Synthetic Methods

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Straightforward Access to a Structurally Diverse Set of Oxacyclic Scaffolds through a Four-Component Reaction**

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Multicomponent reactions (MCRs) constitute an important group of transformations that combine many elements of an ideal synthesis, such as operational simplicity, atom economy, bond-forming efficiency, the access to molecular complexity from simple starting materials, and so on. The modular character of this approach is extremely suitable for drug discovery, and therefore it is widely used for the fast generation of bioactive compounds.[1] Recently, the concept of chemical genomics has sparked the development of diversity-oriented synthesis (DOS)[2] to reach the structural flexibility needed in the small-molecule range, thus demanding new and versatile synthetic methodology. We report herein new processes leading to diversely functionalized oxacycles (privileged structures including carbohydrate-related compounds)[3] based on an MCR that allows access to a variety of scaffolds using commercially available reagents.

The Povarov reaction (the condensation of an aniline, an aldehyde, and an activated olefin), has been useful in the formation of tetrahydroquinoline adducts, including aza- and oxacyclic fused derivatives.[4] Previous reports[5] suggested that the formal [4+2] cycloaddition was nonconcerted and, consequently, opened the possibility to trap the final oxocarbonium intermediate with an external nucleophile (terminator), thus leading to a four-component reaction.[6] Herein, we describe a Lewis acid catalyzed four-component reaction of an amine, an aldehyde, a cyclic enol ether, and an alcohol, which acts as the terminator of the process[7] (Scheme 1).

The first experiment was carried out using equimolar amounts of 3,4-dihydro-2*H*-pyran (**1a**), 3-nitroaniline (**2a**),

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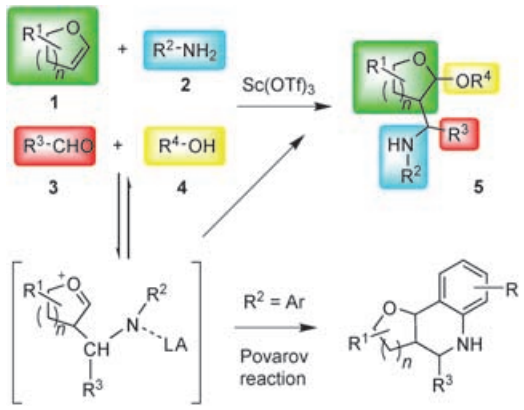
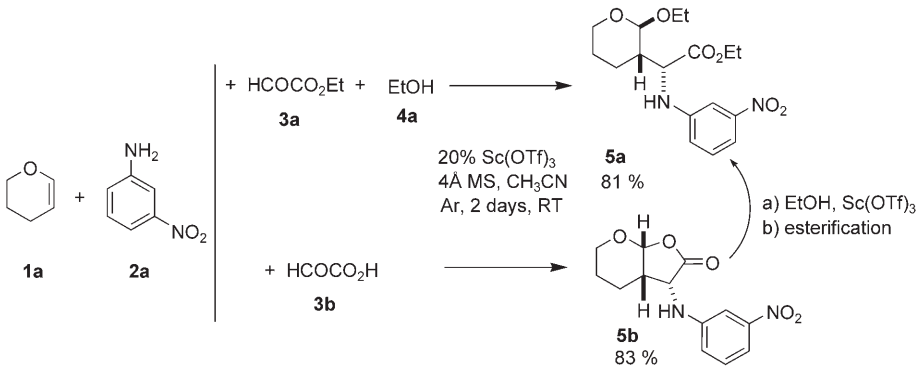


Scheme 1. General four-component reaction and proposed mechanism. LA = Lewis acid.

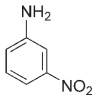
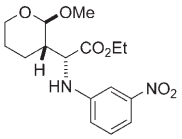
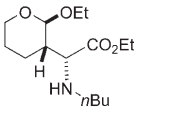
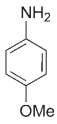
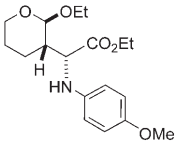
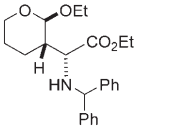
ethyl glyoxylate (**3a**),[8] and an excess of ethanol (**4a**). Under $Sc(OTf)_3$ catalysis,[9] the reaction was successful, and the desired product **5a** (81%) was obtained as a mixture of two isomers in a ratio of 70:30.[10] Similarly, by using glyoxylic acid (**3b**) we obtained the compound **5b** in high yield (83%, isomer ratio 70:30). Purification of this mixture afforded the major component and allowed the stereochemical elucidation of the process[11] by conversion of **5b** into the major isomer of **5a** with EtOH and $Sc(OTf)_3$ and subsequent esterification using Mukaiyama's reagent.[12] As expected, the approach of the imine to the enol ether was similar in both cases whereas the trapping of the oxocarbonium ion took place with opposite stereoselectivity (Scheme 2).



