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# 2,3-Epoxyamide-alcohols in Domino Reactions: En Route to Molecular Diversity

Abderrahman El Bouakher,<sup>[a]</sup> Jérôme Lhoste,<sup>[b]</sup> Arnaud Martel,<sup>[b]</sup> and Sébastien Comesse\*<sup>[a]</sup>

SC dedicates this publication to his mother who passed away 10 years ago.

The synthesis of polycyclic  $\gamma$ - and  $\delta$ -lactams bearing up to four contiguous fully controlled stereocenters is presented. For that purpose, we developed an original approach based on the use of 2,3-epoxyamides in domino reactions by taking advantage of the nucleophilic nitrogen atom and electrophilic epoxide. In reaction with enol ethers bearing gem bis-electrophiles on the double bond as Michael acceptors, four different reaction pathways were observed. They all started with a domino oxa-Michael/aza-Michael/epoxide opening sequence and depending

on substrates engaged could be followed either by a lactonization or a hemiketalization/retro-aldol cascade. Thus, four original fully-substituted piperidine- or pyrrolidine-2-one scaffolds were selectively synthesized in good to high yields. Moreover, these polycyclic lactams were obtained in high stereo- and chemo-selectively highlighting the efficiency and molecular diversity offered by this new methodology that should offer various synthetic opportunities in the future.

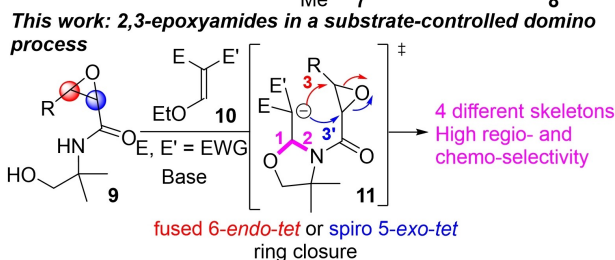
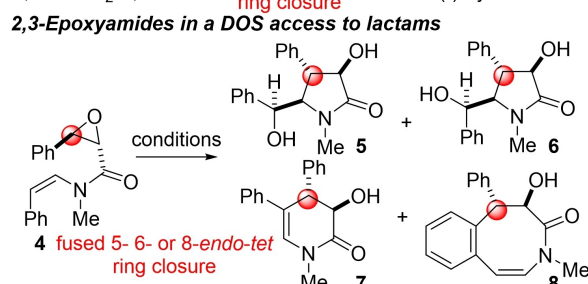
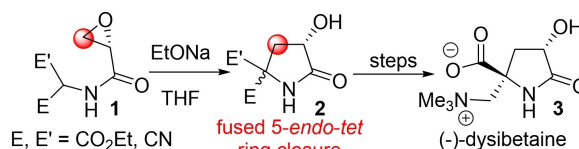
## Introduction

Synthesis of original three-dimensional structures based on  $sp^3$  carbons remains an entertaining arena for organic and medicinal chemists as they are often correlated to many compounds with high biological interest.<sup>[1]</sup> Over the years, many strategies have emerged for the efficient synthesis of such chiral molecules such as the so-called target-oriented (TOS) and diversity-oriented syntheses (DOS).<sup>[2]</sup> The former's goal is directed by the synthesis of targeted molecules when the latter are aimed to generate a range of structurally different small-3D-molecules starting from common starting material. Other powerful tools for the synthesis of three-dimensional edifices are multicomponent<sup>[3]</sup> and domino<sup>[4]</sup> reactions. Another way to achieve this goal can rely on substrate-controlled<sup>[5]</sup> oriented synthesis where well-chosen substituents can lead to molecular diversity by switching domino pathways.

2,3-Epoxyamides (also named glycidamides or glycidic amides) have several strings to one's bow as they are: (i) found in natural products,<sup>[6]</sup> (ii) parts of molecules exhibiting interesting biological activities<sup>[7]</sup> and (iii) versatile building blocks bearing multiple reactive centers.<sup>[8]</sup> For example, Barry B. Snider

and Yonghong Gu have demonstrated the synthetic interest of 2,3-epoxyamides **1** as key intermediates for the total synthesis of (-) and (+)-dysibetaine **3**, a  $\gamma$ -lactam isolated from an aqueous extract of the marine sponge *Dysidea herbacea* (upper part of Scheme 1).<sup>[9]</sup> In their case, only the fused 5-endo-tet<sup>[10]</sup> ring closure product **2**, resulting from a carbanion generated in situ in  $\alpha$  of the electron-withdrawing groups (EWG) by reaction with EtONa, was observed.

