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Access to novel bicyclic fused γ-butyrolactone using [3,3]-sigmatropic rearrangement and acid-lactonization sequence as key transformation

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ABSTRACT

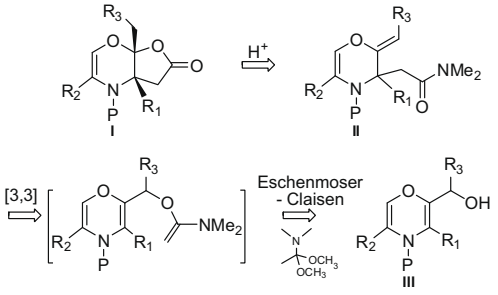
In this Letter, we wish to disclose a new strategy for the construction of substituted γ-butyrolactones. The latter might not only be of potential interest in terms of biological activity and synthesis but also allow access to original heterocyclic scaffolds. According to previous study, efficient two-step sequence involving Eschenmoser–Claisen rearrangement and acid-lactonization reaction was successfully applied for the construction of original fused bicyclic γ-butyrolactones based on an 1,4-oxazine core.

A large number of natural products containing substituted γ-butyrolactone fragments that have been isolated exhibit a broad range of activity against different biological targets.[1] The diversity of their biogenetic origins suggests that this structure may be one of the key elements in their biosynthesis.[2] Therefore γ-butyrolactones, in general, represent remarkable lead structures and have attracted our interest for the development of new drug precursors.[3] Given this interest, we now report a novel methodology for the construction of original fused bicyclic γ-butyrolactones based on an 1,4-oxazine core. According to our previous investigation concerning the easy functionalization of the 1,4-oxazine moiety,[4] we have envisaged a new synthetic route to original bicyclic γ-lactone **I** (Scheme 1). This synthetic methodology relies on a Claisen-type [3,3]-sigmatropic rearrangement[5] from the corresponding allylic alcohols **III** followed by an acidic lactonization sequence.

The interest of this approach lies in the possibility from this original dihydro-1*H*-furo[2,3-*b*]oxazinone **I**[6a] to easily accede to various building blocks which could be used in the construction of core skeletons by ring opening of the lactone (Fig. 1, pathway 1) or of the oxazine ring (via ozonolysis for example) (pathway 2). Thus according to the literature, the newly formed β-amino alcohols[6b] could then for instance be transformed into original oxazoline intermediates[6c,d] which generate an additional level of diversity.

For some time, we have been engaged in the synthesis and the functionalization of new nitrogen-containing heterocyclic derivatives.[4,7] We therefore devised an original synthetic approach to compounds **3** or **5** via an Eschenmoser–Claisen rearrangement starting from adequate allylic alcohols **2** or **4**, bearing an 1,4-oxazine moiety (Table 1). As previously described,[4] allylic alcohols (**2** or **4**) were prepared in good yields under anionic conditions from the corresponding 3,5-disubstituted or non substituted 1,4-oxazines **1a** or **1b**, respectively.

Taking into account previous study reported in the 1,4-benzoxazine field,[7d] allylic alcohols **2** or **4** were then heated in xylenes in the presence of *N,N*-dimethylacetamide dimethylacetal. According to an Eschenmoser–Claisen rearrangement, the desired [3,3]-rearranged products **3** or **5** were thus isolated in fair to good yields. As



Scheme 1. Retrosynthetic pathway for the construction of fused bicyclic γ-butyrolactones.

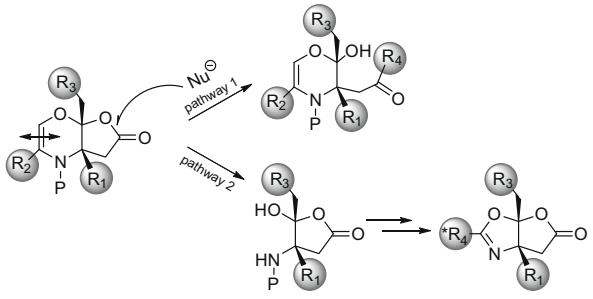


Figure 1. Easy access to various building blocks.

