Pergamon

Tetrahedron Letters 42 (2001) 6797–6801

TETRAHEDRON LETTERS

Novel and convenient method for the syntheses of 2,6-dideoxypyranoses, 3,6-dideoxypyranoses, and azido (amino) analogs of 3,6-dideoxypyranoses

Cheng-Wei Tom Chang,* Terri Clark and Mumbi Ngaara

Department of Chemistry and Biochemistry, Utah State University, 0300 Old Main Hill, Logan, UT 84322-0300, USA

Received 25 June 2001; revised 27 July 2001; accepted 30 July 2001

Abstract—A novel method of regioselective deoxygenation of methyl 4,6-*O*-benzylidene-2,3-di-*O*-tosyl-α-D-glucopyranoside, and its application for the syntheses of 2,6-dideoxypyranoses, 3,6-dideoxypyranoses, and azido (amino) analogs of 3,6-dideoxypyranoses were reported. © 2001 Elsevier Science Ltd. All rights reserved.

The 2,6 and 3,6 dideoxyhexoses are commonly found in microorganisms.[1–5] The formers occur primarily in antibiotics or antitumor agents, such as mithramycin produced by *Streptomyces argillaceus* and urdamycin produced by *Streptomyces fradiae*. The later exist mainly in the *O*-specific side chains of cell-wall lipopolysaccharide (LPS) of a number of gram-negative bacteria such as *Yersinia pseudotuberculosis* and different Salmonella strains, which attract interest due to their immunogenic effects. These unusual sugars, which exhibit various important and interesting biological activities, are synthesized from normal sugars, such as glucose, through a series of enzymes. These enzymes can be found only in bacteria, which make them very attractive targets for new drug development. Inhibitor designs that mimic the substrates or intermediates of these enzymes are valuable in the enzyme mechanistic studies, and have the potential of being used as drug candidates.

In this paper, we report a convenient method for the preparation of both 2,6 and 3,6 dideoxyhexoses (olivose, oliose, abequose, and paratose), as well as the azide-substituted analogs of abequose and paratose (Fig. 1).

Our group is interested in studying the structure–activity relationship of aminosugars. Aminosugars are a group of structurally diverse unusual sugars bearing amino substitution from a normal sugar scaffold, and have been shown to closely relate to the activity of the aminosugar-containing antibiotics[3,6–8] For the ease of purification, the amino groups were masked as azide

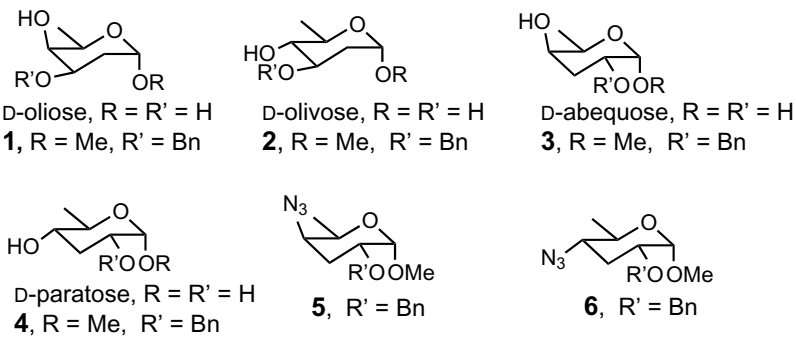


Figure 1. 2,6- and 3,6-Dideoxyhexoses.

Keywords: deoxypyranose; deoxysugar; aminosugar; regioselective deoxygenation.

* Corresponding author. Tel.: 435-797-3545; fax: 435-797-3390; e-mail: chang@cc.usu.edu

PII: S0040-4039(01)01402-2

groups, which can be reduced to amino groups later. We believe that the amino group, which is protonated as ammonium group at physiological pH, can form a stronger hydrogen-bonding network than the hydroxyl group does. The amino-substituted pyranoses are expected to have tighter binding affinity and can be valuable in generating new carbohydrate-containing antibiotics with higher potency.[9,10] Therefore, we are also interested in synthesizing amino-substituted analogs of deoxypyranoses for use as inhibitors or drug candidates that target the enzymes involved in the biosynthesis of deoxypyranoses.

