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Isocyanide Chemistry

Stereoselective Synthesis of Functionalized Bicyclic Scaffolds by Passerini 3-Center-2-Component Reactions of Cyclic Ketoacids

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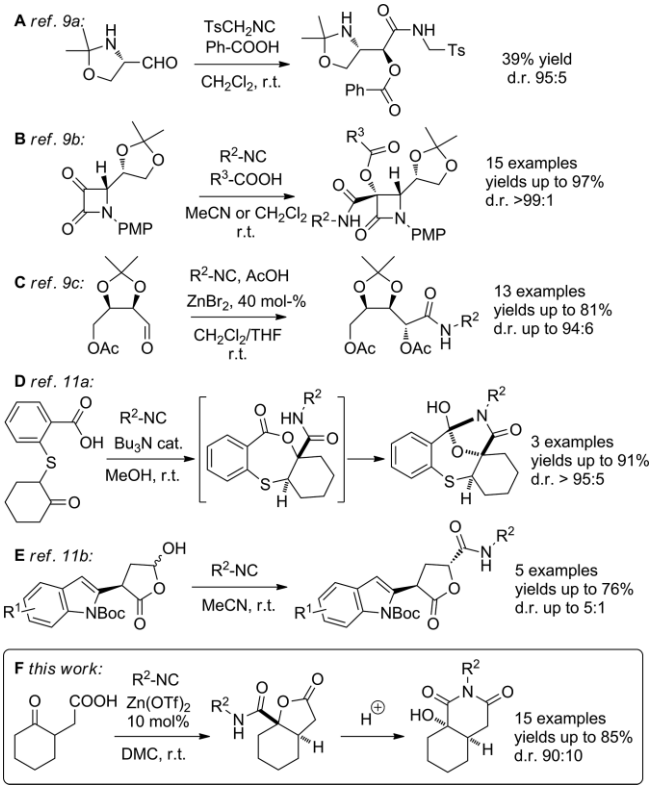
Abstract: We report the use of bifunctional starting materials (ketoacids) in a diastereoselective Passerini three-center-two-component reaction. Study of the reaction scope revealed the required structural features for stereoselectivity in the isocyanide addition. In this system, an interesting isomerization of the primary Passerini product – the α-carboxamido lactone – into an atypical product, an α-hydroxy imide, was found to occur under acidic conditions. Furthermore, enantioenriched Passerini products can be generated from an enantioenriched ketoacid obtained by chemoenzymatic synthesis.

Introduction

Isocyanide-based multicomponent reactions (IMCRs) are essential tools in combinatorial and diversity-oriented synthesis. Based on the unique reactivity of the formally divalent isocyanide carbon atom, this chemistry facilitates the efficient exploration of chemical space, rapidly generating complexity from simple starting materials. Importantly, the primary MCR (multicomponent reaction) products provide numerous opportunities for further synthetic elaboration, for instance into planar heterocycles as well as sp^3-rich structures.[1] The first discovered IMCR, the Passerini reaction, in which an aldehyde (or ketone), a carboxylic acid, and an isocyanide are combined,[2] still represents one of the most widely used IMCRs in various applications[3] owing to its many advantages (convergence, atom economy, simple operation, broad scope).[4] However, its most important limitation, the poor control over the stereochemistry of the newly formed stereocenter, is also well recognized in the multicomponent reaction community.[5] Despite the great efforts that have been made to address this issue, successful asymmetric Passerini reactions are still limited to just a few examples of catalytic enantioselective variants[6] and diastereoselective reactions (with chiral isocyanides,[7] chiral carboxylic acids,[8] or chiral aldehydes/ketones,[9] respectively). Some representative examples of diastereoselective Passerini reactions are shown in Scheme 1. A relatively simple strategy to improve the modest stereocontrol involves the use of bifunctional starting materials (oxoacids), as the (partially) intramolecular reaction benefits



Scheme 1. Diastereoselective Passerini reactions. PMP = *p*-methoxyphenyl; Boc = *tert*-butoxycarbonyl.

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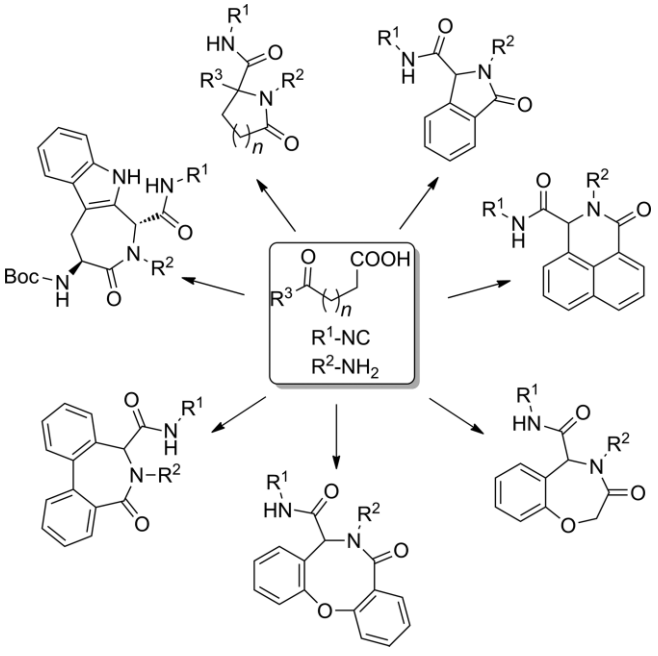
from a more sterically constrained transition state for the isocyanide addition. The bifunctional nature of oxoacid components has been strategically exploited in isocyanide chemistry to create a broad spectrum of heterocycles through the Ugi reaction (Scheme 2).[10] However, similar examples of the Passerini reaction are scarce (Scheme 1D and E).[11]



Scheme 2. Use of oxoacids in Ugi reactions.

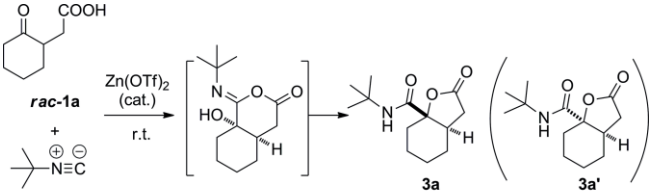
In this paper, we report a new diastereoselective Passerini reaction using simple cyclic oxoacids as starting materials. The reaction proceeds through a fused bicyclic transition state with additional steric constraints, thus leading to improved stereoselectivity. Furthermore, we report the unusual rearrangement of these Passerini products to give unprecedented α-hydroxy bicyclic imides.

Results and Discussion

We began our investigation with the reaction between 2-(2-oxocyclohexyl)acetic acid (**1a**) and *tert*-butyl isocyanide (**2a**; 1.5 equiv.). Under standard Passerini conditions (CH_2Cl_2, room temp.), the reaction proceeded smoothly to give the desired product with already good diastereoselectivity (85:15) in favor of the *trans*-fused isomer (Table 1, entry 1). The stereochemistry corresponds to an axial attack of the isocyanide (expected for a non-sterically-demanding nucleophile[12]) to yield a *cis*-fused *O*-acyl imidate α-adduct, which, upon Mumm rearrangement, gives *trans*-fused bicyclic lactone **3a** (see also Scheme 3). This structure was unambiguously confirmed by X-ray diffraction analysis, as shown in Figure 1.

Encouraged by this initial result, we attempted to improve the diastereomeric ratio of the isocyanide addition by varying the solvent. The reaction was found to proceed in most of the solvents investigated (toluene, dimethyl carbonate, *tert*-butanol, methanol, and even water) but with lower stereoselectivity. We then resorted to Lewis acid catalysis with the hypothesis that

Table 1. Optimization of the intramolecular Passerini reaction with **1a**.[a]



Entry	Solvent	Catalyst loading [mol-%]	Time [h]	Yield [%][b]	**3a**/**3a'**[c]
1	CH_2Cl_2	0	20	100	85:15
2	DMC	0	20	73	72:18
3	CH_2Cl_2	20	20	100	88:12
4	THF	20	20	95	86:14
5	Toluene	20	20	100	83:17
6	*t*BuOH	20	20	93	81:19
7	EtOAc	20	20	98	87:13
8	MeCN	20	20	100	89:11
9	DMC	20	20	100	90:10
11	DMC	20	2	100	90:10
12[d]	DMC	20	2	56	50:50
13	DMC	10	2	100	90:10
14[e]	DMC	10	2	90	90:10
15	DMC	5	2	93	75:25

[a] Standard conditions: ketoacid **1a** (0.5 mmol) and *t*BuNC **2a** (0.75 mmol, 1.5 equiv.) in solvent (1 mL) at room temperature for the indicated time. [b] Yield based on NMR spectrum with mesitylene as an internal standard. [c] Based on NMR spectroscopic analysis of the crude product. [d] Carried out at 0 °C. [e] With 1.1 equiv. of *t*BuNC, ca.10 % of intermolecular Passerini three-component reaction product observed.

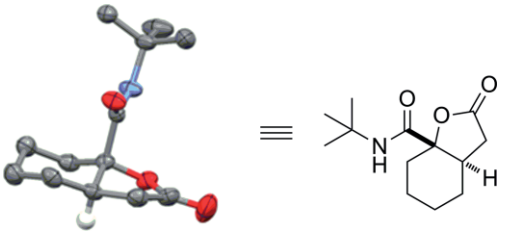


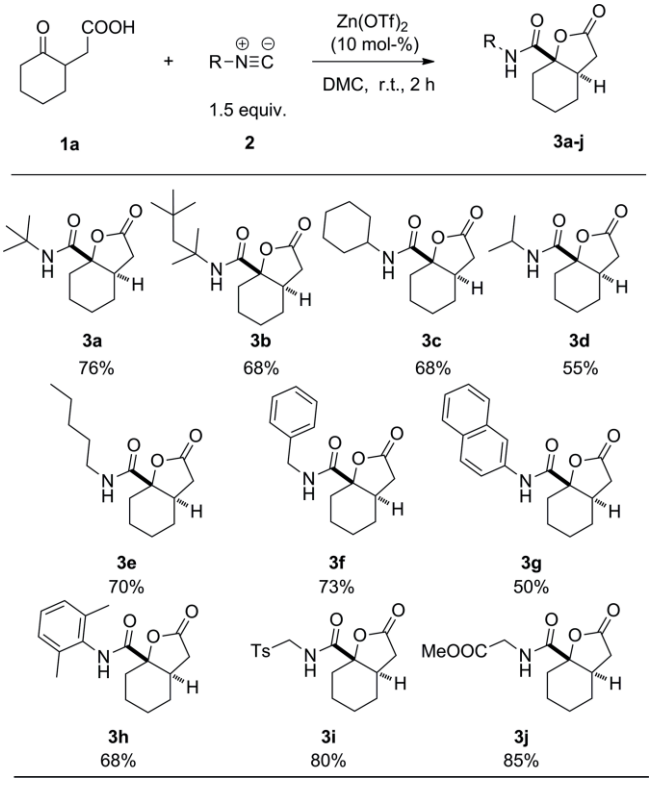
Figure 1. X-ray structure of major *trans* diastereoisomer **3a** (some H atoms omitted for clarity).

coordination of both carbonyl groups (and possibly the isocyanide as well) to a metal center would lead to a more rigid transition state.[9c] A small screening[13] identified $Zn(OTf)_2$ as a promising candidate for improved diastereoselectivity (Table 1, entry 3). Since the Lewis acid also led to an increase in the reaction rate, we repeated the solvent screening and focused on the solvent with the slowest background (uncatalyzed) reaction. Thus, the reaction with $Zn(OTf)_2$ (20 mol-%) in dimethylcarbonate (DMC)[14] gave complete conversion and a 9:1 diastereomeric ratio (Table 1, entry 9). Carrying out the reaction at 0 °C was detrimental to both the yield and the selectivity (possibly due to the insolubility of the catalyst), but we observed that we could significantly decrease both the catalyst loading (to 10 mol-%) and the reaction time (to 2 h) without adverse effects. These conditions turned out to be optimal, as any further

decrease in the amount of isocyanide (Table 1, entry 14) or in the catalyst loading (entry 15) did not lead to improved results.

