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An efficient synthesis of diquinane-based bis-γ-lactones

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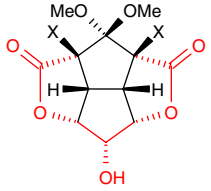
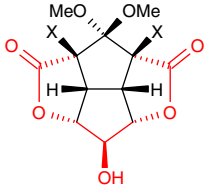
Abstract—An efficient stereoselective synthesis of both the diastereomers of diquinane-based conformationally constrained symmetric bis-γ-lactones starting from tricyclic derivative **9** is reported. The key step involves the intramolecular ring opening of an epoxide by the in situ formed hydrate of a diketone leading to the tetracyclic hemiacetal **10**, which directly leads to the *exo*-hydroxy bis-γ-lactone derivatives **2** and **4** under basic hydrogen peroxide cleavage conditions. Conversion to the *endo*-hydroxy bis-γ-lactone derivatives **1** and **3** was accomplished through lithium hydroxide mediated S_N2 displacements in dimesylate **7**, or more expeditiously, via trimesylate **21** through alkaline H_2O_2 mediated cleavage.

γ-Lactones are among the most abundant substructures found in numerous complex, challenging and biologically active natural products.[1] In continuation of our efforts to synthesize functionalized lactone derivatives,[2] we became interested in diquinane-based symmetric bis-γ-lactones **1**–**6**. These lactones may be regarded as conformationally constrained 1,3-diacylglycerol derivatives, the backbone of which is extended over the three non-fused carbons of the lower part while the 1,3-acyl moiety is present as part of the lactone rings (highlighted part) connected to the two non-fused proximal carbons of the upper half of the diquinane unit.[3]

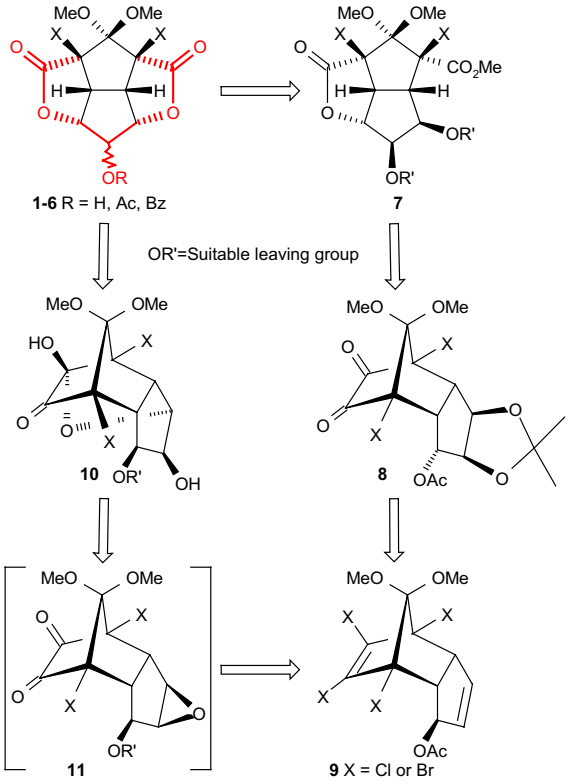


1x X = Cl
3x X = Br
5x X = H



2x X = Cl
4x X = Br
6x X = H

We envisioned that the diquinane-based bis-γ-lactones **1**–**6** could be obtained from easily accessible tricyclic norbornyl acetate derivative **9** as depicted in Scheme 1. Our approach to these compounds is based on the utilization of the synthetically versatile norbornyl α-diketones **8**, which are derived from **9** in a few steps, to obtain the monolactones **7** that would result through intramolecular lactonization upon diketone cleavage reaction. The norbornyl α-diketones are accessible from



Scheme 1. Retrosynthetic analysis of diquinane-based lactones **1**–**6**.