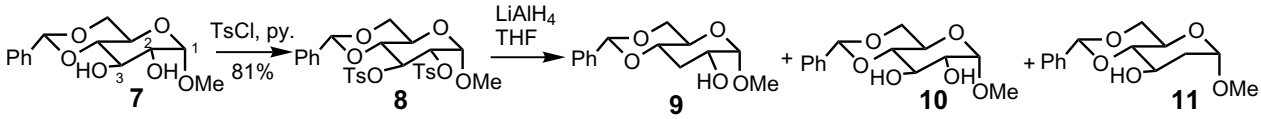
The syntheses of 2,6-dideoxyhexoses[11] and 3,6-dideoxyhexoses[12–16] have been reported in the literatures. However, little effort was devoted to the synthesis of analogs of 2,6 and 3,6 dideoxyhexoses. In addition, most of the reported methods require multiple steps of protection and deprotection to achieve the differentiation of hydroxyl groups on the hexoses scaffold. Finally, two distinct routes are often needed for the syntheses of both 2,6 and 3,6 dideoxyhexoses.

Our method generates not only the analogs of 3,6 dideoxyhexoses in shorter steps, but also the hydroxyl groups on the 2,6 and 3,6 dideoxyhexoses can be selectively protected allowing further modifications to be carried out conveniently. The syntheses began with a common starting material, methyl glucoside, and diverged into two separate routes via a regioselective deoxygenation.

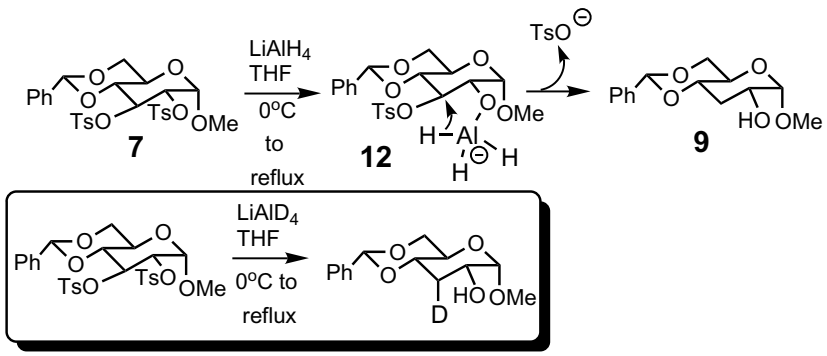
In the attempt to synthesize C-3 deoxygenation product following the literature procedure[17] from ditosylated glucose, **7**, we were surprised to find out that the major compound was actually C-2 deoxygenated (Scheme 1). Upon further investigation, we discovered that the reaction temperature and the order of adding the reagents govern the regioselectivity of deoxygenation. Addition of a solution of ditosylglucopyranoside, **7**, in THF to a cool suspension of $LiAlH_4$ in THF, followed by refluxing as described in the literature furnishes the C-3 deoxygenated product. Alternatively, addition of solid $LiAlH_4$ into a solution of ditosylglucopyranoside in THF at room temperature followed by refluxing, results in the formation of C-2 deoxygenated product.

The C-3 deoxygenation is proposed to proceed through the detosylation at the C-2 position of the ditosylglucopyranoside, which was suggested to occur readily at low temperature. The free C-2 hydroxyl group forms an alkoxyaluminum hydride complex, **12**, that displaces the tosyl group with hydride-attack from the axial position generating the C-3 deoxygenated glucopyranoside. This proposed mechanism has been used for the synthesis of stereospecific deuterium-labeled 3,6-dideoxyhexoses where the deuterium is incorporated at the axial position on the C-3 carbon (Scheme 2).[15]

With this mechanism in mind, we proposed that the formation of 2-deoxyglucopyranoside began with the release of the 3-*O*-tosyl group, and the resulting C-3 hydroxyl group was used to form an alkoxyaluminum hydride complex, **13**, that displaced the C-2 tosyl group with hydride-attack from the axial position generating the C-2 deoxygenated glucopyranoside. The overall transformation is analogous to the previously reported C-3 deoxygenation (Scheme 3(1)). Another possible mechanism is the direct detosylation and deoxygenation pathway, where the reducing agent, $LiAlH_4$, attacks and reduces the C-2 tosyl group directly (Scheme 3(2)).