Scheme 2. Three- and four-component reactions leading to **5a** and **5b**. MS = molecular sieves.

All the components were systematically varied in order to investigate the scope of the reaction, starting with the amine **2** (Table 1). The process seemed to be general to anilines with electron-donating or electron-withdrawing groups, as well as alkyl amines. Therefore, there is no need for deactivated anilines to avoid the formal [4+2] cycloaddition (see Scheme 1). Under these conditions, the reaction progresses through a four-component reaction pathway to yield the corresponding adduct with no evidence of the Povarov compound. *n*-Butylamine (entry 2) was less reactive and the reaction required heating (40 °C for 48 h). The diastereoselectivity in these series seems to depend on the amine used,

Table 1: Range of amines **2**.

Entry	**2**	Yield [%]	**5**	Isomer ratio[a]
1		**2a** 81	 **5c**	2.3:1
2	$nBuNH_2$	**2b** 55	 **5d**	2.3:1
3		**2c** 82	 **5e**	2.3:1
4		**2d** 93	 **5f**	9:1

[a] Determined by ^1H NMR spectroscopic or HPLC methods; see Reference [11].

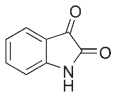
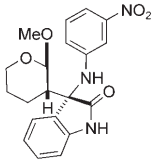
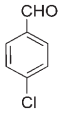
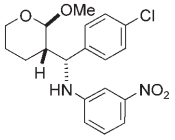
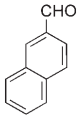
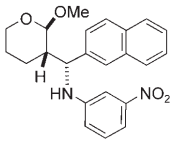
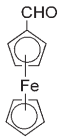
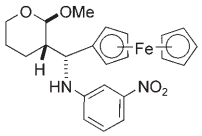
ranging from 2.3:1 with anilines and linear amines (entries 1–3) to 9:1 with more bulky amines (entry 4).

The range of carbonyl compounds was also investigated (Table 2). Besides glyoxylic acid and ethyl glyoxylate, aromatic aldehydes showed convenient reactivity and isatin and 2-ferrocenecarboxaldehyde also yielded the expected adducts.[13]

The range of alcohols (terminators) was studied next (Table 3). Primary alcohols such as MeOH, EtOH (Table 1, entries 1–4), and *n*BuOH (Table 3, entry 1) worked very well. Even secondary and long-chain primary alcohols yielded the desired products (entries 2 and 3), although in low yields. The use of water was more problematic, probably because of the reduced stability of the hemiacetal **5n**. Interestingly, ethanethiol could be efficiently used to afford adduct **5o** (entry 5). As expected, the alcohols do not play a significant role in the stereocontrol of the reaction. We have preliminarily explored the possibility of using quenchers with higher structural and biological relevance, such as terpenes (entry 6) and carbohydrate derivatives.[14] Other oxygen-based species with reduced nucleophilicity (AcOH, CF_3CH_2OH, *p*-nitrophenol) did not afford the expected four-component reaction adducts. With these species, the process furnished the Povarov compound (e.g. **6a**) in a regio- and stereoselective manner (Figure 1).

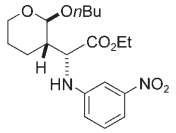
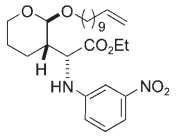
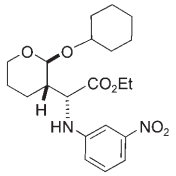
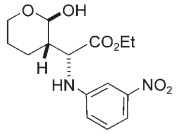
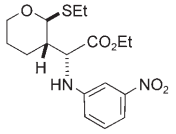
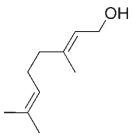
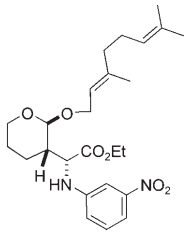
The study of the fourth component (the cyclic enol ether) opened the possibility to further increase the molecular diversity as well as to better control the stereochemical outcome of the reaction (Table 4).

Table 2: Set of carbonyl derivatives **3**.

Entry	**3**	Yield [%]	**5**	Isomer ratio[a]
1	 **3c**	55	 **5g**	4:1
2	 **3d**	42	 **5h**	2.5:1
3	 **3e**	88	 **5i**	2:1
4	 **3f**	40	 **5j**	2.5:1

[a] See Reference [11].

Table 3: Set of terminators **4**.

