Pergamon

Tetrahedron Letters 40 (1999) 5063–5066

TETRAHEDRON LETTERS

A Versatile Approach to the Synthesis of Highly Functionalised Carbocycles

Huib Ovaa, Jeroen D. C. Codée, Bas Lastdrager, Herman S. Overkleeft, Gijs A. van der Marel and Jacques H. van Boom*

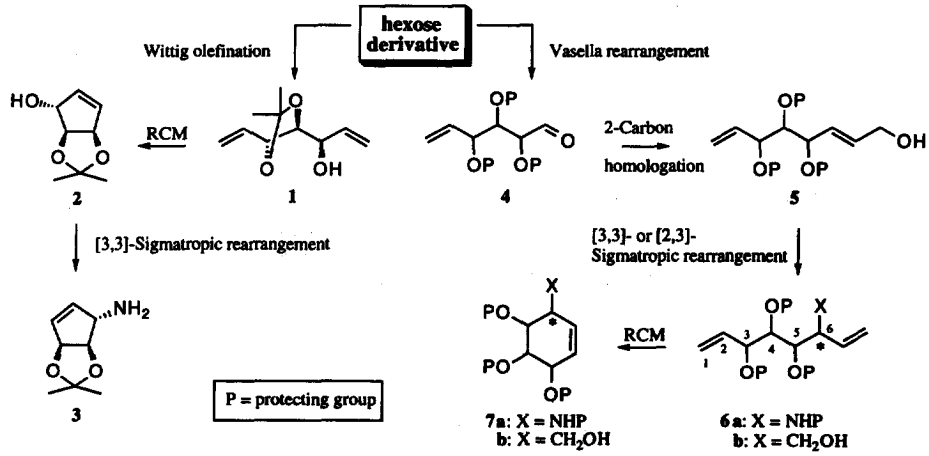
Leiden Institute of Chemistry, Gorlaeus Laboratories, P. O. Box 9502, 2300 RA Leiden, The Netherlands

Received 19 April 1999; accepted 6 May 1999

Abstract: A synthetic route towards conduramine and carbasugar derivatives based on the transformation (*i.e.* two-carbon Wittig olefination and ester reduction) of the Vasella rearrangement product derived from D-galactose followed by either a [3,3] Overman or a [2,3]-Wittig-Still sigmatropic rearrangement, and subsequent ring-closing metathesis, is presented.

Key words: Vasella rearrangement, [3,3] Overman and [2,3] Wittig-Still rearrangements, ring-closing metathesis.

Studies[1-3] from this laboratory revealed that sugars are versatile starting compounds for the construction of scaffolds featuring two terminal olefinic functions suitable for ensuing ring-closing metathesis (RCM).[4] The success of this approach was illustrated in the construction of oxepines[1], pyranopyrans[2] as well as spiroketals.[3] More recently, we reported that this methodology could be extended (Scheme 1) to the synthesis of the acetonide derivative of (3S, 4R, 5S)-4,5-dihydroxycyclopent-1-en-3-ylamine (**3**), a key compound *en route* to the hypermodified nucleoside Q.[5] Thus, Wittig olefination of 2,3-di-*O*-isopropylidene-α-D-*lyxo*-hex-5-enofuranose at the anomeric centre, followed by RCM of the resulting 1,6-diene scaffold **1** and subsequent Overman rearrangement[6] of the corresponding

