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Diisobutylaluminum Hydride Mediated Regioselective O Desilylations: Access to Multisubstituted Cyclodextrins**

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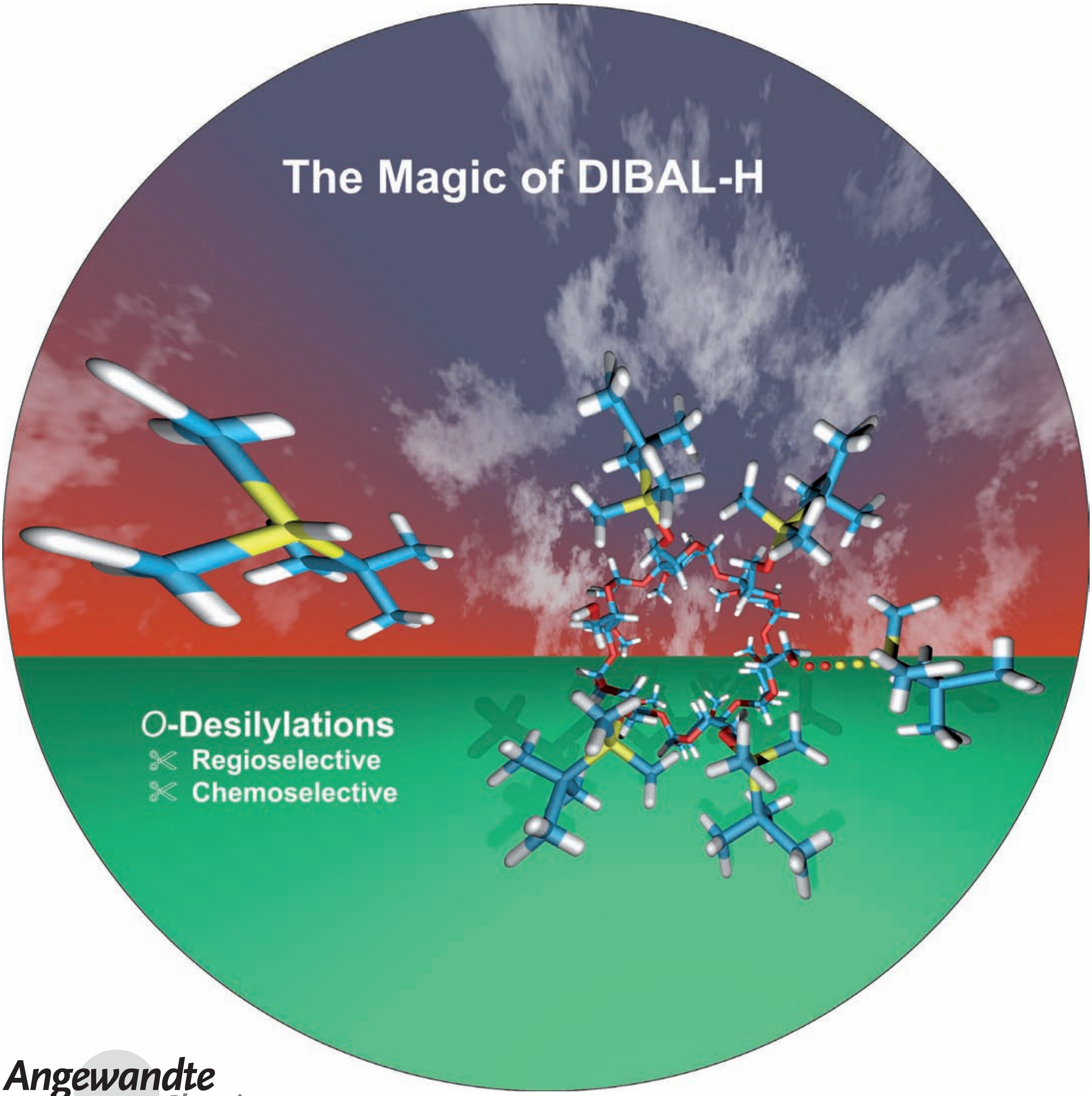