### 2,3-Epoxyamides in the synthesis of (-)-dysibetaine



**Scheme 1.** 2,3-Epoxyamides **1**, **4** and **9** as key partners for the synthesis of lactams.

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Moreover, as beautifully illustrated by Mei-Xiang Wang and co-workers,<sup>[11]</sup> DOS of multiple lactam rings could be achieved by tuning the reaction conditions (middle part of Scheme 1). Indeed, depending on the additive employed, three different pathways were observed from **4**: (i) a fused 5-*endo-tet* ring closure probably resulting from the addition of the  $\alpha$ -carbon of the enamide onto the epoxide leading to diastereoisomers **5** and **6**, (ii) a fused 6-*endo-tet* ring closure based on attack of the  $\beta$ -carbon of the enamide onto the epoxide forming **7** and (iii) a fused 8-*endo-tet* ring closure conducting to **8** via an intramolecular Friedel–Crafts addition onto the epoxide.<sup>[12]</sup>

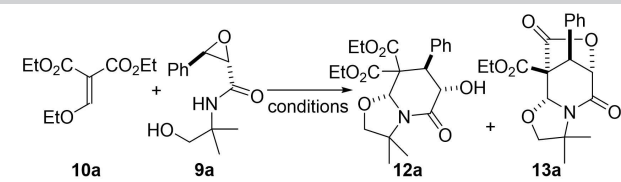
Nevertheless, their use as domino partners, particularly by taking advantage of the nucleophilic nitrogen atom, should offer various synthetic opportunities but is to the best of our knowledge not described. This is particularly astonishing since homolog molecules such as haloacetamides<sup>[13]</sup> and acrylamides<sup>[14]</sup> are widely used in domino reactions. On this basis, we decided to study 2,3-epoxyamido-alcohols **9** as key partners for the direct access to  $\gamma$ - and  $\delta$ -lactams.

In link with previous findings from our group,<sup>[15]</sup> we anticipated that 2,3-epoxyamido-alcohols **9** could, by reaction with commercially or synthetically available Michael acceptors **10**, lead to various non planar bicyclic  $\gamma$ - and  $\delta$ -lactams (lower part of Scheme 1). The original domino process was expected to begin with an oxa-Michael/aza-Michael sequence (formation of bonds **1** and **2**) leading to the anionic intermediate **11** and it was anticipated that, depending on the nature of the substrates, different pathways could occur. Indeed, the R group was expected to influence the intramolecular addition of the carbanion onto the epoxide either via a fused 6-*endo-tet* ring closure (formation of bond **3**) or, contrary to the example cited above, a spiro 5-*exo-tet* ring closure (formation of bond **3'**). Moreover, the nature of the EWG could bring even more molecular diversity by allowing subsequent steps such as lactonization, hemiketalization and retro aldol reactions. Finally, we were able to synthesize with a high regio- and chemo-control four different original polycyclic skeletons in a few steps from simple and easily accessible synthons.

## Results and Discussion

Commercially available Michael acceptor **10a** and 2,3-epoxyamido alcohols **9a** were chosen as benchmark substrates (Table 1). Various bases and solvents were selected based on our previous results in related domino processes.<sup>[15]</sup> The use of 1.2 equivalents of carbonated bases in refluxing acetonitrile proved to be inefficient, the starting materials being fully recovered (entries 1 and 2, Table 1). The same result was observed when shifting to a stronger base, *i.e.* *t*-BuOK in THF at room temperature (entry 3, Table 1). Thankfully, 1.2 equivalent of NaH in THF led to the total conversion of the starting materials, but only traces of the desired lactams were isolated (entry 4, Table 1). Considering that the reaction conditions were too harsh and that a catalytic amount of the base should be sufficient, we then modulated the quantity of NaH engaged. The best results were obtained when 0.5 equivalent were used,

