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ARTICLE TYPE

A Mild Lewis Acid Mediated Epoxy-Ester to Bicyclic Ortho Ester Rearrangement

Awais Ahmed, Steven D. R. Christie,*[a] Mark R. J. Elsegood and Gareth J. Pritchard*[b]

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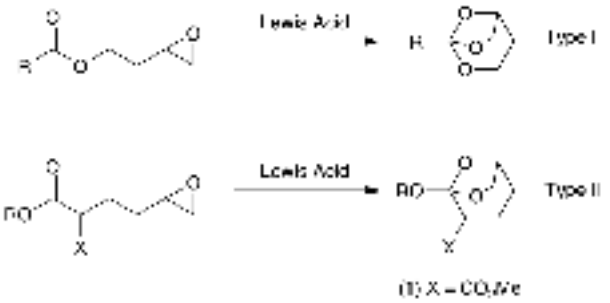
A high yielding rearrangement of epoxy-esters, under Lewis acid conditions, to give bicyclic ortho esters is reported.

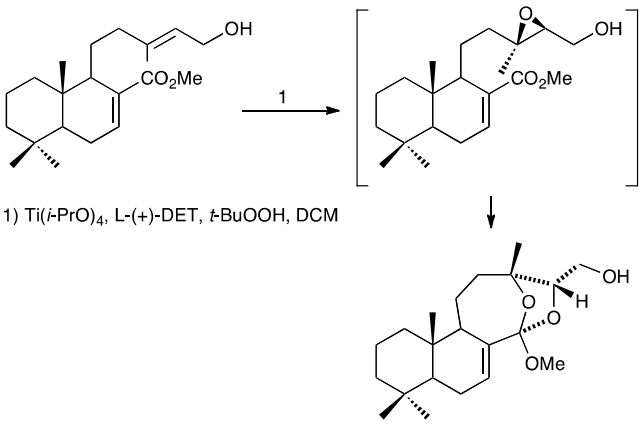
We have an interest in the development of new methods to prepare heterocyclic systems; including stoichiometric organometallics,[1] palladium mediated reactions,[2] biomimetic methods,[3] condensation of reactive electrophilic systems.[4] We now wish to report a new route to methoxy substituted dioxabicyclo[3.2.1]octane systems using a epoxy-ester to ortho ester rearrangement.

The rearrangement of epoxy-esters to ortho esters is a well established reaction.[5] It has found applications in the protection of carboxylic acids,[6] in total synthesis of natural products,[7] and also in numerous elegant biomimetic chemistry.[8] The majority of the reports focused on the formation of a trioxabicyclic ortho ester where the epoxide of the precursor is in the alkoxide part of the ester (Type I, Scheme 1). Our curiosity led us to investigate the formation of a lesser-known configuration of bicyclic ortho ester starting from a precursor where the epoxide is linked to the carbonyl of the ester (Type II, Scheme 1).



Scheme 1 Epoxy-ester to ortho ester rearrangement.

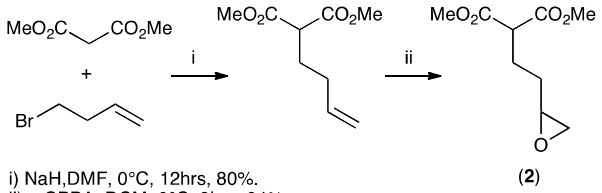
To our knowledge there have been only two reports of this type of reaction, both being in the field of diterpene chemistry (Scheme 2).[9,10] Urones has reported the unexpected formation of such an ortho ester during a Sharpless asymmetric epoxidation of a diterpene.[9] The chemistry was further used in the semisynthesis of bioactive drimanes, pereniporin B and warburganal, but no follow up on the ortho ester chemistry.[10] We believe this reaction warrants further exploration since ortho ester remain an under exploited functional group in organic chemistry, thus giving access to unusual compounds and opens up the development of new chemical space. Herein we report our preliminary studies.



Scheme 2 Formation of ortho ester in an asymmetric epoxidation.

