed by chromatography (AcOEt−hexane 15:85), afforded the bromide **17** (112 mg, 70%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.73 (m, 2H), 7.65 (m, 2H), 7.41 (m, 6H), 6.03 (d, J = 1.4), 5.65 (d, J = 1.4, 1H), 5.58 (d, J = 1.7, 1H), 4.91 (d, J = 2.0, 1H), 4.48 (d, J = 14.6, 1H), 4.41 (d, J = 1.7, 1H), 4.35 (m, 1H), 4.23 (d, J = 14.6, 1H), 3.64 (dd, J = 8.0 and 5.8, 1H), 3.63 (s, 3H), 3.42 (d, J = 8.0, 1H), 1.08 (s, 9H): ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.8, 135.7 (2C), 135.6 (2C), 133.2, 132.6, 129.90, 129.87, 129.0, 127.7 (2C), 127.4 (2C), 117.9, 101.4, 77.2, 75.9, 74.7, 65.34, 65.31, 61.6, 26.7 (3C), 19.3; LRMS *m*/*z* (%) 426 [$(M - C_3H_4Br)^+$; 0.5), 213 (100), 77 (Ph^+; 16), 57 ($t\text{Bu}^+$; 23).

Tetrahydrofuran 19 and (*Z*)-2-*O*-Allyl-1,6-anhydro-4-*O*-(*tert*-butyldiphenylsilyl)-3-deoxi-3-methoxyimino-*β*-D-arabino-hexopyranose (20). A solution of bromide **17** (70 mg, 0.13 mmol), $NaBH_3CN$ (17 mg, 0.26 mmol, 200 mol %), *n*-Bu_3SnCl (6 μL, 0.02 mmol, 15 mol %) and AIBN (3 mg, 0.02 mmol, 15 mol %) in deoxygenated *t*-BuOH (5 mL) was heated at 90 °C for 8 h under Ar. The solvent was rotary-evaporated and the residue was redisolved in CH_2Cl_2 and washed with NH_4OH (3%) and brine. Chromatography (EtOAc−hexane, 25:75) afforded tetrahydrofuran **19** and allyl ether **20** (1:1 mixture, 35 mg, 58%). A careful chromatographic separation allowed to obtain enough quantities of both compounds in pure form for their characterization. **Tetrahydrofuran 19:** ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.86 (m, 4H), 7.44 (m, 6H), 6.67 (s, broad, 1H; NH), 5.38 (d, $J_{1,2}$= 2.5, 1H), 5.00 (s, 1H), 4.81 (d, J = 2.5, 1H), 4.72 (s broad, 2H), 4.24 (m, J = 5.9, 1H), 4.02 (s, 1H), 3.74 (d, J = 2.5, 1H), 3.46 (d, J = 7.5, 1H), 3.39 (s, 3H), 3.29 (dd, J = 7.5 and 5.9, 1H), 1.09 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 148.2, 136.2, 136.0, 133.9, 131.9, 130.1, 129.8, 127.66, 127.61, 106.7, 100.9, 80.8, 76.6, 72.5, 70.3, 66.8, 65.3, 62.4, 26.9, 19.5; LRMS *m*/*z* (%) 436 [$(M - OCH_3)^+$; 5], 410 [$(M - t\text{Bu})^+$; 3]. Anal. Calcd for $C_{26}H_{33}O_5NSi$: C, 66.78; H, 7.11; N 3.00. Found: C, 66.56; H, 7.08; N, 2.96. **Allyl ether 20:** ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.74 (m, 2H), 7.65 (m, 2H), 7.41 (m, 6H), 5.99 (m, 1H), 5.56 (d, J = 1.7, 1H), 5.35 (dd, J = 17.2, J = 1.3, 1H), 5.24 (dd, J = 10.3, J = 1.3, 1H), 4.92 (d, J = 2.1, 1H), 4.45−4.31 (m, 3H), 4.15 (dd, J = 12.9, J = 6.5, 1H), 3.65 (s, 3H), 3.66−3.61 (m, 1H), 3.42 (dd, J = 8.0 and 0.8, 1H), 1.08 (s, 9H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 152.1, 135.7 (2C), 135.6 (2C), 134.4, 133.3, 132.6, 129.85, 129.79, 127.6 (2C), 127.4 (2C), 117.7, 101.4, 77.1, 75.6, 65.3, 72.0, 65.3, 61.5, 26.7 (3C), 19.2; LRMS *m*/*z* (%) 467 (M^+; 2), 426 [$(M - C_3H_5)^+$; 3], 410 [$(M - t\text{Bu})^+$; 5].