Recently, there has been a renewed interest[1] in developing novel methodologies[2–5] to regioselectively obtain multisubstituted cyclodextrin (CD) hosts. These structurally well-defined molecules are key intermediates in the design of artificial enzymes,[6] gene delivery vehicles,[7] sensors,[8] and novel supramolecular assemblies.[9]

In all CD molecules, there exist three types of hydroxy groups attached to the C6, C2, and C3 positions of the D-glucopyranosyl unit. It is relatively straightforward to chemoselectively differentiate one hydroxy group from another,[1] but it is much more challenging to regioselectively differentiate between hydroxy groups of the same type because of their identical chemical reactivity. To obtain multifunctionalized CDs, three innovative strategies were commonly used: 1) the first relies on the use of bulky protecting groups such as trityl[4a,10] and its variants[3a,b] to protect the primary rim; 2) the second involves the use of tethered bifunctional sulfonating,[11] tritylating,[3c,d] or other alkylating reagents[5a,b] which selectively react with two hydroxy groups of the CD according to the length and geometry of the tether; 3) the third was introduced by the Sinaÿ and co-workers, and takes advantage of the reductive O dealkylation by diisobutylaluminum hydride (DIBAL-H)[2] using O-perbenzylated CDs as substrates; either one or two benzyl (Bn) groups are removed from the primary face in moderate to high yields. They also found that the same conditions can be applied to remove methyl groups from permethylated CDs, predominantly at the secondary rim.[2d] The most remarkable feature of the method reported by Sinaÿ and co-workers is the high regioselectivity. For example, in the cases of α/β CDs, only benzyl group(s) attached to O6 positions of the A and D units (see Scheme 1 for labeling of a CD) are affected. We later found that this methodology could also be used to synthesize triply and quadruply O-debenzylated products in gram quantities.[4b,c] A downside of the methodology is that a large excess (> 30 equiv) of DIBAL-H is required. Herein we report a hitherto new method that allows access to multisubstituted CDs from readily available per-6-O-silylated CD derivatives by DIBAL-H-promoted regioselective O desilylation.

Recently, Kuranaga et al. reported[12] that primary silyl ethers such as *tert*-butyldimethylsilyl (TBS), triethylsilyl (TES), and *tert*-butyldiphenylsilyl (TBDPS) could be chemoselectively removed by DIBAL-H (5 equiv) in the presence of secondary TES ethers at low temperatures (−20–−40 °C) to afford primary alcohols in good to excellent yields. Encouraged by this report, we wondered if this methodology could be applied to CD chemistry, specifically if substrates **1**–**3** (Figure 1), which are all per-6-O-*tert*-butyldimethylsilylated, could be used to react with DIBAL-H to produce partially O-desilylated intermediates. Contrary to the reported work, here the challenge is that in each substrate all TBS groups are derived from a primary hydroxy group and have identical chemical environments. However, we thought if we were able to partially remove the TBS groups, we could provide the first examples to demonstrate the utility of DIBAL-H in regioselective O desilylations in CD chemistry. Large quantities of compounds **1**–**3** were conveniently prepared from native α, β, and γ CDs in two steps using literature procedures.[13]

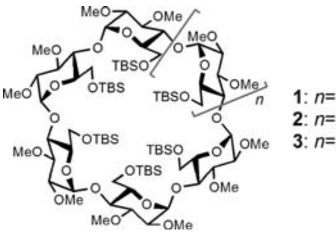
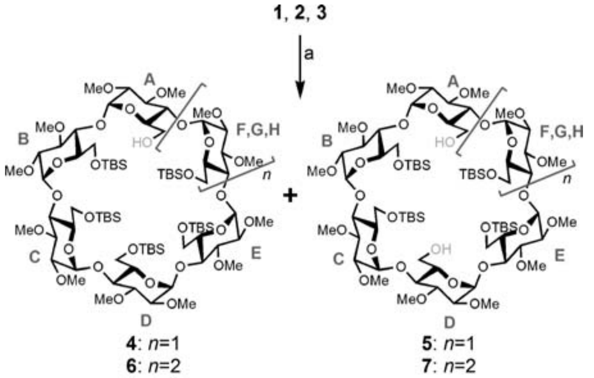


Figure 1. Structures of the 6-*O*-persilylated substartes **1**–**3**.

