BEILSTEIN JOURNAL OF ORGANIC CHEMISTRY

Synthesis of D-*manno*-heptulose via a cascade aldol/hemiketalization reaction

Yan Chen, Xiaoman Wang, Junchang Wang and You Yang*

Letter

Open Access

Address:
Shanghai Key Laboratory of New Drug Design, School of Pharmacy, East China University of Science and Technology, 130 Meilong Road, Shanghai 200237, China

Email:
You Yang* - yangyou@ecust.edu.cn

* Corresponding author

Keywords:
aldol reaction; cascade reaction; D-*manno*-heptulose; higher-carbon sugar; ketoheptose

Beilstein J. Org. Chem. **2017,** *13,* 795–799.
doi:10.3762/bjoc.13.79

Received: 15 February 2017
Accepted: 12 April 2017
Published: 28 April 2017

This article is part of the Thematic Series "Biomolecular systems".

Guest Editor: P. H. Seeberger

Abstract

A [4 + 3] synthesis of D-*manno*-heptulose is described. The cascade aldol/hemiketalization reaction of a C_4 aldehyde with a C_3 ketone provides the differentially protected ketoheptose building block, which can be further reacted to furnish target D-*manno*-heptulose.

Introduction

D-*manno*-Heptulose is a rare naturally occurring seven-carbon sugar first isolated from avocado [1], which exhibited promising diabetogenic effects through suppression of the glucose metabolism and insulin secretion via competitive inhibition of the glucokinase pathway [2-6]. Accordingly, ketoheptoses and fluorinated ketoheptoses were considered to be potential therapeutic agents for hypoglycemia and cancer as well as diagnostic tools for diabetes [7-12]. Amino- and azido-group-containing ketoheptoses were also synthesized for the development of novel antibiotics and the evaluation of carbohydrate–lectin interactions by conjugation with fluorescent quantum dots via click chemistry [13,14]. Besides, differentially protected D-*manno*-heptulose building blocks could serve as valuable precursors for the synthesis of *C*-glycosides [15,16].

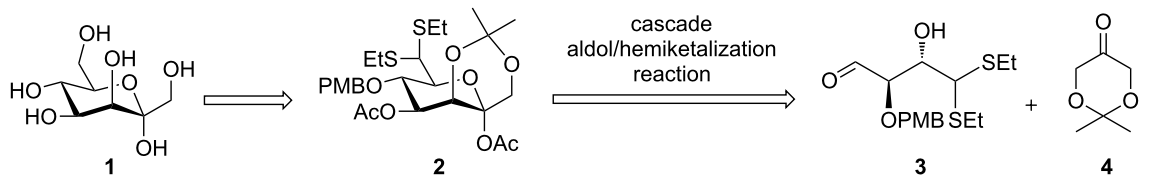
The known synthesis of D-*manno*-heptulose mainly rely on the use of rearrangements and chain elongation reactions [17]. Rearrangement reactions such as the Lobry de Bruyn rearrangement and the Bilik rearrangement employ unprotected aldoses as substrates, usually yielding an equilibrium mixture of aldoses and ketoses [18,19]. In addition to chain elongations of aldoses employing the Henry reaction, the aldol reaction, and the Wittig reaction for the preparation of ketoheptoses [20-22], sugar lactones were also often utilized for the synthesis of D-*manno*-heptulose via reactions with *C*-nucleophiles or conversion into exocyclic glycals followed by dihydroxylation [10-13,23-27]. Remarkably, Thiem et al. reported the highly efficient synthesis of D-*manno*-heptulose from D-mannose in 59% overall yield over five steps [26]. However, the synthesis of D-*manno*-heptu-

lose and its derivatives from the common differentially protected ketoheptose building block is still attractive due to the versatile functionalization possibilities of the building block into various derivatives of D-*manno*-heptulose. A de novo synthesis has proved to be an attractive strategy to produce orthogonally protected carbohydrate building blocks from simple precursors [28-39]. Here, we report a [4 + 3] approach to access differentially protected ketoheptose building blocks, which enables the synthesis of D-*manno*-heptulose. As depicted in Scheme 1, D-*manno*-heptulose (**1**) could be obtained by global deprotection of the differentially protected ketoheptose building block **2**. The ketoheptose **2** can be further divided into C_4 aldehyde **3** and C_3 ketone **4** via a cascade aldol/hemiketalization pathway.

