A Flexible Six-Component Reaction To Access Constrained Depsipeptides Based on a Dihydropyridinone Core

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Highly functionalized and conformationally constrained depsipeptides based on a dihydropyridin-2-one core are prepared by the combination of a four- and a three-component reaction. The synthesis combines a one-pot Horner–Wadsworth–Emmons/cyclocondensation sequence leading to isonitrile-functionalized DHP-2-ones with an isonitrile-based Passerini multicomponent reaction (MCR). Substituents could be independently varied at six different positions. The two MCRs could also be performed as a one-pot procedure, simplifying the protocol and leading to a new and highly variable six-component process.

One of the main challenges in synthetic organic chemistry is the rapid and efficient construction of collections of structurally complex and diverse small molecules. This can be most efficiently achieved by performing multiple reaction steps in a single operation. The development of such processes in which several bonds are formed without isolation of intermediates receives considerable attention.¹ An important class of these reactions is constituted by multicomponent reactions (MCRs),² which are particularly valued because they combine readily available building blocks with a range of functionalities in a single transformation. MCRs form the perfect basis for modular

SCHEME 1. MCR Leading to Isonitrile-Functionalized 3,4-DHP-2-ones



reaction sequences, in which a common intermediate is trapped to create different complex scaffolds in a minimal number of steps.

Although reports on novel MCRs appear regularly in the recent literature,³ MCRs using more than five components are very rare. A landmark in this context is the seven component reaction (7CR) reported by Dömling and Ugi,⁴ which was basically a one-pot combination of a modified Asinger-4CR and Ugi-4CR. In this 7CR, two different aldehydes, NaSH, NH₃, an isocyanide, CO₂, and a primary alcohol are combined to produce thiazolidines efficiently. However, NaSH, NH₃, and CO₂ are invariable components in this reaction.

Recently, we have reported several new MCRs based on a modular sequence.⁵ The common factor in these reactions is the application of 1-azadiene intermediate **4**, generated in situ by reaction of phosphonates **1**, nitriles **2**, and aldehydes **3** via a Horner–Wadsworth–Emmons (HWE) reaction (Scheme 1).⁶ The azadiene intermediate can be trapped by isocyanates or isothiocyanates to afford functionalized 3,4-dihydropyrimidine-2-ones,⁵ 2-aminothiazines,^{5b} and dihydropyrimidine-2-thiones.^{5b} In an elaboration of this chemistry, we examined the application of α -aryl isocyanoacetates **5** as the fourth, cyclizing, component to trap 1-azadiene **4** (Scheme 1).⁷ The resulting 3,4-dihydropyridin-2-ones **6** (3,4-DHP-2-ones) were obtained in good to excellent yields and with full diastereoselectivity in favor of the cis isomer.

The 4CR could be performed with aliphatic and aromatic nitriles and aromatic and α,β -unsaturated aldehydes affording a small library of isonitrile-functionalized 3,4-DHP-2-ones **6**. For convenience, a selection of examples (**6a**–**g**) are also included in Table 1. We only employed isocyanides **5** with an aromatic R³-group, because in these cases the 4CR proceeds in a highly diastereoselective fashion.⁷

We envisioned the ability of isonitrile-functionalized 3,4-DHP-2-ones **6** to react as isocyanide components in a subsequent

