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New Strategy for the Construction of Epoxy-Bridged Tetrahydropyran Frameworks from Trioxane Precursors: Application to a Concise Synthesis of a Riesling Acetal

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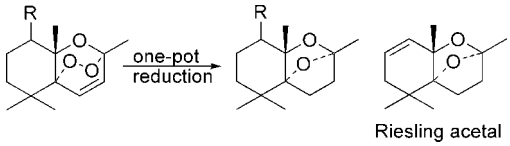
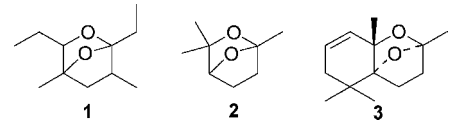


A simple one-pot method to prepare dioxabicyclo[2.2.1] heptane derivatives, from readily available 1,2,4-trioxane frameworks, under catalytic hydrogenation conditions over a platinum surface is reported. The overall transformation involves the hydrogenation of the double bond and a ring contraction rearrangement that presumably proceeds via a hydrogenolytic cleavage of the O−O bond and subsequent intramolecular ketalization. The strategy was successfully applied to the synthesis of a Riesling acetal.

Bicyclic ketal skeletons are core constituents of naturally occurring active molecules. The 2,8-dioxabicyclo- and the 6,8-dioxabicyclo[3.2.1]octane units are structural motifs of biologically important compounds such as zaragozic acids[1] and several kinds of insect pheromones.[2] Although it is less common, the more strained lower homologue 2,7-dioxabicyclo[2.2.1]heptane element is recognized as the central frame in pheromone and flavor compounds. Examples of structurally simple members of this series include compounds such as 1,3-diethyl-4,6-dimethyl-2,7-dioxabicyclo[2.2.1] heptane (**1**), recently identified as a new aggregation pheromone,[3] and 1,3,3-trimethyl-2,7-dioxabicyclo[2.2.1] heptane (**2**)[4] and the terpenoid 2,2,6,8-tetramethyl-7,11-dioxatricyclo[6.2.1.0^{1,6}]undec-4-ene (**3**),[5] both having odorant properties.



Furthermore, this epoxy-bridged tetrahydropyran substructure has been found in a growing number of diverse natural products like chuktabularins A-D,[6] isogosterone,[7] loukacinol B,[8] and leptocladolide C.[9] Bicyclic ketal skeletons are also known as a class of versatile intermediates for the stereocontrolled preparation of cyclic ethers.[10]

One common strategy for accessing the 2,7-dioxabicyclo-[2.2.1]heptane moiety focuses on the generation of an appropriate keto-diol or equivalents, followed by intramolecular ketalization. Thus, structural features such as the relative arrangement of substituents in the precursors and substitution pattern compatibility need to be taken into consideration. Recently, an alternative route to the synthesis of related 1,5-anhydrofuranoses starting from specifically protected anhydroalditols by means of an intramolecular hydrogen abstraction reaction, followed by oxidation and internal glicosidation, has been described.[11] Another method, using an 1,3-dipolar cycloaddition between carbonyl ylides and carbonyl compounds, has been proposed to assemble analogous epoxy-bridged tetrahydropyranone skeletons.[12]

Herein, we wish to report a conceptually different approach to 2,7-dioxabicyclo[2.2.1]heptane systems that, to set the epoxy-linkage, involves the reductive ring contraction reaction of a trioxacyclic peroxy-bridged precursor. We also disclose the application of this strategy to a new synthesis of natural product Riesling acetal **3**.

We recently reported an efficient light-mediated protocol for the transformation of dienones **4** into 1,2,4-trioxanes **5** by a one-pot transformation involving cis−trans isomerization, oxa-6π electrocyclization, and singlet oxygen Diels−Alder type oxygenation[13] (Scheme 1).