Having established this optimal protocol, we went on to investigate the scope of the reaction in terms of the isocyanide component. Gratifyingly, all classes of isocyanides are accepted in this reaction (Table 2): aliphatic (tertiary [products **3a**, **3b**], secondary [products **3c**, **3d**], primary [products **3e**, **3f**]), aromatic (including the bulky 2,6-dimethylphenyl derivative [product **3h**]), and α-acidic (products **3i**, **3j**). In general, the diastereoisomers of the products were readily separated by flash chromatography, and the isolated yields of the pure *trans*-fused Passerini products **3a**–**3j** were moderate to high. As expected for relatively small linear nucleophiles like isocyanides, the diastereoselectivity was well conserved across the series (ca. 9:1, as in the parent example **3a**).

Table 2. Scope of the reaction in terms of isocyanides.[a]

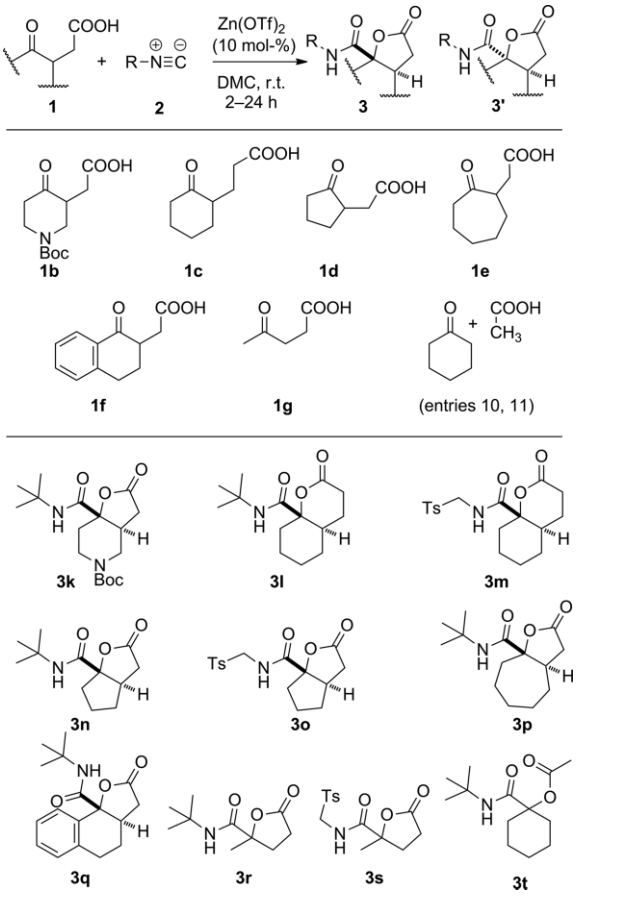


[a] Standard conditions: ketoacid **1a** (1.0 mmol) and isocyanide **2** (1.5 mmol, 1.5 equiv.) in DMC (2 mL) with $Zn(OTf)_2$ (10 mol-%) at room temperature for 2 h; yields refer to isolated yields of the pure major diastereoisomer after flash chromatography.

Next, we sought to extend this intramolecular Passerini reaction to other oxoacids in order to rationalize the structural features required for high diastereoselectivity. In this context, we focused on the ring size, the distance between the ketone and carboxylic acid, and the conformational flexibility of the oxoacid **1**.

First, the introduction of a carbamate group into the cyclohexanone ring (starting material **1b**) led to a drastic decrease in the reaction rate (Table 3, entry 1), possibly due to a preferential binding of the Zn ions to this additional coordinating group. A starting material with the keto and carboxylic groups in a 1,5-relationship reacted somewhat more slowly (the imidate α-adduct is a seven-membered ring in this case) but still gave the products **3l** and **3m** in reasonable yield under the standard conditions (with *t*BuNC and $TsCH_2NC$, Table 3, entries 2 and 3). The diastereoselectivity was found to be lower (3:1), but the direction of isocyanide attack was preserved (*trans*-fused products predominated). Unfortunately, we found that the reaction

Table 3. Scope of the reaction in terms of ketoacids.[a]



Entry	Product	Ketoacid	R	Time [h]	Yield [%][b]	**3**/**3′**[c]
1	**3k**	**1b**	*t*Bu	6	23	5:1
2	**3l**	**1c**	*t*Bu	2	58	3:1
3	**3m**	**1c**	$TsCH_2$	2	50	3:1
4	**3n**	**1d**	*t*Bu	2	n.d.	n.d.
5	**3o**	**1d**	$TsCH_2$	2	n.d.	n.d.
6	**3p**	**1e**	*t*Bu	24	n.d.	n.d.
7	**3q**	**1f**	*t*Bu	24	n.d.	n.d.
8	**3r**	**1g**	*t*Bu	2	11[d]	≈ 1:1
9	**3s**	**1g**	$TsCH_2$	24	82[d]	≈ 1:1
10	**3t**	–[e]	*t*Bu	24	95[f,g]	–
11	**3t**	–[e]	*t*Bu	24	50[f]	–

[a] Standard conditions: ketoacid **1** (1 mmol) and isocyanide **2** (1.5 mmol, 1.5 equiv.) in DMC (2 mL) with $Zn(OTf)_2$ (10 mol-%) at room temperature for the indicated time. [b] Isolated yield of the major diastereoisomer unless indicated otherwise. [c] Based on NMR spectroscopic analysis of the crude product. [d] Combined yield of diastereomers. [e] With cyclohexanone and acetic acid as reactants. [f] Crude yield with mesitylene as internal standard. [g] Without catalyst.

is not tolerant of variation in the nature of the cyclic ketone; starting materials based on a cyclopentanone (**1d**), cycloheptanone (**1e**), or tetralone (**1f**) motif gave slow conversions and side reactions (Table 3, entries 4–7). Due to ring strain, the carbonyl group is particularly reactive in the cyclohexanone system compared to the C_5 and C_7 homologs; conjugation with the aromatic ring drastically decreases the reactivity of **1f**. Furthermore, side reactions (e.g., multiple isocyanide addition) may take place as a result of conformational/strain effects disfavoring the formation of the usual reaction intermediates. Indeed, for starting material **1d**, a more ionic mechanism (i.e., isocyanide addition to generate a nitrilium ion followed by addition of the carboxylate[15]) can be expected, since the nucleophilic attack would presumably take place from the least hindered diastereotopic face of the carbonyl group leading to a strained *trans*-fused α-adduct.[16] This adduct may be difficult to form, and may not evolve cleanly into a single product. Additionally, intermolecular reactions can take place if the transition state for the intramolecular condensation is not favorable. Evidence for these side reactions was obtained in the reaction of **1d** with *t*BuNC under the standard conditions: a complex mixture of products was observed (Table 3, entry 4). Moreover, in the case of the less reactive isocyanide $TsCH_2NC$, the conversion was low, and product formation could not be confirmed. In the case of the seven-membered homolog **1e**, HRMS analysis indicated the formation of the desired product **3p**, but we were unable to isolate it from the complex product mixture. A similar outcome was observed for tetralone-based acid **1f**. On the other hand, the simple acyclic derivative **1g** reacted cleanly, albeit slowly and with no stereoselectivity (Table 3, entry 8). Extending the reaction time to 24 h allowed the isolation of the expected Passerini product of **1g** and $TsCH_2NC$ in 82 % yield (Table 3, entry 9), but for this scaffold the diastereoisomers could not be separated. As a control experiment, the Passerini reaction of *t*BuNC, AcOH, and cyclohexanone proceeded to completion within 24 h, even in the absence of a Lewis acid catalyst (Table 3, entry 10). This result confirms the particularly high electrophilicity of cyclohexanone. Remarkably, the addition of catalytic $Zn(OTf)_2$ gave a much lower yield (ca. 50 %; Table 3, entry 11) due to side reactions. Thus, the Lewis acid not only enhances the rate of the desired pathway but also that of alternative pathways, possibly by a switch in the reaction mechanism. Clearly, the success of the reaction depends on a fine balance between the rigidity of the transition state required for good diastereoselectivity (**1a** vs. **1g**, **1c** vs. **1g**) and some degree of conformational flexibility to prevent side reactions (**1g** vs. **1d**).

Upon crystallization of Passerini product **3j** from ethanol, we were intrigued to find that the structure revealed by X-ray diffraction analysis corresponded to a rearrangement of the scaffold to α-hydroxy imide **4j** (Figure 2). We then investigated this unusual transformation further, and found that it is amenable to Brønsted acid catalysis. Surprisingly, the conditions required to drive this rearrangement [$MeSO_3H$ (1 equiv.), $CHCl_3$, 80 °C] are not as mild as might be expected from the crystallization experiment,[17] and the rate varies significantly and relatively inconsistently with the type of secondary amide substituent.

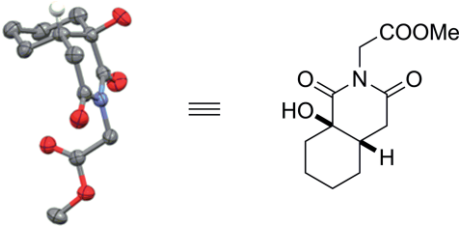
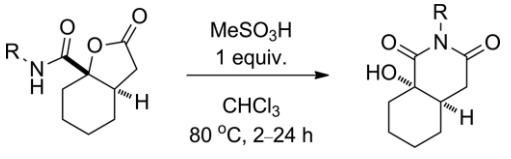


Figure 2. X-ray structure of **4j** (some H atoms omitted for clarity).

