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COMMUNICATION

Tandem Payne/Meinwald *versus* Meinwald rearrangements on the α-hydroxy- or α-silyloxy-spiro epoxide skeleton†

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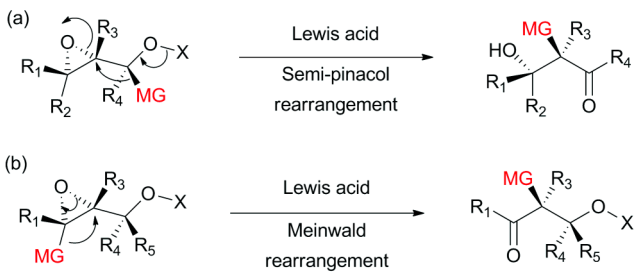
Under Lewis acid activation, the new α-hydroxy-spiro epoxide scaffold 1a underwent an original tandem Payne/Meinwald rearrangement affording the cyclopentyl hydroxymethylketone 6 in a stereospecific manner, while a Meinwald-type epoxide rearrangement occurred when the derived α-trimethylsilyloxy-spiro epoxide 2a was treated with MABR, yielding stereoselectively the cyclohexane carbaldehyde 9.

Introduction

The acid-promoted 1,2-rearrangement of α-hydroxy and α-silyloxy epoxides is an elegant strategy to access β-hydroxy or β-silyloxy carbonyl compounds. The high synthetic interest of this rearrangement lies in the stereospecificity generally observed, allowing quaternary centers to be generated with a high stereoselectivity at the carbonyl's α-position (Scheme 1). Depending on the substitution pattern on the epoxide substrate and on the nature of the Lewis acid used, two alternative mechanisms are known to proceed, *i.e.*, either the semi-pinacol rearrangement (Scheme 1(a)) or the Meinwald rearrangement (Scheme 1(b)). The semi-pinacol rearrangement of α-hydroxy and α-silyloxy epoxides has been thoroughly investigated.[1] Lewis acids like $TiCl_4$,[2] $BF_3{\cdot}OEt_2$,[2a,3] $SnCl_4$,[3d,3e,4] and R_3SiOTf/iPr_2NEt[5,3e] proved efficient to promote vinyl, aryl, alkyl or hydride migration on various acyclic and cyclic systems.



Scheme 1 Semi-pinacol and Meinwald rearrangements on α-hydroxy- and α-silyloxy-epoxides.

Catalytic processes were also developed using Me_3SiI or Me_3SiOTf,[6] $B(C_6F_5)_3$,[7] $ZnBr_2$[8] and rare earth triflates.[9] This powerful methodology has been applied in multi-step synthesis of complex structures,[1,10] and particularly used in this field to carry out clean ring expansions[11] or ring contractions.[12] The Meinwald rearrangement[13] has been reported to proceed with $BF_3{\cdot}OEt_2$ or $SnCl_4$[14] and R_3SiOTf/iPr_2NEt.[15] To overcome the lack of selectivity usually observed on trialkyl-substituted epoxides, Yamamoto's group developed the use of the bulky organoaluminium promoter methylaluminium bis(4-bromo-2,6-di-*tert*-butyl-phenoxide) (MABR)[16] and of the bulky organoboron catalyst $B(C_6F_5)_3$.[7]

The nature of the mechanism involved, as well as the regioselectivity and stereospecificity of the process, are governed by the following parameters: the stability of the carbocations which may be generated under Lewis acid activation of the epoxide,[15] the nature[14b] and the bulkiness[16a] of the Lewis acid used, the steric hindrance and the nature of the epoxide's substituents.[5c,d,f]

Results and discussion

Chemical synthesis

Although numerous α-hydroxy- and α-silyloxy-epoxides have been shown to undergo Lewis acid-induced semi-pinacol or Meinwald rearrangements, only a few examples of stereoselective rearrangements of spiro epoxides have been reported to date.[9b,11c,16b,17] Herein, we report on the unusual behavior of new spiro epoxides derivatives **1** and **2** in the presence of a Lewis acid (Scheme 2). In the course of ongoing studies on the stereoselective synthesis of highly functionalized cyclohexane carbaldehydes, original α-hydroxy- and α-trimethylsilyloxy-spiro epoxides **1** and **2** were stereoselectively prepared from phorenol.[18]

Protection of phorenol as the *tert*-butyldimethylsilyl (TBS) ether was followed by stereoselective *anti*-epoxidation of the

