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Stereoselective synthesis of piperidinone and quinolinone systems via ring opening reactions using $TiCl_4$/silyl reagents

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ABSTRACT

Titanium(IV) chloride and silyl reagents mediated regio- and chemoselective ring opening reactions of oxa-bridged piperidinone ring systems were demonstrated. This methodology interestingly undergoes the stereoselective ring opening at the C–O bond of oxa-bridged piperidinone ring systems. Study of $TiCl_4$ with hydride or non-hydride silyl reagents furnished the product with selectivity. This protocol is highly valuable to synthesize a range of stereoselective piperidinones, quinolinones ring systems.

1. Introduction

The ring opening reaction of oxabicyclic or dioxabicyclic compounds led to synthetically useful intermediates toward a range of carbo- as well as heterocycles, which can readily be maneuvered to furnish natural/unnatural molecules.[1,2] These oxa-bridged carbo- or heterocyclic systems can easily be assembled via [1,3]-dipolar cycloaddition of the rhodium(II) generated carbonyl ylides with C=O, C=C, C≡C or C=N groups as dipolarophiles.[1–3] Interestingly, synthesis[4] of oxazabicyclic systems and their ring opening reactions[5] have been reported by us to afford the functionalized piperidines. Iminosugars are polyhydroxylated aza-heterocycles that they show a wide range of biological activities.[6] For example, polyhydroxylated piperidine derivatives (Fig. 1), such as 1-deoxyfuconojirimycin **1**, 1-deoxymannojirimycin **2**, and fagomine **3** are useful to inhibit glycosidase enzymes and possess biological applications.[7] *N*-Hydroxyethyl-DNJ (Miglitol **4**) has been approved as medicine for a wide range of diseases.[7e] The survey of literature reveals that there are many reports available on ring opening reactions of oxa-bridged systems, such as transition metal-catalyzed asymmetric ring opening reactions of oxa- and azabicyclic alkenes,[8a–d] SmI_2-mediated ring opening of oxanorbornane systems,[8e–g] Lewis acids mediated ring opening reactions of oxa-bridged piperidinones,[1h,2b,8h–k] base-mediated ring opening reactions,[1j] and $TiCl_4$-promoted ring opening reaction of oxanorbornenes.[8l,m] The silyl reagents, such as trimethylsilyl cyanide and allyltrimethylsilane are known to act as nucleophiles,[9a,b] for example, nucleophilic additions to cyclic oxocarbenium ions and ring opening reactions of bicyclic lactams.[9c] In the continuation our interest[5] on the ring opening reaction, we herein report the stereoselective synthesis of piperidinones and quinolinones via the ring opening reaction of oxa-bridged piperidines using $TiCl_4$/silyl reagents.

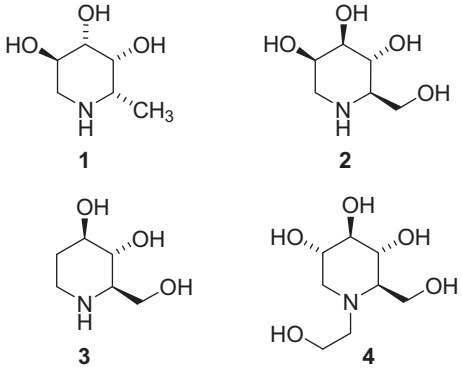

Fig. 1. Structure of 1-deoxyfuconojirimycin (**1**), 1-deoxymannojirimycin (**2**), fagomine (**3**), miglitol (**4**).

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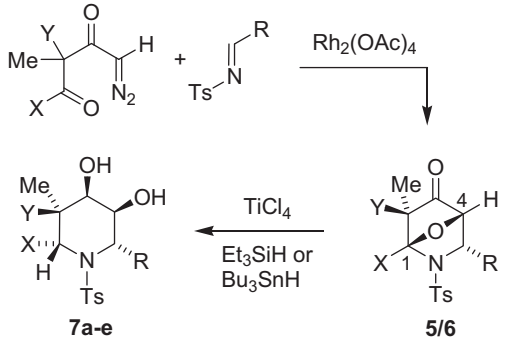
2. Results and discussion

Initially, we were interested in studying the ring opening reactions of the oxa-bridged piperidinones **5**/**6** using $TiCl_4$ and silyl hydrides. The *endo* isomers of oxa-bridged piperidinone/fused piperidinone systems **5**/**6** were synthesized[4] via the 1,3-dipolar cycloaddition of five-membered-ring carbonyl ylide with *N*-tosylimine. Subsequent investigation of the oxa-bridged piperidinones **5**/**6** on reaction with titanium(IV) chloride and Et_3SiH afforded[5] compounds **7** as a single diastereomer via reductive ring opening reaction at the C_1–O bond (Scheme 1). There is no product formation via the cleavage at the C_4–O bond. Based on this protocol, the synthesis of *cis*-diol or *trans*-diol of piperidines **7** was successfully demonstrated. To study the effect of other hydride sources, the reaction was planned using Bu_3SnH. Toward this, the reaction of oxa-bridged piperidinone **5a** with $TiCl_4$ and Bu_3SnH was performed to furnish ring opened product **7a** in 48% yield (Table 1). The product was characterized as *cis*-diol stereochemistry based on the interrelated spectroscopic analyses. Reaction of oxa-bridged piperidinones **5b**,**c** under the above conditions afforded the corresponding 2-arylpiperidin-3,4-diol derivatives **7b**,**c**. Similarly, decahydroquinoline-3,4-diol derivatives **7d**,**e** were obtained from the corresponding fused oxa-bridged piperidinones **6a**,**b**. The yield of the products **7** obtained via Bu_3SnH is relatively less compared to reactions using Et_3SiH. The reason may be Et_3SiH reagent is better hydride source than Bu_3SnH. The initial study of the oxa-bridged piperidinone **6c** with $TiCl_4$ alone led to decomposition.



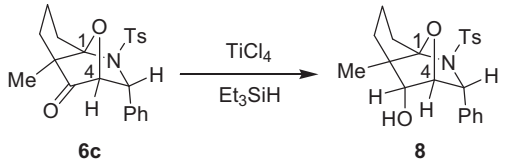
Scheme 1.

Table 1
Synthesis of functionalized piperidinediols/quinolinediols **7**

Entry	R	X	Y	Product **7**	Yield[a] %	
					Et_3SiH	Bu_3SnH
1	**5a** C_6H_5	CH_3	CH_3	**a**	67	48
2	**5b** 3-FC_6H_4	CH_3	CH_3	**b**	71	50
3	**5c** 3-BrC_6H_4	CH_3	CH_3	**c**	80	56
4	**6a** C_6H_5	$-(CH_2)_4-$		**d**	63	41
5	**6b** 3-FC_6H_4	$-(CH_2)_4-$		**e**	75	46

[a] Yields (unoptimized) refer to isolated pure compounds **7**.

The ring opening reaction of cyclopentane fused piperidine **6c** was carried out in the presence of $TiCl_4$ and triethylsilane to afford the corresponding reduction product **8** (Scheme 2). This result indicates that the reduction of keto group present on **6c** took place,



Scheme 2.

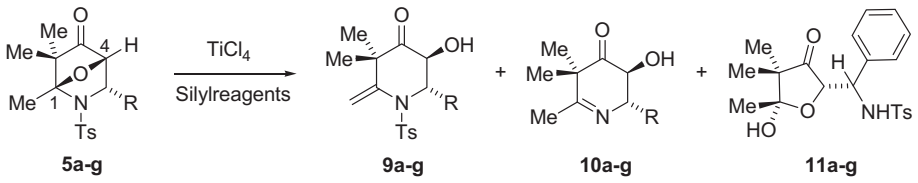
whereas the ring opening at the C_1–O was not observed even at reflux conditions.

Based on the above strategy, further efforts were made to study the effect of non-hydride silyl reagents on ring opening reactions of oxa-bridged ring systems. Thus, non-hydride silyl reagents, such as allyl(trimethyl)silane, ethynyltrimethylsilane, trimethyl(prop-1-ynyl)silane, (trimethylsilyl)acetonitrile, and *tert*-butyldimethylsilyl cyanide were chosen for this study. The ring opening reaction of compound **5a** was carried out with equimolar amount of $TiCl_4$ and allyl(trimethyl)silane to afford a mixture of products **9a**/**10a** (Scheme 3, Table 2, entry 1) in the ratio of 2:1 (based on the crude NMR data). The formation of major product methylenepiperidinone **9a** bearing *N*-tosyl substituent was confirmed based on the characteristic resonance signals at 5.29 and 5.37 ppm; for the each geminal proton attached on the *exo*-cyclic olefin in the ^1H NMR spectrum. The presence of *N*-tosyl substituent in compound **9a** was confirmed based on the characteristic resonance signal at 2.30 ppm for a methyl group. The structure of minor product dihydropyridinone **10a** was established based on the interrelated NMR spectral data, where the absence of a characteristic resonance signal at 2.30 ppm for a methyl group confirmed the oxa-bridge opening followed by clean N-deprotection of compound **5a**. Further, the reaction of oxa-bridged piperidinones **5b**–**f** under similar reaction conditions afforded methylenepiperidinones **9b**–**f** and dihydropyridinones **10b**–**f** as a mixture of products in the ratio of 2:1 (Table 2, entries 2–6). Reaction of **5g** with $TiCl_4$ and allyl(trimethyl) silane afforded only α-methylenepiperidinone **9g** with a trace amount of dihydropyridinone **10g** (entry 7). The structures of compounds **9**,**10** have evidently been characterized based on their interrelated spectral data. The proposed structures of **9**/**10** were unequivocally corroborated based on the representative single-crystal X-ray analyses of **9f** (Fig. 2) and **10f** (Fig. 3). The related piperidine systems of compounds **9**,**10** are known to have a core unit of many azasugars[6,7] and building blocks for many natural and non-natural products.[10]

This interesting observation encouraged us to investigate the selectivity of products **9**/**10**. To this end, we planned to use ethynyltrimethylsilane reagent in the above ring opening reactions. Consequently, reaction of oxa-bridged piperidinone **5a** was performed using $TiCl_4$ and ethynyltrimethylsilane to afford dihydropyridinone **10a** as a single product (Scheme 3, Table 2). This notable result led to investigate the reaction of other oxa-bridged systems **5b**–**f** as described above, furnishing dihydropyridinones **10b**–**f** in good yields (Table 2, entries 2–6). The reaction of oxa-bridged system having 2-bromophenyl substituent **5f** was found to provide more yield of the corresponding dihydropyridinones.