Nevertheless, this transformation is general in the series of Passerini products **3a**–**3j** and can be pushed to near completion over 24 h (Table 4). The tertiary derivatives **3a** and **3b** represent a special case as they undergo dealkylation under these conditions: for **3a**, the conversion was slow, and led to a mixture of products, whereas for the *tert*-octyl derivative **3b** the corresponding free α-hydroxy imide (**4b**, R = H) could be isolated in reasonable yield (Table 4, entry 2). We hypothesize that ring strain plays an important role in this rearrangement, which corresponds to a formal 1,3(O–N) acyl transfer in the Passerini α-adduct instead of acyl migration to the OH group. The thermodynamic driving force for this isomerization is most probably the release of strain in moving from the *trans*-fused [4.3.0] bicyclic system to the more relaxed *cis*-hexahydroisoquinolinedione scaffold. This premise is supported by negative control experiments: the minor diastereoisomer **3h′** was stable under the rearrangement conditions, whereas homolog **3m** and monocyclic lactone **3r** gave at best low conversions over 24 h (Scheme 3).

Table 4. Rearrangement of Passerini products to α-hydroxyimides.[a]

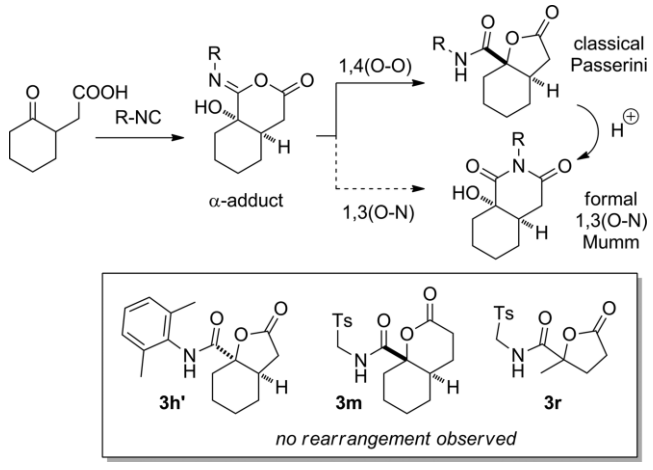


3 **4**

Entry	**3**	R	Time [h]	Yield [%][b]	**4**/**3**[c]
1	**3a**	*t*Bu	24	n.d.[d]	n.d.
2	**3b**	*t*Oct	7	60[e]	>95:5
3	**3c**	cHex	24	89	94:6
4	**3d**	*i*Pr	24	96	95:5
5	**3e**	*n*-pentyl	2	75	94:6
6	**3f**	benzyl	4	93	>95:5
7	**3g**	2-naphthyl	24	64[f]	91:9
8	**3h**	2,6-$Me_2C_6H_4$	3	99	>95:5
9	**3i**	$TsCH_2$	1	83	>95:5
10	**3j**	MeO_2CCH_2	3	76[f]	>95:5

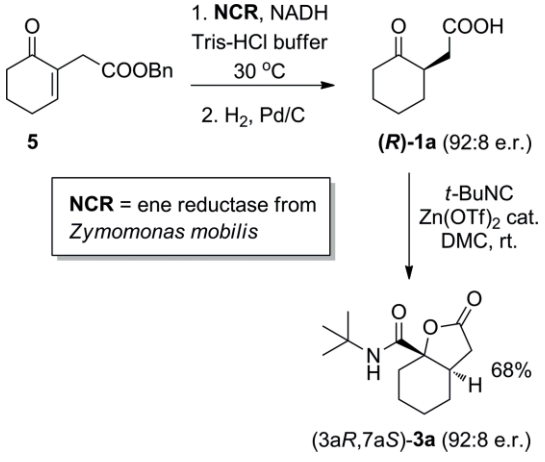
[a] Standard conditions: Passerini product (0.1 mmol) and $MeSO_3H$ (1 equiv.) in $CHCl_3$ (0.3 mL) at 80 °C for the indicated time. [b] Isolated yield of **4** with minor amounts of **3**. [c] Based on the NMR spectrum of the crude product mixture. [d] Complex product mixture. [e] Free imide (**4b**, R = H) isolated after column chromatography. [f] Minor impurity observed.

Finally, we attempted to control not only the diastereoselectivity, but also the absolute stereochemistry during our intramolecular Passerini reaction.[18] Thus, asymmetric bioreduction of unsaturated keto ester **5** with the nicotinamide-dependent



Scheme 3. Negative control experiments in the formal 1,3(O–N) Mumm rearrangement of scaffold **3**.

ene-reductase NCR from *Zymomonas mobilis*[19] and subsequent hydrogenolysis delivered (*R*)-**1a**.[20] This can then react with isocyanides to give enantioenriched Passerini products,[21] as exemplified for **3a** (Scheme 4). This result underlines the fruitful complementarity of biocatalysis and multicomponent reactions in the asymmetric synthesis of valuable small molecules.[22]



Scheme 4. Chemoenzymatic preparation of enantioenriched **3a**. NADH = nicotinamide adenine dinucleotide.

Conclusions

In conclusion, we report a new diastereoselective intramolecular Passerini reaction with cyclic ketoacids leading to interesting sp^3-rich bicyclic lactones. The structural features required for high stereoselectivity in the isocyanide addition were identified and discussed. Interestingly, these Passerini products can isomerize to α-hydroxy imide derivatives as formal 1,3(O–N) Mumm rearrangement products of the α-adducts. Furthermore, complete stereocontrol can be achieved by combining this diastereoselective isocyanide addition with a chemoenzymatic preparation of the nonracemic ketoacid building block.

Experimental Section

General Information: Unless stated otherwise, all solvents and commercially available reagents were used as purchased. Melting points were recorded with a Büchi M-565 melting-point apparatus. Nuclear magnetic resonance (NMR) spectra were recorded with a Bruker Avance 500 (125.78 MHz for ^{13}C) or Bruker Avance 400 (100.62 MHz for ^{13}C) instrument with the residual solvent as an internal standard (^1H: δ = 7.26 ppm, $^{13}C\{^1H\}$: δ = 77.16 ppm for $CDCl_3$; ^1H: δ = 2.50 ppm, $^{13}C\{^1H\}$: δ = 39.52 ppm for [D_6]DMSO). Chemical shifts (δ) are given in ppm, and coupling constants (J) are quoted in Hertz (Hz). Resonances are described as s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), sex (sextet), sep (septet), br. (broad singlet), and m (multiplet) or combinations thereof. Infrared (IR) spectra were recorded neat by using a Shimadzu FTIR-8400s spectrophotometer, and data are reported in wavenumbers (cm^{-1}). Electrospray ionization (ESI) high-resolution mass spectrometry (HRMS) was carried out by using a Bruker microTOF-Q instrument in positive-ion mode (capillary potential of 4500 V). Chiral GC analysis was carried out with a Shimadzu GC-2010 Plus chromatograph. Flash chromatography was carried out on Silicycle Silia-P flash silica gel (particle size 40–63 μm, pore diameter 60 Å) by using the indicated eluent. Thin-layer chromatography (TLC) was carried out with TLC plates from Merck (SiO_2, Kieselgel 60 F254 neutral, on aluminium with fluorescence indicator). X-ray structures were determined with an Agilent Supernova diffractometer equipped with a Cu microsource, mirror monochromator, and Atlas CCD detector. Omega scans were used at liquid-nitrogen temperatures. Additional experimental details can be found in the CIFs in the Supporting Information. The ketoacids **1a** and **1c**–**1f** are known compounds, and were prepared according to literature procedures: **1a**,[23] **1c**,[24] **1d**,[25] **1e**,[25] **1f**.[26] Compound **1g** is commercially available.

General Optimization Procedure: $Zn(OTf)_2$ (0.05 mmol, 0.1 equiv.) and isocyanide **2a** (0.75 mmol, 1.5 equiv.) were added to a solution of ketoacid **1a** (0.5 mmol, 1 equiv.) in solvent (1 mL). The solution was stirred at room temperature for 2–20 h. Then the mixture was diluted with CH_2Cl_2, and quenched with a saturated $NaHCO_3$ solution. The organic layer was separated, and the aqueous layer was extracted again with CH_2Cl_2. The combined organic layers were dried with Na_2SO_4, and concentrated in vacuo. The crude yield of **3a** and the ratio **3a**/**3a**′ were determined by NMR spectroscopic analysis with mesitylene as an internal standard.

Procedure A – Intramolecular Passerini Reaction: $Zn(OTf)_2$ (0.1 mmol, 0.1 equiv.) and isocyanide **2** (1.5 mmol, 1.5 equiv.) were added to a solution of ketoacid **1** (1 mmol, 1 equiv.) in dimethyl carbonate (2 mL). The solution was stirred at room temperature for 2 h. Then the mixture was diluted with CH_2Cl_2, and quenched with a saturated $NaHCO_3$ solution. The organic layer was separated, and the aqueous layer was extracted again with CH_2Cl_2. The combined organic layers were dried with Na_2SO_4, and concentrated in vacuo. The crude product **3** was purified by column chromatography on silica gel.

Procedure B – Rearrangement of Passerini Products: Passerini product **3** (0.1 mmol) was dissolved in $CHCl_3$, and CH_3SO_3H (0.1 mmol, 1 equiv.) was added. The solution was heated at 80 °C in a sealed vial for 1–24 h (conversion monitored by TLC). The solution was then diluted with CH_2Cl_2, and quenched with a saturated $NaHCO_3$ solution. The organic layer was separated, and the aqueous layer was extracted again with CH_2Cl_2. The combined organic layers were dried with Na_2SO_4, and concentrated in vacuo. The yield and the ratio **4**/**3** were determined by NMR spectroscopic analysis.

***N*-(*tert*-Butyl)-2-oxohexahydrobenzofuran-7a(2*H*)-carboxamide (3a/3a′):** Prepared from 2-(2-oxocyclohexyl)acetic acid (**1a**; 156 mg, 1 mmol, 1 equiv.) and *tert*-butyl isocyanide (170 μL, 1.5 mmol, 1.5 equiv.) according to Procedure A. Purification: column chromatography on silica (cyclohexane/ethyl acetate, 4:1); the diastereoisomers could be separated [R_f = 0.50 (*major*) and R_f = 0.34 (*minor*)].