**Table 1.** Optimization of the reaction conditions.<sup>[a]</sup>

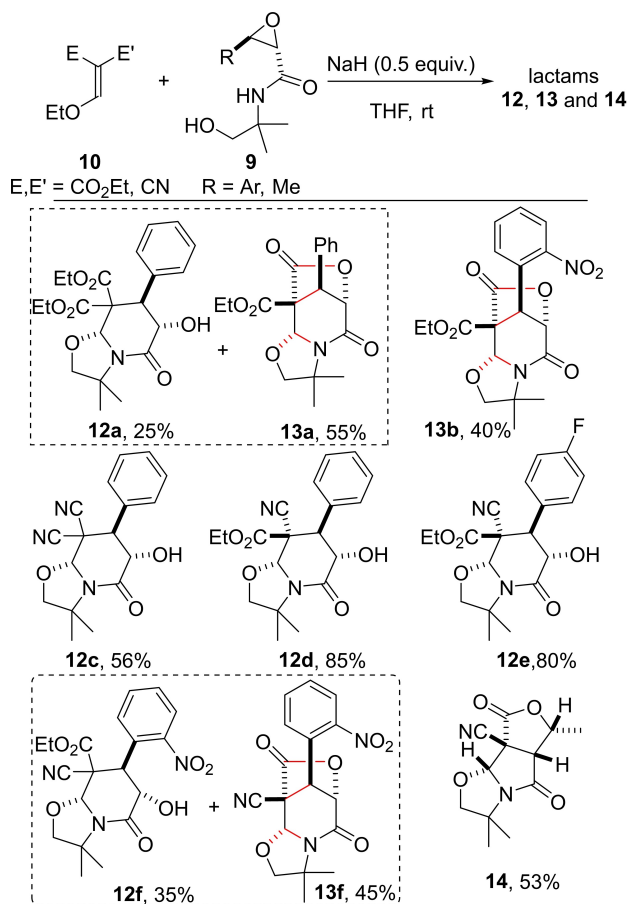


| Entry | Base (equiv.)                         | Solvent            | T °C   | Yield (%) <sup>[b]</sup> | Ratio <b>12a</b> : <b>13a</b> <sup>[c]</sup> |
|-------|---------------------------------------|--------------------|--------|--------------------------|--|
| 1     | K <sub>2</sub> CO <sub>3</sub> (1.2)  | CH <sub>3</sub> CN | reflux | nr <sup>[d]</sup>        | –  |
| 2     | Cs <sub>2</sub> CO <sub>3</sub> (1.2) | CH <sub>3</sub> CN | reflux | nr <sup>[d]</sup>        | –  |
| 3     | <i>t</i> -BuOK (1.2)                  | THF                | rt     | nr <sup>[d]</sup>        | –  |
| 4     | NaH (1.2)                             | THF                | rt     | 3                        | nd <sup>[d]</sup>                            |
| 5     | NaH (0.8)                             | THF                | rt     | 12                       | nd <sup>[d]</sup>                            |
| 6     | NaH (0.6)                             | THF                | rt     | 53                       | 3:7  |
| 7     | NaH (0.2)                             | THF                | rt     | 32                       | 3:7  |
| 8     | NaH (0.5)                             | THF                | rt     | 80                       | 3:7  |

[a] Base was added to a solution of 2,3-epoxyamido-alcohol **9a** (0.25 mmol, 1 equiv) and Michael acceptor **10a** (0.26 mmol, 1.05 equiv) in freshly distilled solvent (2 mL). [b] Isolated Yields. [c] dr: diastereomeric ratio determined on the crude mixture. [d] nd: not determined.

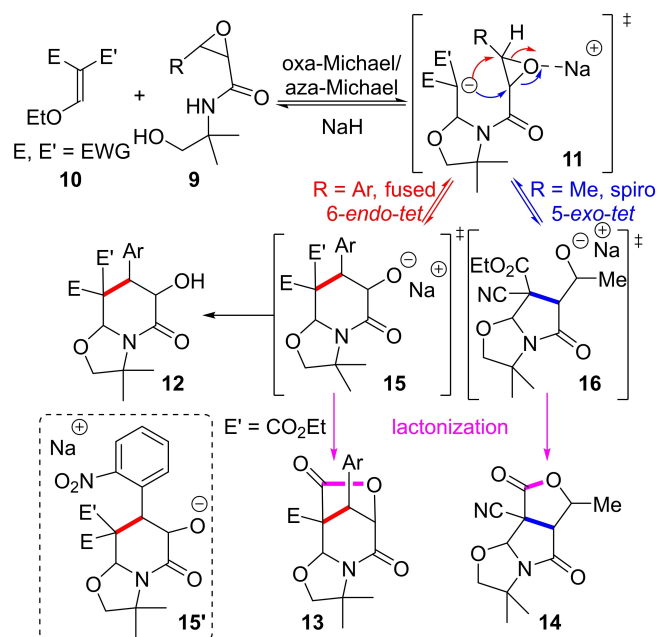
allowing the formation of the lactams **12a** and **13a** in a good 80% overall yield and a 3:7 ratio (entry 8, Table 1). The uncommon bridged tricyclic 5/6/5 system **13a**<sup>[16]</sup> bearing 4 contiguous stereocenters results from a complementary intramolecular lactonization step between the alcoholate resulting from the epoxide opening and one of the ester functions. The ratio was the same with 0.2 or 0.6 equivalent of NaH, only the yields being impacted (compared entries 5–8, Table 1). It is worth noticing that both lactams **12a** and **13a**, resulting from a fused 6-*endo-tet* ring closure, were isolated as a single diastereomer, demonstrating that the newly created stereocenters were fully controlled by the stereochemistry of the epoxide ring.<sup>[15b]</sup>

