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Ring closing metathesis as an efficient approach to branched cyclitols and aminocyclitols : a short synthesis of valiolamine

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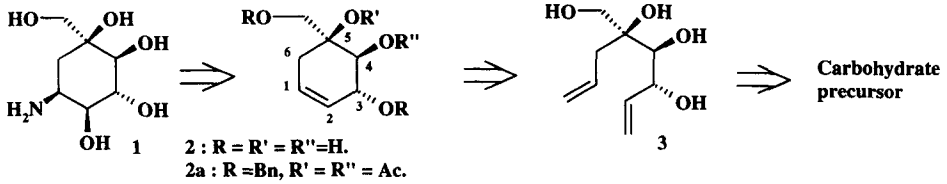
Abstract : Ring closing metathesis of sugar-derived 1,6 dienes is the key step for the construction of highly functionnalized cyclohexenes, precursors of branched cyclitols and aminocyclitols. The method has been used for a short synthesis of valiolamine.

Ring closing metathesis (RCM) has emerged as a powerful tool for the synthesis of medium (5-8) to large (10-13 and higher) carbo- or heterocycles.[1] However, to the best of our knowledge, the method has not been applied to the preparation of polysubstituted, sterically congested carbocyclic systems[2] as found in several classes of naturally occuring glycosidase inhibitors.[3,4,5] In particular, valiolamine (**1**), a potent glucosidase inhibitor with potential antidiabetic activity, has been the target of numerous synthetic efforts. In a recent preparation, the dehydrocyclitol **2a** (R = Bn, R' = R" = Ac) was used as a crucial intermediate. **2a** itself was obtained from quinic acid, in 9 steps (scheme 1).[6] In this paper we show that metathesis is a very efficient, alternative method for the synthesis of highly functionnalized dehydrocyclitols (similar to **2a**). We also describe the facile conversion of these versatile intermediates into polyhydroxylated and aminohydroxylated carbocycles, "pseudo sugars",[7] some of which, (or their derivatives) may be useful therapeutic agents.[8,9,10] In particular the present work presents a very short synthesis of valiolamine.

Conceptually, structure **2** can be considered to arise from an 1,6 diene (**3**), by RCM (scheme 1). **3**, in turn should be readily accessible from a suitable carbohydrate derivative. This suggested that the new approach summarized in scheme 1 offered a simple alternative to available strategies for the synthesis of pseudo sugars.



Scheme 1

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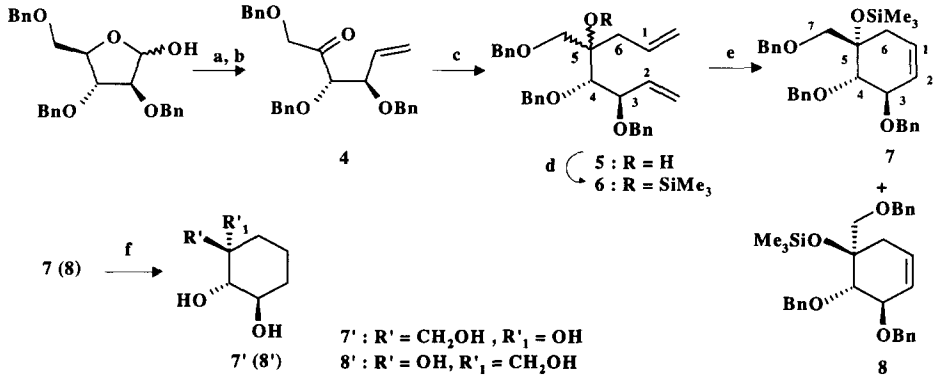
The realization of this approach is shown in scheme 2. The ketone **4,** prepared in two steps from commercially available 2,3,5-tri-*O*-benzyl-D-arabinose,[11] was treated with allylmagnesium bromide, affording in high yield a 7 : 3 mixture of 5(*S*) and 5(*R*) diene-ols **5**. After protection of the tertiary alcohol in **5** as its trimethylsilyl derivative, the resulting mixture (**6**) was submitted to RCM conditions. In initial experiments the relatively easy to handle ruthenium alkylidene catalysts developed by Grubbs were used with limited success.[12] When switching to $PhMe_2CCH{=}Mo{=}N(2,6\text{-}(i\text{-}Pr)_2C_6H_3)(OCMe(CF_3)_2)_2$ (Schrock's catalyst),[13] however, the reaction proceeded smoothly at room temperature to afford in high yield a 7 : 3 mixture of cyclohexene derivatives **7** and **8**, which were separated by HPLC (Kromasil C18, MeOH / H_2O 9 : 1). Measurement of nuclear Overhauser effects in **7** and **8** indicated that **7**, the major isomer had the 5(*S*) configuration, implying that **8** had the 5(*R*) configuration (fig.1).



