Application of a Ring Closing Metathesis Based Linker to the Solid Phase Synthesis of Oligosaccharides

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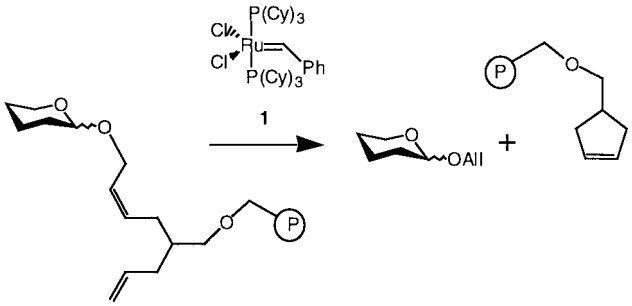
Abstract: A linker allowing a ring closing metathesis mediated cleavage of resin bound oligosaccharides in the form of their 1-*O*-allyl derivatives was designed. This new linker system for the solid phase synthesis of oligosaccharides via the trichloroacetimidate approach demonstrated highly promising results.

Key words: solid phase synthesis, oligosaccharides, linker, ring closure metathesis

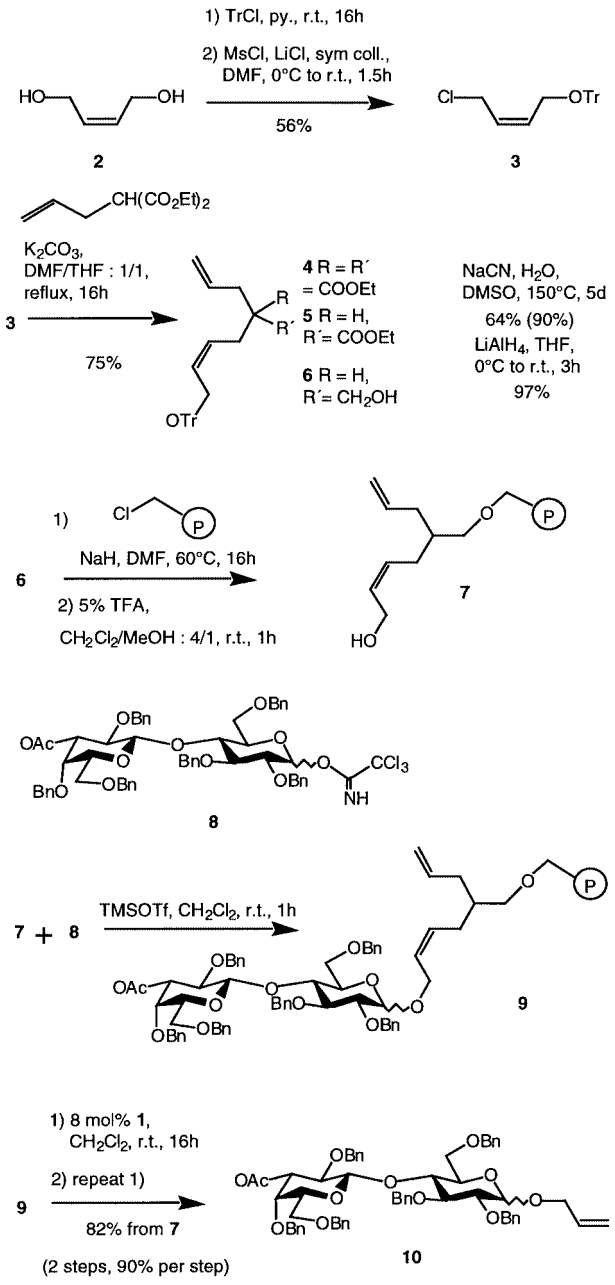
The synthesis of oligosaccharides on solid support has attracted considerable interest over the last years.[1] Our[2,3] and other[4] groups have already demonstrated the usefulness of the trichloroacetimidate glycosylation approach in this field. To this end, extension of the oligosaccharide chain is achieved by alternating basic deprotection steps of temporary ester protecting groups and acidic glycosylation steps. Thus, the linker has to be stable both in basic and acidic media and must be cleaved in high yields. Therefore, the design of new efficient linker systems for the solid phase synthesis of oligosaccharides remains a very challenging task. We present here our results concerning the preparation and first application on Merrifield resin of a new type of linker using a ring closing metathesis (RCM) reaction as the cleavage step.