Although the unusual 1,2,4-trioxane unit present in heterocycles **5** is rarely found in nature, it constitutes the pharmacophoric portion of the potent antimalarial artemisinin and has therefore gained great interest in synthetic and medicinal chemistry. Due to their specific structure which includes a weak O−O bond, trioxane substrates represent suitable entities for synthetic transformations, becoming emerging starting points for the development of new methods in organic synthesis. In this regard, it has been demonstrated that due to their chemical

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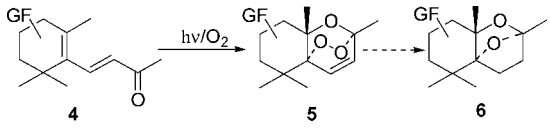
SCHEME 1. Oxidative Cyclization/Reductive Ring Contraction Strategy for the Synthesis of 2,7-Dioxabicyclo[2.2.1]heptane Moieties



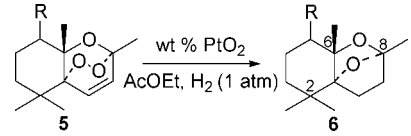
nature of cyclic peroxyacetals, spiro-1,2,4-trioxanes and related trioxa-heterocycles can be used as protecting groups for carbonyl compounds, and remarkable results concerning their stability under different reaction conditions have been uncovered.[14] Also, based on the homolytic cleavage of the O−O bond followed by rearrangement reactions, dispiro-1,2,4-trioxanes have been proposed as precursors for medium- to large-ring lactones.[15]

To pursue the synthetic potential of the 1,2,4-trioxane functionality,[16] we became interested in the inherent reactivity displayed by compounds **5** due to their particular structural features, examining a rather different aspect of the chemistry of peroxidic systems. We envisioned that double bond hydrogenation and reductive ring contraction involving the peroxide linkage would provide a simple and straightforward entry to dioxabicyclo[2.2.1]heptane derivatives **6**, functionalized analogues of natural product **3**.

Attempts to identify precedent for such a process revealed that, compared to the extensive study on deoxygenative processes in cyclic endoperoxides, little is known about similar transformations on bridged 1,2,4-trioxanes substructures, formally oxa-analogues of bicyclic 1,2-dioxins and -dioxanes. Although synthetically interesting, this type of ring reorganization is rare and, to our knowledge, literature reports only one example in which the ring contraction of the trioxane function within artemisinin is accomplished under reductive conditions promoted by zinc-acetic acid.[17] The same result could also be obtained by hydrogenation using palladium on carbon as the catalyst. The former reduction is proposed to proceed via a hydrogenolytic cleavage of the O−O bond and subsequent intramolecular cyclization. In the present context, the use of catalytic hydrogenation to induce the ring contraction would be very advantageous since the process holds the potential to perform both reductive transformations under the same reaction conditions, besides the practical advantages associated with the use of heterogeneous catalysts.

Consequently, to develop this one-pot process, the reactivity of compounds **5** toward hydrogenation was investigated. Initial experiments using palladium on carbon in different solvents led to disappointing results affording only in some cases low yield of the target molecules. By using Rh/Al_2O_3, the reaction was quite sluggish with low conversion (50%), even at high catalyst loading, giving no reproducible results. After considerable experimentation, we found that platinum oxide was an efficient catalyst to promote both reductive reactions in a one-pot process and the results are shown in Table 1. Compounds **5a-f** were hydrogenated using PtO_2 under atmospheric pressure in ethyl acetate, affording the corresponding saturated dioxabicyclo[2.2.1]-heptane derivatives **6a-f** in moderate to good yields. (Table 1)

TABLE 1. One-Pot Reduction of Unsaturated 1,2,4-Trioxanes with PtO_2 Catalyst[a]



entry	substrate	PtO_2 (wt %)	reaction time (h)	yield[b] (%)
1	**5a**	10	3	80[c]
2	**5b**	10	3	85
3	**5c**	10	12	90
4	**5d**	20	70	70
5	**5e**	10	6	75
6	**5f**	10	12	80

[a] The reactions were carried out at rt in ethyl acetate (20 mM) under 1 atm of hydrogen. **5**: R = (**a**) H; (**b**) OH_{ax}; (**c**) OH_{eq}; (**d**) OAc_{ax}; (**e**) OAc_{eq}; (**f**) O. [b] Isolated yield. [c] Reference 16a.

