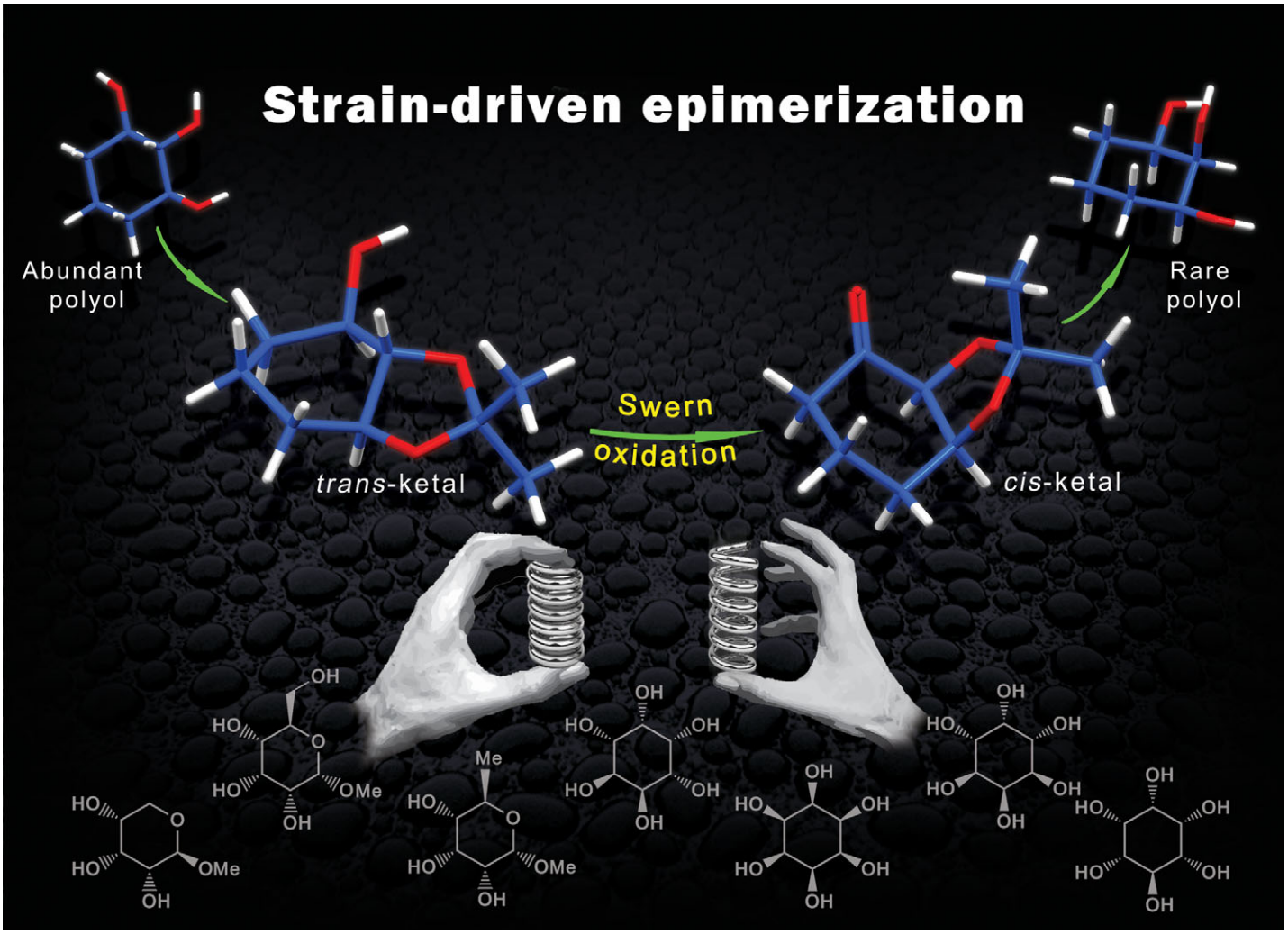

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Bio-inspired synthesis of rare and unnatural carbohydrates and cyclitols through strain driven epimerization