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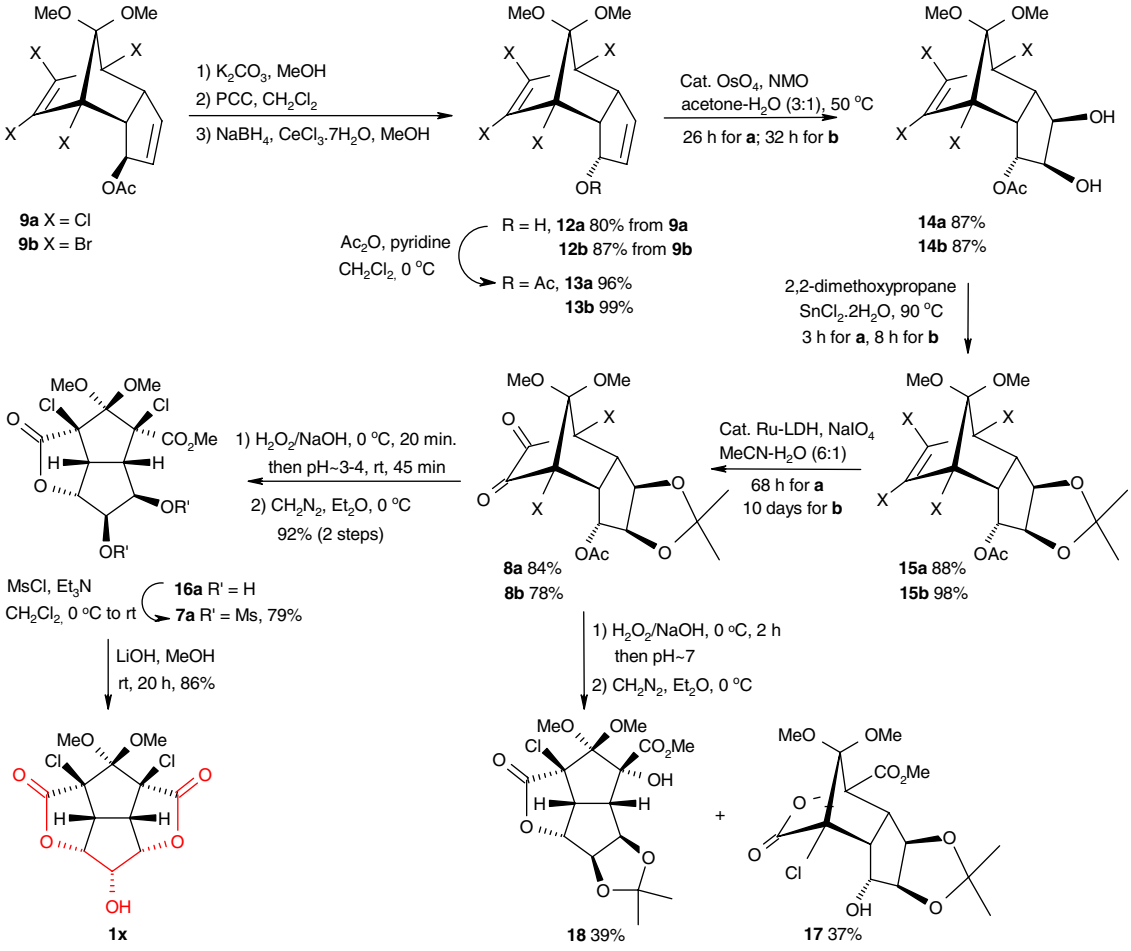
the corresponding tetrahalonorbornyl derivatives via an efficient methodology developed in our laboratory.[4] Monolactones **7** could be transformed into diquinane-based bis-γ-lactones **1** (or **3**) via an intramolecular S_N2 displacement reaction. An alternative approach was based on the conversion of **9** to the tetracyclic hemiacetal **10** equipped with a suitable leaving group as the key step. The formation of hemiacetal **10** from epoxy diketone **11** was based on the premise that norbornyl α-diketones have a high propensity to form monohydrates, especially in the presence of an interacting *endo*-group.[2b] It was hoped that the reactive epoxide moiety in **11** would undergo ring opening in situ leading directly to **10**, which on cleavage would furnish **2** (or **4**).

The tricyclic norbornyl acetate derivatives **9a**,**b**[5] were prepared via Diels–Alder reaction between tetrahalo-5,5-dimethoxycyclopentadiene and cyclopentadiene followed by allylic oxidation of the resulting adducts with manganese(III) acetate generated in situ from manganous acetate.[6] The *exo*-acetate groups in **9a**,**b** were conveniently transformed into the corresponding *endo*-acetates following a four-step protocol involving hydrolysis to the alcohol, oxidation to the ketone and finally selective reduction from the *exo*-face to furnish *endo*-alcohols **12a**,**b**[7] which were reprotected as acetates **13a**,**b** in an excellent overall yield (Scheme 2). The allylic double bond in acetates **13a**,**b** was dihydroxylated from the sterically more accessible convex face employing OsO_4 (cat.)–NMO to obtain **14a**,**b** in 87% yield. Protection of the vicinal diols as acetonides **15a**,**b** followed by treatment with supported Ru–LDH catalyst (ruthenium trichloride supported on layered double hydroxide, LDH), an efficient recyclable system reported from our laboratory for the conversion of 1,2-haloalkenes in norbornyl derivatives to the corresponding α-diketones,[4a] furnished diketones **8a**,**b**. The alkaline hydrogen peroxide mediated cleavage of the α-diketone moiety in **8a** and a subsequent work-up under neutral conditions, followed by esterification of the crude product with diazomethane furnished an unwanted but separable mixture of bridged-lactone **17** along with lactone **18**. Fortunately, reducing the reaction time from 2 h to 20 min and allowing the reaction mixture to stir at room temperature whilst maintaining an acidic pH (in order to hydrolyze the acetonide) directly furnished, after esterification, the lactone **16a** in high yield. A similar attempt on bromo analogue **8b** furnished a mixture of acetonide deprotected compounds, similar to **17** but with the acetate group intact (41%) and **18** (47%). The chloro analogue **16a** was then converted into dimesylate **7a**.

