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An Expeditious Route to the Synthesis of Highly Functionalized Chiral Oxepines from Monosaccharides

Huib Ovaa, Michiel A. Leeuwenburgh, Herman S. Overkleeft, Gijs A. van der Marel and Jacques H. van Boom*

Leiden Institute of Chemistry, Gorlaeus Laboratories, Leiden University, P.O. Box 9502, 2300 RA Leiden, The Netherlands

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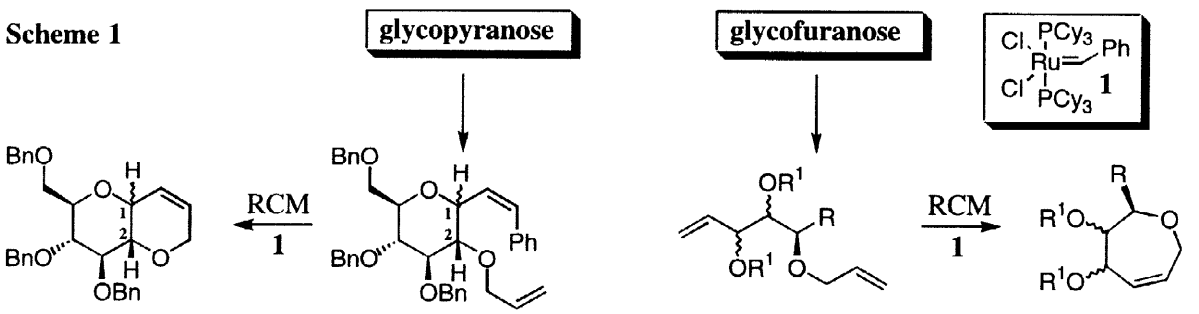
Abstract: The transformation of partially protected aldofuranoses into dienes by Wittig olefination of the anomeric center followed by either allylation or oxopalladation of alkoxy-1,2-propadienes is described. Ring-closing metathesis of the linear dienes gives rise to a variety of highly functionalized and chiral ring-expanded oxepines. © 1998 Elsevier Science Ltd. All rights reserved.

A recent publication from this laboratory[1] revealed that glycopyranoside derivatives containing a set of neighbouring vinyl-*O*-allyl functions are ideal starting compounds for the synthesis of functionalized pyranopyrans *via* a ring-closing metathesis[2] (RCM) reaction. For example, ruthenium-complex **1** catalyzed RCM reaction (see Scheme 1) of a 1α- or β-vinyl-2-*O*-allyl spatial arrangement as in the individual α/β-*C*-glycopyranosides **2** gave the corresponding 1,2-*cis*- or *trans*-fused bicyclic derivatives **3** in good yields.

Scheme 1



It occurred to us that a glycofuranose, instead of a glycopyranose, would be an alternative substrate for the installation of the desired vinyl-*O*-allyl arrangement suitable for the execution of a RCM reaction. Thus it was expected that RCM reaction of the linear chain diene derivative **4**, obtained by elaboration of an appropriately protected glycofuranose, would give access to seven-membered oxacyclic rings **5**, which are common structural elements of many natural products (*e.g.* zoapatanol, montanol[3] and (+)-isolaurepinnacin).[4]

In order to assess the viability of the aforementioned concept, we first explored the RCM of the vinyl-*O*-allyl adduct **8**, which in turn is readily accessible by olefination of 2,3,5-tri-*O*-benzyl-D-arabinofuranose (**6**)[5] and subsequent allylation of the Wittig product **7** with allyl bromide. It was established that treatment of **8** with the Ru-cat. **1** (5 mass%) in toluene for 24h at 50 °C resulted in the isolation of the expected cyclization product **9**, as evidenced[6] by NMR-spectroscopy and mass-spectrometry.