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TABLE 1. Passerini Follow-up Chemistry Using Several DHP-2-ones 6	To Afford the	Corresponding De	epsipeptides 7 th
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		EtO-P EtO 1 R ¹ Ct	`MeO₂ + N R ²	R ³ С ∩NC 5 − 2°СНО 3	<u>nBuLi</u> THF (0.2 M) -78°C to rt				$\mathbb{R}^{1} \xrightarrow{\mathbb{R}^{2} \mathbb{R}^{3}}_{\mathbb{N}} \xrightarrow{\mathbb{R}^{1} \mathbb{R}^{3}}_{\mathbb{N}} \xrightarrow{\mathbb{R}^{1} \mathbb{R}^{1}}_{\mathbb{N}} \mathbb{R}^{1}$	$\mathcal{A}_{\mathcal{A}}^{\mathcal{A}} \mathcal{B}^{\mathcal{B}}$
Entry	R ¹	\mathbb{R}^2	R ³	DHP- 2-one	R ⁴	R ⁵	R ⁶	Passerini Product	Yield $6 \rightarrow 7$ (%) ^b	Overall yield (%) ^b
1	iPr	PMP	Ph	6a	iPr	Н	Et	7a	72	41
2	\mathbf{Ph}	PMP	Ph	6b	<i>i</i> Pr	Н	Et	7b	66	42
3	Ph	PCP	Ph	6c	iPr	Н	Et	7c	73	53
4	\mathbf{Ph}	Ph	Ph	6d	<i>i</i> Pr	Н	Et	7d	76	74
5	Ph	PMP	PCP	6e	<i>i</i> Pr	Н	Et	7e	89	53
6	Ph	PMP	Ph	6b	iPr	Н	Ph	7f	61	39
7	Ph	PCP	Ph	60	iPr	Н	CbzHN ,	7g ^d	80	58
8	Ph		Ph	6f	<i>i</i> Pr	н	Bn	7h	89	57
9	Ph	Ph	Ph	6d	Ph	Н	Et	7i	57	56
10	Ph	Ph	Ph	6d	PCP	Н	Et	7j	57	56
11	\mathbf{Ph}	Ph	Ph	6d	PCP	Н	Bn	7k	65	64
12	Ph	PCP	Ph	6c	2-furyl	Н	Bn	71	47 ^e	34
13	Ph	PMP	Ph	6b	Et	Me	Bn	7m	43	28
14	\mathbf{Ph}	Ph	PCP	6g	\mathbf{H}^{c}	Н	Et	7 n	98	59
15	Ph	PMP	Ph	6b	H°	Н	Et	70	95	61

^{*a*} Unless otherwise noted (see the Supporting Information), the Passerini-3CRs were carried out using 0.7 M of DHP-2-one **6** and 1.1 equiv of both aldehyde/ketone and acid. Full conversion to **7** was reached after stirring for 1–6 days at room temperature in CH₂Cl₂, after which the Passerini products **7** were isolated as a 1:1 mixture of diastereomers. ^{*b*} Isolated yields are reported. ^{*c*} A large excess of paraformaldehyde (6 equiv) was used. ^{*d*} **7g** was obtained as a 1:1:1:1 mixture of four diastereomers. ^{*e*} Along with the product, 34% of side product **8** was also isolated. PMP = *p*-methoxyphenyl, PCP = *p*-chlorophenyl.



SCHEME 2. Formation of Side Product 8

Passerini-3CR reaction.⁸ In this way, conformationally constrained depsipeptides based on the DHP-2-one core should be accessible in only two steps. Depsipeptides, and cyclodepsipeptides in particular, represent an important class of natural products displaying diverse biological activities.⁹ The 3,4-DHP-2-ones like **6** have great potential in the construction of Freidinger-type β -turn mimics.^{9a} Conformationally constrained depsipeptides based on the 3,4-DHP-2-one core such as those resulting from the current multicomponent approach are therefore promising candidates for lead discovery. The modular setup of our approach allows for optimal flexibility with respect to the diversity points, and independent variation of all of the components involved in both MCRs, with the exception of **1**, should be possible. Furthermore, the generally mild reaction conditions for both the HWE/cyclocon-densation-4CR as well as for the Passerini-3CR led us to study the one-pot combination of both reactions to give a novel 6CR, thus simplifying the procedure and offering unprecendented opportunities for complexity generation and diversification. In this paper, we wish to report the results of our study.

3,4-DHP-2-ones 6a-g were reacted with a range of commercially available aldehydes and acids under standard Passerini conditions (CH₂Cl₂, rt). The expected depsipeptides 7a-owere successfully obtained in reasonable to excellent yield. Table 1 shows the broad substrate scope of this reaction typical for Passerini reactions. Due to the absence of stereochemical induction that is intrinsic to the Passerini reaction, a 1:1 mixture of inseparable diastereomers was obtained.¹⁰ No limitations were found in the aldehyde component since aliphatic, aromatic, and heteroaromatic aldehydes could be used. The use of ketones as the carbonyl component was also allowed, albeit with a slight decrease in yield (Table 1, entry 13). Furthermore, several acids (including an N-protected amino acid, entry 7) were successfully applied and afforded the corresponding products 7 in good to excellent yield. Moreover, no restriction was found with respect to the DHP-2-one input in the efficiency of the Passerini reaction. The low

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TABLE 2. One-Pot DHP-2-one-Passerini Reaction To Produce Depsipeptides 7^a

