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Nucleophilic Trapping of Alkoxy-Stabilized Oxyallyl Systems Generated from Inosose 2-*O*-Mesylates

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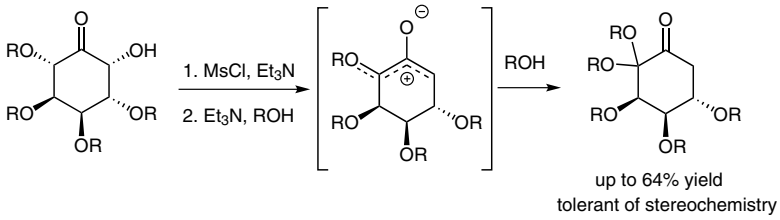

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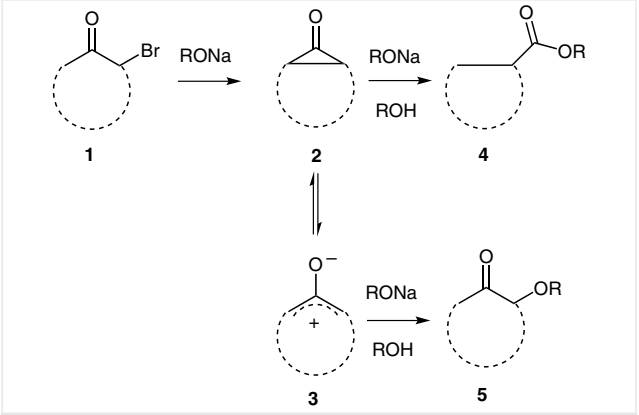
Abstract Protected inosose 2-*O*-mesylates generate oxyallyl systems by elimination of the mesylate group after enolization. The reaction is promoted by weak bases such as triethylamine and azide, and the oxyallyl systems are then trapped by nucleophilic alcohols or azide. Computations using DFT/B3LYP confirm that the singlet planar oxyallyl is stabilized by the exocyclic alkoxy group.

Key words nucleophilic addition, carbocycle, carbohydrates, rearrangement, carbocation

The oxyallyl system is a transient reactive group often used in [4+3]-cycloaddition reactions to form seven-membered and bicyclic structures.[1–3] Macmillan et al. has recently expanded their use as electrophiles that react with heteroatoms and soft π-systems when generated in the solvent 2,2,2-trifluoroethanol.[4] Stabilization of the oxyallyl system can be promoted by heteroatoms such as nitrogen[5–7] and oxygen,[1b,2] and a methoxy-stabilized oxyallyl was recently proposed as an intermediate following a cyclopropane ring-opening reaction.[8]

Oxyallyls have most notably been implicated as intermediates in the Favorskii rearrangement which transforms cyclic α-halo ketones into ring-contracted cycloalkanecarboxylic acids and acyclic alkanones into chain-extended carboxylic acids or derivatives (Scheme 1).[9,10] Evidence suggests that the reaction proceeds by the intramolecular cyclization of an enolate generated from an α-halo ketone **1** to give a cyclopropanone **2**, in equilibrium with the oxyallyl intermediate **3** (Scheme 1).[10–12] The cyclopropanone intermediate is attacked by alcohol or water giving a hemiacetal which then undergoes cyclopropane ring opening affording the final product **4**. The rearrangement is usually conducted using alkoxide or hydroxide as both base and nucleophile, affording esters or acids, respectively. When conformationally constrained α-halo ketones are used, both ring-contracted products **4** and alkoxide α-addition products **5** can be observed.[10] The retention of stereochemistry observed in some addition products,[13] trapping reactions,[14] as well as reaction rates for alcoholysis reactions[15] have been used as evidence for the oxyallyl intermediate **3**, while stereospecific examples of the rearrangement provide evidence for direct synchronous cyclopropanone formation.[9,16]