As a part of our ongoing interest in the stereoselective ring opening reaction, we envisioned the use of a range of silyl reagents as nucleophiles that might permit easy access to these two different piperidines **9**/**10** in a selective manner. As a result, we were curious to accomplish the selective product of methylenepiperidinones **9** from compound **5**. Thus, ring opening reaction of **5a** was carried out with equimolar amounts of $TiCl_4$ and trimethyl(prop-1-ynyl)silane to afford a mixture of two products in the ratio of 1:11. The major product was characterized as methylenepiperidinone **9a** and the minor product[5] as hydroxyfuranone **11a** (Scheme 3, Table 2). This reaction surprisingly has not produced the *N*-deprotected dihydropyridinone **10a**. Reactions of oxa-bridged piperidinones **5b**,**d**,**e** under similar conditions afforded the respective methylenepiperidinones **9b**,**d**,**e** with high selectivity. Attempts to test the selectivity of product **9** using other silyl nucleophiles, such as (trimethylsilyl)acetonitrile and *tert*-butyldimethylsilyl cyanide were unsuccessful.

We could not isolate any product arising from the reaction of **5** and $TiCl_4$ in the absence of silyl compound. Thus, the interesting role of silyl reagent may be obvious to explain the reaction



Scheme 3.

Table 2
Synthesis of piperidinones **9**, dihydropyridinones **10** and methylenepiperidinones **11**

Entry	R	Product	Yield[a] %								
			Allyltrimethylsilane			Ethynyltrimethylsilane			Trimethyl(prop-1-ynyl)silane		
			9	**10**	**11**	**9**	**10**	**11**	**9**	**10**	**11**
1	**5a** C_6H_5	**a**	43	30	—	—	68	—	55	—	5
2	**5b** 3-FC_6H_4	**b**	45	30	—	—	64	—	63	—	Trace
3	**5c** 3-BrC_6H_4	**c**	47	35	—	—	70	—	—	—	—
4	**5d** 4-FC_6H_4	**d**	42	28	—	—	60	—	68	—	Trace
5	**5e** 2-ClC_6H_4	**e**	52	38	—	—	73	—	71	—	—
6	**5f** 2-BrC_6H_4	**f**	54	42	—	—	79	—	—	—	—
7	**5g**-MeC_6H_4	**g**	40	Trace							

[a] Yields (unoptimized) refer to isolated pure compounds **9**, **10** and **11**.

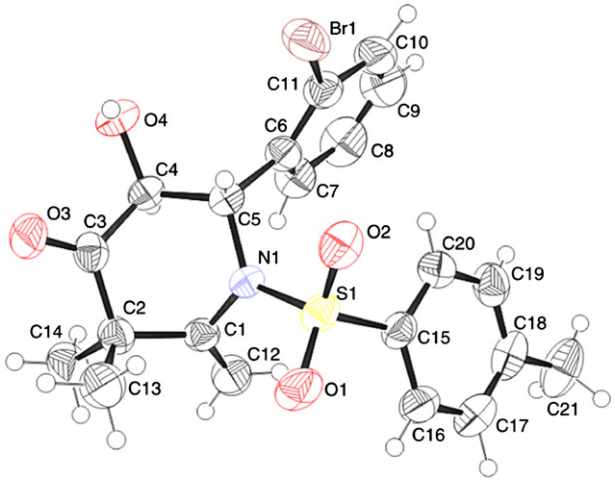


Fig. 2. ORTEP view of compound **9f**.

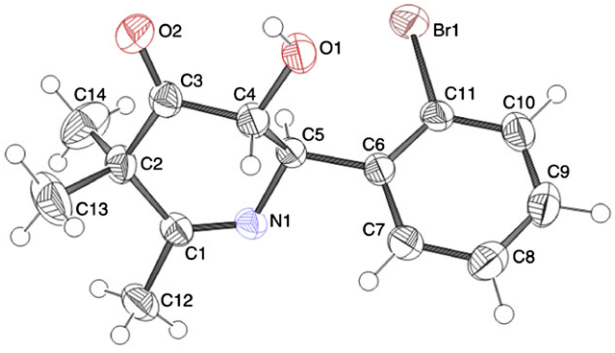
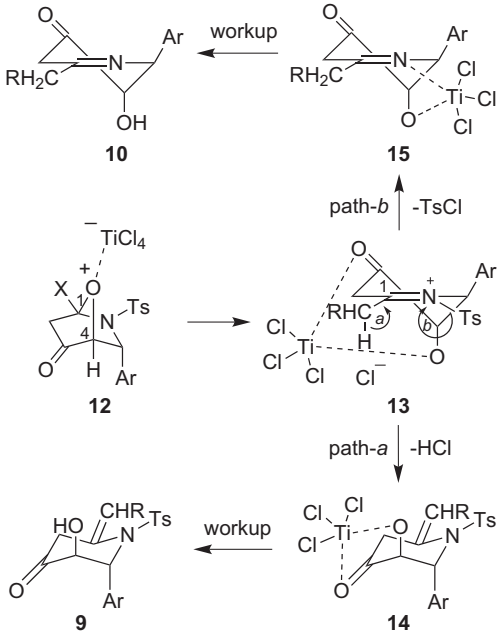


Fig. 3. ORTEP view of compound **10f**.

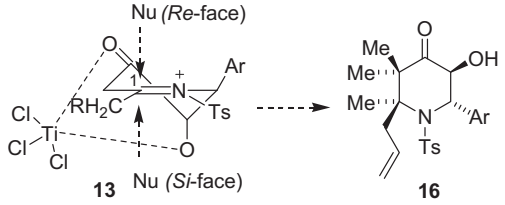
mechanism of these reactions. Mechanistically, the formation of *exo*-cyclic olefin products **9** was clearly confirmed that the titanium(IV) chloride would probably coordinate initially to oxygen atom of oxa-bridged piperidinone due to more oxophilicity of titanium metal forming an oxonium ion **12** followed by the chemoselective ring opening of oxygen bridge produces tosyliminium ion **13** (Scheme 4). The *N*-tosyliminium ion is neutralized by the formation of α-methylene group via proton elimination. The proton elimination is activated by free chloride ion as shown in **13**. The proton abstraction might be the deciding factor for the formation of the selective product **9**. To understand the role of silyl nucleophile with free chloride ion is mechanistically complex, but we can tentatively reason that the nucleophilicity factor of silyl reagent leads to the desired product. We also found that triethylsilane played a role of nucleophile to reduce the *N*-tosyliminium ion (Table 1). Notably, the reaction of oxa-bridged piperidinones **5** with $TiCl_4$ and allyl(trimethyl)silane furnished a mixture of products. However, the silyl nucleophile, such as trimethyl(prop-1-ynyl) silane favors the ring opening followed by proton elimination of **13** (path a) to afford the selective product **9** via **14**. On the other hand, the reaction with ethynyltrimethylsilane directs to ring opening followed by detosylation might produce **15** (path b) to yield the selective product **10**. The steric hindrance (adjacent



Scheme 4.

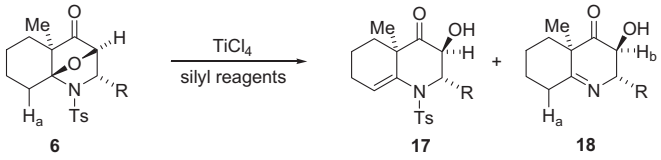
quaternary stereocentre to iminium ion **13**) is also presumably an important retarding factor. An alternative explanation may be that the different organosilicon additives, which direct the partitioning by directly reacting with the intermediate iminium, instead of chloride ion.

Alternatively, there was no observation of product, such as **16**, which normally obtained when 2-hydroxy or alkoxypiperidines were treated with $TiCl_4$ and allyl(trimethyl)silane.[9] We reasoned that both faces (*Re* or *Si*) of *N*-tosyliminium ion intermediate **13** might be hindered by *N*-tosyl part as well as titanium complex, thus diminishing the attack of silyl nucleophile on iminium ion (Scheme 5).



Scheme 5.

In continuation of the above ring opening reaction, studies were extended to synthesize functionalized quinolines. Toward this, reaction of compound **6a** was carried out with $TiCl_4$ and allyl(trimethyl)silane to afford a mixture of quinolines **17a**,**18a** in the ratio of 1:2 (Scheme 6, Table 3). ^{1}H NMR spectrum of the major product **18a** showed the absence of tosyl CH_3 group. Furthermore, ^{13}C NMR and DEPT-135 experiments disclosed the presence of characteristic quaternary carbon (C_1) at 175.5 ppm and a C–H_b signal at 71.7 ppm, which confirm the formation of imine bond of **18a**. All other data were in good agreement with the assigned structure. The ratio of compounds **17a**,**18a** got reversed when compared to the similar reaction as shown in Table 2 for products **9**,**10**. It might be reasoned that the elimination of proton in intermediate **13** is less favored than N–Ts bond cleavage. Extension of this interesting strategy with the substrate **6d** also furnished the corresponding ring opened products **17b** and **18b** in moderate yields (Table 3). The structure of minor product **17b**, which contains a bridgehead olefin in the bicyclic unit, was unequivocally confirmed by the single-crystal X-ray structure analysis (Fig. 4).



Scheme 6.

After investigating the ring opening reaction of fused epoxy-bridged systems using $TiCl_4$ and ethynyltrimethylsilane as a nucleophile, the product selectivity of **17**,**18** was aimed. To this end, the ring opening reactions of **6** were performed using $TiCl_4$ and ethynyltrimethylsilane to furnish only the N–Ts bond cleavage products **18a**–**d** (Scheme 6, Table 3). To our delight, this strategy proved to be beneficial for the product selectivity via ring opening of **6**.

