A Multicomponent Reaction between α-Substituted Acroleins, Nitroalkanes and Paraformaldehyde: Efficient Construction of Nitro δ-Lactol

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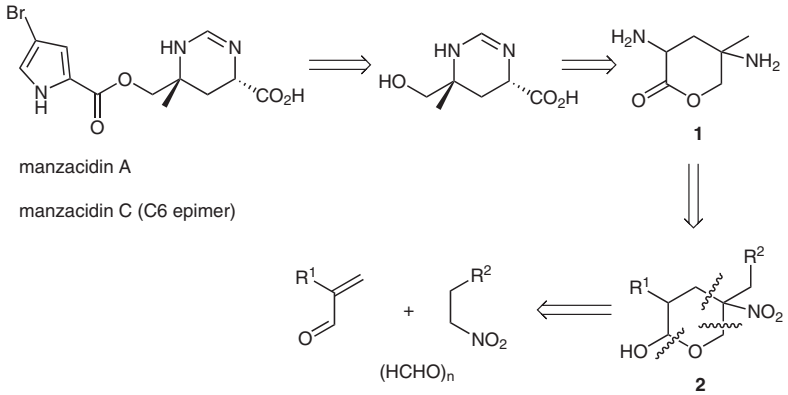
Abstract: A base-catalyzed multicomponent cascade reaction between α-substituted acroleins, nitroalkanes, and paraformaldehyde that proceeded smoothly to give high yields of functionalized δ-lactols under mild conditions, is described. This methodology is useful in the development of a concise synthetic route to natural products (±)-manzacidin A and C.

Key words: multicomponent reaction, α-substituted acroleins, 1,8-diazabicyclo[5.4.0]undec-7-ene, δ-lactols

Organocatalytic multicomponent reactions are powerful tools in natural products synthesis and drug discovery that have attracted much attention because they typically proceed in a highly efficient and atom-economical manner through the formation of multiple new bonds in a one-pot system, which saves time and energy by avoiding purification of intermediates and the protection/deprotection of functional groups.[1] Bromopyrrole alkaloids, such as manzacidin A and C,[2] have shown potent bioactivities as α-adrenoceptor blockers, antagonists of serotonergic receptors, and actomyosin ATPase activators.[3] The biological profiles of these molecules, combined with the synthetic interest in constructing unusual structures, have resulted in a number of successful total syntheses of manzacidin A[4] and C.[5] Nevertheless, the development of facile and efficient strategies to access these molecules is still an unmet challenge.

We are interested in the rational design of new multicomponent approaches to reach this goal. Retrosynthetic analysis of manzacidin A and C leads to the identification of the key motif δ-lactone **1**[4a] and then to δ-lactols **2** (Scheme 1). In this paper, we report one highly chemo- and regioselective synthetic method that enables access to δ-lactol **2** through a three-component cascade reaction between α-substituted acrolein, nitroalkane, and paraformaldehyde. From the synthetic point of view, this kind of δ-lactol core is not only a very important precursor in the synthesis of natural products[4a,5] and biologically active compounds[6] such as dysibetaine[5a] and NK_1 antagonists,[6e] but also, as a versatile synthetic platform, can be easily converted into useful products such as tetrahydropyran, γ-lactam, and prolinol, among others.[7]

The desired δ-lactol **2** would be generated when α-substituted acroleins **3**, nitroalkanes **4** and paraformaldehyde were mixed together in the presence of an appropriate catalyst through the pathways outlined in Scheme 2. For Path a, nitroalkane **4** first reacts with paraformaldehyde to give β-nitro alcohol **A**, which then undergoes a Michael-hemiacetalization with α-substituted acrolein **3** to afford δ-lactol **2**. Alternatively, with the aid of base, nitroalkane **4** could also react with α-substituted acrolein **3** to give Michael adduct **B**.[8] The generated intermediate **B** further reacts with paraformaldehyde through hydroxymethylation and subsequent intramolecular hemiacetalization to produce δ-lactol **2**. Thus, the chemo- and regioselectivity



Scheme 1 Retrosynthetic analysis of manzacidin A and C

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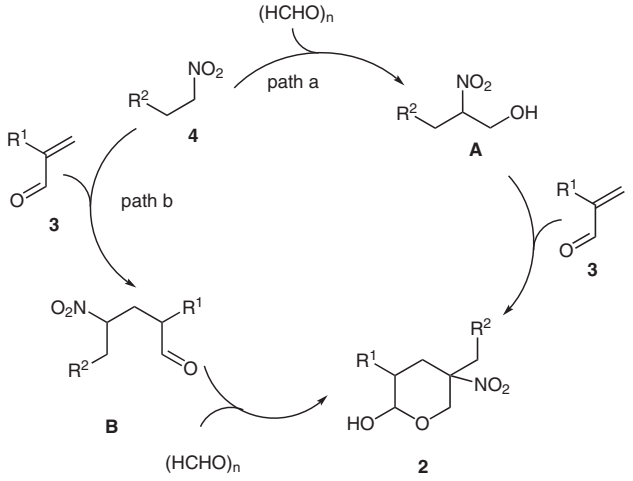


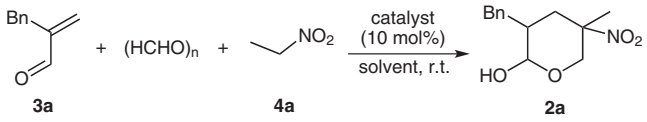
Scheme 2 Possible pathways of the three-component cascade reaction

was the first issue to address for the development of this cascade reaction.

