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## Tricycles by a New Ugi Variation and Pictet–Spengler Reaction in One Pot

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### Keywords

multicomponent reactions; natural products; Pictet–Spengler reaction; Ugi reaction

Chemical diversity and complexity of scaffolds are key for the design- or screening-based discovery of useful materials. Series of compounds based on a particular scaffold are often used to optimize properties. Although scaffolds are traditionally built up by sequential multistep syntheses, a convergent alternative pathway involves one-pot multicomponent reactions (MCRs).<sup>[1]</sup> A useful definition of the scaffold in the context of MCR has been introduced recently by us, and accordingly it is defined “as the smallest atomic denominator and its connectivity as resulting from a reaction or reaction sequence by using starting materials with common functional groups.”<sup>[2]</sup> A very large variety of MCR scaffolds have been described in the past based on different strategies.<sup>[3]</sup> For example, there are more than 40 piperazine scaffolds accessible by MCR.<sup>[2]</sup> The two-step Ugi MCRs/ring-forming Pictet–Spengler reaction is of particular interest, because it gives access to rather rigid, complex polycyclic products, which can lead to entropically preferred receptor binding (Scheme 1). This reaction sequence has been used for the synthesis of drugs and natural products, as well as for chemical-biology tools.

We described the shortest scalable synthesis of the schistosomiasis drug praziquantel **1** by an Ugi–Pictet–Spengler sequence.<sup>[4]</sup> The same route can be used for the synthesis of bioactive Praziquantel derivatives otherwise not amenable.<sup>[5]</sup> Almorexant **2**, a selective and orally bioavailable orexin I antagonist recently began phase III clinical trials and was discovered by a sequence Ugi–Pictet–Spengler reactions.<sup>[6]</sup> By using a bifunctional oxocarboxylic acid, compounds, such as **3** with even more condensed cycles, can be conveniently synthesized.<sup>[7]</sup> Tyagi et al. performed the Ugi reaction in the Groebcke–Blackburn–Bienaymé variation followed by a Pictet–Spengler reaction to give several distinct skeletons of fused ring systems, for example, **4**.<sup>[8]</sup> Phenylethylamine-derived isocyanides can be converted in just two steps to polycyclic products with unprecedented complexity (**5**).<sup>[9]</sup> Lesma et al.

described the synthesis of 1,2,3,4-tetrahydro- $\beta$ -carboline (THBC)-based tetracyclic peptidomimetics from an Ugi–Pictet–Spengler reaction sequence with  $\beta$ -turn-like conformations.<sup>[10]</sup> El Ka m et al. described the synthesis of 1,4-diketopiperazines (**6**) by using  $\alpha$ -ketocarboxylic acids and homoveratryl isocyanide in the Ugi–Pictet–Spengler sequence.<sup>[11]</sup> Fukuyama et al. used an Ugi–Pictet–Spengler reaction in their total synthesis of the anticancer natural-product drug ecteinascidin 784 and the related naphthyridinomycin and lemonomycin.<sup>[12]</sup> Cano-Herrera and Miranda described an expedient entry to the piperazinohydroisoquinoline ring system (**7**) present in the tetrahydroisoquinoline antitumor alkaloids family by a sequential Ugi–Pictet–Spengler/reductive methylation reaction protocol.<sup>[13]</sup> Znabet et al. described an interesting biocatalytic desymmetrization of 3,4-*cis*-substituted *meso*-pyrrolidines (**8**) with an Ugi-type multi-component reaction followed by an in situ Pictet–Spengler-type cyclization-reaction sequence for the rapid asymmetric synthesis of alkaloid-like polycyclic compounds.<sup>[14]</sup> Other MCRs, such as the van Leusen reaction, have also been combined with the Pictet–Spengler reaction.<sup>[15]</sup> Most of the scaffolds are new and cannot be easily synthesized by methods other than by MCR chemistry methods. They thus provide an excellent source for the search for bioactive compounds.