(a) BuLi (2 eq), $CH_3PPh_3^+Br^-$ (2eq), THF, 0°C to RT, 92% ; (b) CrO_3 (8 eq.), pyridine (20 eq.), CH_2Cl_2, 0°C, 30 min then r.t.,16h, 87% ; (c) $CH_2{=}CH\text{-}CH_2MgBr$ (1M in THF), THF, -78°C → 20°C, 16 h, 97% ; (d) TMSOTf (1.6 eq.), 2,6-lutidine (2.5 eq.), r.t.,16 h, 82% ; (e) Schrock's catalyst, (8 mol%), benzene, r.t.,16h, 92% (mixture of isomers), 42% (**7**), 19 % (**8**) ; (f) i. $Bu_4N^+F^-$ (3 eq), THF, 0°C → 20°C, 16 h ; ii. H_2 (P = 50 bar), Pd/C 10%, MeOH, 24 h, 86% (**7'**), 91% (**8'**).

Scheme 2

To confirm our structural assignment, **7** and **8** were desilylated and hydrogenated to give the corresponding substituted cyclohexanes **7'** and **8'**. Comparison of NMR data and optical rotation with those previously reported showed that **7'** corresponds to the known 1α,2β,3α-trihydroxy-1β-hydroxymethyl-cyclohexane.[14]

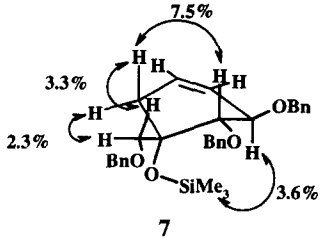
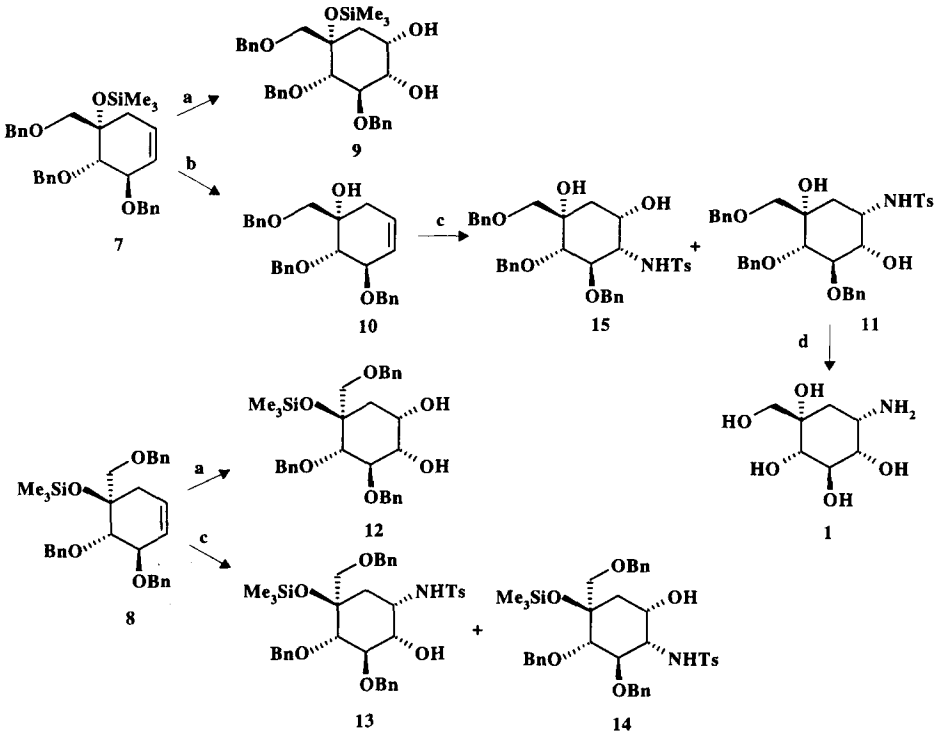