With the optimized conditions in hands, we focused on the substrate scope (Scheme 2). During the reaction between the same Michael acceptor **10a** (E = E' = CO<sub>2</sub>Et) and 2,3-epoxyamido alcohols bearing an ortho-nitro substituent onto the aromatic ring, only the tricyclic lactam **13b** was isolated in 40% yield. Another symmetrical Michael acceptor **10** (E = E' = CN) was then engaged in the domino process with **9a** (R = Ph) and the resulting lactam **12c** was obtained in 56% yield and >95:5 diastereomeric ratio. The use of commercially available unsymmetrical enol ether Michael acceptor **10** (E = CN and E' = CO<sub>2</sub>Et) was then considered. Good yields of 85% and 80% for lactams **12d** and **12e** respectively were secured with all four contiguous stereocenters fully controlled. Surprisingly, with 2,3-epoxyamido alcohol **9** (R = *o*-NO<sub>2</sub>-Ph) the course of the domino process was different since a mixture of lactam **12f** and **13f** with a total yield of 80% and a 7:9 ratio was obtained. Another different result was observed when replacing the R group onto the 2,3-epoxyamido alcohol **9** by a methyl substituent (R = Me).

Scheme 2. Access to polycyclic lactams **12**, **13** and **14**.

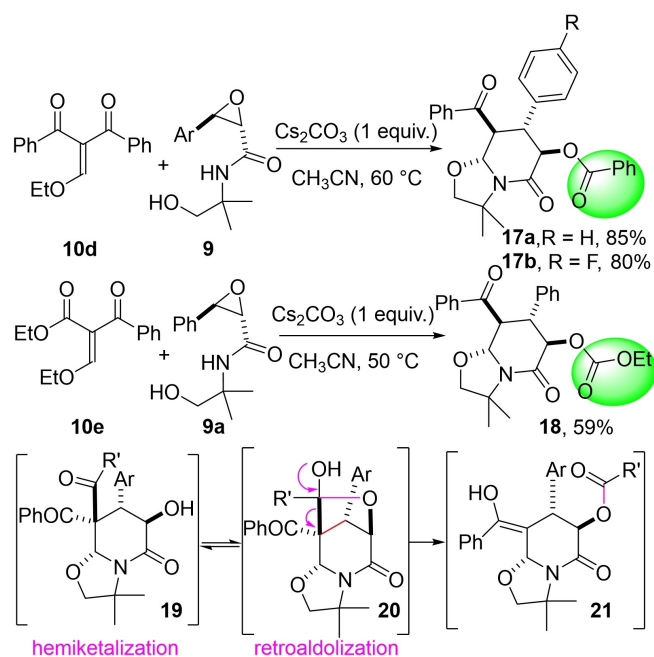
Indeed, the new linear tricyclic 5/5/5 skeleton **14**<sup>[17]</sup> resulting from the alteration of the domino pathway was isolated in 53% yield, showing that this time a spiro 5-*exo-tet* ring closure occurred instead of the fused 6-*endo-tet* ring closure observed for all the other substrates.