Recently, We introduced an extension of the Ugi reaction of  $\alpha$ -amino acids by introducing primary or secondary amines as additional reactants, thus rendering the U-5C-4CR into a truly four-component reaction with four highly variable starting materials.<sup>[16]</sup> Herein, chiral iminodicarboxamides can be formed by the variation of an  $\alpha$ -amino acid, an oxocomponent, an isocyanide, and a primary or secondary amine as unprecedented components for this Ugi variation. The reaction is compatible with many functional groups and different fragments. For example, we have previously shown in one example that aminoacetaldehyde dimethylacetal can react together with the electron-rich aromatic amino acid tryptophan to give an unprecedented polycyclic ring system after a Pictet–Spengler ring closure in one pot.<sup>[16]</sup> We believe that such compounds are of interest to natural-product synthesis and for medicinal chemists, and therefore we would like to give full experimental detail, report the scope and stereochemistry of this new reaction by variation of different amino acids, isocyanides and oxocomponents, and several molecular structures (Scheme 2).

We first reacted tryptophan amino acid (**11**), a ketone (**10**), an isocyanide (**9**), and aminoacetaldehyde dimethyl acetal (**12**) in MeOH/H<sub>2</sub>O (4:1) at room temperature to form the U-5C-4CR product **13** as shown in Scheme 2. The Pictet–Spengler reaction product was not obtained by using various conditions, such as sulfonic acid, *para*-toluenesulfonic acid, and camphorsulfonic acid in toluene, however, by using concentrated formic acid at room temperature surprisingly gave the Pictet–Spengler cyclization product **14**. The reaction sequence was also conveniently performed in one pot without loss of yield of final product by evaporation of the crude U-5C-4CR mixture followed by addition of formic acid. Furthermore, we found that the reaction also worked with 5-hydroxy tryptophan according to Scheme 3. We made variations by using different isocyanides and ketones or aldehydes as shown in Table 1, and all reactions worked giving satisfactory yields. Use of benzaldehyde (**28**) and cyclopentanecarbaldehyde (**29**) produced two diastereomers (4:1 by <sup>1</sup>H NMR analysis, Table 1). In the case of valeraldehyde (**36**), two diastereomers in a ratio of 3.6:1 (by HPLC analysis, Table 1) were formed. All stereoisomers could be easily separated by using preparative supercritical fluid chromatography (SFC) HPLC analysis. By using TMS-oxy ethyl isocyanide, ethyl formate polycyclic compound **32** was obtained in good yield likely by an acid-catalyzed deprotection/esterification. All reactions are believed to work by the proposed mechanism shown in Scheme 3.<sup>[17]</sup> The reaction mechanism might occur by an initial deprotection step of the acetal groups in acidic condition to form the iminium ion (**17**) followed by electrophilic substitution (**18**). After subsequent deprotonation, the desired product (**16**) was obtained.

We also investigated the use of phenylalanine amino acid derivatives to form the Ugi–Pictet–Spengler isoquinoline (**39**). Although the U-5C-4CR product was formed in all cases, only when using 3-methoxy phenylalanine and 3,4-dimethoxy phenylalanine, the Pictet–Spengler isoquinoline product (**39**) was produced. However, if no electron-donating group is available on the *meta* position of the phenyl ring, such as phenylalanine or 4-methoxy phenylalanine, the Pictet–Spengler isoquinoline was not formed. The reaction might occur as shown in Scheme 4. The acetal group is removed in acidic condition to form the iminium ion (**38**) followed by electrophilic substitution and deprotonation to give the desired product (**39**).<sup>[17]</sup> Several analogous reactions were applied, and all analogs gave satisfactory yield even with diethyl (cyanomethyl)phosphonate (**47**) as shown in the Table 2.

To investigate the absolute structure, the relative stereochemistry and intermolecular contacts with respect to potential receptor–ligand interactions, several compounds were crystallized, and their single-crystal structures were solved (Figure 1).

Although there have been several previous attempts to use the Ugi–Pictet–Spengler combination in natural-product chemistry, we believe its potential is far from being fully tapped. A substructure search of the herein formed molecular skeletons in alkaloid- and natural-product databases revealed several potentially interesting targets, for example, the antitumor quinocarcin or the insecticidal notoamide B (Scheme 5).