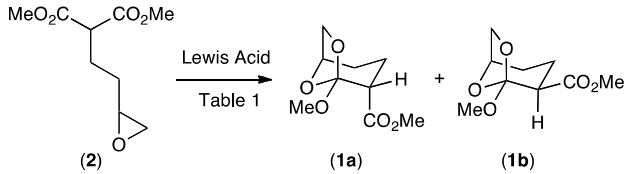
Our initial ortho ester target is the methoxy substituted dioxabicyclo[3.2.1]octane (**1**). It was chosen because the bridged 5,6-membered ring system was expected to be the both kinetically and thermodynamically stable, thus improving our prospect of isolating the desired bicyclic ortho ester. The use of alkylated dimethyl malonate derivatives as starting materials allowed quick access to the epoxy ester precursors. Also the desymmetrization of the malonic ester center during the reaction would give additional insights into the reaction (Scheme 1, Type II, X = CO_2Me). The required epoxy ester (**2**) was prepared by alkylation of dimethyl malonate with 4-bromo-1-butene and subsequent epoxidation with mCPBA in good over all yield (Scheme 3).

With the required epoxy ester in hand, we attempted the Lewis acid catalysed rearrangement by straightforward treatment with $ZnBr_2$ in DCM. After 8 hours at room temperature, it was gratifying to isolate the targeted ortho ester product as two separable diastereoisomers in a good combined yield of 80% (Scheme 4). The relative stereochemistry of diastereoisomers (**1a**)



i) NaH,DMF, 0°C, 12hrs, 80%.
ii) mCPBA, DCM, 0°C, 8hrs, 94%.

Scheme 3 Preparation of the epoxy ester.



Scheme 4 Trial Lewis acid catalysed rearrangement reaction.

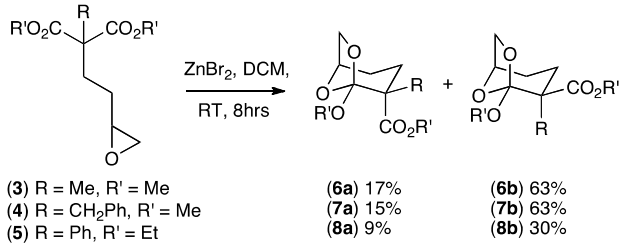
and (**1b**) where confirmed by nOe experiments and single crystal X-ray structures.

This successful initial result was followed up by possible optimisation under a range of reaction conditions (Table 1). The same substrate (**2**) was reacted using a limited range of Lewis Acids, solvents and conditions. The most successful Lewis acids were found to be $ZnBr_2$ and $Yb(OTf)_3$. Some variations in the diastereoselectivity was seen with $ZnBr_2$ depending on the reaction conditions while $Yb(OTf)_3$ giving essentially one diastereoisomer. The chlorinated solvents DCM and DCE appear to be best solvents for this reaction and it typically ran smoothly at room temperature over a period 8 hours.

Lewis Acid	Solvent	Equiv.	Temp.	Time	Yield % (**1a**:**1b**)
$ZnBr_2$	DCM	1.0	RT	8h	80 (17:63)
$ZnBr_2$	DCM	0.1	Reflux	12h	80 (30:50)
$ZnBr_2$	DCE	0.1	50°C	12h	90 (30:60)
$ZnBr_2$	DCE	1.0	RT	8h	90 (30:60)
$ZnBr_2$	Toluene	0.1	40°C	18h	58 (24:34)
$ZnBr_2$	THF	1.0	60°C	6h	-
$MgBr_2$	DCM	1.0	RT	10h	-
$BF_3.OEt_2$	DCM	0.1	RT	1h	-
$Sc(OTf)_3$	DCM	0.01	Reflux	20min	30 (0:30)
$Yb(OTf)_3$	DCM	0.1	Reflux	8h	75 (0:75)

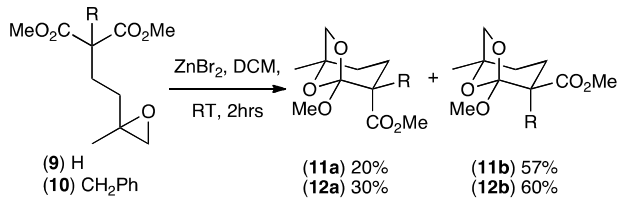
Table 1 Results of Lewis acids used and reaction conditions.

