Carbohydrate Research 343 (2008) 2740–2743

Contents lists available at ScienceDirect

Carbohydrate Research

journal homepage: www.elsevier.com/locate/carres

A facile synthesis of 4,6-*O*-benzylidene-D-glycals via 1,5-anhydro-4,6-*O*-benzylidene-D-hex-1-en-3-ulose

Tohru Sakakibara *, Tsubasa Ito, Chika Kotaka, Yasuhiro Kajihara, Yuhya Watanabe, Aki Fujioka

Department of Chemistry, Graduate School of Integrated Science, Yokohama City University, Seto Kanazawa-ku, Yokohama 236, Japan

ARTICLE INFO

Article history:
Received 22 April 2008
Received in revised form 20 May 2008
Accepted 22 May 2008
Available online 14 June 2008

Keywords:
Glycal
Benzylidenation
1-En-3-ulose
Lipase PS

ABSTRACT

Benzylidenation of readily available 1,5-anhydro-D-hex-1-en-3-ulose, followed by sodium borohydride reduction, afforded the title compounds in high yields. Separation of 4,6-*O*-benzylidene-D-allal and -D-glucal was accomplished by selective acetylation with lipase PS.

1. Introduction

Glycals (1,5-anhydro-1-enitols) have proven to be excellent starting materials for various syntheses of sugar derivatives. Particularly noteworthy in this regard is their use as substrates for oligosaccharide synthesis,[1] for Ferrier rearrangement (glycosidation),[2] and for Danishefsky's glycosylation method.[3] Selective 4,6-O-protection of a glycal is useful since it allows modification of the remaining 3-hydroxyl group. In this context, 4,6-*O*-benzylidene glucal is extremely desirable since the regioselective cleavage of the protecting group has already been established to afford the desired 4-*O*-benzyl (6-hydroxyl)[4] or the 6-*O*-benzyl (4-hydroxyl) derivative.[5] 4,6-*O*-Benzylidene glucal was originally prepared from the free glucal under standard, acidic conditions.[6] However, the yield was low because of the acid sensitivity of the glucal. Improved methods for preparation of these target compounds have thereafter been reported from methyl,[7] thiophenyl,[8] selenophenyl,[9] sulfone,[8,10] and sulfinyl glycosides.[11]

We have employed 1,5-anhydro-hex-1-en-3-uloses **1** and **5** for the preparation of 4,6-*O*-benzylidene-D-glycals, because these compounds, which are readily prepared from per-*O*-acetyl-D-glycals in high yield,[12] should withstand acidic conditions. Although expensive Pd/C was used as a catalyst in the preparation of **1** and **5**, it is recycled at least three times.[13] Furthermore, a very recently improved method, using nitrobenzene as hydrogen acceptor, is reported.[14]

2. Results and discussion

Treatment of D-*threo*-hex-1-en-3-ulose (**1**) with benzaldehyde dimethylacetal in the presence of (±)-10-camphorsulfonic acid afforded 4,6-*O*-benzylidene-D-*threo*-hex-1-en-3-ulose (**2**) in 94% yield. However, a similar reaction of the *erythro* isomer **5** did not go to completion, and starting material **5** still remained, even when the reaction time was prolonged and additional benzaldehyde dimethylacetal was added. Thus, the acid sensitivities for the *threo* **2** and *erythro* isomer **6** seem to be fairly different. In fact when *erythro* isomer **6** was treated with (±)-10-camphorsulfonic acid in the presence of benzaldehyde dimethylacetal and methanol (generated as the benzylidenation occurs) for 3 h at 80 °C, about half the amount of **6** was debenzylidenated, whereas similar treatment of *threo* isomer **2** resulted in the recovery of **2**.

To get some information about stability, we performed an ab initio calculation (B3LYP/6-31+G*)[15] of starting materials **1** and **5** as well as benzylidene derivatives **2** and **6**. The most stable conformers calculated are shown in Figure 1, in which, as expected, hydrogen bonding was observed between the hydroxyl group at C-4 (4-OH) and the carbonyl group as well as between 6-OH and O-4. For the 4,6-*O*-benzylidene derivative, the *threo* isomer **2** is more stable than *erythro* one **6** by 1.1 kcal/mol, whereas for starting materials *threo* isomer **1** is less stable than the *erythro* isomer **5** by 1.5 kcal/mol. These results are not in conflict with the experimental results.

When less acidic pyridinium *p*-toluenesulfonate (PPTS)[16] was used instead of (±)-10-camphorsulfonic acid, the intended **6** was obtained in 80% yield (Scheme 1).