Thus we first subjected the persilylated α-CD derivative **1** to react with DIBAL-H (3.5 equiv, 0.1 mol L^{-1}) in anhydrous toluene at −40 °C (Scheme 1). However, it was found that reaction proceeded very slowly, as most starting materials remained unchanged even after 16 hours. When we slowly raised the temperature to 0 °C, we observed an accelerated reaction rate. The starting material was gradually consumed along with the formation of two new products—both of them being more polar. After stirring for 3 hours, the less polar product (**4**) became the major product and was isolated by column chromatography on silica gel in 71 % yield as was based on the consumed material. The more polar product **5** was also isolated in 16 % yield (Table 1, entry 1). Some starting material (**1**) remained and was never completely consumed even after 48 hours. However, if we increased the



Scheme 1. DIBAL-H-mediated O desilylations. a) DIBAL-H in toluene. See the Supporting Information for detailed reaction conditions and yields.

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Table 1: Reaction conditions and yields of the DIBAL-H mediated stepwise O desilylations

Entry	Substrate	Conditions[a]	Yield [%][b]				
			4	5	6	7	8
1	**1**	3.5 equiv, 0.1 M, 0 °C, 3 h	71	16	–	–	–
2	**1**	7 equiv, 0.3 M, 0 °C, 4 h	10	68	–	–	–
3	**2**	3 equiv, 0.15 M, 0 °C, 3 h	–	–	62	22	–
4	**2**	6 equiv, 0.3 M, 0 °C, 4 h	–	–	12	71	–
5	**3**	3 equiv, 0.1 M, 0 °C, 4 h	–	–	–	–	58[c]
6	**3**	6 equiv, 0.1 M, 0 °C, 4 h	–	–	–	–	16 [c]

[a] For all reactions, DIBAL-H in toluene (1.0 M) was used. [b] Yield of isolated product. [c] The reaction also afforded a mixture of unseparable O-di-desilylated compounds (26 % for entry 5 and 53 % for entry 6).

amount of DIBAL-H to 7 equivalents (0.3 mol L^{-1}), we observed complete consumption of the starting material after 4 hours (Table 1, entry 2). In this case, the more polar product **5** was formed as the major product and was isolated in 68 % yield, and the less polar product **4** was isolated in 10 % yield. Thin-layer chromatography (TLC) also showed that some even more polar products were formed, but they were minor and therefore not characterized.

High resolution mass spectrometry (HRMS) confirmed that the less polar product **4** corresponded to a compound that lost only one TBS group (m/z: 1728.0709, $M+NH_4^+$). Thus the structure of **4** was assigned as indicated in Scheme 1, and the structure was supported by NMR experiments wherein no symmetry was observed in both the ^{1}H and ^{13}C NMR spectra (see the Supporting Information). The HRMS of the more polar product **5** corresponded to a compound that lost two TBS groups (m/z: 1619.8438, $M+Na^+$). Theoretically, there are three possible regioisomers (6^A,6^B; 6^A,6^C; and 6^A,6^D) that could arise form the loss of two TBS groups. Surprisingly, from the ^{1}H and ^{13}C NMR spectra, we found that only one regioisomer was present and identified as the symmetric 6^A,6^D-di-*O*-desilylated compound **5**, as evidenced by the presence of C_2 symmetry. For example, in the ^{1}H NMR spectra, three pairs of anomeric protons were observed at $\delta = 5.10$, 5.07, and 5.03 ppm, and this symmetry is additionally supported by the observation of three pairs of H2 protons at $\delta = 3.14$, 3.09, and 3.08 ppm (Figure 2 A).

Thus, it appeared that the DIBAL-H-mediated O desilylations follow a similar deprotection pattern as the related O debenzylations. Therefore, we continued our investigations using the persilylated compounds **2** and **3** (Scheme 1) as substrates to confirm the observations.