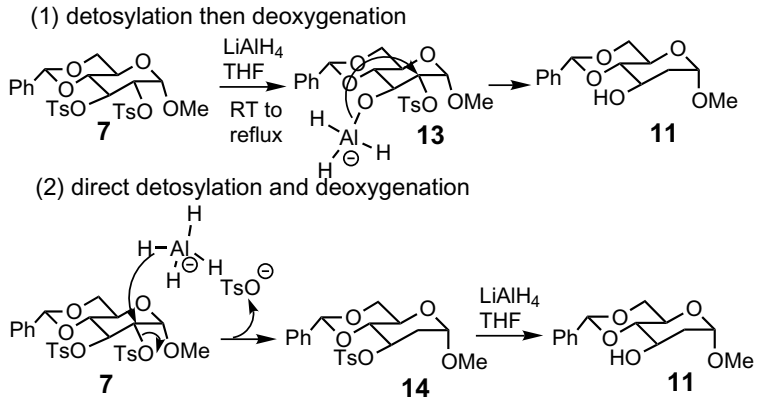
Scheme 1. Regioselective deoxygenation.



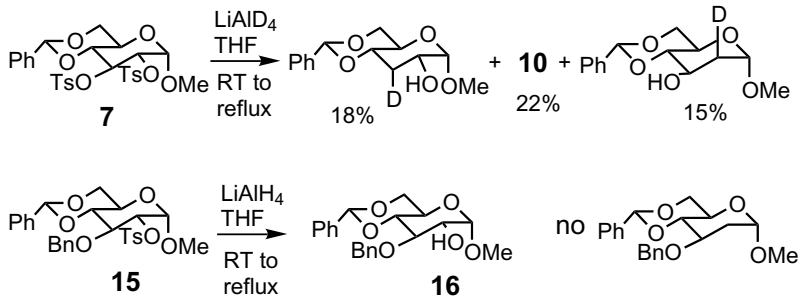
Scheme 2. Proposed mechanism for C-3 deoxygenation.

When we treated methyl 3-*O*-benzyl-4,6-*O*-benzylidene-2-*O*-tosyl-α-D-glucopyranoside, **15**, in identical condition as for the C-2 deoxygenation, no C-2 deoxygenated product was obtained. This result rules out the mechanism of direct detosylation and deoxygenation (Scheme 4). Then, we used $LiAlD_4$ as the reducing agent to confirm the stereochemistry of the hydride (deuteride) that will incorporate onto the hexose to confirm the proposed mechanism in Scheme 3(1).

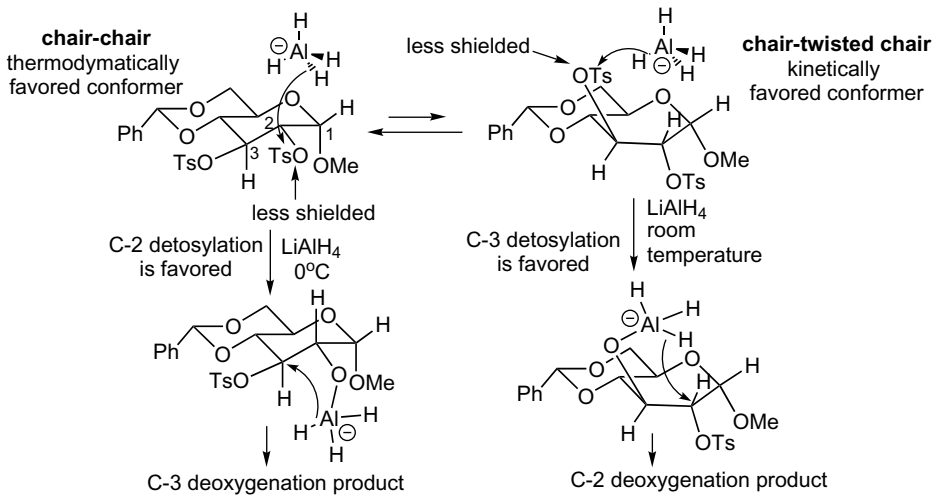
Since the tosyl group is relatively bulky, it is likely that the ditosylated glucopyranoside exists with equilibrium between two conformations, the chair–chair and chair–twisted-chair (Scheme 5). The chair–chair conformer is favored thermodynamically while the chair–twisted-chair one is favored kinetically. We proposed that the C-3 deoxygenation adduct is the thermodynamic product, which comes from the chair–chair conformer. The C-2 tosyl group is less shielded than the C-3 tosyl group in this chair–chair conformation. In the condi-



Scheme 3. Proposed mechanism for C-2 deoxygenation.



