ChemComm

# Zinc-mediated domino elimination–alkylation of methyl 5-iodopentofuranosides: an easy route to unsaturated carbohydrates for transition metal-catalyzed carbocyclizations

**Lene Hyldtoft, Carina Storm Poulsen and Robert Madsen***

*Department of Organic Chemistry, Technical University of Denmark, DK-2800 Lyngby, Denmark. E-mail: okrm@pop.dtu.dk*

*Received (in Cambridge, UK) 27th August 1999, Accepted 16th September 1999*

**5-Iodopentofuranosides are converted with zinc and allyl/propargyl bromide into dienes/enynes which are further used in carbohydrate annulation reactions.**

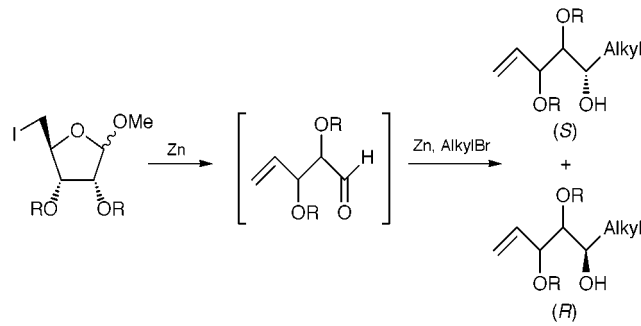
Domino reactions are becoming a very attractive tool for enhancing synthetic efficiency by allowing several bond-forming transformations to be carried out in a single synthetic operation.[1] Such a strategy could be particularly important in the area of carbohydrate chemistry: because carbohydrates are densely functionalized, synthetic applications are often hampered by the need for many reaction steps, usually for manipulation of different protecting groups. In particular, the conversion of carbohydrates into carbocycles is a major task and has been the subject of intense study due to the biological significance of the products.[2] Herein, we report a zinc-mediated domino elimination–alkylation of methyl 5-deoxy-5-iodopentofuranosides to prepare carbohydrate-derived dienes and enynes. These are important substrates for transition metal-catalyzed carbocyclizations,[3] and we demonstrate the use of the obtained dienes in the ring-closing metathesis reaction.[4,5]

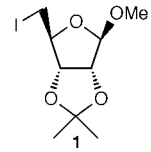
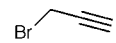
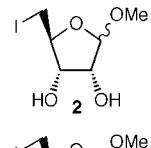
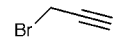
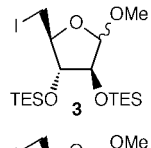
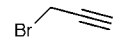
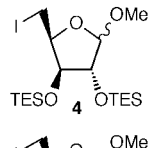
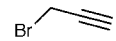
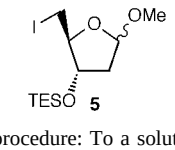
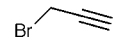
Zinc-mediated reductive elimination of ω-iodoglycosides is a valuable reaction for introducing a terminal double bond in carbohydrates,[6] but the instability of the liberated aldehyde can be a problem leading to side reactions and decomposition. We reasoned that the aldehyde could be trapped *in situ* by a Barbier-type alkylation[7] (Table 1). Zinc would then serve a dual purpose by promoting both the reductive elimination and reacting with an alkyl halide to perform the Barbier reaction. Hereby, a C–C double bond, a C–C single bond and a new stereocenter would be generated in the same pot.

Allyl and propargyl bromide were selected as the alkyl halides. Initial experiments were carried out on isopropylidene ribofuranoside **1**.[8] When **1** was reacted with allyl bromide and zinc, the desired diene was obtained in quantitative yield as a 4:1 diastereomeric mixture (entry 1, Table 1). Switching to propargyl bromide gave rise to the corresponding enyne, but now in an improved 9:1 diastereomeric ratio (entry 2). Notably, no isomerization from alkyne to allene was observed under these conditions. In general, for these sequential transformations to go to completion, 3 equiv. of allyl bromide was needed while the reaction with propargyl bromide required 5 equiv. Allyl bromide was added at the beginning of the reaction while propargyl bromide was added during the course of the reaction to minimize the formation of Wurtz coupling products. The reactions were carried out under sonication in aq. THF.[7] The THF:$H_2O$ ratio influenced the rate, but had little effect on the diastereoselectivity. Addition of more $H_2O$ generally enhanced the rate of the overall transformation.