Due to the appearance of catalysts with increased stability, greater reactivity and excellent functional group tolerance such as the Grubbs catalyst **1**,[5,6] the RCM has emerged as a very powerful reaction for both solution and solid phase organic synthesis.[7] Different cleavage strategies for the production of cyclic alkenes using RCM have been recently published[8] but to our knowledge only one example of production of acyclic alkene by RCM mediated cleavage was recently reported for the preparation of styrene derivatives.[9] This interesting result prompted us to prepare a linker that could allow the synthesis of oligosaccharides and their cleavage as 1-*O*-allyl derivatives. These compounds could permit further functionalisation of the allyl moiety or selective deallylation and transformation of the newly synthesized oligosaccharide. This approach could be of particular interest for the synthesis of glycopeptides. To this end, we designed a linker, allowing the liberation of 1-*O*-allyl derivatives and concomitant production of a cyclopentene on the solid support (Scheme 1).



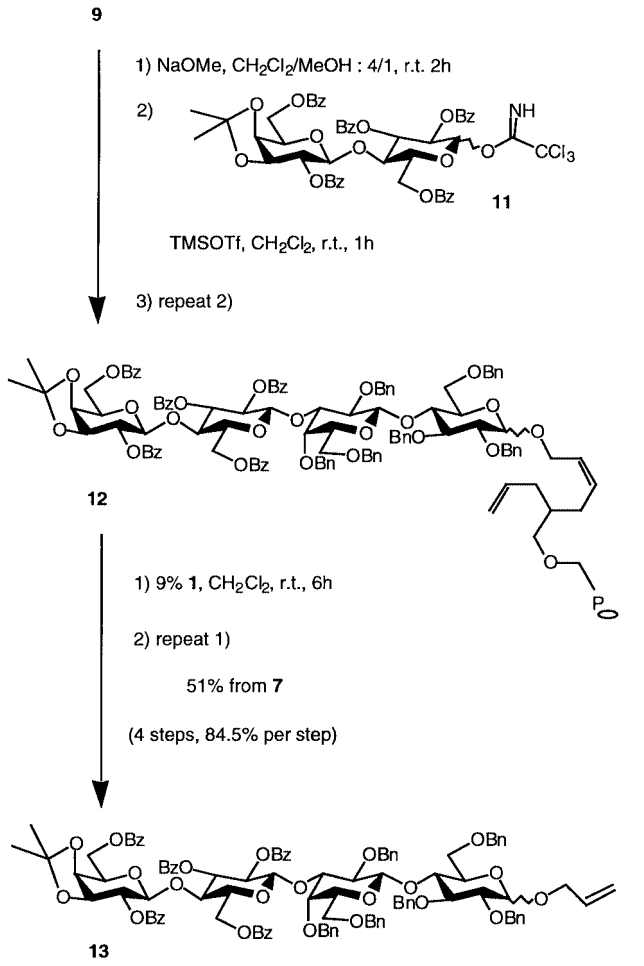
Scheme 1

The synthesis of the linker (Scheme 2) started from cis-1,4-butenediol **2**, which is monotritylated and chlorinated under Meyers conditions[10] in 56% overall yield to give chloride **3**. Alkylation of diethyl allylmalonate with **3** led to **4** (75%) which was then decarboxylated using the Krapcho procedure[11] to give **5** in 64% yield (90% conversion). Ester **5** was smoothly reduced affording alcohol **6** in 97% yield. At this stage **6** was coupled in a Williamson ether synthesis (NaH, DMF, 60°C, 16h) to the Merrifield resin (Fluka, 0.8 mmol/g, 1% crosslinked). The resulting protected linker was then detritylated (5% TFA in CH_2Cl_2/MeOH: 4/1, r.t., 1h) to give **7**. The loading of **7** was calculated to be 0.2 mmol/g by 3-nitrobenzoyl derivatization (excess 3-nitrobenzoyl chloride, pyridine, r.t., 16h, followed by extensive washing and drying) and nitrogen analysis. Resin **7** was then glycosylated using the lactosyl trichloroacetimidate **8**[12] which is a useful building-block for our ongoing program on human milk oligosaccharide syntheses. With resin **9** in hand, RCM mediated cleavage was then performed using 9 mol% of **1** in CH_2Cl_2 at rt for 18h. The cleavage reaction was performed twice under these conditions to afford **10** in encouraging 82% isolated yield (1/1 : α/β mixture) based on the loading of **7** (2 steps, 90% per step). It is to be noticed that completion of the cleavage can be monitored by the disappearance of the terminal double bond stretching band (1639-1641cm^{-1}) using FTIR. With this reaction time or when shorter reaction times and higher temperatures (80°C in toluene or refluxing CH_2Cl_2) were used for the cleavage step, small amounts of products resulting from the cross metathesis dimerization of **10** were isolated.