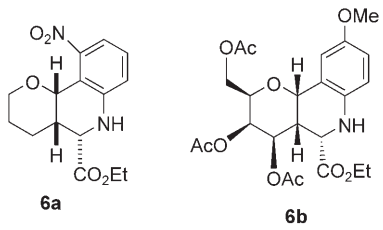
Entry	**4**	Yield [%]	**5**[a]
1	*n*BuOH **4c**	83	 **5k**
2	 **4d**	10	 **5l**
3	 **4e**	15	 **5m**
4	H_2O **4f**	35	 **5n**
5	EtSH **4g**	83	 **5o**
6	 **4h**	62	 **5p**

[a] The isomer ratio in all cases was around 2.5:1; see Reference [11].

A hydroxymethyl substituent at position 2 of the dihydropyran ring (**1c**) efficiently traps the oxocarbonium intermediate to yield adduct **5q** (entry 1), a compound which is structurally related to the sexual attractant insect pheromone brevicomin.[15] An acetoxymethyl at position 6 did not exert relevant streodirecting effects on the MCR, and mixtures of stereoisomers were isolated as shown in entry 2. In sharp contrast, glycals bearing a substituent at position 4 displayed excellent facial stereoselectivity and enabled access to enantiopure compounds. For instance, compound **5s** (36%) was obtained from tri-*O*-acetyl-D-galactal in a process carried out at 40°C during 14 days.[16] Extension of this methodology to the D-glucal derivative afforded **5t** (20%). Microwave irradiation efficiently promoted faster and cleaner reactions, and **5s** and **5t** were obtained in 71% and 45% yield, respectively, in only 2 minutes (entries 3 and 4). Remarkably, we did not observe Ferrier-type or ring-opening transformations, which are common in acid-promoted reactions involving glycals and other enol ethers.[17] Additionally, the Povarov reaction proceeds with improved stereoselectivity to yield compound **6b** as a single stereoisomer (Figure 1).[18]

Tailored enol ethers also worked in this MCR. For example, substrates **1g** and **1h**, respectively prepared by Heck[19] and hetero-Diels–Alder reactions,[20] afforded the desired adducts stereoselectively with diastereomeric ratios of 4:1 for **5u** (the minor isomer is the epimer at the *p*-methoxyphenyl center) and 2.5:1 for **5v**[11] (Scheme 3).

One interesting application of this methodology is the ready access to new α-amino acid derivatives that bear an oxacycle substituent. This was done in just one additional step by hydrogenolysis of the benzhydryl derivative **5f** to afford the corresponding α-amino ester **7a** (78%). Interestingly, the oxidation of the *p*-methoxyaniline derivative **5e** with CAN



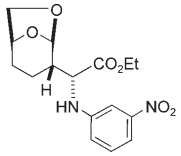
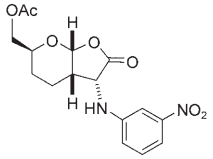
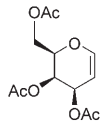
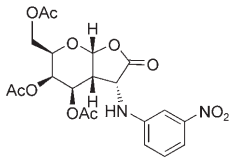
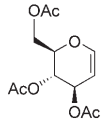
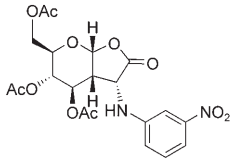
6a **6b**

Figure 1. Povarov-type compounds **6a** and **6b**.

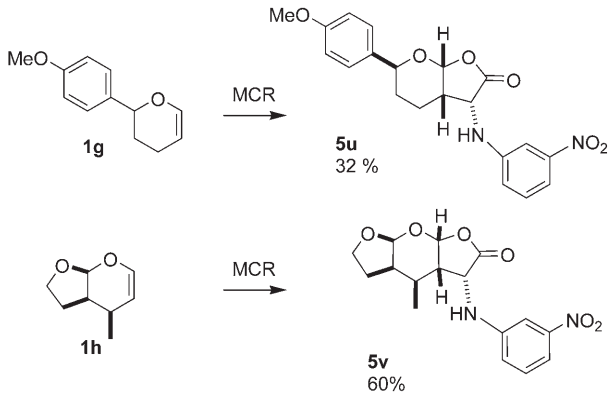
afforded the quinoline **8a** (55%). An improved protocol (71%) for this transformation involved treatment of **5e** with TFA in open atmosphere (O_2 as the oxidant). Analogously, oxidative treatment of **6b** produced the quinoline derivative **8b** (58%) bearing a stereodefined polyoxygenated chain at position 3 (Scheme 4).

