Amino Sugar Synthesis

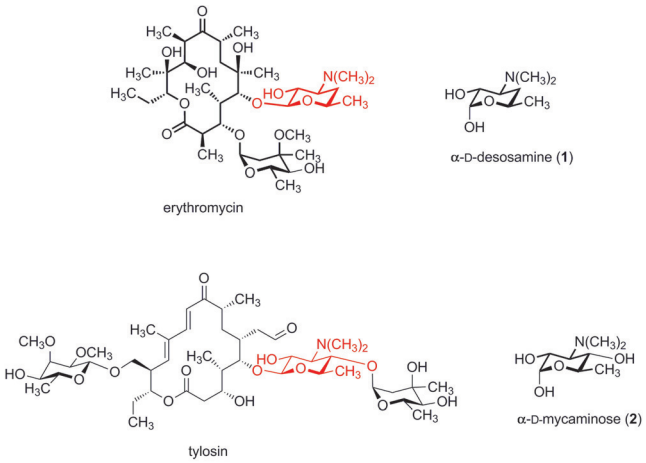
Deutsche Ausgabe: DOI: 10.1002/ange.201507357
Internationale Ausgabe: DOI: 10.1002/anie.201507357

Synthesis of D-Desosamine and Analogs by Rapid Assembly of 3-Amino Sugars

*Ziyang Zhang, Takehiro Fukuzaki, and Andrew G. Myers**

Abstract: *D-Desosamine is synthesized in 4 steps from methyl vinyl ketone and sodium nitrite. The key step in this chromatography-free synthesis is the coupling of (R)-4-nitro-2-butanol and glyoxal (trimeric form) mediated by cesium carbonate, which affords in crystalline form 3-nitro-3,4,6-trideoxy-α-D-glucose, a nitro sugar stereochemically homologous to D-desosamine. This strategy has enabled the syntheses of an array of analogous 3-nitro sugars. In each case the 3-nitro sugars are obtained in pure form by crystallization.*

D-Desosamine (**1**) and its 4-hydroxylated counterpart D-mycaminose (**2**) are 3-amino sugars that are constituents of the macrolide antibiotics erythromycin and tylosin, respectively (Scheme 1).[1] X-ray crystallographic studies reveal that

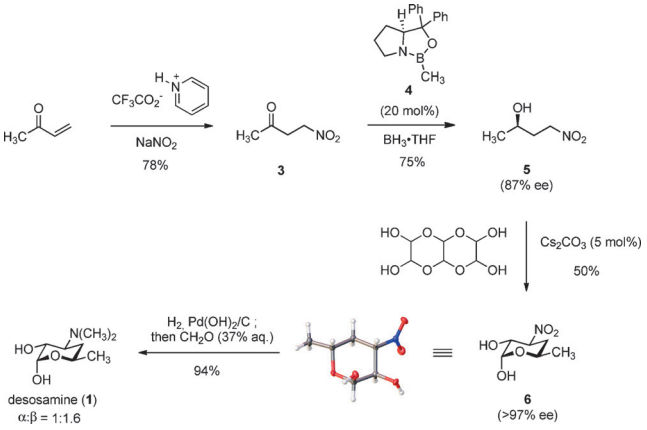


Scheme 1. Structures of erythromycin, tylosin, desosamine (**1**) and mycaminose (**2**).

both sugars make extensive contacts within the 23S subunit of bacterial ribosomal RNA, and thus it is thought that they play key roles in antibiotic activity.[2] This idea is supported by antimicrobial testing data of macrolides lacking these residues, which reveal them to be inactive. Since the structure of desosamine was determined in 1962,[3] a number of syntheses of this substance have been reported,[4] including three stereospecific approaches to the naturally occurring enantiomer, D-desosamine.[4c,e,f] In 1964 Richardson reported a synthesis of D-desosamine from methyl 3-acetamido-4,6-*O*-benzylidene-3-deoxy-α-D-glucopyranoside that proceeded in 8 steps and 1.6% yield.[4c] Davidson and McDonald reported an 11-step synthesis of D-desosamine-1,2-diacetate in 2004 that featured a tungsten-catalyzed alkynol cycloisomerization. This route employed (*R*)-3-*tert*-butyldimethylsiloxybutanal as starting material and proceeded in 13% overall yield.[4e] Most recently, Velvadapu and Andrade published a 5-step route to D-desosamine employing methyl α-D-glucopyranoside as starting material that proceeded in 16% overall yield.[4f] Desosamine can also be obtained from erythromycin by acidic hydrolysis,[1] a process that we have found to be somewhat laborious.