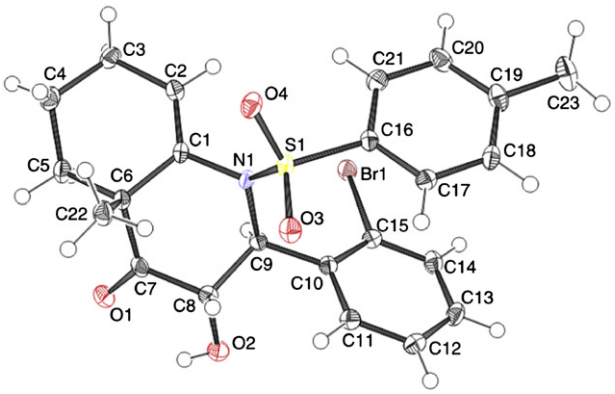
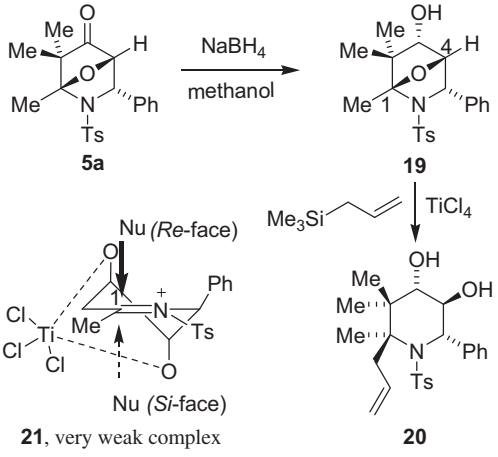


Fig. 4. ORTEP view of compound **17b**.

Next, we attempted the ring opening reaction of **6a** with $TiCl_4$ and trimethyl(prop-1-ynyl)silane for the selectivity of product **17**. In this case, we were unable to obtain the better selectivity, instead a mixture of products **17a**,**18a** were obtained (Scheme 6).

Finally, the ring opening reaction of alcohols **19**,**22** derived from the respective oxa-bridged piperidinones **5a**,**6a** was studied. The *endo*-alcohol **19** was obtained as described in the literature[5] by reducing the oxa-bridged piperidinone **5a** with $NaBH_4$. The *endo*-alcohol **19** was treated with $TiCl_4$ and allyl(trimethyl)silane to furnish **20** in good yield (Scheme 7). Interestingly, the NMR analysis of product **20** revealed the formation of *trans*-diol having allyl substituent. Based on this result, a possible reaction mechanism rationalizing the formation of allyl product **20** during the addition of allyltrimethylsilane to *N*-tosyliminium ion **13** as depicted in Scheme 5. The allyl anion might react with *N*-tosyliminium ion **21** via *Re*-face addition due to weak Ti-complexation with 1,2-diaxial hydroxyl groups.



Scheme 7.

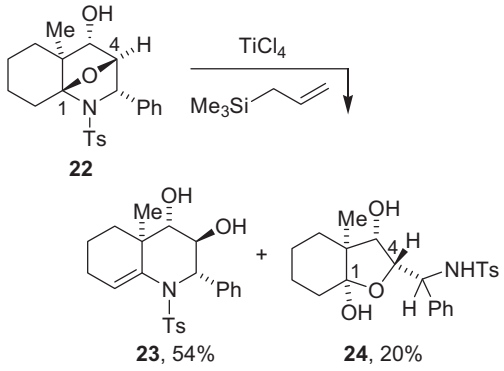
After the reduction of carbonyl group in **5a**, the steric hindrance arising from the proximity of Ti-complex, which coordinated with two oxygen atoms as shown in **21**, may be spatially allowing the

Table 3
Synthesis of 3-hydroxyquinolinones **17** and **18**

Entry	R	Product	Yield[a] %					
			Allyltrimethylsilane		Ethynyltrimethylsilane		Trimethyl(prop-1-ynyl)silane	
			17	**18**	**17**	**18**	**17**	**18**
1	**6a**[4] C_6H_5	**a**	22	45	—	64	31	28
2	**6d** 2-BrC_6H_4	**b**	25	54	—	81	—	—
3	**6e**[4] 4-FC_6H_4	**c**	—	—	—	68	—	—
4	**6f** 2-ClC_6H_4	**d**	—	—	—	76	—	—

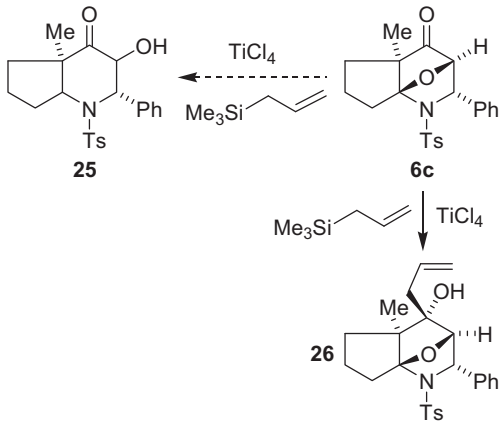
[a] Yields (unoptimized) refer to isolated pure compounds **17** and **18**.

nucleophilic attack upon the less hindered *Re*-face. Similarly, the *endo*-alcohol **22** was then investigated using $TiCl_4$ and allyltrimethylsilane to afford a mixture of products **23**,**24** (Scheme 8). These products were characterized based on their interrelated spectroscopic analyses. The formation of major product **23** may be explained by the ring opening followed by proton elimination. The minor product formation can be attributed by the ring opening at the C–N bond. This may be due to the strong coordination of two hydroxyl groups with Ti-metal and tend not to allow the intermediate **13** as depicted in Scheme 5. The hydrolysis of *N*-tosyliminium intermediate type **13** led to minor product **24**. In this case, the addition product of allyl nucleophile was not observed. This may be reasoned that the *Re*-face in **21** might be sterically hindered due to the proximity of fused cyclohexane ring (when X,Y=$-(CH_2)_4-$).



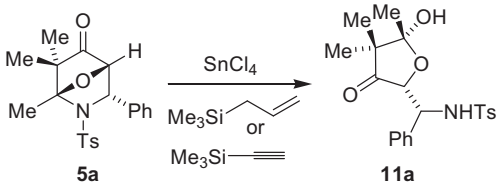
Scheme 8.

The present protocol was extended to cyclopentane fused oxa-bridged system using trimethyl(allyl)silane reagent. We expected the formation of ring opened product **25**, but the product **26** produced by the nucleophilic addition on carbonyl functionality of **6c** (Scheme 9). The reason may be due to the rigidity of cyclopentane and tend not to allow the Ti-metal to make coordination with oxa-bridge oxygen atom. Further treatment of **6c** with $SnCl_4$ and silyl nucleophiles led to the decomposition of starting material ^1H NMR shows unidentified junk products.



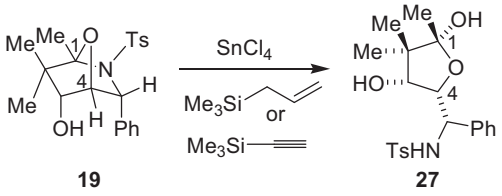
Scheme 9.

Ring opening reaction of oxa-bridged piperidinone **5a** was carried out with tin(IV) chloride and trimethyl(allyl)silane in dichloromethane to afford the product **11a** as a single diastereomer in 85% yield (Scheme 10). Similarly, reaction with trimethyl(silyl) acetylene also afforded the same product **11a** in good yield. This observation showed that the similar results were also obtained when mild acid, such as Amberlyts-15 treated[5] with oxa-bridged systems **5**/**6**.



Scheme 10.

The *endo*-alcohol **19** was also subjected to study the ring opening reaction with $SnCl_4$ and silyl nucleophiles. Reaction between **19** and $SnCl_4$ in the presence of either trimethyl(silyl)acetylene or trimethyl(allyl)silane afforded the furan product **27** via the ring opening of **19** at the C–N bond (Scheme 11).



Scheme 11.

3. Conclusion

In summary, titanium(IV) chloride, and silyl reagents mediated regio- and chemoselective ring opening reactions of oxa-bridged piperidinone ring systems were demonstrated. This methodology interestingly undergoes the reductive ring opening at the selective C–O bond of oxa-bridged piperidinone ring systems. Use of $TiCl_4$ and non-hydride silyl reagents on the ring opening reaction protocol is highly valuable to synthesize a range of functionalized piperidines, quinolines, furanose, and epoxycyclopentapyridinol systems, which are bearing the skeleton of azasugars.

4. Experimental section

4.1. General

All reactions were carried out in oven-dried glassware under an atmosphere of argon. Dry dichloromethane (dried over phosphorous pentoxide) has freshly been prepared for every reaction. Analytical thin layer chromatography (TLC) was performed on alumina plates and components were visualized by observation under iodine, sulfuric acid charring or UV-Light. Column chromatography was performed on a silica gel (100–200 mesh) column. The melting points are uncorrected. The FT-IR spectra were recorded using KBr method. ^1H NMR and ^{13}C NMR spectra (200 MHz and 50.3 MHz, respectively) were referenced to TMS. Multiplicities are indicated by singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m). Coupling constants (*J*) were reported in hertz (Hz). Carbon types were determined from DEPT ^{13}C NMR experiments. Mass spectra were determined on a high resolution liquid chromatography/mass spectrometer with ESI method on a Waters QTof-micro mass spectrometer.

4.2. Typical procedure for the synthesis of oxa-bridged heterocyclic compounds 5 and 6

In an oven-dried flask, a solution containing the appropriate *N*-tosylimine (1 mmol) and rhodium(II) acetate dimer (1.0 mol %) in

anhydrous CH_2Cl_2 (dried over phosphorous pentoxide) was degassed under argon. To this reaction mixture, a solution of the appropriate α-diazo ketone (1.2 mmol) in anhydrous CH_2Cl_2 was added very slowly over a period of 2 h. The progress of the reaction was monitored by TLC. The solvent was removed under reduced pressure and the resulting residue was purified by column chromatography (neutral alumina, hexane/EtOAc) to afford oxa-bridged piperidinone ring systems **5**/**6**.

*4.2.1. 1,6,6-Trimethyl-3-phenyl-2-(toluene-4-sulfonyl)-7-oxa-2-aza-bicyclo[2.2.1]heptan-5-one (**5a**).* Colorless solid, yield: 330 mg (74%); mp 136–138 °C (chloroform/hexane). ν_{max} (KBr)/cm^{-1} 2974, 1770, 1350, 1166, 1137, 685, 577. ^1H NMR (300 MHz, $CDCl_3$) δ 1.09 (s, 3H), 1.39 (s, 3H), 1.89 (s, 3H), 2.39 (s, 3H), 4.56 (d, 1H, J=5.1 Hz), 4.99 (d, 1H, J=5.1 Hz), 7.29–7.17 (m, 7H), 7.70 (d, 2H, J=8.4 Hz). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 14.4, 17.8, 21.4, 21.8, 55.6, 66.9, 84.0, 105.9, 127.1, 127.9, 128.1, 129.5, 133.5, 138.2, 144.0, 211.0. HRMS (ESI) for $C_{21}H_{23}NO_4S$ [(M+Na)$^+$] calcd 408.1245, found 408.1264.