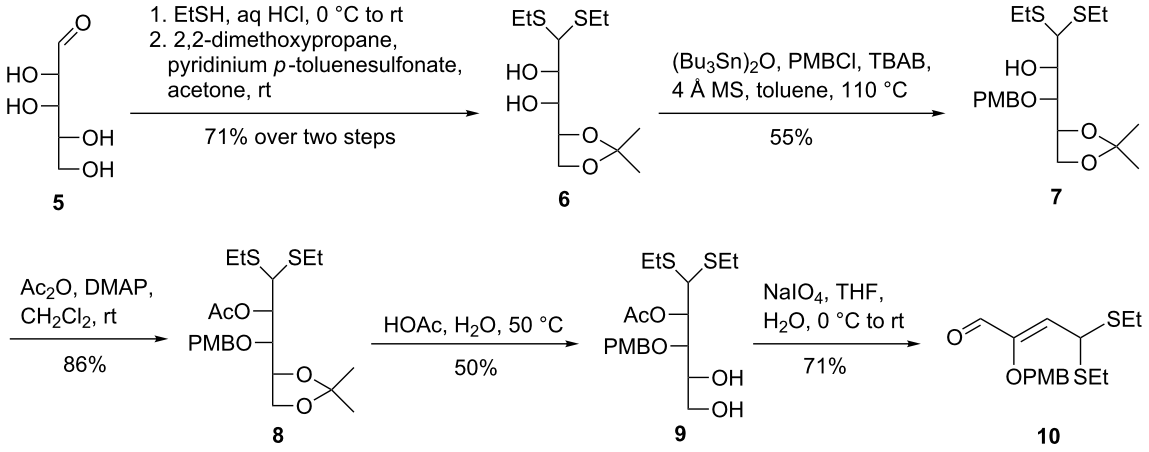
Results and Discussion

The synthesis of the C_4 aldehyde commenced with commercially available D-lyxose (**5**, Scheme 2). The reaction of **5** with ethanethiol in the presence of hydrochloric acid followed by selective protection of the 4,5-diol with 2,2-dimethoxypropane using pyridinium *p*-toluenesulfonate as the promoter gave the 4,5-*O*-isopropylidene derivative **6** in 71% yield over two steps [40]. Treatment of diol **6** with bis(tributyltin) oxide and subsequent exposure to *p*-methoxybenzyl (PMB) chloride in the presence of tetra-*n*-butylammonium bromide (TBAB) at 110 °C led to regioselective protection of the 3-OH with the PMB group, affording the 3-*O*-PMB protected alcohol **7** (55%) [41]. At this stage, we initially planned to synthesize the 2-OH-protected C_4 aldehyde for the assembly of the seven-carbon skeleton. Thus, acetylation of the 2-OH group in **7** with acetic anhydride and DMAP in dichloromethane provided ester **8** in 86% yield. The positions of the 2-acetyl and 3-PMB groups were determined by ^{1}H, ^{13}C and 2D NMR spectra of **8** (see Supporting Information File 1 for details). Cleavage of the isopropylidene acetal group in **8** under acidic conditions gave diol **9** (50%). However, oxidative cleavage of diol **9** with sodium periodate resulted in the unexpected formation of α,β-unsaturated aldehyde **10** in 71% yield, indicating that the 2-acetyl group might be prone to initiate the elimination reaction. The double bond of **10** was assigned to have *Z*-configuration based on the analysis of the NOEs between the olefinic hydrogen and the aldehyde hydrogen (see Supporting Information File 1 for details). In addition, when alcohol **7** was subjected to benzoyl chloride and DMAP in dichloromethane at room temperature or *tert*-butyldimethylsilyl chloride and imidazole in DMF at room temperature, no reaction occurred probably because of the steric hindrance between the 2-OH group and the surrounding functional groups.

