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Highly Regio- and Chemoselective Ring Opening of Oxa-Bridged Piperidinones toward Functionalized Furanones and Piperidines

Sengodagounder Muthusamy,*,† Janagiraman Krishnamurthi,† and Eringathodi Suresh‡

School of Chemistry, Bharathidasan University, Tiruchirappalli, Tamilnadu-620 024, India, and Central Salt & Marine Chemicals Research Institute, Bhavnagar, Gujarat-364 002, India

muthu@bdu.ac.in

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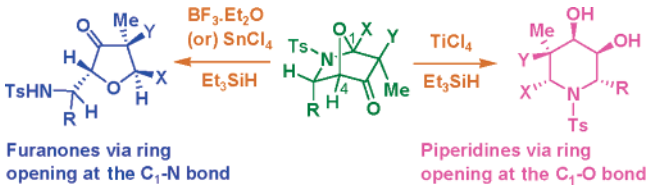
ABSTRACT



Lewis acid mediated competitive ring-opening reactions of *N*-tosyl-substituted oxa-bridged piperidinone ring systems are demonstrated. A majority of the Lewis acids furnished the regio- and chemoselective reductive ring opening at the C_1–N bond, whereas $TiCl_4$ furnished at the C_1–O bond in the presence of triethylsilane, affording functionalized furanones and dihydroxypiperidines, respectively.

Iminosugars are polyhydroxylated aza-heterocycles or piperidines that show a wide range of biological activities.[1] For example, polyhydroxylated piperidine derivatives such as 1-deoxyfuconojirimycin **1** and 1-deoxymannojirimycin **2** (Figure 1) are useful to inhibit glycosidase enzymes and possess biological applications.[2] Thus, we envisaged constructing the hydroxylated piperidine systems via ring-opening reactions of recently reported substituted oxa-bridged piperidinones.[3] The survey of literature reveals that there are many reports available on ring-opening reactions, such as transition-metal-catalyzed asymmetric ring opening reactions of oxa- and azabicyclic alkenes,[4a−d] SmI_2-mediated ring opening of oxanorbornane systems,[4e−g] Lewis acids mediated ring opening reactions of oxa-bridged piperidinones,[4h−m] base-mediated ring-opening reactions,[4n] and $TiCl_4$-promoted ring-opening reaction of oxanorbornenes.[4o,p]

Herein, we report highly regio- and chemoselective reductive ring opening of oxa-bridged piperidinones toward

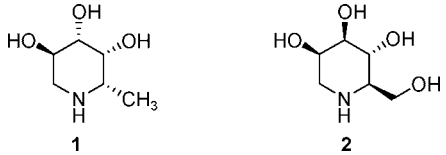


Figure 1. Structure of 1-deoxyfuconojirimycin (**1**) and 1-deoxymannojirimycin (**2**).

* To whom correspondence should be addressed. Fax: 91-431-2407043.
† Bharathidasan University.
‡ Central Salt and Marine Chemicals Research Institute.

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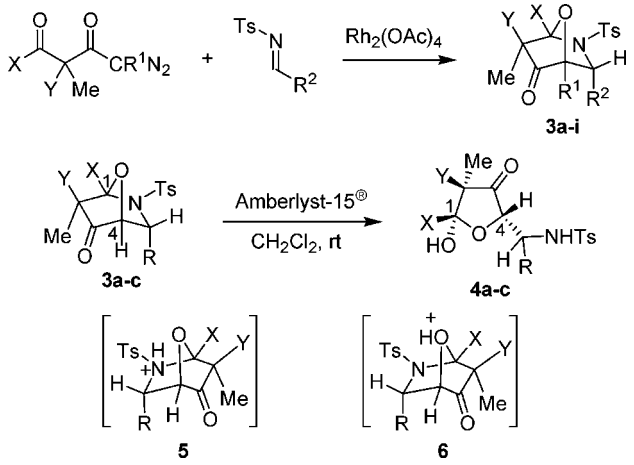
functionalized furanones, 2-aryldecahydroquinoline-3,4-diols, and 2-arylpiperidine-3,4-diols (iminosugars).