All the proposed mechanism paths explaining the above results have in common the 2 first steps, *i.e.* an oxa-Michael/aza-Michael sequence triggered by the deprotonation of the alcohol function of **9** by NaH (Scheme 3). The resulting intermediate carbanion **11** can then follow two different paths depending on the R group onto the epoxide ring. In the case of a methyl substituent (R=Me), a spiro 5-*exo-tet* ring closure occurred leading, after lactonization of alcoholate **16**, to the tricyclic  $\gamma$ -butyrolactone-fused  $\gamma$ -lactam **14**. The aromatic moiety (R=Ar), probably due to the better stabilization of a higher partial positive charge, in the transition state on the carbon bearing this substituent, making it more reactive toward nucleophiles, favor the formation of intermediate **15** via a fused 6-*endo-tet* ring closure in accordance with Mei-Xiang Wang and co-workers' findings (see middle part of Scheme 1). The bicyclic alcoholate **15** could furnish **12** after protonation, either during the process due to a default of base, or during work-up. It could also afford the tricyclic 5/6/5 lactone **13** when at least one of the electron-withdrawing groups is an ester function being on the same face of the alcoholate. The peculiar formation of the

Scheme 3. Proposed mechanism's pathways for the access to **12**, **13** and **14**.

tricyclic 5/6/5 lactone **13f**, implying that in this case the ester function was on the same side than the alcoholate contrary to **12d** and **12e** (compare stereochemistry of the lactams **12d**, **12e** and **13f**, Scheme 2), could be explained by the complexation of the sodium atom by the *o*-NO<sub>2</sub> substituent<sup>[15c]</sup> in **15'** (Scheme 3) changing the otherwise *trans* selectivity between the ester and the alcoholate.

Hence, we turned our attention to Michael acceptor **10d** bearing two benzoyl moieties (Scheme 4). The experimental conditions used above proved to be detrimental to the process leading to a complex mixture. Thus, 1 equivalent of cesium carbonate (Cs<sub>2</sub>CO<sub>3</sub>)<sup>[15a]</sup> as a base in freshly distilled CH<sub>3</sub>CN at 60 or 50 °C were employed (for more details see SI). The course of the domino process changes dramatically to lead to rearranged lactams **17a** and **17b** in 85% and 80% yield and high dr, respectively.<sup>[18]</sup> More surprising, in the case of Michael acceptor **10e** bearing a benzoyl and an ester function, it was the latter which was fully transferred to furnish the totally unexpected bicyclic lactam **18** in 59% yield with no trace of another diastereoisomer. It is important to notice that we didn't observe the formation of a bridged tricyclic lactone like products **13** obtained above (Scheme 2). An oxa-Michael/aza-Michael would first lead to the intermediate carbanion **11** as depicted in Scheme 3. Then, after a fused 6-*endo-tet* ring closure the bicyclic alcohol **19** could evolve toward the bridged intermediate **20** after an intramolecular hemiketalization. The last step is a retroaldol mechanism<sup>[20]</sup> leading to the formation of the enol intermediate **21**. After a diastereoselective keto-enol tautomerism favoring a pseudo-equatorial position for all the substituent onto the piperidin-2-one rings, the rearranged products **17a,b** and **18** are formed. The reactivity shift explaining these surprising results barely disclosed before<sup>[19]</sup> could be rationalized both by the use of less basic conditions (Cs<sub>2</sub>CO<sub>3</sub> instead of



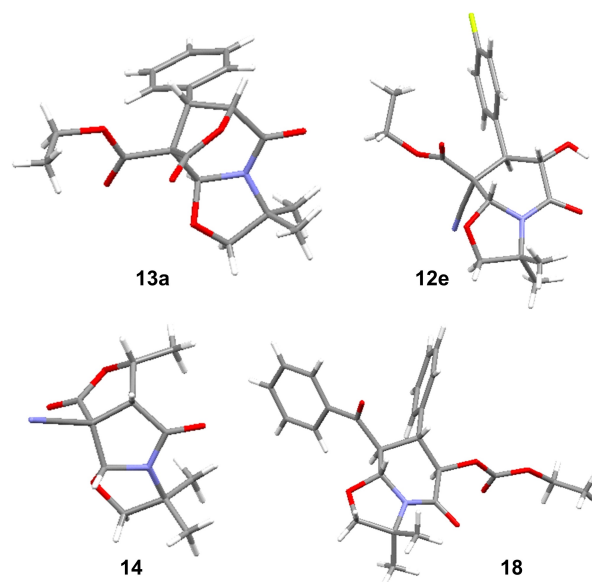
**Scheme 4.** Unexpected rearrangement products **17** and **18** and proposed mechanism.