(*Z*)-1,6-Anhydro-4-*O*-(*tert*-butyldiphenylsilyl)-3-deoxy-3-methoxyimine-2-*O*-(prop-2′-inyl)-*β*-D-arabino-hexopyranose (21). A solution of alcohol **10** (750 mg, 1.75 mmol) in dry THF (13.3 mL) was added to a cold (0 °C) suspension of NaH (60% in parafine, 105 mg, 2.63 mmol, 150 mol %) in 3.8 mL of the same solvent. When evolution of H_2 ceased, 3-bromopropine (0.28 mL, 2.63 mmol, 150 mol %) was added and the ice−water bath removed. Additional 3-bromopropine (100 mol %) was needed to completely transform **10**. Et_2O was then added, the mixture was washed with saturated NH_4Cl and the aqueous layer extracted with more Et_2O. The combined organic extracts were dried, filtered and concentrated. Chromatography through silica gel (EtOAc−hexane, 20:80) afforded alkyne **21** (820 mg, quant): ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.75 (m, 2H), 7.67 (m, 2H), 7.41 (m, 6H), 5.59 (d, J = 1.4 Hz, 1H), 4.92 (d, J = 2.0 Hz, 1H), 4.70 (d, J = 1.4 Hz, 1H), 4.48 (m, 2H), 4.38 (m, 1H), 3.66 (dd, J = 8.0 Hz, J = 5.9 Hz, 1H), 3.59 (s, 3H), 3.42 (d, J = 8.0 Hz, 1H), 2.52 (t, J = 2.4 Hz, 1H) 1.09 (s, 9H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 151.8, 135.7 (2C), 135.6 (2C), 133.7, 133.1, 129.9, 129.8, 127.6 (2C), 127.4 (2C), 101.4, 79.2, 77.2, 75.4, 74.3, 65.3, 65.2, 61.5, 57.9, 26.7 (3C), 19.2; LRMS *m*/*z* (%) 465 [3, M^+]; HRMS calcd for $C_{26}H_{31}NO_5Si$ (M^+) 465.197152, found 465.196081; $[\alpha]_D$ 67.2° (*c* 1.06, CH_2Cl_2).

Cyclization of Alkyne 21 with *n*-Bu_3SnH−Et_3B. A solution of **21** (450 mg, 0.97 mmol), *n*-Bu_3SnH (0.30 mL, 1.06 mmol, 110 mol %) and Et_3B (0.36 mL, 0.24 mmol, 25 mol %) in toluene (121 mL) was heated at 75 °C, first under Ar (36 h) and then allowing entrance of air through a $CaCl_2$ tube (24 h). Chromatographic purification of the residue obtained by evaporation of the solvent afforded **22a** (230 mg, 31%), **(2′*E*)-23a** (224 mg, 30%), **(2′*Z*)-23a** (59 mg, 8%) and **24a** (18 mg, 2%) as colorless oils. ***O*-Methyl-hydroxylamine 22a:** ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.87 (m, 4H, ArH_o), 7.43 (m, 6H, ArH_m, ArH_p), 6.63 (br s, 1H, NH), 5.73 (t, J_{9-7} = 2.4 Hz, 1H, H9), 5.38 (d, J_{1-2} = 2.6 Hz, 1H, H1), 4.65 (m, 2H, H7), 4.23