Data for major diastereoisomer **3a** (*trans*): Isolated as a slowly crystallizing solid (182 mg, 0.76 mmol, 76 %). M.p. 50–54 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.08 (br., 1 H), 2.52 (qd, J = 12.5, J = 3.5 Hz, 1 H), 2.46–2.34 (m, 2 H), 2.18–2.06 (m, 2 H), 2.01–1.87 (m, 2 H), 1.78 (d, J = 13.0 Hz, 1 H), 1.76–1.66 (m, 2 H), 1.47–1.37 (m, 1 H), 1.35 (s, 9 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 175.9 (C), 170.2 (C), 86.5 (C), 51.6 (C), 48.5 (CH), 34.6 (CH_2), 33.8 (CH_2), 28.7 (CH_3), 25.3 (CH_2), 24.0 (CH_2), 22.1 (CH_2) ppm. IR (neat): $\tilde{\nu}$ = 3396 (m), 2924 (w), 2868 (w), 1790 (s), 1665 (s), 1522 (s), 1452 (m), 1180 (s), 1024 (s), 901 (m), 881 (m), 552 (m) cm^{-1}. HRMS (ESI): calcd. for $C_{13}H_{22}NO_3$ [M + H]$^+$ 240.1595; found 240.1594. Crystals for single-crystal X-ray diffraction were grown from dichloromethane.

Data for minor diastereoisomer **3a′** (*cis*): Isolated as a white solid (14 mg, 0.06 mmol, 6 %). M.p. 93–105 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.15 (br., 1 H), 2.88–2.77 (m, 1 H), 2.51 (dd, J = 17.0, J = 7.0 Hz, 1 H), 2.19 (dd, J = 17.0, J = 2.0 Hz, 1 H), 1.97–1.87 (m, 3 H), 1.73–1.57 (m, 2 H), 1.47–1.34 (m, 2 H), 1.32 (s, 9 H), 1.21–1.10 (m, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 176.2 (C), 171.8 (C), 87.2 (C), 51.6 (C), 36.4 (CH), 36.3 (CH_2), 31.3 (CH_2), 28.7 (CH_3), 28.0 (CH_2), 22.3 (CH_2), 20.4 (CH_2) ppm. IR (neat): $\tilde{\nu}$ = 3354 (m), 2951 (w), 1780 (s), 1736 (s), 1670 (s), 1533 (m), 1414 (m), 1188 (s), 1011 (s), 935 (s), 885 (s), 710 (m), 548 (m) cm^{-1}.

***N*-(2,4,4-Trimethylpentan-2-yl)-2-oxohexahydrobenzofuran-7a(2*H*)-carboxamide (3b):** Prepared from 2-(2-oxocyclohexyl)acetic acid (**1a**; 156 mg, 1 mmol, 1 equiv.) and 1,1,3,3-tetramethylbutyl isocyanide (263 μL, 1.5 mmol 1.5 equiv.) according to Procedure A. Purification: column chromatography on silica (cyclohexane/ethyl acetate, 4:1); the diastereoisomers could be separated [R_f = 0.50 (*major*) and R_f = 0.37 (*minor*)]. The major diastereoisomer **3b** (*trans*) was isolated as a white solid (200 mg, 0.68 mmol, 68 %). M.p. 59–67 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.11 (br., 1 H), 2.52 (qd, J = 12.7, J = 4.0 Hz, 1 H), 2.42–2.32 (m, 2 H), 2.13–2.04 (m, 2 H), 1.94–1.82 (m, 2 H), 1.79–1.61 (m, 5 H), 1.39–1.31 (m, 1 H), 1.35 (s, 6 H), 0.96 (s, 9 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 175.7 (C), 169.6 (C), 86.3 (C), 55.4 (C), 55.8 (CH_2), 48.3 (CH), 34.2 (CH_2), 33.6 (CH_2), 31.6 (C), 31.4 (CH_3), 28.8 (CH_3), 25.0 (CH_2), 23.7 (CH_2), 21.8 (CH_2) ppm. IR (neat): $\tilde{\nu}$ = 3394 (m), 2948 (w), 2868 (w), 1788 (s), 1675 (s), 1522 (s), 1454 (m), 1177 (s), 1018 (s), 878 (m), 718 (m) cm^{-1}. HRMS (ESI): calcd. for $C_{17}H_{30}NO_3$ [M + H]$^+$ 296.2220; found 296.2215.

***N*-Cyclohexyl-2-oxohexahydrobenzofuran-7a(2*H*)-carboxamide (3c):** Prepared from 2-(2-oxocyclohexyl)acetic acid (**1a**; 156 mg, 1 mmol, 1 equiv.) and cyclohexyl isocyanide (187 μL, 1.5 mmol, 1.5 equiv.) according to Procedure A. Purification: column chromatography on silica (cyclohexane/ethyl acetate, 4:1); the diastereoisomers could be separated [R_f = 0.46 (*major*) and R_f = 0.23 (*minor*)]. The major diastereoisomer **3c** (*trans*) was isolated as a white solid (180 mg, 0.68 mmol, 68 %). M.p. 111–114 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.19 (br., 1 H), 3.75–3.64 (m, 1 H), 2.49 (qd, J = 12.0, J = 4.0 Hz, 1 H), 2.42–2.28 (m, 2 H), 2.17–2.06 (m, 2 H), 1.90–1.62 (m, 9 H), 1.62–1.53 (m, 1 H), 1.44–1.27 (m, 3 H), 1.20–1.06 (m, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 175.9 (C), 169.8 (C), 86.5 (C), 48.5 (CH), 34.5 (CH_2), 33.7 (CH_2), 33.1 (CH_2), 32.8 (CH_2), 31.1 (CH), 25.5 (CH_2), 25.3 (CH_2), 24.9 (CH_2), 24.9 (CH_2), 23.9 (CH_2), 22.1 (CH_2) ppm. IR (neat): $\tilde{\nu}$ = 3323 (w), 2930 (m), 2851 (m), 1784 (s), 1643 (s), 1518 (s), 1445 (m), 1194 (m), 1180 (m), 1024 (s), 918 (m), 883 (m), 725 (w), 694 (s), 538 (m) cm^{-1}. HRMS (ESI): calcd. for $C_{15}H_{24}NO_3$ [M + H]$^+$ 266.1751; found 266.1751.

***N*-Isopropyl-2-oxohexahydrobenzofuran-7a(2*H*)-carboxamide (3d):** Prepared from 2-(2-oxocyclohexyl)acetic acid (**1a**; 156 mg, 1 mmol, 1 equiv.) and isopropyl isocyanide (141 μL, 1.5 mmol 1.5 equiv.) according to Procedure A. Purification: column chromatography on silica (cyclohexane/ethyl acetate, 3:1); the diastereoisomers could be separated [R_f = 0.5 (*major*) and R_f = 0.25 (*minor*)]. The major diastereoisomer **3d** (*trans*) was isolated as a white solid (124 mg, 0.55 mmol, 55 %). M.p. 84–86 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.19 (d, J = 12.0 Hz, 1 H), 4.04–3.96 (m, 1 H), 2.49 (qd, J = 12.6, J = 3.8 Hz, 1 H), 2.44–2.30 (m, 2 H), 2.16–2.07 (m, 2 H), 1.98–1.84 (m, 2 H), 1.80–1.65 (m, 3 H), 1.43–1.31 (m, 1 H), 1.11 (d, J = 6.5 Hz, 6 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 175.6 (C), 169.5 (C), 86.1 (C), 48.1 (CH), 41.1 (CH), 34.1 (CH_2), 33.4 (CH_2), 24.9 (CH_2), 23.6 (CH_2), 22.4 (CH_3), 22.2 (CH_3), 21.7 (CH_2) ppm. IR (neat): $\tilde{\nu}$ = 3310 (w), 2927 (m), 1784 (s), 1645 (s), 1521 (s), 1450 (m), 1196 (m), 1026 (s), 906 (m), 883 (m), 696 (s) cm^{-1}. HRMS (ESI): calcd. for $C_{12}H_{20}NO_3$ [M + H]$^+$ 226.1438; found 226.1437.

***N*-Pentyl-2-oxohexahydrobenzofuran-7a(2*H*)-carboxamide (3e):** Prepared from 2-(2-oxocyclohexyl)acetic acid (**1a**; 156 mg, 1 mmol, 1 equiv.) and *n*-pentyl isocyanide (188 μL, 1.5 mmol, 1.5 equiv.) according to Procedure A. Purification: column chromatography on silica (cyclohexane/ethyl acetate, 5:1); the diastereoisomers could be separated [R_f = 0.30 (*major*)]. The major diastereoisomer **3e** (*trans*) was isolated as a white solid (177 mg, 0.70 mmol, 70 %). M.p. 55–57 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.33 (br., 1 H), 3.25–3.14 (m, 2 H), 2.50 (dq, J = 12.6, J = 3.9 Hz, 1 H), 2.44–2.29 (m, 2 H), 2.18–2.09 (m, 2 H), 1.99–1.83 (m, 2 H), 1.81–1.64 (m, 3 H), 1.50–1.33 (m, 3 H), 1.32–1.19 (m, 4 H), 0.87 (t, J = 6.9 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 175.7 (C), 170.5 (C), 86.5 (C), 48.4 (CH), 39.1 (CH_2), 34.3 (CH_2), 33.5 (CH_2), 29.0 (CH_2), 28.9 (CH_2), 25.1 (CH_2), 23.7 (CH_2), 22.2 (CH_2), 21.8 (CH_2), 13.9 (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 3312 (w), 2928 (m), 2866 (w), 1788 (s), 1651 (s), 1533 (s), 1439 (m), 1194 (m), 1184 (m), 1026 (s), 943 (m), 881 (m), 704 (m), 561 (w) cm^{-1}. HRMS (ESI): calcd. for $C_{14}H_{24}NO_3$ [M + H]$^+$ 254.1751.1751; found 254.1745.

***N*-Benzyl-2-oxohexahydrobenzofuran-7a(2*H*)-carboxamide (3f):** Prepared from 2-(2-oxocyclohexyl)acetic acid (**1a**; 156 mg, 1 mmol, 1 equiv.) and benzyl isocyanide (183 μL, 1.5 mmol 1.5 equiv.) according to Procedure A. Purification: column chromatography on silica (cyclohexane/ethyl acetate, 4:1); the diastereoisomers could be separated [R_f = 0.5 (*major*) and R_f = 0.3 (*minor*)]. The major diastereoisomer **3f** (*trans*) was isolated as a yellowish solid (200 mg, 0.73 mmol, 73 %). M.p. 56–66 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.32–7.29 (m, 2 H), 7.27–7.25 (m, 1 H), 7.20 (d, J = 7.3 Hz, 2 H), 6.78 (br., 1 H), 4.33 (dd, J = 14.8, J = 5.5 Hz, 1 H), 4.45 (dd, J = 14.8, J = 6.1 Hz, 1 H), 2.51 (dq, J = 12.7, J = 4.0 Hz, 1 H), 2.44–2.34 (m, 2 H), 2.17–2.10 (m, 2 H), 1.98–1.88 (m, 2 H), 1.80–1.78 (m, 1 H), 1.74–1.69 (m, 2 H), 1.42–1.35 (m, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 175.6 (C), 170.5 (C), 137.7 (C), 128.7 (CH), 127.5 (CH), 127.3 (CH), 86.5 (C), 48.3 (CH), 34.2 (CH_2), 33.5 (CH_2), 29.6 (CH_2), 25.0 (CH_2), 23.7 (CH_2), 21.8 (CH_2) ppm. IR (neat): $\tilde{\nu}$ = 3315 (w), 2930 (m), 1782 (s), 1653 (s), 1522 (s), 1427 (m), 1194 (m), 1183 (m), 1021 (s), 938 (m), 885 (m), 733 (s), 693 (s), 557 (s) cm^{-1}. HRMS (ESI): calcd. for $C_{16}H_{20}NO_3$ [M + H] $^+$ 274.1438; found 274.1435.