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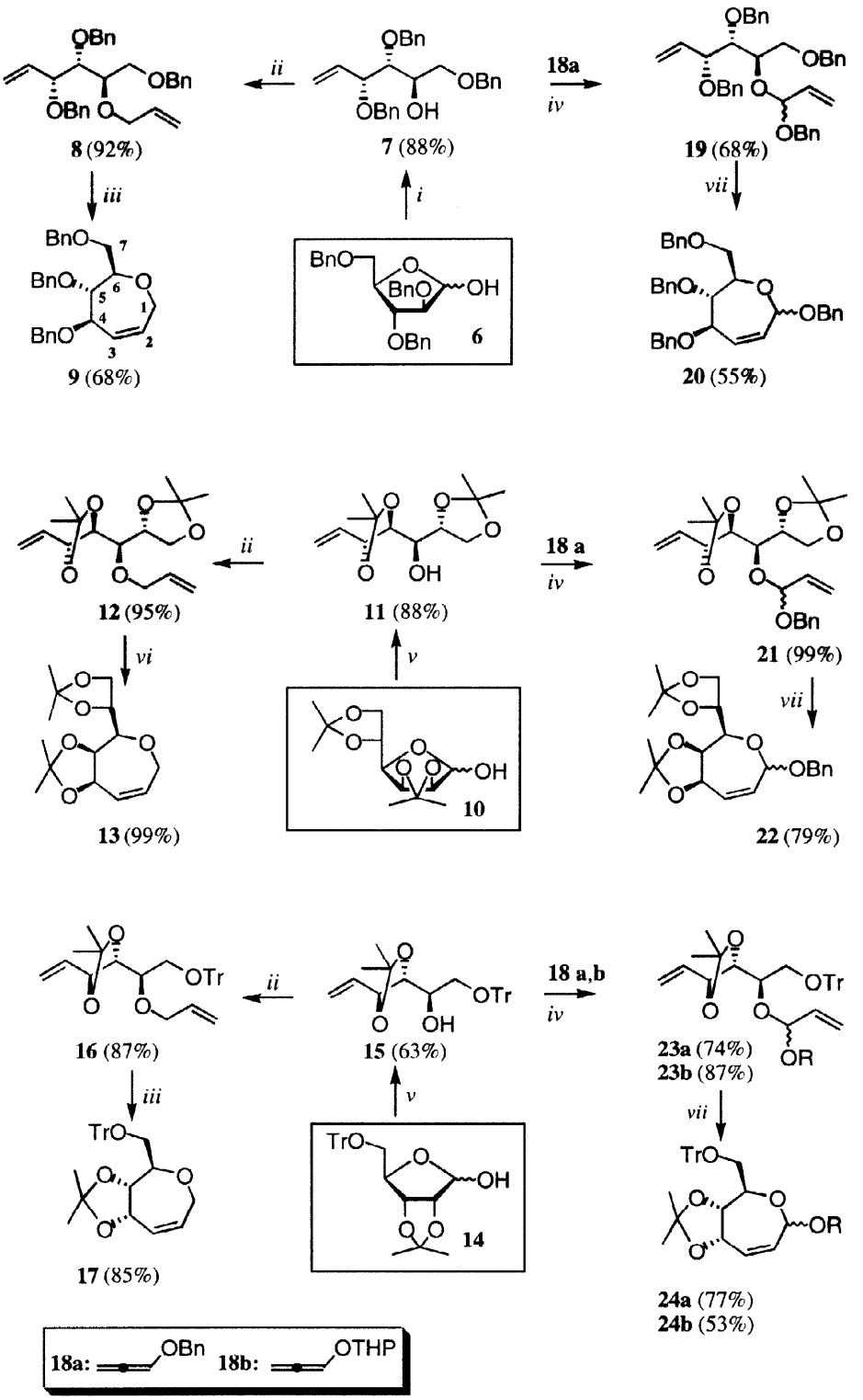
Scheme 2



Reagents and conditions: *i.* $Ph_3P^+MeBr^-$ (2.0 eq.), *n*BuLi (2.0 eq), THF, then **6**. *ii.* AllylBr, NaH, DMF. *iii.* $Cl_2(PCy_3)_2Ru{=}CHPh$ (**1**, 5 mass%), PhMe, 50 °C, 24 h. *iv.* **18a** or **b**, $Pd(OAc)_2$ (5 mol%), dppp (5 mol%), Et_3N, MeCN, 80 °C. *v.* $Ph_3P^+MeBr^-$ (1.0 eq.), NaHMDS (2.0 eq.), THF. *vi.* $Cl_2(PCy_3)_2Ru{=}CHPh$ (**1**, 5 mass%), CH_2Cl_2, 20°C., 24 h. *vii.* $Cl_2(PCy_3)_2Ru{=}CHPh$ (**1**, 5 mass%), PhMe, 80 °C, 24 h.