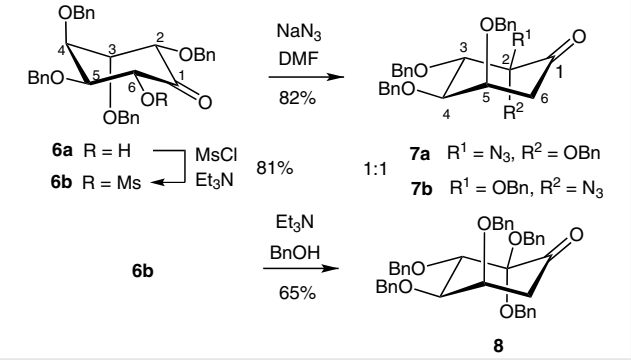


Scheme 1 General form of the Favorskii reaction

We have recently observed nucleophilic addition to 2-*O*-alkyl-6-*O*-mesylinososе derivatives through an oxyallyl intermediate without ring contraction and now detail our findings, mechanistic investigations and the scope of the reaction.

In a recent report, we described the synthesis of a series of tetra-*O*-alkylinosose derivatives from tetra-*O*-alkyldialdoses using organocatalysis and converted the products into *allo*- and *epi*-inositol.[17] To examine the utility of the primary products of cyclization such as **6a** described in this report, we attempted the synthesis of some aminodeoxyinositols. Thus, *allo*-inosose derivative **6a** was converted into mesylate **6b** using mesyl chloride and an equivalent of triethylamine in good yield (Scheme 2). Treating the mesylate with sodium azide in DMF did not give the expected 6-azido-6-deoxyinosose, rather two diastereomers of azidoketal **7a** and **7b** were isolated in a 1:1 ratio in excellent yield. An evaluation of the reaction outcome suggested

that the products arose from a Favorskii-type process with opening of the cyclopropanone or direct formation of a dipolar alkoxy-stabilized oxyallyl intermediate. If this was the case, then other nucleophiles might also be used to trap the intermediate formed in the reaction. Thus, mesylate **6b** was stirred with triethylamine in benzyl alcohol which fulfilled the role of solvent and nucleophile and to our delight afforded a good yield of ketal **8**.

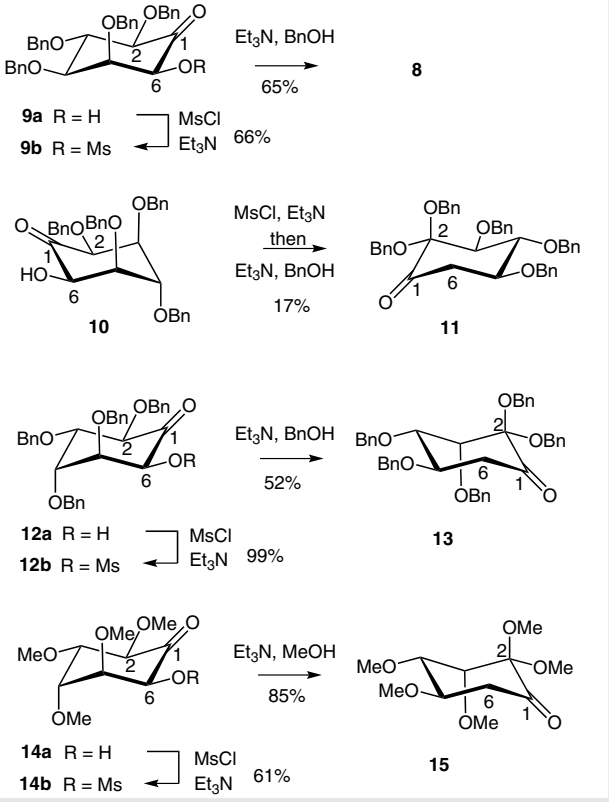


Scheme 2 Rearrangement of mesylate **6b**

The observed reaction outcome is similar to the Mattox rearrangement which converts a steroidal dihydroxyacetone motif into an enol aldehyde under acidic conditions.[18] A base-promoted variant of this rearrangement on betamethasone dipropionate has been reported by Li et al. who proposed hydrolysis and rearrangement of an intermediate enol.[19]