Inspection of Table 1 reveals that the time required to achieve complete reduction is highly modulated by the functionalities associated with our system, namely the nature and stereochemistry of the functional group present at C-5 in the carbocyclic ring, and unanticipated trends were observed during these studies. The hydrogenation of **5b** bearing the axial hydroxyl group, proceeded at comparable rate to that of the unsubstituted compound **5a** (Entries 1 and 2). However, for substrates **5c**−**f** (Entries 3−6), longer reaction times were required, reflecting a retardation effect exerted by the substituents. While compounds **5c**, **5e**, and **5f** (Entries 3, 5, and 6) could still be efficiently reduced maintaining the amount of catalyst, in the case of **5d** (Entry 4), a very slow reaction was observed and a high loading of catalyst was needed to attain an acceptable yield of **6d**. These differences, difficult to justify simply by a steric argument, may also be attributed to a combination of several other factors that modify the substrate affinity for the platinum surface, including an increased haptophilic[18] effect due to the presence of the hydroxyl group and the electronic nature of the substituent.

Having established a one-pot protocol for the preparation of heterocycles **6**, our efforts were then directed toward the synthesis of **3**. The target molecule required the installation of the double bond into the carbocyclic ring, and a methanesulfonylation-elimination protocol, starting from **6b**, appeared to be the procedure of choice.

However, these reactions proved to be surprisingly difficult. Typical procedures for the synthesis of sulfonic esters led to incomplete esterification, a problem that could only be circumvented when pyridine was used as solvent and base markedly improving the yield of **7**. (Scheme 2) Unfortunately, elimination of mesylate **7** using DBU or potassium tert-butoxide in toluene or tetrahydrofuran failed to introduce the olefin moiety and only traces of alkene **3** along with variable amounts of the unexpected alcohol **6b** were found when a great excess of sodium methoxide was used. These results may be explained by assuming that the stereoelectronic requirement for an E2-like elimination reaction cannot be satisfied for isomer **6b**. Considering that **6b** cannot attain a chair conformation with the antiperiplanar arrangement of the leaving group and the axial hydrogen at C-4, a syn-elimination of alcohol **6c** using Burgess's inner salt[19] was then attempted but again without any success, suggesting a

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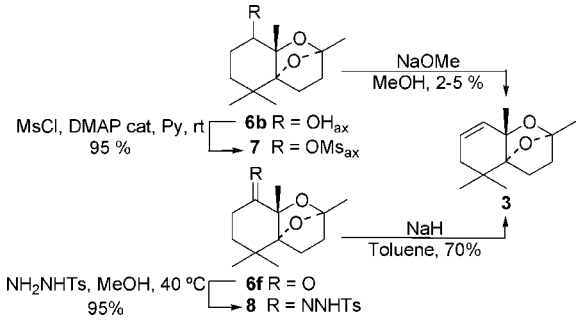
SCHEME 2. Completion of the Synthesis of Riesling Acetal 3



severe steric crowding around C-4 position. Attempts to promote direct dehydration using classic protocols resulted in extensive decomposition of the substrate.

Given the difficulties encountered in the elimination process, we decided to explore an alternative methodology involving a Bamford-Stevens[20] type reaction starting from ketone **6f**. Since base-promoted decomposition of arylsulfonylhydrazones generates a carbene intermediate (aprotic conditions), it was believed that its formation would permit conformational adjustments that minimize the steric hindrance around the α-carbon, allowing the proper alignment of the C−H bond and carbene orbitals for the 1,2-hydrogen shift to form the requisite olefin.

