ORGANIC LETTERS

2003
Vol. 5, No. 24
4541−4544

Use of Olefin Cross-Metathesis to Release Azide-Containing Sugars from Solid Support

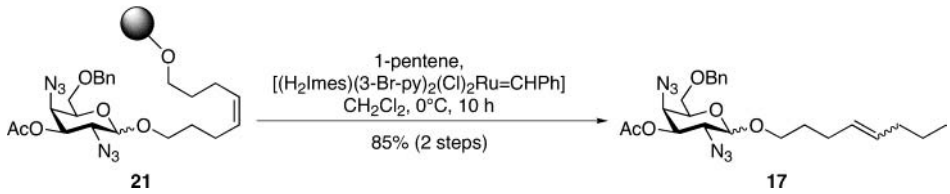
Takuya Kanemitsu[†] and Peter H. Seeberger*[,‡]

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

seeberger@org.chem.ethz.ch

Received August 4, 2003

ABSTRACT



The octenediol linker used during automated oligosaccharide assembly is cleaved by olefin cross-metathesis. Until now, this linker could not be applied to sugars containing azides. A detailed study of the cleavage reaction served as basis for the development of a new protocol using the [(H$_2$Imes)(3-Br-py)$_2$(Cl)$_2$Ru=CHPh] catalyst and 1-pentene. Efficient release of azide-protected carbohydrates from solid support can be readily achieved.

Automated solid-phase oligosaccharide synthesis has greatly accelerated the process of assembling even complex oligosaccharides from monosaccharide building blocks.[1] Several factors are of critical importance when designing a synthetic strategy for the solid phase assembly of carbohydrates, including the choice of protecting groups, anomeric leaving group and the linker. The linker that connects the first monosaccharide to the polymeric support can be viewed as a support-bound protecting group and presents possibly the most important strategic decision during synthetic planning. The selection of the linker determines all reaction conditions that can be applied during assembly and influences the form in which the oligosaccharide is released from the support.

The octenediol linker we developed[2] for the automated synthesis of oligosaccharides on solid support has proven versatile. The double bond serves as an unique and robust functional group that can be selectively cleaved via cross-metathesis with ethylene.[2] Until now, this linker had been exclusively used with oligosaccharides that did not contain any azide protecting groups masking amino functions. The protection of amines as azides is a common and convenient strategy applied to the assembly of oligosaccharides, aminoglycoside antibiotics[3] and glycosaminoglycans including heparin.[4] With the automated assembly of aminoglycoside antibiotics and heparin coming within reach, this limitation of the octene diol linker system had to be addressed.

[†] Current address: Division of Organic and Bioorganic Chemistry, Kyoritsu College of Pharmacy, Shibakoen 1-5-30, Minatoku, Tokyo 105, Japan.

[‡] New address: Laboratorium für Organische Chemie, ETH Hönggerberg/HCI F 315, Wolfgang-Pauli-Strasse 10, 8093 Zürich, Switzerland.

(1) (a) Seeberger, P. H.; Haase, W.-C. *Chem. Rev.* **2000**, *100*, 4349−4394. (b) Plante, O. J.; Palmacci, E. R.; Seeberger, P. H. *Science* **2001**, *291*, 1253−1257. (c) Sears, P.; Wong, C.-H. *Science* **2001**, *291*, 2344−2350. (d) *Solid Support Oligosaccharide Synthesis and Combinatorial Carbohydrate Libraries*; Seeberger, P. H., Ed.; Wiley: New York, 2001. (e) Kanemitsu, T.; Kanie, O. *Comb. Chem. High Throughput Screening* **2002**, *5*, 339−360.