We were initially interested in studying the ring-opening reactions of the oxa-bridged piperidinones **3** using mild acids. The *endo* isomers of oxa-bridged piperidinone/fused piperidinone systems **3** were synthesized[3] via the 1,3-dipolar cycloaddition of rhodium(II) acetate to generate a 5-membered-ring carbonyl ylide with *N*-tosylimine. Further, the ring-opening reaction of oxa-bridged piperidinone **3** would provide three possible competitive ring openings via C_1-N, C_1-O, and/or C_4-O bonds. With this in view, the fused oxa-bridged piperidinone **3a** was treated with a solid matrix like Amberlyst-15 in dichloromethane to afford the product **4a** as a single diastereomer in 95% yield (Scheme 1, Table 1).

Scheme 1. Amberlyst-15 Mediated C_1-N Bond Cleavage of Oxa-Bridged Piperidinones **3**



The structure was characterized as hydroxy furanone **4a** on the basis of the spectral data. The proposed structure of **4a** was unequivocally corroborated on the basis of the single-crystal X-ray[5] analysis. The formation of product **4a** clearly indicates that the regioselective nucleophilic ring opening occurs at the C_1-N bond of oxa-bridged compound **3a**.

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(5) For ORTEP view of the compounds **4a** and **7a**, see the Supporting Information.

Table 1. Synthesis of Hydroxy Furanones **4**

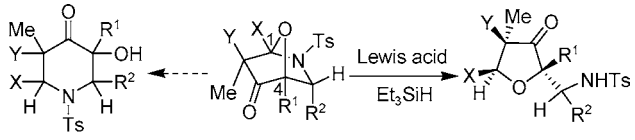
entry	R	X	Y	product **4**	yield[a] (%)
1	**3a**, C_6H_5	$-(CH_2)_4-$		**a**	95
2	**3b**, C_6H_5	CH_3	CH_3	**b**	87
3	**3c**, 4-FC_6H_4	$-(CH_2)_4-$		**c**	90

[a] Yields are unoptimized and refer to isolated yields.

Reaction of substituted/fused oxa-bridged piperidinones **3b**,**c** with Amberlyst-15 also furnished the functionalized hydroxy furanones **4b**,**c**, respectively. The reason for the selective cleavage at the C_1-N bond of **3a**−**c** may be due to the formation of tosylammonium ion **5** as an intermediate rather than oxonium ion **6** in the presence of an *N*-tosyl group, which subsequently hydrolyzed to yield hydroxy furanones **4**.

Successful ring-opening reactions of similar oxa-bridged piperidines were also reported[4h−k] using Lewis acids to yield the functionalized piperidine ring systems. To this end, we planned to perform the reactions of oxa-bridged piperidinones **3** with various Lewis acids. The initial study of the oxa-bridged piperidinone **3a** with $BF_3{\cdot}OEt_2$ led to decomposition. The above reaction was intended to perform in the presence of hydride nucleophile. Thus, the reaction of **3a**, Et_3SiH, and

Scheme 2. Lewis Acid Mediated C_1-N Bond Cleavage of Oxa-Bridged Piperidinones **3** in the Presence of Et_3SiH



$BF_3{\cdot}OEt_2$ afforded a single diastereomer **7a** in 85% yield (Scheme 2, Table 2, entry 1). The structure and stereochem-