***N*-(2-Naphthyl)-2-oxohexahydrobenzofuran-7a(2*H*)-carboxamide (3g):** Prepared from 2-(2-oxocyclohexyl)acetic acid (**1a**; 78 mg, 0.5 mmol, 1 equiv.) and 2-naphthyl isocyanide (115 mg, 0.75 mmol, 1.5 equiv.) according to Procedure A. Purification: column chromatography on silica (cyclohexane/ethyl acetate, 7:1); the diastereoisomers could be partially separated [R_f = 0.20 (*major*) and R_f = 0.18 (*minor*)]. The major diastereoisomer **3g** (*trans*) was isolated

as a white solid (77 mg, 0.25 mmol, 50 %). M.p. 115–129 °C (dec.). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.23 (br., 1 H), 8.22 (d, J = 13.5 Hz, 1 H), 7.78 (t, J = 8.0 Hz, 3 H), 7.46 (t, J = 8.0 Hz, 1 H), 7.42 (t, J = 7.0 Hz, 2 H), 2.65 (qd, J = 13.0, J = 4.2 Hz, 1 H), 2.54–2.46 (m, 2 H), 2.37–2.29 (m, 1 H), 2.28–2.17 (m, 1 H), 2.07–1.92 (m, 2 H), 1.91–1.75 (m, 3 H), 1.52–1.40 (m, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 175.5 (C), 169.2 (C), 134.5 (C), 133.8 (C), 131.0 (C), 129.0 (CH), 127.8 (CH), 127.6 (CH), 126.7 (CH), 125.4 (CH), 120.2 (CH), 117.2 (CH), 86.7 (C), 48.5 (CH), 34.4 (CH_2), 33.7 (CH_2), 25.2 (CH_2), 23.9 (CH_2), 22.0 (CH_2) ppm. IR (neat): $\tilde{\nu}$ = 3332 (w), 2937 (w), 1772 (s), 1684 (s), 1540 (m), 1223 (m), 1021 (s), 810 (m) cm^{-1}. HRMS (ESI): calcd. for $C_{20}H_{23}NNaO_4$ [M + MeOH + Na]$^+$ 364.1519; found 364.1564.

***N*-(2,6-Dimethylphenyl)-2-oxohexahydrobenzofuran-7a(2*H*)-carboxamide (3h/3h′):** Prepared from 2-(2-oxocyclohexyl)acetic acid (**1a**; 156 mg, 1 mmol, 1 equiv.) and 2,6-dimethylphenyl isocyanide (196 mg, 1.5 mmol, 1.5 equiv.) according to Procedure A. Purification: column chromatography on silica (cyclohexane/ethyl acetate, 4:1); the diastereoisomers could be separated [R_f = 0.21 (*major*) and R_f = 0.10 (*minor*)].

Data for major diastereoisomer **3h** (*trans*): Isolated as a white solid (194 mg, 0.68 mmol, 68 %). M.p. 157–159 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.61 (br., 1 H), 7.14–7.04 (m, 3 H), 2.58 (qd, J = 13.0, J = 3.5 Hz, 1 H), 2.51 (d, J = 10.5 Hz, 2 H), 2.36 (d, J = 12.5 Hz, 1 H), 2.28–2.18 (m, 1 H), 2.18 (s, 6 H), 2.01–1.83 (m, 4 H), 1.74 (d, J = 12.5 Hz, 1 H), 1.50–1.38 (m, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 175.7 (C), 169.3 (C), 135.3 (C), 132.9 (C), 128.4 (CH), 127.7 (CH), 87.1 (C), 48.5 (CH), 34.7 (CH_2), 33.8 (CH_2), 25.3 (CH_2), 23.9 (CH_2), 22.1 (CH_2), 18.5 (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 3294 (w), 2922 (w), 1782 (s), 1655 (m), 1499 (m), 1190 (m), 1020 (s), 912 (m), 883 (m), 770 (m), 706 (m), 519 (m) cm^{-1}. HRMS (ESI): calcd. for $C_{17}H_{22}NO_3$ [M + H]$^+$ 288.1595; found 288.1594.

Data for minor diastereoisomer **3h′** (*cis*): Isolated as a white solid (23 mg, 0.08 mmol, 8 % (contains 10 % of the *trans* diastereoisomer). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.71 (br., 1 H), 7.15–7.03 (m, 3 H), 3.02–2.92 (m, 1 H), 2.68 (dd, J = 17.0, J = 7.0 Hz, 1 H), 2.29 (d, J = 17.0 Hz, 1 H), 2.21–2.14 (m, 1 H), 2.16 (s, 6 H), 2.09–1.93 (m, 2 H), 1.80–1.65 (m, 2 H), 1.56–1.35 (m, 2 H), 1.28–1.17 (m, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 176.0 (C), 171.0 (C), 135.3 (C), 132.7 (C), 128.4 (CH), 127.8 (CH), 87.7 (C), 36.6 (CH_2), 36.3 (CH), 31.5 (CH_2), 28.1 (CH_2), 22.3 (CH_2), 20.3 (CH_2), 18.4 (CH_3), ppm. IR (neat): $\tilde{\nu}$ = 3288 (w), 2924 (w), 1782 (s), 1655 (m), 1499 (m), 1190 (m), 1113 (s), 912 (m), 883 (m), 770 (m), 706 (m), 519 (m) cm^{-1}.

***N*-(Tosylmethyl)-2-oxohexahydrobenzofuran-7a(2*H*)-carboxamide (3i):** Prepared from 2-(2-oxocyclohexyl)acetic acid (**1a**; 156 mg, 1 mmol, 1 equiv.) and tosylmethyl isocyanide (196 mg, 1 mmol, 1 equiv.) according to Procedure A. Purification: column chromatography on silica (cyclohexane/ethyl acetate, 3:1 to cyclohexane/ethyl acetate, 1:1); the diastereoisomers could be separated [R_f = 0.15 (*major*) in cyclohexane/ethyl acetate, 3:1]. The major diastereoisomer **3i** (*trans*) was isolated as a gummy white solid (280 mg, 0.80 mmol, 80 %). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.71 (d, J = 7.5 Hz, 2 H), 7.53 (t, J = 6.3 Hz, 1 H), 7.28 (d, J = 7.5 Hz, 2 H), 4.66 (d, J = 6.5 Hz, 2 H), 2.36 (s, 3 H), 2.33–2.11 (m, 2 H), 2.11–2.93 (m, 3 H), 1.76–1.50 (m, 4 H), 1.40–1.17 (m, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 175.4 (C), 170.1 (C), 145.3 (C), 133.8 (C), 129.9 (CH), 128.9 (CH), 86.4 (C), 59.6 (CH_2), 47.9 (CH), 33.8 (CH_2), 33.3 (CH_2), 24.7 (CH_2), 23.4 (CH_2), 22.6 (CH_3), 22.5 (CH_2) ppm. IR (neat): $\tilde{\nu}$ = 3377 (w), 2935 (w), 1786 (s), 1686 (s), 1597 (w), 1499 (m), 1321 (m), 1286 (m), 1140 (s), 1018 (s), 925 (m), 727 (s) cm^{-1}. HRMS (ESI): calcd. for $C_{18}H_{25}NNaO_6S$ [M + MeOH + Na]$^+$ 406.1295; found 406.1341.

Methyl (2-Oxooctahydrobenzofuran-7a-carbonyl)glycinate (3j): Prepared from 2-(2-oxocyclohexyl)acetic acid (**1a**; 156 mg, 1 mmol, 1 equiv.) and methyl isocyanoacetate (136 μL, 1.5 mmol, 1.5 equiv.) according to Procedure A. Purification: column chromatography on silica (cyclohexane/ethyl acetate, 4:1); the diastereoisomers could be separated [R_f = 0.07 (*major*)]. The major diastereoisomer (*trans*) was isolated as a colorless oil (217 mg, 0.85 mmol, 85 %). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.79 (s, 1 H), 3.99 (d, J = 5.5 Hz, 2 H), 3.74 (s, 3 H), 2.52–2.38 (m, 3 H), 2.27–2.12 (m, 2 H), 1.96–1.85 (m, 2 H), 1.84–1.67 (m, 3 H), 1.50–1.35 (m, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 175.7 (C), 171.5 (C), 169.8 (C), 86.6 (C), 52.6 (CH), 48.5 (CH_3), 41.0 (CH_2), 34.2 (CH_2), 33.6 (CH_2), 25.2 (CH_2), 23.9 (CH_2), 21.9 (CH_2) ppm. IR (neat): $\tilde{\nu}$ = 3356 (m), 2951 (w), 1780 (m), 1736 (s), 1672 (s), 1531 (m), 1414 (s), 1188 (s), 1011 (s), 935 (s), 885 (s) cm^{-1}. HRMS (ESI): calcd. for $C_{12}H_{18}NO_5$ [M + H]$^+$ 256.1180; found 256.1179.

***tert*-Butyl 7a-(*tert*-Butylcarbamoyl)-2-oxohexahydrofuro[3,2-*c*]-pyridine-5(4*H*)-carbamate (3k):** Prepared from 2-[1-(*tert*-butoxycarbonyl)-4-oxopiperidin-3-yl]acetic acid (**1b**; 132 mg, 0.51 mmol, 1 equiv.) and *tert*-butyl isocyanide (87 μL, 0.77 mmol 1.5 equiv.) according to Procedure A (reaction time 6 h). Purification: column chromatography on silica (cyclohexane/ethyl acetate, 3:1); the diastereoisomers could be separated [R_f = 0.40 (*major*) and R_f = 0.23 (*minor*)]. The major diastereoisomer **3k** (*trans*) was isolated as a white solid (40 mg, 0.12 mmol, 23 %). M.p. 132–144 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.15 (s, 1 H), 4.42–37.74 (m, 3 H), 3.55–3.25 (m, 1 H), 2.49 (dd, J = 16.2, J = 6.4 Hz, 1 H), 2.43–2.33 (m, 1 H), 2.31–2.21 (m, 1 H), 2.14–2.00 (m, 1 H), 1.96–1.84 (m, 1 H), 1.45 (s, 9 H), 1.33 (s, 9 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.5 (C), 169.3 (C), 155.0 (C), 84.1 (C), 80.1 (C), 51.8 (C), 46.7 (CH), 41.8 (CH_2), 39.6 (CH_2), 33.8 (CH_2), 31.3 (CH_2), 28.5 (CH_3), 28.3 (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 3342 (w), 2972 (w), 1793 (s), 1664 (s), 1526 (m), 1418 (s), 1163 (s), 1015 (s), 974 (w), 849 (m) cm^{-1}. HRMS (ESI): calcd. for $C_{18}H_{33}N_2O_6$ [M + H]$^+$ 373.2333; found 373.2330.