* Corresponding author. Tel.: +81 45 787 2183.
E-mail address: baratoru@yokohama-cu.ac.jp (T. Sakakibara).

0008-6215/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.carres.2008.05.018

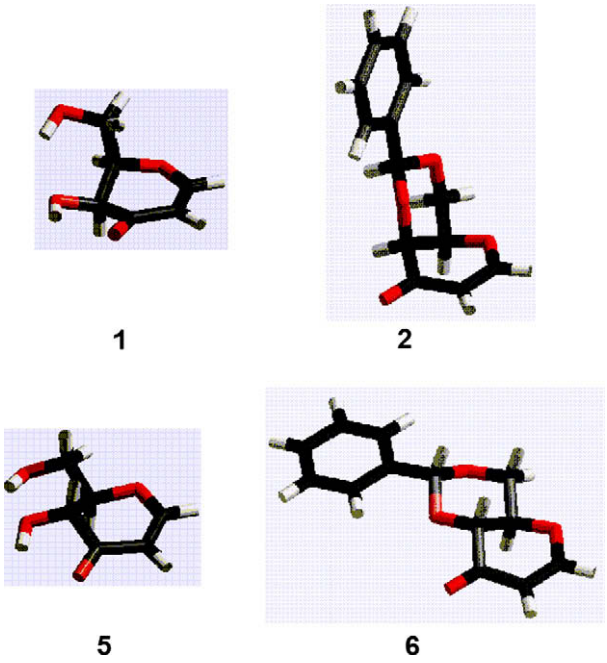


Figure 1. Most stable conformers obtained by ab initio calculation.

Sodium borohydride reduction of the enone **2** in the presence of $CeCl_3{\cdot}7H_2O$ proceeded with high stereoselectivity to afford the galactal **3** in 86% yield. Similar reduction of *erythro* isomer **6** gave a ca. 2.6:1 mixture of glucal **7** and allal **9** in 91% yield.

Although we managed to separate these two products by silica gel column chromatography, selective acetylation with lipase PS (*Burkholderia*) is much superior; only the glucal was acetylated. Thus, the acetate **11** and 3-O-free **9** were obtained in 72% and 28% yields, respectively, after short column chromatography on silica gel. Deacetylation of **11** was accomplished by treatment with NaOMe in methanol to give glucal **7** in 98% yield. Without separation of these two products, **7** and **9**, their acetates should become substrates for the Ferrier glycosidation, because the reaction is believed to proceed via the same oxocarbonium ion. To investigate the reaction mechanism, formation of both glucal **7** and allal **9** from **6** and their facile separation have advantage.

The 3-deuterio-derivatives **4**, **8**, and **10** were readily prepared by the use of sodium borodeuteride.

In conclusion, a facile, high-yielding, inexpensive synthesis of 4,6-*O*-benzylidene glycals has been achieved. Not only the 4,6-*O*-benzylideneglycals, but also their precursors, 1,5-anhydro-4,6-*O*-benzylidene-D-hex-1-en-3-ulose, have potential utility as glycosidation donors.[17]