The general usefulness of the latter three-step procedure is further illustrated in the successful synthesis of the cyclic products **13** and **17**, the protecting groups of which can be removed selectively under appropriate[7] conditions. Thus Ru-cat. (**1**) mediated cyclization of **12**, prepared in two consecutive steps from the 2,3:5,6-di-*O*-isopropylidene-D-mannofuranose (**10**),[8] gave 1,6-anhydro-4,5:7,8-di-*O*-isopropylidene-D-*manno*-oct-2-enitol (**13**) in a quantitative yield. Similarly, RCM reaction of **16**, obtained by subjecting 5-*O*-trityl-2,3-*O*-isopropylidene-D-ribofuranose (**14**) to olefination (→ **15**) and then allylation (→ **16**), led to the isolation of the homogeneous cyclic product **17** in 85% yield.[6]

The ease of preparation and smooth cyclization of the vinyl-*O*-allyl derivatives **8**, **12** and **16** was an incentive to find out whether the corresponding vinyl-allylic acetal derivatives **19**, **21** and **23a** could be converted into the interesting higher carbon sugars **20**, **22** and **24a**.[9] The key step in the preparation of the derivatives **19**, **20** and **23a** entails allylic acetalization of the terminal olefinic derivatives **7**, **11** and **15**. The latter could be readily accomplished by treatment of **7**, **11** and **15** with benzyloxy-1,2-propadiene (**18a**) under the recently by Rutjes *et al.*[10] optimized original procedure of Alper *et al.*[11] Indeed, acetalization of **11** with excess **18a**, obtainted by isomerization of benzyl propargylic ether with KOtBu at 70 °C,[12] under the influence of catalytic amounts of $Pd(OAc)_2$ and the ligand 1,3-bis(diphenylphosphino)propane (dppp) led to the isolation of the vinyl-allylic acetal adduct **21**, as a mixture of diastereoisomers (ratio 1:1) in a near quantitative yield. Subsequent RCM reaction of **21** gave a cyclic product, the spectoscopic data of which were in full accord with an anomeric mixture (ratio 1:1) of benzyl-4,5:7,8-di-*O*-isopropylidene-D-*manno*-oct-2-enoseptanoside (**22**).[6] Similarly, acetalization of the olefines **7** and **15** followed by RCM reaction of the resulting mixed acetals **19** and **23a** gave the respective α/β-septanosides **20** and **24a**. On the other hand, RCM reaction of the mixed acetal derivative **23b**, resulting as mentioned before by reaction of **15** with tetrahydropyranyloxy-1,2-propadiene (**18b**) under the influence of $Pd(OAc)_2$ and dppp, gave **24b** as a mixture of diastereoisomers in an acceptable yield of 53%.

In conclusion, a novel and versatile route to highly functionalized chiral oxepines which is based on a simple sequential three-step (*i.e.*, olefination, *O*-allylation and then ring-closing metathesis) transformation of differently protected glycofuranoses has been developed. In addition, introduction of an allylic acetal function, instead of an allyl ether, in the second step of the synthetic sequence provides another type of ring-expanded oxepines, which are potential useful chiral synthons for the construction of higher carbon sugars.[9] In this respect, it is of interest to note that our new approach nicely complements the recently by Ramana *et al.*[13] reported preparation of chiral oxepines, starting from 1,2-cyclopropanated sugars. Application of the methodology presented in this paper to the synthesis of oxepane-containing natural products and higher carbon sugars are in progress.