To overcome the difficulties in the synthesis of the 2-OH-protected C_4 aldehyde and to improve the synthetic efficiency in



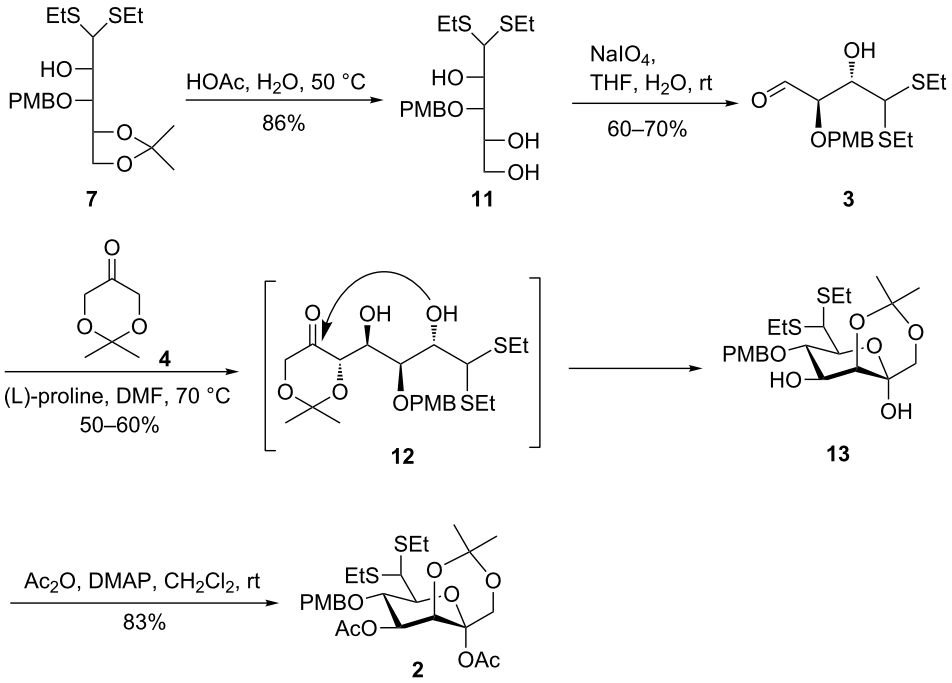
Scheme 1: Retrosynthetic analysis of D-*manno*-heptulose.



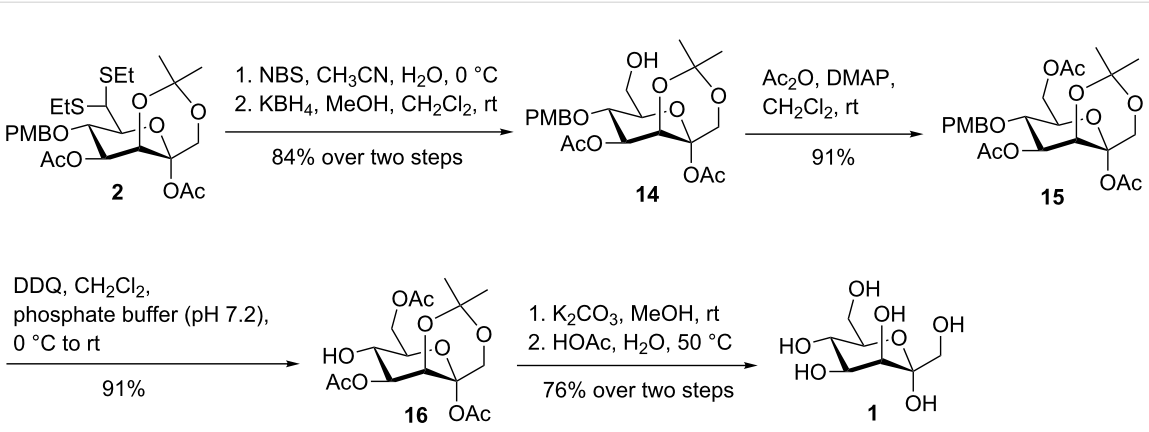
Scheme 2: Initial attempt on the synthesis of the C_4 aldehyde from D-lyxose (**5**).