As part of an ongoing program to develop a practical and scalable route to novel macrolide antibiotics, we required a simple and efficient method to prepare D-desosamine and its analogs on 10-g scale, with potential for further scaling. Existing routes to D-desosamine were considered to be nonideal as a consequence of their lengths or reliance upon a number of chromatographic purifications. Here we describe a four-step route to highly enantiomerically enriched D-desosamine (**1**) from methyl vinyl ketone that is suitable for large-scale synthesis and requires no chromatography. Strategically, the amino sugar scaffold is assembled from (*R*)-4-nitro-2-butanol and glyoxal (trimeric form) in a single-step process that forms three stereogenic centers, one of them the stereomerically labile anomeric center.

The optimized 4-step sequence to D-desosamine (**1**) is shown in Scheme 2, and begins with the transformation of methyl vinyl ketone to 4-nitro-2-butanone (**3**). Miyakoshi et al. have reported that conjugate addition of sodium nitrite to methyl vinyl ketone in a mixed solvent of acetic acid and



Scheme 2. Synthesis of D-desosamine (**1**).[19]

[*] Z. Zhang, Dr. T. Fukuzaki, Prof. Dr. A. G. Myers
Department of Chemistry and Chemical Biology, Harvard University
Cambridge, MA 02138 (USA)
E-mail: myers@chemistry.harvard.edu

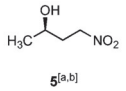
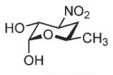
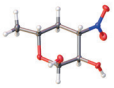
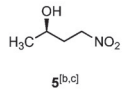
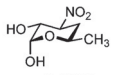
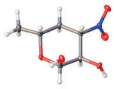
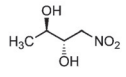
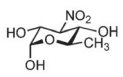
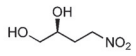
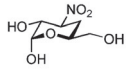
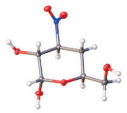
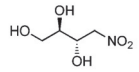
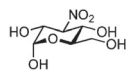
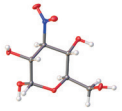
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201507357.