As indicated by the TLC analysis, treatment of either the β-CD derivative **2** or γ-CD derivative **3** with 3.0 equivalents of DIBAL-H (Table 1, entries 3 and 5) also generated two new products, both of which are more polar than the respective starting material. In both cases, the less polar compounds **6** and **8** were formed as major products, and were isolated in 62 % (from **2**) and 58 % (from **3**) yield, respectively. Both compounds were characterized as the mono O-desilylated compound by HRMS as well as ^{1}H and ^{13}C NMR spectroscopy. Their structures were assigned as shown for **6** and **8**. The more polar product **7** from the reaction of compound **2** was isolated in 22 %, whereas the more polar product arising from **3** was obtained in 26 % yield. Consistent with the O desilylaion of **1**, the degree of O desilylation seems to correlate well with the amount of DIBAL-H used. For example, when increasing the amount of DIBAL-H to 6.0 equivalents for reaction with **2** (Table 1, entry 4), the more polar compound **7** became the major product after 4 hours at 0 °C, and was isolated in 71 % yield.

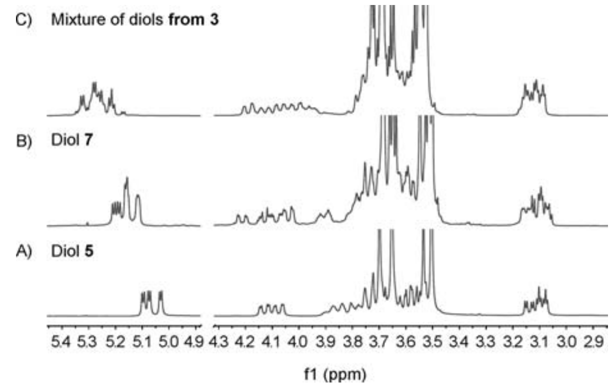
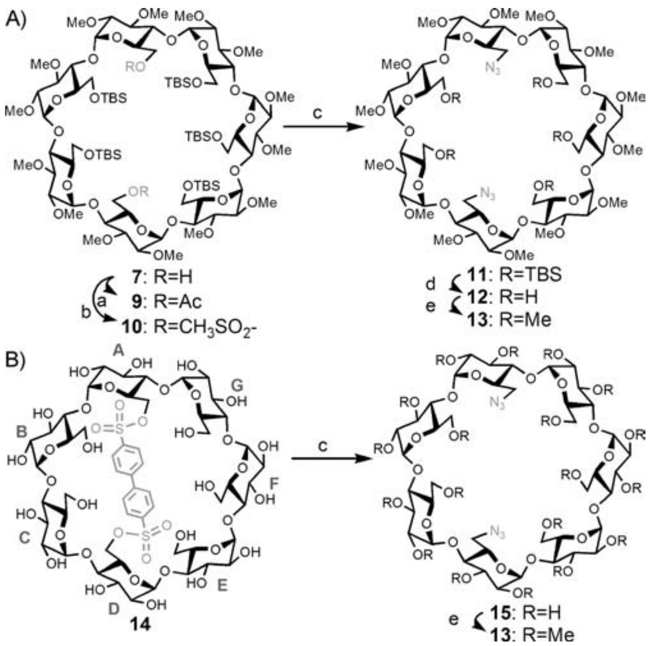


Figure 2. The ^{1}H NMR spectra of the di-6-*O*-desilylated A) products **5** and B) **7**, as well as C) a mixture of the diols obtained from the reaction of substrate **3** with DIBAL-H.