To this end, derivative **8** was prepared in nearly quantitative yield by treatment of **6f** with tosylhydrazide under standard conditions. Consistent with our expectation, natural product **3** was indeed cleanly obtained by treatment of **8** with sodium hydride in toluene. The spectral data of compound **3** are in agreement with those reported for synthetic Riesling acetal.[21] The new synthesis, combined with the possibility of obtaining **5f** by direct allylic oxidation of β-ionone[22] and subsequent photooxygenation,[13b] presents the advantages of short route, use of stable intermediates and ease of operation, highlighting the utility of 1,2,4-trioxane systems as valuable precursors in the construction of oxygenated targets.

In summary, we present an unconventional approach to dioxabicyclic ketal containing targets by exploiting the chemistry of 1,2,4-trioxane systems. The developed reductive process capitalizes on the ability of platinum to promote two catalytic transformations under the same reaction conditions: the hydrogenation of carbon−carbon double bond and the ring contraction of the peroxide linkage. The simplicity of the experimental procedure as well as good chemical yields render this method a synthetically useful alternative to classic deoxygenative protocols. The combination of the one-pot oxidative cyclization of β-ionone type dienones with the one-pot hydrogenation/deoxygenative ring contraction rearrangement allowed for an efficient new synthesis of natural product **3** while providing a convenient short access to previously unknown closely related functional derivatives.

Experimental Section

General Procedure for Hydrogenation. To a solution of 1 mmol of trioxane **5** in EtOAc (50 mL, 20 mM) was added PtO_2 (wt % according to Table 1), and the resulting suspension was degassed three times (three vacuum/hydrogen cycles to remove air). The suspension was vigorously stirred under a hydrogen atmosphere (balloon, ca.1 atm) at room temperature for the time indicated in Table 1, filtered through celite, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography with hexanes/EtOAc as eluent to obtain the desired reduced product (**6**).

***syn*-2,2,6,8-Tetramethyl-7,11-dioxatricyclo[6.2.1.0^{1,6}]undecan-5-ol (6b).** To a solution of trioxane **5b** (180 mg, 0.75 mmol) in EtOAc (37.5 mL, 20 mM) was added PtO_2 (18 mg, 10 wt %), and the resulting suspension was degassed three times (three vacuum/hydrogen cycles to remove air). The suspension was vigorously stirred under a hydrogen atmosphere (balloon, ca.1 atm) at room temperature for 3 h, filtered through celite and concentrated under reduced pressure. The residue was purified by silica gel column chromatography with hexanes/EtOAc as eluent to obtain 144 mg of **6b** (0.64 mmol, 85%). Colorless oil. IR (film): ν = 3555, 2944, 1476, 1396, 1024 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.52 (bs, 1H), 3.04 (bs, 1H), 2.05 (td, J = 13.7, 3.5 Hz, 1H), 1.98−1.60 (m, 6H), 1.61 (s, 3H), 1.35 (s, 3H), 1.12 (dt, J = 13.6, 3.4 Hz, 1H), 1.10 (s, 3H), 0.98 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 107.9, 93.6, 81.3, 72.9, 36.7, 33.6, 30.4, 25.8, 25.6, 25.5, 24.1, 22.6, 18.9. HRMS *m*/*z* calcd for $C_{13}H_{23}O_3$ (M + H$^+$) 227.1642, found 227.1643.

2,2,6,8-Tetramethyl-7,11-dioxatricyclo[6.2.1.0^{1,6}]undecan-5-one (6f). To a solution of trioxane **5f** (250 mg, 1.05 mmol) in EtOAc (52.5 mL, 20 mM) was added PtO_2 (25 mg), and the resulting suspension was degassed three times (three vacuum/hydrogen cycles to remove air). The suspension was vigorously stirred under a hydrogen atmosphere (balloon, ca.1 atm) at room temperature for 12 h, filtered through celite and concentrated under reduced pressure. The residue was purified by silica gel column chromatography with hexanes/EtOAc as eluent to obtain 188 mg of **6f** (0.83 mmol, 80%). Colorless crystals. Mp: 95.5−96.0 °C (Hexane). IR (KBr): ν = 2968, 2943, 1726, 1011, 937 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.62 (td, J = 14.7, 5.7 Hz, 1H), 2.35 (ddd, J = 14.7, 4.0, 3.0 Hz, 1H), 2.09 (td, J = 14.7, 4.0 Hz, 1H), 2.01−1.60 (m, 5H), 1.55 (s, 3H), 1.43 (s, 3H), 1.19 (s, 3H), 1.14 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 210.4, 107.8, 95.4, 85.4, 37.3, 36.2, 35.1, 33.8, 25.1, 24.1, 22.8, 20.0, 18.6. HRMS *m*/*z* calcd. for $C_{13}H_{21}O_3$ (M + H$^+$) 225.1485, found 225.1487.

