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Atorvastatin (Lipitor) by MCR

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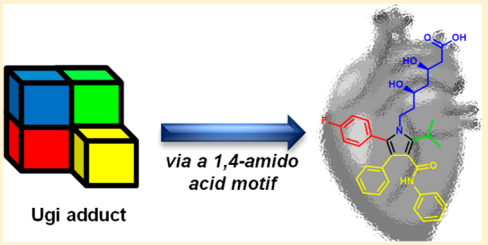
Supporting Information

ABSTRACT: A concise and convergent synthesis of the atorvastatin, the best-selling cardiovascular drug of all time, is presented. Our approach is based on an Ugi reaction, which shortens the current synthetic route and is advantageous over the published syntheses.



KEYWORDS: *Atorvastatin, Ugi reaction, münchnone, convergent synthesis, generics*

Multicomponent reactions (MCRs) are an advanced class of organic reactions which, opposite to classical organic reactions, allow for the easy, fast, and efficient generation of chemical diversity in just one assembly step.[1−3] These features make them an attractive area in research and development.[4] Surprisingly, the number of applications in drug discovery is rather limited regarding the superb advantages of this chemistry.[5] An analysis of the currently marketed drugs, however, shows that approximately 5% can be synthesized with the use of MCR, even so they are synthesized by a classical sequential pathway.[6] Examples of drugs synthesized by MCR clearly show the immense advantages of them in this context, e.g., lidocaine,[7] praziquantel,[8,9] telaprevir,[10] olanzapine,[11] clopidogrel,[12] lacosamide,[13] carfentanil,[14] ivosidenib,[15] and levetiracetam (Figure 1).[16] Epelsiban[17] and almorexant[18] are examples of compounds currently or recently in clinical trials and actually synthesized by utilization of the MCR repertoire (Figure 1).

Here we report an MCR-based synthesis of atorvastatin (common trade name: Lipitor), one of the world's best-selling medication of all time. Only in 2005, Lipitor made $12 billion in sales and was used by more than 45 million people worldwide.[19] It belongs to the drug class of statins, lipid-lowering drugs for the prevention of events associated with cardiovascular disease.[20] It is an example of a competitive HMG-CoA-reductase inhibitor, which consists of a pentasubstituted pyrrole core. The importance of atorvastatin until today[21−23] led to much interest in its synthesis. The main retrosynthetic scheme of the atorvastatin synthesis as described in literature focuses on the assembly of its five different substituents on a pyrrole hub.[24,25] By this way, which consists also the industrial route,[26] the pyrrole ring could be formed by a Paal−Knorr cyclocondensation[27,28] of the highly substituted 1,4-diketone **2** with primary amine **3** (Paal−Knorr route, Scheme 1, blue color).[21,22,26,29−34] In 2015, a total synthesis of atorvastatin via a late-stage, regioselective 1,3-dipolar münchnone cycloaddition[35] of the amido acid **4** with the acetylene

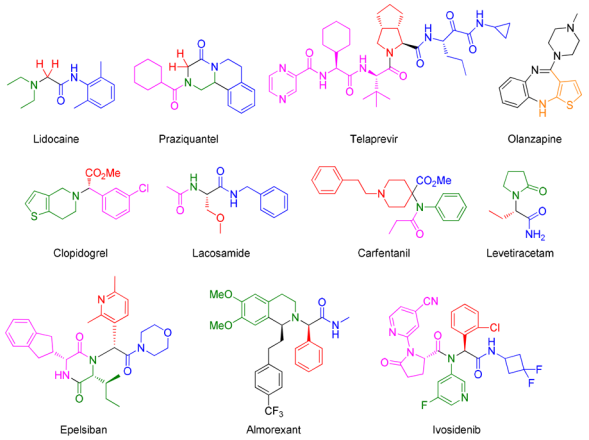


Figure 1. Examples of marketed drugs and drugs in clinical trials which have been discovered using MCR chemistry; the amine, aldehyde, isocyanide, and acid components are depicted with green, red, blue, and magenta color, respectively.

derivative **5** (münchnone route, Scheme 1, red color) was described.[36] Although this synthesis provided a nice solution to the problem of regioselectivity of the cycloaddition,[30] the synthesis of derivative **4** required five sequential steps which contributed to eight steps for the total synthesis of atorvastatin. Regarding the latter approach, we envisioned the synthesis of the amido acid **4** in only two steps utilizing the Ugi four-component reaction (U-4C, Scheme 2).