THF provides 4-nitro-2-butanone (**3**) in 82% yield.[5] When we employed this method to prepare **3** we did successfully obtain the desired product, but it was contaminated with 4-acetoxy-2-butanone as a by-product (ca. 4:1 ratio, respectively) and the mixture proved challenging to separate. We found that this problem was obviated by substituting pyridinium trifluoroacetate for acetic acid. Thus, in one larger-scale experiment, solid pyridinium trifluoroacetate (173 g, 898 mmol, 1.10 equiv) was added portionwise over 10 min to a stirred heterogeneous mixture of methyl vinyl ketone (68.1 mL, 816 mmol, 1 equiv) and sodium nitrite (61.9 g, 898 mmol, 1.10 equiv) in THF (408 mL) at 0°C. Upon completion of addition, the mixture was allowed to warm to 23°C over 1 h. After 17 h, a second portion of sodium nitrite (11.3 g, 164 mmol, 0.200 equiv) and pyridinium trifluoroacetate (31.5 g, 164 mmol, 0.200 equiv) was added at 23°C and the mixture was further stirred for 3 h. 4-Nitro-2-butanone (**3**) was obtained in a high state of purity in 78% yield (74.2 g) after extractive isolation (ether-hydrochloric acid) and filtration of the crude product through a pad of silica gel (see Supporting Information for details). While it has been reported that **3** can be purified by distillation, we do not recommend this, as we have observed that more often than not attempted distillation leads to decomposition (browning) with bumping, perhaps due to retro-Michael addition to form nitrous acid and methyl vinyl ketone. Because **3** is formed in a high state of purity by our modified method, we find that no further purification is necessary. Enantioselective reduction of **3** was achieved by slow addition over 1 h of a solution of the "crude" ketone **3** (46.0 g, 393 mmol, 1 equiv) in THF (100 mL) to a stirred mixture of a solution of the Corey–Bakshi–Shibata oxazaborolidine catalyst **4**[6] in toluene (1.0 M, 79 mL, 79 mmol, 20 mol%), a solution of borane-tetrahydrofuran complex in THF (1.0 M, 275 mL, 275 mmol, 0.70 equiv), and THF (982 mL) at −10°C. Dilution of the reaction mixture with 2 N hydrochloric acid, extraction of the product with ethyl acetate, concentration of the product extract and distillation of the residue (1.5 mmHg, 85°C) afforded the secondary alcohol **5** in 75% yield (35.1 g) and 87% *ee* (Mosher ester analysis).[7] We find that the use of a substoichiometric amount of borane and slow addition of the ketone are key factors to achieve reproducibly high enantioselectivities. The amino alcohol ligand (*S*)-1,1-diphenylprolinol was readily recovered by neutralization of the acidic aqueous layer with solid sodium hydroxide, extraction with dichloromethane, concentration of the extracts, and recrystallization of the residue from hot heptane (16.9 g, 84% recovery, m.p. 72–74°C). The recovered ligand can be used to regenerate the catalyst **4** in one step, as reported by Corey et al.[6a] (see Supporting Information for details).

In the key step of the sequence, an aqueous solution of cesium carbonate (5.0 M, 2.52 mL, 12.6 mmol, 0.050 equiv) was added to a stirred heterogeneous mixture of glyoxal trimer dihydrate (24.8 g, 118 mmol, 1.41 equiv of monomeric glyoxal), nitro alcohol **5** (30.0 g, 252 mmol, 1 equiv) and 1:1 *n*-butanol:dichloromethane (50.4 mL) at 0°C. The α-D nitro sugar **6** precipitated from the reaction mixture over the course of 17 h at 23°C. The precipitate was not isolated at this stage; instead, 6 N aqueous hydrochloric acid (6.0 mL) and ether (100 mL) were added to the suspension. Further stirring for 24 h at 23°C led to additional precipitation of product **6**, presumably due to acid-catalyzed conversion of the soluble β-anomer in the mother liquor to the less soluble α-anomer. Filtration of the reaction suspension through a sintered glass funnel (medium porosity) afforded the first crop of **6** in pure form as a white powder (20.1 g, 45%, m.p. 178–180°C). A second crop of **6** was obtained by extracting the filtrate with ethyl acetate, concentration of the extracts, and trituration of the residue with ether (2.2 g, 5%, m.p. 178–180°C, see Supporting Information for details). Chiral HPLC analysis established that both crops of the product were of >97% *ee*, which is substantially higher than the *ee* of the starting nitro alcohol **5**. Although further purification of **6** is unnecessary, if desired, it can be recrystallized from hot *n*-butanol (75% recovery, m.p. 185–187°C). X-ray crystallographic analysis of crystals obtained from *n*-butanol confirmed that the stereochemistry of the nitro sugar was fully homologous with D-desosamine and further revealed that the anomeric configuration was α (^{1}H NMR analysis of a solution of **6** in deuterated methanol showed it to exist as a 15:1 mixture of α- and β-anomers, respectively). The cyclization reaction can also be performed with 40 wt % aqueous glyoxal solution (1.05 equiv) and sodium carbonate (5 mol%) in 3:1 dichloromethane:water, but proceeds in lower yield (41%, entry 2, Table 1). Completion of the synthesis was achieved in one final operation wherein nitro reduction and reductive amination were conducted sequentially. Thus, a suspension of **6** (15.0 g, 85.0 mmol, 1 equiv) and palladium hydroxide on carbon (20 wt %, 6.0 g) in 9:1 methanol:acetic acid (420 mL) was stirred under H_2 (1 atm) at 23°C. Aqueous formaldehyde (37 wt %, 15.8 mL, 2.50 equiv) was added after 7–8 h, when TLC analysis indicated that full consumption of nitro sugar **6** had occurred, and the mixture was stirred under hydrogen for an additional 12 h. Filtration of the reaction suspension through Celite, concentration of the filtrate and neutralization of the ammonium acetate salt with Amberlyst A26 resin afforded D-desosamine (**1**) as a yellow oil in 94% yield (13.9 g, 94% yield, 1:1.6 α:β). The yield of the 4-step sequence from methyl vinyl ketone is 27.5%.

