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Modular, Flexible, and Stereoselective Synthesis of Pyrroloquinolines: Rapid Assembly of Complex Heterocyclic Scaffolds

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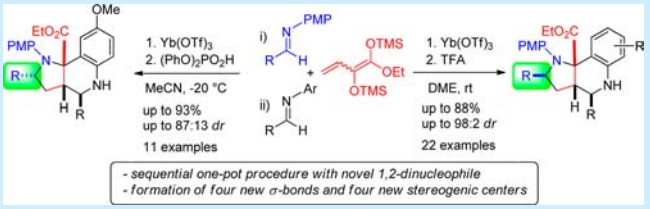
Supporting Information

ABSTRACT: A novel 1,2-dinucleophile engages two imines in a sequential vinylogous Mannich–Mannich–Pictet–Spengler process to generate complex hexahydropyrrolo[3,2-*c*]quinolines in a one-pot operation. This methodology provides a rapid, highly modular, and flexible access toward a wide range of products and forms four new σ-bonds and chiral centers each. The diastereoselectivity may be inverted by fine-tuning of reaction conditions and the electronic nature of the imines.



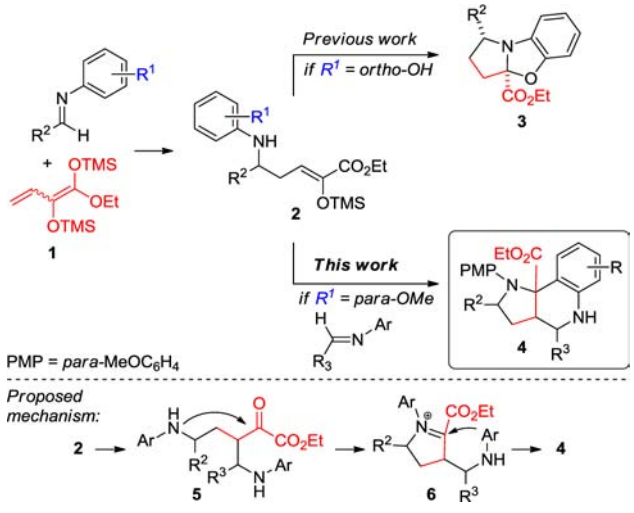
The diversity-oriented synthesis (DOS), the rapid assembly of structurally complex and highly functionalized molecules from simple and readily available starting materials, has become an important and intensely investigated research topic in recent years in view of its role in medicinal chemistry and chemical biology.[1] Ideally, various components react in a one-pot process,[2] form carbon–carbon bonds in a domino-type fashion with full stereochemical control,[3] and generate molecular complexity in an efficient manner. In general, the rapid generation of diverse compound libraries that subsequently provide valuable information in biological screenings is the goal of this approach. In addition, avoiding purification steps and isolating intermediates results in time-, cost-, and waste-reducing procedures getting close to an ideal synthesis.[4]

The hexahydropyrrolo[3,2-*c*]quinoline motif is a rather unusual nitrogen-containing heterocycle. It can be found in the alkaloids of *Martinella iquitosensis*, which exhibit interesting biological activity.[5] The combination of its intriguing architecture with this activity makes these alkaloids highly attractive targets and accordingly various synthetic strategies have been developed to access the hexahydropyrrolo[3,2-*c*]quinoline backbone.[6−10]

We report herein a novel, stereoselective, and highly flexible one-pot synthesis of polysubstituted hexahydropyrrolo[3,2-*c*]quinolines **4** starting from simple bis-silylated 1,2-dinucleophile **1** and two imines. In the course of this process, altogether three carbon–carbon bonds and one carbon–nitrogen bond as well as four stereogenic centers are formed with good stereocontrol. In addition, we can modulate the stereoselectivity by fine-tuning of the reaction conditions and produce the formerly minor stereoisomer as the major one.