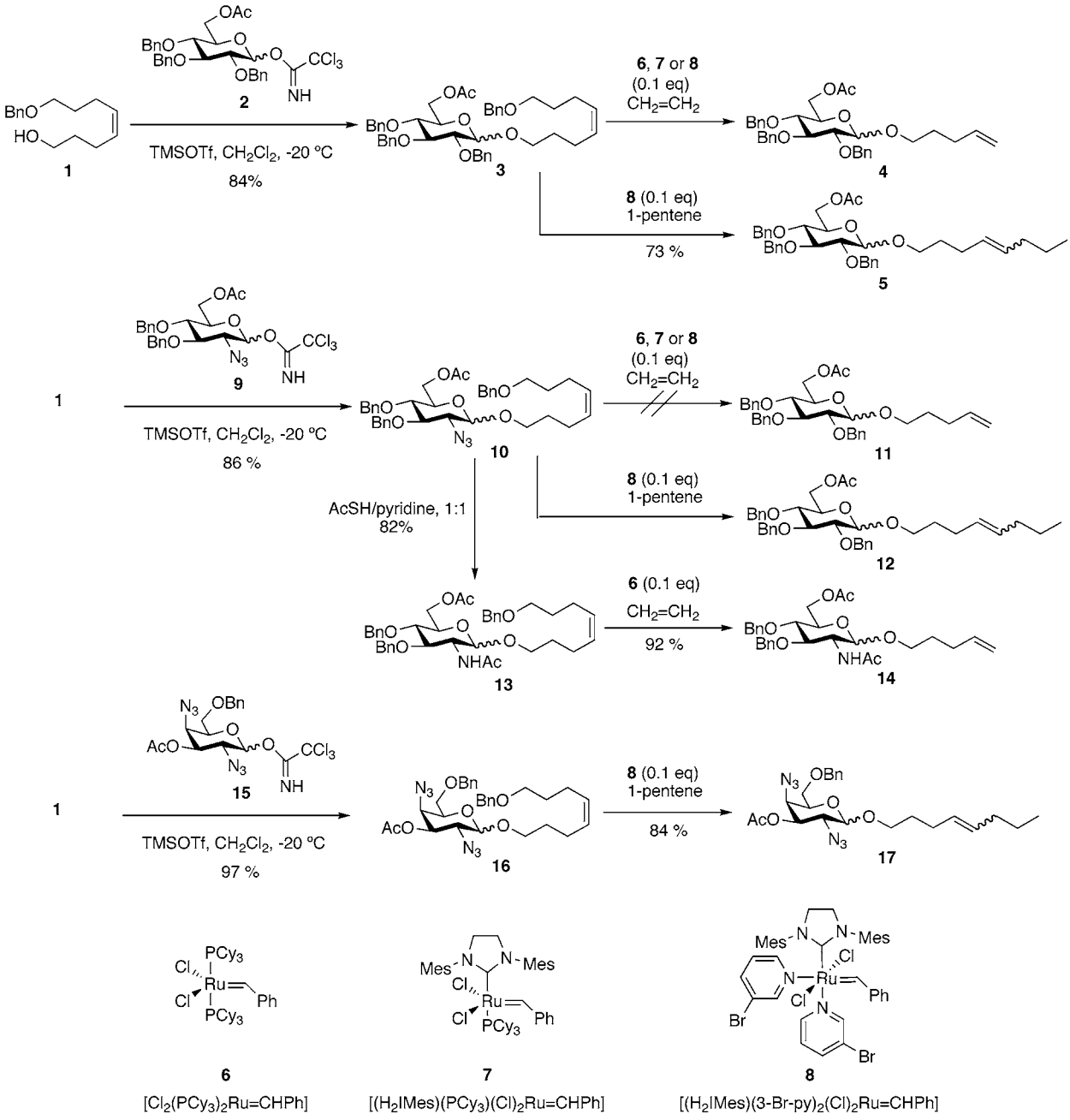
(2) Andrade, R. B.; Plante, O. J.; Melean, L. G.; Seeberger, P. H. *Org. Lett.* **1999**, *1*, 1811−1814.

(3) (a) Alper, P. B.; Hendrix, M.; Sears, P.; Wong, C.-H. *J. Am. Chem. Soc.* **1998**, *120*, 1965−1978. (b) Wong, C.-H.; Hendrix, M.; Manning, D. D.; Rosenbohm, C.; Greenberg, W. A. *J. Am. Chem. Soc.* **1998**, *120*, 8319−8327. (c) Greenberg, W. A.; Priestley, E. S.; Sears, P. S.; Alper, P. B.; Rosenbohm, C.; Hendrix, M.; Hung, S.-C.; Wong, C.-H., *J. Am. Chem. Soc.* **1999**, *121*, 6527−6541. (d) Nyffeler, P. T.; Liang, C.-H.; Koeller, K. M.; Wong, C.-H. *J. Am. Chem. Soc.* **2002**, *124*, 10773−10778.

(4) (a) For a review, see: van Boeckel, C. A. A., Petitou, M. *Angew. Chem., Int. Ed.* **1993**, *32*, 1671−1690. (b) Orgueira, H. A.; Bartolozzi, A.; Schell, P.; Seeberger, P. H. *Angew. Chem., Int. Ed.* **2002**, *41*, 2128−2131.