Figure 1

We then examined the functionalization of **7** and **8** (Scheme 3). *Cis*-dihydroxylation of **7** according to Sharpless, proceeded smoothly to give the protected cyclitol **9** in quantitative yield. *Cis*-aminohydroxylation was only possible using the desilylated compound **10** and afforded protected valiolamine **11** in good (55 %) yield [15, 16] accompanied by less than 5% of the "wrong" isomer **15** . Single step removal of all protective groups gave

valiolamine **1**. Starting from **8**, *cis*-dihydroxylation afforded diol **12** in nearly quantitative yield and *cis*-aminohydroxylation provided a 2 : 1 mixture of protected 5-*epi*-valiolamine **13** and isomer **14** (combined yield 54 %).



(a) OsO_4 (2.5% w/v in *tert*-BuOH, 20 mol%), *N*-methylmorpholine -*N*-oxide, THF/acetone/H_2O 4/4/1, r.t.,16 h, 85% (**9**), 90% (**12**) ; (b) $Bu_4N^+F^-$ (3 eq), THF, 0°C → 20°C, 16 h, 92% ; (c) OsO_4 (2.5% w/v in *tert*-BuOH, 5 mol%), chloramine T (2.1 eq.), $Et_3BnN^+Cl^-$ (0.05 eq.), $CHCl_3/H_2O$ 1/1, 50°C, 16 h, 36 % (**13**), 18% (**14**), 55 % (**11**) and 5 % (**15**) ; (d) Na/NH_3 liq, -78°C, 7 h, 50%.

Scheme 3

Thus, RCM appears as a very powerful tool for the preparation of branched cyclitols or aminocyclitols (pseudo sugars). In particular, the present work describes, to the best of our knowledge, the shortest synthesis of valiolamine reported so far. Although individual steps have not been optimized, the present preparation is competitive when compared to other published syntheses. It should be noted that, in the present case, the outcome of the RCM was strongly influenced by the catalyst, high yields and mild reaction conditions being obtained using the extremely sensitive Schrock's catalyst. We are currently applying RCM to the synthesis of other, highly functionalized, very sterically demanding systems, derived from monosaccharides.

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[15] New compounds have satisfactory analytical data. The NMR data of **1** are identical with those reported in the literature.[10] Data obtained for selected examples are as follow :

7 ^{1}H-NMR (C_6D_6, 250MHz) δ 0.20 (9H, s), 2.24 (1H, ddt, *J* = 18, 4.5, 1.5 Hz), 2.57 (1H, dq, *J* = 18, 3 Hz), 3.37 (1H, *J* = 8.5 Hz), 3.74 (1H, *J* = 8.5 Hz), 3.87 (1H, d, *J* = 7.5 Hz), 4.22 (1H, *J* = 12 Hz), 4.27 (1H, *J* = 12 Hz), 4.53 (1H, m), 4.57 (2H, s), 4.70 (1H, *J* = 11.5 Hz), 5.01 (1H, *J* = 11.5 Hz), 5.50 (1H, m), 5.62 (1H, m). ^{13}C-NMR (C_6D_6, 62.9MHz) δ 2.81, 36.76, 71.83, 73.44, 74.23, 75.13, 78.74, 79.75, 81.87, 125.57, 126.83, 127.50-128.61, 138.72, 139.73, 139.96. Anal. Calcd for $C_{31}H_{38}O_4Si$: C, 74.06; H, 7.62. Found : C, 74.16; H, 7.79. $[\alpha]_D^{20}$ = -51.5 (*c* 1.2, $CHCl_3$).