Acknowledgement

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6. All new compounds were obtained in an analytically pure form and fully characterized by spectroscopic techniques (^{1}H-NMR, ^{13}C-NMR, MS). Representative data: **17**: **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 7.50-7.15 (m, 15H, C<u>H</u>Ph), 5.65-5.59 (ddd, 1H, H-2), 5.49-5.44 (ddd, 1H, H-3), 4.99-4.96 (m, 1H, H-4), 4.50-4.28 (m, 2H, H-1), 4.22-4.18 (dd, 1H, H-5), 3.77-3.71 (m, 1H, H-6), 3.34-3.23 (m, 2H, H-7), 1.34 (s, 3H, CH_3 isopr.), 1.27(s, 3H, CH_3 isopr.). **^{13}C-NMR** (APT, 75 MHz, $CDCl_3$): δ 143.99 (C_q, Ph), 128.67 (<u>C</u>H, Ph), 127.71 (C-3), 127.63 (<u>C</u>H, Ph) 126.79 (<u>C</u>H, Ph), 126.77 (C-2), 108.84 (C_q, isopr.), 86.34 (C_q, Tr), 78.95 (C-6), 78.17 (C-5), 75.64 (C-4), 71.43 (C-1), 65.32 (C-7), 27.59 (CH_3 ispopr.), 25.29 (CH_3 isopr.). **22**β: **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 7.36-7.26 (m, 5H, C<u>H</u>Ph), 5.98-5.91 (ddd, 1H, H-3), 5.79-5.74 (dd, 1H, H-2), 5.21-5.20 (dd, 1H, H-1), 4.81 (d, 1H, PhCH<u>H</u>), 4.75-4.71 (dd, 1H, H-4), 4.68 (d, 1H, PhC<u>H</u>H), 4.41-4.38 (dd, 1H, H-5), 4.37-4.31 (m, 1H, H-7), 4.18-4.13 (dd, 1H, H- 8), 3.41-2.76 (dd, 1H, H-8'), 1.53 (s, 3H, CH_3 isopr.), 1.43 (s, 3H, CH_3 isopr.), 1.39 (s, 3H, CH_3 isopr.), 1.37 (s, 3H, CH_3 isopr.), the configuration of the anomeric proton was confirmed by NOE-experiments. **^{13}C-NMR** (APT, 75 MHz, $CDCl_3$): δ 137.80 (C-3), 133.77 (C-2), 128.60 (C_q, Ph), 128.33, 127.86, 127.63 (3x <u>C</u>HPh), 109.23, 108.91 (2x C_q, isopr.), 101.02 (C-1), 76.88, 75.06, 74.76, 72.73 (C-4, C-5, C-6, C-7), 68.65, 66.77 (<u>C</u>H_2Ph, C-8), 27.01, 26.74, 25.73, 25.21 (4x CH_3 isopr.). Characteristic **^{13}C-NMR** (APT) data (*i.e.* C-1, C-2, C-3) of compounds **9**, **13**, **17**, **20**, **22**, and **24a** are as follows: **9**: δ 129.14, 128.31, 71.99; **13**: δ 135.33, 123.55, 71.56; **17**: δ 127.71, 126.77, 71.43; **20**: δ 133.43, 132.51, 132.40, 99.56, 97.95; **22**: δ 137.80, 137.22, 135.49, 133.77, 101.02, 99.05; **24a**: δ 131.38, 131.24, 126.99, 126.47, 100.67, 98.54. Mass spectrometric data of compounds **9**, **13**, **17**, **20**, **22**, **24a** and **24b** are as follows: **9**: (ESI): 431.0 $[M+H]^+$. **13**: (ESI): 465.2 $[M+H]^+$. **17**: (ESI): 271.0 $[M+Na]^+$. **20**: (ESI): 559.0 $[M+Na]^+$. **22**: (ESI): 399.1 $[M+Na]^+$. **24a**: (EI): 548.0 $[M]^+$. **24b**: (ESI): 565.0 $[M+Na]^+$.
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