Highly Regio- and Stereo-selective Annulation–Elimination Reactions of 1-Cycloalkenyl 3-Hydroxypropyl Ethers

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Highly regio- and stereo-selective annulation–elimination reactions of 1-cycloalkenyl 3-hydroxypropyl ethers in the presence of triflic anhydride and tertiary amines are described; the bicyclic vinyl ethers produced are converted to 2-substituted δ-lactones, macrocyclic oxolactones and bicyclic hydroxy ethers by ozonolysis and stereoselective hydroboration.

A few years ago we reported a stereospecific annulation of hydroxy vinyl ethers **2** to bicyclic hemiacetals **3**,[1] which were prepared by regio- and stereo-specific ring opening of 1,3-dioxanes **1**.[2] Synthetic and mechanistic interests in the annulation led to further investigation. Here we report new regio- and stereo-selective annulation–elimination reactions of **2** to yield bicyclic vinyl ethers **4** and **5** (Scheme 1). Subsequent oxidations of **4** and **5** lead to useful functionalized cyclic compounds.

While investigating the annulation reaction of 1-cyclohexenyl 3-hydroxypropyl ether **2a**, we found that a mixture of 2-oxabicyclo[4.4.0]dec-1(6)-ene **4a** and 2-oxabicyclo-[4.4.0]dec-1(10)-ene **5a** was obtained by warming the reaction solution of **2a** and triflic anhydride (Tf_2O) to 25 °C (Scheme 1). The progress of the reaction was followed by ^1H NMR as the bicyclic vinyl ethers **4a** and **5a** are highly acid sensitive. The reaction proceeded gradually above 0 °C and was completed upon stirring for over 12 h at 25 °C. These experimental results are consistent with the production of a bicyclic triflate at −78 °C, which, after adding water at −78 °C, is hydrolysed upon warming to 25 °C to give **3a**, but is transformed to the compounds **4a** and **5a** upon warming to 25 °C under anhydrous conditions.

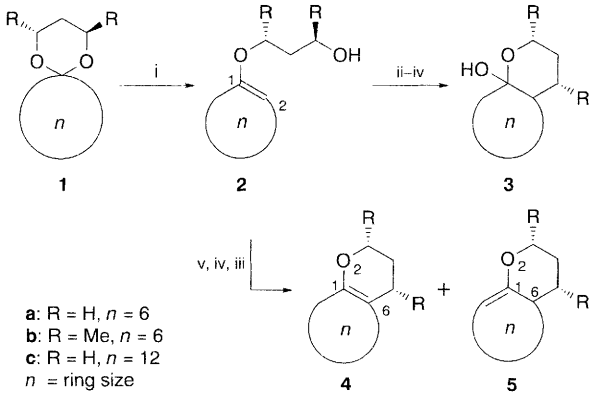
A variety of amines and other reaction conditions were screened to investigate the regioselectivity (**4a** *vs.* **5a**) in the elimination reaction (Table 1). The results strongly suggest a crucial role of the steric hindrance of amine; the use of sterically hindered trialkylamines, *e.g. N,N*-dicyclohexylmethylamine or *N,N*-diisopropylethylamine in dichloromethane gave **5a** as the major product (entries 1–3), while the use of non-nucleophilic and relatively less hindered trialkylamines, *e.g.* triisobutylamine in dichloromethane gave principally **4a** (entry 5). These results can be understood on the basis that the direction of the elimination of the cationic intermediate in dichloromethane is governed by the degree of steric hindrance to approach of amine to the β-proton under kinetic control.[3] Solvent effects are also important factors in the regioselectivity: the use of *N,N*-diisopropylethylamine in toluene gave **4a** as a major isomer (entry 3 *vs.* 6). This result is understandable based on the direction of the elimination being governed by thermodynamic control. These mechanistic considerations can explain that the ratio **4a**:**5a** is changed by the concentrations of amine: high concentrations of amine favour **5a** (entry 2 *vs.* 3) while high dilutions of amine favour **4a** (entry 6 *vs.* 7). Thus, the procedures used in the reactions of entry 7 (Method A)[4] and entry 2 (Method B) were established as representative procedures for the regioselective annulation– elimination reaction of **2**, and were used to explore the generality and scope of the annulation (Scheme 2, Table 2). To our knowledge, the regioselective reaction using Method B is the first example of a practical synthesis of **5**.[4]