The initial derived MCR adduct can be considered as a synthetic hub to a vast diversity of other scaffolds.[2] Thus, the 1,4 amido acid motif could easily be derived from an Ugi adduct with the cleavage of the isocyanide moiety (Scheme 2).[37,38] Indeed, the reaction at rt of *p*-fluorobenzaldehyde **6**,

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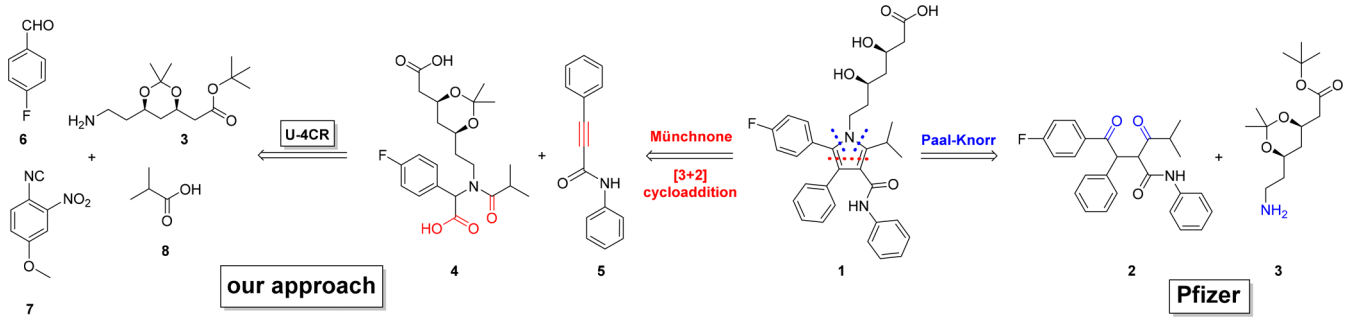
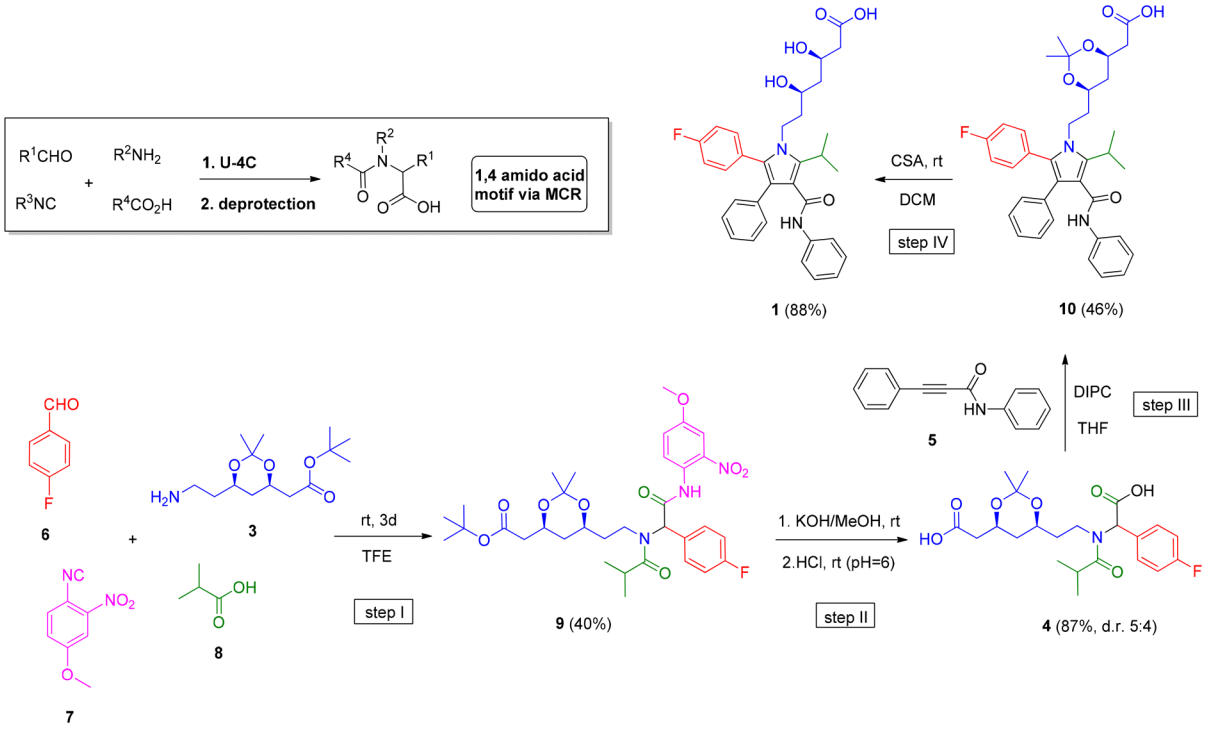
Scheme 1. Main Retrosynthetic Scheme for the Synthesis of Atorvastatin (Paal–Knorr Route, Blue Color); A Novel Approach to the Intermediate 4 Is Proposed by MCR (Münchnone Route, Red Color)