The scope of this ortho ester formation reaction was then explored using a range of epoxy ester substrates. The first variation was the introduction of an additional alkyl group to the malonic ester. This would examine the effect of steric bulk at this position and allow the incorporation of a quaternary centre into the molecule. It is also interesting to note that the quaternary centre is adjacent the quaternary centre of the ortho ester, since the generation of vicinal quaternary carbon centers, always a challenge for organic synthesis. The substrates (**3-5**) were readily prepared by standard alkylation chemistry, as outlined above (Scheme 3). Yields for all three examples, Me, Ph, CH_2Ph, (**6-8**) ranged from reasonable to good (Scheme 5). The stereoselectivity of the reactions saw no major changes. This observation is consistent with our proposed reaction mechanism with Lewis acid coordination directing the orientation of the product's ester group instead of simply a result of steric effect.



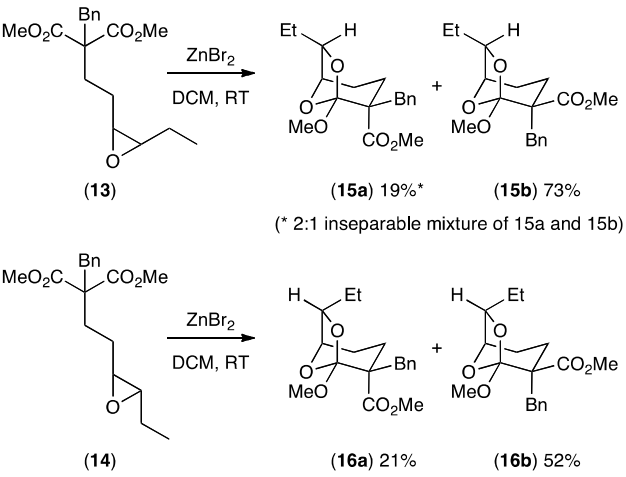
Scheme 5 Introduction of a substituent and the malonate centre.

The next extension to the work was to explore the possibility of introducing a substituent on the epoxide. To this end gem-disubstituted expoxides (**9-10**) were prepared in order to examine the additional alkyl group's influence on cyclisation under Lewis acid conditions. It was gratifying to find that both examples worked well giving products (**11-12**) combined yields of 77% and 90% respectively, in a rough ration of 1:2, showing a substituient at this position has little impact on the reaction (Scheme 6).



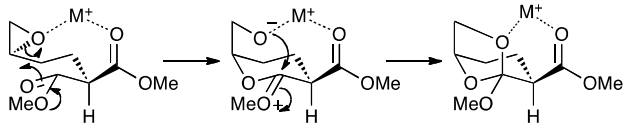
Scheme 6 Reactions using a substituted epoxide starting material.

Following the above positive results, we turned our attention to 1,2-disubstituted epoxides (**13**) and (**14**) analogous to investigation by Sum and Weiler into the stereochemical outcome of the Lewis acid catalysed isomerisation of epoxides to give ketals.[11] They have shown the epoxide ring opening was stereospecific by using *cis* and *trans* epoxides. We therefore undertook similar work to see if the rearrangement of epoxy-ester to ortho ester reaction was also stereospecific. The epoxides (**13**) and (**14**) were readily prepared by alkylation, subsequent epoxidation from respective *Z* and *E* alkenes (Scheme 7).