Et(Et	0 D-P 1 R ¹ CN 2	MeO ₂ C + R ² CHO 3	<i>n</i> BuLi THF (0.2 M) -78°C to rt	R	$\begin{bmatrix} R^2 & R^3 \\ R^3 & NC \\ R^4 & O \\$	R4´	0 0 0 R ⁵ R ⁶ THF, rt	[`] ОН R ¹	$ \begin{array}{c} $
	Entry	$r = \mathbf{R}^1$	\mathbb{R}^2	R ³	\mathbb{R}^4	R ⁵	R ⁶	Product	Yield (%) ^b
	1	iPr	PMP	Ph	iPr	Н	Et	7a	40
	2	Ph	$\bigcap_{i=1}^{n}$	Ph	iPr	Н	Bn	7h	44
	3	Ph	Ph	Ph	PCP	Н	Et	7j	48
	4	Ph	PCP	Ph	iPr	Η	Et	7c	36
	5	Ph	РСР	Ph	iPr	Н	Et	7c	40°

^{*a*} In general, the reactions were carried out using 0.2 M of 1, 1.1 equiv of *n*-BuLi, and 1 equiv of 2, 3, and 5. After formation of 6 was complete (TLC), the mixture was concentrated to 0.6-0.7 M, and 1.1 equiv of aldehyde and acid were added. Depsipeptides 7 were usually obtained by allowing the reactions to stir for an additional 7–9 days at rt. For more details, see the Supporting Information. ^{*b*} Isolated yields are reported. ^{*c*} The whole sequence was performed at 0.2 M concentration for 7 days at rt. PMP = *p*-methoxyphenyl, PCP = *p*-chlorophenyl.

yield of product **71** is caused by a side reaction leading to formamide **8**, most likely the result of a reaction between the isonitrile and the acid component followed by an acyl migration involving the free amide NH in the DHP-2-one (Scheme 2). No acylated Passerini product was observed, excluding an intermolecular process. A similar side reaction was observed in two reports describing the Passerini reaction in aqueous media; in these cases, the primary reaction was followed by hydrolysis rather than acyl migration.¹¹ This side reaction occurs primarily upon dilution, which was required for this specific Passerini reaction (0.25 M instead of 0.7 M) for solubility reasons.

The reported Passerini reactions generally reached full conversion in 1-6 days, with some exceptions.¹² Such reaction rates are quite typical for the Passerini reaction.¹³

To accelerate the reaction, an additional 1 equiv of aldehyde and acid was added in some cases.¹² Furthermore, it is known that the use of water as a cosolvent can accelerate the Passerini reaction.^{11,13} However, performing the reaction of entry 2 (Table 1) in H₂O or THF/H₂O mixtures instead of CH₂Cl₂ did not result in significant rate enhancement of the reaction. With this rather flexible two-step procedure for constrained depsipeptides in hand, we now turned to study the combination of both MCRs in one pot resulting in a six-component reaction. The rather mild reaction conditions under which both the HWE/cyclocondensation-4CR and the Passerini-3CR operate suggested that only slight modifications of the original conditions would be required. For the HWE/cyclocondensation-4CR, we decided to apply stoichiometric amounts of all components except for the slight excess of n-BuLi (1.1 equiv). In addition, THF was used as the solvent in the whole sequence, which is a slight modification for the Passerini-3CR. Under these conditions, the one-pot synthesis of depsipeptide 7a was first investigated (Table 2, entry 1).

Thus, diethyl methylphosphonate, isobutyronitrile, *p*-methoxybenzaldehyde, and methyl 2-isocyano-2-phenylacetate were combined to form the corresponding 3,4-DHP-2-one **6a**. The concentration for this HWE/cyclocondensation-4CR was kept similar (0.2 M) compared to that of the reaction used in the two-step sequence (see entry 1, Table 1). After the in situ formation of **6a** was complete, the solution was concentrated to 0.6-0.7 M (similar to the Passerini conditions described in Table 1) and isobutyraldehyde and propionic acid were added. The one-pot six-component procedure performed surprisingly well and after the reaction was complete, we could isolate depsipeptide **7a** in 40% yield. In fact, this yield was the same as the overall yield obtained via the two-step procedure (41%, see entry 1, Table 1).

The initial conditions proved more generally applicable and, in addition to 7a, the conformationally constrained depsipeptides 7c, 7h, and 7j were formed smoothly (see Table 2). Actually, the reaction performs very well in one pot considering the complexity of the reaction system, and all the isolated yields are comparable with the combined yields of the two separate MCRs, indicating that no additional side reactions occur. It should be noted, however, that in the one-pot procedure the Passerini reaction proceeded relatively slow, with reaction times up to 10 days, probably due to the use of THF instead of CH₂Cl₂ as a solvent.¹⁴ Performing the whole sequence at 0.2 M concentration leads to comparable reaction rates and overall yield of the depsipeptide with respect to the same reaction in which the Passerini reaction is performed at 0.6-0.7 M concentration (compare entries 4 and 5, Table 2). This result makes the tandem DHP-2-one/Passerini reaction in fact a true one-pot 6CR.