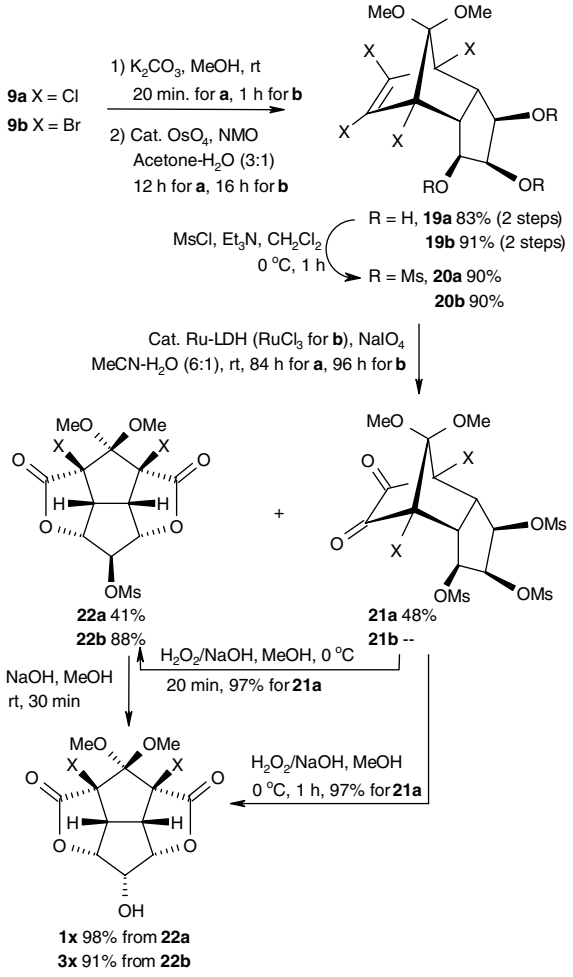


Scheme 2. Synthesis of diquinane-based lactone **1x**.

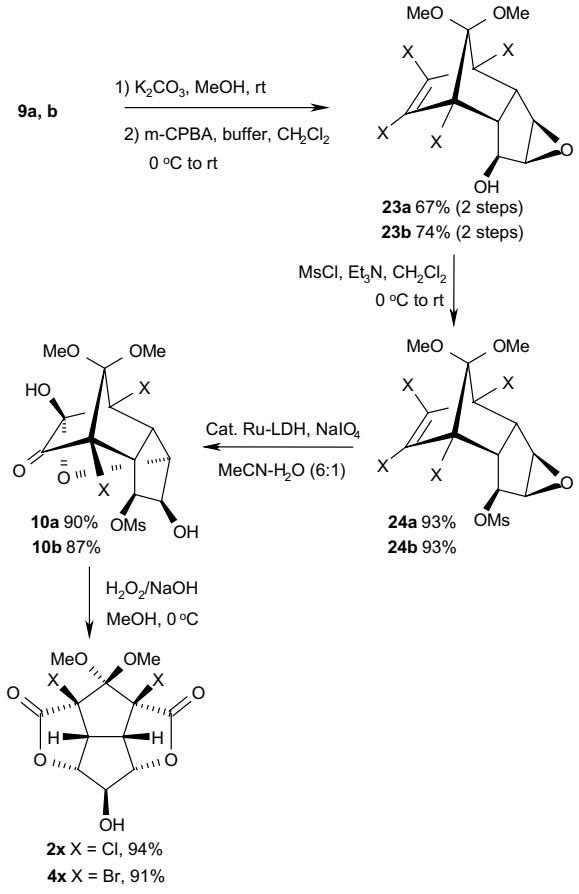
The densely functionalized dimesylate **7a** is highly susceptible to a variety of unwanted side reactions under aqueous alkaline conditions. This is due to the in situ release of nucleophilic carboxylates (or alkoxides) in close proximity to intramolecularly displaceable leaving groups such as chlorines or mesylates. The conversion of norbornyl α-diketones under alkaline H_2O_2 conditions via the intermediacy of bridged lactones similar to **17** to eventually form oxabridged compounds has been reported from our laboratory for a variety of other derivatives.[8] Fortunately, treatment of **7a** with LiOH in methanol furnished the diacylglycerol analogue **1x** in high yield. Both the mesylate groups were displaced in an S_N2 fashion, the proximal by the carboxylate anion and the distal by the hydroxide ion, resulting in the inversion of stereochemistry. The highly symmetric nature was evident from ^1H as well as ^{13}C spectra and was unambiguously confirmed by single crystal X-ray analysis of its benzoate ester **1z**.[9]