HRMS confirmed that the more polar compound from each reaction correlated to a di-6-O-desilylated derivative. However, from the analysis of recorded ^{1}H and ^{13}C NMR spectra, it was found that the more polar product from the reaction of **3** comprised a mixture of two compounds (Figure 2 C), whereas the more polar product **7** from the desilylation of **2** consisted of only one single isomer (Figure 2 B). For example, in the ^{1}H NMR spectra of compound **7**, seven anomeric protons were observed; two of them are well separated from the rest ($\delta = 5.21$ and 5.19 ppm), while the remaining five anomeric protons were observed in two regions within the range of $\delta = 5.17$–4.14 ppm (3 × H1) and $\delta = 5.13$–5.10 (2 × H1). We tried to assign the structures of the di-O-desilylated compounds by a series of 2D experiments (GCOSY and GHSQC); however, because of extensive overlaps of the NMR signals, our attempts were unsuccessful. Since the di-O-desilylation of compound **1** followed a path similar to the corresponding di-O-debenzylation, we tentatively assigned the structure of the di-O-desilylated compound from **2** to be the 6^A,6^D-di-*O*-desilylated β-CD isomer **7**. The di-O-desilylated products from **3** could be the 6^A,6^D/6^E-di-*O*-desilylated γ-CD isomers according to the literature;[2a] however, attempts to separate the two regioisomers using different chromatographic conditions were unsuccessful.

To unambiguously prove the structure of **7**, it was acetylated to provide the diacetate **9** (Scheme 2 A). We hoped that the deshielding effect of the acetyl groups would reduce the overlapping of the NMR signals, thus allowing us to determine the substitution patterns of **7** by 2D NMR experiments. However, this did not yield success. We then decided to convert **7** into **13** through a multistep transformation and then compare **13** with an identical compound that could be obtained from the known 6^A,6^D-capped disulfonate **14** (Scheme 2 B). First, compound **7** was treated



Scheme 2. A) Chemical transformation of **7** into **13**. B) Chemical transformation of **14** into **13**. a) Ac_2O, pyridine; b) CH_3SO_2Cl, Et_3N, CH_2Cl_2; c) NaN_3, DMF; d) $n$$Bu_4NF$, THF; e) MeI, NaH, DMF. See the Supporting Information for detailed reaction conditions and yields.

with MsCl to provide the dimesylate **10** (75%), which was then substituted with azide (**11**, 93%). The five TBS groups were then removed by the treatment with tetra-*n*-butylammonium fluoride in THF to provide the pentaol **12** (93%), which was methylated to afford the desired **13** (85%). In parallel, the previously known compound **14** was treated with an excess amount of sodium azide to afford the 6^{A},6^{D}-diazide **15**. After a conventional permethylation, we obtained a compound that had identical ^{1}H NMR spectra to that of **13** as obtained from **7** (Figure 3). Thus the structure of compound **7** was confirmed.

Considering that the TBS group is considerably larger than the benzyl group, we can predict that for the per-6-O-silylated substrates, there must exist greater steric hindrance at the primary rim compared to that of the perbenzylated analogues. The fact that DIBAL-H is able to react with both classes of substrates and performs deprotections with similar regioselectivities is remarkable. Furthermore, we also note that even though our substrates had methyl groups at the secondary rim, the previously observed O demethylation did not occur. This observation illustrates that the DIBAL-H-mediated O desilylation is highly chemoselective. To further demonstrate the versatility of the method, we decided to use two additional substrates, namely **16** and **17**,[13c] which are analogues of compound **1** and **2** having removable benzyl groups at the secondary rim (Scheme 3). Selective O desilylations on these substrates would effectively create CD derivatives with three orthogonal functional groups (Bn, OH, TBS) that can be manipulated independently. These compounds are valuable intermediates for the design of artificial enzymes and complex supramolecular systems that are difficult to obtain through other methods.