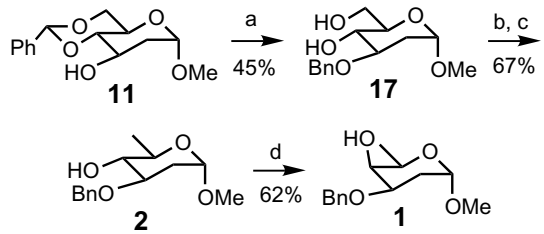
Scheme 4. Mechanistic studies for the C-2 deoxygenation.



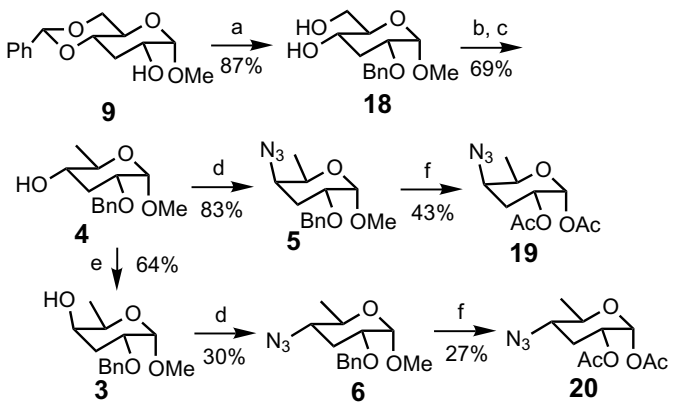
Scheme 5. Proposed rationale for the regioselective deoxygenation.

tion where $LiAlH_4$ is abundant, the C-2 tosyl group will be readily removed. The C-3 detosylation adduct is the kinetic product, which is favored at higher temperature. In this chair–twisted chair conformation, the C-3 tosyl group is less shielded, and can be removed easier with $LiAlH_4$.

The completed syntheses of aminosugars with C-2 or C-3 deoxygenation are outlined in Schemes 6 and 7. The branched step of the syntheses is the regioselective reduction/deoxygenation of methyl 4,6-*O*-benzylidene-2,3-di-*O*-tosyl-α-D-glucopyranoside, which can be prepared from modified literature procedure from methyl glucoside with overall yield of 81% with no purification of column chromatography needed. After the regioselective deoxygenation, the hydroxyl group on C-3 or C-2 of **9** and **11** were protected with benzyl group. The crude products can be treated with catalytic toluenesulfonic acid in methanol for the deprotection of benzylidene group resulting in the diols, **17** and **18**. The primary hydroxyl group of **17** and **18** were selectively tosylated then reduced providing 2,6 and 3,6 dideoxyhexoses. The free hydroxyl group can be epimerized generating different naturally occurring 2,6 and 3,6 dideoxyhexoses. The azide incorporation was carried out through a Mistunobu type azide substitution with diphenylphosphoryl azide, triphenylphosphine, and



Scheme 6. (a) (i) BnBr, NaH, THF, TBAI, rt, 16 h, (ii) TsOH–H_2O, MeOH, 6 h; (b) TsCl, py. 16 h; (c) $LiAlH_4$, THF, rt, 12 h; (d) (i) $(COCl)_2$, DMSO, CH_2Cl_2, −60 to −20°C, then DIPEA, (ii) $NaBH_4$, MeOH, 0°C, 6 h.



Scheme 7. (a) (i) BnBr, NaH, THF, TBAI, rt, 16 h, (ii) TsOH–H_2O, MeOH, 6 h; (b) TsCl, py. 16 h; (c) $LiAlH_4$, THF, rt, 12 h; (d) $(PhO)_2P(O)N_3$, PPh_3, DEAD, THF, −60°C to rt; (e) (i) $PhCO_2H$, PPh_3, DEAD, −60°C to rt, (ii) NaOMe, MeOH, rt, 0.5 h; (f) Ac_2O, conc. H_2SO_4, 0°C to rt, 16 h.

diethyl azodicarboxylate for the benzyl-protected 3,6-dideoxyhexoses, **3** and **4**. We have also converted the azido analogs, **5** and **6**, into acetyl glycosides, **19** and **20**,[18] which can be used for glycosylation directly[19] or can be transformed to other glycosyl donors, such as glycosyl halide,[20] glycosyl trichloroacetimidate,[20] alkylthioglycoside,[21] and glycose with a hydroxyl group on the anomeric carbon,[22] if needed.