The characterization of ketal **8** was performed using 1D and 2D ^{1}H and ^{13}C NMR spectroscopy. A methylene group, not present in the starting material, was assigned on the basis of two upfield resonances at δ = 2.87 and 2.73 ppm in the ^{1}H NMR spectrum. Assignment of protons around the ring was straightforward using the COSY spectrum, and the relative stereochemistry of the product was found to match the starting material although the conformation was ring-flipped, on the basis of the *trans*-diaxial coupling constant (J = 8.8 Hz) observed between H-3 and H-4 and a gauche H-4 to H-5 coupling. Ketal **8** exhibited both ketone (δ = 202 ppm) and ketal (δ = 102 ppm) resonances in the ^{13}C NMR spectrum consistent with the proposed structure.

Many reactions on carbohydrates and inositols show dependence on the stereochemistry of the substrate. In addition, the Favorskii reaction on cyclohexyl substrates is influenced by the relative geometry of both the acidic proton and the leaving group.[10] To examine the scope of the reaction and the effect of stereochemistry, a series of inososes were subjected to the reaction conditions (Scheme 3). Mesylation of the alcohols under standard conditions afforded **9b**, **12b**, and **14b** which were then treated with triethylamine in benzyl alcohol or in the case of **14b** with triethylamine in methanol. The reaction was generally tolerant to stereochemistry and good yields of ketal **8**, **13**, and **15** were obtained from **9b**, **12b**, and **14b**, respectively. The product isolated from the reaction of **9b** was spectroscopically identical to the product obtained from the reaction of **6b** as both of the epimeric α-centers are eliminated in the rearrangement. Attempted isolation of the mesylate from **10** was unsuccessful and so the crude mesylate obtained after precipitating ammonium salts using ethyl acetate was treated with benzyl alcohol and triethylamine which afforded minor amounts of ketal **11**. Inosose **10** was a difficult substrate, prone to decomposition, especially on silica which may have contributed to the low yield of **11**. Conformations of the products were assigned on the basis of coupling constants which indicated that the products **11**, **13**, and **15** were ring-flipped relative to the starting materials.

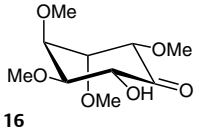
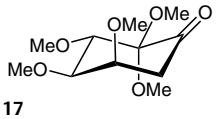


Scheme 3 Synthesis and rearrangements of **9b**, **10**, **12b**, and **14b** showing conformations of the products

All mesylates underwent varying degrees of decomposition on silica so we applied our chromatography-free procedure for **10** to the other hydroxy ketones (Table 1).

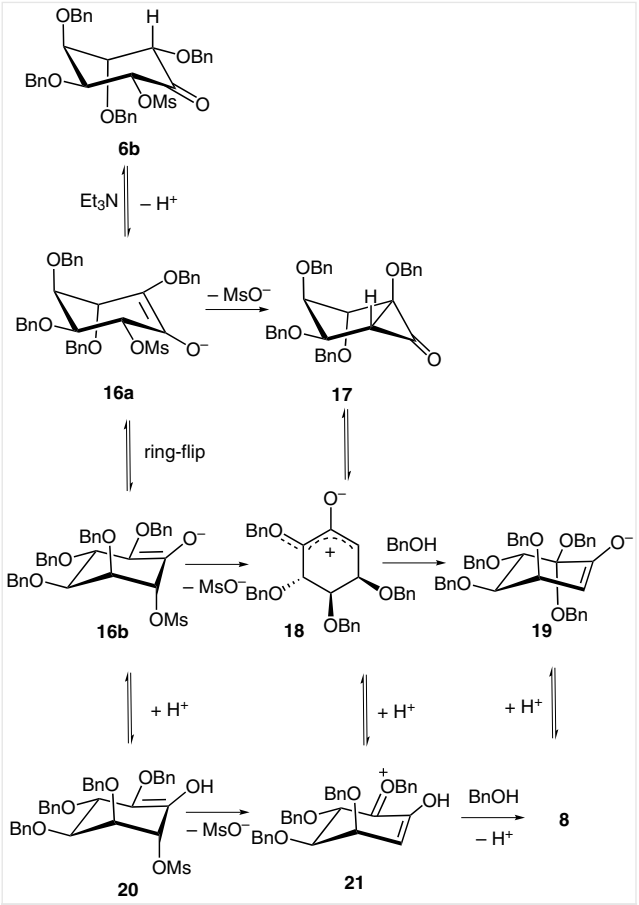
The yields obtained from **6a** and **12a** were superior using this chromatography-free methodology, however, both **9a** and **14a** afforded inferior isolated yields of ketals. Application of the conditions to the methyl ether **16** afforded a poor yield of ketal **17**.