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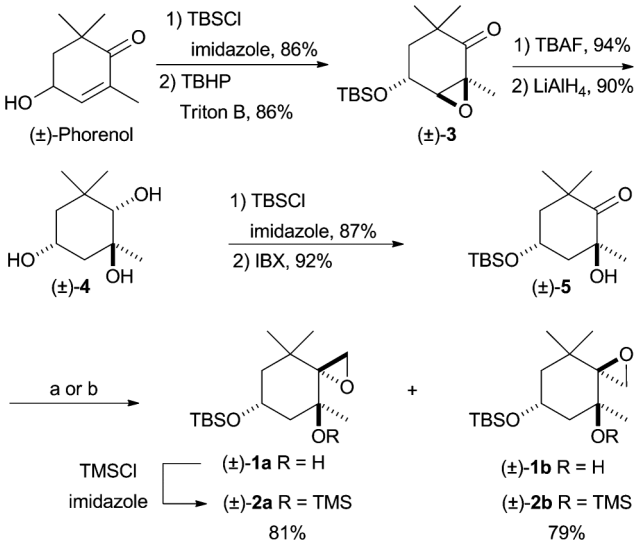


Scheme 2 Reagents and conditions: (a) Me_3S^+O,I^-, NaH, LiI, DMSO/THF, 50 °C; **1a** : **1b** = 82 : 18; 55% (**1a**), 18% (**1b**). (b) Me_3S^+,I^-, NaH, DMSO/THF, 0 °C; **1a** : **1b** = 14 : 86; 9% (**1a**), 65% (**1b**).

electro-deficient double bond with the nucleophilic system *tert*-BuOOH/Triton B.[19] Deprotection of **3** with TBAF allowed the hydroxy-directed reductive opening of the epoxide[20] to proceed in 90% yield using excess $LiAlH_4$.[21] Selective protection of the less hindered alcohol as its TBS ether and clean re-oxidation of the hindered secondary alcohol using IBX in EtOAc[22] afforded the α-hydroxy ketone **5** in 80% yield over two steps.

The latter was then stereoselectively epoxidized by sulfur ylides.[23] In accordance with the stereodivergence classically observed on cyclohexanic substrates, trimethylsulfoxonium ylide[24] favored an equatorial attack on the carbonyl (**1a** : **1b** = 82 : 18), while trimethylsulfonium ylide favored the axial attack (**1a** : **1b** = 14 : 86). Good overall yields were obtained and clean separation of **1a** and **1b** could be achieved by chromatography. TMS-protected derivatives **2a** and **2b** were obtained by treatment with TMSCl/imidazole. The *cis* relative configuration between the hydroxyl group and the epoxide in α-hydroxyepoxide **1b** was established by X-ray diffraction analysis (Fig. 1).

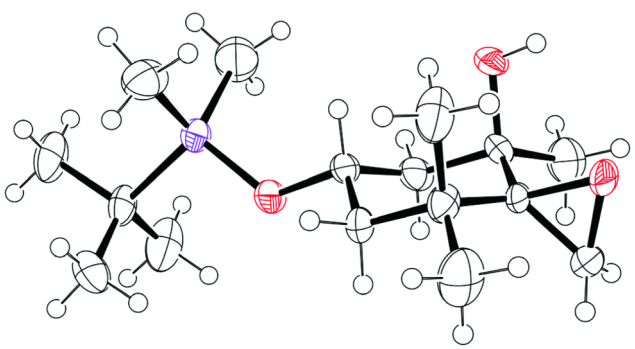


Fig. 1 ORTEP diagram of *cis*-diastereoisomer **1b**.

Rearrangement of α-hydroxy-spiro epoxide 1a

We investigated first the behaviour of original α-hydroxy-spiro epoxides **1** towards various Lewis acids in catalytic or stoichiometric amounts. The *cis* diastereoisomer **1b** proved unreactive whatever the Lewis acid used. Extending the reaction times and increasing the temperature only led to degradation. By contrast, the *trans* diastereoisomer **1a** proved reactive in the presence of $BF_3{\cdot}OEt_2$, $SnCl_4$ and $Yb(OTf)_3$ but led unexpectedly to the cyclopentyl hydroxymethylketone **6**[25] as a single diastereoisomer in 55–84% yields (Table 1, entries 1–5). The structure and the relative configuration in **6** were established by X-ray diffraction analysis of the derived 3,5-dinitrobenzoate ester **8** (Fig. 2). Interestingly, the diastereopure cyclopentyl-substituted ketone scaffold of **6** is found in several carotenoids.[26] Although excesses of $BF_3{\cdot}OEt_2$ or $SnCl_4$ are usually used to induce epoxide rearrangements, higher yields of **6** were attained using 0.25 equiv. of $BF_3{\cdot}OEt_2$ (Table 1, entry 2) and 0.5 equiv. of $SnCl_4$ (Table 1, entry 4). The latter proved the most efficient, leading to **6** in a high 84% yield. When the hindered MABR was used as a promoter, a complex mixture was obtained, from which a 47 : 53 mixture of compound **6** and β-hydroxyaldehyde **7**[27] was isolated in a modest 34% yield (Table 1, entry 7). No reactivity was observed with Jung's system (TBSOTf/*i*Pr$_2$NEt) (Table 1, entry 6) or using the bulky catalyst $B(C_6F_5)_3$ (entry 8).