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Bio-inspired synthesis of rare and unnatural carbohydrates and cyclitols through strain driven epimerization†‡

Raja Mohanrao, Aromal Asokan and Kana M. Sureshan*

We report a bio-inspired, strain driven epimerization of *trans*-ketals to *cis*-ketals through an enolate intermediate. Swern oxidation of a hydroxyl group adjacent to a *trans*-ketal effects both oxidation and its epimerization to *cis*-ketal. This novel and general strategy allows inversion of up to three contiguous stereocenters and has been illustrated by the synthesis of several unnatural/rare isomers of carbohydrates/cyclitols from their naturally abundant isomers.

Carbohydrates and cyclitols are two important classes of biologically active polyols involved in many physiological processes such as cellular signaling, structure, and storage, *etc.*[1] However, only seven of the many possible pentoses and hexoses and one (*myo*-inositol) of the nine possible inositols (major class of cyclitols) are naturally abundant. Hence there has been a tremendous interest in the synthesis of especially the unnatural or rare isomers of these polyols as tools for biological investigations.[2] Synthesis of rare/unnatural polyols from their cheaply available isomers by inversion of one or more hydroxyl groups through oxidation–reduction,[3] the Mitsunobu reaction[4] or S_N2 substitution[5] are the common methods. However, these methods are not suitable for efficient synthesis of isomers with more than one configurational difference with respect to the starting isomer. We herein report a novel and general strategy for inversion of up to three contiguous stereocenters.

Many isomerases, enzymes involved in the biosynthesis of unusual sugars from common sugars, use enolate chemistry for the isomerization of a carbon center adjacent to a carbonyl group (Fig. 1A).[6] In such cases, factors such as increased stability of the product (at least in the enzyme environment) dictate the direction of the reaction. While synthetically mimicking such a strategy, exploiting the stability difference for the stereochemical inversion, is appealing, creating such a stability difference is a formidable challenge. Ketalization is one of the best methods to protect vicinal diols of cyclitols and carbohydrates.[7] It is known that a simple *trans*-ketal, formed from *anti*-diols has a greater steric strain than the *cis*-ketal, formed from *syn*-diols.[8] We envisioned that this steric strain can be exploited for the epimerization of a *trans*-ketal adjacent to a keto group to a *cis*-ketal through the enolate (Fig. 1B). Oxidation of a hydroxyl group adjacent to a *trans*-ketal to ketone and its subsequent enolization using a base would result in the epimerization of a *trans*-ketal to a *cis*-ketal. Furthermore, the keto group can be reduced selectively by using appropriate reducing agents, thus allowing stereochemical inversion of more than one center.

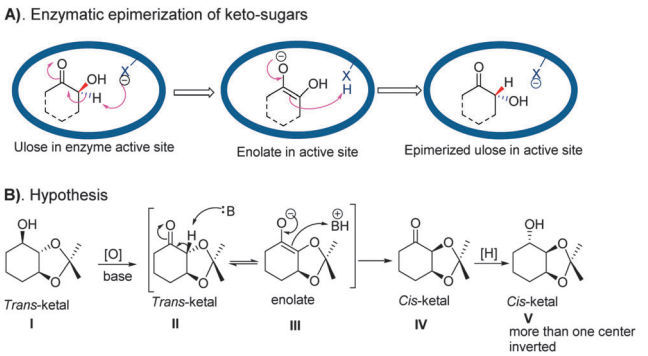

Fig. 1 (A) Mechanism of enzyme mediated epimerization of uloses, (B) proposed strain driven epimerization of a *trans*-ketal to a *cis*-ketal.

In order to test this hypothesis, ketone **2**, prepared from the D-xylose derivative **1** was treated with triethylamine. Gratifyingly, the *cis*-ketal ketone **3** could be isolated in good yield, which could be reduced to D-ribose derivative **4**. Similarly, *myo*-inositol derivative **5** upon oxidation gave ketone **7**, which could be epimerized to the symmetrical ketone **9** by treatment with triethylamine. As anticipated, only the *trans*-ketal underwent epimerization. Ketone **8** obtained from the cyclohexylidene derivative **6** also underwent smooth epimerization to **10** under basic conditions.