Table 2. Synthesis of Substituted Furanones **7**

entry	R^2	Lewis acid	X	Y	product **7**	yield[a] (%)
1	**3a**, C_6H_5	$BF_3{\cdot}OEt_2$	$-(CH_2)_4-$		**a**	85
2	**3b**, C_6H_5	$BF_3{\cdot}OEt_2$	CH_3	CH_3	**b**	82
3	**3c**, 4-FC_6H_4	$BF_3{\cdot}OEt_2$	$-(CH_2)_4-$		**c**	89
4	**3d**, 4-FC_6H_4	$BF_3{\cdot}OEt_2$	CH_3	CH_3	**d**	88
5[b]	**3e**, C_6H_5	$BF_3{\cdot}OEt_2$	$-(CH_2)_4-$		**e**	75
6	**3f**, 4-MeC_6H_4	$BF_3{\cdot}OEt_2$	CH_3	CH_3	**f**	77
7	**3a**, C_6H_5	$SnCl_4$	$-(CH_2)_4-$		**a**	80
8	**3a**, C_6H_5	TBSOTf	$-(CH_2)_4-$		**a**	90
9	**3b**, C_6H_5	TBSOTf	CH_3	CH_3	**b**	92
10	**3a**, C_6H_5	$Cu(OTf)_2$	$-(CH_2)_4-$		**a**	95
11	**3a**, C_6H_5	$ZnBr_2$	$-(CH_2)_4-$		**a**	
12	**3a**, C_6H_5	$InCl_3$	$-(CH_2)_4-$		**a**	

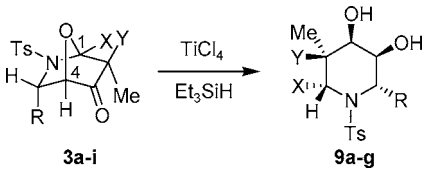
[a] Yields are unoptimized and refer to isolated pure compounds, and the substituent $R^1 = H$ for **7** except for entry 5. [b] $R^1 = COOEt$.

istry of furanone **7a** were characterized on the basis of spectral and single-crystal X-ray[5] analysis, which indicate the chemoselective reductive ring opening. Further, the reaction of oxa-bridged piperidinones **3b**−**f** under similar conditions afforded furanone derivatives **7b**−**f** (entries 2−6). In order to attain the piperidine ring system from oxa-bridged piperidinones **3**, a subsequent investigation was proposed to study other Lewis acids in the presence of Et_3SiH. Toward this end, the appropriate piperidinone **3a** was treated with tin(IV) chloride at 0 °C to furnish the furanone **7a** in 80% yield (entry 7). Reactions of **3a**,**b** with other Lewis acids such as TBSOTf and Cu(II) triflate afforded the respective furanones **7a**,**b** as single diastereomers in excellent yield (entries 8−10). In the above reactions, no detectable quantities of other possible products such as **8** via the ring opening at the C_1−O bond (Scheme 2) were observed.

Treatment of piperidinones **3** with other Lewis acids such as $ZnBr_2$ or $InCl_3$ was not successful. Contrary to the literature reports,[4h−k] the above reactions furnished the products via ring opening at the C_1−N bond of **3** instead of the C_1−O bond. Hence, we rationalized that the presence of the electron-withdrawing (tosyl) group tethered on the nitrogen atom of **3** favored the formation of tosylammonium ion **5**, which led to the selective cleavage at the C_1−N bond rather than the C_1−O bond (Scheme 2). The intermediate **6** is expected to be as stable as **5**. Further, the tertiary carbocation that results from the C_1−N heterolysis is expected to be more stable than the tosylaminium ion in order to furnish products **4** and **7**.

Subsequent investigation was carried out toward the synthesis of piperidinones **8** via the cleavage at the C_1−O bond of **3**. Thus, the fused oxa-bridged piperidinone **3a** on reaction with Et_3SiH in the presence of $TiCl_4$ as a Lewis acid at 0 °C afforded product **9a** in 63% yield as a single diastereomer (Scheme 3, Table 3). Interestingly, the spectral

Scheme 3. $TiCl_4$ Mediated C_1−O Bond Cleavage of Oxa-Bridged Piperidinone Systems



3a-i **9a-g**

analysis clearly confirmed the formation of piperidine skeleton **9a** via ring opening at the C_1−O bond. Notably, the spectral data of product **9a** indicate it to be a *cis*-diol. The stereochemistry of **9a** was further established by single-crystal X-ray crystallographic analysis[6] (Figure 2). It is

(6) Crystal data for the compound **9a**: $C_{23}H_{29}NO_4S$, $M = 415.54$, 0.23 × 0.14 × 0.10 mm^3, orthorhombic, space group *Pca*21 with $a = 13.841(9)$ Å, $b = 10.407(7)$ Å, $c = 28.006(18)$ Å, $\alpha = 90°$, $\beta = 90°$, $\gamma = 90°$, $V = 4034.4(5)$ Å^3, $T = 100(2)$ K, $R_1 = 0.0567$, w$R_2 = 0.1205$ on observed data, $z = 4$, $D_{calcd} = 1.368$ g cm^{-3}, $F(000) = 1776$, Absorption coefficient = 0.191 mm^{-1}, $\lambda = 0.71073$ Å, 23236 reflections were collected, 6924 observed reflections ($I \geq 2\sigma(I)$). The largest difference peak and hole = 0.578 and −0.341 e Å^{-3}, respectively.