***N*-(*tert*-Butyl)-2-oxooctahydro-8a*H*-chromene-8a-carboxamide (3l):** Prepared from 3-(2-oxocyclohexyl)propanoic acid (**1c**; 170 mg, 1 mmol, 1 equiv.) and *tert*-butyl isocyanide (124 μL, 1.1 mmol, 1.1 equiv.) according to Procedure A (reaction time 2 h). Purification: column chromatography on silica (cyclohexane/ethyl acetate, 6:1); the diastereoisomers could be separated [R_f = 0.22 (*major*) and R_f = 0.13 (*minor*)]. The major diastereoisomer **3l** (*trans*) was isolated as a white solid (148 mg, 0.58 mmol, 58 %). M.p. 101–104 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.00 (br., 1 H), 2.69–2.65 (m, 2 H), 2.23 (qd, J = 13.5, J = 3.5 Hz, 1 H), 2.01 (d, J = 9.0 Hz, 1 H), 1.93–1.58 (m, 9 H), 1.33 (s, 9 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.6 (C), 171.1 (C), 85.0 (C), 51.4 (C), 42.2 (CH), 37.4 (CH_2), 29.8 (CH_2), 29.0 (CH_2), 28.9 (CH_3), 25.3 (CH_2), 23.0 (CH_2), 21.8 (CH_2) ppm. IR (neat): $\tilde{\nu}$ = 3327 (w), 2932 (m), 2868 (w), 1744 (s), 1666 (s), 1537 (m), 1450 (m), 1354 (m), 1244 (m), 1157 (m), 1059 (m), 1032 (s), 989 (m), 631 (w), 542 (m), 488 (m) cm^{-1}. HRMS (ESI): calcd. for $C_{14}H_{24}NO_3$ [M + H]$^+$ 254.1751; found 254.1751.

***N*-(Tosylmethyl)-2-oxooctahydro-8a*H*-chromene-8a-carboxamide (3m):** Prepared from 3-(2-oxocyclohexyl)propanoic acid (**1c**; 85 mg, 0.5 mmol) and tosylmethyl isocyanide (148 mg, 0.75 mmol, 1.5 equiv.) according to Procedure A (reaction time 2 h). Purification: column chromatography on silica (cyclohexane/ethyl acetate, 1:1); the diastereoisomers could be partially separated. The major diastereoisomer contained a small amount of the minor diastereoisomer. The major diastereoisomer (*trans*) was isolated as a gummy white solid (91 mg, 0.50 mmol, 50 %). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.75 (d, J = 7.6 Hz, 2 H), 7.46 (t, J = 7.0 Hz, 1 H), 7.32 (d, J = 7.6 Hz, 2 H), 4.80–4.70 (m, 1 H), 4.68–4.58 (m, 1 H), 2.57 (t, J = 6.2 Hz, 2 H), 2.40 (s, 3 H), 2.05–1.93 (m, 1 H), 1.88 (d, J = 12.5 Hz, 1 H), 1.80–1.47 (m, 7 H), 1.30–1.05 (m, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.0 (C), 171.0 (C), 145.4 (C), 134.1 (C), 130.0 (CH), 128.9 (CH),

85.0 (C), 59.7 (CH_2), 42.0 (CH), 37.8 (CH_2), 29.7 (CH_2), 28.4 (CH_2), 25.0 (CH_2), 22.6 (CH_2), 21.7 (CH_3), 21.3 (CH_2) ppm. IR (neat): $\tilde{\nu}$ = 3315 (w), 2938 (w), 1742 (s), 1686 (s), 1501 (m), 1448 (m), 1321 (s), 1286 (m), 1229 (m), 1140 (s), 1084 (s), 1030 (s), 914 (w), 727 (s) cm^{-1}. HRMS (ESI): calcd. for $C_{18}H_{23}NNaO_5S$ $[M + Na]^+$ 388.1189; found 388.1181.

***N*-(*tert*-Butyl)-2,3-dimethyl-5-oxotetrahydrofuran-2-carboxamide (3r):** Prepared from 3-methyl-4-oxopentanoic acid (**1g**; 130 mg, 1 mmol, 1 equiv.) and *tert*-butyl isocyanide (170 µL, 1.5 mmol, 1.5 equiv.) according to Procedure A (reaction time 2 h). The diastereoisomers were not separated by chromatographic purification. Isolated as a colorless oil (24 mg, 0.11 mmol, 11 %). In the NMR spectroscopic data, D1 and D2 denote the two diastereomers. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.26 (br., 1 H, D1), 6.19 (br., 1 H, D2), 2.88 (dd, *J* = 10.0, *J* = 8.0 Hz, 1 H, D1), 2.75–2.57 (m, 1 H, D1/D2, 1 H, D2), 2.57–2.49 (m, 1 H, D2/D1), 2.28–2.15 (m, 1 H, D1, 1 H, D2), 1.53 (s, 3 H, D2), 1.42 (s, 3 H, D1), 1.33 (s, 9 H, D1), 1.32 (s, 9 H, D2), 1.20 (d, *J* = 7.0 Hz, 3 H, D2), 1.04 (d, *J* = 7.0 Hz, 3 H, D1) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 175.2 (C, D1/D2), 174.8 (C, D2/D1), 171.6 (C, D1/D2), 169.2 (C, D2/D1), 88.5 (C, D2), 87.6 (C, D1), 51.7 (C, D1), 51.3 (C, D2), 38.2 (CH, D1), 37.1 (CH, D2), 36.7 (CH_2, D2), 36.3 (CH_2, D1), 28.7 (CH_3, D1), 28.7 (CH_3, D2), 24.0 (CH_3, D1), 18.9 (CH_3, D2), 16.4 (CH_3, D1/D2), 15.2 (CH_3, D2/D1) ppm. IR (neat): $\tilde{\nu}$ = 2972 (w), 1784 (s), 1670 (s), 1521 (m), 1456 (m), 1365 (m), 1223 (s), 1194 (m), 1123 (s), 1059 (m), 1010 (w), 926 (m), 768 (w) cm^{-1}. HRMS (ESI): calcd. for $C_{12}H_{23}NNaO_4$ $[M + MeOH + Na]^+$ 268.1519; found 268.1513.

***N*-(Tosylmethyl)-2,3-dimethyl-5-oxotetrahydrofuran-2-carboxamide (3s):** Prepared from 3-methyl-4-oxopentanoic acid (**1g**; 130 mg, 1 mmol, 1 equiv.) and tosylmethyl isocyanide (294 mg, 1.5 mmol, 1.5 equiv.) according to Procedure A (reaction time 2 h). Purification: column chromatography on silica (cyclohexane/ethyl acetate, 2:1 to cyclohexane/ethyl acetate, 1:1); the diastereoisomers could not be separated (R_f = 0.32 and R_f = 0.27). Isolated as a gummy white solid containing 2 wt.-% EtOAc. Yield (corrected): 266 mg, 0.82 mmol, 82 %. In the NMR spectrascopic data, D1 and D2 denote the two diastereomers. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.76 (d, *J* = 8.0 Hz, 2 H, D1, 2 H, D2), 7.70 (t, *J* = 6.6 Hz, 1 H, D1/D2), 7.69 (t, *J* = 7.0 Hz, 1 H, D2/D1), 7.30 (d, *J* = 8.0 Hz, 2 H, D1, 2 H, D2), 4.73–4.53 (m, 2 H, D1, 2 H, D2), 2.80 (dd, *J* = 17.0, *J* = 9.0 Hz, 1 H, D2), 2.57 (dd, *J* = 17.0, *J* = 9.0 Hz, 1 H, D1), 2.50–2.38 (m, 1 H, D1, 1 H, D2), 2.37 (s, 3 H, D1), 2.37 (s, 3 H, D2), 2.23–2.14 (m, 1 H, D1, 1 H, D2), 1.40 (s, 3 H, D2), 1.26 (s, 3 H, D1), 1.00 (d, *J* = 7.5 Hz, 3 H, D1), 0.81 (d, *J* = 7.5 Hz, 3 H, D2) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.9 (C, D2), 174.6 (C, D1), 171.9 (C, D1), 170.1 (C, D2), 145.4 (C, D1, D2), 133.9 (C, D2), 133.8 (C, D1), 129.9 (CH, D1), 129.8 (CH, D2), 129.0 (CH, D2), 129.0 (CH, D1), 88.4 (C, D2), 87.3 (C, D1), 59.9 (CH_2, D1), 59.8 (CH_2, D2), 38.5 (CH, D2), 37.1 (CH, D1), 36.2 (CH_2, D2), 35.6 (CH_2, D1), 23.9 (CH_3, D1/D2), 21.7 (CH_3, D1, D2), 18.2 (CH_3, D2/D1), 15.9 (CH_3, D2), 14.3 (CH_3, D1) ppm. IR (neat): $\tilde{\nu}$ = 3354 (w), 1784 (s), 1676 (s), 1518 (s), 1294 (s), 1220 (m), 1148 (s), 1088 (s), 1053 (m), 926 (m), 750 (m) cm^{-1}. HRMS (ESI): calcd. for $C_{16}H_{23}NNaO_6S$ [M + MeOH + Na]$^+$ 380.1138; found 380.1178.

8a-Hydroxyhexahydroisoquinoline-1,3-(2*H*,4*H*)-dione (4b): Prepared from **3b** (6 mg, 0.2 mmol) according to Procedure B (reaction time 7 h). Purification: column chromatography on silica (cyclohexane/ethyl acetate, 4:1, to cyclohexane/ethyl acetate, 2:1, R_f = 0.13). Isolated as a white solid (22 mg, 0.12 mmol, 60 %). M.p. 150–158 °C. ^{1}H NMR (500 MHz, $CDCl_3$/[D_6]DMSO): δ = 9.32 (br., 1 H), 4.73 (br., 1 H), 2.76 (d, *J* = 16.6 Hz, 1 H), 2.20 (d, *J* = 16.6 Hz, 1 H), 2.11–1.97 (m, 1 H), 1.95–1.84 (m, 1 H), 1.67–1.45 (m, 2 H), 1.43–1.31 (m, 1 H), 1.28–0.95 (m, 4 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$/[D_6]DMSO):[27] δ = 172.5 (C), 71.4 (C), 37.5 (CH), 34.4 (CH_2), 32.8 (CH_2), 29.5 (CH_2), 22.6 (CH_2), 22.2 (CH_2) ppm. IR (neat): $\tilde{\nu}$ = 3166 (m), 2923 (m), 1722 (s), 1668 (s), 1358 (s), 1209 (s), 1068 (s), 1041 (m), 840 (m), 732 (m) cm^{-1}. HRMS (ESI): calcd. for $C_9H_{13}NNaO_3$ $[M + Na]^+$ 206.0788; found 206.0786.