(m, 1H, H5), 4.06 (d, J_{4-5} = 1.5 Hz, 1H, H4), 3.75 (d, J_{2-1} = 2.6 Hz, 1H, H2), 3.45 (dd, $J_{6endo-6exo}$ = 7.3 Hz, 1H, H6endo), 3.35 (s, 3H, OCH_3), 3.26 (dd, $J_{6exo-6endo}$ = 7.3 Hz, J_{6exo-5} = 5.8 Hz, 1H, H6exo), 1.45 (m, 6H, $(CH_3CH_2CH_2CH_2)_3Sn$), 1.29 (m, 6H, $(CH_3CH_2CH_2CH_2)_3Sn$), 1.09 (s, 9H, *t*-Bu), 0.88 (m, 15H, $(CH_3CH_2CH_2CH_2)_3Sn$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 156.4 (C8), 136.3 (Ar, 2C, C_o), 136.0 (Ar, 2C, C_o), 134.0 (Ar, C_i), 132.0 (Ar, C_i), 130.0 (Ar, C_p), 129.8 (Ar, C_p), 127.6 (Ar, 4C, C_m), 119.8 (C9), 101.0 (C1), 81.1 (C2), 76.6 (C5), 73.8 (C7), 70.7 (C4), 67.3 (C3), 65.3 (C6), 62.3 (OCH_3), 29.1 (3C, $CH_3CH_2CH_2CH_2)_3Sn$), 27.2 (3C, $CH_3CH_2CH_2CH_2)_3Sn$), 26.9 (C(CH_3)$_3$), 19.5 (*C*(CH_3)$_3$), 13.6 (3C, $CH_3CH_2CH_2CH_2)_3Sn$), 9.6 (3C, $CH_3CH_2CH_2CH_2)_3Sn$); IR (neat) 3248 (medium, sharp, NH) cm^{-1}; LRMS *m*/*z* (%) 697 [5, (M − *t*Bu)$^+$]; HRMS calcd for $C_{38}H_{59}NO_5SiSn$ (M^+ + H) 757.329039, found 757.325799; $[\alpha]_D$ −65° (*c* 1.15, CH_2Cl_2). **(3*Z*,2′*E*)-23a:** ^1H NMR ($CDCl_3$, 300 MHz) δ 7.73 (m, 2H), 7.64 (m, 2H), 7.41 (m, 6H), 6.29 (d, *J* = 19.1 Hz, 1H), 6.13 (ddd, *J* = 19.1 Hz, *J* = 5.7 Hz, *J* = 4.5 Hz, 1H), 5.56 (d, *J* = 1.8 Hz, 1H), 4.91 (d, *J* = 2.2 Hz, 1H), 4.44 (ddd, *J* = 12.8 Hz, *J* = 4.5 Hz, *J* = 1.2 Hz, 1H), 4.41 (d, *J* = 1.8 Hz, 1H), 4.30 (m, 1H), 4.14 (ddd, *J* = 12.8 Hz, *J* = 5.7 Hz, *J* = 0.9 Hz, 1H), 3.66 (s, 3H), 3.63 (dd, *J* = 8.0 Hz, *J* = 5.7 Hz, 1H), 3.42 (dd, *J* = 8.0 Hz, *J* = 1.0 Hz, 1H), 1.50 (m, 6H), 1.31 (m, 6H), 1.07 (s, 9H), 0.90 (m, 15H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 152.3, 144.4, 135.9 (2C), 135.7 (2C), 133.5, 132.7, 132.2, 129.9, 129.8, 127.7 (2C), 127.5 (2C), 101.5, 77.2, 75.7, 74.9, 65.4, 65.37, 61.5, 29.1 (3C), 27.3 (3C), 26.7 (3C), 19.3, 13.7 (3C), 9.6 (3C); IR (neat): 1588 (weak, sharp, C=N) cm^{-1}; LRMS *m*/*z* (%) 697 [4, (M − *t*Bu)$^+$]. **(3*Z*,2′*Z*)-23a:** ^1H NMR ($CDCl_3$, 300 MHz) δ 7.74 (m, 2H), 7.65 (m, 2H), 7.41 (m, 6H), 6.63 (ddd, *J* = 13.0 Hz, *J*- *J* − 6.3 Hz, 1H), 6.13 (d, *J* = 13.0 Hz, 1H), 5.55 (d, *J* = 1.7 Hz, 1H), 4.90 (d, *J* = 2.1 Hz, 1H), 4.42 (m, 1H), 4.39 (d, *J* = 1.7 Hz, 1H), 4.28 (m, 1H), 4.14 (m, *J* = 12.1 Hz, *J* = 6.3 Hz, *J* = 1.0 Hz, 1H), 3.68 (s, 3H), 3.62 (dd, *J* = 7.9 Hz, *J* = 5.7 Hz, 1H), 3.40 (dd, *J* = 7.9 Hz, *J* = 1.0 Hz, 1H), 1.51 (m, 6H), 1.30 (m, 6H), 1.08 (s, 9H), 0.90 (m, 15H). **(*Z*)-1,6-Anhydro-4-*O*-(*tert*-butyldiphenylsilyl)-3-deoxy-3-methoxyimine-2-*O*-(2′-tributylstannyl-prop-2′-enyl)-*β*-D-arabino-hexopyranose (24a):** ^1H NMR ($CDCl_3$, 300 MHz) δ 7.74 (m, 2H), 7.65 (m, 2H), 7.42 (m, 6H), 5.97 (d, *J* = 2.4 Hz, 1H), 5.53 (d, *J* = 1.7 Hz, 1H), 5.33 (d, *J* = 2.4 Hz, 1H), 4.92 (d, *J* = 2.1 Hz, 1H), 4.59 (dd, *J* = 13.1 Hz, *J* = 1.5 Hz, 1H), 4.39 (d, *J* = 1.7 Hz, 1H), 4.30 (m, 1H), 4.23 (d, *J* = 13.1 Hz, 1H), 3.65 (s, 3H), 3.61 (dd, *J* = 8.0 Hz, *J* = 5.8 Hz, 1H), 3.41 (dd, *J* = 8.0 Hz, *J* = 0.9 Hz, 1H), 1.53 (m, 6H), 1.30 (m, 6H), 1.08 (s, 9H), 0.87 (m, 15H).