NaH) favoring the formation of protic intermediates and of higher temperatures (50 or 60 °C vs rt) favoring such rearrangements. These mild basic conditions allow to isolate the rearrangement product without further side-reactions. It is also assumed that the presence of traces of hydrogen carbonates plays an important role in the various proton transfers involved during this rearrangement.

The structure and relative stereochemistry of products **13a**, **12e**, **14** and **18** were secured by X-ray analysis and the relative stereochemistry of other lactams extrapolated from them (see SI and Figure 1).<sup>[21]</sup> For the tricyclic lactone **13a** a *syn* relationship between the phenyl and ester moieties is observed. The same *syn* relationship between the aromatic ring and the ester on one hand and the hydroxyl and nitrile function on the other hand is shown for the bicyclic lactam **12e**. The X-ray structure of the tricyclic 5/5/5 lactone **14** displays that the nitrile moiety and the H atoms onto the three other asymmetric carbons are on the same face. An all trans relationship between adjacent substituents onto lactam **18** is observed. Finally, in all cases, the 4 contiguous stereocenters including the 2 created during the domino process were fully controlled.

## Conclusions

An original access to polycyclic  $\gamma$ - and  $\delta$ -lactams based on substrate-controlled oriented synthesis was presented. The key partners of the divergent domino processes were 2,3-epoxyamido-alcohols and Michael acceptors. The main finding of this study was the possibility to fully switch the epoxide opening in order to access 5- or 6-membered lactam rings. Moreover, the concomitant formation of tricyclic lactones was observed when



**Figure 1.** X-ray structures of domino products **13a**, **12e**, **14** and **18**.

at least one of the EWG was an ester function or the transfer of one of the EWG onto the alkoxide formed after the epoxide opening could occur. Whatever the domino sequence, good yields and high diastereoselectivity were achieved. We are now working on expanding the scope of these new domino sequences to other Michael acceptors and chiral 2,3-epoxyamido-alcohols. Moreover, DFT calculations to elucidate and rationalize the role of the substrate substituents are underway and will be published in due course.

## Supporting Information

The authors have cited additional references within the Supporting Information.<sup>[22]</sup>

2,3-Epoxyamido-alcohol **9** (0.25 mmol) and Michael acceptor **10** (0.26 mmol, 1.05 eq) were dissolved in freshly distilled THF (2 mL). Sodium hydride (3 mg, 0.125 mmol, 0.5 eq.) was then added. The mixture was stirred for 12 to 48 hours and was then quenched carefully at 0 °C by addition of a saturated aqueous solution of  $\text{NH}_4\text{Cl}$  (2 mL). The aqueous layer was extracted with EtOAc (3x5 mL), the organic layers were combined, brined, dried over  $\text{MgSO}_4$  and the solvent was removed under vacuum. The residue was then chromatographed on silica gel to provide the desired domino compound.

Experimental procedures, characterization data, and copy of the  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra for all new compounds (**9**, **12–14**, **17** and **18**).

## Acknowledgements

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## Conflict of Interests

The authors declare no conflict of interest.

## Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

**Keywords:** 2,3-epoxyamido-alcohols · domino reaction · polycyclic lactams · epoxide opening · molecular diversity

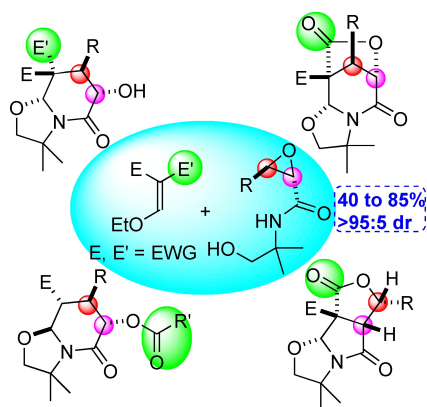
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## RESEARCH ARTICLE

Molecular diversity was achieved by reaction between easily accessible 2,3-epoxyamido-alcohols and Michael acceptors. 4 different  $\gamma$ - and  $\delta$ -lactam skeletons were selectively synthesized in good yields with up to 4 contiguous stereo-centres fully controlled. Depending on the R substituent and the electron-withdrawing groups different domino pathways, all triggered by an oxa-Michael/aza-Michael/epoxide opening sequence, occurred.



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1 – 6

**2,3-Epoxyamide-alcohols in Domino Reactions: En Route to Molecular Diversity**