In conclusion, we showed that the retained isocyanide functionality in 3,4-DHP-2-ones **6** synthesized via a HWE/ cyclocondensation-4CR allows subsequent isonitrile-based multicomponent follow-up chemistry. The isocyano group proved indeed an excellent synthetic handle for additional MCRs. A follow-up Passerini-3CR reaction led to a series of complex DHP-2-one based conformationally constrained depsipeptides

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7. The combination of our MCR and the Passerini reaction in one pot was also demonstrated, affording a novel one-pot 6CR. The yields of the one-pot, six-component process were comparable to those of the two-step procedure. All of the six components in the novel 6CR can be varied, opening the way to efficient generation of arrays of DHP-2-one-functionalized depsipeptidic scaffolds from simple, commercially available starting materials. These results demonstrate the strength of the concept of unification of MCRs.

Experimental Section

General Procedure I for the Passerini Reaction. The reactions were generally carried out at a concentration of 0.70 M of DHPone and 0.77 M of the other two components in CH₂Cl₂. Deviations from these concentrations are due to solubility problems and are reported for every product. The dihydropyridone was dissolved in DCM, followed by addition of 1.1 equiv of carbonyl compound and 1.1 equiv of carboxylic acid. After being stirred at rt until completion, the reaction mixture was concentrated in vacuo and the crude product purified by column chromatography. The resulting diastereomeric mixture could not be separated in any case and the diastereomeric ratio was determined via ¹H NMR analysis for all the products with the exception of **7g** (HPLC).

General Procedure II for the One-Pot DHP-one-Passerini MCR. The synthesis was always carried out at a concentration of 0.20 M of phosphonate 1, 0.22 M of *n*-BuLi, 0.20 M of nitrile 2, aldehyde 3, and isocyanoacetate 5 in dry THF. Always 1.0 mmol of the limiting reagent, the phosphonate, was used. 1.1 Equiv. of *n*-BuLi (1.6 M solution in hexanes) were added at -78 °C to a stirred solution of phosphonate in THF. After the mixture was stirred at -78 °C for 1.5 h, the nitrile (1.0 equiv) was added, and the mixture was then stirred at -78 °C for 45 min, at -40 °C for 1 h, and at -5 °C for 30 min. The aldehyde (1.0 equiv) was added, and after being stirred at -5 °C for 30 min, the mixture was allowed to warm to rt and stirred for 1.5 h. Finally, the isocyanoacetate (1.0 equiv) was added, and the mixture was stirred overnight at rt and then concentrated in vacuo up to a concentration of phosphonate of 0.6-0.7 M. After addition of 1.1 equiv of carbonyl compound and of acid, the mixture was stirred at rt until completion. The mixture was concentrated, and the crude product was purified by chromatography.

Passerini Product 7a. General Procedure I. Reaction between **6a**, isobutyraldehyde, and propionic acid afforded after 2 days **7a** (104 mg, 72%) as a 1:1 mixture of diastereoisomers. A concentration of 0.59 M of **6a** was used. Column chromatography was performed with *c*-hexane/EtOAc 9:1 \rightarrow 85:15. **General Procedure II.** Compound **7a** (201 mg) was obtained in 40% overall yield from phosphonate **1** after stirring for 8 days: ¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.71–7.26 (m, 7H + 7H), 7.18 (d, *J* = 8.7 Hz, 2H), 6.76 (d, *J* = 8.6 Hz, 2H + 2H), 5.36 (d, *J* = 6.6 Hz, 1H), 5.32 (d, *J* = 6.7 Hz, 1H), 5.06 (d, *J* = 6.7 Hz, 1H),