The advantages of our new combination of Ugi–Pictet–Spengler reactions is the expedited and convergent access to polycyclic natural-product-like skeletons. The yields over two steps are good to acceptable. The stereochemistry of the amino acid is conserved, and therefore stereochemically pure (symmetrical ketones, formaldehyde) or diastereomeric (aldehyde other than formaldehyde) compounds were obtained. Many variations in the oxo and isocyanide starting materials can lead to synthetic handles to further elaborate the primary synthetic structures. Work is ongoing to investigate the further synthetic applications and biological properties of the new compounds.

## Experimental Section

### General procedure of Ugi–Pictet–Spengler reaction

A mixture of *L*-amino acid (0.5 mmol), ketone (0.5 mmol), isocyanide (0.5 mmol), and aminoacetaldehyde dimethyl acetal (0.5 mmol) in 0.1 M of MeOH/H<sub>2</sub>O (4:1) were stirred for 24–72 h at RT (in the case of 3,4-dimethoxy-*L*-phenylalanine, the reaction mixture was heated at 50°C for 72 h). Solvents were evaporated under reduced pressure. The crude Ugi product was dissolved in formic acid (2 mL) and stirred for another 16 h at RT. Reaction mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub>, and solid K<sub>2</sub>CO<sub>3</sub> was added in portion to neutralize the mixture. The excess K<sub>2</sub>CO<sub>3</sub> was filtered off by using Celite, and solvents were evaporated to get crude product, which was purified by supercritical fluid chromatography, column-flash chromatography, or preparative TLC to give title compound in decent yield.

Characterization of compound **20**: <sup>1</sup>H NMR (600 MHz, [D<sub>6</sub>]DMSO): δ = 1.25–1.55 (m, 9H), 1.73–1.78 (m, 1H), 1.95–2.04 (m, 2H), 2.68–2.75 (m, 3H), 2.93–2.98 (m, 2H), 3.28 (q, *J* = 13.8, 7.2 Hz, 2H), 3.49 (dd, *J* = 11.4, 4.2 Hz, 1H), 3.85 (d, *J* = 5.4 Hz, 1H), 4.04 (d, *J* = 3.6 Hz, 1H), 6.94 (t, *J* = 7.2 Hz, 1H), 7.03 (t, *J* = 7.2 Hz, 1H), 7.16–7.21 (m, 3H), 7.26–7.31 (m, 3H), 7.35 (d, *J* = 7.8 Hz, 1H), 7.39 (d, *J* = 3.6 Hz, 1H), 7.86 (t, *J* = 5.4 Hz, 1H), 10.73 ppm (s, 1H); <sup>13</sup>C NMR (150 MHz, [D<sub>6</sub>]DMSO): δ = 23.0, 33.8, 24.8, 29.3, 29.5, 32.5, 35.1, 35.3, 40.5, 46.3, 47.2, 54.6, 68.6, 106.9, 111.2, 117.5, 118.5, 120.8, 126.0, 126.5, 128.3, 128.5, 134.3, 135.4, 139.5, 171.5, 175.4 ppm. SFCMS (atmospheric pressure chemical ionization (APCI)) *m/z* calcd for C<sub>29</sub>H<sub>34</sub>N<sub>4</sub>O<sub>2</sub>: 471.61 [*M*]<sup>+</sup>; found: 471.25.