Cyclization of Alkyne 21 with Ph_3SnH−Et_3B. A solution of Ph_3SnH (226 mg, 0.64 mmol, 300 mol %) and Et_3B (0.32 mL, 0.32 mmol, 150 mol %), in 2 mL of benzene was slowly added (syringe pump, 3 h) to a refluxing solution of alkyne **21** (100 mg, 0.21 mmol) in 22 mL of the same solvent. After refluxing for additional 5.5 h, the solvent was removed and the residue purified by column chromatography through silica gel, to afford **22b** (72 mg, 41%), **(3Z,2′Z)-23b** (14 mg, 8%) and **(3Z,2′*E*)-23b** (49 mg, 28%) and **24b** (5 mg, 3%). ***O*-Methylhydroxylamine 22b:** ^1H NMR ($CDCl_3$, 300 MHz) δ 7.90 (m, 4H), 7.63−7.35 (m, 21H), 6.69 (br s, 1H), 6.03 (t, *J* = 2.4 Hz, 1H), 5.40 (d, *J* = 2.5 Hz, 1H), 4.58 (dd, *J* = 13.3 Hz, *J* = 2.4 Hz, 1H), 4.48 (dd, *J* = 13.3 Hz, *J* = 2.4 Hz, 1H), 4.31 (m, 1H), 4.15 (br s, 1H), 3.78 (d, *J* = 2.5 Hz, 1H), 3.60 (d, *J* = 7.5 Hz, 1H), 3.39 (s, 3H), 3.34 (dd, *J* = 7.5 Hz, *J* = 5.8 Hz, 1H), 1.13 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 160.2, 137.5 (3C), 136.8 (6C), 136.3 (2C), 136.0 (2C), 133.8, 131.9, 130.1, 129.8, 129.2 (3C), 128.7 (6C), 127.7 (2C), 127.6 (2C), 115.9, 100.9, 81.0, 76.6, 74.1, 70.6, 67.9, 65.4, 62.4, 26.9 (3C), 19.4; LRMS *m*/*z* (%) 349 [39, (Ph_3Sn)$^+$], 196 [16, (M − Ph_3Sn − *t*BuPh_2Si − MeO)$^+$]; HRMS calcd for $C_{44}H_{47}NO_5SiSn$ (M^+) 816.248642, found 816.246401; $[\alpha]_D$ 226.6° (*c* 1.72, CH_2Cl_2). **(3*Z*,2′*E*)-23b:** ^1H NMR ($CDCl_3$, 300 MHz) δ 7.76−7.34 (m, 25H), 6.62 (d, *J* = 19.0 Hz, 1H), 6.38 (ddd, *J* = 19.0 Hz, *J* = 5.0 Hz, *J* = 4.2 Hz, 1H), 5.58 (s, 1H), 4.93 (d, *J* = 1.6 Hz, 1H), 4.58 (dd, *J* = 13.5 Hz, *J* = 4.2 Hz, 1H), 4.43 (s, 1H), 4.32 (m, 1H), 4.24 (dd, *J* = 13.5 Hz, *J* = 5.0 Hz, 1H, H7), 3.64 (s, 3H), 3.67−3.62 (m, 1H), 3.43 (d, *J* = 7.9 Hz, 1H), 1.06 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 152.2, 148.1, 138.0 (3C), 137.0 (6C), 135.8 (2C), 135.7 (2C), 133.4, 132.7, 129.9, 129.8, 129.0 (3C), 128.5 (6C), 127.7 (2C), 127.4 (2C), 126.7, 101.4, 77.2, 76.4, 65.4, 74.3, 65.3, 61.6, 26.7 (3C), 19.3; LRMS *m*/*z* (%) 426 [6, (M − $Ph_3SnCHCHCH_2$)$^+$]. **(3*Z*,2′*Z*)-1,6-Anhydro-4-*O*-(*tert*-butyldiphenylsilyl)-3-deoxy-3-(*Z*)-methoxyimine-2-*O*-(3′-triphenylstannyl-prop-2′-enyl)-*β*-D-arabino-hexopyranose (23b).** ^1H NMR ($CDCl_3$, 300 MHz) δ 7.74−7.30 (m, 25H), 7.03 (m, 1H), 6.49 (d, *J* = 12.7 Hz, 1H), 5.04 (d, *J* = 1.7 Hz, 1H), 4.81 (d, *J* = 1.9 Hz, 1H), 4.41 (m, 1H), 4.21 (m, 1H), 4.08 (dd, *J* = 12.2 Hz, *J* = 6.4 Hz, 1H), 3.94 (d, *J* = 1.7 Hz, 1H), 3.56 (s, 3H), 3.64−3.52 (m, 1H), 3.30 (d, *J* = 8.0 Hz, 1H), 1.03 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 151.9, 148.0, 138.8 (3C), 136.8 (6C), 135.8 (2C), 135.7 (2C), 133.4, 132.7, 129.9, 129.8, 129.0 (3C), 128.6 (6C), 127.7 (2C), 127.4 (2C), 127.6, 101.2, 77.2, 76.2, 65.3, 73.5, 65.2, 61.5, 26.8 (3C), 19.3; LRMS *m*/*z* (%) 227 [6, (M − Ph_3Sn-*t*BuPh_2-Si)$^+$]. **(*Z*)-1,6-Anhydro-4-*O*-(*tert*-butyldiphenylsilyl)-3-deoxy-3-methoxyimine-2-*O*-(2′-triphenylstannyl-prop-2′-enyl)-*β*-D-arabino-hexopyranose 24b.** ^1H NMR ($CDCl_3$, 300 MHz) δ 7.71−7.53 (m, 10H), 7.45−7.30 (m, 15H), 6.19 (d, *J* = 1.4 Hz, 1H), 5.57 (d, *J* = 1.4 Hz, 1H), 4.87−4.76 (m, 3H), 4.37 (d, *J* = 13.1 Hz, 1H), 4.20 (m, 2H), 3.57 (s, 3H), 3.53 (dd, *J* = 7.8 Hz, *J* = 5.8 Hz, 1H), 3.33 (d, *J* = 7.8 Hz, 1H), 1.06 (s, 9H).