Recently, we have reported a novel Lewis acid catalyzed, stepwise [3 + 2]-cycloannulation process that converts bis-silyldienediolate **1**, aldehydes, and 2-aminophenols directly and with excellent diastereoselectivity into tetrahydropyrrolo[2,1-*b*]benzoxazoles **3** (Scheme 1).[11] In this process, **1** adds to the in situ generated imine in a vinylogous Mannich reaction to furnish silyl enol ether **2** as the first intermediate which under the acidic, aqueous reaction conditions employed hydrolyzes into the corresponding α-keto ester, which then spontaneously cyclizes into the final benzoxazole **3**. We reasoned that under nonaqueous conditions this reaction pathway may be diverted in that silyl enol ether **2** may engage a second imine in a normal Mannich reaction to give rise to diamino α-keto ester **5**. This highly reactive intermediate should spontaneously cyclize into

Scheme 1. Design Plan for the Synthesis of Pyrroloquinolines



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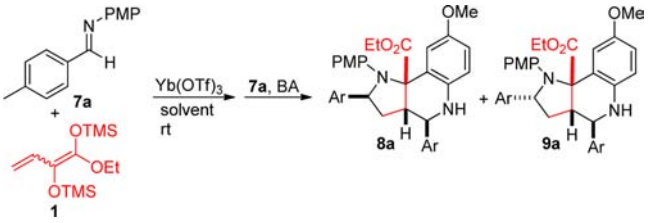
iminium ion **6**, which would now be in an ideal position to trap the electronrich anisidine moiety in a Pictet–Spengler reaction and produce the final pyrroloquinoline skeleton **4**.

To put these plans into practice, we started our studies with the model reaction of bis-silyldienediolate **1**, two equivalents of PMP-imine **7a** and 10 mol % of $Yb(OTf)_3$ in dry acetonitrile as solvent (Table 1). To our delight, the first vinylogous Mannich

Table 1. Optimization Studies[a]



entry	solvent	Brønsted acid (BA)	yield[b] (%)	dr[c]
1	MeCN	$(PhO)_2PO_2H$	80	56:34:10
2	CH_2Cl_2	$(PhO)_2PO_2H$	68	71:12:17
3	toluene	$(PhO)_2PO_2H$	66	77:12:11
4	MeOH	$(PhO)_2PO_2H$	71	50:40:10
5[d]	THF	$(PhO)_2PO_2H$	55	76:12:12
6	Et_2O	$(PhO)_2PO_2H$	72	71:16:13
7	DME	$(PhO)_2PO_2H$	80	82:12:6
8	DME	CH_3CO_2H	85	49:38:13
9	DME	CF_3CO_2H	64	81:13:6
10[e]	DME	CF_3CO_2H	80	91:4:5

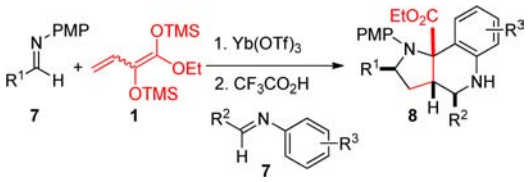
[a]Reaction conditions (unless otherwise noted): **7a** (1 equiv, 0.2 mmol), **1** (1.1 equiv), $Yb(OTf)_3$ (10 mol %) in 3 mL solvent for 10–60 min; then **7a** (1 equiv), Brønsted acid (1 equiv) for 10–30 min. [b]Combined yield of all diastereomers. [c]Ratio of **8a**:**9a**:combined minor diastereomers, dr determined by ^1H NMR. [d]Reaction time for the first step: 160 min. [e]CF_3CO_2H (3.26 M aq solution, 0.5 equiv). Ar = 4-MeC_6H_4, TMS = trimethylsilyl, PMP = *p*-methoxyphenyl, OTf = trifluoromethanesulfonate.

reaction proceeded quickly within 20 min at rt as expected and formed the stable intermediate **2a**. The second normal-type Mannich reaction, however, required further activation and it turned out that Brønsted acids proved to be suitable for this purpose.[12] Thus, the addition of one full equivalent of diphenyl phosphate to the intermediate **2a** delivered the pyrroloquinoline in 80% yield within only 10 min at rt with promising selectivity in favor of the first two isomers (**8a**, **9a**) (entry 1).