Table 3. Synthesis of Functionalized *cis*-Decahydroquinoline-3,4-diols and *cis*-Piperidine-3,4-diols **9**

entry	R	X	Y	product **9**	yield[a] (%)
1	**3a**, C_6H_5	−$(CH_2)_4$−		**a**	63
2	**3g**, 3-FC_6H_4	−$(CH_2)_4$−		**b**	75
3	**3c**, 4-FC_6H_4	−$(CH_2)_4$−		**c**	70
4	**3h**, 3-FC_6H_4	CH_3	CH_3	**d**	71
5	**3i**, 3-BrC_6H_4	CH_3	CH_3	**e**	80
6	**3d**, 4-FC_6H_4	CH_3	CH_3	**f**	68
7	**3b**, C_6H_5	CH_3	CH_3	**g**	67

[a] Yields are unoptimized and refer to isolated pure compounds **9**.

important to note that there is no product formation via the cleavage at C_4-O bond. Similar reactions of the fused oxa-

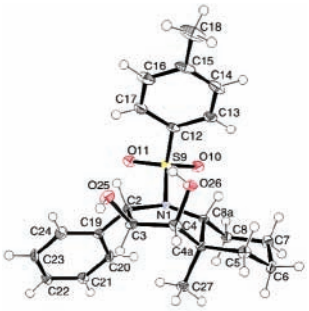
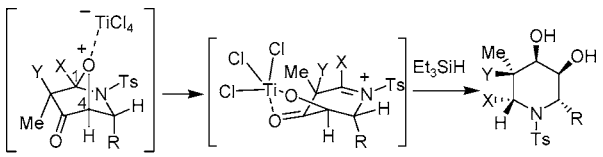


Figure 2. X-ray crystal structure of **9a**. There are two molecules in the asymmetric unit; only one is shown.

bridged piperidinones **3** furnished functionalized decahydroquinoline-3,4-diols **9b**,**c** as single diastereomers. Subsequent reaction of the piperidinone **3h** afforded the arylpiperidine-3,4-diol **9d** in 71% yield (entry 4). Further, 2-arylpiperidine-3,4-diol derivatives **9e**−**g** with *cis*-geometry were synthesized from the appropriate oxa-bridged piperidinones **3** (entries 5−7).

Mechanistically, titanium(IV) chloride would probably coordinate to the oxa-bridged oxygen atom[4o] forming an oxonium ion **10** rather than tosylammonium ion followed by the chemoselective ring opening of oxygen bridge produces tosyliminium ion **11**. The simultaneous hydride nucleophilic addition on imine as well as carbonyl group of **11** would lead to the desired stereoselective product **9** (Scheme 4).

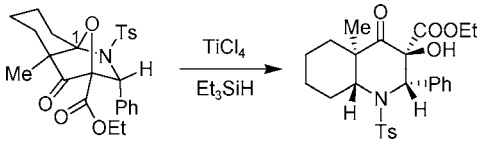
Scheme 4. Tentative Mechanistic Pathway of Ring Opening of Oxa-Bridged Piperidinone toward **9**



10 **11** **9**

The above reaction was performed on oxa-bridged piperidinone **3e** having an ester substituent led to the monohydroxy piperidinone **12**. It is observed that the keto group of **3e** is intact under the similar experimental conditions. This may be due to the absence of titanium metal coordination with carbonyl group when the substrate has an ester substituent (Scheme 5).