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† Dedicated to Prof. Horst Kunz.

‡ Electronic supplementary information (ESI) available: Quantum mechanical calculations, experimental procedures, characterization data and crystallographic data for **33A**, **37**, **38**, **39**, **38A**, **49** & **50**. CCDC 973079–973085. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c4cc00868e

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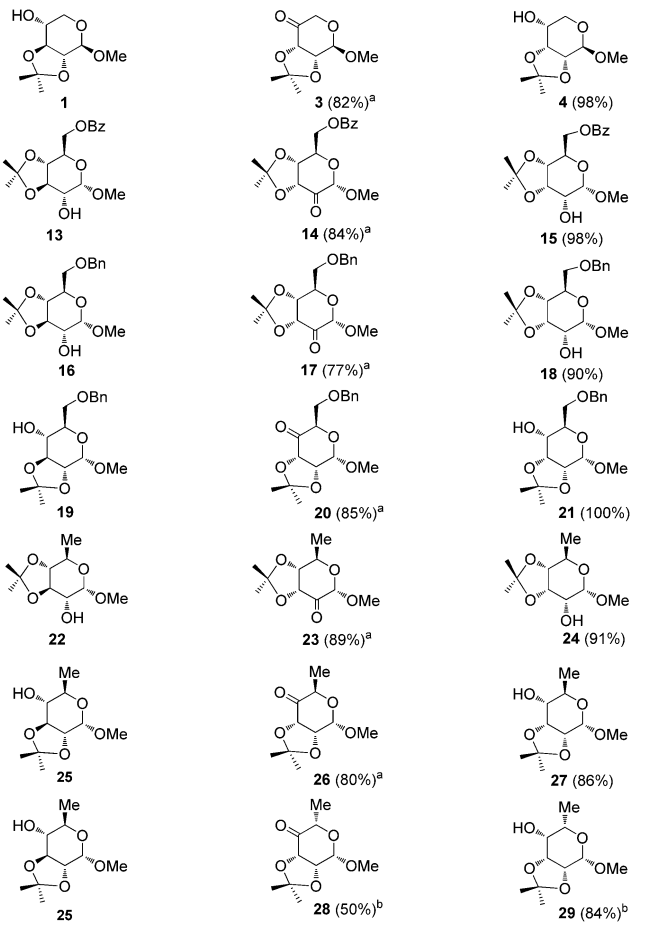
Both the ketones **9** and **10** upon reduction gave the corresponding *epi*-inositol derivatives **11** and **12**, respectively.

Having established the proof of concept, we, next, were curious to know whether Swern oxidation would directly lead to the formation of the epimerized product (ketone with *cis*-ketal) as the triethylamine used in the Swern oxidation reaction can, in principle, effect the epimerization of the *trans*-ketal to the *cis*-ketal *in situ*. To test this hypothesis, xylose derivative **1** was subjected to Swern oxidation. To our satisfaction, ketone **3** was obtained in good yield. Ketone **3** on reduction gave the D-ribose derivative **4** (98%) as expected (Table 1). To check the generality of this methodology, D-glucose derivative **13** was subjected to Swern oxidation. As anticipated, epimerised pyranosid-2-ulose **14** was formed in very good yield, which on reduction with sodium borohydride gave D-allose derivative **15** as a single isomer in almost quantitative yield. Similarly, differently protected ketals **16** and **19** underwent a smooth oxidation–epimerization reaction giving corresponding uloses **17** and **20**, respectively, which could be reduced to D-allopyranoside derivatives **18** and **21** in good yields. D-Quinovose derived ketals **22** and **25** also gave epimerized ketones **23** and **26**, respectively, which on reduction gave the derivatives **24** and **27** of the very rare sugar, 6-deoxy-allopyranose,[9] in good yields. Interestingly, a prolonged reaction of **25** gave ketone **28** with inverted stereochemistry at both C3 and C5, which could be reduced to get L-pneumose derivative **29**. This provides possible access to other rare and biologically important L-hexoses such as L-rhamnose (C4 epimer).