Ethereal and aromatic solvents were found to be optimal for this reaction (entries 2–7). In particular, 1,2-dimethoxyethane (DME) gave rise to 80% of product with an improved diastereomeric ratio of 82:12:6 (entry 7). Other Brønsted acids were also studied as mediators for the second step (entries 8–10). It turned out that an aqueous solution of trifluoroacetic acid (0.5 equiv) gave the best results in terms of yield and stereoselectivity. Thus, the mixture of **8a**/**9a** was obtained in 80% combined yield and with 91:4:5 dr (entry 10). The major stereoisomer **8a** was obtained in pure form by subsequent flash chromatography in 59% yield. The relative configuration of the major diastereomer was elucidated by X-ray crystallography of **8j** (see the Supporting Information).[13]

A broad range of aldimines were subsequently converted into pyrroloquinolines **8a**–**v** using the optimized conditions (Table 2). As the two imines were added sequentially to the reaction mixture and the second step was only triggered through addition of a second Brønsted acid, two different imines could

Table 2. Substrate Scope[a]



entry	R^1	R^2	R^3	**8**	yield[b] (%)	dr[c]
1	4-MeC_6H_4	4-MeC_6H_4	4-MeO	**a**	80	91:9
2	Ph	Ph	4-MeO	**b**	83	92:8
3	3-MeC_6H_4	3-MeC_6H_4	4-MeO	**c**	80	93:7
4	4-*t*-BuC_6H_4	4-*t*-BuC_6H_4	4-MeO	**d**	80	91:9
5	4-$MeOC_6H_4$	4-$MeOC_6H_4$	4-MeO	**e**	88	96:4
6	Ph	4-$MeOC_6H_4$	4-MeO	**f**	81	92:8
7	4-*t*-BuC_6H_4	4-$MeOC_6H_4$	4-MeO	**g**	82	93:7
8	4-ClC_6H_4	4-$MeOC_6H_4$	4-MeO	**h**	76	93:7
9	4-FC_6H_4	4-$MeOC_6H_4$	4-MeO	**i**	84	95:5
10	4-CNC_6H_4	4-$MeOC_6H_4$	4-MeO	**j**	83	92:8
11	3-ClC_6H_4	4-MeC_6H_4	4-MeO	**k**	81	91:9
12	4-$NO_2C_6H_4$	4-MeC_6H_4	4-MeO	**l**	85	93:7
13	2-naphthyl	4-$MeOC_6H_4$	4-MeO	**m**	72	95:5
14	2-furyl	4-$MeOC_6H_4$	4-MeO	**n**	82	80:20
15	2-thiophenyl	4-$MeOC_6H_4$	4-MeO	**o**	54	84:16
16	Ph	3-furyl	4-MeO	**p**	78	84:16
17	*t*-Bu	4-$MeOC_6H_4$	4-MeO	**q**	75	98:2
18	Cy	4-$MeOC_6H_4$	4-MeO	**r**	57	95:5
19	Ph	Ph	4-Me	**s**	83	86:14
20	Ph	Ph	H	**t**	64	89:11
21	Ph	Ph	4-NMe_2	**u**	64	80:20
22	Ph	4-$MeOC_6H_4$	2-MeO	**v**	50	92:8

[a]Reaction conditions: imine (1 equiv, 0.2 mmol), **1** (1.1 equiv), $Yb(OTf)_3$ (10 mol %) in 3 mL of DME for 0.5–6 h; then imine (1 equiv), CF_3CO_2H (3.26 M aq solution, 0.5 equiv) at rt for 9–24 h. [b]Combined yield of all diastereomers. [c]dr of **8** with respect to all other possible diastereomers, determined by ^1H NMR.

easily be employed in this process substantially broadening the scope of this transformation. PMP-protected imines carrying either electron-donating or electron-withdrawing groups at different positions of the benzylidene ring were readily tolerated and gave rise to the corresponding pyrroloquinolines in good yields and high diastereoselectivities of at least 90:10 dr in favor of the major isomer **8** versus the sum of the other isomers (entries 1–13). Again, the major isomers **8** were obtained in pure form through chromatography. In addition, heterocyclic and aliphatic aldimines were successfully transformed into the products with a maximum diastereoselectivity of 98:2 dr (entries 14–18). Linear aliphatic aldimines currently do not give the products in good yields. In addition, several aldimines with different substituents on the aniline ring component could be applied in the second step further expanding the scope of this process and furnishing more diversely substituted pyrroloquinolines (entries 19–22).