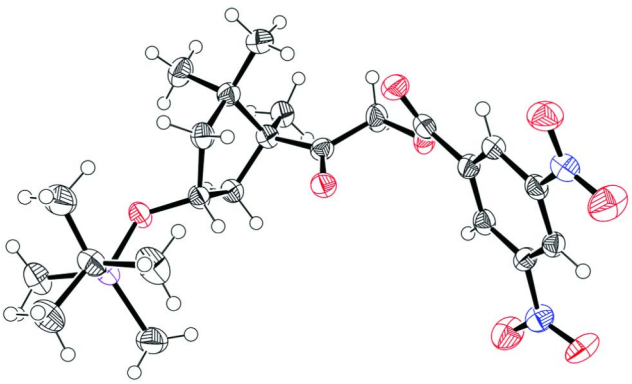


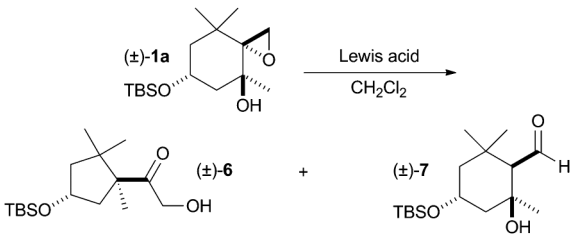
Fig. 2 ORTEP diagram of compound **8**.

To rationalize the stereoselective formation of the cyclopentyl hydroxymethylketone **6**, we propose an original stereospecific tandem rearrangement, involving an acid-induced Payne rearrangement on the α-hydroxy epoxide scaffold **1a**, followed by a Meinwald rearrangement of the resulting tetrasubstituted epoxide **A** with ring contraction (Scheme 3). Acid-induced Payne rearrangements have been scarcely reported in the literature, induced either by Brønsted acids,[28] $Yb(OTf)_3$,[9b] trialkylsilyl halides[29] or triflates.[5c,30]

We presume that the proposed Meinwald rearrangement[13] would begin by the *axial cleavage*[25,31] of the intermediate tetrasubstituted epoxide **A**, thus following the Fürst–Plattner rule.[5f,32] Ring contraction of the cationic intermediate **B** through 1,2-alkyl shift would then furnish stereospecifically ketone **6**.

The tandem Payne/Meinwald rearrangement proposed is supported by the absence of reactivity of the *cis*-diasteroisomer **1b**, for which the C–O bond of the hydroxyl group and the adjacent C–O bond of the epoxide are nearly perpendicular to each other, thus preventing the Payne rearrangement from occurring (Fig. 1). The observation that neither semi-pinacol nor Meinwald rearrangements took place instead could be interpreted by the fact that the geometric requirements for such

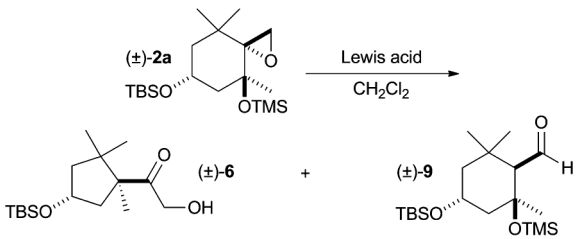
Table 1 Lewis acid-promoted rearrangement of α-hydroxy-spiro epoxide **1a**



Entry	Lewis acid (equiv.)	*T* (reaction time)	Yield of **6** (%)[a]	Yield of **7** (%)[a]
1	$BF_3{\cdot}OEt_2$ (1.1)	−78 °C (1 h)	55	
2	$BF_3{\cdot}OEt_2$ (0.25)	−78 °C (1.5 h) → −20 °C (1 h)	64	
3	$SnCl_4$ (1.1)	−78 °C (1 h)	73	
4	$SnCl_4$ (0.5)[b]	−78 °C (1 h) → −20 °C (1 h)	84	
5	$Yb(OTf)_3$ (0.2)	RT (6.5 h)	60	
6	TBSOTf (3)/*i*-Pr_2NEt (3)	−50 °C (1 h) → RT (48 h)	—[c]	
7	MABR (2)	−78 °C (1 h)	16[d]	18[d]
8	$B(C_6F_5)_3$ (0.1)[e]	RT (1 h) → 60 °C (12 h)	—[c]	

[a] Isolated yields. [b] With 0.25 equiv., the reaction did not go to completion. [c] Substrate recovered unchanged. [d] Isolated as a 47 : 53 mixture of **6** and **7** (ratio determined by ^{1}H NMR integration). [e] Reaction carried out in THF.