*4.2.2. 3-(3-Fluoro-phenyl)-1,6,6-trimethyl-2-(toluene-4-sulfonyl)-7-oxa-2-aza-bicyclo[2.2.1]heptan-5-one (**5b**).* Colorless solid, yield: 288 mg (66%); mp 125–127 °C (chloroform/hexane). ν_{max} (KBr)/cm^{-1} 1767, 1594, 1453, 1322, 1153, 1136, 1090, 867, 689, 576. ^1H NMR (300 MHz, $CDCl_3$) δ 1.05 (s, 3H, CH_3), 1.34 (s, 3H, CH_3), 1.85 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 4.56 (d, 1H, J=5.0 Hz, CH), 5.00 (d, 1H, J=5.0 Hz, CH), 7.00–6.87 (m, 3H, ArH), 7.23–7.14 (m, 3H, ArH), 7.68 (d, 2H, J=8.2 Hz, ArH). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 14.1 (*C*H_3), 17.5 (*C*H_3), 21.2 (*C*H_3), 21.6 (*C*H_3), 55.4 (*quat-C*), 66.1 (CH), 83.6 (CH), 105.9 (*quat-C*), 113.9 (*C*H), 114.4 (*C*H), 114.9 (*C*H), 122.7 (*C*H), 127.9 (*C*H), 129.5 (*C*H), 129.6 (*C*H), 135.9 (*quat-C*), 136.2 (*quat-C*), 136.3 (*quat-C*), 144.1 (*quat-C*), 159.6 (*quat-C*), 164.5 (*quat-C*), 210.7 (*C*=O). HRMS (ESI) for $C_{21}H_{22}FNO_4S$ [(M+Na)$^+$] calcd 426.1151, found 426.1167.

*4.2.3. 3-(3-Bromo-phenyl)-1,6,6-trimethyl-2-(toluene-4-sulfonyl)-7-oxa-2-aza-bicyclo[2.2.1]heptan-5-one (**5c**).* Colorless solid, yield: 327 mg (60%); mp 177–179 °C (chloroform/hexane). 2945, 1757, 1510, 1452, 1345, 1233, 1159, 1080, 699, 554. ^1H NMR (300 MHz, $CDCl_3$) δ 0.87 (s, 3H), 1.35 (s, 3H), 1.89 (s, 3H), 2.35 (s, 3H), 4.55 (d, 1H, J=5.0 Hz), 4.94 (d, 1H, J=5.0 Hz), 7.34–7.08 (m, 6H), 7.66 (d, 2H, J=8.2 Hz). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 14.3, 17.6, 21.3, 21.6, 55.6, 66.1, 83.7, 106.1, 122.0, 125.7, 128.0, 129.5, 130.1, 130.8, 135.8, 144.2, 210.8. HRMS (ESI) for $C_{21}H_{22}BrNO_4S$ [(M+Na)$^+$] calcd 486.0351, found 486.0358.

*4.2.4. 3-(4-Fluoro-phenyl)-1,6,6-trimethyl-2-(toluene-4-sulfonyl)-7-oxa-2-aza-bicyclo[2.2.1]heptan-5-one (**5d**).* Colorless solid, yield: 436 mg (64%); mp 159–161 °C (chloroform/hexane). ν_{max} (KBr)/cm^{-1} 2991, 1767, 1511, 1349, 1165, 1135, 1088, 822, 686, 577. ^1H NMR (300 MHz, $CDCl_3$) δ 1.08 (s, 3H), 1.36 (s, 3H), 1.88 (s, 3H), 2.39 (s, 3H), 4.53 (d, 1H, J=5.0 Hz), 4.96 (d, 1H, J=5.0 Hz), 6.99–6.90 (m, 2H), 7.27–7.13 (m, 4H), 7.68 (d, 2H, J=8.4 Hz). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 14.4, 17.8, 21.4, 21.8, 55.8, 66.3, 84.0, 106.1, 114.9, 115.4, 128.1, 128.8, 129.0, 129.6, 136.2, 144.2, 159.8, 164.8, 211.1. HRMS (ESI) for $C_{21}H_{22}FNO_4S$ [(M+Na)$^+$] calcd 426.1151, found 426.1154.

*4.2.5. 3-(2-Chloro-phenyl)-1,6,6-trimethyl-2-(toluene-4-sulfonyl)-7-oxa-2-aza-bicyclo[2.2.1]heptan-5-one (**5e**).* Colorless solid, yield: 212 mg (74%); mp 164–166 °C (chloroform/hexane). ν_{max} (KBr)/cm^{-1} 2944, 1765, 1512, 1448, 1344, 1230, 1154, 1095, 688, 540. ^1H NMR ($CDCl_3$, 200 MHz) δ 1.07 (s, 3H), 1.40 (s, 3H), 1.90 (s, 3H), 2.36 (s, 3H), 4.82 (d, 1H, J=4.8 Hz), 5.37 (d, 1H, J=4.8 Hz), 7.40–7.14 (m, 6H), 7.72 (d, 2H, J=8.2 Hz). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 14.7, 18.1, 22.0, 22.4, 56.2, 65.1, 82.6, 106.6, 126.9, 128.8, 129.7, 129.9, 130.0, 130.3, 131.8, 132.7, 144.9, 211.7. HRMS (ESI) for $C_{21}H_{22}ClNO_4S$ [(M+Na)$^+$] calcd 442.0856, found 442.0874.

*4.2.6. 3-(2-Bromo-phenyl)-1,6,6-trimethyl-2-(toluene-4-sulfonyl)-7-oxa-2-aza-bicyclo[2.2.1]heptan-5-one (**5f**).* Colorless solid, yield: 332 mg (81%); mp 179–181 °C (chloroform/hexane). ν_{max} (KBr)/cm^{-1} 2954, 1761, 1510, 1451, 1345, 1227, 1158, 1076, 692, 554. ^1H NMR ($CDCl_3$, 200 MHz) δ 1.08 (s, 3H), 1.42 (s, 3H), 1.90 (s, 3H), 2.36 (s, 3H), 4.83 (d, 1H, J=4.8 Hz), 5.32 (d, 1H, J=4.8 Hz), 7.20–7.08 (m, 2H), 7.35–7.23 (m, 3H), 7.49–7.45 (m, 1H), 7.72 (d, 2H, J=8.2 Hz). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 14.8, 18.1, 22.0, 22.4, 56.4, 67.4, 82.6, 106.8, 122.9, 127.5, 128.8, 130.2, 130.0, 130.3, 133.2, 136.2, 144.9, 211.7. HRMS (ESI) for $C_{21}H_{22}BrNO_4S$ [(M+Na)$^+$] calcd 486.0351, found 486.0369.

*4.2.7. 1,6,6-Trimethyl-2-(toluene-4-sulfonyl)-3-p-tolyl-7-oxa-2-aza-bicyclo[2.2.1]heptan-5-one (**5g**).* Colorless solid, yield: 183 mg (62%); mp 115–117 °C (chloroform/hexane). ^1H NMR (300 MHz, $CDCl_3$) δ 1.08 (s, 3H), 1.38 (s, 3H), 1.87 (s, 3H), 2.29 (s, 3H), 2.39 (s, 3H), 4.52 (d, 1H, J=5.0 Hz), 4.94 (d, 1H, J=5.0 Hz), 7.07 (s, 4H), 7.24 (d, 2H, J=8.2 Hz), 7.69 (d, 2H, J=8.2 Hz). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 14.4, 17.9, 21.0, 21.4, 21.8, 55.7, 66.9, 84.1, 105.8, 127.1, 128.1, 128.5, 129.5, 130.5, 136.4, 137.7, 143.9, 211.2. HRMS (ESI) for $C_{22}H_{25}NO_4S$ [(M+Na)$^+$] calcd 422.1401, found 422.1437.

*4.2.8. 9-(3-Fluoro-phenyl)-6-methyl-10-(toluene-4-sulfonyl)-11-oxa-10-aza-tricyclo[6.2.1.0^{1,6}]undecan-7-one (**6b**).* Colorless solid, yield: 325 mg (70%); mp 163–165 °C (chloroform/hexane). ν_{max} (KBr)/cm^{-1} 2945, 1769, 1595, 1447, 1355, 1268, 1165, 1092, 677, 588. ^1H NMR (200 MHz, $CDCl_3$) δ 1.37 (s, 3H), 1.83–1.43 (m, 8H), 2.38 (s, 3H), 4.65 (d, 1H, J=5.2 Hz), 5.02 (d, 1H, J=5.2 Hz), 7.01–6.86 (m, 3H), 7.26–7.17 (m, 3H), 7.69 (d, 2H, J=8.2 Hz). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 14.3, 19.3, 21.3, 22.6, 25.8, 31.6, 54.0, 66.4, 84.2, 105.9, 114.1, 114.5, 114.6, 115.0, 122.7, 128.1, 129.6, 129.7, 136.4, 136.5, 144.2, 159.8, 164.7, 210.2. HRMS (ESI$^+$) for $C_{23}H_{24}NO_4FS$ [(M+Na)$^+$] calcd 452.1307, found 452.1318.

*4.2.9. 5-Methyl-8-phenyl-9-(toluene-4-sulfonyl)-10-oxa-9-aza-tricyclo [5.2.1.0^{1,5}]decan-6-one (**6c**).* Colorless solid, yield: 331 mg (54%); mp 133–135 °C (chloroform/hexane). ^1H NMR ($CDCl_3$, 200 MHz) δ 0.97–0.90 (m, 1H), 1.11 (s, 3H), 1.60–1.25 (m, 2H), 2.03–1.72 (m, 1H), 2.25–2.12 (m, 1H), 2.43 (s, 3H), 2.75–2.65 (m, 1H), 4.72 (d, 1H, J=5.6 Hz), 5.22 (d, 1H, J=5.6 Hz), 7.44–7.25 (m, 7H), 7.80 (d, 2H, J=8.2 Hz). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 17.0, 21.5, 21.6, 26.8, 33.0, 60.3, 67.1, 82.6, 112.0, 126.9, 128.0, 128.3, 128.6, 129.7, 133.9, 135.4, 144.4, 209.1. HRMS (ESI) for $C_{22}H_{23}NO_4S$ [(M+Na)$^+$] calcd 420.1245, found 420.1268.