Table 1 Isomerization of sugars

Substrate $\xrightarrow{a \text{ or } b}$ Oxidised product $\xrightarrow{c}$ Reduced product



[a] $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, 0.5–1 h. [b] $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, 96 h. [c] $NaBH_4$, MeOH, 0 °C, 0.5 h.

It is worthy of note that by using our method, we could synthesize expensive sugars such as allose and ribose in their orthogonally protected form from cheaply available sugars. Since all but one hydroxyl groups are protected, the corresponding epimeric sugars can be accessed easily, in principle, *via* conventional epimerization methods. For instance, allose derivatives **18** and **21**, in principle, provide easy access to their epimeric hexoses *viz.* D-gulose (C4 epimer) and D-altrose (C2 epimer), respectively. Also there is a possibility of stereoselective reduction of the keto group using different reducing agents.

Having shown the utility of this methodology in carbohydrates, we turned our attention to cyclitols. As quinic acid is a chiral pool cyclitol for the synthesis of natural products,[10] application of isomerisation would be of tremendous interest synthetically. Thus, quinic acid derivative **30** was subjected to Swern oxidation (Table 2). Ketone **31** and enone **34** were isolated as a mixture both with *cis*-isopropylidene groups. A prolonged reaction leads to the formation of protocatechuic acid methyl ester (Scheme S5, ESI‡), a natural product with antioxidant, anti-inflammatory and anti-cancer activities, biosynthesized from shikimic acid. While the reduction of enone **34** gave alcohol **35** irrespective of the reducing agent, ketone **31** gave exclusively lactone **32** and alcohol **33** when reduced with $NaBH_4$ and $NaBH(OAc)_3$, respectively.

Of all nine inositols, *allo*-, *neo*-, *epi*-, *muco*- and *cis*-inositols are unnatural isomers. However, these unnatural inositols and derivatives are essential for chemical biology exploration of inositide signaling. This prompted us to investigate the possibility of adopting our methodology for the synthesis of unnatural inositol derivatives from the cheaply available *myo*-inositol. Thus, *myo*-inositol derivative **5**, was subjected to Swern oxidation. As anticipated, the symmetric ketone **9** was obtained in very good yield, which on reduction gave *epi*-inositol derivative **11** as before (Scheme 1). Similarly, the dicyclohexylidene derivative **6** also underwent a smooth oxidation–epimerization sequence to form the symmetrical ketone **10** under the Swern oxidation conditions as expected.

Swern oxidation of *myo*-inositol derivative **36** gave inosose **37**, whose crystal structure (ESI‡) showed the presence of two *cis*-isopropylidene groups. Reduction of **37** with sodium borohydride gave a 1 : 1 mixture of *allo*-inositol derivative **38**, wherein two contiguous centers are inverted, and *neo*-inositol derivative **39**, whose structures were confirmed by solving their X-ray crystal structures (ESI‡). Interestingly, reduction of **37** with K-selectride gave exclusively *neo*-inositol derivative **39** (93%). The best condition in favour of *allo*-inositol derivative **38** was the use of sodium triacetoxyborohydride for reduction and the selectivity was 2 : 1 (Table S5, ESI‡). Thus by choosing appropriate conditions, the required isomeric inositol derivative **38** or **39** could be obtained. Similarly, Swern oxidation of *myo*-inositol derivative **40** gave the