A remarkable feature of our synthesis of desosamine is the efficient and operationally simple cyclization reaction that provides the crystalline nitro sugar **6**. This key cyclization certainly involves both a Henry reaction and hemiacetalization, though the ordering of these events is not known. We surmise that the nitroalcohol **5** and glyoxal first form a diastereomeric mixture of open-chain hemiacetals, which then undergo an intramolecular Henry reaction to give the product (as an α-anomeric mixture), but we have no direct evidence to support this. ^{1}H NMR analysis of the reaction solution reveals that other minor diastereomers are present in the mother liquor, but the desired product **6** is formed preferentially and precipitates selectively from the reaction mixture. Presumably the C–C bond-forming (Henry) reaction is reversible under the reaction conditions, allowing for equilibration of diastereomers in solution; when the concentration of diastereomer **6** reaches saturation, this isomer precipitates, driving the production of the desired diastereomer (**6**). Although the yield (50%) may be regarded as

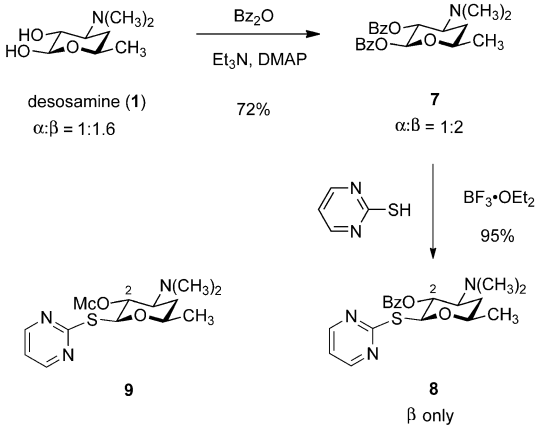
Table 1: Synthesis of 3-nitro sugars by condensation of γ-nitro alcohols and glyoxal.

entry	γ-nitro alcohol	3-nitro sugar	X-ray structure[19]
1	 **5**[a,b]	 **6** (50%)	
2	 **5**[b,c]	 **6** (41%)	
3	 **13**[c]	 **14** (41%)	
4	 **15**[c]	 **16** (43%)	
5	 **17**[c]	 **18** (43%)	

[a] Reaction conditions: γ-nitroalcohol (1 equiv), glyoxal trimer (1.41 equiv of monomeric glyoxal), cesium carbonate (0.05 equiv). [b] The *ee* of this starting material was 87%; all other starting materials were >98% *ee*. [c] Reaction conditions: γ-nitroalcohol (1 equiv), 40 wt% aqueous glyoxal (1.20–1.30 equiv), sodium carbonate (0.05–0.20 equiv), water (2.5–5.0 M). See the Supporting Information for detailed procedures and syntheses of starting materials.

moderate, the availability and affordability of starting materials allows the reaction to be performed on large scale and isolation of pure product is facile. We believe that further optimization of the process is possible.