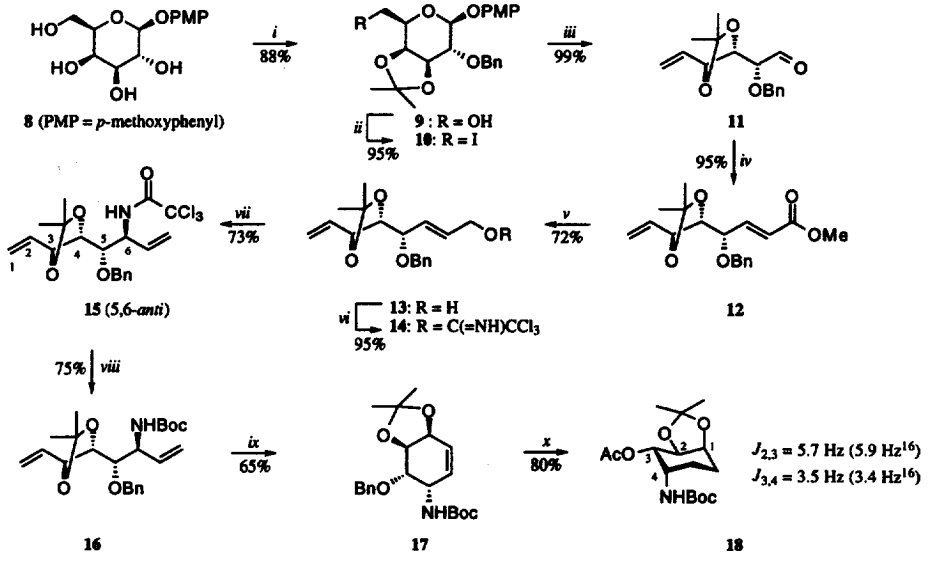


Scheme 1

PII: S0040-4039(99)00911-9

imidate derivative of **2** gave after further elaboration the aminocyclopentenediol **3**. It occurred to us that RCM of the 1,7-diene constellation **6** bearing different substituents (*i.e.* nitrogen or carbon) on the C-6 position would lead (see Scheme 2) to similarly substituted cyclohexitols **7**. The construction of the highly functionalised eight carbon framework **6** can in principle be achieved in transforming the Vasella rearrangement[7] product **4** via Wittig extension, subsequent reduction followed either by a [3,3] Overman or a [2,3] Wittig-Still[8] sigmatropic rearrangement of **5**. We here wish to report that the Vasella rearrangement product **4** serves as a convenient chiral source for the preparation of stereodefined carbocycles **7a,b**.

In the first instance, attention was focused on the preparation, as outlined in Scheme 2, of the conduramine derivative **17**. To this end, the known[9] *p*-methoxyphenyl-β-D-galactopyranoside (**8**) was converted into the primary iodide **10**[10] via the following well established five-step sequential procedure: regioselective silylation and acetonation, benzylation, desilylation of the *t*-butyldiphenylsilyl group and treatment of resulting **9** with 2,4,5-triiodoimidazole and triphenylphosphine according to the method of Garegg.[11] Vasella rearrangement of **10** proceeded smoothly[12] to give the open-chain aldehyde **11**,



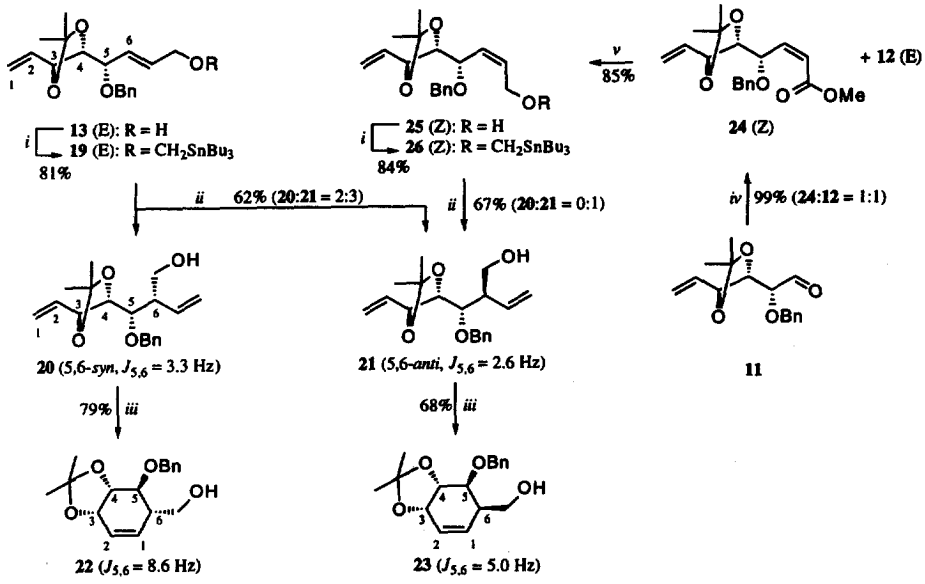
Reagents and conditions: *i.* a) TBDPSCl, pyridine, b) acetone, dimethoxypropane, pTsOH (cat.), c) NaH, BnBr, DMF, d) TBAF, THF. *ii.* imidazole, 2,4,5-triiodoimidazole, $(Ph)_3P$, toluene, reflux. *iii.* Zn, EtOH, reflux. *iv.* $(Ph)_3P{=}CHCO_2Me$ (1.5 eq.), CH_3CN, reflux. *v.* $LiAlH_4$, THF, 0 °C. *vi.* CCl_3CN, DBU, CH_2Cl_2, 0 °C. *vii.* $PdCl_2(MeCN)_2$ (8 mol%), toluene, rt, 12 h. *viii.* a) NaOH, EtOH, H_2O, 70 °C, b) Boc_2O, Et_3N, CH_2Cl_2. *ix.* $Cl_2(PCy_3)_2Ru{=}CHPh$ (10 mol%), CH_2Cl_2, 40 °C, 5 days. *x.* a) H_2, Pd/C, b) Ac_2O, pyridine.