Moreover, the reaction may also be performed as a five-component reaction on a 0.2 mmol or even 2.0 mmol scale with two different aldehydes, 2 equiv of *p*-anisidine and bis-silyldienediolate **1**. Thus, mixing the first aldehyde, *p*-anisidine, and **1** with 10 mol % of $Yb(OTf)_3$ in DME resulted in the formation of silyl enol ether **2f** as intermediate. Subsequently, a second aldehyde and *p*-anisidine were added with 0.5 equiv of TFA to effect the second Mannich and Pictet–Spengler

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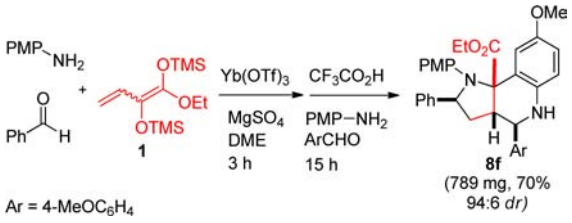
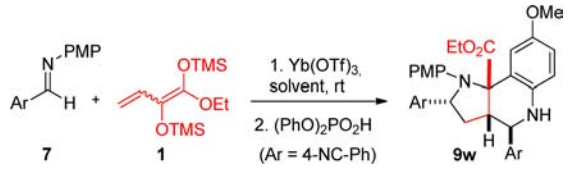
reactions upon which pyrroloquinoline **8f** was obtained in 70% combined yield and 94:6 dr on a 2.0 mmol scale (Scheme 2). The pure stereoisomer **8f** was isolated in 55% yield (626 mg).

Scheme 2. Sequential Five-Component, Gram-Scale Reaction



In the course of our studies, we observed that reactions with electronpoor imines employed as reaction partners for the second Mannich reaction gave rise to only low selectivity and shifted the selectivity toward stereoisomer **9** (Table 3). This

Table 3. Optimization Studies toward Stereoisomer 9[a]



entry	solvent	temp (°C)	yield[b] (%)	dr[c]
1	MeCN	rt	76	71:22:7
2	CH_2Cl_2	rt	68	38:46:16
3	MeOH	rt	73	43:40:17
4	MeCN	0	84	76:19:5
5[d]	MeCN	−20	86	83:15:2

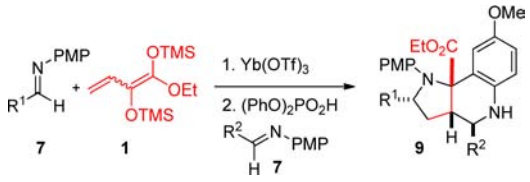
[a]Reaction conditions: **7** (1 equiv, 0.2 mmol), **1** (1.1 equiv), $Yb(OTf)_3$ (10 mol %) in 3 mL of solvent at rt for 15−30 min; then **7** (1 equiv), $(PhO)_2PO_2H$ (1.0 equiv) for 15−50 min. [b]Combined yield of all diastereomers. [c]Ratio of **9w**:**8w**:combined minor diastereomers, dr determined by ^{1}H NMR. [d]Reaction time for the second step: 8 h.

trend was particularly pronounced when we used diphenylphosphate as Brønsted acid and acetonitrile as solvent (entries 1−3). By lowering the reaction temperature, the diastereoselectivity was further increased and eventually at −20 °C the product was obtained in 86% combined yield and with 83:17 dr in favor of the major isomer **9w** versus the sum of the other isomers (entries 4 and 5). Its relative configuration was again unambiguously assigned by X-ray crystallography (see the Supporting Information).[14] We assume that this reversal of diastereoselectivity is caused by different modes of hydrogen bonding in the respective transition states due to the different strengths of the Brønsted acids employed as well as the basicity of the imines used.