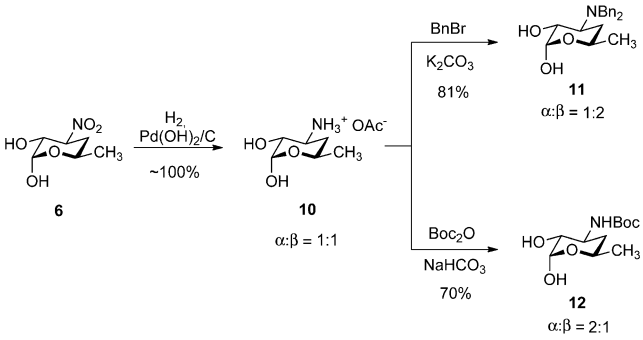
Thioglycoside **9** is an anomerically activated, *O*-protected form of desosamine developed for glycosidic coupling reactions of desosamine by Woodward and co-workers in their landmark synthesis of erythromycin A.[8] During our research on the synthesis of macrolide antibiotics, we have found that glycosylation reactions of certain challenging (sterically hindered) substrates proceed more efficiently and with higher β-anomeric selectivity using the slightly modified thioglycoside **8**, in which the 2-hydroxy group is protected as a benzoate ester rather than a methyl carbonate group (Scheme 3).[9] We have developed a two-step transformation that allows for convenient preparation of **8** on >10-g scale from D-desosamine. Thus, benzoic anhydride (39.9 g, 176 mmol, 3.00 equiv) was added in one portion to a mixture of D-desosamine (10.3 g, 58.8 mmol, 1 equiv), triethylamine (16.4 mL, 118 mmol, 2.00 equiv) and 4-dimethylaminopyridine (7.18 g, 58.8 mmol, 1.00 equiv) in ethyl acetate (294 mL) at 23 °C, and the mixture was stirred at 23 °C for 16 h. After an aqueous workup, D-desosamine 1,2-dibenzoate (**7**) was



Scheme 3. Synthesis of thioglycoside **8**.

obtained as an orange foam (16.2 g, 72%, α:β = 1:2). Addition of boron trifluoride ethyl etherate (8.87 mL, 70.0 mmol, 2.20 equiv) to a heterogeneous mixture of **7** (12.2 g, 31.8 mmol, 1 equiv), 2-mercaptopyrimidine (4.64 g, 35.0 mmol, 1.10 equiv), dry Celite (12.2 g) and 1,2-dichloroethane (159 mL) at 23 °C with stirring of the mixture at 60 °C for 24 h afforded thioglycoside **8** (11.2 g, 95%, exclusively β) after purification by column chromatography. We found that inclusion of dry Celite was essential to achieving reproducibly high yields. When the reaction was performed in the absence of Celite, gum-like precipitates formed as the reaction proceeded, preventing efficient stirring and mixing of reactants, and **8** was obtained in low yield.

N-protected derivatives of *N*,*N*-didesmethyl desosamine **11** and **12** are readily obtained from the nitro sugar **6** in two steps (Scheme 4). Stirring a suspension of **6** (1.72 g, 9.71 mmol, 1 equiv) and palladium hydroxide on carbon



Scheme 4. Synthesis of two *N*-protected derivatives of *N*,*N*-didesmethyl desosamine.

(20 wt%, 682 mg) in 9:1 methanol:acetic acid (48 mL) under 1 atmosphere of H_2 at 23 °C for 6 h, filtration of the reaction mixture through a thin pad of Celite (2 mm), and concentration of the filtrate afforded the ammonium acetate salt **10** (2.01 g, quantitative). Heating a mixture of **10** (100 mg, 0.483 mmol, 1 equiv), potassium carbonate (267 mg, 1.93 mmol, 4.00 equiv) and benzyl bromide (115 μL,

0.965 mmol, 2.00 equiv) at 80 °C for 1 h led to formation of *N*,*N*-dibenzyl derivative **11** (136 mg, 81 %, α:β = 1:2). Alternatively, *N*-*tert*-butoxycarbonyl derivative **12** was prepared by stirring a mixture of **10** (415 mg, 1.60 mmol, 1 equiv), di-*tert*-butyl dicarbonate (446 μL, 1.92 mmol, 1.20 equiv) and sodium bicarbonate (538 mg, 6.41 mmol, 4.00 equiv) in 2:3 ethanol: water (8 mL) at 23 °C for 16 h (278 mg, 70 %, α:β = 2:1).