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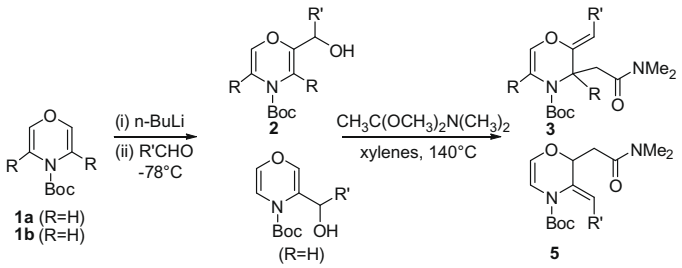
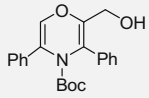
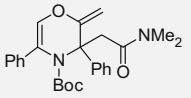
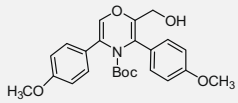
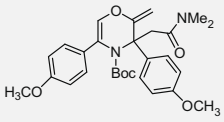
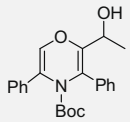
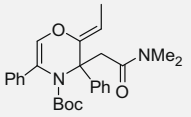
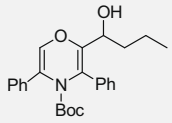
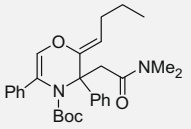
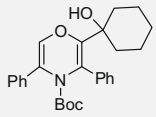
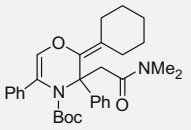
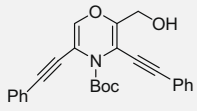
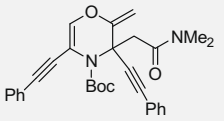
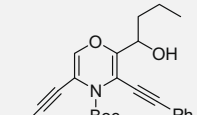
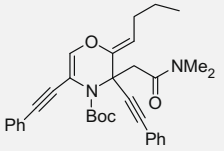
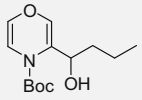
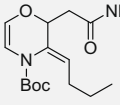
Table 1
Preparation of allylic alcohols **2** or **4** and Eschenmoser–Claisen rearrangement



Entry	Allylic alcohols	Yields (%)	[3,3]-Rearranged products[b]	Yields (%)
1		**2a**[b] (99)		**3a**[d] (69)
2		**2b**[b] (85)		**3b**[d] (56)
3		**2c**[a] (64)		**3b**[d] (55)
4		**2c**[a] (89)		**3c**[d] (70)
5		**2d**[a] (82)		**3d**[d] (0)
6		**2e**[b] (100)		**3e**[d] (28)
7		**2f**[a] (45)		**3f**[d] (30)
8		**4**[c] (100)		**5**[e] (37)

Reagents and conditions: (a) (i) *n*-BuLi (1.5 equiv), HMPA (1.5 equiv), THF, −78 °C, 40 min. (ii) R′CHO (5 equiv), THF, −78 °C, 2 h. (b) (i) cf. Ref. 4d. (ii) $NaBH_4$ (3 equiv), MeOH, rt 10 min. (c) (i) *n*-BuLi (1.2 equiv), THF, −78 °C, 5 min. (ii) C_4H_9CHO (5 equiv), THF, −78 °C, 45 min. (d) $CH_3C(OCH_3)_2N(CH_3)_2$ (10 equiv), xylenes, 140 °C, 45 min. (e) $CH_3C(OCH_3)_2N(CH_3)_2$ (10 equiv), xylenes, M.W., 140 °C, 40 min.

a consequence, a novel quaternary carbon alpha to the nitrogen atom was created. The Z configuration of the newly formed carbon–carbon double bond was demonstrated by NOE NMR experiments.[8] In all cases no traces of the E isomer could be detected. This revealed that the rearrangement only proceeded via the sterically less hindered six-membered ring transition state, where the R′ substituent (Me, Pr) occupies the equatorial position (TS1, Fig. 2). The rearrangement was found to be highly influenced by the substitution on the allyl moiety. Lower yields were thus observed in the case of *bis*-ethynyl compounds **3e** and **3f** (entries 5 and 6) because of decomposition process. It is noteworthy that this Eschenmoser–Claisen rearrangement could also be performed in

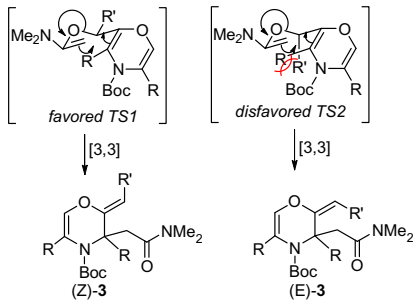
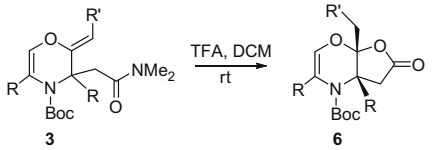
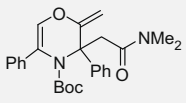
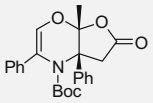
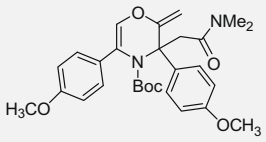
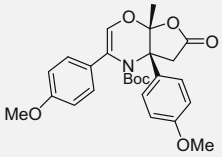
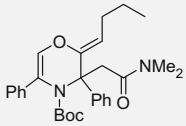
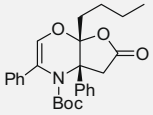
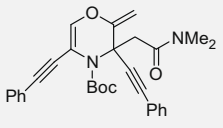
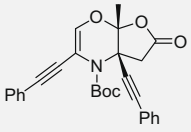