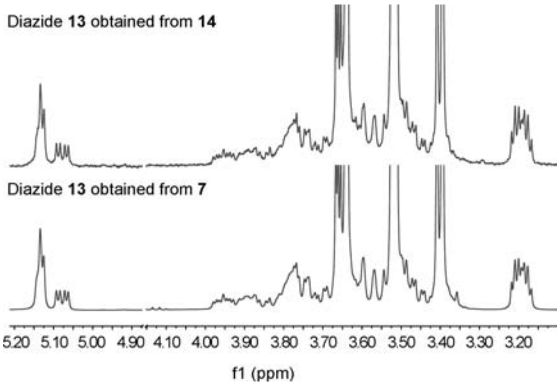
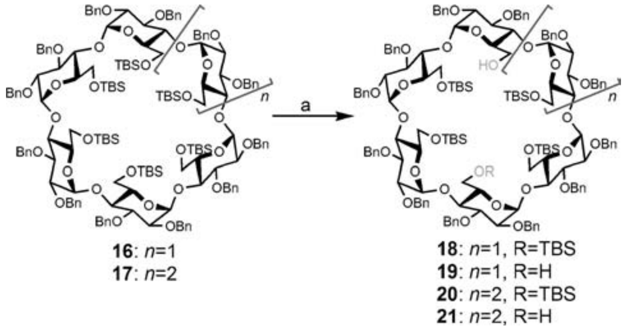


Figure 3. Comparison of the ^{1}H NMR spectra of compound **13**, obtained from **7** and from **14**.



Scheme 3. O Desilylations using per-2,3-O-benzylated substrates **16** and **17**. a) DIBAL-H in toluene. See the Supporting Information for detailed reaction conditions and yields.

To our delight, these two substrates behaved in an analogous manner as the other methylated analogues. For example, when **16** and **17** were subjected to 3–3.5 equivalents of DIBAL-H, the corresponding O-monodesilylated products **18** and **20** were obtained in 70% and 71% yields, respectively. When more DIBAL-H (6.0–7.0 equiv) was used, the corresponding di-O-desilylated products **19** and **21** were obtained in even better yields (82% for **21** and 87% for **23**). The structure of compound **19** was confirmed by the presence of C_2 symmetry in both the ^{1}H and ^{13}C NMR spectra. To unambiguously prove the substitution patterns of the β-CD analogue **21**, we converted **21** into a per-*O*-benzylated 6^{A},6^{D}-diazido analogue in a similar manner as **7**, and confirmed its structure by comparing its ^{1}H NMR spectra with an identical compound obtained from the known perbenzylated β-CD 6^{A},6^{D}-diol[2c] (see the Supporting Information).

In conclusion, the work presented here demonstrates that DIBAL-H is an excellent reagent that can be used to promote regioselective O desilylations of primary silyl ethers on CD derivatives. This method will allow the preparation of orthogonally protected, multisubstituted CD derivatives in an efficient manner. Compared to the previously known O debenzylations, the O desilylation requires easily accessible starting materials, but a much smaller amount of the reagent, and the reaction can be carried out under mild reaction conditions. Based on results obtained from this work, we note that the degree of O desilylation is responsive to the amount of reagent used. When combined with the high chemoselectivity of the method, we think that the DIBAL-H mediated O desilylations will be likely to find ample applications in CD chemistry.

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[1] a) A. R. Khan, P. Forgo, K. J. Stine, V. T. D'Souza, *Chem. Rev.* **1998**, *98*, 1977–1996; b) M. Sollogoub, *Eur. J. Org. Chem.* **2009**, 1295–1303; c) E. Engeldinger, D. Armspach, D. Matt, *Chem. Rev.* **2003**, *103*, 4147–4173.

[2] a) A. J. Pearce, P. Sinaÿ, *Angew. Chem.* **2000**, *112*, 3756–3758; *Angew. Chem. Int. Ed.* **2000**, *39*, 3610–3612; b) B. du Roizel, J. P. Baltaze, P. Sinaÿ, *Tetrahedron Lett.* **2002**, *43*, 2371–2373; c) T. Lecourt, A. Herault, A. J. Pearce, M. Sollogoub, P. Sinaÿ, *Chem. Eur. J.* **2004**, *10*, 2960–2971; d) S. Xiao, M. Yang, P. Sinaÿ, Y. Blériot, M. Sollogoub, Y. Zhang, *Eur. J. Org. Chem.* **2010**, 1510–1516.