Scheme 2

which was subjected without further extensive purification to a Wittig two carbon elongation. Thus, reaction of crude **11** with methyl triphenylphosphoranylidene acetate in acetonitrile[13] resulted in the exclusive isolation of the E-alkene **12** in a yield of 95% (based on **10**). The requisite trichloroacetimidate **14** was in turn readily accessible by the reaction of the allylic hydroxyl group in **13**, generated by $LiAlH_4$ reduction of **12**, with trichloroacetonitrile in the presence of the base DBU. Overman rearrangement of **14** with catalytic $PdCl_2(MeCN)_2$ in toluene[14] gave the 1,7-diene **15**. Unfortunately, compound **15** resisted,

despite prolonged heating, in undergoing the expected RCM under the agency of the Grubbs catalyst $Cl_2(PCy_3)_2Ru$=CHPh.[15] Gratifyingly, RCM of the corresponding *N*-Boc protected derivative **16**, obtained by deacetylation of **15** and reaction of the free amino group with di-*t*-butyl dicarbonate, gave after prolonged heating the conduramine **17** in 65% yield. The stereochemistry of **17** was determined as follows: hydrogenation (H_2/Pd-C) and acetylation (Ac_2O, pyridine) of HO-5 led to **18**, the NMR data of which were in full accord with those reported for the same compound by Ogawa *et al.*[16] The latter finding also implies that the RCM precursor (**15/16**) has the 5,6-*anti*-configuration.[17]

Apart from the successful metal catalysed 1-aza-[3,3] sigmatropic rearrangement of **13**(E) to **15**(5,6-*anti*), it was envisaged that **13**(E) would also be amenable, due to the presence of the allylic stereocentre at C-5, to a diastereocontrolled [2,3] Wittig-Still rearrangement[18] resulting in the 1,7-diene **6b** (Scheme 1). Accordingly, the α-methoxystannylidene adduct **19**(E) (see Scheme 3), prepared by reaction of **13**(E) with Bu_3SnCH_2I[8] in the presence of potassium hydride, was subjected to *n*-butyllithium in THF[19]



Reagents and conditions: *i*. Bu_3SnCH_2I, KH, THF, 0 °C. *ii*. *n*BuLi, THF, -65 °C, 4h. *iii*. $Cl_2(PCy_3)_2Ru$=CHPh (5 mol%), CH_2Cl_2, RT, 5 days. *iv*. Ph_3P=$CHCO_2Me$ (excess), MeOH. *v*. $LiAlH_4$, THF, 0 °C.

Scheme 3

to give, after separation by flash chromatography, the individual isomers **21**(5,6-*anti*) and **20**(5,6-*syn*) in a ratio of 3:2. Subsequent RCM of both diastereoisomers proceeded slowly to give the expected diastereomeric carbasugars **22** and **23** in a yield of 79 and 68%, respectively. The stereochemistry of the newly created stereocentre at C-6 in the two isomers **20** and **21** as determined by NMR spectroscopy was also established independently by executing the following experiment. It was anticipated[18] that [2,3] sigmatropic rearrangement of the corresponding Z-isomer **26** would lead to the main formation of the 5,6-*anti*-1,7-diene **21**. The requisite precursor **25**(Z) was accessible by submitting **11** to the Mulzer[20] variant of Wittig's (methoxycarbonyl)methylenation. Separation of the resulting E- and Z-isomers and reduction of **24**(Z) with $LiAlH_4$ gave after α-methoxystannylidenation the adduct **26**(Z). Tin-lithium exchange of

26(Z) led to the exclusive formation of the 5,6-*anti* product **21**, which was in every aspect identical with the same product derived from [2,3] sigmatropic rearrangement of **19**(E).