Our present strategy for the assembly of the fully equatorial (save the α-anomeric center) nitro sugar **6** has successfully enabled the syntheses of an array of analogous 3-nitro sugars by condensation of various γ-nitro alcohols[10] and glyoxal (Table 1).[11] In all cases, the products were isolated as crystalline solids in diastereomerically pure form, although in the case of entries 2–4, the products did not precipitate from the reaction mixture and additional operations were necessary to induce crystallization (see Supporting Information for details). The stereochemistry of all four products of Table 1 was confirmed by X-ray crystallographic analysis. Product **14** serves as a precursor to D-mycaminose (**2**), the amino sugar constituent of the 16-membered macrolide antibiotic tylosin.

Diastereoselective Henry reactions of nitro alkanes with α-oxygenated aldehyde substrates have led to successful construction of 3-amino sugars. Notable examples include the syntheses of daunosamine by Hanessian and Kloss[12] and by Brandange and Lindqvist,[13] of ristosamine by Hanessian and Kloss,[12] by Brandange and Lindqvist,[13] by Suami et al.,[14] and by Barco et al.,[15] and of acosamine by Barco et al.[15] and by Menzel et al.[16] Each of these prior works targeted 2-deoxy-3-amino sugars and involved stepwise construction of the C3–C4 and O–C1 bonds.[17] Seeberger and co-workers have reported a conceptually distinct tandem Michael addition–Henry reaction sequence (employing a β-hydroxyaldehyde as nucleophile and a nitroalkene as Michael acceptor) to prepare the 2-amino sugar D-glucosamine,[18] whereas the present method provides access to 2-hydroxy-3-amino sugars, which are readily obtained in pure form by crystallization, without the need for chromatography.

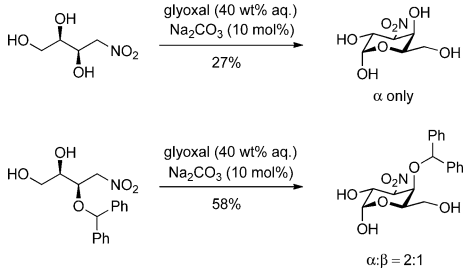
Acknowledgements

We most gratefully acknowledge funding from Alastair and Celine Mactaggart, from a private family foundation, and from the Blavatnik Biomedical Accelerator Program at Harvard University. We also thank Dr. Shao-Liang Zheng for conducting X-ray crystallographic analysis. Z.Z. is a Howard Hughes Medical Institute International Student Research Fellow. T.F. acknowledges Daiichi-Sankyo Co., Ltd. for financial support.

Keywords: 3-amino sugars · desosamine · Henry reaction · macrolide antibiotics · γ-nitro alcohols

How to cite: *Angew. Chem. Int. Ed.* **2016**, *55*, 523–527
Angew. Chem. **2016**, *128*, 533–537