8 ^{1}H-NMR (C_6D_6, 250MHz) δ 0.23 (9H, s), 2.08 (1H, ddq, *J* = 17.5, 1, 2.5 Hz), 2.80 (1H, ddt, *J* = 17.5, 1, 5 Hz), 3.47 (1H, *J* = 9.5 Hz), 3.81 (1H, *J* = 9.5 Hz), 3.90 (1H, d, *J* = 7.5 Hz), 3.95 (1H, m), 4.15 (1H, *J* = 12 Hz), 4.35 (1H, *J* = 12 Hz), 4.49 (1H, *J* = 12 Hz), 4.58 (1H, *J* = 12 Hz), 4.83 (1H, *J* = 12 Hz), 5.05 (1H, *J* = 12 Hz), 5.45 (1H, m), 5.62 (1H, m). ^{13}C-NMR (C_6D_6, 62.9MHz) δ 2.73, 35.50, 71.26, 71.93,73.43, 75.90, 79.17, 79.68, 86.47, 126.50, 126.74, 175.50-128.61, 138.72, 139.73, 140.07. $[\alpha]_D^{20}$ = -87.5 (*c* 0.7, $CHCl_3$).

11 ^{1}H-NMR ($CDCl_3$, 400MHz) δ 1.38 (1H, dd, *J* = 15, 3 Hz), 1.74 (1H, ddd, *J* = 15, 4, 2 Hz), 2.43 (3H, s), 2.82 (1H, d, *J* = 2 Hz), 2.84 (1H, d, *J* = 8 Hz), 3.01 (1H, *J* = 8.5 Hz), 3.32 (1H, *J* = 8.5 Hz), 3.56 (1H, m), 3.60 (1H, d, *J* = 9 Hz), 3.61 (1H, m), 3.76 (1H, t, *J* = 9 Hz), 4.31 (1H, *J* = 12 Hz), 4.39 (1H, *J* = 12 Hz), 4.43 (1H, *J* = 11 Hz), 4.75 (1H, *J* = 11 Hz), 4.88 (1H, *J* = 11 Hz), 5.01 (1H, *J* = 11 Hz), , 6.34 (1H, brd, *J* = 8 Hz), 7.14-7.39 (17H, m), 7.78 (2H, d, *J* = 8.5 Hz).^{13}C-NMR ($CDCl_3$, 62.9MHz) δ 21.56, 32.03, 53.60, 72.92, 73.14, 73.52, 75.64, 75.70, 76.05, 79.64, 81.88, 127.23-128.39, 129.77, 137.03, 137.40, 137.80, 138.59, 143.56. $[\alpha]_D^{20}$ = + 14.5 (*c* 1.6, $CHCl_3$).

1 ^{1}H-NMR (D_2O, 250MHz) δ 1.68 (1H, dd, *J* = 15, 4 Hz), 1.88 (1H, dd, *J* = 15, 3 Hz), 3.34 (1H, ddd, *J* = 9.5, 4, 3 Hz), 3.41 (1H, d, *J* = 9.5 Hz), 3.48 (2H, ABq, *J* = 11.5 Hz), 3.57 (1H, dd, *J* = 4, 10 Hz), 3.83 (1H, t, *J* = 9.5 Hz).

[16] In a previous report, attempts to perform a Sharpless's *cis*-aminohydroxylation on **2a** failed completely. *Cis*-dihydroxylation using classical conditions (OsO_4, NMO) was also ineffective, and an alternative method ($RuCl_3$ / $NaIO_4$) was developed.[6]