2-Cyclohexyl-8a-hydroxyhexahydroisoquinoline-1,3-(2*H*,4*H*)-dione (4c): Prepared from **3c** (27 mg, 0.1 mmol) according to Procedure B (reaction time 24 h). Isolated as a white solid (24 mg, 0.089 mmol, 89 %). M.p. 110–117 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.48 (tt, *J* = 12.5, *J* = 4.0 Hz, 1 H), 3.25 (br., 1 H), 2.82–2.64 (m, 2 H), 2.28–2.08 (m, 3 H), 1.97–1.40 (m, 12 H), 1.37–1.06 (m, 4 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.9 (C), 72.4 (C), 53.9 (CH), 35.2 (CH_2), 34.5 (CH), 32.6 (CH_2), 29.3 (CH_2), 28.7 (CH_2), 26.4 (CH_2), 26.4 (CH_2), 25.6 (CH_2), 25.3 (CH_2), 21.0 (CH_2), 20.4 (CH_2) ppm. IR (neat): $\tilde{\nu}$ = 3377 (w), 2927 (m), 1719 (m), 1654 (m), 1358 (s), 1225 (s), 1136 (m), 1043 (m), 729 (m) cm^{-1}. HRMS (ESI): calcd. for $C_{15}H_{23}NNaO_3$ $[M + Na]^+$ 288.1570; found 288.1572.

2-Isopropyl-8a-hydroxyhexahydroisoquinoline-1,3-(2*H*,4*H*)-dione (4d): Prepared from **3d** (23 mg, 0.1 mmol) according to Procedure B (reaction time 24 h). Isolated as a white solid (22 mg, 0.096 mmol, 96 %). M.p. 81–89 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.90 (sep, *J* = 7.9 Hz, 1 H), 2.82–2.64 (m, 2 H), 2.22–2.12 (m, 1 H), 1.97–1.70 (m, 3 H), 1.55–1.42 (m, 4 H), 1.41–1.28 (m, 1 H), 1.36 (d, *J* = 7.0 Hz, 3 H), 1.34 (d, *J* = 7.0 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 177.5 (C), 171.9 (C), 72.4 (C), 45.4 (CH), 35.2 (CH_2), 34.4 (CH), 32.6 (CH_2), 25.6 (CH_2), 21.0 (CH_2), 20.4 (CH_2), 19.8 (CH_3), 19.4 (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 3400 (w), 2935 (m), 1719 (m), 1668 (s), 1346 (m), 1244 (m), 1221 (m), 1116 (w), 1045 (w) cm^{-1}. HRMS (ESI): calcd. for $C_{12}H_{19}NNaO_3$ $[M + Na]^+$ 248.1257; found 248.1249.

2-Pentyl-8a-hydroxyhexahydroisoquinoline-1,3-(2*H*,4*H*)-dione (4e): Prepared from **3e** (25 mg, 0.1 mmol) according to Procedure B (reaction time 2 h). Isolated as a colorless oil (19 mg, 0.075 mmol, 75 %). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.83–3.63 (m, 2 H), 2.90–2.70 (m, 3 H), 2.24–2.12 (m, 1 H), 1.99–1.65 (m, 3 H), 1.57–1.40 (m, 6 H), 1.38–1.15 (m, 5 H), 0.87 (t, *J* = 7.0 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.9 (C), 72.2 (C), 40.4 (CH_2), 34.8 (CH), 34.7 (CH_2), 32.7 (CH_2), 29.1 (CH_2), 27.7 (CH_2), 25.9 (CH_2), 22.4 (CH_2), 21.6 (CH_2), 20.7 (CH_2), 14.1 (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 3411 (w), 2932 (m), 1724 (m), 1653 (s), 1346 (s), 1254 (m), 1176 (s), 1118 (s), 1047 (m), 734 (w) cm^{-1}. HRMS (ESI): calcd. for $C_{14}H_{23}NNaO_3$ $[M + Na]^+$ 276.1570; found 276.1558.

2-Benzyl-8a-hydroxyhexahydroisoquinoline-1,3-(2*H*,4*H*)-dione (4f): Prepared from **3f** (28 mg, 0.1 mmol) according to Procedure B (reaction time 4 h). Isolated as a pale yellow oil (26 mg, 0.093 mmol, 93 %). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.34–7.19 (m, 5 H), 4.95 (d, *J* = 13.5 Hz, 1 H), 4.93 (d, *J* = 13.5 Hz, 1 H), 3.01 (br., 1 H), 2.86 (dd, *J* = 19.0, *J* = 4.5 Hz, 1 H), 2.74 (dd, *J* = 19.0, *J* = 9.0 Hz, 1 H), 2.21 (sex, *J* = 5.0 Hz, 1 H), 1.98–1.85 (m, 2 H), 1.85–1.73 (m, 1 H), 1.55–1.37 (m, 4 H), 1.33–1.25 (m, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.5 (C), 136.9 (C), 128.6 (CH), 128.5 (CH), 127.6 (CH), 72.3 (C), 43.5 (CH_2), 34.8 (CH), 34.7 (CH_2), 32.7 (CH_2), 26.0 (CH_2), 21.2 (CH_2), 20.7 (CH_2) ppm. IR (neat): $\tilde{\nu}$ = 3445 (w), 2929 (m), 1726 (m), 1670 (s), 1346 (s), 1173 (m), 1076 (w), 733 (w) cm^{-1}. HRMS (ESI): calcd. for $C_{16}H_{19}NNaO_3$ $[M + Na]^+$ 296.1257; found 296.1249.

2-(Naphthalen-2-yl)-8a-hydroxyhexahydroisoquinoline-1,3-(2*H*,4*H*)-dione (4g): Prepared from **3g** (31 mg, 0.1 mmol) according to Procedure B (reaction time 24 h). Isolated as a brown solid containing 15 % 2-naphthylamine. Yield (corrected): 20 mg, 0.064 mmol, 64 %. M.p. 141–147 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.93 (d, *J* = 8.5 Hz, 1 H), 7.88 (d, *J* = 8.0 Hz, 1 H), 7.83 (d, *J* = 8.5 Hz, 1 H), 7.60 (s, 1 H), 7.56–7.46 (m, 2 H), 7.16 (dd, *J* = 8.5, *J* = 2.0 Hz, 1 H), 3.06 (dd, *J* = 18.5, *J* = 5.0 Hz, 1 H), 2.93 (dd, *J* = 18.5, *J* = 10.0 Hz,

1 H), 2.41 (sex, *J* = 4.0 Hz, 1 H), 2.16 (t, *J* = 11.0 Hz, 1 H), 2.10–2.01 (m, 1 H), 1.92–1.80 (m, 1 H), 1.71–1.44 (m, 6 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.9 (C), 133.5 (C), 133.2 (C), 132.3 (C), 129.4 (CH), 128.2 (CH), 128.0 (CH), 127.4 (CH), 127.0 (CH), 126.7 (CH), 125.8 (CH), 72.8 (C), 34.8 (CH), 34.7 (CH_2), 32.7 (CH_2), 26.0 (CH_2), 21.2 (CH_2), 20.7 (CH_2) ppm. IR (neat): $\tilde{\nu}$ = 3446 (w), 2936 (w), 1734 (m), 1680 (s), 1370 (m), 1202 (m), 1073 (w), 746 (w) cm^{-1}. HRMS (ESI): calcd. for $C_{20}H_{23}NNaO_4$ $[M + MeOH + Na]^+$ 364.1519; found 364.1564.

2-(2,6-Dimethylphenyl)-8a-hydroxyhexahydroisoquinoline-1,3-(2*H*,4*H*)-dione (4h): Prepared from **3h** (29 mg, 0.1 mmol) according to Procedure B (reaction time 3 h). Isolated as a colorless oil (29 mg, 0.01 mmol, 99 %). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.21 (t, *J* = 7.5 Hz, 1 H), 7.16–7.10 (m, 2 H), 3.08 (dd, *J* = 18.5, *J* = 5.0 Hz, 1 H), 2.89 (dd, *J* = 18.5, *J* = 10.0 Hz, 1 H), 2.77 (br., 1 H), 2.36 (sex, *J* = 4.5 Hz, 1 H), 2.20–2.11 (m, 1 H), 2.08–1.98 (m, 1 H), 2.06 (s, 3 H), 2.04 (s, 3 H), 1.92–1.80 (m, 1 H), 1.68–1.44 (m, 5 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 175.8 (C), 171.0 (C), 135.4 (C), 135.1 (C), 133.3 (C), 129.0 (CH), 128.7 (CH), 128.6 (CH), 72.8 (C), 35.5 (CH), 35.1 (CH_2), 33.1 (CH_2), 26.6 (CH_2), 21.6 (CH_2), 21.3 (CH_2), 18.2 (CH_3), 17.6 (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 3390 (w), 2927 (m), 1734 (m), 1670 (s), 1364 (s), 1238 (s), 1207 (s), 1186 (s), 1132 (m), 1003 (m), 768 (m), 725 (m) cm^{-1}. HRMS (ESI): calcd. for $C_{17}H_{22}NO_3$ $[M + H]^+$ 288.1594; found 288.1597.

2-Tosylmethyl-8a-hydroxyhexahydroisoquinoline-1,3-(2*H*,4*H*)-dione (4i): Prepared from **3i** (29 mg, 0.1 mmol) according to Procedure B (reaction time 1 h). Isolated as a white solid (24 mg, 0.083 mmol, 83 %). M.p. 149–163 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.76 (d, *J* = 7.5 Hz, 2 H), 7.34 (d, *J* = 7.5 Hz, 2 H), 5.26 (s, 2 H), 3.08 (br., 1 H), 2.99 (dd, *J* = 18.5, *J* = 5.0 Hz, 1 H), 2.65 (dd, *J* = 18.5, *J* = 7.0 Hz, 1 H), 2.44 (s, 3 H), 2.21–2.12 (m, 2 H), 1.94–1.64 (m, 2 H), 1.65–1.27 (m, 5 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.3 (C), 145.4 (C), 136.0 (C), 130.0 (CH), 128.6 (CH), 72.7 (C), 59.4 (CH_2), 35.7 (CH), 34.5 (CH_2), 33.5 (CH_2), 27.1 (CH_2), 21.9 (CH_2), 21.8 (CH_2), 21.8 (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 3420 (w), 2939 (m), 1734 (m), 1686 (s), 1304 (s), 1288 (s), 1138 (s), 1043 (m), 927 (m), 820 (m), 735 (m) cm^{-1}. HRMS (ESI): calcd. for $C_{17}H_{21}NNaO_5S$ $[M + Na]^+$ 374.1033; found 374.1025.