2,2,6,8-Tetramethyl-7,11-dioxatricyclo[6.2.1.0^{1,6}]undecan-5-one tosylhydrazone (8). *p*-Toluenesulfonyl hydrazide (0.2 g, 1.07 mmol) was added to a stirred solution of ketone **6f** (0.2 g, 0.89 mmol) in dry methanol (16.4 mL). After stirring at 40 °C for 12 h, the solvent was evaporated and the residue dissolved in ether (60 mL). The solution was washed with water (20 mL), sodium carbonate (10% P/V, 2 × 20 mL) and brine (20 mL), and dried (Na_2SO_4). The solvent was evaporated to give 0.42 g of the title compound, a colorless glass that did not require further purification (isolated yield: 95%). IR (KBr): ν = 3200, 2978, 1476, 1448, 1351, 1169 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 10.48 (sb, 1H), 7.79 (m, 2H), 7.28 (m, 2H), 2.42 (s, 3H), 2.39−2.19 (m, 2H), 1.91−1.60 (m, 5H), 1.46 (s, 3H), 1.37 (ddd, J = 13.3, 4.5, 3.1 Hz, 1H), 1.33 (s, 3H), 1.05 (s, 3H), 1.01 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 156.0, 143.3, 136.2, 129.2 × 2, 127.4 × 2, 108.2, 94.7, 85.9, 37.0, 35.4, 33.7, 29.4, 25.6, 23.6, 22.5, 21.4, 19.5, 18.2. HRMS *m*/*z* calcd. for $C_{20}H_{29}N_2O_4S$ (M + H$^+$) 393.1848, found 393.1854.

2,2,6,8-Tetramethyl-7,11-dioxatricyclo[6.2.1.0^{1,6}]undec-4-ene (3). Sodium hydride (40%, 0.104 g, 1.73 mmol) was added to a stirred solution of tosylhydrazone **8** (0.4 g, 1.02 mmol) in dry toluene (16.5 mL). After 10 min, the solution was diluted (16.5 mL of toluene) and then refluxed for 3 h. The reaction was quenched with water (14 mL) and extracted with ether (3 × 30 mL). The organic extracts were combined, washed with brine (2 × 14 mL), and dried (Na_2SO_4). Then the solvent was evaporated and the residue purified by silica gel column chromatography (2% gradient elution: 100% hexanes − % hexanes/EtOAc) to give the title compound **3** (0.149 g, 0.71 mmol, 70%) as a colorless oil. IR (film): ν = 3020, 2972,

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2939, 1473, 1394, 1165, 1055 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 5.52$ (ddd, $J = 10.2, 5.5, 2.2$ Hz, 1H), 5.36 (dd, $J = 10.2, 2.9$ Hz, 1H), 2.28 (dt, $J = 17.6, 2.2$ Hz, 1H), 2.00−1.69 (m, 5H), 1.52 (s, 3H), 1.37 (s, 3H), 1.13 (s, 3H), 0.97 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 131.1, 123.6, 106.7, 91.5, 79.2, 37.6, 37.3, 33.1, 25.2, 24.15, 24.12, 23.9, 19.4$.

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Supporting Information Available: Detailed experimental procedures, compound characterization data, and copies of ^1H and ^{13}C NMR spectra of all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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