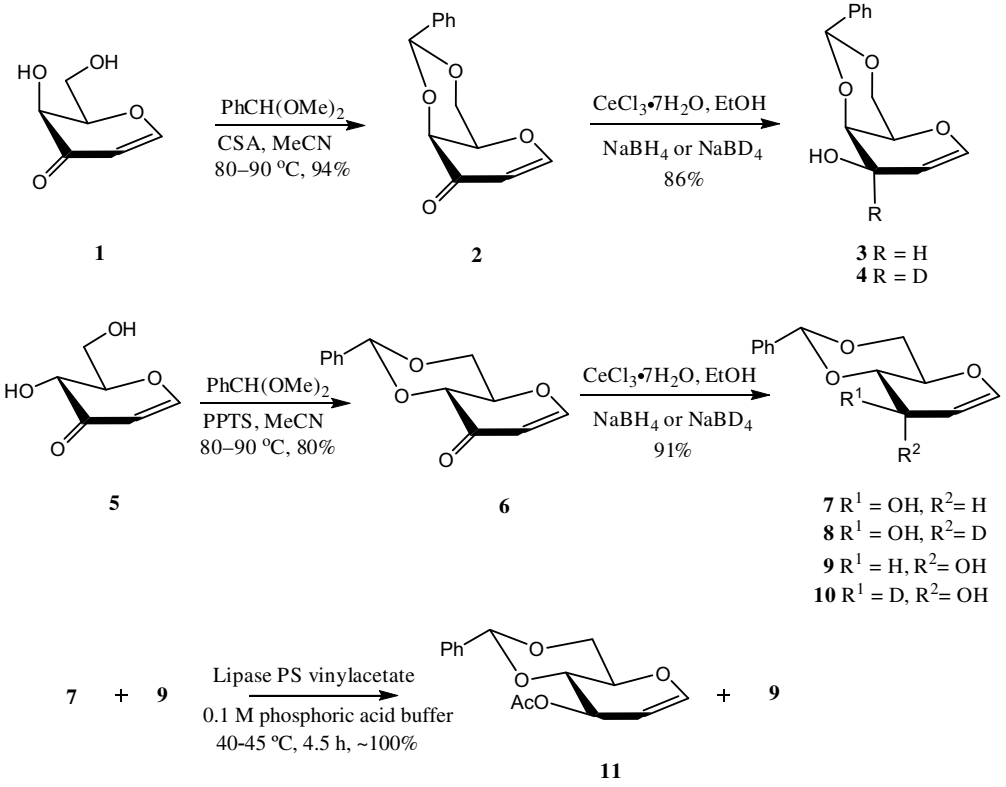
3. Experimental

3.1. General methods

All melting points are uncorrected. ^1H and ^{13}C NMR spectra (Bruker Advance 400, 400, and 100.6 MHz, respectively) were recorded using Me_4Si as an internal standard. IR spectra were recorded for KBr pellets. The reaction mixture was dried over $MgSO_4$ and evaporated under diminished pressure. Column chromatography was conducted on silica gel (Wakogel C-300).

3.2. Preparation of 1,5-anhydro-4,6-*O*-benzylidene-2-deoxy-D-threo-hex-1-en-3-ulose (2)

A solution of 1,5-anhydro-D-*threo*-hex-1-en-3-ulose (**1**)[12] (200 mg, 1.39 mmol) in distd MeCN (0.58 mL) and benzaldehyde dimethyl acetal (320 mg, 2.10 mmol) was warmed at 80–90 °C under an Ar atmosphere, to which (±)-10-camphorsulfonic acid



Scheme 1.

(64 mg, 0.28 mmol) was added and kept for 10 min. After addition of Et_3N (57.8 μL, 0.42 mmol), the solvent was evaporated, and the residue was extracted with EtOAc. The extracts were washed with satd aq NaCl, dried, and evaporated. The residue was chromatographed on silica gel with 2:1, v/v, hexane–EtOAc to give 304 mg (94%) of **2**, ^{1}H NMR data of which were identical with an authentic sample of **2**: mp 170–171 °C, lit.[18] mp 165–166 °C, $[\alpha]_D$ 170.4 (*c* 1.1, $CHCl_3$), lit.[18] 186 (*c* 1, $CHCl_3$); *ν* 668, 1596 cm^{-1}, lit.[18] 1680, 1600 (C=O, C=C); ^{1}H NMR of **6** ($CDCl_3$): *δ* 7.26–7.52 (m, 6H, H-1 and aryl), 5.36 (dd, 1H, $J_{1,2}$ 6.2, $J_{2,4}$ 1.2 Hz, H-2), 4.21–4.22 (m, 2H, H-4, H-5), 4.16 (dd, 1H, $J_{5,6a}$ 1.2, $J_{6a,6e}$ 13.0 Hz, H-6a), 4.51 (dd, 1H, $J_{5,6e}$ 1.6 Hz, H-6e), 5.63 (s, 1H, PhCH). ^{13}C NMR ($CDCl_3$): *δ* 186.1, 164.7, 137.3, 129.7, 128.7, 126.6, 105.9, 101.1, 75.6, 73.6, 68.4.