Having accomplished the synthesis of chloro analogue **1x**, we turned our attention to modify the scheme such that the elusive bromo analogue could also be obtained with ease. To this end, trimesylates **20a**,**b** obtained from **9a**,**b** via hydrolysis, dihydroxylation and mesylation (Scheme 3) were subjected to ruthenium catalyzed oxidation. Interestingly, **20a** furnished the expected diketone **21a** along with the symmetric bislactone **22a**, resulting from the cleavage of the diketone moiety in the former to the corresponding dicarboxylate followed by S_N2 displacement of the proximal mesylate groups. Bislactone **22a** could be smoothly transformed to bis-γ-lactone **1x** in near quantitative yield. Diketone **21a** was also converted directly to *endo*-alcohol **1x** or to bislactone **22a** depending on the reaction time as shown in Scheme 3. On the other hand, bromo analogue **20b** which reacted sluggishly with Ru–LDH, gave exclusively **22b** when $RuCl_3$ was employed as the catalyst. Brief exposure of **22b** to NaOH furnished bis-γ-lactone **3x** in excellent yield.

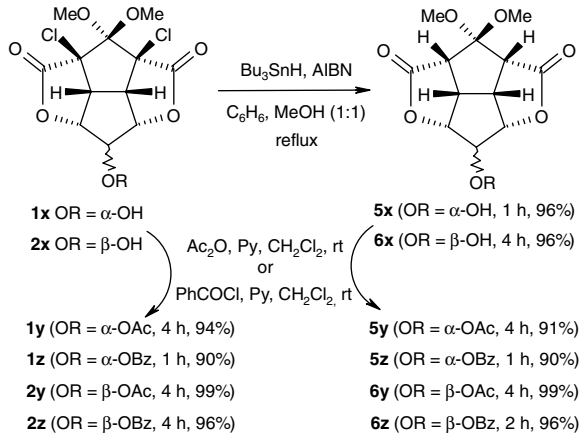
For the acquisition of the diastereomeric *exo*-alcohols a de novo approach as depicted in Scheme 1 involving the epoxide intermediate **11** was followed. This approach was based on the fact that the reactive *exo*-epoxide in **11** opens up instantaneously upon conversion of the dihaloalkene to the diketone leading to hemiacetal **10** as a result of hydration. It was indeed gratifying to note that the *exo*-epoxy mesylates **24** obtained from acetates **9** upon hydrolysis and epoxidation follwed by mesylation furnished, upon ruthenium catalyzed oxidation, the hemiactals **10** in high overall yield (Scheme 4). Hydrolyses of acetates **9** was essential for the progress of the *m*-CPBA mediated epoxidation to obtain **23**.



Scheme 3. Synthesis of diquinane-based lactones **1x** and **3x**.



Scheme 4. Synthesis of diquinane-based lactones **2x** and **4x**.



Scheme 5. Synthesis of diquinane-based lactones **5x**–**z** and **6x**–**z**.

Alkaline hydrogen peroxide mediated cleavage of **10** furnished the diastereomeric *exo*-alcohols **2x** and **4x** in excellent yields.

Bis-γ-lactones **5x** and **6x** devoid of halogens were obtained by the Bu_3SnH mediated reduction of **1x** and **2x**, respectively (Scheme 5). These alcohols were converted to the corresponding acetates (**1y**, **2y**, **5y**, **6y**) and benzoates (**1z**, **2z**, **5z**, **6z**) in high yields for characterization purposes (Scheme 5).

In conclusion, we have developed a highly efficient method for the synthesis of diastereomeric diquinane-based bis-γ-lactones **1**–**6**. The overall yields are impressive, ranging from 65% to 66% for the *endo*-hydroxy 1,3-diacylglycerol derivatives **1x** and **3x** and 53% to 54% for the *exo*-hydroxy 1,3-diacylglycerol analogues **2x** and **4x**.

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9. Details of the X-ray analysis will be published in a full account in the future (CCDC 614515).