## Supplementary Material

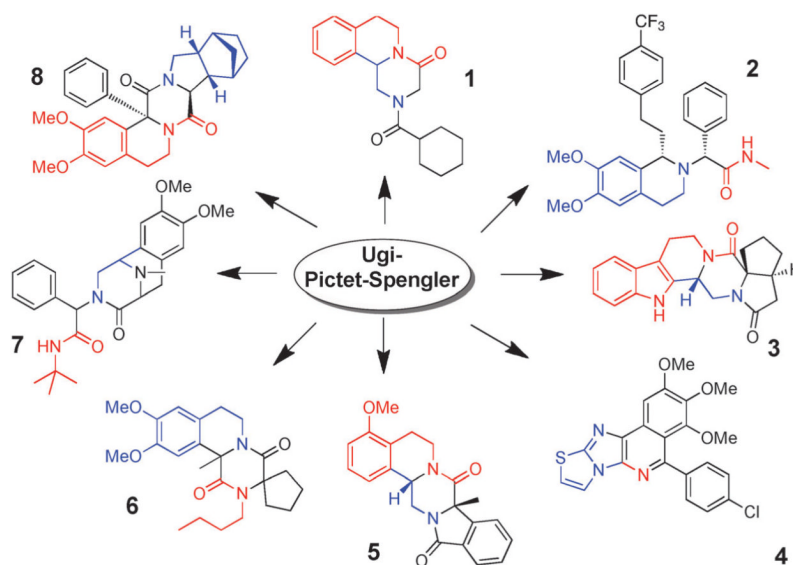
Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

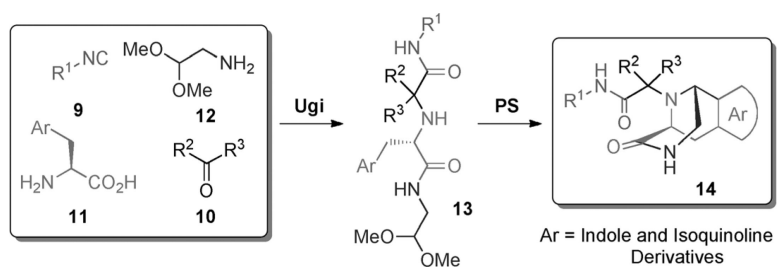
This work was financially supported by the NIH (1R21 M087617, 1R01M097082, and 1P41M094055 for A.D.). K.K. acknowledges the ACS Medicinal Chemistry predoctoral fellowship (2011–2012).

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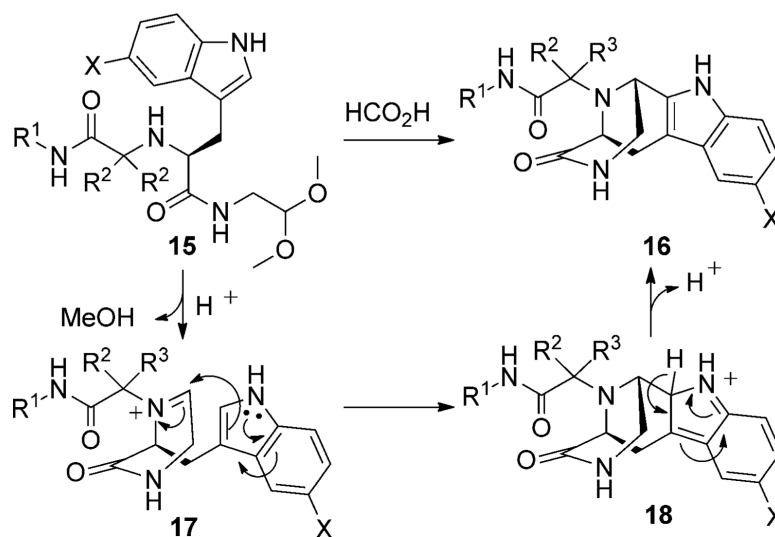
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**Scheme 1.**

Some previously described molecular skeletons assembled by the Ugi–Pictet–Spengler sequence. The isocyanide component, the amine component, and the oxo/acid components are marked in red, blue, and black, respectively.