3.3. Preparation of 4,6-*O*-benzylidene-D-galactal (3)

To a stirred ethanolic solution (7.6 mL) of **2** (176 mg, 0.758 mmol) was added $CeCl_3{\cdot}7H_2O$ (423 mg, 1.14 mmol) under an Ar atmosphere. After the $CeCl_3{\cdot}7H_2O$ was dissolved, the mixture was cooled with ice-water, sodium borohydride (42.9 mg, 1.13 mmol)[19] was added, and the mixture was kept for 5 min with stirring, to which aq M HCl was added. After evaporation of the solvent, the mixture was extracted with CH_2Cl_2, and the extracts were washed with water, satd aq NH_4Cl, and satd aq NaCl, dried, and filtered, and then the filtrate was evaporated. The residue was chromatographed on silica gel eluting with 2:1, v/v, hexane–EtOAc to afford 153 mg (86%) of **3**: mp 151–152 °C, lit.[8] mp 151–152 °C, $[\alpha]_D$ 47.3 (*c* 1.0, $CHCl_3$), lit.[8] 47 (*c* 1, $CHCl_3$). The ^{1}H NMR data for **3** were almost the same as those reported in the literature.[8] ^{1}H NMR ($CDCl_3$): *δ* 6.49 (dd, 1H, $J_{1,2}$ 6.4, $J_{1,3}$ 1.9 Hz, H-1), 4.80 (ddd, 1H, $J_{2,3}$ 1.7, $J_{2,4}$ 1.8 Hz, H-2), 4.56 (m, 1H, H-3), 4.26 (br d, 1H, $J_{3,4}$ 5.1 Hz, H-4), 3.96 (br s, 1H, H-5), 4.42 (dd, 1H, $J_{5,6a}$ 1.9, $J_{6a,6e}$ 12.4 Hz, H-6a), 4.09 (dd, 1H, $J_{5,6e}$ 0.9 Hz, H-6e), 7.34–7.60 (m, 5H, aryl), 5.73 (s, 1H, PhCH), 2.55 (br d, 1H, $J_{3,OH}$ 11.0 Hz, OH). ^{13}C NMR ($CDCl_3$): *δ* 144.2, 137.9, 129.7, 128.7, 126.7, 102.5, 101.7, 72.8, 69.8, 68.5, 63.3.

Similar reduction of **2** (50 mg, 0.2 mmol) with $NaBD_4$ gave 50.1 mg (99%) of **4**.

3.4. Preparation of 1,5-anhydro-4,6-*O*-benzylidene-2-deoxy-D-erythro-hex-1-en-3-ulose (6)

A solution of 1,5-anhydro-D-*erythro*-hex-1-en-3-ulose (**5**)[12] (760 mg, 5.27 mmol) and benzaldehyde dimethyl acetal (1613 mg, 10.60 mmol) in distd MeCN (53 mL) was warmed at 80–90 °C under an Ar atmosphere, to which PPTS (266 mg, 1.06 mmol) was added. After 170 min, an additional benzaldehyde dimethyl acetal (1613 mg) was added to the mixture, which was kept for 120 min, and cooled at room temperature. After addition of Et_3N (150 μL, 1.1 mmol), the mixture was concentrated, and the residue was chromatographed on silica gel with 3:1, v/v, hexane–EtOAc to give 975 mg (80%) of **6**: mp 127–129 °C, lit.[20] mp 128–129 °C, $[\alpha]_D$ 189 (*c* 0.5, $CHCl_3$), lit.[21] 189 (*c* 0.8, $CHCl_3$). The ^{1}H NMR data of which were taken in $CDCl_3$,[20] but some signals were overlapped. The spectrum in C_6D_6 gave better signals for analysis. ^{1}H NMR of **6** (C_6D_6): *δ* 6.39 (d, 1H, $J_{1,2}$ 6.0 Hz, H-1), 5.15 (d, 1H, H-2), 3.83 (d, 1H, $J_{4,5}$ 12.3 Hz, H-4), 3.94 (ddd, $J_{5,6a}$ 9.5, $J_{5,6e}$ 4.9 Hz, H-5), 3.44 (dd, 1H, $J_{6a,6e}$ 9.6 Hz, H-6a), 4.00 (dd, 1H, H-6e), 5.23 (s, 1H, PhCH), 7.20–7.75 (m, 5H, aryl).

3.5. Preparation of 4,6-*O*-benzylidene-D-glucal (7) and allal (9)

To a stirred ethanolic solution (42 mL) of **6** (975 mg, 4.20 mmol) under an Ar atmosphere was added $CeCl_3{\cdot}7H_2O$ (2.3 g, 6.2 mmol). After the addition of $CeCl_3{\cdot}7H_2O$, the mixture was cooled with ice-water, and then sodium borohydride (240 mg, 6.35 mmol) was added. After stirring for 20 min, aq M HCl was added to the solution, and the solvent was evaporated. The residue was extracted with Et_2O, and the extracts were washed with water, satd NH_4Cl, and satd NaCl, dried, and filtered. The filtrate was then concentrated. The residue was chromatographed on silica gel eluting with 3:1, v/v, hexane–EtOAc to afford a ca. 2.6:1 mixture of D-glucal and D-allal (895 mg, 91%).