(*Z*)-1,6-Anhydro-3-deoxy-3-methoxyimine-2-*O*-(prop-2′-inyl)-*β*-D-arabino-hexopyranose (25). TBAF (1M in THF, 1.62 mL, 1.62 mmol, 110 mol %) was added to a solution of the silyl ether **21** (688 mg, 1.48 mmol) in dry THF (18 mL), kept under Ar at −78 °C. The cold bath was immediately removed and the progress of the reaction was monitored by TLC. Once the starting material was completely consumed, the reaction mixture was concentrated, redisolved in EtOAc and washed successively with saturated aqueous solutions of NH_4Cl and NaCl. The organic layer was dried, filtered and concentrated. The oily residue was purified by column chromatography through silica gel (EtOAc−hexane, 60:40) to afford alcohol **25** (300 mg, 89%) as a pale yellow oil: ^1H NMR ($CDCl_3$, 300 MHz) δ 5.52 (d, *J* = 2.3 Hz, 1H), 4.85 (d, *J* = 1.3 Hz, 1H), 4.56 (m, 1H), 4.43 (m, 3H), 3.88 (s, 3H), 3.81 (dd, *J* = 8.0 Hz, *J* = 5.8 Hz, 1H), 3.63 (dd, *J* = 8.0 Hz, *J* = 1.2 Hz, 1H), 3.08 (br s 1H), 2.47 (t, *J* = 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 153.3, 100.6, 79.1, 76.6, 75.4, 73.2, 65.7, 64.6, 62.2, 58.3; IR (neat) 3432 (medium, broad, OH), 2215 (weak, sharp, C + N) cm^{-1}; LRMS *m*/*z* (%)196 [0.4, (M − MeO)$^+$], 188 [100, (M − $CHCCH_2$)$^+$].