Table 1 Chromatography-Free Rearrangement Starting with Hydroxy Ketone[a]

Entry	Starting material	Product	Yield (%)
1	**6a**	**8**	58
2	**9a**	**8**	30
4	**12a**	**13**	64
5	**14a**	**15**	45
6	 **16**	 **17**	27

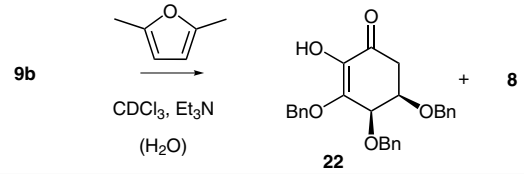
[a] Reactions were performed on 40–60 mg of hydroxy ketone using 2 equiv of MsCl and Et_3N and once complete, amine salts were precipitated using EtOAc, the mixture filtered, concentrated, and BnOH or MeOH (2 mL) and Et_3N (4 equiv) were added.

A mechanism for the reaction of **6b** which explains the observed product **8** is shown in Scheme 4. Axial α-hydrogens are more acidic than equatorial hydrogens as the orbitals are aligned such that the developing carbanion can be stabilized by the carbonyl group. Equatorial leaving groups are required for the formation of the cyclopropanone as this makes the C–X σ* orbital accessible to the enolate carbanion.[10] The conformation in solution for **6b** is shown in Scheme 3 based upon the 10 Hz *trans*-diaxial coupling seen for H-3 and H-4. Thus, starting with **6b**, the triethylamine in the reaction mixture promotes the formation of enolate **16a** from which the cyclopropanone **17** can form by direct ring closure due to the equatorial mesylate. Ring opening of the cyclopropanone **17** promoted by the benzyloxy group gives the alkoxy oxyallyl intermediate **18**. Alternatively, a ring flip of enolate **16a** to give **16b** makes the mesylate axial and elimination can afford **18** without the involvement of the cyclopropanone **17**. Formation of the final product could proceed by protonation of **18** to give **21** and then nucleophilic addition of the alcohol, or by addition of alcohol, to give **19** and then protonation. Formation of tautomer **20** from mesylate **6b** could avoid oxyallyl **18**, proceeding through the oxocarbenium ion **21**, and such a mechanism would be similar to that proposed for the Mattox rearrangement.



Scheme 4 Mechanism for the rearrangement of **6b**

Attempted small-scale trapping of the proposed benzyloxyoxyallyl species from **9b** with two equivalents of 2,6-dimethylfuran in $CDCl_3$ gave only reaction with adventitious water, then tautomerism affording unstable **22** as well as **8** formed from eliminated benzyl alcohol (Scheme 5). Attempted trapping with furan and cyclopentadiene gave complex mixtures with no clear evidence for any [4+3] reactions.



