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Novel azetidinones for carbapenems and fragmentation in the allylamine precursor analogue

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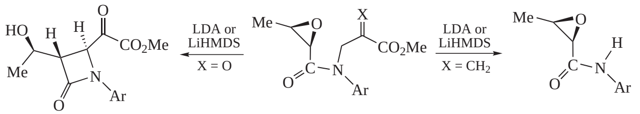
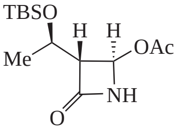
(2*R*,3*R*)-*N*-(3-Methoxy-2,3-dioxopropyl)-*N*-(4-methoxyphenyl)-2,3-epoxybutanamide on treatment with strong bases (LDA, LHMDS) gives 3-[(1*R*)-1-hydroxyethyl]azetidin-2-one derivative, while the *N*-(3-methoxy-2-methylidene-3-oxopropyl) analogue undergoes fragmentation.



Ar = 4-MeOC$_6$H$_4$

Antibiotics of the carbapenem series (Meropenem, Ertapenem, Biapenem, Orapenem, Tebipenem, *etc.*) belong to much-in-demand antimicrobial agents.[1,2] Properly functionalized key azetidinone blocks, such as compounds **1** and **2**, are widely used in the synthesis of carbapenem antibiotics.[3]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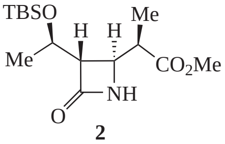
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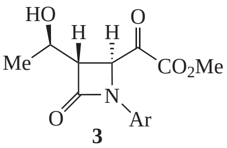
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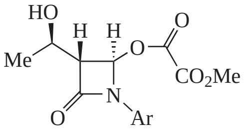
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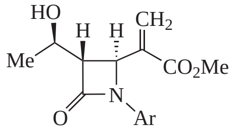
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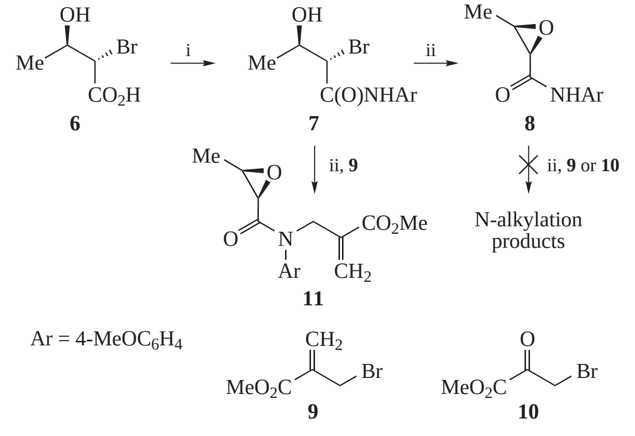
TBS = Bu^{t}Me$_2$Si Ar = 4-MeOC$_6$H$_4$

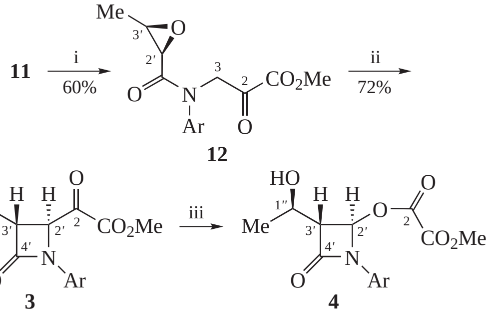
Within the approaches to carbapenems that we are developing, we planned to obtain similar new azetidinones **3**–**5** from L-threonine using a version of intramolecular ‘epoxide-enolate’ cyclization.[4] Threonine contains 3*R*-chiral center with β-oriented hydroxy group whose stereochemistry matches that of the side hydroxyethyl moieties in azetidinones **1** and **2** (*cf*. ref. 5).