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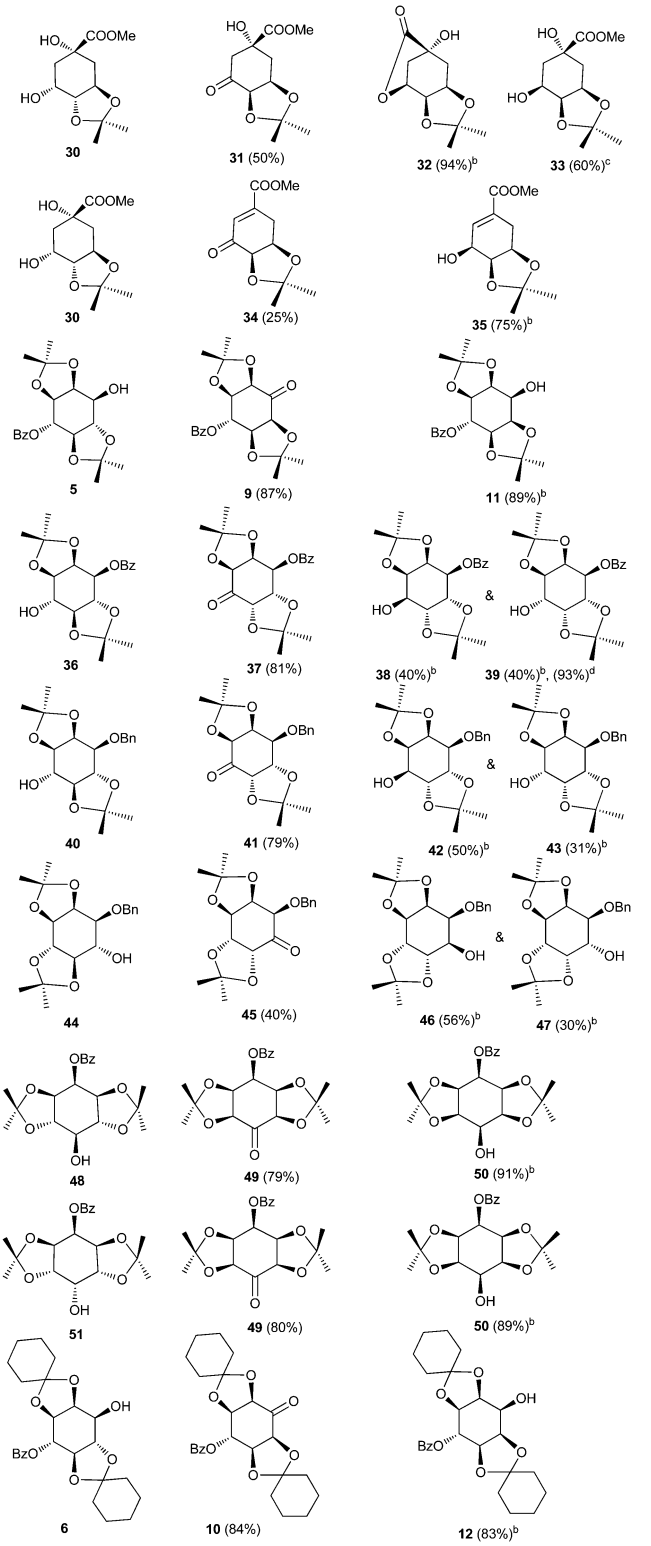
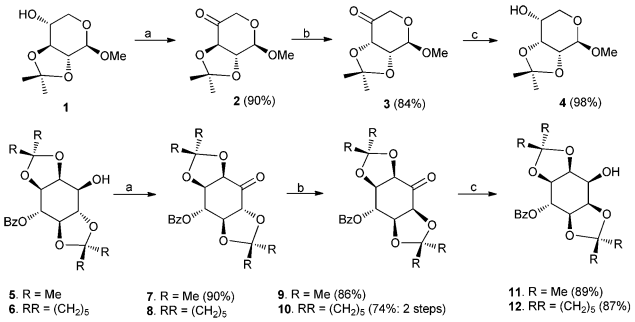
Table 2 Isomerization of cyclitols[e]

Substrate $\xrightarrow{a}$ Oxidised product $\xrightarrow{b/c/d}$ Reduced product



[a] $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, 0.5–1 h. [b] $NaBH_4$, MeOH, 0 °C, 0.5 h. [c] $NaBH(OAc)_3$, CH_2Cl_2, rt. [d] K-selectride, THF, −78 °C. [e] All the inositols derivatives are either racemic or *meso* compounds.