The synthetic utility of the unstable compounds **4** and **5** is clear from oxidative transformations to the useful synthetic intermediates **6**, **7** and **8** or **9** (Scheme 2, Table 2).† Ozonolysis of **4** and **5** gave (2 + *n*)-oxolactones **6**[5] and 2-substituted-5-pentanolides **7**, respectively. Hydroboration of **5** using borane·THF or 9-BBN (9-borabicyclo[3.3.1]nonane) gave

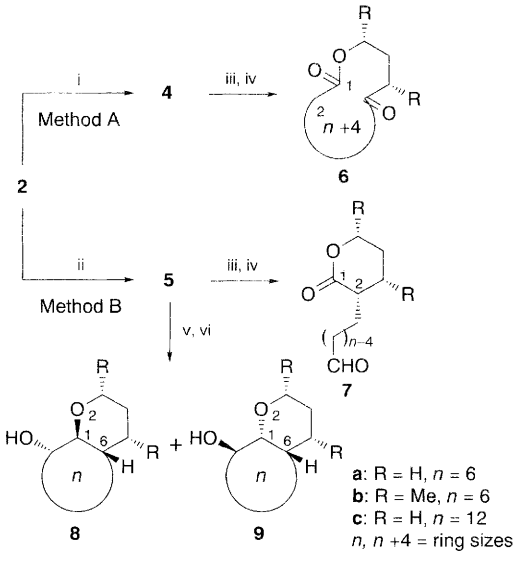
Table 1 The effects of bases and solvents on the regioselectivity[a]

Entry	Amine (ml per 1 mmol of **2a**)	Solvent (ml per 1 mmol of **2a**)	Ratio[b] **4a**:**5a**
1	$(C_6H_{11})_2MeN$, 1	CH_2Cl_2, 5	10:90
2	Pr^i_2EtN, 2	CH_2Cl_2, 5	13:87
3	Pr^i_2EtN, 1	CH_2Cl_2, 5	16:84
4	collidine, 1	CH_2Cl_2, 5	40:60
5	Bu^i_3N, 1	CH_2Cl_2, 5	91:9
6	Pr^i_2EtN, 1	Toluene, 5	91:9
7	Pr^i_2EtN, 1	Toluene, 10	97:3

[a] The reaction of **2a** was carried out using 1.2 equiv. of triflic anhydride (see Scheme 1). [b] The ratio was determined by ^1H NMR analysis of the crude products.



Scheme 1 *Reagents and conditions*: i, Bu^i_3Al (4 equiv.), CH_2Cl_2, 0 °C; ii, Tf_2O (1.2 equiv.), Pr^i_2EtN, CH_2Cl_2, −78 °C; iii, aq. $NaHCO_3$, −78 °C; iv, warm to 25 °C; v, Tf_2O (1.2 equiv.), base, solvents, −78 °C



Scheme 2 *Reagents and conditions*: i, Tf_2O, Pr^i_2EtN, toluene, −78 to 25 °C; ii, Tf_2O, Pr^i_2EtN, CH_2Cl_2, −78 to 25 °C; iii, O_3, MeOH, −78 °C; iv, Me_2S; v, BH_3·THF or 9-BBN; vi, H_2O_2, NaOH

(6 + *n*)-hydroxy-2-oxabicyclo[4.*n*.0]alkanes **8** or **9** with high stereoselectivity.

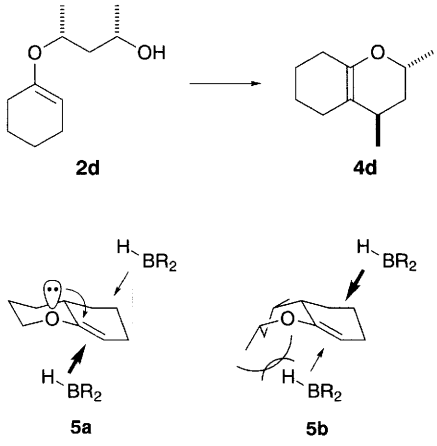
For each case, product stereochemistry was confirmed by ^{1}H and ^{13}C NMR spectroscopy. The structural assignment of **8a** and **9a** was based on comparison with the spectral assignments of *cis*- and *trans*-2-oxabicyclo[4.4.0]octanes reported in the literature.[6]‡ In addition, for product **9b**, the *cis* structure and absolute configuration were determined by single-crystal X-ray crystallographic analysis of the *p*-nitrobenzoate.§ The X-ray structure indicates that the annulation–elimination reaction of **2b** proceeds with complete inversion of stereochemistry at the triflate function¶ and by stereospecific attack to *re*-face of vinyl ether carbon. The absolute stereochemistries of **6b** and **7b** were assigned by analogy with **9b**.