*4.2.10. 9-(2-Bromo-phenyl)-6-methyl-10-(toluene-4-sulfonyl)-11-oxa-10-aza-tricyclo[6.2.1.0^{1,6}]undecan-7-one (**6d**).* Colorless solid, yield: 468 mg (77%) as a colorless solid: mp 191–193 °C (chloroform/hexane). ν_{max} (KBr)/cm^{-1} 2972, 1771, 1443, 1349, 1155, 1137, 689, 580. ^1H NMR ($CDCl_3$, 200 MHz) δ 1.41 (s, 3H, CH_3), 1.78–1.47 (m, 7H), 2.36 (s, 3H, CH_3), 2.52–2.46 (m, 1H), 4.92 (d, 1H, J=4.8 Hz, CH), 5.37 (d, 1H, J=4.8 Hz, CH), 7.39–7.14 (m, 6H, ArH), 7.71 (d, 2H, J=8.0 Hz, ArH). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 14.8 (*C*H_3), 20.0 (*C*H_2), 22.0 (*C*H_3), 23.2 (*C*H_2), 26.3 (*C*H_2), 32.2 (*C*H_2), 54.6 (*quat-C*), 65.3 (*C*H), 82.9 (*C*H), 106.4 (*quat-C*), 126.9 (=*C*H), 128.8 (=*C*H), 129.7 (=*C*H), 129.8 (=*C*H), 130.1 (=*C*H), 130.3 (=*C*H), 132.0 (*quat-C*), 132.7 (*quat-C*), 136.7 (*quat-C*), 144.8 (*quat-C*), 211.1 (*C*=O). HRMS (ESI) for $C_{23}H_{24}ClNO_4S$ [(M+Na)$^+$] calcd 512.5552, found 512.5559.

*4.2.11. 9-(2-Chloro-phenyl)-6-methyl-10-(toluene-4-sulfonyl)-11-oxa-10-aza-tricyclo[6.2.1.0^{1,6}]undecan-7-one (**6f**).* Colorless solid, yield: 468 mg (77%); mp 191–193 °C (chloroform/hexane). ν_{max} (KBr)/cm^{-1} 2972, 1771, 1443, 1349, 1155, 1137, 689, 580. ^1H NMR

($CDCl_3$, 200 MHz) δ 1.41 (s, 3H), 1.78–1.47 (m, 7H), 2.36 (s, 3H), 2.52–2.46 (m, 1H), 4.92 (d, 1H, J=4.8 Hz), 5.37 (d, 1H, J=4.8 Hz), 7.39–7.14 (m, 6H), 7.71 (d, 2H, J=8.0 Hz). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 14.8, 20.0, 22.0, 23.2, 26.3, 32.2, 54.6, 65.3, 82.9, 106.4, 126.9, 128.8, 129.7, 129.8, 130.1, 130.3, 132.0, 132.7, 136.7, 144.8, 211.1. HRMS (ESI) for $C_{23}H_{24}ClNO_4S$ [(M+Na)$^+$] calcd 468.1012, found 468.1044.

*4.2.12. 4a-Methyl-1-(toluene-4-sulfonyl)-2-phenyloctahydro-3,7a-epoxycyclopenta[b]pyridin-4-ol (**8**).* Colorless solid, yield: 187 mg, (85%); mp 145–147 °C, R_f 0.60 (1:5 EtOAc/hexane). ν_{max} (KBr)/cm^{-1} 3515, 2962, 2926, 1598, 1493, 1449, 1340, 1153, 1018, 704, 559. ^{1}H NMR (200 MHz, CD_3OD+$CDCl_3$) δ 1.08 (s, 3H), 1.99–181 (m, 5H), 2.38 (s, 3H), 3.46 (m, 1H), 2.75–2.64 (m, 1H), 4.50 (d, J=5.0 Hz, 1H), 5.02 (d, J=5.0 Hz, 1H), 7.36–7.19 (m, 5H), 7.48–7.41 (m, 2H), 7.75 (d, J=8.0 Hz, 2H). ^{13}C NMR (50.3 MHz, CD_3OD+$CDCl_3$) δ 24.2, 25.2, 25.6, 29.4, 33.5, 63.1, 70.6, 81.2, 89.3, 115.8, 130.7, 131.0, 132.1, 132.2, 133.4, 139.4, 140.2, 147.9. HRMS (ESI) calcd for $C_{22}H_{25}NO_4SNa$ (M+Na)$^+$: 422.1401, found 422.1432.

4.3. Typical procedure for the synthesis of compounds 9 and 10

To a solution of appropriate oxa-bridged piperidinones **5** (0.5 mmol) in CH_2Cl_2 (25 ml) at 0 °C were added equivalent amounts of allyltrimethylsilane and $TiCl_4$. All the reaction mixture was stirred for 2 h and allowed to gradually warm to room temperature. The reaction was quenched by the addition of saturated $NaHCO_3$, and diluted with H_2O. The aqueous phase was extracted with DCM (3×20 ml) then ethyl acetate (1×20 ml). The combined organic extracts were washed with brine, desiccated with Na_2SO_4, and the solvents removed under reduced pressure, and a portion of crude product was subjected to ^{1}H NMR analysis for determination of the product ratio. The crude product was purified by flash chromatography on silica gel by using hexane/EtOAc as eluent to obtain products **9** and **10**.

*4.3.1. 5-Hydroxy-3,3-dimethyl-2-methylene-1-[(4-methylphenyl)sulfonyl]-6-phenyl piperidin-4-one (**9a**).* Colorless solid, yield: 86 mg (43%); mp 96–98 °C ($CHCl_3$/hexane). ν_{max} (KBr)/cm^{-1} 3404, 2983, 2926, 1730, 1344, 1164, 1091, 1049, 670, 568. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.33 (s, 3H), 1.38 (s, 3H), 2.30 (s, 3H), 3.46 (br s, 1H), 4.42 (d, 1H, J=9.6 Hz), 4.77 (d, 1H, J=9.6 Hz), 5.29 (s, 1H), 5.37 (d, 1H, J=1.2 Hz), 6.67 (d, 2H, J=8.4 Hz), 7.09 (d, 2H, J=8.4 Hz), 7.31–7.24 (m, 5H). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 21.8, 23.9, 24.7, 52.1, 64.8, 76.5, 112.3, 128.1, 128.2, 128.8, 129.1, 129.4, 138.5, 139.6, 143.8, 148.8, 211.7. HRMS (ESI) for $C_{21}H_{23}NO_4S$ [(M+Na)$^+$] calcd 408.1245, found 408.1270.

*4.3.2. 3-Hydroxy-5,5,6-trimethyl-2-phenyl-2,5-dihydropyridin-4(3H)-one (**10a**).* Semi-solid, yield: 36 mg (30%); ($CHCl_3$/hexane). ν_{max} (KBr)/cm^{-1} 3423, 2977, 2927, 1723, 1656, 1591, 1449, 1381, 1263, 1158, 1048, 692. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.45 (s, 3H), 1.47 (s, 3H), 2.23 (s, 3H), 4.09 (br s, 1H), 4.26 (d, 1H, J=10.6 Hz), 4.43 (d, 1H, J=10.6 Hz), 7.47–7.45 (m, 5H). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 21.5, 22.1, 26.1, 50.3, 68.8, 74.7, 128.1, 128.9, 115.0, 141.1, 174.2, 211.1. HRMS (ESI) for $C_{14}H_{17}NO_2$ [(M+Na)$^+$] calcd 254.1156, found 254.1160.

*4.3.3. 5-Hydroxy-3,3-dimethyl-2-methylene-1-[(4-methylphenyl) sulfonyl]-6-(3-fluoro-phenyl)piperidin-4-one (**9b**).* Colorless solid, yield: 135 mg (45%); mp 121–123 °C ($CHCl_3$/hexane). ν_{max} (KBr)/cm^{-1} 3449, 2987, 2927, 1729, 1592, 1339, 1158, 1090, 1050, 694, 545. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.32 (s, 6H), 2.32 (s, 3H), 3.52 (br s, 1H), 4.36 (d, 1H, J=9.6 Hz), 4.75 (d, 1H, J=9.6 Hz), 5.32 (d, 1H, J=1.0 Hz), 5.45 (d, 1H, J=1.4 Hz), 7.12–6.93 (m, 6H), 7.20 (d, 2H, J=8.4 Hz). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 21.9, 24.1, 24.7, 52.1, 64.4, 76.3, 112.9, 114.6, 115.0, 115.5, 116.0, 124.0, 128.3, 129.6, 130.6, 130.8, 138.2, 142.3, 142.5, 144.3, 148.6, 160.8, 165.8, 211.4. HRMS (ESI) for $C_{21}H_{22}FNO_4S$ [(M+Na)$^+$] calcd 426.1151, found 426.1180.

*4.3.4. 3-Hydroxy-5,5,6-trimethyl-2-(3-fluorophenyl)-2,5-dihydropyridin-4(3H)-one (**10b**).* Colorless solid, yield: 55 mg (30%); mp 89–91 °C ($CHCl_3$/hexane). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.37 (s, 3H), 1.39 (s, 3H), 2.15 (d, 3H J=2.0 Hz), 3.54 (br s, 1H), 4.17 (d, 1H, J=10.6 Hz), 4.39–4.33 (m, 1H), 7.17–7.00 (m, 3H, J=7.0 Hz), 7.38–7.28 (m, 1H). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 21.6, 22.4, 26.2, 50.3, 68.3, 74.6, 114.9, 115.3, 124.0, 128.9, 130.3, 130.5, 161.0, 174.5, 211.1. HRMS (ESI) for $C_{14}H_{16}FNO_2$ [(M+Na)$^+$] calcd 272.1062, found 272.1050.

*4.3.5. 5-Hydroxy-3,3-dimethyl-2-methylene-1-[(4-methylphenyl) sulfonyl]-6-(3-bromophen yl)piperidin-4-one (**9c**).* Colorless solid, yield: 141 mg (47%); mp 154–156 °C ($CHCl_3$/hexane). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.35 (s, 3H), 1.38 (s, 3H), 2.35 (s, 3H), 3.42 (br s, 1H), 4.33 (d, 1H, J=9.6 Hz), 4.71 (d, 1H, J=9.6 Hz), 5.34 (s, 1H), 5.46 (s, 1H), 7.36–7.02 (m, 8H). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 22.0, 24.0, 24.9, 52.0, 64.2, 76.4, 113.1, 127.4, 128.3, 129.8, 130.3, 130.8, 131.9, 136.7, 144.4, 148.6, 152.7, 155.1, 211.4. HRMS (ESI) for $C_{21}H_{22}BrNO_4S$ [(M+Na)$^+$] calcd 486.0350, found 486.0373.