Scheme 5

To examine the reaction mechanism further we have used computational chemistry to study a model methoxyoxyallyl system using DFT B3LYP/6311++G**.[20] Previous computational studies have examined the semibenzylic and cyclopropanone pathways for the Favorskii rearrangement but have not examined the effect of alkoxy substitu-

tion adjacent to the ketone.[21] The oxyallyl species has previously been studied computationally which has shown the ground state to be a singlet diradical.[23]

There were three energy-minimized structures found for 2-methoxyoxyallyl **23**, corresponding to the planar singlet structure **23P**, the chair cyclopropanone **24C**, and the boat cyclopropanone **24B** (Figure 1,Table 2). Both **24C** and **24B** are drawn with a formal cyclopropyl ring as these energy-minimized structures are isoenergetic to those found starting with **23**. In vacuum, the planar conformation **23P** was 0.9 kcal·mol^{-1} more stable than the lowest-energy boat cyclopropanone **24B**, while the alternative chair **24C** was destabilized by 4.9 kcal·mol^{-1} as the methoxy group eclipsed the neighbouring C–H bond. In vacuum, the triplet diradical was calculated to be 10.8 kcal·mol^{-1} higher in energy than **23P**.

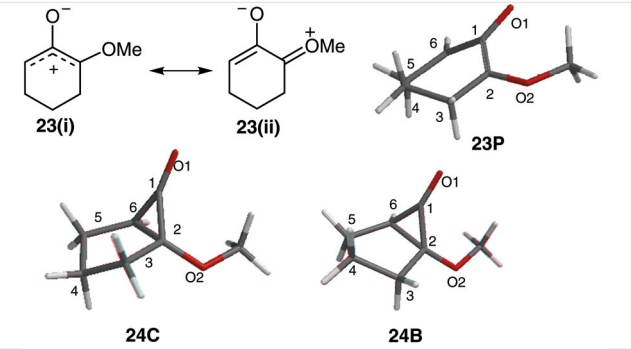


Figure 1 Energy-minimized structures for the model system **23**

The p-type lone pair found on the alkoxy oxygen stabilizes the planar conformation **23P** as rotation around the C–O bond taking these electrons out of conjugation causes the structure to collapse to the cyclopropanone **24B**. The empirical solvation model[22] implemented in Spartan '14 shows significant stabilization of the planar **23P** relative to the cyclopropanones. The polar solvents used would stabilize **23P** as an intermediate and this may explain why ring-contraction products are not observed.

The long C1–O1 bond favors resonance hybrid **23** and the short C1–C6 bond relative to the C1–C2 bond as well as the short C2–O2 bond relative to the same bond in **24C** or **24B** favor canonical form **23(ii)**. Calculation of the natural charges[24] showed cationic character at C2 (+0.52) and anionic character at C6 (–0.16). The charges and bond lengths explain why addition is observed adjacent to the alkoxy group at C2 and not at the allylic C6 position. In addition, the enolate formed by reaction of methanol at C2 of **23P** is computed to be 11.4 kcal·mol^{-1} more stable than the enolate formed from addition at C6.

In conclusion, we have demonstrated that 2-*O*-alkyl-6-*O*-mesylinososes undergo an oxyallyl or oxyallyl cation mediated rearrangement in the presence of alcohols and amine base yielding solely addition products. We were able to trap the intermediates (**18** or **21**) using both azide and alcohols. Importantly, the conditions are extremely mild and the examples demonstrate the reaction is general and tolerant to stereochemistry around the ring. The reaction could find use transferring oxidation within carbohydrate structures and in generating masked 1,2-diones.

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1379490. Included are experimental procedures, characterization data, NMR spectra for **6**–**9**, **11**, **13**, **15**, and **17**, and atomic coordinates for **23** and **24**.