Methyl 2-[8a-Hydroxy-1,3-dioxooctahydroisoquinolin-2(1*H*)-yl]acetate (4j): Prepared from **3j** (26 mg, 0.1 mmol) according to Procedure B (reaction time 3 h). Isolated as a white solid (20 mg, 0.076 mmol, 76 %). M.p. 122–126 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.57 (d, *J* = 16.5 Hz, 1 H), 4.52 (d, *J* = 16.5 Hz, 1 H), 3.73 (s, 3 H), 2.96 (dd, *J* = 19.0, *J* = 5.5 Hz, 1 H), 2.80 (br., 1 H), 2.75 (dd, *J* = 19.0, *J* = 8.0 Hz, 1 H), 2.28–2.19 (m, 1 H), 2.16–2.05 (m, 1 H), 1.98–1.88 (m, 1 H), 1.86–1.75 (m, 1 H), 1.64–1.40 (m, 5 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.3 (C), 168.5 (C), 72.4 (C), 52.5 (CH_3), 40.8 (CH_2), 35.6 (CH), 34.5 (CH_2), 33.3 (CH_2), 26.7 (CH_2), 21.7 (CH_2), 21.7 (CH_2) ppm. IR (neat): $\tilde{\nu}$ = 3404 (w), 2948 (w), 1753 (s), 1720 (m), 1664 (s), 1380 (s), 1329 (s), 1218 (s), 1173 (s), 1130 (s), 1070 (s), 1022 (s), 940 (m), 744 (m) cm^{-1}. HRMS (ESI): calcd. for $C_{12}H_{17}NNaO_5$ $[M + Na]^+$ 278.0999; found 278.0989. Crystals for single-crystal X-ray diffraction were grown by slow evaporation of an ethanolic solution.

(3a*R*,7a*S*)-*N*-(*tert*-butyl)-2-oxohexahydrobenzofuran-7a(2*H*)-carboxamide [(3a*R*,7a*S*)-3a]: $Zn(OTf)_2$ (4 mg, 0.011 mmol, 0.1 equiv.) and *tert*-butyl isocyanide (18.5 µL, 0.165 mmol 1.5 equiv.) were added to a solution of (*R*)-**1a** (17 mg, 0.11 mmol, 1 equiv.) in dimethyl carbonate (0.45 mL). The solution was stirred at room temperature for 6 h. Then the mixture was diluted with CH_2Cl_2, and quenched with saturated $NaHCO_3$ solution. The organic layer was separated, and the aqueous layer was extracted again with CH_2Cl_2. The combined organic layers were dried with Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (cyclohexane/ethyl acetate, 6:1) to give (3a*R*,7a*S*)-**3a** (18 mg, 0.075 mmol, 68 %). The spectroscopic data are in accordance with racemic **3a**. The enantiomeric ratio was determined by chiral GC on the chiral phase ChiraSil Dex CB (25 m × 0.25 µm); temperature program 130 °C, hold for 60 min. Retention times: $t_{R(major)}$ = 23.5 min, $t_{R(minor)}$ = 25.6 min; *er* = 92:8. $[\alpha]_D^{20}$ = –54 (*c* = 0.67, $CHCl_3$).

CCDC 1511110 [for **3a** (*trans*)] and 1511111 (for **4j**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

Supporting Information (see footnote on the first page of this article): Copies of the ^{1}H and ^{13}C NMR spectra for all new compounds, and CIF files for **3a** and **4j**.

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[1] a) S. Sadjadi, M. M. Heravi, N. Nazari, *RSC Adv.* **2016**, *6*, 53203–53272; b) G. Koopmanschap, E. Ruijter, R. V. A. Orru, *Beilstein J. Org. Chem.* **2014**, *10*, 544–598; c) A. Váradi, T. Palmer, R. Notis Dardashti, S. Majumdar, *Molecules* **2016**, *21*, 19; d) U. K. Sharma, N. Sharma, D. D. Vachhani, E. V. Van der Eycken, *Chem. Soc. Rev.* **2015**, *44*, 1836–1860.
[2] M. Passerini, L. Simone, *Gazz. Chim. Ital.* **1921**, *51*, 126–129.
[3] A. R. Kazemizadeh, A. Ramazani, *Curr. Org. Chem.* **2012**, *16*, 418–450.
[4] R. C. Cioc, E. Ruijter, R. V. A. Orru, *Green Chem.* **2014**, *16*, 2958–2975.
[5] a) C. de Graaff, E. Ruijter, R. V. A. Orru, *Chem. Soc. Rev.* **2012**, *41*, 3969–4009; b) S. S. van Berkel, B. G. M. Bögels, M. A. Wijdeven, B. Westermann, F. Rutjes, *Eur. J. Org. Chem.* **2012**, 3543–3559.
[6] a) J. Zhang, S. X. Lin, D. J. Cheng, X. Y. Liu, B. Tan, *J. Am. Chem. Soc.* **2015**, *137*, 14039–14042; b) T. Yue, M. X. Wang, D. X. Wang, G. Masson, J. P. Zhu, *J. Org. Chem.* **2009**, *74*, 8396–8399; c) S. X. Wang, M. X. Wang, D. X. Wang, J. P. Zhu, *Angew. Chem. Int. Ed.* **2008**, *47*, 388–391; *Angew. Chem.* **2008**, *120*, 394–397; d) P. R. Andreana, C. C. Liu, S. L. Schreiber, *Org. Lett.* **2003**, *5*, 4021–4024; e) U. Kusebauch, B. Beck, K. Messer, E. Herdtweck, A. Dömling, *Org. Lett.* **2004**, *6*, 4231–4233.
[7] H. Bock, I. Ugi, *J. Prakt. Chem.* **1997**, *339*, 385–389.
[8] R. Frey, S. G. Galbraith, S. Guelfi, C. Lamberth, M. Zeller, *Synlett* **2003**, 1536–1538.
[9] a) P. Radha Krishna, G. Dayaker, P. V. Narasimha Reddy, *Tetrahedron Lett.* **2006**, *47*, 5977–5980; b) B. Alcaide, P. Almendros, C. Aragoncillo, R. Callejo, M. P. Ruiz, M. R. Torres, *J. Org. Chem.* **2012**, *77*, 6917–6928; c) L. Moni, L. Banfi, A. Basso, E. Martino, R. Riva, *Org. Lett.* **2016**, *18*, 1638–1641.
[10] a) M. Jida, C. Betti, Z. Urbanczyk-Lipkowska, D. Tourwé, S. Ballet, *Org. Lett.* **2013**, *15*, 5866–5869; b) J. Zhang, A. Jacobson, J. R. Rusche, W.

Herlihy, *J. Org. Chem.* **1999**, *64*, 1074–1076; c) W. Wang, E. Herdtweck, A. Dömling, *Chem. Commun.* **2010**, *46*, 770–772; d) V. P. Mehta, S. G. Modha, E. Ruijter, K. Van Hecke, L. Van Meervelt, C. Pannecouque, J. Balzarini, R. V. A. Orru, E. Van der Eycken, *J. Org. Chem.* **2011**, *76*, 2828–2839.

[11] a) S. Marcaccini, D. Miguel, T. Torroba, M. García-Valverde, *J. Org. Chem.* **2003**, *68*, 3315–3318; b) M. Bos, E. Riguet, *J. Org. Chem.* **2014**, *79*, 10881–10889.

[12] a) L. E. Kaïm, L. Grimaud, J. Oble, S. Wagschal, *Tetrahedron Lett.* **2009**, *50*, 1741–1743; b) C. B. Gilley, M. J. Buller, Y. Kobayashi, *Org. Lett.* **2007**, *9*, 3631–3634.

[13] Other Lewis acids such as BF_3•Et_2O and $Sc(OTf)_3$ were explored, but gave lower conversions and stereoselectivities.

[14] Dimethyl carbonate is one of the most environmentally benign aprotic solvents and recommended for sustainable chemistry applications. See, for example: D. Prat, A. Wells, J. Hayler, H. Sneddon, C. R. McElroy, S. Abou-Shehada, P. J. Dunn, *Green Chem.* **2016**, *18*, 288–296. For a recent discussion on the sustainability aspects of MCRs, see ref.[4]

[15] R. Ramozzi, K. Morokuma, *J. Org. Chem.* **2015**, *80*, 5652–5657.

[16] In Ugi reactions, ketoacid **1d** does indeed preferentially (3:1 ratio) give the *cis*-bicyclic lactam corresponding to an *anti* addition, see ref.[10c]

[17] Crystal packing forces may be relevant in the transformation of **3j** into **4j** during crystallization.

[18] For a recent example of the use of enzymes to prepare optically pure precursors for Passerini reactions, see ref.[9c]

[19] A. Müller, B. Hauer, B. Rosche, *Biotechnol. Bioeng.* **2007**, *98*, 22–29.

[20] N. G. Turrini, R. C. Cioc, D. J. van der Niet, E. Ruijter, R. V. A. Orru, M. Hall, K. Faber, *Green Chem.* **2017**, *19*, 511–518.

[21] Chiral oxoacid **1a** was observed to racemize slowly upon prolonged storage.

[22] For other examples from our group combining biocatalysis and MCRs in the asymmetric synthesis of medicinally relevant heterocycles, see: a) A. Znabet, E. Ruijter, F. J. J. de Kanter, V. Köhler, M. Helliwell, N. J. Turner, R. V. A. Orru, *Angew. Chem. Int. Ed.* **2010**, *49*, 5289–5292; *Angew. Chem.* **2010**, *122*, 5417–5420; b) A. Znabet, M. M. Polak, E. Janssen, F. J. J. de Kanter, N. J. Turner, R. V. A. Orru, E. Ruijter, *Chem. Commun.* **2010**, *46*, 7918–7920.

[23] S. M. Allin, S. L. James, M. R. J. Elsegood, W. P. Martin, *J. Org. Chem.* **2002**, *67*, 9464–9467.

[24] W. Yang, X. Sun, W. Yu, R. Rai, J. R. Deschamps, L. A. Mitchell, C. Jiang, A. D. MacKerell, F. Xue, *Org. Lett.* **2015**, *17*, 3070–3073.

[25] C. A. Holloway, M. E. Muratore, R. I. Storer, D. J. Dixon, *Org. Lett.* **2010**, *12*, 4720–4723.

[26] L. Carro, M. Torrado, E. Raviña, C. F. Masaguer, S. Lage, J. Brea, M. I. Loza, *Eur. J. Med. Chem.* **2014**, *71*, 237–249.

[27] Due to cyclohexane ring flipping, some peaks in the ^{13}C NMR spectra of compounds **4** appear broad and have low intensities.

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