*4.3.6. 3-Hydroxy-5,5,6-trimethyl-2-(3-bromophenyl)-2,5-dihydropyridin-4(3H)-one (**10c**).* Colorless solid, yield: 63 mg (35%); mp 125–127 °C ($CHCl_3$/hexane). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.37 (s, 3H), 1.39 (s, 3H), 2.15 (d, 3H, J=1.8 Hz), 4.13 (d, 1H, J=10.6 Hz), 4.35–4.30 (m, 1H), 7.31–7.19 (m, 2H), 7.43 (d, 1H, J=7.0 Hz), 7.52 (s, 1H). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 21.6, 22.4, 26.2, 50.3, 68.2, 74.6, 123.2, 127.2, 130.5, 131.2, 131.3, 143.6, 174.7, 211.1. HRMS (ESI) for $C_{14}H_{16}BrNO_2$ [(M+Na)$^+$] calcd 332.0261, found 332.0293.

*4.3.7. 5-Hydroxy-3,3-dimethyl-2-methylene-1-[(4-methylphenyl) sulfonyl]-6-(4-fluoro-phenyl)piperidin-4-one (**9d**).* Colorless solid, yield: 126 mg (42%); mp 147–149 °C ($CHCl_3$/hexane). ν_{max} (KBr)/cm^{-1} 3412, 2965, 2928, 1733, 1340, 1163, 1091, 1047, 556. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.34 (s, 6H), 2.33 (s, 3H), 3.44 (br s, 1H), 4.37 (d, 1H, J=9.6 Hz), 4.76 (d, 1H, J=9.6 Hz), 5.31 (s, 1H), 5.42 (s, 1H), 7.05–6.89 (m, 4H), 7.30–7.16 (m, 4H). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 21.9, 24.0, 24.7, 52.1, 64.2, 76.5, 112.7, 115.8, 116.3, 128.3, 129.6, 129.8, 129.9, 135.7, 138.1, 144.2, 148.7, 211.6. HRMS (ESI) for $C_{21}H_{22}FNO_4S$ [(M+Na)$^+$] calcd 426.1151, found 426.1160.

*4.3.8. 23-Hydroxy-5,5,6-trimethyl-2-(4-fluorophenyl)-2,5-dihydropyridin-4(3H)-one (**10d**).* Colorless solid, yield: 51 mg (28%); mp 116–118 °C ($CHCl_3$/hexane). ν_{max} (KBr)/cm^{-1} 3424, 2936, 1738, 1346, 1162, 1093, 1048, 677, 572. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.47 (s, 3H), 1.48 (s, 3H), 2.24 (s, 3H), 3.53 (br s, 1H), 4.47–4.39 (m, 2H), 7.13–7.00 (m, 2H), 7.41–7.34 (m, 2H). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 20.9, 21.6, 25.5, 51.3, 68.0, 74.9, 115.6, 116.0, 129.8, 130.0, 137.5, 160.4, 165.3, 174.5, 211.3. HRMS (ESI) for $C_{14}H_{16}FNO_2$ [(M+Na)$^+$] calcd 272.1062, found 272.1098.

*4.3.9. 5-Hydroxy-3,3-dimethyl-2-methylene-1-[(4-methylphenyl) sulfonyl]-6-(2-chlorophen yl)piperidin-4-one (**9e**).* Colorless solid, yield: 181 mg (52%); mp 163–165 °C ($CHCl_3$/hexane). ν_{max} (KBr)/cm^{-1} 3434, 2977, 2936, 1745, 1346, 1163, 1090, 1052, 677, 564. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.35 (s, 3H), 1.36 (s, 3H), 2.30 (s, 3H), 3.40 (br s, 1H), 4.54 (d, 1H, J=10.4 Hz), 5.29 (d, 1H, J=10.4 Hz), 5.34 (s, 1H), 5.47 (s, 1H), 7.18–6.97 (m, 4H), 7.32–7.19 (m, 4H). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 21.9, 23.9, 25.0, 51.9, 61.1, 76.1, 113.2, 127.6, 128.2, 129.6, 129.8, 130.6, 134.8, 136.7, 138.1, 144.0, 148.3, 211.7. HRMS (ESI) for $C_{21}H_{22}ClNO_4S$ [(M+Na)$^+$] calcd 442.0855, found 442.0877.

*4.3.10. 3-Hydroxy-5,5,6-trimethyl-2-(2-chlorophenyl)-2,5-dihydropyridin-4(3H)-one (**10e**).* Colorless solid, yield: 84 mg (38%); mp 134–136 °C ($CHCl_3$/hexane). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.40 (s, 3H), 1.43 (s, 3H), 2.14 (d, 3H J=2.4 Hz), 3.65 (br s, 1H), 4.45 (d, 1H,

J=11.0 Hz), 5.00–4.93 (m, 1H), 7.41–7.22 (m, 4H). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 21.6, 22.3, 26.0, 50.7, 65.9, 74.9, 127.9, 129.5, 129.8, 130.4, 132.6, 134.8, 175.2, 211.2. HRMS (ESI) for $C_{14}H_{16}ClNO_2$ [(M+Na)$^+$] calcd 288.0767, found 288.0795.

*4.3.11. 5-Hydroxy-3,3-dimethyl-2-methylene-1-[(4-methylphenyl) sulfonyl]-6-(2-bromophen yl)piperidin-4-one (**9f**).* Colorless solid, yield: 162 mg (54%); mp 175–177 °C ($CHCl_3$/hexane). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.34 (s, 3H), 1.35 (s, 3H), 2.29 (s, 3H), 3.33 (br s, 1H), 4.49 (d, 1H, J=10.2 Hz), 5.32 (d, 1H, J=10.2 Hz), 5.34 (s, 1H), 5.48 (s, 1H), 7.09–6.96 (m, 4H), 7.29–7.19 (m, 3H), 7.51–7.46 (m, 1H). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 21.9, 23.8, 24.8, 51.9, 62.6, 76.7, 113.2, 124.9, 128.2, 128.3, 129.5, 129.9, 133.7, 138.0, 138.2, 144.0, 148.4, 211.5. HRMS (ESI) for $C_{21}H_{22}BrNO_4S$ [(M+Na)$^+$] calcd 486.0350, found 486.0364. Crystal data for compound **9f**: (CCDC 785049) $C_{21}H_{22}BrNO_4S$, M=464.37, 0.44×0.34×0.29 mm, monoclinic, $C2/c$, a=21.813 (6) Å, b=15.043 (4) Å, c=13.102 (3) Å, α=90°, β=105.132 (4)°, γ=90°, V=4150.4 (18) Å^3, T=293 (2) K, R_1=0.0581, wR_2=0.1508 on observed data, z=8, $D_{calcd.}$=1.486 Mg m^{-3}, F(000)=1904, absorption coefficient=2.108-mm^{-1}, λ=0.71073 Å, 4783 reflections were collected on a CAD-4 diffractometer, 3051 observed reflections ($I\geq 2\sigma$ (I)). The largest difference peak and hole=1.002 and −0.352 e Å^{-3}, respectively.

*4.3.12. 3-Hydroxy-5,5,6-trimethyl-2-(2-bromophenyl)-2,5-dihydropyridin-4(3H)-one (**10f**).* Colorless solid, yield: 84 mg (42%); mp 144–146 °C ($CHCl_3$/hexane). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.38 (s, 3H), 1.40 (s, 3H), 2.12 (d, 3H, J=2.2 Hz), 3.55 (br s, 1H), 4.38 (d, 1H, J=10.8 Hz), 4.99–4.92 (m, 1H), 7.19–7.15 (m, 1H), 7.36–7.34 (m, 2H), 7.57 (s, 1H, J=8.0 Hz). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 21.6, 22.2, 25.8, 50.5, 67.7, 75.0, 125.0, 128.4, 129.7, 129.8, 133.5, 140.1, 174.4, 210.9. HRMS (ESI) for $C_{14}H_{16}BrNO_2$ [(M+Na)$^+$] calcd 332.0261, found 332.0263. Crystal data for compound **10f**: (CCDC 785050) $C_{14}H_{16}BrNO_2$, M=310.19, 0.54×0.39×0.30 mm, monoclinic, $P21/n$, a=7.5187 (15) Å, b=19.492 (4) Å, c=9.431 (2) Å, α=90°, β=92.588 (4)°, γ=90°, V=1380.7 (5) Å^3, T=293 (2) K, R_1=0.0337, wR_2=0.0861 on observed data, z=4, $D_{calcd.}$=1.492 Mg m^{-3}, F(000)=632, absorption coefficient=2.971 mm^{-1}, λ=0.71073 Å, 3169 reflections were collected on a CAD-4 diffractometer, 2526 observed reflections ($I\geq 2\sigma$ (I)). The largest difference peak and hole=0.718 and −0.309 e Å^{-3}, respectively. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

*4.3.13. 5-Hydroxy-3,3-dimethyl-2-methylene-1-[(4-methylphenyl) sulfonyl]-6-(4-methylphenyl)piperidin-4-one (**9g**).* Colorless solid, yield: 80 mg (40%); mp 102–104 °C ($CHCl_3$/hexane). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.33 (s, 3H), 1.36 (s, 3H), 2.32 (s, 3H), 2.33 (s, 3H), 3.42 (br s, 1H), 4.42 (d, 1H, J=9.6 Hz), 4.73 (d, 1H, J=9.6 Hz), 5.28 (s, 1H), 5.37 (d, 1H, J=1.0 Hz), 7.16–7.00 (m, 8H). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 21.7, 22.0, 24.0, 24.8, 52.2, 64.7, 76.6, 112.3, 128.1, 128.4, 129.5, 129.8, 136.7, 138.7, 138.8, 143.8, 148.9, 211.9. HRMS (ESI) for $C_{22}H_{25}NO_4S$ [(M+Na)$^+$] calcd 422.1401, found 422.1387.