We have reported a novel method for the regioselective C-2 or C-3 deoxygenation, and the application of this method for the syntheses of biologically important 2,6 and 3,6 dideoxypyranoses with differentiation on their hydroxyl groups, and the analogs of 2,6 and 3,6 dideoxypyranoses. We are currently examining various glycosylation approaches for the synthesis of 2,6 and 3,6 dideoxysugar-containing antimicrobials.

Experimental procedure for the preparation of methyl 4,6-O-benzylidene-3-deoxy-α-D-glucopyranoside, ***9***. Please refer to Ref. 17.

Experimental procedure for the preparation of methyl 4,6-O-benzylidene-2-deoxy-α-D-glucopyranoside, ***11***. To a solution of methyl 4,6-*O*-benzylidene-2,3-di-*O*-tosyl-α-D-glucopyranoside (9.3 g, 15.8 mmol) in 300 mL anhydrous THF, $LiAlH_4$ (1.2 g, 31.6 mmol) was added in small portion at room temperature. After the complete addition of $LiAlH_4$, the reaction was refluxed for 2 days. Another 0.5 g of $LiAlH_4$ was added after 1 day when TLC (hexane/ethyl acetate = 1/1) showed the reaction was incomplete. The reaction mixture was refluxed for another day then cooled to room temperature and slowly poured into ice. Ethyl acetate was added. The resulting solution with white precipitate was filtered through Celite. The residue was washed thoroughly with ethyl acetate. The combined organic solutions were washed with 1N $HCl_{(aq)}$, water, saturated $NaHCO_{3(aq)}$, brine, then dried over Na_2SO_4. After removal of solvent, the crude product was purified with flash-column chromatography. The products were obtained as the following order with R_f values determined in a solution of hexane and ethyl acetate (1/1 ratio): starting material (0.42 g, 0.71 mmol, 5%, R_f = 0.7); **11** (2.39 g, 9.0 mmol, 57%, R_f = 0.55); undetermined mixture (0.29 g, R_f = 0.50), **10** (0.08 g, 0.28 mmol, 2%, R_f = 0.1).

Acknowledgements

We thank the financial support from the Utah State University and the support from Department of Chemistry and Biochemistry, Utah State University.

References

1. Kirschning, A.; Bechthold, A. F.-W.; Rohr, J. *Top. Curr. Chem.* **1997**, *188*, 1–84.
2. Johnson, D. A.; Liu, H.-w. *Curr. Opin. Chem. Biol.* **1998**, *2*, 642–649.