Cyclization of Alkyne 25. A solution of Ph_3SnH (0.2 mL, 0.77 mmol, 250 mol %) and Et_3B (0.46 mL, 0.46 mmol, 150 mol %) in 5 mL of benzene was slowly added (syringe pump, 5 h) to a refluxing solution of **25** (70 mg, 0.31 mmol) in 31 mL of the same solvent. Chromatography of the residue obtained by solvent removal (EtOAc−hexane, 50:50), afforded **26** (122 mg, 68%) **27** (5 mg, 3%) and **28** (5 mg, 3%). **Tetrahydrofuran 26:** ^1H NMR ($CDCl_3$, 250 MHz) δ 7.61−7.55 (m, 6H), 7.45−7.38 (m, 9H), 6.39 (t, *J* = 2.5 Hz, 1H), 6.04 (br s, 1H), 5.39 (d, *J* = 2.6 Hz, 1H), 4.66 (m, 1H), 4.60 (dd, *J* = 13.4 Hz, *J* = 2.5 Hz, 1H), 4.44 (dd, *J* = 13.4 Hz, *J* = 2.5 Hz, 1H), 4.25 (m, 1H), 3.91 (d, *J* = 7.5 Hz, 1H), 3.77 (d, *J* = 2.6 Hz, 1H), 3.67 (dd, *J* = 7.5 Hz, *J* = 5.6 Hz, 1H), 3.55 (s, 3H), 3.44 (d, *J* = 4.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 159.5, 137.3 (3C), 136.7 (6C), 129.3 (3C), 128.7 (6C), 116.4, 100.6, 80.1, 76.9, 68.3, 73.8, 67.5, 65.7, 62.7. IR (neat): 3422 (medium, broad, OH) cm^{-1}; LRMS *m*/*z* (%) 546 [0.3, (M − MeO)$^+$], 197 [100, (M − MeO − Ph_3-Sn)$^+$]; HRMS calcd for $C_{28}H_{29}NO_5Sn$ (M^+) 578.964183, found 578.965235; $[\alpha]_D$ −36.3° (*c* 1.07, CH_2Cl_2). **Vinylstannane 27:** ^1H NMR ($CDCl_3$, 250 MHz) δ 7.57 (m, 6H), 7.39 (m, 9H), 6.62 (d, *J* = 19.0 Hz, 1H), 6.36 (ddd, *J* = 19.0,_4.9 and -_4.9 Hz, 1H), 5.56 (d, *J* = 1.9 Hz, 1H), 4.91 (m, 1H, H4), 4.61−4.53 (m, 2H), 4.31 (dd, *J* = 13.5 and 4.9 Hz, 1H), 4.25 (d, *J* = 1.9 Hz, 1H), 3.92 (s, 3H), 3.87 (dd, *J* = 8.0 and 5.8 Hz, 1H), 3.72 (dd, *J* = 8.0 and 0.9 Hz, 1H), 2.69 (s, broad, 1H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 153.6, 147.8, 137.9 (3C), 137.0 (6C), 129.0 (3C), 128.5 (6C), 127.2, 100.7, 76.7, 74.9, 65.0, 74.7, 65.9, 62.3; LRMS *m*/*z* (%) 502 (4), 500 [3, (M − Ph)$^+$], 349 [21, (Ph_3Sn)$^+$], 197 [47, (M − MeO − Ph_3Sn)$^+$], 195 [35, (PhSn)$^+$], 188 [100, (M − $Ph_3SnCHCHCH_2$)$^+$]. **Vinylstannane 28:** ^1H NMR ($CDCl_3$, 250 MHz) δ 7.63 (m, 6H), 7.40 (m, 9H), 6.21 (d, *J* = 1.4 Hz, 1H), 5.59 (d, *J* = 1.4 Hz, 1H), 4.93 (d, *J* = 2.0 Hz, 1H), 4.87−4.81 (m, 2H), 4.50−4.44 (m, 2H), 4.04 (d, *J* = 2.0 Hz, 1H), 3.85 (s,

3H), 3.78 (dd, J = 7.9 and 5.9 Hz, 1H), 3.61 (d, J = 7.9 Hz, 1H), 2.04 (d, J = 6.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 153.3, 149.0, 137.9 (3C), 137.2 (6C), 129.6, 128.9 (3C), 128.4 (6C), 100.4, 77.1, 76.5, 74.3, 64.7, 65.7, 62.2; LRMS m/z (%) 502 (18), 500 [14, $(M - Ph)^+$], 462 [24, $(M - Ph - MeO)^+$], 349 [75, $(Ph_3Sn)^+$], 272 [12, $(Ph_2Sn)^+$], 197 [81, $(M - MeO - Ph_3Sn)^+$], 195 [60, $(PhSn)^+$].

(*Z*)-1,6-Anhydro-2-*O*-(1′-ethoxy-2′-iodoethyl)-3-deoxy-3-methoxyimine-*β*-D-arabino-hexopyranose (29). It was prepared from iodoacetals **11** (5.53 g, 8.84 mmol) and TBAF (1 M in THF, 9.72 mL, 9.72 mmol, 110 mol %) in dry THF (100 mL), as described for **25**. Purification (EtOAc−hexane, 50:50) afforded iodoacetals **29** (3.24 g, 95%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.48 (d, J = 2.3 Hz, 1H), 5.45 (d, J = 2.2 Hz, 1H), 4.90 (m, 2H), 4.85 (m, 2H), 4.57 (m, 2H), 4.46 (br s, 2H), 3.90 (s, 3H), 3.89 (s, 3H) 3.85−3.18 (m, 12H), 3.07 (br s, 2H), 1.20 (t, J = 7.0 Hz, 3H), 1.19 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 153.2, 153.0, 102.5, 101.8, 101.1, 100.9, 76.6, 72.3, 64.8, 76.6, 69.9, 64.8, 65.8 (2C), 62.9, 62.4, 62.2, 61.7, 14.9, 14.7, 5.0, 4.8.