10.1021/ol035463z CCC: $25.00
Published on Web 10/29/2003

Scheme 1. Olefin Metathesis Cleavage of an Octenediol Linker Model in Solution Phase



Here, we report the development of reaction conditions that allow for the cleavage of azide-containing monosaccharides connected to a solid support via an octene diol linker using olefin cross-metathesis. A series of olefin metathesis catalysts[5] were tested and resulted in an efficient cleavage protocol.

To study the performance of different metathesis catalysts[4] for the cleavage of an octenediol linker by cross-metathesis,[6] we used a solution-phase model system. The polystyrene resin was represented by a benzyl group (Scheme 1). Linker model **1** was glycosylated using differentially protected glucose trichloroacetimidate **2** in good yield to fashion **3**. Olefin metathesis of **3** with ethylene in the presence of catalyst **6** proceeded at room temperature in 48 h to yield 90% of the desired *n*-pentenyl glucoside **4** (Table 1). Use of [$(H_2IMes)(PCy_3)$ $(Cl)_2Ru{=}CHPh$] catalyst **7** to affect this metathesis reaction at 40 °C yielded only 50% of the desired

(5) (a) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100−101. (b) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3013. (c) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18−29. (d) Choi, T.-L.; Lee, C. W.; Chatterjee, A. K.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 10417−10418. (e) Lee, C. W.; Choi, T.-L.; Grubbs, R. H. *J. Am. Chem. Soc.* **2002**, *124*, 3224. (f) Choi, T.-L.; Rutenberg, I. M.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2002**, *41*, 3839−3841. (g) Love, J. A.; Morgan, J. P.; Trnka, T. M.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2002**, *41*, 4035−4037.

(6) For a review see: Connon, S. J., Blechert, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1900−1923.

Table 1. Olefin Cross-Metathesis for the Cleavage of a Model Linker in Solution

substr.	cat.	olefin	solvent	*T* (°C)	time (h)	yield (%)
3	**6**	ethylene	CH_2Cl_2	rt	48	90
3	**7**	ethylene	CH_2Cl_2	40	48	50
3	**8**	ethylene	DCE	80	48	trace
3	**8**	1-pentene	DCE	80	12	73
10	**7**	ethylene	CH_2Cl_2	rt	48	0
10	**8**	ethylene	DCE	80	48	trace
10	**6**	1-pentene	DCE	rt	24	22
10	**7**	1-pentene	DCE	rt	24	47
10	**8**	1-pentene	DCE	rt	16	62
10	**8**	1-pentene	CH_2Cl_2	0	10	79
13	**6**	ethylene	CH_2Cl_2	rt	48	92
16	**8**	1-pentene	CH_2Cl_2	0	10	84

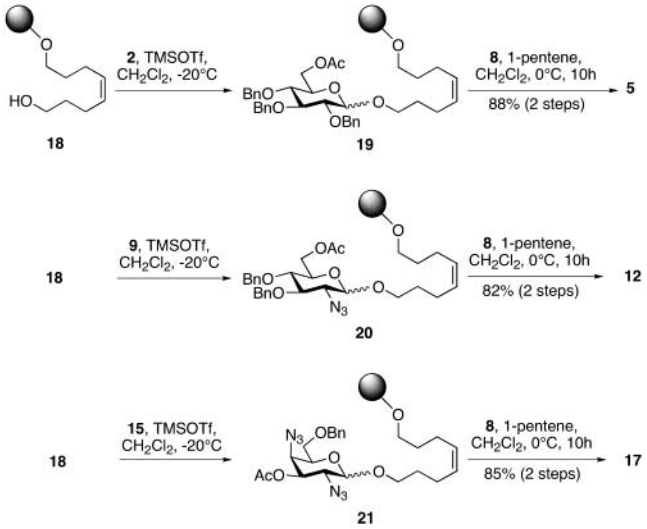
product **4**. The phosphine-free catalyst [$(H_2Imes)(3\text{-Br-py})_2(Cl)_2Ru{=}CHPh$] **8** produced only trace amounts of **4** when reacted with **3** and ethylene at 80 °C in dichloroethane for 48 h. It was reasoned that 1-pentene, a liquid, would perform better in this reaction than the gas ethylene. Indeed, cross-metathesis of **3** and 1-pentene in the presence of **8** yielded 73% of desired product **5** in 12 h.