3. Weymouth-Wilson, A. C. *Nat. Prod. Rep.* **1997**, 99–110.
4. Trefzer, A.; Salas, J. A.; Bechthold, A. *Nat. Prod. Rep.* **1999**, *16*, 283–299.
5. Liu, H.-w.; Thorson, J. S. *Annu. Rev. Microbiol.* **1994**, *48*, 223–256.
6. Dwek, R. A. *Chem. Rev.* **1996**, *96*, 683–720.
7. Wells, L.; Vosseller, K.; Hart, G. W. *Science* **2001**, *291*, 2376–2378.
8. Rudd, P. M.; Elliott, T.; Cresswell, P.; Wilson, I. A.; Dwek, R. A. *Science* **2001**, *291*, 2371–2376.
9. For reviewing of the activity of aminoglycoside antibiotics: Hooper, I. R. *Aminoglycoside Antibiotics*; Springer: New York, 1982.
10. Examples related to the increase or decrease of the potency of aminoglycoside antibiotics with the introduction and the deletion of amino groups on the aminoglycoside antibiotics: (a) Tor, Y.; Wang, H. *J. Am. Chem. Soc.* **1997**, *119*, 8734–8735; (b)Wang, H.; Tor, Y. to RNA. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 109–111; (c) Roestamadji, J.; Grapsas, I.; Mobashery, S. *J. Am. Chem. Soc.* **1995**, *117*, 11060–11069.
11. Toshima, K.; Matsuo, G.; Nakata, M. *J. Chem. Soc., Chem. Commun.* **1994**, 997–998.
12. Jutten, P.; Scharf, H.-D. *J. Carbohydr. Chem.* **1990**, *9*, 675–681.
13. Pinto, M. B.; Bundle, D. R. *Carbohydr. Res.* **1984**, *133*, 333–338.
14. Zegelaar-Jaarsveld, K.; van der Plas, S.; van der Marel, G. A.; van Boom, J. H. *J. Carbohydr. Chem.* **1996**, *201*, 665–689.
15. Russell, R. N.; Weigel, T. M.; Han, O.; Liu, H.-w. *Carbohydr. Res.* **1990**, *201*, 95–114.
16. Yu, H. N.; Zhang, P.; Ling, C.-C.; Bundle, D. R. *Tetrahedron: Asymmetry* **2000**, *11*, 465–479.
17. Bear, H. H.; Hanna, H. R. *Carbohydr. Res.* **1982**, *110*, 19–41.
18. Spectroscopic data for **19**: ^{1}H NMR (270 MHz, $CDCl_3$): δ 6.19 (d, $J_{HH}=3.3$ Hz, 1H, H-1), 5.18 (ddd, $J_{HH}=11.2$ Hz, $J_{HH}=5.9$ Hz, $J_{HH}=3.3$ Hz, 1H, H-2), 4.10 (dq, $J_{HH}=1.9$ Hz, $J_{HH}=6.5$ Hz, 1H, H-5), 3.72 (ddd, $J_{HH}=2.6$ Hz, $J_{HH}=2.6$ Hz, $J_{HH}=1.9$ Hz, 1H, H-4), 2.1–2.2 (m, 2H, H-3), 2.12 (s, 3H, CH_3CO_2), 2.01 (s, 3H, CH_3CO_2), 1.24 (d, $J_{HH}=6.5$ Hz, 3H, H-6); ^{13}C NMR (68 MHz, $CDCl_3$): δ 169.08 (s), 169.02 (s), 89.4 (s), 67.7 (s), 64.5 (s), 61.0 (s), 28.5 (s), 21.1 (s), 20.8 (s), 17.3 (s). **20**: ^{1}H NMR (270 MHz, $CDCl_3$): δ 6.13 (d, $J_{HH}=3.3$ Hz, 1H, H-1), 4.95 (ddd, $J_{HH}=12.2$ Hz, $J_{HH}=5.0$ Hz, $J_{HH}=3.3$ Hz, 1H, H-2), 3.67 (dq, $J_{HH}=10.0$ Hz, $J_{HH}=6.3$ Hz, 1H, H-5), 3.18 (ddd, $J_{HH}=12.2$ Hz, $J_{HH}=10.0$ Hz, $J_{HH}=4.6$ Hz, 1H, H-4), 2.29 (ddd, $J_{HH}=12.2$ Hz, $J_{HH}=5.0$ Hz, $J_{HH}=4.6$ Hz, 1H, H-3$_{eq}$), 2.14 (s, 3H, CH_3CO_2), 2.02 (s, 3H, CH_3CO_2), 1.94 (ddd, $J_{HH}=12.2$ Hz, $J_{HH}=12.2$ Hz, $J_{HH}=12.2$ Hz, 1H, H-3$_{ax}$), 1.26 (d, $J_{HH}=6.3$ Hz, 3H, H-6); ^{13}C NMR (68 MHz, $CDCl_3$): δ 169.9 (s), 169.3 (s), 88.5 (s), 69.4 (s), 67.1 (s), 60.7 (s), 29.1 (s), 21.1 (s), 20.8 (s), 18.1 (s).
19. (a) Salvador, L. A.; Eloffson, M.; Kihlberg, J. *Tetrahedron* **1995**, *51*, 5643–5656; (b) Hanessian, S.; Banoub, J. *Carbohydr. Res.* **1977**, *59*, 261–267.
20. *Preparative Carbohydrate Chemistry Part III*; Hanessian, S., Ed.; Marcel Dekker, 1996, pp. 263–464.
21. (a) Crich, D.; Sun, S. *J. Am. Chem. Soc.* **1998**, *120*, 435–436; (b) Crich, D.; Sun, S. *J. Org. Chem.* **1997**, *62*, 1198–1199; (c) Crich, D.; Sun, S. *J. Org. Chem.* **1997**, *62*, 4506–4507; (d) Crich, D.; Cai, W. *J. Org. Chem.* **1999**, *64*, 4926–4930; (e) Garegg, P. J.; Olsson, L.; Oscarson, S. *J. Org. Chem.* **1995**, *60*, 2200–2204.
22. (a) Garcia, B. A.; Gin, D. Y. *Org. Lett.* **2000**, *2*, 2135–2138; (b) Garcia, B. A.; Gin, D. Y. *J. Am. Chem. Soc.* **2000**, *122*, 4269–4279.