the assembly of ketoheptose skeletons, we envisioned ketoheptoses could be assembled by a cascade aldol/hemiketalization reaction between 2-OH-unprotected C_4 aldehyde **3** and C_3 ketone **4**. As such, the isopropylidene acetal group in **7** was cleaved under acidic conditions to produce triol **11** in 86% yield (Scheme 3). Cleavage of the resulting vicinal diol in **11** with sodium periodate led to the C_4 aldehyde **3** in nearly 60–70% yield. In this oxidative cleavage reaction, almost no elimination product was found based on TLC monitoring. Given that the C_4 aldehyde **3** was unstable upon purification by silica gel column chromatography, it was immediately used for the subsequent coupling after the extraction procedure. The aldol reaction of aldehyde **3** with the readily available ketone **4** [42,43] under the catalysis of L-proline at room temperature for three days proceeded sluggishly, leading to the desired product in a very low yield. Gratifyingly, when the L-proline-catalyzed aldol reaction was performed at 70 °C for one day, the TLC indicated the complete consumption of aldehyde **3**, and the generated 4,5-*anti*-selective coupling intermediate **12** underwent in situ cyclization to provide hemiketal **13** as the major product in about 50–60% yield (35% overall yield from compound **11**). Notably, trace amounts of a stereoisomer and a minor highly polar unknown byproduct were also observed in this cascade reaction. The excellent *anti*-selectivity for the L-proline-catalyzed aldol reaction can be explained by the Houk–List transition state model [43-45]. Compound **13** was then acetylated to afford differentially protected ketoheptose building block **2** in 83% yield. The structure of **2** was unambiguously confirmed by ^{1}H, ^{13}C, and 2D NMR spectra (see Supporting Information File 1 for details). The anomeric α-configuration of compound **2** was confirmed by analysis of the NOE effects between the C-1 hydrogen and the C-5 hydrogen.

With the ketoheptose building block **2** in hand, we turned our attention to the synthesis of D-*manno*-heptulose (**1**). Upon exposure to NBS in acetonitrile and water, the dithioacetal in **2** was cleaved to give the corresponding aldehyde [46,47], which was then reduced by potassium borohydride in a methanol and dichloromethane solvent mixture to produce alcohol **14** as the predominant product (84% over two steps, Scheme 4). In addition, a trace amount of the deacetylated product was also detected . DDQ-mediated oxidative cleavage of the PMB group in alcohol **14** produced only a moderate yield (≈50%) of the 5,7-diol probably due to the presence of the free 7-hydroxy group. We envisaged that protection of the free 7-hydroxy group in **14** followed by treatment with DDQ could yield the desired 5-hydroxy product in high yield. Indeed, acetylation of alcohol **14** with acetic anhydride delivered ester **15** in 91% yield. Removal of the PMB group in **15** with DDQ resulted in a very clean reaction, affording alcohol **16** in an excellent yield (91%). Saponification of all esters in **16** with potassium carbonate followed by acidic cleavage of the isopropylidene



Scheme 3: Synthesis of differentially protected ketoheptose building block **2**.



Scheme 4: Synthesis of D-*manno*-heptulose (**1**).

acetal group with aqueous acetic acid furnished D-*manno*-heptulose (**1**, 76% over two steps). The structure of **1** was found to be in good agreement with those reported for α-D-*manno*-heptulose (**1**) by comparison of the NMR spectra (see Supporting Information File 1 for details) [26].

Conclusion

In summary, we have described a [4 + 3] approach for the synthesis of D-*manno*-heptulose (**1**) starting from D-lyxose (**5**). The key step is a cascade aldol/hemiketalization reaction for the construction of the differentially protected ketoheptose building block, which was finally converted into D-*manno*-heptulose for subsequent biological evaluation. Although the synthesis of D-*manno*-heptulose (5% overall yield, 13 steps) is not so efficient as the Thiem's method (59% overall yield, 5 steps), the reported differentially protected ketoheptose building blocks may find further application in the preparation of structurally diverse D-*manno*-heptulose derivatives.

Supporting Information

Supporting Information File 1

Experimental details, characterization data, and NMR spectra of all new compounds.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-13-79-S1.pdf]

Acknowledgements

Financial support from the National Thousand Young Talents Program (YC0130518, YC0140103), the Shanghai Pujiang Program (15PJ1401500), the Fundamental Research Funds for the Central Universities (WY1514052), and the Opening Project of State Key Laboratory of Bio-organic and Natural Products Chemistry (Y100-D-1501) is gratefully acknowledged.