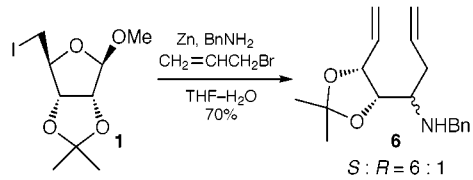
These conditions were then applied to substrates **2**–**5** (Table 1). Interestingly, the reaction of unprotected ribofuranoside **2** with allyl bromide now gave the opposite diastereomer as the major product as compared to isopropylidene-protected **1** (entries 1 and 3). However, the reaction of **2** with propargyl bromide failed to give any of the desired enyne. The reason for this is not clear, but is probably associated with the unprotected hydroxy groups. As a result, the remaining furanosides were

**Table 1** Domino elimination–alkylation of methyl 5-iodofuranosides[a]




| Entry | Furanoside | Alkyl Br | Yield (%) (*S*:*R*)[b] |
|---|---|---|---|
| 1 |  **1** |  | quant. (4 :1)[c] |
| 2 | |  | 73 (9 : 1) |
| 3 |  **2** |  | quant. (3 : 7) |
| 4 | |  | 0 |
| 5 |  **3** |  | 82 (3 : 7)[c] |
| 6 | |  | 56 (3 : 7) |
| 7 |  **4** |  | 89 (3 : 1) |
| 8 | |  | 61 (7 : 3) |
| 9 |  **5** |  | 94 (5 : 6)[c] |
| 10 | |  | 64 (2 : 3) |

[a] General procedure: To a solution of the iodofuranoside (1.6 mmol) and allyl bromide (0.4 ml) in THF–$H_2O$ (4:1, 10 ml) was added zinc (1 g, pre-activated with aq. HCl). The mixture was sonicated at 40 °C for 4 h under Ar atmosphere, filtered through Celite, and worked up by extraction with $CH_2Cl_2$ or stirring with ion-exchange resin followed by flash chromatography. [b] The stereochemistry of the enynes from the propargylations was assigned after hydrogenation to the corresponding dienes with Lindlar catalyst. In entry 10 the stereochemistry of the major enyne isomer was determined after conversion into its known MEM-protected derivative (ref. 9). Hydrogenation with Lindlar catalyst subsequently showed that the major diene isomer in entry 9 had the same absolute stereochemistry. [c] Protecting group removed in the work-up by acidic ion-exchange resin.



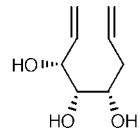
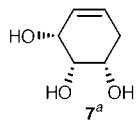
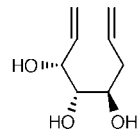
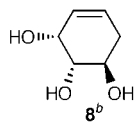
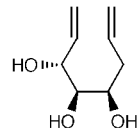
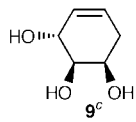
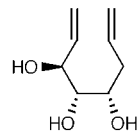
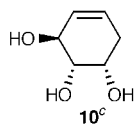
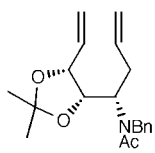
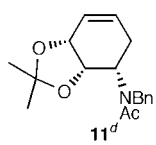

**Scheme 1**

protected as triethylsilyl (TES) ethers **3**–**5**. The reaction of these in the presence of allyl/propargyl bromide proceeded smoothly to give the dienes/enynes in good to excellent yields (entries 5–10). Unfortunately, the 2-deoxyribose substrate **5** gave a poor diastereoselectivity in the alkylation. For the protected furanosides **1**, **3** and **4**, on the other hand, the selectivity for addition to the intermediate aldehyde generally followed the Felkin–Anh model.[10]

The intermediate aldehyde can potentially be intercepted with an amine prior to the alkylation (Scheme 1). The alkylation would then take place on the formed imine resulting in the introduction of an amino group. In fact, treatment of **1** with zinc, benzylamine and allyl bromide succeeded in giving the amino diene product **6** in both good yield and diastereoselectivity. To prevent significant allylation of the intermediate aldehyde, it was important to add allyl bromide slowly during the course of the reaction.

Dienes and enynes are useful in transition metal-catalyzed carbocyclizations.[3] Hydroxylated enynes have previously been used in palladium-catalyzed coupling of the A-ring in vitamin D derivatives[9,11] and in cobalt-mediated Pauson–Khand reactions.[12] Hydroxylated dienes are useful for carbocyclization by ring-closing olefin metathesis. We have carried out the metathesis reaction on the major dienes from the allylations by the use of 5–10% Grubbs catalyst $[RuCl_2(CHPh)\{PCy_3\}_2]$[13] in $CH_2Cl_2$ (Table 2). These reactions also allow the stereochemical outcome of the allylations to be determined. The unprotected dienes in entries 1–4 all gave the desired cyclohexenes **7**–**10** in near quantitative yields. When the ammonium salt of diene **6** (Scheme 1) was subjected to Grubbs catalyst, significant decomposition took place and only a moderate yield of the cyclohexene could be obtained. However, when **6** was N-acetylated the ring-closing metathesis reaction went smoothly to give **11** in very high yield (entry 5, Table 2).