This modified procedure was then employed to convert a wide range of imines with different substituents in the benzylidene ring into pyrroloquinoline stereoisomers **9** (Table 4, entries 1−9). Excellent yields of up to 93% were again observed for this multiple bond-forming event. Furthermore, heterocyclic imines reacted likewise to form the corresponding pyrroloquinolines in good yields and selectivities (entries 10 and 11).

We have briefly investigated structural modifications of the pyrroloquinolines. Thus, hydrolysis of the ester moiety with

Table 4. Substrate Scope Regarding 9[a]

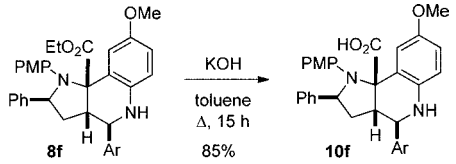


entry	R^1	R^2	**9**	yield[b] (%)	dr[c]
1	4-NCC_6H_4	4-NCC_6H_4	**w**	86	83:17
2	$4\text{-NO}_2C_6H_4$	$4\text{-NO}_2C_6H_4$	**x**	83	82:18
3	Ph	$4\text{-NO}_2C_6H_4$	**y**	87	82:18
4	4-FC_6H_4	4-NCC_6H_4	**z**	83	86:14
5	4-MeC_6H_4	4-NCC_6H_4	**aa**	93	79:21
6	4-MeOC_6H_4	4-NCC_6H_4	**ab**	84	85:15
7	4-FC_6H_4	$4\text{-NO}_2C_6H_4$	**ac**	82	87:13
8	3-ClC_6H_4	$4\text{-NO}_2C_6H_4$	**ad**	91	78:22
9	1-naphthyl	$4\text{-NO}_2C_6H_4$	**ae**	91	62:38
10	2-furyl	$4\text{-NO}_2C_6H_4$	**af**	80	87:13
11	2-furyl	4-NCC_6H_4	**ag**	83	75:25

[a]Reaction conditions: imine (1 equiv, 0.2 mmol), **1** (1.1 equiv), $Yb(OTf)_3$ (10 mol %) in 3 mL of MeCN for 15−30 min; then imine (1 equiv), $(PhO)_2PO_2H$ (1.0 equiv) at −20 °C for 7−8 h. [b]Combined yield of all diastereomers. [c]dr of **9** vs the sum of all other diastereomers as determined by ^{1}H NMR.

potassium hydroxide in toluene at reflux for 15 h generated amino acid **10f** in 85% yield (Scheme 3). Selective removal of the PMP group from the pyrrolidine N atom has not been possible so far.

Scheme 3. Ester Hydrolysis



In conclusion, we have established a rapid, modular, and high-yielding synthesis of complex hexahydropyrrolo[3,2-*c*]-quinolines from simple precursors. Four σ-bonds and four stereogenic centers were formed in a one-pot, sequential transformation. Out of eight possible diastereomers, one major isomer was obtained typically with good yield and selectivity. We were able to modulate the selectivity and obtain two different stereoisomers at will by careful adjustment of reaction conditions. Finally, a sequential five-component process was developed further simplifying the overall transformation. We believe that this latter reaction constitutes a particularly striking example of a multicomponent one-pot reaction for the rapid assembly of molecular complexity which should prove highly valuable in the context of the diversity-oriented synthesis. Ongoing studies aim at a full investigation of this reaction, an asymmetric variant, and its extension toward the synthesis of other heterocyclic scaffolds.

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■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, and X-ray structures of **8j** and **9w**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(14) The two minor diastereomers could not be separated. Coupling constants (J = 2 Hz for 3a-H and 4-H) support the assumed *cis*-configuration. Crystallograhic data for **9w**: CCDC 993568 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.