5.01 (d, J = 6.7 Hz, 1H), 4.90 (d, J = 4.3 Hz, 1H), 4.74 (d, J =4.3 Hz, 1H), 3.78 (s, 3H), 3.76 (s, 3H), 2.42 (q, *J* = 7.5 Hz, 2H), 2.21-1.87 (m, 4H + 2H), 1.20 (t, J = 7.6 Hz, 3H), 0.98 (t, J =7.6 Hz, 3H), 0.94-0.87 (m, 6H + 6H), 0.72 (d, J = 6.9 Hz, 6H), 0.69 (d, J = 6.8 Hz, 3H), 0.48 (d, J = 6.8 Hz, 3H); ¹³C NMR (63 MHz, CDCl₃) δ (ppm) 173.4 (C), 172.5 (C), 171.5 (C), 171.4 (C), 168.5 (C), 168.1 (C), 159.4 (2 × C), 141.0 (C), 140.3 (C), 138.9 (C), 138.8 (C), 130.9 (C), 130.2 (CH), 129.8 (C), 129.7 (CH), 128.5 (CH), 128.3 (CH), 128.1 (CH), 128.0 (CH), 127.8 (CH), 127.5 (CH), 114.4 (2 × CH), 105.6 (CH), 105.0 (CH), 78.3 (CH), 77.4 (CH), 64.1 (C), 63.7 (C), 55.7 (CH₃), 55.6 (CH₃), 42.4 (CH), 41.4 (CH), 31.6 (2 × CH), 30.9 (CH), 30.5 (CH), 28.0 (CH₂), 27.7 (CH₂), 20.5 (CH₃), 20.1 (CH₃), 20.0 (CH₃), 19.3 (CH₃), 18.9 (CH₃), 17.0 (CH₃), 16.8 (CH₃), 9.6 (CH₃), 9.3 (CH₃); IR (NaCl) 2966 (s), 1749 (s), 1668 (s), 1510 (s), 1178 (s); HRMS (EI, 70 eV) calcd for C₂₉H₃₆N₂O₅ (M⁺) 492.2624, found 492.2624; MS (EI, 70 eV) m/z 320 (28), 319 (100), 318 (46), 215 (10), 172 (12), 104 (9), 57 (14).

Passerini Product 7c. General Procedure I. Reaction between 6c, isobutyraldehyde, and propionic acid afforded after 1 day 7c (40 mg, 73%) as a 1:1 mixture of two diastereoisomers. Column chromatography was performed with c-hexane/EtOAc 7:3. General **Procedure II.** Compound **7c** (190 mg) was obtained in 36% overall yield from phosphonate 1 after stirring for 8 days: ¹H NMR (250 MHz, CDCl₃) δ (ppm) 7.74–7.18 (m, 16H + 16H), 5.88 (d, J = 6.9 Hz, 1H), 5.85 (d, J = 7.0 Hz, 1H), 5.31 (d, J = 6.7 Hz, 1H), 5.27 (d, J = 6.8 Hz, 1H), 4.86 (d, J = 4.6 Hz, 1H), 4.72 (d, J =4.4 Hz, 1H), 2.44 (q, J = 7.8 Hz, 2H), 2.23–1.91 (m, 3H + 1H), 1.20 (t, J = 7.6 Hz, 3H), 1.00 (t, J = 9.4 Hz, 3H), 0.74–0.68 (m, 6H + 3H), 0.52 (d, J = 6.8 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃) δ (ppm) 173.5 (C), 172.7 (C), 170.7 (C), 168.8 (C), 168.4 (C), 138.4 (C), 138.3 (C), 136.8 (C), 136.1 (C), 136.0 (C), 135.4 (C), 134.2 (2 × C), 134.0 (C), 133.9 (C), 130.7 (CH), 130.2 (CH), 129.7 (2 × CH), 129.4 (CH), 129.3 (CH), 129.2 (CH), 128.9 (CH), 128.7 (CH), 128.6 (CH), 128.5 (CH), 128.3 (CH), 127.5 (CH), 127.3 (CH), 125.4 (CH), 108.0 (CH), 107.7 (CH), 78.1 (CH), 77.5 (CH), 63.8 (C), 63.5 (C), 43.4 (CH), 42.2 (CH), 30.9 (CH), 30.5 (CH), 27.9 (CH₂), 27.7 (CH₂), 19.3 (CH₃), 18.8 (CH₃), 17.2 (CH₃), 16.8 (CH₃), 9.6 (CH₃), 9.3 (CH₃); IR (NaCl) 2352 (m), 2343 (m), 1733 (s), 1717 (s), 1652 (s), 1635 (s), 739 (s); HRMS (EI, 70 eV) calcd for C₃₁H₃₁ClN₂O₄ (M⁺) 530.1972, found 530.1967; MS (EI, 70 eV) *m*/*z* 359 (38), 358 (37), 357 (100), 244 (33), 242 (99), 215 (17), 71 (27), 57 (42).

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Supporting Information Available: Full experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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