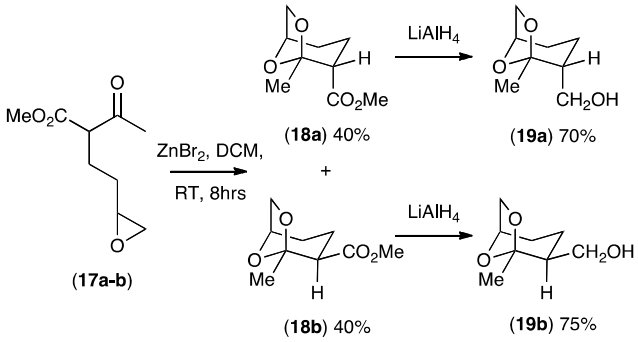
Scheme 7 Reactions using substituted *cis* and *trans* epoxides.

The results are inline with the findings of Sum and Weiler[11] that the reaction occurs with nucleophilic ring opening of the epoxide by the oxygen lone pair leading to inversion of stereochemistry at that centre to give ortho ester (**15a-b**) and (**16a-b**). The mechanism and stereoselectivity of the reaction can be rationalised as below (Scheme 8). The variation in diastereoselectivity with the Lewis acid (Table 1) and the evidenced of inversion of epoxide (Scheme 7) suggest to us there is some coordination, or pre-organisation, between the epoxide and non-reacting ester before ring opening of the epoxide. Simple models suggest that a 7-membered chelate would still allow for backside attack on the epoxide by the non-chelated ester. Further experimental work and modelling on this aspect is ongoing.



Scheme 8 Mechanism and explanation of stereoselectivity.

Another aspect of the reaction we wish to explore is its chemoselectivity. There have been numerous reports on the rearrangement of epoxy-ketones into dioxabicyclo[3.2.1]octanes which is related to our ortho ester rearrangement chemistry.11 The rearrangement precursor (**17**) would serve as the ideal starting material to determine whether the ester carbonyl or the ketone carbonyl would be more reactive under the Lewis acid rearrangement reaction condition. It was prepared as a pair of inseparable diastereomers (**17a-b**) by alkylation of ethyl acetoacetate with 4-bromo-1-butene, followed by epoxidation with mCPBA. Reaction between the ester and the epoxide will give the ortho ester, otherwise reaction between the ketone and the epoxide will give the ketal product. After treatment of (**17a-b**) with $ZnBr_2$ in DCM, only two out of the four potential products were exclusively formed (Scheme 9). The two separable products were isolated with a combined yield of 80% in a 1:1 ratio. The NMR studies suggested diastereoisomers (**18a**) and (**18b**) were formed which was confirmed by $LiAlH_4$ reduction giving the ketals (**19a**) and (**19b**) respectively in preference to their ortho esters counterparts. To date no kinetic studies have been carried out to see if the ortho ester is formed initially, however when the ketals (**18a**) and (**18b**) are re-subjected to the reaction conditions no change is observed. The result was somewhat unexpected since the ester group is marginally more nucleophilic due to electron donating effect of the alkoxy group. However it may be



Scheme 9 Reactions using an acetoacetate derived epoxide.

the case that the Lewis acid is coordinating strongly to the ester group thus reducing its nucleophilicity.

Conclusions

We have thus established a high yielding versatile route to methoxy substituted dioxabicyclo[3.2.1]octane, we believe this is a useful addition to the field of ortho esters synthesis. The chemistry also is an interesting example of desymmetrisation of the malonic ester center during the reaction that could be proved useful. We are currently looking at expanding the reaction, by controlling the stereochemistry, cascade reactions and applications in synthesis.

Notes and references

[a] *Department of Chemistry, University of Loughborough, Loughborough, Leicestershire, LE11 3TU, UK. Fax: +44(0)1509 22395; Tel; +44(0)1509 222587; E-mail: S.D.Christie@lboro.ac.uk*

[b] *Department of Chemistry, University of Loughborough, Loughborough, Leicestershire, LE11 3TU, UK. Fax: +44(0)1509 22395; Tel; +44(0)1509 222586; E-mail: G.J.Pritchard@lboro.ac.uk*

† Electronic Supplementary Information (ESI) available: Experimental procedures, analytical data, crystal structure diagarams for **1a**, **1b**, **15b**, and **16b**, and copies of NMR spectra are available in the ESI. See DOI: 10.1039/b000000x/

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