References

1. La Forge, F. B. *J. Biol. Chem.* **1917,** *28,* 511–522.
2. Roe, J. H.; Hudson, C. S. *J. Biol. Chem.* **1936,** *112,* 443–449.
3. Simon, E.; Kraicer, P. F. *Arch. Biochem. Biophys.* **1957,** *69,* 592–601. doi:10.1016/0003-9861(57)90523-4
4. Paulsen, E. P.; Richenderfer, L.; Winick, P. *Nature* **1967,** *214,* 276–277. doi:10.1038/214276b0
5. Coore, H. G.; Randle, P. J. *Biochem. J.* **1964,** *91,* 56–59. doi:10.1042/bj0910056
6. Zelent, D.; Najafi, H.; Odili, S.; Buettger, C.; Weik-Collins, H.; Li, C.; Doliba, N.; Grimsby, J.; Matschinsky, F. M. *Biochem. Soc. Trans.* **2005,** *33,* 306–310. doi:10.1042/BST0330306
7. Paulsen, E. P. *Ann. N. Y. Acad. Sci.* **1968,** *150,* 455–456. doi:10.1111/j.1749-6632.1968.tb19069.x
8. Board, M.; Colquhoun, A.; Newsholme, E. A. *Cancer Res.* **1995,** *55,* 3278–3285.
9. Malaisse, W. J. *Diabetologia* **2001,** *44,* 393–406. doi:10.1007/s001250051635
10. Leshch, Y.; Waschke, D.; Thimm, J.; Thiem, J. *Synthesis* **2011,** 3871–3877. doi:10.1055/s-0031-1289598
11. Waschke, D.; Leshch, Y.; Thimm, J.; Himmelreich, U.; Thiem, J. *Eur. J. Org. Chem.* **2012,** 948–959. doi:10.1002/ejoc.201101238
12. Malaisse, W. J.; Zhang, Y.; Louchami, K.; Sharma, S.; Dresselaers, T.; Himmelreich, U.; Novotny, G. W.; Mandrup-Poulsen, T.; Waschke, D.; Leshch, Y.; Thimm, J.; Thiem, J.; Sener, A. *Arch. Biochem. Biophys.* **2012,** *517,* 138–143. doi:10.1016/j.abb.2011.11.014
13. Leshch, Y.; Jacobsen, A.; Thimm, A.; Thiem, J. *Org. Lett.* **2013,** *15,* 4948–4951. doi:10.1021/ol4021699
14. Schmidtke, C.; Kreuziger, A.-M.; Alpers, D.; Jacobsen, A.; Leshch, Y.; Eggers, R.; Kloust, H.; Tran, H.; Ostermann, J.; Schotten, T.; Thiem, J.; Thimm, J.; Weller, H. *Langmuir* **2013,** *29,* 12593–12600. doi:10.1021/la402826f
15. Levy, D. E.; Tang, C. *The chemistry of C-glycosides;* Pergamon: Oxford, 1995.
16. Du, Y.; Linhardt, R. J.; Vlahov, I. R. *Tetrahedron* **1998,** *54,* 9913–9959. doi:10.1016/S0040-4020(98)00405-0
17. Jacobsen, A.; Thiem, J. *Curr. Org. Chem.* **2014,** *18,* 2833–2841. doi:10.2174/1385272819666141016215205
18. Montgomery, E. M.; Hudson, C. S. *J. Am. Chem. Soc.* **1939,** *61,* 1654–1658. doi:10.1021/ja01876a007