References

(1) (a) Harmata, M. *Chem. Commun.* **2010**, *46*, 8886. (b) Harmata, M. *Chem. Commun.* **2010**, *46*, 8904.
(2) Lee, J. C.; Jin, S.-j.; Cha, J. K. *J. Org. Chem.* **1998**, *63*, 2804.
(3) Meilert, K. T.; Schwenter, M.-E.; Shatz, Y.; Dubbaka, S. R.; Vogel, P. *J. Org. Chem.* **2003**, *68*, 2964.
(4) Vander Wal, M. N.; Dilger, A. K.; MacMillan, D. W. C. *Chem. Sci.* **2013**, *4*, 3075.
(5) Lohse, A. G.; Hsung, R. P. *Chem. Eur. J.* **2011**, *17*, 3812.
(6) Du, Y.; Krenske, E. H.; Antoline, J. E.; Lohse, A. G.; Houk, K. N.; Hsung, R. P. *J. Org. Chem.* **2013**, *78*, 1753.
(7) Krenske, E. H.; He, S.; Huang, J.; Du, Y.; Houk, K. N.; Hsung, R. P. *J. Am. Chem. Soc.* **2013**, *135*, 5242.
(8) Goodell, J. R.; Poole, J. L.; Beeler, A. B.; Aubé, J.; Porco, J. A. *J. Org. Chem.* **2011**, *76*, 9792.
(9) Kende, A. S. *Org. React.* **1960**, *11*, 261.
(10) Baretta, A.; Waegell, B. In *Reactive Intermediates*; Springer: Berlin, **1982**, 527.
(11) Loftfield, R. B. *J. Am. Chem. Soc.* **1951**, *73*, 4707.
(12) Hamblin, G. D.; Jimenez, R. P.; Sorensen, T. S. *J. Org. Chem.* **2007**, *72*, 8033.
(13) House, H. O.; Thompson, H. W. *J. Org. Chem.* **1963**, *28*, 164.
(14) Fort, A. W. *J. Am. Chem. Soc.* **1962**, *84*, 4979.
(15) Fort, A. W. *J. Am. Chem. Soc.* **1962**, *84*, 2620.
(16) Stork, G.; Borowitz, I. J. *J. Am. Chem. Soc.* **1960**, *82*, 4307.

Table 2 Selected Properties of Energy-Minimized Structures Using DFT B3LYP/6311++G**

	Interatomic distance (Å)					Relative energy (kcal·mol^{-1})	Solvation energy (kcal·mol^{-1})	Natural charges	
	C1–C6	C1–C2	C2–C6	C1–O1	C2–O2			C2	C6
24C	1.48	1.47	1.61	1.20	1.39	+4.9	+6.30	+0.21	–0.33
23P	1.41	1.46	2.33	1.26	1.31	0	0	+0.52	–0.16
24B	1.47	1.47	1.65	1.21	1.38	+0.9	+6.16	+0.23	–0.30

(17) Stockton, K. P.; Greatrex, B. W.; Taylor, D. K. *J. Org. Chem.* **2014**, *79*, 5088.
(18) Mattox, V. R. *J. Am. Chem. Soc.* **1952**, *74*, 4340.
(19) Li, M.; Chen, B.; Lin, M.; Chan, T.-M.; Fu, X.; Rustum, A. *Tetrahedron Lett.* **2007**, *48*, 3901.
(20) *Spartan '14*; Wavefunction Inc: Irvine, CA, **2014**, 1.1.4 ed..
(21) Moliner, V.; Castillo, R.; Safont, V. S.; Oliva, M.; Bohn, S.; Tuñón, I.; Andrés, J. *J. Am. Chem. Soc.* **1997**, *119*, 1941.
(22) Chambers, C. C.; Hawkins, G. D.; Cramer, C. J.; Truhlar, D. G. *J. Phys. Chem.* 1996, *100*, 16385.
(23) Ichino, T.; Villano, S. M.; Gianola, A. J.; Goebbert, D. J.; Velarde, L.; Sanov, A.; Blanksby, S. J.; Zhou, X.; Hrovat, D. A.; Borden, W. T. *Angew. Chem. Int. Ed.* **2009**, *48*, 8509.
(24) Reed, A. E.; Weinstock, R. B.; Weinhold, F. *J. Chem. Phys.* **1985**, *83*, 735.