**Table 2** Ring-closing olefin metathesis of the major diene products from the allylations

| Entry | Diene | Cyclohexene | Yield (%) |
|---|---|---|---|
| 1 |  |  **7**[a] | 96 |
| 2 |  |  **8**[b] | 95 |
| 3 |  |  **9**[c] | 97 |
| 4 |  |  **10**[c] | 95 |
| 5 |  |  **11**[d] | 94 |

[a] Ref. 14, [b] Ref. 15. [c] Ref. 16. [d] Ref. 17.

In conclusion, we have developed a zinc-mediated elimination–alkylation of 5-iodopentofuranosides which permits 'one-pot' formation of several bonds and a stereocenter in a controlled manner. The obtained dienes and enynes are valuable in carbohydrate annulation by transition metal catalysis, and we have processed the dienes in the ring-closing metathesis reaction. Hereby, a range of complex carbocyclic structures are easily available as chiral building blocks from cheap sugar starting materials by two consecutive organometallic transformations.

We thank the Danish Natural Science Research Council for financial support.

## Notes and references

1 L. F. Tietze, *Chem. Rev.*, 1996, **96**, 115; L. F. Tietze and U. Beifuss, *Angew. Chem., Int. Ed. Engl.*, 1993, **32**, 131.
2 D. I. Dalko and P. Sinaÿ, *Angew. Chem., Int. Ed.*, 1999, **38**, 773; R. J. Ferrier and S. Middleton, *Chem. Rev.*, 1993, **93**, 2779.
3 I. Ojima, M. Tzamarioudaki, Z. Li and R. J. Donovan, *Chem. Rev.*, 1996, **96**, 635.
4 For recent reviews, see: U. K. Pandit, H. S. Overkleeft, B. C. Borer and H. Bieräugel, *Eur. J. Org. Chem.*, 1999, 959; D. L. Wright, *Curr. Org. Chem.*, 1999, **3**, 211; A. Fürstner, *Top. Organomet. Chem.*, 1998, **1**, 37.
5 For recent applications of ring-closing olefin metathesis in carbohydrate chemistry, see: P. Kapferer, F. Sarabia and A. Vasella, *Helv. Chim. Acta*, 1999, **82**, 645; H. Ovaa, J. D. C. Codée, B. Lastdrager, H. S. Overkleeft, G. A. van der Marel and J. H. van Boom, *Tetrahedron Lett.*, 1999, **40**, 5063; A. Kornienko and M. d'Alarcao, *Tetrahedron: Asymmetry*, 1999, **10**, 827; O. Sellier, P. Van de Weghe, D. Le Nouen, C. Strehler and J. Eustache, *Tetrahedron Lett.*, 1999, **40**, 853.
6 B. Bernet and A. Vasella, *Helv. Chim. Acta*, 1979, **62**, 1990, 2400, 2411; M. Nakane, C. R. Hutchinson and H. Gollman, *Tetrahedron Lett.*, 1980, **21**, 1213; A. Fürstner, D. Jumbam, J. Teslic and H. Weidmann, *J. Org. Chem.*, 1991, **56**, 2213.
7 J.-L. Luche, L. A. Sarandeses, in *Organozinc Reagents—A Practical Approach*, ed. P. Knochel and P. Jones, OUP, Oxford, 1999, p. 307.
8 L. M. Lerner, *Carbohydr. Res.*, 1977, **53**, 177.
9 R. M. Moriarty, J. Kim and H. Brumer III, *Tetrahedron Lett.*, 1995, **36**, 51.
10 M. Chérest, H. Felkin and N. Prudent, *Tetrahedron Lett.*, 1968, 2199; N. T. Anh, *Top. Curr. Chem.*, 1980, **88**, 145.
11 B. M. Trost, J. Dumas and M. Villa, *J. Am. Chem. Soc.*, 1992, **114**, 9836; R. M. Moriarty and H. Brumer III, *Tetrahedron Lett.*, 1995, **36**, 9265.
12 C. Mukai, J. S. Kim, M. Uchiyama and M. Hanaoka, *Tetrahedron Lett.*, 1998, **39**, 7909.
13 P. Schwab, R. H. Grubbs and J. W. Ziller, *J. Am. Chem. Soc.*, 1996, **118**, 100.
14 Structure confirmed by acetylation to the known triacetate: J. Bange, A. F. Haughan, J. R. Knight and J. Sweeney, *J. Chem. Soc., Perkin Trans. 1*, 1998, 1039.
15 T. Hudlicky, H. Luna, H. F. Olivo, C. Andersen, T. Nugent and J. D. Price, *J. Chem. Soc., Perkin Trans. 1*, 1991, 2907.
16 The structure of enantiomeric **9** and **10** was determined by $OsO_4$ catalyzed dihydroxylation to the same symmetrical quercitol, (1β,2β,3α,4β,5β)-pentahydroxycyclohexane: S. J. Angyal and L. Odier, *Carbohydr. Res.*, 1982, **100**, 43.
17 Structure assigned after hydrogenation of the double bond and $^1H$ NMR analysis of the resulting cyclohexane.

*Communication 9/06953D*