*4.3.14. 3-Hydroxy-4a-methyl-1-(toluene-4-sulfonyl)-2-phenyl-2,3,4a,5,6,7-hexahydroquinolin-4(1H)-one (**17a**).* Colorless solid, yield: 88 mg (22%); mp 147–149 °C ($CHCl_3$/hexane). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.78–1.64 (m, 2H), 1.83 (s, 3H), 1.95–1.89 (m, 2H), 2.16–2.12 (m, 2H,), 2.48 (s, 3H), 3.45 (s, 1H), 4.44 (d, 1H, J=11.0 Hz), 5.65 (d, 1H, J=11.0 Hz), 6.36 (t, 1H J=4.4 Hz), 7.31–7.20 (m, 4H), 7.41–7.37 (m, 5H). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 18.0, 20.1, 25.7, 26.5, 32.3, 50.7, 68.6, 72.6, 128.8, 129.3, 130.2, 132.0, 134.4, 137.2, 138.9, 142.8, 211.9. HRMS (ESI) for $C_{23}H_{25}NO_4S$ [(M+Na)$^+$] calcd 434.1401, found 434.1380.

*4.3.15. 3-Hydroxy-4a-methyl-2-phenyl-2,4a,5,6,7,8-hexahydroquinolin-4(3H)-one (**18a**).* Colorless solid, yield: 113 mg (45%); mp 89–91 °C ($CHCl_3$/hexane). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.44 (s, 3H), 1.76–1.59 (m, 4H), 2.14–1.94 (m, 2H), 2.60–2.40 (m, 2H), 3.67 (br s, 1H), 4.36 (s, 2H), 7.37–7.29 (m, 5H). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 21.0, 23.9, 28.1, 33.7, 35.3, 50.9, 71.7, 74.4, 128.2, 129.0, 141.5, 175.5, 211.4. HRMS (ESI) for $C_{16}H_{19}NO_2$ [(M+Na)$^+$] calcd 280.1315, found 280.1326.

*4.3.16. 3-Hydroxy-4a-methyl-1-(toluene-4-sulfonyl)-2-(2-bromophenyl)-2,3,4a,5,6,7-hexahydroquinolin-4(1H)-one (**17b**).* Colorless solid, yield: 75 mg (25%); mp 182–184 °C ($CHCl_3$/hexane). ν_{max} (KBr)/cm^{-1} 3464, 2993, 2929, 1746, 1342, 1164, 1088, 1052, 574. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.84–1.57 (m, 2H), 1.87 (s, 3H, CH_3), 1.97–1.93 (m, 2H), 2.19–2.15 (m, 2H), 2.48 (s, 3H, CH_3), 4.52 (d, 1H, J=11.6 Hz, CH), 5.71 (d, 1H, J=11.6 Hz, CH), 6.42 (t, 1H J=3.0 Hz, =CH), 7.24–7.07 (m, 5H, ArH), 7.60–7.47 (m, 2H, ArH), 7.99 (d, 1H, J=7.8 Hz, ArH). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 18.0 (CH_2), 21.9 (CH_3), 25.8 (CH_3), 25.9 (CH_2), 32.0 (CH_2), 51.1 (*quat*-C), 66.9 (=CH), 71.9 (=CH), 127.5 (=CH), 129.0 (=CH), 130.2 (=CH), 130.6 (=CH), 131.4 (*quat*-C), 132.7 (=CH), 133.7 (=CH), 138.3 (*quat*-C), 138.6 (*quat*-C), 143.0 (*quat*-C), 176.2 (*quat*-C), 211.8 (C=O). HRMS (ESI) for $C_{23}H_{24}BrNO_4S$ [(M+Na)$^+$] calcd 512.0506, found 512.0508. Crystal data for compound **17b**: (CCDC 785051) $C_{23}H_{24}BrNO_4S$, M=490.40, 0.22×0.12×0.08 mm, monoclinic, $P21/c$, a=9.3427 (7) Å, b=14.9368 (11) Å, c=15.1482 (11) Å, α=90°, β=91.4220 (10)°, γ=90°, V=2113.3 (3) Å^3, T=273 (2) K, R_1=0.0339, wR_2=0.0812 on observed data, z=4, D_{calcd}=1.541 Mg m^{-3}, F(000)=1008, absorption coefficient=2.075 mm^{-1}, λ=0.71073 Å, 4898 reflections were collected on a CAD-4 diffractometer, 4052 observed reflections ($I\geq 2\sigma$ (I)). The largest difference peak and hole=0.591 and −0.289 e Å^{-3}, respectively.

*4.3.17. 3-Hydroxy-4a-methyl-2-(2-bromophenyl)-2,4a,5,6,7,8-hexahydroquinolin-4(3H)-one (**18b**).* Colorless solid, yield: 110 mg (54%); mp 144–146 °C ($CHCl_3$/hexane). ν_{max} (KBr)/cm^{-1} 3464, 2923, 1726, 1360, 1144, 1076, 1049, 671, 570. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.49 (s, 3H, CH_3), 1.75–1.71 (m, 3H), 2.16–2.02 (m, 3H), 2.59–2.48 (m, 2H), 4.10 (br s, 1H, OH), 4.63 (d, 1H, J=10.4 Hz, CH), 4.99 (dd, 1H, J_1=10.4 Hz, J_2=2.4 Hz, CH), 7.19–7.15 (m, 1H, ArH), 7.35–7.29 (m, 2H, ArH), 7.58 (d, 1H, J=8.0 Hz, ArH). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 20.9 (CH_2), 23.5 (CH_3), 28.1 (CH_2), 33.7 (CH_2), 35.2 (CH_2), 51.3 (*quat*-C), 70.8 (=CH), 74.5 (=CH), 124.8 (*quat*-C), 128.4 (=CH), 129.9 (=CH), 130.0 (=CH), 133.7 (=CH), 140.1 (*quat*-C), 176.2 (*quat*-C), 210.9 (C=O). HRMS (ESI) for $C_{16}H_{18}BrNO_2$ [(M+Na)$^+$] calcd 358.0418, found 358.0427.

*4.3.18. 3-Hydroxy-4a-methyl-2-(4-fluorophenyl)-2,4a,5,6,7,8-hexahydro quinolin-4(3H)-one (**18c**).* Colorless solid, yield: 131 mg (68%); mp 110–112 °C ($CHCl_3$/hexane). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.47 (s, 3H), 1.76–1.55 (m, 4H), 2.18–1.98 (m, 2H), 2.62–2.34 (m, 2H), 3.53 (br s, 1H), 4.45–4.31 (m, 2H), 7.10–7.01 (m, 2H), 7.36–7.29 (m, 2H). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 21.0, 24.0, 28.2, 33.8, 35.5, 50.9, 70.9, 74.5, 115.6, 116.0, 129.6, 129.8, 137.4, 160.4, 165.3, 175.8, 211.3. HRMS (ESI) for $C_{16}H_{18}FNO_2$ [(M+Na)$^+$] calcd 298.1219, found 298.1246.

*4.3.19. 3-Hydroxy-4a-methyl-2-(2-chlorophenyl)-2,4a,5,6,7,8-hexahydroquinolin-4(3H)-one (**18d**).* Colorless solid, 150 mg (76%); mp 154–156 °C ($CHCl_3$/hexane). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.48 (s, 3H), 1.74–1.65 (m, 3H), 2.15–1.96 (m, 3H), 2.59–2.38 (m, 2H), 3.50 (br s, 1H), 4.63 (d, 1H, J=10.4 Hz), 4.98–4.93 (m, 1H), 7.39–7.19 (m, 4H). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 20.9, 23.5, 28.1, 33.6, 35.3, 51.2, 69.0, 74.2, 127.8, 129.4, 129.9, 130.4, 134.5, 138.9, 175.9, 211.0. HRMS (ESI) for $C_{16}H_{18}ClNO_2$ [(M+Na)$^+$] calcd 314.0923, found 314.0957.

*4.3.20. 6-Allyl-2-phenyl-5,5,6-trimethyl-1-(toluene-4-sulfonyl)piperidine-3,4-diol (**20**).* Colorless solid, yield: 180 mg, (82%); mp

148–150 °C ($CHCl_3$/hexane). ^1H NMR ($CDCl_3$, 200 MHz) δ 0.91 (s, 3H), 0.95 (s, 3H), 1.03 (s, 3H), 1.99–1.87 (m, 1H), 2.33 (s, 3H), 3.02–2.83 (m, 1H), 3.21 (m, 1H), 4.02 (m, 1H), 4.28–4.22 (m, 1H), 4.81 (t, 1H, J=9.0 Hz), 4.98–4.92 (m, 2H), 5.58–5.53 (m, 1H), 5.82–5.63 (m, 1H), 7.19–6.94 (m, 7H), 7.47 (d, J=8.2 Hz, 2H). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 17.8, 20.2, 21.2, 24.8, 42.7, 47.5, 58.2, 81.0, 81.6, 86.3, 116.2, 127.1, 127.2, 128.0, 129.1, 136.3, 136.8, 138.6, 143.0. HRMS (ESI) for $C_{24}H_{31}NO_4S$ [(M+Na)$^+$] calcd 452.1871, found 452.1894.

4.4. Synthesis of compounds 23 and 24

*4.4.1. 4a-Methyl-1-(toluene-4-sulfonyl)-2-phenyl-1,2,3,4,4a,5,6,7-octahydroquinoline-3,4-diol (**23**).* Yield: 225 mg, (54%); ^1H NMR ($CDCl_3$, 200 MHz) δ 1.73–0.98 (m, 9H), 2.27 (s, 3H), 3.94–3.85 (m, 2H), 4.34–4.28 (m, 2H), 4.56 (t, 1H, J=9.0 Hz), 5.87 (d, J=10.2 Hz, 1H), 7.03–6.97 (m, 7H), 7.46–7.43 (m, 2H). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 15.5, 21.5, 22.0, 23.1, 32.4, 34.2, 48.7, 59.2, 80.7, 83.0, 107.8, 128.0, 128.8, 129.9, 137.8, 139.6, 144.0. HRMS (ESI) for $C_{23}H_{27}NO_4S$ [(M+Na)$^+$] calcd 436.1559, found 436.1578.

*4.4.2. N-[(3,7a-Dihydroxy-3a-methyloctahydro-1-benzofuran-2-yl)(phenyl)methyl]toluene-4-sulfonamide (**24**).* Yield: 82 mg, (20%); ^1H NMR ($CDCl_3$, 200 MHz) δ 1.32 (s, 3H), 2.01–1.54 (m, 7H), 1.96–2.01 (m, 1H), 2.29–2.20 (m, 1H), 2.31 (s, 3H), 3.31 (d, J=8.4 Hz, 1H), 2.63 (br s, 1H), 4.25–4.19 (m, 1H), 4.45 (t, 1H, J=9.0 Hz), 6.13 (m, 1H), 6.94 (d, J=8.2 Hz, 2H), 7.19–7.05 (m, 7H). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 17.4, 18.8, 21.2, 28.2, 35.8, 40.4, 69.0, 74.2, 81.7, 126.3, 126.9, 127.6, 127.9, 128.7, 131.1, 132.8, 139.1, 140.3, 141.9. HRMS (ESI) for $C_{23}H_{29}NO_5S$ [(M+Na)$^+$] calcd 454.1664, found 454.1687.