The results presented in this paper clearly show that Vasella rearrangement products are versatile chiral synthons for the construction of highly functionalised and stereodefined carbocycles. Application of this strategy to the synthesis of biologically interesting conduramines and carbasugars will be reported in due course.

Acknowledgements: This work was financially supported by the Netherlands Foundation for Chemical Research (SON). We wish to thank Fons Lefeber and Cees Erkelens for recording the NMR spectra.

References and notes

[1] Ovaa, H.; Leeuwenburgh, M. A.; Overkleeft, H. S.; van der Marel, G. A.; van Boom, J. H. *Tetrahedron Lett.* **1998**, *39*, 3025.

[2] a) Leeuwenburgh, M. A.; Overkleeft, H. S.; van der Marel, G. A.; van Boom, J. H. *Synlett* **1997**, 1263. b) Leeuwenburgh, M. A.; Kulker, C.; Duynstee, H. I.; Overkleeft, H. S.; van der Marel, G. A.; van Boom, J. H. *Tetrahedron* **1999**, in press.

[3] van Hooft, P. A. V.; Leeuwenburgh, M. A.; Overkleeft, H. S.; van der Marel, G. A.; van Boeckel, C. A. A.; van Boom, J. H. *Tetrahedron Lett.* **1998**, *39*, 6061.

[4] a) Schuster, M.; Blechert, S. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2036. b) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. c) Armstrong, S. K. *J. Chem. Soc. Perkin Trans. 1* **1998**, 371.

[5] a) Ovaa, H.; Codée, J. D. C.; Lastdrager, B.; Overkleeft, H. S.; van der Marel, G. A.; van Boom, J. H. *Tetrahedron Lett.* **1998**, *39*, 7987. See for recently reported syntheses of carbocycles employing RCM on carbohydrate derivatives: b) Sellier, O.; van de Weghe, P.; Le Nouen, D.; Strehler, C.; Eustache, J. *Tetrahedron Lett.* **1999**, *40*, 853. c) Ziegler, F. E.; Wang, Y. *J. Org. Chem.* **1998**, *63*, 7920.

[6] a) Overman, L. E. *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 579. b) Berger, D.; Overman, L. E.; Renhove, P. A. *J. Am. Chem. Soc.* **1993**, *115*, 9305.

[7] Bernet, B.; Vasella, A. *Helv. Chim. Acta* **1979**, *62*, 1990.

[8] Still, W. C. *J. Am. Chem. Soc.* **1978**, *100*, 1481.

[9] Murakata, C.; Ogawa, T. *Carbohydr. Res.* **1992**, *235*, 95.

[10] All new compounds were obtained in an analytically pure form and fully characterised by spectroscopic techniques ($^{1}H/^{13}C$-NMR, MS) as well as elemental analysis.

[11] Garegg, P. J.; Samuelsson, B. *J. Chem. Soc. Perkin Trans. 1* **1980**, 2866.

[12] Vasella rearrangement of the *p*-methoxyphenyl galactoside **10** proved to be more effective than the corresponding methyl galactosides.

[13] Mayranoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863.

[14] Gonda, J.; Helland, A.-C.; Ernst, B.; Bellus, D. *Synthesis* **1993**, 729.

[15] Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100.

[16] Chida, N.; Tobe, T.; Murai, K.; Yamazaki, K.; Ogawa, S. *Heterocycles* **1994**, *38*, 2383.

[17] In this respect it is of interest to note that the same stereochemistry was observed by Bellus *et al.*[14] in the palladium catalysed Overman rearrangement of (*E*, *4R*)-4-(*tert*-butyloxycarbonylamino)-2-penten-1-ol.

[18] a) Brückner, R.; Priepke, H. *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 278. b) Priepke, H.; Brückner, R. *Chem. Ber.* **1990**, *123*, 153.

[19] Contrary to the recommendation of Brückner *et al.*[18b], addition of HMPA (4 eq.) did not increase the yield.

[20] Mulzer, J.; Kappert, M. *Angew. Chem. Int. Ed. Engl.* **1983**, *22*, 63.