[1] E. H. Flynn, M. V. Sigal, P. F. Wiley, K. Gerzon, *J. Am. Chem. Soc.* **1954**, *76*, 3121–3131.
[2] a) D. Tu, G. Blaha, P. B. Moore, T. A. Steitz, *Cell* **2005**, *121*, 257–270; b) A. S. Mankin, *Curr. Opin. Microbiol.* **2008**, *11*, 414–421.
[3] a) C. H. Bolton, A. B. Foster, M. Stacey, J. M. Webber, *J. Chem. Soc.* **1961**, 4831–4836; b) P. W. K. Woo, H. W. Dion, L. Durham, H. S. Mosher, *Tetrahedron Lett.* **1962**, *3*, 735–739; c) W. Hofheinz, H. Grisebach, *Tetrahedron Lett.* **1962**, *3*, 377–379.
[4] a) F. Korte, A. Bilow, R. Heinz, *Tetrahedron* **1962**, *18*, 657–666; b) H. Newman, *J. Org. Chem.* **1964**, *29*, 1461–1468; c) A. C. Richardson, *J. Chem. Soc.* **1964**, 5364–5370; d) H. H. Baer, C.-W. Chiu, *Can. J. Chem.* **1974**, *52*, 122–124; e) M. H. Davidson, F. E. McDonald, *Org. Lett.* **2004**, *6*, 1601–1603; f) V. Velvadapu, R. B. Andrade, *Carbohydr. Res.* **2008**, *343*, 145–150.
[5] a) T. Miyakoshi, S. Saito, J. Kumanotani, *Chem. Lett.* **1981**, *10*, 1677–1678; b) T. Miyakoshi, S. Saito, *Nippon Kagaku Kaishi* **1984**, *1984*, 458–462.
[6] a) E. J. Corey, R. K. Bakshi, S. Shibata, *J. Am. Chem. Soc.* **1987**, *109*, 5551–5553; b) E. J. Corey, C. J. Helal, *Angew. Chem. Int. Ed.* **1998**, *37*, 1986–2012; *Angew. Chem.* **1998**, *110*, 2092–2118.
[7] a) J. A. Dale, H. S. Mosher, *J. Am. Chem. Soc.* **1973**, *95*, 512–519; b) T. R. Hoye, C. S. Jeffrey, F. Shao, *Nat. Protocols* **2007**, *2*, 2451–2458.
[8] R. B. Woodward, E. Logusch, K. P. Nambiar, K. Sakan, D. E. Ward, B. W. Au-Yeung, P. Balaram, L. J. Browne, P. J. Card, C. H. Chen, *J. Am. Chem. Soc.* **1981**, *103*, 3215–3217.
[9] J. R. Hauske, G. R. Schulte (Pfizer, Inc.), WO1993018042, **1993**.
[10] a) Alcohol **15** was prepared according to the procedures reported by Zindel and de Meijere: J. Zindel, A. de Meijere, *J. Org. Chem.* **1995**, *60*, 2968–2973; b) Alcohol **17** was prepared according to the procedures reported by Estévez et al.: J. M. Otero, R. G. Soengas, J. C. Estévez, R. J. Estévez, D. J. Watkin, E. L. Evinson, R. J. Nash, G. W. J. Fleet, *Org. Lett.* **2007**, *9*, 623–626.
[11] At the suggestion of a reviewer, we have applied our method to the preparation of nitro sugars bearing an axial hydroxy group. In an intital study, a single 1-g-scale reaction, coupling of (2*S*, 3*S*)-4-nitrobutane-1,2,3-triol and glyoxal afforded the crystalline nitrosugar shown below in 27 % yield. Examination of its NMR spectrum indicated that this nitrosugar differs from compound **18** in that the 4-hydroxy group adopts an axial configuration. We believe that with additional experimentation further optimization is possible. In addition, when the 3-hydroxy group was protected as a benzhydryl ether, the cyclization reaction afforded the corresponding protected nitro sugar in 58 % yield after purification by column chromatography.



[12] S. Hanessian, J. Kloss, *Tetrahedron Lett.* **1985**, *26*, 1261–1264.
[13] S. Brandänge, B. Lindqvist, *Acta Chem. Scand. B* **1985**, *39*, 589–592.
[14] T. Suami, K.-I. Tadano, A. Suga, Y. Ueno, *J. Carbohydr. Chem.* **1984**, *3*, 429–441.
[15] A. Barco, S. Benetti, C. De Risi, G. P. Pollini, G. Spalluto, V. Zanirato, *Tetrahedron* **1996**, *52*, 4719–4734.

[16] A. Menzel, R. Öhrlein, H. Griesser, V. Wehner, V. Jäger, *Synthesis* **1999**, 1691 – 1702.
[17] For graphical summaries of these syntheses, see the Supporting Information.
[18] A. Adibekian, M. S. M. Timmer, P. Stallforth, J. van Rijn, D. B. Werz, P. H. Seeberger, *Chem. Commun.* **2008**, 3549 – 3551.
[19] CCDC 1431780–1431783 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

Received: August 7, 2015
Revised: October 23, 2015
Published online: November 27, 2015