Scheme 2

Following this result, resin **9** was submitted to deacetylation conditions (Scheme 3). Here too, the reaction is easily monitored by FTIR (disappearance of bands at 1744 and 1236cm^{-1}). Extension of the chain was then achieved using the known lactosyl donor **11**,[13] under conditions similar to those used for the preparation of **9**, leading to resin bound tetrasaccharide **12**.[14] At this stage we developed an analytical cleavage procedure which allows a fast and efficient monitoring of the chain extension by MALDI-TOF MS.[15] Cleavage[16] was performed as for **9** but with a shorter reaction time of 6h and gave tetrasaccharide **13**[17] (1/1 : α/β mixture) in 51% yield from **7** (4 steps, 84.5% per step). No dimerization products were detected in this case.



Scheme 3

In conclusion, the preliminary results obtained using this RCM based linker system are promising in terms of cleavage and glycosylation efficiencies. Extension of this strategy to more complex synthetic targets are underway.

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(14) **Protocol for solid phase glycosylation:** to deacetylated resin **9** (0.052 mmol) was added **11** (275 mg, 0.26 mmol, 5 eq.) in 5 ml CH_2Cl_2. The mixture was shaken 15min under argon. TMSOTf (0.25 M in CH_2Cl_2, 50µl, 0.0125 mmol, 0.24 eq.) was then added and the mixture was shaken 1h at r.t. under argon. The resin was filtered and washed four times each with 5 ml of THF and 5 ml of CH_2Cl_2. After extensive drying under high vacuum the resin was glycosylated a second time (1.7 eq. **11**, 0.1 eq. TMSOTf) to ensure a complete reaction.

(15) **Protocol for RCM mediated cleavage:** resin **12** (0.04 mmol) was swollen in 10 ml of dry CH_2Cl_2. The resulting suspension was degassed for 30 min using a steam of argon. **1** (3 mg, 3.6 µmol, 9 mol%) was then added and the mixture was shaken for 6h at r.t. under argon. The reaction solvent was collected and the resin was washed three times each with 5 ml of THF and 5 ml of CH_2Cl_2. The combined filtrates were evaporated. The resin was dried for 18h under high vacuum and submitted a second time to the cleavage conditions. The combined filtrates of both cleavage reactions were then submitted to silica gel column chromatography to afford 37 mg of **13** (51% from **7**).

(16) **Protocol for Maldi-TOF analytical cleavage:** 4 mg of resin **12** in 500 µl of dry CH_2Cl_2 were degassed. A few crystals of **1** were added to this suspension. The mixture was stirred for 4h at r.t.. Satisfactory TLCs are obtained from the crude reaction. The catalyst was then filtered over a small pad of silica gel (0.4*1cm) and the cleaved compounds were eluted with ethyl acetate (10 ml). The solvents were then evaporated and the resulting crude was analyzed by Maldi-TOF in the usual way.

(17) Analytical data of compound **13**:
MALDI-TOF (DHB/THF), calcd: $M(C_{107}H_{106}O_{26})$ = 1808.02 m/z; $(M+Na)^+$ = 1831.02 m/z. Found: 1830 m/z.
13β: ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.53 [$C(CH_3)_2$], 3.06 (5a-H), 3.20 (6b-H), 3.23 (5b-H), 3.27 (2a-H), 3.32 (3a-H), 3.34 (6b-H'), 3.42 (6a-H), 3.46 (2b-H), 3.51 (6d-H), 3.52 (6a-H'), 3.53 (3b-H), 3.70 (5d-H), 3.71 (5c-H), 3.76 (4a-H), 3.77 (4b-H), 3.99 [C*H*HCH=CH_2], 4.00 (4d-H), 4.02-4.92 [6CH_2Ph], 4.13 (4c-H), 4.16 (6d-H'), 4.18 (3d-H), 4.21 (1b-H), 4.24 (1a-H, $J_{1,2}$ = 8Hz), 4.27 [CH*H*CH=CH_2], 4.40 (6c-H), 4.54 (1d-H), 4.62 (6d-H'), 5.02 (1c-H), 5.08 (2d-H), 5.09 [CH_2CH=C*H*H], 5.23 [CH_2CH=CH*H*], 5.47 (2c-H), 5.67 (3c-H), 5.83 [CH_2C*H*=CH_2], 6.90-8.0 [6CH_2*Ph*, 5CO*Ph*].
13α (selected data)**:** ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.57 [$C(CH_3)_2$], 3.84 [C*H*HCH=CH_2], 3.95 [CH*H*CH=CH_2], 4.07 (1b-H), 4.54 (1d-H), 4.61 (1a-H, $J_{1,2}$ = 3Hz), 5.00 (1c-H), 5.09 [CH_2CH=C*H*H], 5.19 [CH_2CH=CH*H*], 5.81 [CH_2C*H*=CH_2].

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