Following these initial studies concerning different metathesis catalysts to affect linker cleavage, we approached substrates containing azide moieties.[7] The automated solid phase assembly of glycosaminoglycans and aminoglycoside antibiotics would result in solid support-bound, azide-containing carbohydrates. Recovery of these precious reaction products mandates an efficient cleavage. To mimic the solid-phase scenario, the simple monosaccharide model **10** was prepared by reacting differentially protected glucosamine **9** with linker model **1** (Scheme 1). Exposure of **10** to currently used octenediol cleavage conditions involving Grubbs' catalyst **6** in the presence of ethylene did not yield any of the desired product **11**. This failure was expected due to the incompatibility of the azide groups with the phosphine ligands of **6**. Reduction of the azide present in **10** by treatment with thioacetic acid-pyridine to form the protected *N*-acetyl glucosamine **13** provided a viable substrate for cross-metathesis with ethylene. Grubbs catalyst **6** facilitated this reaction to form desired product **14** in 92% yield.

To avoid the potential complications of a two-step cleavage protocol, alternatives for the metathesis reaction using ethylene in the presence of **6** were sought. Catalyst **7** did also fail to produce any of the desired product while phosphine-free catalyst **8** in the presence of ethylene resulted in the formation of traces of **11** to be formed after 48 h. When 1-pentene was used in place of ethylene in these cross-metathesis reactions, even catalyst **6** fashioned 22% of desired metathesis product **12**. The more active catalyst **7** resulted in improved yield (47%) while **8** ensured even better returns (62%). The cleavage protocol was optimized to proceed in just 10 h at 0 °C to give 79% of **12** in the presence of **8**. Carbohydrates containing more than one azide group can also be cleaved from solid support using this protocol. Diazidogalactoside **16** was prepared by reaction of **1** and **15**. Metathesis of **16** and 1-pentene proceeded smoothly to give **17** in 84% yield to mirror a cleavage reaction from solid support.

After establishing a cross-metathesis protocol for the cleavage of an octenediol linker in a solution phase model, the viability of this procedure in a solid-phase setting had to be demonstrated (Scheme 2). Octenediol functionalized

Scheme 2. Cleavage of Monosaccharides from Solid Support Using Olefin Metathesis



polystyrene resin **18** was reacted with monosaccharide building block **2** to fashion solid support-bound glucose **19**. Using the procedure established for the solution-phase model, treatment of the resin with 1-pentene and **8** for 10 h at 0 °C yielded 88% of monosaccharide **5**. This yield combines the glycosylation and cleavage events. Cleavage of support-bound glucosamine **20** under the same conditions resulted in 82% of **12**. Diazido galactose **21** was also efficiently cleaved (85%) using this protocol when treated with 1-pentene and **8** for 10 h at 0 °C.

In conclusion, we have developed an efficient cleavage protocol for the release of azide-containing oligosaccharides from solid support. Olefin cross-metathesis was achieved using the catalyst [$(H_2Imes)(3\text{-Br-py})_2(Cl)_2Ru{=}CHPh$] **8** and 1-pentene to release the reaction products from the solid support. This protocol is a key step toward the automated synthesis of aminoglycoside antibiotics and glycosaminoglycans including heparin on solid support. The octenediol linker may also prove useful to tether other highly functionalized molecules to sold support.

Acknowledgment. Financial support from NIH (1RO1-HL64799), ISIS Pharmaceuticals, GlaxoSmithKline (Research Scholar Award to P.H.S.), the Alfred P. Sloan

(7) (a) Wu, B.; Yang, J.; He, Y.; Swayze, E. E. *Org. Lett.* **2002**, *4*, 3455−3458. (b) Wang, J.; Li, J.; Tuttle, D.; Takemoto, J. Y.; Chang, C.-W. T. *Org. Lett.* **2002**, *4*, 3997−4000. (c) Chang, C.-W. T.; Hui, Y.; Elchert, B.; Wang, J.; Li, J.; Rai, R. *Org. Lett.* **2002**, *4*, 4603−4606.

Foundation (Scholar Award to P.H.S.), and Merck (Academic Development Award to P.H.S.) is gratefully acknowledged. Funding for the MIT-DCIF Avance (DPX) 400 NMR was provided by the NIH (Award No. 1S10RR13886-01). We thank Dr. A. Chatterjee and Prof. R. Grubbs for helpful discussions.

Supporting Information Available: Experimental procedures for the preparation of new compounds and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL035463Z