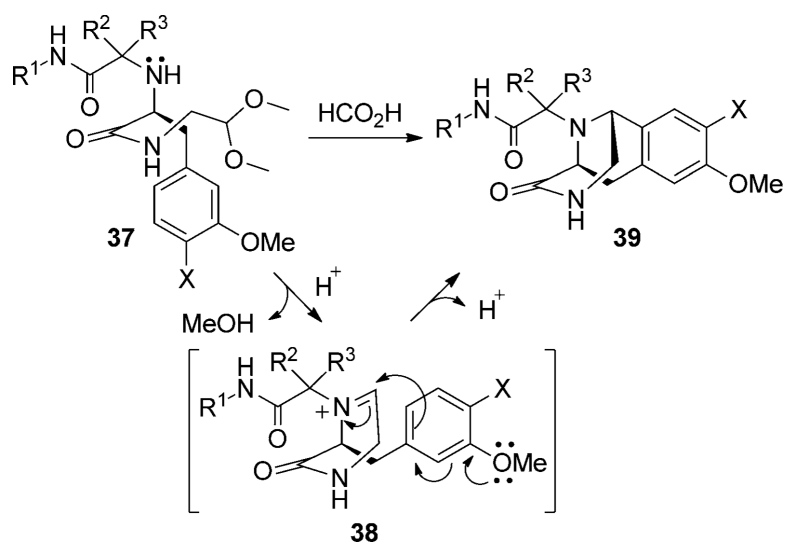
**Scheme 2.**  
Synthesis of Ugi–Pictet–Spengler indole and isoquinoline derivatives.



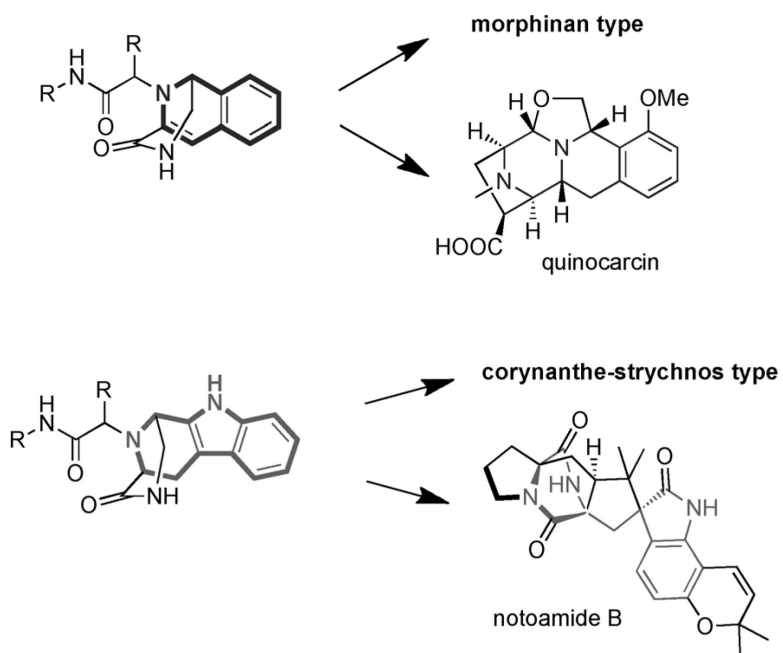
**Scheme 3.**  
Proposed reaction mechanism of Pictet–Spengler reaction for indole derivatives.







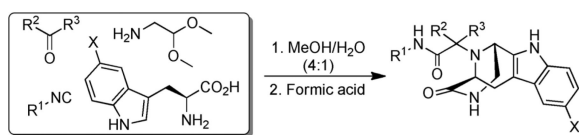
**Scheme 4.**  
Proposed reaction mechanism of the Pictet-Spengler isoquino-line derivative formation.



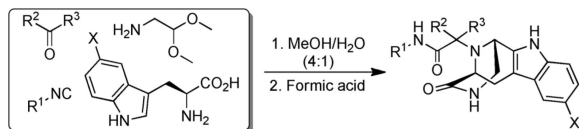
**Scheme 5.**  
Substructures in potential natural-product targets.

Table 1

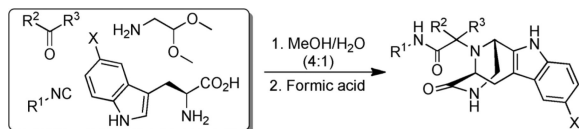
Synthesis of Ugi-Pictet-Spengler reaction for indole derivative.