Similar reduction of **6** (50 mg, 0.2 mmol) with $NaBD_4$ gave a mixture of **8** and **10**. Compounds **7** and **9** were separated by the following method.

3.6. Separation of 4,6-*O*-benzylidene-D-glucal 7 and D-allal 9 with lipase PS

To a mixture of **7** and **9** (150 mg, ca. 2.6:1, 0.640 mmol) in vinyl acetate (13 mL) were added lipase PS (*Burkholderia*) (172 mg) on Celite (577 mg) and 0.1 M phosphoric acid buffer solution (575 μL) with stirring. (lipase PS on Celite was prepared by stirring Celite, lipase PS, and 0.1 M phosphoric acid (575 μL) overnight, followed by drying over P_2O_5 under reduced pressure using a vacuum pump.) The stirred mixture was warmed at 40–45 °C for 4.5 h and then filtered. The filtrate was concentrated, and the residue was chromatographed with 6:1, and 3:1, v/v, hexane–EtOAc to give the acetate **11**[6] (127 mg, 72%) and 3-O-free **9** (42 mg, 28%): mp 81–84 °C, lit.[22] mp 83–84 °C, lit.[23] mp 83.5 °C, $[\alpha]_D$ 208.2 (*c* 0.5, EtOH), lit.[22] 219 (*c* 3.2, EtOH), lit.[23] 209.5 (*c* 2, EtOH). Compound **11** is known, but its NMR spectrum was determined in pyridine-d_6. NMR data in $CDCl_3$ are described in the following.

^{1}H NMR of **11**: *δ* 6.39 (dd, 1H, $J_{1,2}$ 6.1, $J_{1,3}$ 1.7 Hz, H-1), 4.80 (dd, 1H, H-2), 5.45 (dt, 1H, $J_{2,3}$ 1.9, $J_{3,4}$ 8.8 Hz, H-3), 4.02 (d, 1H, $J_{4,5}$ 10.2 Hz, H-4), 3.99 (dt, 1H, $J_{5,6a}$ 10.2, $J_{5,6e}$ 4.2 Hz, H-5), 3.84 (t, 1H, $J_{6a,6e}$ 10.4 Hz, H-6a), 4.39 (dd, 1H, H-6e), 7.49 (d, 2H, Ph), 7.37 (d, 2H, Ph), 5.59 (s, 1H, PhCH), 2.08 (s, 3H, OCOMe). ^{13}C NMR ($CDCl_3$): *δ* 145.1 (C-1), 100.6 (C-2), 68.8 (C-3), 68.64 (C-4), 68.7 (C-5), 68.2 (C-6), 170.7 (OCO), 21.1 (OCOMe).

3.7. Deacetylation of 11 with NaOMe in MeOH

To a stirred methanolic solution of **11** (100 mg, 0.362 mmol) was added M NaOMe (2 mg, 0.04 mmol). After stirring for 105 min, the solution was deionized with Amberlite IR-120 (H^+) and filtered. The filtrate was concentrated and the residue was chromatographed on silica gel with 3:1, v/v, hexane–EtOAc to give 83 mg (98%) of **7**: mp 144–145 °C, lit.[6] mp 142–143 °C, lit.[9] mp 140–143 °C, $[\alpha]_D$ −15.8 (*c* 2.3, $CHCl_3$), lit.[6] −19 (*c* 0.63, $CHCl_3$), lit.[9] −15.8 (*c* 0.83, $CHCl_3$).

3.8. Treatment of benzylidene derivatives 2 and 6 with (±)-10-camphorsulfonic acid

To a stirred solution of 30 mg (0.13 mmol) of the *threo* isomer **2**, benzaldehyde dimethylacetal (19.7 mg, 0.13 mmol), MeOH (5.0 μL, 0.12 mmol), and MeCN (0.58 mL) at 80 °C under an Ar atmosphere was added (±)-10-camphorsulfonic acid (6.0 mg, 0.03 mmol), and the solution was kept for 3 h. After addition of Et_3N (5.4 μL, 0.39 mmol), the solvents were evaporated. The residue was extracted with EtOAc and the extracts were washed with satd aq NaCl, dried, and filtered. The filtrate was concentrated, and the ^{1}H NMR spectrum of the residue revealed the recovery of **2**.

Similar treatment of *erythro* isomer **6** gave ca. 1:1 mixture of **6** and debenzylidenated **5**.

Acknowledgment

We gratefully acknowledge Dr. Masakiko Hayashi for kind advice to preparation of compounds **1** and **5**.