It is presumed that the annulation of **2b** into **3b**, **4b** or **5b** proceeds through an S_N2-like mechanism, *i.e.* with inversion of stereochemistry at hydroxy function. Evidence that the mechanism of the annulation is not S_N1 was based upon the following experimental result: the annulation–elimination reaction of **2d** prepared from the *meso* acetal, a diastereoisomer of **1b**, by Method A gave the (4*RS*, 5*RS*)-3,5-dimethyl-2-oxabicyclo-[4.4.0]dec-1(6)-ene **4d**, a diastereoisomer of **4b**.

Table 2 Regioselective synthesis of bicyclic vinyl ethers **4** and **5** from spiroacetals **1** and subsequent oxidations[a]

	Annulation[b]		Ozonolysis[e]		Hydroboration[g]	
Starting Material	Method[c]	**4**:**5**[d]	Yield (%)[f]	**6**:**7**[d]	Yield (%)[f]	**8**:**9**[h]
1a	A	97:3	58	88:12		
	B	13:87	61	22:78	48[i](89)[j]	94:6
1b	A	96:4	52	97:3		
	B	31:69	54	35:65	53	<1:>99
1c	A	87:13	43	79:21		
	B	9:91	77	24:76	65	70:30[k]

[a] The crude product **2**, which was prepared from **1** using Bu^i_3Al, was used immediately in the next cyclization step (see Scheme 2). [b] The crude mixture of **4** and **5** was used immediately in the next oxidation steps. [c] Method A: entry 7, Table 1; Method B: entry 2, Table 1. [d] Determined by ^{1}H NMR analysis. [e] Ozonolysis was carried out in methanol at −78 °C. [f] Overall yield from **1**. [g] Hydroboration was carried out in THF using 1.5 equiv. of BH_3·THF at 25 °C. [h] Determined by GLC analysis. [i] 9-BBN was used. [j] **5a** purified by chromatography was used. Isolated yield from **5a** is indicated. [k] The stereochemistries of **8c** and **9c** were not determined.



Scheme 3 Stereoselectivity of the hydroboration of bicyclic vinyl ethers **5a** and **5b**

Hydroboration reactions on vinyl ether double bonds are highly stereo- and regio-selective.[7] The hetero atom directs the addition of diborane nearly exclusively to the β-position to give β-hydroxy ether. The observed relative stereochemical preferences for the formation of **8** or **9** are consistent with the pathway shown in Scheme 3. In the hydroboration of **5a**, the borane reagent stereoselectively approaches the antiperiplanar side of the axial lone pair on the ether oxygen by anomeric interaction between π-orbital of the alkene and its lone pair, to afford **8a** as the major product.[8] In the reaction of **5b**, in contrast, the borane reagent stereoselectively approaches the less hindered side of the alkene, to afford **9b** as a major product, since the antiperiplanar arrangement of lone pairs on the ether oxygen and the π-orbital of the alkene is obstructed by steric hindrance of the two dimethyl groups.

We believe that the stereospecific annulation which we previously developed has advanced to a new level of practicality and versatility as a result of the present investigation which delineated the outstanding and predictable regio- and stereoselectivities of the annulation–elimination reactions and subsequent oxidations.

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Footnotes

† All new compounds gave satisfactory analytical and/or spectral data.
‡ *trans*-2-Oxabicyclo[4.4.0]octane:[6] ^{13}C NMR δ 82.02 [C(1)], 68.28 [C(3)], 42.14 [C(6)]; *cis*-isomer: ^{13}C NMR δ 75.21 [C(1)], 68.91 [C(3)], 34.7 [C(6)]; the acetate of **8a**: ^{13}C NMR ($CDCl_3$) δ 83.45 [C(1)], 68.37 [C(3)], 40.14 [C(6)]; ^{1}H NMR ($CDCl_3$) δ 4.77 [C(10)H(axial)]; the acetate of **8b**: ^{13}C NMR ($CDCl_3$) δ 70.37 [C(1)], 67.51 [C(3)], 32.11 [C(6)]; ^{1}H NMR ($CDCl_3$) δ 5.00 [C(10)H(axial)].
§ The *p*-nitrobenzoate of **9a** gave satisfactory crystallographic data. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Information for Authors, Issue No. 1.
¶ We earlier clarified that the annulation of **2b** to **3b** proceeds with complete inversion of stereochemistry at the triflate function; see ref 1.

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