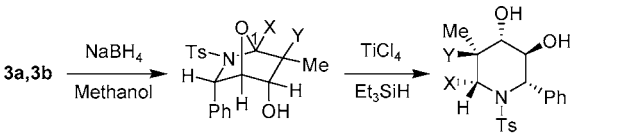
Scheme 5. Oxa-Bridge Ring Opening of an Ester-Substituted Piperidinone **3e**



3e **12**

Further, we considered synthesizing the product **9** with *trans*-diol stereochemistry. To this end, the fused oxa-bridged piperidinone **3a** was reduced with $NaBH_4$ in methanol. The desired *endo*-alcohol **13** was obtained in 75% yield along with furanone **7a** in 15% yield (Scheme 6). The *endo*-alcohol

Scheme 6. Synthesis of Functionalized *trans*-Decahydroquinoline-3,4-diol and *trans*-Piperidine-3,4-diol



Major diastereomer
13: X, Y = $-(CH_2)_4-$
15: X, Y = CH_3

14: X, Y = $-(CH_2)_4-$ (72%)
16: X, Y = CH_3 (76%)

13 was treated with $TiCl_4$ in the presence of Et_3SiH to afford *trans*-diol **14** in good yield.

The reductive ring opening at C_1-O bond of an *endo*-alcohol **13** will tend to furnish the *trans*-diol stereochemistry. The presence of *trans*-diol geometry in piperidine **14** was also established by the single-crystal X-ray crystallographic analysis[7] (Figure 3). Similar reaction of oxa-bridged piperidinone **3b** furnished *trans*-diol **16**. In the above reactions, the ratio of compound **3**/Lewis acid is 1:2. Even in the presence of an excess amount of Lewis acid reaction afforded

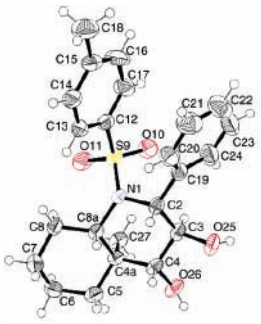


Figure 3. X-ray crystal structure of **14**. There are two molecules in the asymmetric unit; only one is shown.

the same above products. Thus, the chemoselectivity is not dependent on the ratio of substrate/Lewis acid used in the present study.

In conclusion, we have demonstrated the Lewis acid mediated regio- and chemoselective reductive ring-opening reactions of oxa-bridged piperidinone ring systems. A majority of the Lewis acids yielded the selective ring opening at the C−N bond, whereas $TiCl_4$ yielded the reductive ring opening at the C−O bond of oxa-bridged piperidinone **3** in the presence of triethylsilane affording functionalized furanones and dihydroxypiperidines, respectively. Further, this methodology is highly useful to synthesize *cis*- as well as *trans*-dihydroxypiperidines. The synthesis of iminosugars using this methodology and detailed mechanistic studies are in progress.

Acknowledgment. This research was supported by DST, New Delhi. J.K. thanks CSIR, New Delhi, for a fellowship.

Supporting Information Available: Experimental procedures, spectral data for all new compounds, copies of spectra for the products, and X-ray structural data for compounds **4a**, **7a**, **9a**, and **14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) Crystal data for the compound **14**: $C_{23}H_{29}NO_4S$, $M = 415.54$, 0.22 × 0.12 × 0.06 mm^3, monoclinic, space group $P21/n$ with $a = 12.0025(12)$ Å, $b = 10.0400(10)$ Å, $c = 35.627(4)$ Å, $\alpha = 90°$, $\beta = 94.042(2)°$, $\gamma = 90°$, $V = 4282.6(7)$ $Å^3$, $T = 296(2)$ K, $R_1 = 0.0638$, w$R_2 = 0.1504$ on observed data, $z = 4$, $D_{calcd} = 1.317$ g cm^{-3}, $F(000) = 1816$, absorption coefficient = 0.183 mm^{-1}, $\lambda = 0.71073$ Å, 20861 reflections were collected, 7509 observed reflections ($I \geq 2\sigma(I)$). The largest difference peak and hole = 0.353 and −0.356 e $Å^{-3}$, respectively. The structures were solved by direct methods and refined by full-matrix least squares on F^2 using SHELXL-97 software.