[3] a) D. Armspach, D. Matt, *Carbohydr. Res.* **1998**, *310*, 129–133; b) L. Poorters, D. Armspach, D. Matt, *Eur. J. Org. Chem.* **2003**, 1377–1381; c) D. Armspach, L. Poorters, D. Matt, B. Benmerad, F. Balegroune; L. Toupet, *Org. Biomol. Chem.* **2005**, *3*, 2588–2592; L. Toupet, *Org. Biomol. Chem.* **2005**, *3*, 2588–2592; d) R. Gramage-Doria, D. Rodriguez-Lucena, D. Armspach, C. Egloff, M. Jouffroy, D. Matt, L. Toupet, *Chem. Eur. J.* **2011**, *17*, 3911–3921.

[4] a) S. Ward, P. Zhang, C.-C. Ling, *Carbohydr. Res.* **2009**, *344*, 808–814; b) G. K. Rawal, S. Rani, C.-C. Ling, *Tetrahedron Lett.* **2009**, *50*, 4633–4636; c) G. K. Rawal, S. Rani, S. Ward, C.-C. Ling, *Org. Biomol. Chem.* **2010**, *8*, 171–180.

[5] a) N. Masurier, O. Lafont, R. Le Provost, D. Lesur, P. Masson, F. Djedaini-Pilard, F. Estour, *Chem. Commun.* **2009**, 589–591; b) P. Balbuena, D. Lesur, M. J. G. Alvarez, F. Mendicuti, C. O. Mellet, J. M. G. Fernandez, *Chem. Commun.* **2007**, 3270–3272; c) M. Petrillo, L. Marinescu, C. Rousseau, M. Bols, *Org. Lett.* **2009**, *11*, 1983–1985; d) R. F. Gómez-Biagi, M. Nitz, *Chem. Commun.* **2011**, *47*, 8614–8616.

[6] a) J. Bjerre, C. Rousseau, L. Marinescu, M. Bols, *Appl. Microbiol. Biotechnol.* **2008**, *81*, 1–11; b) R. Breslow, *Acc. Chem. Res.* **1995**, *28*, 146–153.

[7] a) C. O. Mellet, J. M. G. Fernandez, J. M. Benito, *Chem. Soc. Rev.* **2011**, *40*, 1586–1608; b) A. McMahon, E. Gomez, R. Donohue, D. Forde, R. Darcy, C. M. O'Driscoll, *J. Drug Delivery Sci. Technol.* **2008**, *18*, 303–307.

[8] a) J. M. Haider, Z. Pikramenou, *Chem. Soc. Rev.* **2005**, *34*, 120–132; b) T. Ogoshi, A. Harada, *Sensors* **2008**, *8*, 4961–4982.

[9] a) G. K. Rawal, P. Zhang, C.-C. Ling, *Org. Lett.* **2010**, *12*, 3096–3099; b) H. S. Christensen, B. W. Sigurskjold, T. G. Frihed, L. G. Marinescu, C. M. Pedersen, M. Bols, *Eur. J. Org. Chem.* **2011**, 5279–5290.

[10] a) J. Boger, D. G. Brenner, J. R. Knowles, *J. Am. Chem. Soc.* **1979**, *101*, 7630–7631; b) C.-C. Ling, A. W. Coleman, M. Miocque, *Carbohydr. Res.* **1992**, *223*, 287–291.

[11] I. Tabushi, K. Shimokawa, N. Shimizu, H. Shirakata, K. Fujita, *J. Am. Chem. Soc.* **1976**, *98*, 7855–7856.

[12] K. Kuranaga, S. Ishihara, N. Ohtani, M. Satake, K. Tachibana, *Tetrahedron Lett.* **2010**, *51*, 6345–6348.

[13] a) P. Fügedi, *Carbohydr. Res.* **1989**, *192*, 366–369; b) P. Zhang, C.-C. Ling, A. W. Coleman, H. Parrot-Lopez, H. Galons, *Tetrahedron Lett.* **1991**, *32*, 2769–2770; c) G. Uccello-Barretta, G. Sicoli, F. Balzano, P. Salvadori, *Carbohydr. Res.* **2005**, *340*, 271–281.