Acetal 30. A deoxygenated solution of Ph_3SnH (3.1 mL, 12.2 mmol, 140 mol %) and AIBN (411 mg, 2.5 mmol, 30 mol %) in 25 mL of dry toluene was slowly added (syringe pump, 8 h) to a deoxygenated and preheated (100 °C) solution of the iodoacetals **29** (3.23 g, 8.34 mmol) in 334 mL of the same solvent. The reaction was concentrated and the residue was redissolved in CH_2Cl_2 and treated with 10% aqueous KF. After vigorous stirring for 15 min, the solid was removed by filtration, the phases were separated and the aqueous layer extracted with CH_2Cl_2. The combined organic extracts were dried, filtered and concentrated in vacuo obtaining an oil which was purified through silica gel (EtOAc−hexane, 75:25). Cyclic acetals **30** were obtained as colorless oils in 58% yield (1.26 g). **Fast moving epimer:** ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.15 (br s, 1H), 5.35 (d, J = 2.8 Hz, 1H), 5.27 (d, J = 5.9 Hz, 1H), 4.64 (m, 1H), 4.16 (m, 1H), 3.82−3.69 (m, 5H), 3.58 (s, 3H), 3.54−3.45 (m, 1H), 2.58 (d, J = 13.7 Hz, 1H), 1.87 (dd, J = 13.7 Hz, J = 5.9 Hz, 1H), 1.21 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 103.9, 99.5, 78.4, 77.2, 69.0, 66.4, 65.2, 63.6, 61.5, 38.8, 15.2; LRMS m/z (%) 261 [0.2, $(M)^+$], 215 [100, $(M - MeONH)^+$]; HRMS calcd for $C_{11}H_{19}NO_6$ (M^+) 261.121238, found 261.121835; $[\alpha]_D$ 65° (c 1.93, CH_2Cl_2). **Slow moving epimer:** ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.15 (br s, 1H), 5.39 (m, 2H), 4.62 (m, 1H), 3.94−3.73 (m, 4H), 3.66−3.44 (m, 1H), 3.58 (s, 3H), 3.40 (d, J = 2.8 Hz, 1H), 3.34 (br s, 1H), 2.56 (dd, J = 13.3 Hz, J = 5.2 Hz, 1H), 1.72 (dd, J = 13.3 Hz, J = 7.0 Hz, 1H), 1.22 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 105.1, 99.7, 78.1, 77.4, 70.0, 67.7, 65.7, 65.1, 63.2, 39.5, 15.3; LRMS m/z (%) 261 [1, $(M)^+$].

Aldehyde 31. Powdered molecular sieves 3A (75 mg, activated) and a solution of methylentetrahydrofurane **22a** (51 mg, 0.072 mmol) in dry CH_2Cl_2 (0.5 mL) were added to a suspension of CrO_3 (143 mg, 1.43 mmol, 2000 mol %) in dry pyridine (0.14 mL) and dry CH_2Cl_2 (1.5 mL) previously stirred at room temperature for 30 min. The resulting mixture was refluxed and, when finished (TLC), filtered and washed with saturated $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2, the combined organic extracts washed with 2 N HCl, dried, filtered and concentrated. p-TLC (EtOAc−hexane, 16:84) of the residue so obtained afforded α,β-unsaturated aldehyde **31** (9 mg, 29%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.83 (s, 1H), 7.71 (m, 2H), 7.65 (m, 2H), 7.43 (m, 6H), 5.56 (d, J = 1.6 Hz, 1H), 5.09 (m, 1H), 4.82−4.65 (m, 4H), 3.72 (dd, J = 8.0 Hz, J = 5.7 Hz, 1H), 3.36 (d, J = 8.0 Hz, 1H), 1.09 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 183.9, 149.9, 137.1, 135.8 (2C), 135.6 (2C), 132.5, 132.2, 130.6, 130.4, 128.1 (2C), 128.0 (2C), 102.9, 86.1, 78.2, 67.9, 74.4, 66.5, 26.7 (3C), 19.3; IR (neat) 1676 (strong, sharp, CO) cm^{-1}; LRMS m/z (%) 437 [0.1, $(M + 1)^+$], 436 [1, $(M)^+$]. HRMS m/z $C_{25}H_{28}O_5Si$ calcd: 436.1706, found: 436.1706.