Table 2 Lewis acid-promoted rearrangement of α-silyloxy-spiro epoxide **2a**



Entry	Lewis acid (equiv.)	*T* (reaction time)	Yield of **6** (%)[a]	Yield of **9** (%)[a]
1	$BF_3{\cdot}OEt_2$ (1.1)	−20 °C (1 h)	58	
2	$BF_3{\cdot}OEt_2$ (0.25)	−20 °C (3 h) → 0 °C (1 h)	67	
3	$SnCl_4$ (1.1)	−78 °C (1 h)	80	
4	$SnCl_4$ (0.5)	−78 °C (1 h) → −20 °C (1 h)	82	
5	$Yb(OTf)_3$ (0.2)	RT (15 h)	—[b]	
6	TMSOTf (1.7)/*i*-Pr_2NEt (1.8)	−50 °C → 35 °C (1 h)	—[c]	
7	MABR (2)	−78 °C (1 h)		98
8	$B(C_6F_5)_3$ (0.1)[d]	RT (15 h) → 50 °C (15 h)	—[b]	

[a] Isolated yields. [b] Substrate recovered unchanged. [c] A complex mixture was formed. [d] Reaction carried out in THF.

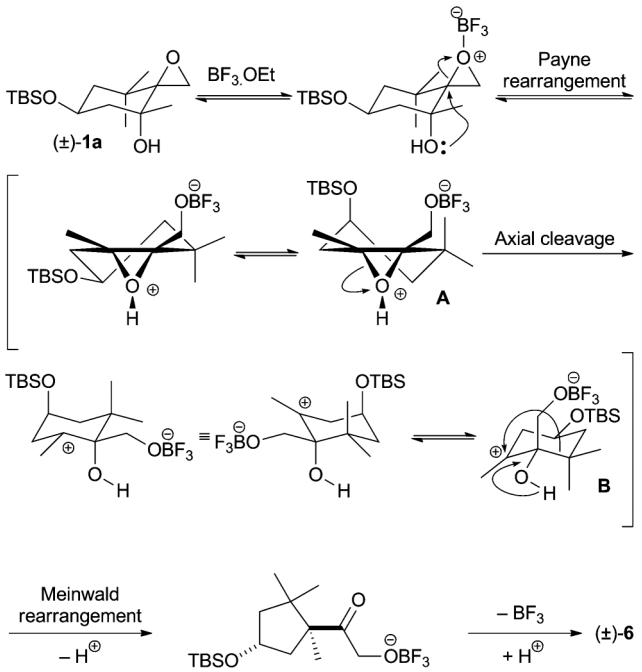
processes could not be achieved on this conformationally restricted substrate.

Rearrangement of α-trimethylsilyloxy-spiro epoxide 2a

We then extended the study to the trimethylsilyloxy epoxides **2** (Table 2). Whereas the *cis*-diastereoisomer **2b** showed no reactivity or underwent deprotection or degradation, interesting results were observed with the diastereoisomer **2a**. Surprisingly, two different rearrangement pathways proved to take place, depending on the nature of the Lewis acid used. Whereas $BF_3{\cdot}OEt_2$ and $SnCl_4$ induced the above tandem Payne/Meinwald rearrangement, leading to **6** in moderate to good yields (Table 2, entries 1–4), MABR allowed a stereoselective Meinwald rearrangement to proceed, affording the cyclohexane carbaldehyde **9** in 98% yield (Table 2, entry 7).[33] Contrary to the unprotected substrate **1a**, **2a** proved unreactive in the presence of $Yb(OTf)_3$ (Table 2, entry 5). Similarly, no reaction was observed in the presence of a catalytic amount of $B(C_6F_5)_3$ (Table 2, entry 8).

Conclusions

In summary, we reported herein an original Lewis acid-induced tandem Payne/Meinwald rearrangement occurring on the α-hydroxy- and α-silyloxy-spiro epoxides **1a** and **2a**. A high yielding seven-step sequence was developed to give stereoselectively the original diastereoisomeric substrates **1a** and **1b**. The new tandem process was cleanly achieved in good yields using a catalytic amount of $Yb(OTf)_3$, or substoichiometric amounts of $BF_3{\cdot}OEt_2$ or $SnCl_4$. The use of MABR as the acidic promoter led to an interesting divergence of mechanism on the trimethylsilyl-protected substrate **2a**. A stereoselective Meinwald rearrangement



Scheme 3 Proposed mechanism for the formation of **6**.

took place, allowing to access the cyclohexane carbaldehyde **9** of high synthetic interest[34] in quantitative yield.

Acknowledgements

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