19. Hricoviniova, Z.; Hricovini, M.; Petrusoa, M.; Matulova, M.; Petrus, L. *Chem. Pap.* **1998,** *52,* 238–243.
20. Sowden, J. C. *J. Am. Chem. Soc.* **1950,** *72,* 3325. doi:10.1021/ja01163a558
21. Schaffner, R.; Isbell, H. S. *J. Org. Chem.* **1962,** *27,* 3268–3270. doi:10.1021/jo01056a069
22. Cheng, J.; Fang, Z.; Li, S.; Zheng, B.; Jiang, Y. *Carbohydr. Res.* **2009,** *344,* 2093–2095. doi:10.1016/j.carres.2009.06.020
23. Kampf, A.; Dimant, E. *Carbohydr. Res.* **1974,** *32,* 380–382. doi:10.1016/S0008-6215(00)82116-3
24. Bessières, B.; Morin, C. *J. Org. Chem.* **2003,** *68,* 4100–4103. doi:10.1021/jo0342166
25. Liu, X.; Yin, Q.; Yin, J.; Chen, G.; Wang, X.; You, Q.-D.; Chen, Y.-L.; Xiong, B.; Shen, J. *Eur. J. Org. Chem.* **2014,** 6150–6154. doi:10.1002/ejoc.201402757
26. Waschke, D.; Thimm, J.; Thiem, J. *Org. Lett.* **2011,** *13,* 3628–3631. doi:10.1021/ol2012764
27. Li, X.; Takahashi, H.; Ohtake, H.; Shiro, M.; Ikegami, S. *Tetrahedron* **2001,** *57,* 8053–8066. doi:10.1016/S0040-4020(01)00775-X
28. Northrup, A. B.; MacMillan, D. W. C. *Science* **2004,** *305,* 1752–1755. doi:10.1126/science.1101710
29. Timmer, M. S. M.; Adibekian, A.; Seeberger, P. H. *Angew. Chem., Int. Ed.* **2005,** *44,* 7605–7607. doi:10.1002/anie.200502742
30. Ahmed, M. M.; Berry, B. P.; Hunter, T. J.; Tomcik, D. J.; O'Doherty, G. A. *Org. Lett.* **2005,** *7,* 745–748. doi:10.1021/ol050044i
31. Adibekian, A.; Timmer, M. S. M.; Stallforth, P.; van Rijn, J.; Werz, D. B.; Seeberger, P. H. *Chem. Commun.* **2008,** 3549–3551. doi:10.1039/B805159C
32. Stallforth, P.; Adibekian, A.; Seeberger, P. H. *Org. Lett.* **2008,** *10,* 1573–1576. doi:10.1021/ol800227b
33. Shan, M.; Xing, Y.; O'Doherty, G. A. *J. Org. Chem.* **2009,** *74,* 5961–5966. doi:10.1021/jo9009722
34. Ohara, T.; Adibekian, A.; Esposito, D.; Stallforth, P.; Seeberger, P. H. *Chem. Commun.* **2010,** *46,* 4106–4108. doi:10.1039/c000784f
35. Calin, O.; Pragani, R.; Seeberger, P. H. *J. Org. Chem.* **2012,** *77,* 870–877. doi:10.1021/jo201883k
36. Babu, R. S.; Chen, Q.; Kang, S.-W.; Zhou, M.; O'Doherty, G. A. *J. Am. Chem. Soc.* **2012,** *134,* 11952–11955. doi:10.1021/ja305321e
37. Gati, W.; Rammah, M. M.; Rammah, M. B.; Couty, F.; Evano, G. *J. Am. Chem. Soc.* **2012,** *134,* 9078–9081. doi:10.1021/ja303002a
38. Mlynarski, J.; Gut, B. *Chem. Soc. Rev.* **2012,** *41,* 587–596. doi:10.1039/C1CS15144D
39. Wang, H.-Y.; Yang, K.; Yin, D.; Liu, C.; Glazier, D. A.; Tang, W. *Org. Lett.* **2015,** *17,* 5272–5275. doi:10.1021/acs.orglett.5b02641
40. van Delft, F. L.; Rob, A.; Valentijn, P. M.; van der Marel, G. A.; van Boom, J. H. *J. Carbohydr. Chem.* **1999,** *18,* 165–190. doi:10.1080/07328309908543989
41. Grindley, T. B. *Adv. Carbohydr. Chem. Biochem.* **1998,** *53,* 17–142. doi:10.1016/S0065-2318(08)60043-8
42. Suri, J. T.; Mitsumori, S.; Albertshofer, K.; Tanaka, F.; Barbas, C. F., III. *J. Org. Chem.* **2006,** *71,* 3822–3828. doi:10.1021/jo0602017
43. Grondal, C.; Enders, D. *Tetrahedron* **2006,** *62,* 329–337. doi:10.1016/j.tet.2005.09.060
44. Bahmanyar, S.; Houk, K. N.; Martin, H. J.; List, B. *J. Am. Chem. Soc.* **2003,** *125,* 2475–2479. doi:10.1021/ja028812d
45. Hoang, L.; Bahmanyar, S.; Houk, K. N.; List, B. *J. Am. Chem. Soc.* **2003,** *125,* 16–17. doi:10.1021/ja028634o
46. Corey, E. J.; Erickson, B. W. *J. Org. Chem.* **1971,** *36,* 3553–3560. doi:10.1021/jo00822a019
47. Crich, D.; de la Mora, M. A.; Cruz, R. *Tetrahedron* **2002,** *58,* 35–44. doi:10.1016/S0040-4020(01)01087-0

License and Terms