Urethane 32. A solution of triphosgene (483 mg, 1.62 mmol, 50 mol %) in dry CH_2Cl_2 (10 mL) was added dropwise at −78 °C to a solution of amino alcohols **30** (1:1 epimeric mixture, 850 mg, 3.25 mmol) and pyridine (1.93 mL, 19.52 mmol, 600 mol %) in the same solvent (16.3 mL). The cold bath was removed and the reaction was allowed to warm to room temperature. A saturated aqueous solution of NH_4Cl was added and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were washed with 10% aqueous $CuSO_4$, dried, filtered and concentrated in vacuo. Purification of the crude mixture (EtOAc−hexane, 70:30) afforded **32** (1:1 mixture of epimers, 801 mg, 86%) as a white solid (mp = 121 °C): ^{1}H NMR ($CDCl_3$, 250 MHz) δ 5.45 (d, J = 3.1 Hz, 1H), 5.38 (d, J = 3.0 Hz, 1H), 5.32 (m, 1H), 5.27 (dd, J = 5.9 Hz, J = 0.9 Hz, 1H), 4.70 (m, 2H), 4.38 (br s, 1H), 4.32 (br s, 1H), 4.24 (d, J = 3.0 Hz, 1H), 4.02 (d, J = 3.1 Hz, 1H), 3.85 (s, 3H), 3.83 (s, 3H), 3.92−3.70 (m, 6H), 3.59−3.36 (m, 2H), 2.51 (dd, J = 13.9 Hz, J = 5.1 Hz, 1H), 2.37 (dd, J = 14.5 Hz, J = 0.9 Hz, 1H), 2.23 (dd, J = 14.5 Hz, J = 5.9 Hz, 1H), 2.05 (dd, J = 13.9 Hz, J = 6.1 Hz, 1H), 1.17 (t, J = 7.0 Hz, 3H), 1.15 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 156.4, 155.6, 104.1, 103.4, 98.3, 98.2, 77.4, 75.5, 73.2, 77.3, 75.2, 73.1, 67.0, 66.6, 65.1, 64.9, 64.9, 64.6, 64.8, 63.1, 44.7, 41.8, 15.0, 14.9; IR (neat) 1783 (strong, sharp, NCOO) cm^{-1}; LRMS m/z (%) 288 [2, $(M + 1)^+$], 287 [13, $(M)^+$]; HRMS m/z $C_{12}H_{17}NO_7$ calcd: 287.1005, found 287.1003.

Lactone 33. Jones reagent (4 mL, prepared from 2 g of CrO_3 in 4 mL of water and 2 mL of H_2SO_4) was added to a mixture of acetals **32** (232 mg, 0.81 mmol) in 2.7 mL of acetone. A few drops of 2-propanol were added and the mixture was neutralized with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 and the organic extracts were dried, filtered and concentrated. Purification of the crude residue (EtOAc−hexane, 65:35) afforded **33** as a white solid (168 mg, 80%, mp = 230−231 °C): ^{1}H NMR (CD_3CN, 300 MHz) δ 5.54 (d, J = 2.5 Hz, 1H), 4.87 (m, 1H), 4.63 (br s, 1H), 4.55 (d, J = 2.5 Hz, 1H), 4.06 (d, J = 9.0 Hz, 1H), 3.86 (s, 3H), 3.80 (dd, J = 9.0 Hz, J = 5.4 Hz, 1H), 3.02 (d, J = 19.2 Hz, 1H), 2.93 (d, J = 19.2 Hz, 1H); ^{13}C NMR (CD_3CN, 75 MHz) δ 173.2, 156.0, 97.3, 77.8, 73.7, 65.7, 65.5, 64.4, 37.0; IR (neat): 1784 (strong, sharp, 2 × COO) cm^{-1}; LRMS m/z (%) 257 [10, $(M)^+$]; HRMS m/z $C_{10}H_{11}NO_7$ calcd: 257.0535, found: 257.0538. Anal. calcd for $C_{11}H_{11}NO_7$: C, 46.70; H, 4.31; N, 5.44. Found: C, 46.72; H, 4.76; N, 5.48.

α-Methylenelactone 34. NaH (60% in parafine, 78 mg, 1.96 mmol, 120 mol %) was added to a mixture of lactone **33** (420 mg, 1.63 mmol) and paraformaldehyde (490 mg, 16.33 mmol, 1000 mol %) in 25 mL of dry THF. Additional NaH (50 mol %) and heating to 45 °C were needed to completely consume **33**. Saturated aqueous NH_4Cl was added and the mixture was extracted with CH_2Cl_2. The combined extracts were dried, filtered and concentrated. Chromatography through silica gel (EtOAc−hexane, 60:40) gave α-methylenelactone **34** as a white solid (355 mg, 81%, mp = 218EC): ^{1}H NMR (CD_3CN, 250 MHz) δ 6.71 (br s, 1H), 6.44 (d, J = 1.0 Hz, 1H), 5.56 (d, J = 2.6 Hz, 1H), 4.87 (m, 1H), 4.70 (m, 2H), 3.77−3.70 (m, 1H), 3.70 (s, 3H), 3.66 (dd, J = 8.7 Hz, J = 1.1 Hz, 1H); ^{13}C NMR (CD_3CN, 75 MHz) δ 168.0, 155.5, 134.6, 130.2, 97.2, 76.0, 75.4, 73.3, 65.7, 65.6, 63.5; IR (neat) 1777 (strong, sharp) cm^{-1}; LRMS m/z (%) 270 [1, $(M + 1)^+$], 269 [27, $(M)^+$]; HRMS calcd for $C_{11}H_{11}NO_7$ (M^+) 269.053552, found 269.054059; $[\alpha]_D$ −110.1° (c 0.85, CH_2Cl_2).

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Supporting Information Available: Spectral data for compounds **4**, **6**, **11**, **15**, **17**, **19**, **21**, **22a**, **22b**, **25**, **26**, and **29**−**34**. This material is available free of change via the Internet at http://pubs.acs.org.

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