The structural flexibility of this protocol is remarkable and allows the formation of four different scaffolds (Scheme 5) by applying post-condensation reactions to the MCR. Thus, it is possible to obtain compounds such as **5e** by a four-component reaction, **6c** by the Povarov three-compo-

Table 4: Range of cyclic enol ethers.

Entry	1	Yield [%]	5	Isomer ratio[a]
1	 **1c**	46	 **5q**	2.5:1
2	 **1d**	77	 **5r**	1.5:1[b]
3	 **1e**	71[c]	 **5s**	99:1
4	 **1f**	45[c]	 **5t**	99:1

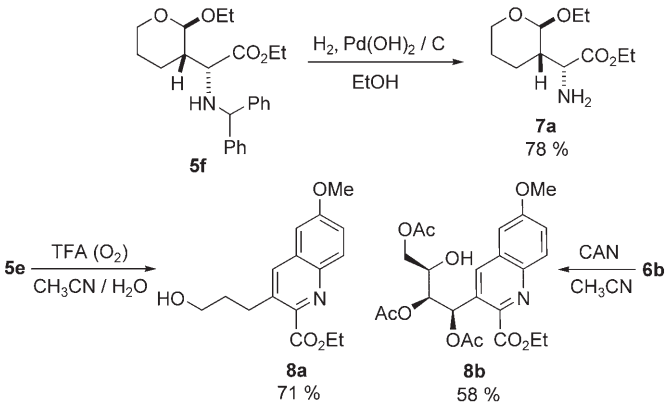
[a] See Reference [11]. [b] The minor isomer is the epimer at the acetoxymethyl center. [c] Microwave-promoted reaction.



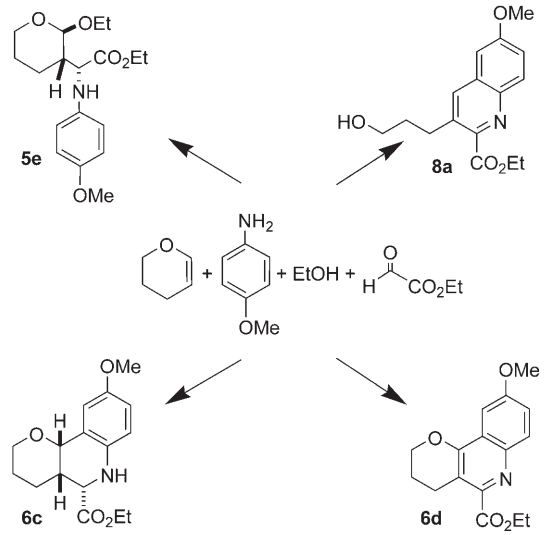
Scheme 3. Multicomponent reactions (MCRs) with preformed enol ethers.

nent reaction, **8a** by treatment of either **5e** or **6c** with acid, and **6d** by oxidation of **6c** with DDQ.[21]

In conclusion, we have developed a four-component reaction based on the nucleophilic interference of the Povarov reaction. The process is general and allows a broad range of variations in every component. The stereoselectivity of the reaction strongly depends on the substrates and ranges from low to moderate to excellent, Good stereocontrol is observed when sterically demanding amines and enol ethers are used.[22] The modular character of this approach, the simplicity and availability of most building blocks used, and the remarkable level of structural diversity attained make this process attractive for combinatorial, target-oriented, and diversity-oriented synthesis.[23]



Scheme 4. Preparation of α-amino ester **7a** and quinolines **8a** and **8b**. TFA = trifluoroacetic acid; CAN = cerium ammonium nitrate.



Scheme 5. MCR-derived scaffolds.

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Keywords: glycosides · Lewis acids · multicomponent reactions · oxygen heterocycles · synthetic methods

[1] For an overview of MCRs, see: a) *Multicomponent Reactions* (Eds.: J. Zhu, H. Bienaymé), Wiley-VCH, Weinheim, **2005**. For recent reviews, see: b) D. J. Ramón, M. Yus, *Angew. Chem.* **2005**, *117*, 1628; *Angew. Chem. Int. Ed.* **2005**, *44*, 1602; c) C. Simon, T. Constantieux, J. Rodriguez, *Eur. J. Org. Chem.* **2004**, 4957; d) R. V. A. Orru, M. de Greef, *Synthesis* **2003**, *10*, 1471; e) J. Zhu, *Eur. J. Org. Chem.* **2003**, 1133; f) H, Bienaymé, C. Hulme, G. Oddon, P. Schmitt, *Chem. Eur. J.* **2000**, *6*, 3321; g) A. Dömling, I. Ugi, *Angew. Chem.* **2000**, *112*, 3300; *Angew. Chem. Int. Ed.* **2000**, *39*, 3168.

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