*4.4.3. 4-Allyl-4a-methyl-1-(toluene-4-sulfonyl)-2-phenyloctahydro-3,7a-epoxycyclopenta [b]pyridin-4-ol (**26**).* Yield: 150 mg, (70%); ^1H NMR ($CDCl_3$, 200 MHz) δ 1.26–1.14 (m, 4H), 1.94–1.65 (m, 4H), 2.34–2.01 (m, 1H), 2.39 (s, 3H), 2.80–2.60 (m, 2H), 3.22 (s, 1H), 4.64–4.55 (m, 1H), 4.90–4.82 (m, 1H), 5.00–4.96 (m, 1H), 5.12–5.09 (m, 1H), 5.64–5.43 (m, 1H), 7.21–7.14 (m, 1H), 7.39–7.28 (m, 3H), 7.57–7.49 (m, 2H), 7.75 (d, 2H, J=8.2 Hz), 8.07 (d, 1H, J=7.4 Hz). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 21.5, 22.0, 24.2, 27.7, 32.5, 37.0, 41.0, 60.8, 68.4, 82.9, 85.2, 118.9, 127.4, 129.2, 130.1, 133.4, 133.6, 135.3, 135.9, 144.7. HRMS (ESI) for $C_{25}H_{29}NO_4S$ [(M+Na)$^+$] calcd 462.1715, found 462.1736.

*4.4.4. 1,3,6-Trideoxy-3,3-dimethyl-6-[(toluene-4-sulfonyl)amino]-6-phenylhex-2-ylofuranose (**27**).* Yield: 182 mg, (90%). ^1H NMR ($CDCl_3$, 200 MHz) δ 0.69 (s, 3H), 1.14 (s, 3H), 1.16 (s, 3H), 2.50 (s, 3H), 3.96–3.91 (m, 1H), 4.27–4.20 (m, 1H), 4.69 (t, 1H, J=9.2 Hz), 5.40 (d, 1H, J=6.8 Hz), 7.21–7.10 (m, 5H), 7.47 (d, J=7.8 Hz, 2H), 8.08 (d, J=7.8 Hz, 2H). ^{13}C NMR (DMSO-d_6, 50.3 MHz) δ 18.0, 21.2, 23.1, 48.0, 57.7, 78.9, 81.7, 108.1, 126.8, 127.8, 128.5, 129.1, 139.3, 140.0, 141.9. HRMS (ESI) for $C_{21}H_{27}NO_5S$ [(M+Na)$^+$] calcd 428.1507, found 428.1524.

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Supplementary data

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References and notes

1. (a) Kinder, F. R., Jr.; Bair, K. W. *J. Org. Chem.* **1994**, *59*, 6965–6967; (b) Padwa, A.; Curtis, E. A.; Sandanayaka, V. P. *J. Org. Chem.* **1997**, *62*, 1317–1325; (c) McMorris, T. C.; Hu, Y.; Yu, J.; Kelner, M. J. *J. Chem. Soc., Chem. Commun.* **1997**, 315–316; (d) McMorris, T. C.; Yu, J.; Hu, Y.; Estes, L. A.; Kelner, M. J. *J. Org. Chem.* **1997**, *62*, 3015–3018; (e) Curtis, E. A.; Sandanayaka, V. P.; Padwa, A. *Tetrahedron Lett.* **1995**, *36*, 1989–1992; (f) Wood, J. L.; Thompson, B. D.; Yusuff, N.; Pflum, D. A.; Matthäus, M. S. P. *J. Am. Chem. Soc.* **2001**, *123*, 2097–2098; (g) Chiu, P.; Chen, B.; Cheng, K. F. *Org. Lett.* **2001**, *3*, 1721–1724; (h) Chen, B.; Ko, R. Y. Y.; Yuen, M. S. M.; Cheng, K.-F.; Chiu, P. *J. Org. Chem.* **2003**, *68*, 4195–4205; (i) Chiu, P. *Pure Appl. Chem.* **2005**, *77*, 1183–1189; (j) Mcmorris, T. C.; Staake, M. D.; Kelner, M. J. *J. Org. Chem.* **2004**, *69*, 619–623.
2. (a) Graening, T.; Friedrichsen, W.; Lex, J.; Schmalz, H.-G. *Angew. Chem., Int. Ed.* **2002**, *41*, 1524–1525; (b) Graening, T.; Bette, V.; Neudorfl, J.; Lex, J.; Schmalz, H.-G. *Org. Lett.* **2005**, *7*, 4317–4320; (c) Mejia-Oneto, J. M.; Padwa, A. *Org. Lett.* **2006**, *8*, 3275–3278; (d) Hong, X.; France, S.; Mejia-Oneto, J. M.; Padwa, A. *Org. Lett.* **2006**, *8*, 5141–5144 and reference cited therein.
3. (a) Mehta, G.; Muthusamy, S. *Tetrahedron* **2002**, *58*, 9477–9504; (b) Padwa, A.; Weingarten, M. D. *Chem. Rev.* **1996**, *96*, 223–269; (c) Padwa, A. *Top. Curr. Chem.* **1997**, *189*, 121–158; (d) Padwa, A.; Krumpe, K. E. *Tetrahedron* **1992**, *48*, 5385–5453; (e) Hodgson, D. M.; Pierard, F. Y. T. M.; Stupple, P. A. *Chem. Soc. Rev.* **2001**, *30*, 50–61; (f) Padwa, A. *Helv. Chim. Acta* **2005**, *88*, 1357–1374; (g) McMills, M. C.; Wright, D. In *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*; Padwa, A., Pearson, W. H., Eds.; John Wiley: Hoboken, 2003, Chapter 4, p 253.
4. Muthusamy, S.; Krishnamurthi, J.; Suresh, E. *Synlett* **2005**, 3002–3004.
5. Muthusamy, S.; Krishnamurthi, J.; Suresh, E. *Org. Lett.* **2006**, *8*, 5101–5104.
6. (a) Sears, P.; Wong, C.-H. *Angew. Chem., Int. Ed.* **1999**, *38*, 2301–2324; (b) Butters, T. D.; Dwek, R. A.; Platt, F. M. *Chem. Rev.* **2000**, *100*, 4683–4696; (c) Lillelund, V. H.; Jensen, H. H.; Liang, X.; Bols, M. *Chem. Rev.* **2002**, *102*, 515–553; (d) Martin, O. R.; Compain, P. *Curr. Top. Med. Chem.* **2003**, *3*, i–iv; (e) Robina, I.; Moreno-Vargas, A. J.; Crmona, A. T.; Vogel, P. *Curr. Drug Metab.* **2004**, *5*, 329–361.
7. (a) Reese, E. T.; Parrish, F. W.; Ettlinger, M. *Carbohydr. Res.* **1971**, *18*, 381–388; (b) Fleet, G. W. J.; Shaw, A. N.; Evans, S. V.; Fellows, L. E. F. *J. Chem. Soc., Chem. Commun.* **1985**, 841–842; (c) Stutz, A. E. *Iminosugars as Glycodidase inhibitors: Nojirimycin and Beyond*; Wiley-VCH: Weinheim, Germany, 1999; (d) Kato, A.; Asano, N.; Kizu, H.; Matsui, K.; Watson, A. A.; Nash, R. J. *J. Nat. Prod.* **1997**, *60*, 312–314 and references cited therein; (e) Butters, T. D.; Dwek, R. A.; Platt, F. M. *Curr. Top. Med. Chem.* **2003**, *3*, 561–574.
8. (a) Lautens, M.; Fagnou, K.; Hiebert, S. *Acc. Chem. Res.* **2003**, *36*, 48–58; (b) Chen, C.-L.; Martin, S. F. *J. Org. Chem.* **2006**, *71*, 4810–4817; (c) Cho, Y.-H.; Zunic, V.; Senboku, H.; Olsen, M.; Lautens, M. *J. Am. Chem. Soc.* **2006**, *128*, 6837–6846; (d) Parthasarathy, K.; Jeganmohan, M.; Cheng, C.-H. *Org. Lett.* **2006**, *8*, 621–623; (e) Padwa, A.; Sandanayaka, V. P.; Curtis, E. A. *J. Am. Chem. Soc.* **1994**, *116*, 2667–2668; (f) Winkler, J. D.; Mikochic, P. J. *Org. Lett.* **2004**, *6*, 3735–3737; (g) Maier, M. E.; Evertz, K. *Tetrahedron Lett.* **1988**, *29*, 1677–1681; (h) Marino, J. P., Jr.; Osterhout, M. H.; Padwa, A. *J. Org. Chem.* **1995**, *60*, 2704–2713; (i) Padwa, A.; Brodney, M. A.; Marino, J. P., Jr.; Osterhout, M. H.; Price, A. T. *J. Org. Chem.* **1997**, *62*, 67–77; (j) Padwa, A.; Brodney, M. A.; Marino, J. P., Jr.; Osterhout, M. H.; Price, A. T. *J. Org. Chem.* **1997**, *62*, 78–87; (k) Brodney, M. A.; Padwa, A. *J. Org. Chem.* **1999**, *64*, 556–565; (l) Padwa, A.; Crawford, K. R.; Straub, C. S.; Pieniazek, S. N.; Houk, K. N. *J. Org. Chem.* **2006**, *71*, 5432–5439; (m) Vogel, P.; Cossy, J.; Plumet, J.; Arjona, O. *Tetrahedron* **1999**, *55*, 13521–13642.
9. (a) Fleming, I.; Barbero, A.; Walter, D. *Chem. Rev.* **1997**, *97*, 2063–2192; (b) Shenoy, S. R.; Smith, D. M.; Woerpel, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 8671–8677 and reference cited therein; (c) Amat, M.; Llor, N.; Hidalgo, J.; Escolano, C.; Bosch, J. *J. Org. Chem.* **2003**, *68*, 4810–4817.
10. O'Hagan, D. *Nat. Prod. Rep.* **2000**, *17*, 435–446.