The syntheses of compounds **3**–**5**, we reasoned, can be started from bromo hydroxy acid **6**[6] (Scheme 1). It was first converted into amide **7** and then into epoxide **8**. Attempts to N-alkylate epoxy amide **10** with active bromides **9**[7] or **10**[8] were unsuccessful. At the same time, the reaction of bromo hydroxy amide **7** with compound **9** smoothly occurred under phase transfer conditions to afford product **11**. Its ^{1}H NMR spectrum contained a double 1 : 1 set of rotamer signals (*cf*. ref. 9).

At the next stage, α-keto ester **12**, a precursor for intramolecular cyclization, was obtained by ozonolytic cleavage of the double bond in compound **11** (Scheme 2). The intramolecular cyclization of compound **12** was carried out in THF at –30 °C by treatment with 1.5 equiv. LiHMDS to afford azetidinone **3** whose subsequent Baeyer–Villiger oxidation gave the target derivative **4**. The ^{1}H NMR spectrum of **3** demonstrates characteristic coupling constants of H(2) and H(3) of the azetidinone ring whose small values of 2.2 Hz indicate *trans*-orientation of the substituents.[9]



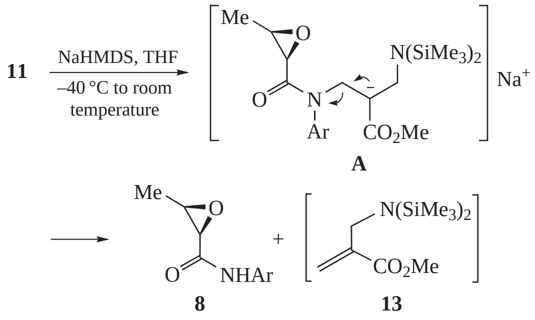
Scheme 1 *Reagents and conditions*: i, 4-MeOC$_6$H$_4$NH$_2$, DMAP, DCC, CH$_2$Cl$_2$, 0 °C; ii, 50% NaOH, Bu$_4$NI (cat.), CH$_2$Cl$_2$, ~20 °C.



Ar = 4-MeOC$_6$H$_4$

Scheme 2 *Reagents and conditions*: i, O$_3$, CH$_2$Cl$_2$, –78 °C, then Me$_2$S; ii, LiHMDS, THF, –40 to –10 °C; iii, mCPBA, CH$_2$Cl$_2$.

The approaches to compound **5** included an attempt to generate a carbaninon from **11** by treatment with bases (LDA, NaHMDS or LiHMDS). However, in all cases epoxy amide **8** was obtained as the fragmentation product (Scheme 3) in 49–60% yields. Note that a similar ‘deallylation’ of molecule **11** to give **8** was observed upon Ru-catalyzed oxidation (RuCl$_3$–K$_2$OsO$_4$–NaIO$_4$).



Scheme 3

A tentative mechanism of this fragmentation (see Scheme 3) involves a ‘conjugate addition–β-elimination’ passing through a low-temperature metallation with generation of Li(Na)-derivative **A**. Though allylamine **13**, the second product, was not isolated, TLC monitoring of the reaction mixture revealed formation of some new product along with traces of **5** (presumably, non-protonated **13**), which is lost during column chromatography on SiO_2. As one can see, the carbaninon centre α-positioned to the N atom in **11** necessary to drive reaction towards **5** is not formed. This fragmentation can be formally considered as removal of the allyl-containing group by the N-deallylation protocol. In literature, Pd-catalyzed N-deallylation of imides[10] and amines,[11] Ru-catalyzed isomerizations of *N*-allylamides followed by oxidation,[12] use of 2-arylallyl moieties at an N atom as readily removable protective groups[13] were reported.

In summary, we have developed a synthesis of novel azetidinone blocks **3** and **4** and indicated an unexpected deallylation of compound **11** proceeding under the action of strong bases (NaHMDS) or oxidizing systems. The **11** → **8** transformation can be regarded as a demonstration that N-‘methyleneacrylated’ amines can be selectively deprotected by treatment with LDA or similar bases at low temperatures.

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Online Supplementary Materials

Supplementary data associated with this article (synthetic procedures and characteristics of products) can be found in the online version at doi: 10.1016/j.mencom.2018.03.005.

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