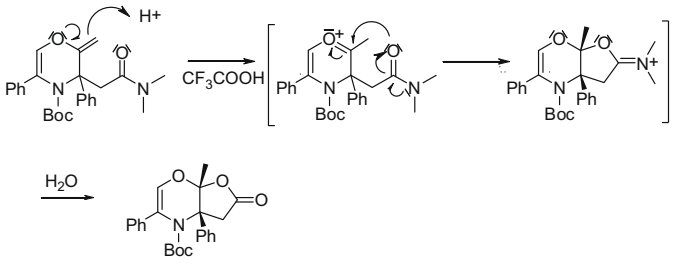
Figure 2. Stereochemical model of the rearrangement.

Table 2
Preparation of *syn* γ-butyrolactones **6** via acidic cyclization sequence

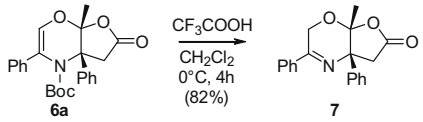


Entry	[3,3]-Rearranged compounds	γ-Butyrolactones	Yields (%)
1	 **3a**		**6a** (70)
2	 **3b**		**6b** (45)
3	 **3c**		**6c** (52)
4	 **3e**		**6e** (20)

Reagents and conditions: (a) TFA (6 equiv), DCM, rt 10 min.



Scheme 2. Proposed mechanism for acid-catalyzed formation of γ-butyrolactone *syn*.



Scheme 3.

fair yield from compound **4** which bears the allylic alcohol function at the C-3 position onto the oxazine ring (entry 7). In this case, best yield was obtained under microwave activation.[9] Under classical heating, 5 was recovered in only 26% yield.

Yields are comparable with primary or secondary allylic alcohol. Unfortunately, no rearrangement occurred starting from tertiary allylic alcohol (compound **2d**, entry 5) even by performing the reaction under microwave activation. It should be pointed out that one of the attractive features of our approach lies in its inherent versatility since a wide range of aldehydes (R′CHO) could be used in the first step. According to our previous methodology,[4] diversity onto R groups at C-3 and C-5 position of **1** can also be easily envisaged.

Given these results, our intent, therefore, was turned to synthesize original γ-butyrolactones from alkylidene **3** (Table 2). In this context, rearranged-compounds **3a**, **3b**, **3c**, and **3e** were submitted for short time to acidic conditions and afforded spontaneously in good yields fused bicyclic γ-butyrolactones **6**-*syn*.[10]

This outcome is consistent with the reaction mechanism outlined in Scheme 2. Under acidic conditions, we anticipated the formation of an oxonium ion which could undergo a nucleophilic attack and afford an unstable iminium species which was subsequently hydrolyzed during workup.

It is noteworthy that with a longer acidic treatment at 0 °C, removal of the Boc group occurred which afforded the original imine **7** isolated in good yields (Scheme 3).

To sum up, we have developed a new and easy method that provides a useful tool for the synthesis of fused bicyclic γ-butyrolactones employing an efficient tandem Eschenmoser–Claisen rearrangement and acid-lactonization sequence. In addition, it is worth noting that the presence of different functional groups in

many positions of the skeleton makes such compounds useful for further structural modifications and suitable as intermediates for various heterocyclic scaffolds. Access to various lactams, oxazolines, and also to chiral γ-butyrolactones could be easily envisaged. A chiral N-substituted quaternary carbon center was also successfully created. Further studies and their applications to natural product synthesis are currently in progress in our laboratory. Experiments designed to explore the potentiality offered by this original heterocyclic scaffold will be described in due course.

Acknowledgments

We are grateful to the CNRS and the Region Centre for their financial support.

Supplementary data

Supplementary data (experimental procedures and full spectroscopic data for all new compounds. Decomposition products were formed for longer reaction time at room temperature) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.04.041.

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8. A NOESY ^{1}H NMR experiment revealed an interaction between the ethylenic proton and one of the protons of the methylene group adjacent to the quaternary center.
9. The microwave irradiation was performed in an open vessel which allows the evaporation of the methanol formed.
10. A NOESY ^{1}H NMR experiment revealed an interaction between the alkyl chain (Me, Et, Pr) and aromatic protons of the phenyl group.