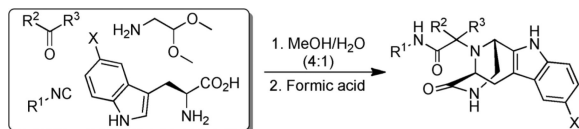
Compd.	R <sup>1</sup> -NC	R <sup>2</sup>	R <sup>3</sup>	X	Yield <sup>[a]</sup> [%]
19		Me		H	42
20				H	52



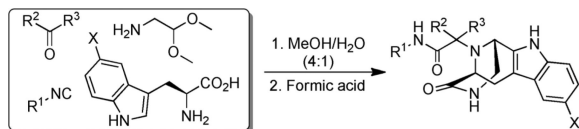
Compd.	R <sup>1</sup> -NC	R <sup>2</sup>	R <sup>3</sup>	X	Yield <sup>[a]</sup> [%]
21				H	48
22				OH	35
23				H	27



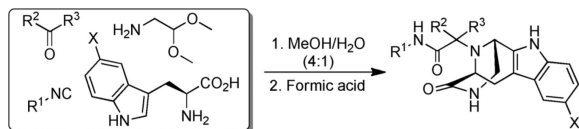
Compd.	R <sup>1</sup> -NC	R <sup>2</sup>	R <sup>3</sup>	X	Yield <sup>[a]</sup> [%]
24				OH	35
25		H	H	H	28
26				OH	44



Compd.	R <sup>1</sup> -NC	R <sup>2</sup> R <sup>3</sup>	X	Yield <sup>[a]</sup> [%]
27			OH	29
28			H	61 (4:1) <sup>[b]</sup>
29			OH	38 (4:1) <sup>[c]</sup>
30			OH	40



Compd.	R <sup>1</sup> -NC	R <sup>2</sup> R <sup>3</sup>	X	Yield <sup>[a]</sup> [%]
31			OH	27
32			OH	51
33			H	25



Compd.	R <sup>1</sup> -NC	R <sup>2</sup>	R <sup>3</sup>	X	Yield <sup>[a]</sup> [%]
34				H	19
35				OH	24
36				H	52 (3.6:1) <sup>[c]</sup>

<sup>[a]</sup> Overall yield in two steps (crude Ugi reaction product was directly used for the Pictet–Spengler reaction).

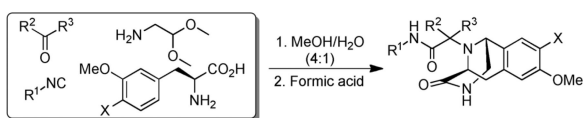
<sup>[b]</sup> Diastereomeric ratio (d.r.) was determined by <sup>1</sup>H NMR spectroscopy.

<sup>[c]</sup> d.r. was determined by UV spectroscopy.

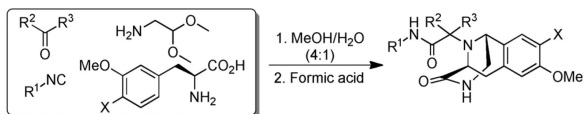


Table 2

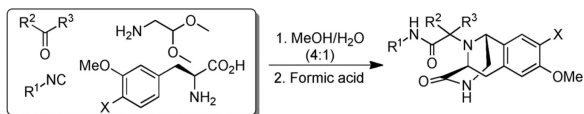
Synthesis of Ugi–Pictet–Spengler isoquinoline derivatives.



Compd.	R <sup>1</sup> -NC	R <sup>2</sup> C(=O) R <sup>3</sup>	X	Yield <sup>[a]</sup> [%]
40			OMe	64
41			OMe	59
42			OMe	62



Compd.	R <sup>1</sup> -NC	R <sup>2</sup>	R <sup>3</sup>	X	Yield <sup>[a]</sup> [%]
43				H	35
44				OMe	72
45				OMe	49



Compd.	R <sup>1</sup> -NC	R <sup>2</sup> -C(=O)-R <sup>3</sup>	X	Yield <sup>[a]</sup> [%]
46			H	44
47			OMe	76
48			H	47
49			OMe	52

<sup>[a]</sup>Yield in two steps (crude Ugi reaction product was directly used for the Pictet–Spengler reaction).