References

1. For review, see: Danishefsky, S. J.; Bilodeau, M. T. *Angew. Chem., Int. Ed.* **1996**, *35*, 1380–1419.
2. Ferrier, R. J.; Prasad, N. J. *J. Chem. Soc. (C)* **1969**, 570–575. For a recent review of the Ferrier glycosidation, see: Ferrier, R. J. *Top. Curr. Chem.* **2001**, *215*, 153–175; Ferrier, R. J.; Zubkov, O. A. *Org. React.* **2003**, *62*, 569–736.
3. Seeberger, P. H.; Bilodeau, M. T.; Danishefsky, S. J. . *Aldrichim. Acta* **1997**, *30*, 75–92.
4. For example: (a) Gelas, J. *Adv. Carbohydr. Chem. Biochem.* **1981**, *39*, 71–156; (b) Lipták, A.; Jodál, I.; Nánási, P. *Carbohydr. Res.* **1975**, *44*, 1–11.
5. For example: Garegg, J.; Hultberg, H.; Wallin, S. *Carbohydr. Res.* **1982**, *108*, 97–101.
6. For example: Sharma, M.; Brown, R. K. *Can. J. Chem.* **1966**, *44*, 2825–2835.
7. Chambers, D. J.; Evans, G. R.; Fairbanks, A. J. *Tetrahedron: Asymmetry* **2003**, *14*, 1767–1769.
8. Fernandez-Mayoralas, A.; Marra, A.; Trumtel, M.; Veyrières, A.; Sinaÿ, P. *Carbohydr. Res.* **1989**, *188*, 81–95.
9. Osborn, H. M. I.; Meo, P.; Nijjar, R. K. *Tetrahedron: Asymmetry* **2005**, *16*, 1935–1937.
10. de Pouilly, P.; Chénedé, A.; Mallet, J.-M.; Sinaÿ, P. *Tetrahedron Lett.* **1992**, *33*, 8065–8068; Pedretti, V.; Mallet, J.-M.; Sinaÿ, P. *Carbohydr. Res.* **1993**, *244*, 247–257.
11. Griffith, D. A.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1996**, *118*, 9526–9538.
12. Hayashi, M.; Yamada, K.; Arikita, O. *Tetrahedron* **1999**, *55*, 8331–8340.
13. Hayashi, M.; Yamada, K.; Nakayama, S.; Hayashi, H.; Yamazaki, S. *Green Chem.* **2000**, *2*, 257–260.
14. Tanaka, T.; Kawabata, H.; Hayashi, M. *Tetrahedron Lett.* **2005**, *46*, 4989–4991.
15. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Baboul, A. G.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98, Revision A.9*; Gaussian: Pittsburgh, PA, 1998.
16. Miyashita, M.; Yoshikoshi, A.; Grieco, P. A. *J. Org. Chem.* **1977**, *42*, 3772–3774.
17. For example: (a) Csuk, R.; Schaade, M.; Krieger, C. *Tetrahedron* **1996**, *52*, 6397–6408; (b) Takiya, M.; Ishii, M.; Shibata, K.; Mikami, Y.; Mitsunobo, O. *Chem. Lett.* **1991**, 1917–1920; (c) Thiem, J.; Elvers, J. *Chem. Ber.* **1981**, *114*, 1442–1454; (d) Paulsen, H.; Biuensch, H. *Chem. Ber.* **1978**, *111*, 3484–3496; (e) Yunker, M. B.; Plaumann, D. E.; Fraser-Reid, B. *Can. J. Chem.* **1977**, *55*, 4002–4009; (f) Fraser-Reid, B.; Holder, N. L.; Hicks, D. R.; Walker, D. L. *Can. J. Chem.* **1977**, *55*, 3978–3985.
18. Beynon, P. J.; Collins, P. M.; Doganges, P. T.; Overend, W. G. *J. Chem. Soc. (C)* **1966**, 1131–1136.
19. Gemal, A. L.; Luche, J.-L. . *J. Am. Chem. Soc.* **1981**, *103*, 5454–5459.
20. Fisher, J.-C.; Horton, D.; Weckerle, W. *Can. J. Chem.* **1977**, *55*, 4078–4089.
21. Collins, P. M. *Carbohydr. Res.* **1969**, *11*, 125–128.
22. Fűrstner, A.; Weidmann, H. *J. Org. Chem.* **1989**, *54*, 2307–2311.
23. Lemieux, R. U.; Fraga, E.; Watanabe, K. A. *Can. J. Chem.* **1968**, *46*, 61–69.