Scheme 2. MCR-Based Synthesis of 4 and the Subsequent Synthesis Towards Atorvastatin 1



the suitably functionalized, commercially available amine **3**,[29,39−41] the convertible isocyanide **7**,[42−45] and isobutyric acid **8** in 2,2,2-trifluoroethanol (TFE) afforded the Ugi adduct (U-4C) **9** in 40% yield. The choice of the corresponding isocyanide was the easiness of its cleavage at basic pH, keeping intact the other functional groups. Thus, in a one-pot acid deprotection and isocyanide cleavage, we obtained the valuable intermediate **4** in a *dr* 5:4 in 87% yield. Then, we performed the regioselective [3 + 2] cycloaddition[36] of **4** with the *N*,3-diphenylpropiolamide **5** and *N*,*N*′-diisopropylcarbodiimide (DIPC) in THF, yielding the advanced intermediate **10** in 46% yield which can be readily converted by acidic deprotection with 10-camphorsulfonic acid (CSA) to atorvastatin **1** (Scheme 2).

The industrial atorvastatin synthesis via the Paal–Knorr route is a synthesis consisting of six steps excluding the synthesis of amine **3**, which is commercially available (Table 1). MCR chemistry has also been employed in order to improve and optimize this synthetic route. These modifications include a one-pot Stetter/Paal–Knorr reaction sequence catalyzed by NHC[46] or a Hantzsch pyrrole synthesis (Table 1).[47] Regarding the münchnone route, this is the first time to the best of our knowledge, that MCR chemistry is utilized. On the basis of MCR chemistry, we synthesized the intermediate **4** in only two steps, and with two additional steps, we successfully obtained atorvastatin (Scheme 2). The Ugi reaction was performed at 10 mmol scale, see Supporting Information).

Our current approach effectively reduces the number of steps toward atorvastatin to only four compared with the seven reported in literature and establish this methodology equally or even better than the Paal–Knorr route. We can classify the recent syntheses of atorvastatin in four different routes (Table 1). Most of the published Paal–Knorr route syntheses include different variations of the synthesis of the amine (entry 1) or differentiation in the amine vector of the pyrrole core (entries 1–3). The required steps vary from six to 10. A Stetter/Paal–Knorr reaction sequence (entry 4) and a Hantzsch pyrrole synthesis (entry 5) were presented as alternatives with four and five steps, respectively. Our synthetic strategy can be ranked among the most competitive one with four steps (entry 7).[48]

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Table 1. Comparison of the Most Important, Recent Atorvastatin Syntheses in Literature along with Our MCR Approach

	routes	reference/ report	steps	remarks
1	Paal–Knorr	22,34,29[a]	6[b]	different variations on the synthesis of amine **3**/ differentiation in the amine vector of the pyrrole core
2		40	8	differentiation in the amine vector of the pyrrole core
3		23	10	differentiation in the amine vector of the pyrrole core
4	Stetter/ Paal–Knorr	46	4[b,c]	NHC-catalyzed Stetter/ Paal–Knorr sequence
5	Hantzsch	47	5[d]	Hantzsch variation of the pyrrole synthesis
6	Münchnone	36	7	
7		this work	4	

[a]The corresponding methyl ester of the amine **3** was employed in the Paal–Knorr [b]Excluding the steps required for the synthesis of amine **3** [c]The final product of the synthesis is the fully protected atorvastatin. [d]The final product of the synthesis is the atorvastatin lactone.

It is noteworthy that our current synthetic methodology of utilizing an MCR adduct bears convertible isocyanides, yielding the 1,4-amido acid motif. This strategy is beneficial not only because we have a faster access to atorvastatin but also by this way more derivatives are accessible. Thus, we can readily synthesize substituted bioactive pyrroles with a great diversity on substituents in 1-, 2-, and 5-positions, for example, positron emission tomography (PET) labeled derivatives.[36]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsmedchemlett.8b00579.

Experimental procedures and full characterization for compounds (PDF)

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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Notes

The authors declare no competing financial interest.

■ ABBREVIATIONS USED

TFE, 2,2,2-trifluoroethanol; DIPC, *N,N′*-diisopropylcarbodiimide; CSA, 10-camphorsulfonic acid; DCM, dichloromethane; PET, positron emission tomography.

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