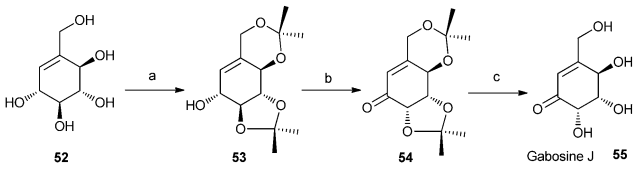
Scheme 1 Proof of concept: (a) Dess–Martin periodinane, CH_2Cl_2 (b) Et_3N, CH_2Cl_2, rt (c) $NaBH_4$, MeOH, 0 °C, 0.5 h.

inosose **41**, which on reduction with sodium borohydride gave a mixture of *allo*-inositol derivative **42** and *neo*-inositol derivative **43**. Swern oxidation of *myo*-inositol derivative **44** gave the epimerized product **45**. A prolonged reaction leads to the E1cB elimination giving an α,β-unsaturated ketone (ESI‡). Reduction of **45** with sodium borohydride yielded two differently protected *allo*- and *neo*-inositol derivatives **46** and **47**, respectively, in a 2 : 1 ratio (ESI‡).

One of the interesting unnatural isomers among the inositols is *cis*-inositol, which forms complexes with metal cations.[11] We were curious to know whether we can make a *cis*-inositol derivative from a *myo*-inositol derivative by epimerization of two *trans*-ketals, simultaneously. Swern oxidation of **48**[12] gave the epimerized ketone **49**, whose crystal structure (ESI‡) showed the presence of two *cis*-isopropylidene groups. As anticipated, sodium borohydride reduction of **49** gave *cis*-inositol derivative **50** exclusively. The structural identity of **50** could be proved by solving its single crystal X-ray structure (ESI‡). As both the *trans*-ketals could be isomerized to *cis*-ketals, it is possible to invert three contiguous stereocenters by adopting our methodology. This was exemplified by the Swern oxidation of *neo*-inositol derivative **51** which gave the ketone **49**, which on reduction gave the *cis*-inositol derivative **50**, where in three contiguous stereocenters are inverted compared to starting alcohol **51**. It is worthy of note that stereochemical inversions of more than one adjacent chiral center are difficult by existing methods due to complications arising from neighbouring group participation, other side reactions or steric crowding.[13]

In order to exploit the utility of this methodology in natural product synthesis, we have synthesized the natural product, Gabosine J from the known pentol **52**.[14] As Gabosine J can be synthesized by oxidation of the allylic alcohol and inversion of the homoallylic center in pentol **52**, our strategy seems to be ideal for its synthesis. Ketalization of **52** gave the known diketal **53** exclusively in very good yield, which on Swern oxidation gave the epimerized enone **54**. Acidic hydrolysis of enone **54** gave Gabosine J in overall excellent yield (Scheme 2).

In summary, taking a cue from Nature, for the first time, we reported a reliable strain driven epimerization of *trans*-ketals to *cis*-ketals under Swern oxidation conditions. Judicious selection of reagents for the reduction of the resultant keto group offers additional stereochemical control. While stereochemical



Scheme 2 Synthesis of Gabosine J: (a) 2-methoxypropene, CSA, DMF, 1 h, 90%; (b) $(COCl)_2$, DMSO, Et_3N, DCM, −78 °C, 5–6 h, 84%; (c) TFA (10% in DCM), rt, 1 h, 92%.

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inversions of more than one adjacent chiral center are difficult by existing methods, our methodology allows inversion of up to three contiguous chiral centers. The fact that the epimerization of an alcoholic center can be done without removing the protecting groups is beneficial in the context of multistep synthesis. The use of our novel methodology has been illustrated by the expedient syntheses of several expensive, rare and unnatural sugars and cyclitols from cheaply available isomers. As Swern oxidation is one of the common synthetic transformations, there is great potential for the application of this methodology for oxidation-cum-epimerization in natural product synthesis.

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