The three-component cascade reaction between 2-benzylacrolein (**3a**), nitroethane (**4a**), and paraformaldehyde was first performed in toluene using various bases, such as 1,4-diazabicyclo[2.2.2]octane (DABCO), *N*,*N*-dimethyl-4-aminopyridine (DMAP), triethylamine, imidazole, or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as the catalyst at room temperature (Table 1, entries 1–5). It was found that DBU showed the best catalytic activity among these bases, although δ-lactol **2a** was generated in all the other cases. Thus, DBU was chosen for further examination of reaction media (Table 1, entries 6–13). In the presence of 10 mol% DBU, ethanol was found to be the best solvent, and the desired product δ-lactol **2a** was isolated in excellent yield (Table 1, entry 13). In fact, under the optimized reaction conditions, the respective reactions of preformed 2-nitropropan-1-ol with 2-benzylacrolein (**3a**) or of preformed 2-benzyl-4-nitropentanal with paraformaldehyde proceeded smoothly to afford δ-lactol **2a** with excellent yields (Table 1, entries 14 and 15). Based on these observations, we believe that the δ-lactol **2** can be generated through both of the pathways shown in Scheme 2. Diastereoselectivity for the above reaction was moderate in all the cases, which was determined by ^{1}H NMR spectroscopy after **2a** was reduced into the corresponding tetrahydropyran by the action of $Et_3SiH/BF_3{\cdot}Et_2O$ in order to differentiate the chemical shifts.

With the optimized reaction conditions in hand, the substrate scope of this cascade reaction was investigated. Because it was difficult to purify and analyze δ-lactols **2**, they were first converted into tetrahydropyrans (Method A) or δ-lactones (Method B), respectively, and then isolated and characterized; the results are summarized in Table 2. With respect to the nitroalkanes, not only were simple aliphatic and aromatic nitroethanes accepted in the reaction, but also functionalized nitroalkanes **4h–i** were well-tolerated, and the corresponding products **5a–i** were obtained in good yields with moderate diastereoselectivities. For α-substituted acroleins, which were prepared by application of the Pihko methylenation,[9] to our delight, the cascade reaction accommodated a range of alkyl groups at the α-position of the substituted acroleins (R^1 = Bn, *n*-pentyl, *n*-Pr, and *i*-Pr). Most importantly, a number of functionalized groups (R^1 = PhthNCH$_2$, BnO, and BocNH) were well-tolerated (products **5m**, **5n**, and **5o**, respectively).

Table 1 Optimization of the Three-Component Cascade Reaction of Nitroethane, 2-Benzylacrolein, and Paraformaldehyde[a]



3a 4a 2a

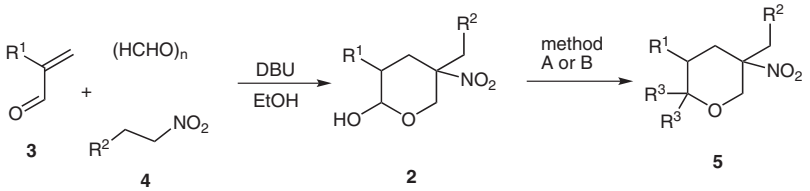
Entry	Catalyst	Solvent	Time (h)	Yield (%)[b]	dr[c]
1	DABCO	toluene	24	28	70:30
2	DMA	toluene	24	37	72:28
3	Et_3N	toluene	24	21	63:37
4	Imidazole	toluene	48	<10	–
5	DBU	toluene	12	82	75:25
6	DBU	$CHCl_3$	12	73	71:29
7	DBU	CH_2Cl_2	12	80	66:34
8	DBU	*n*-hexane	36	78	80:20
9	DBU	EtOAc	12	89	71:29
10	DBU	THF	12	87	63:37
11	DBU	MeCN	12	75	74:26
12	DBU	MeOH	12	90	73:27
13	DBU	EtOH	12	94	78:22
14[d]	DBU	EtOH	12	96	78:22
15[e]	DBU	EtOH	12	96	78:22

[a] Reaction conditions: nitroethane (0.55 mmol), 2-benzylacrolein (0.5 mmol), paraformaldehyde (0.6 mmol), catalyst (10 mol%), solvent (1 mL), r.t.
[b] Isolated yield of **2a**.
[c] Diastereoselectivity determined by ^{1}H NMR analysis of crude tetrahydropyran.
[d] Reactions performed with 2-nitropropan-1-ol (0.55 mmol) and 2-benzylacrolein (0.5 mmol).
[e] Reactions performed with 2-benzyl-4-nitropentanal (0.5 mmol) and paraformaldehyde (0.6 mmol).

As a synthetic application of this cascade procedure, the semisynthesis of (±)-manzacidin A and C was then undertaken. The major diastereoisomer of **5o** was first separated by silica gel column chromatography and then reduced to δ-lactone **6** with hydrogen over Pd/C. The δ-lactone **6** could be readily converted into the γ-lactam **7** in excellent yields at 40 °C in methanol (Scheme 3). Nuclear Overhauser effect (NOE) experiments with **7** clearly showed

that the methyl group at the 5-position and the proton at the 3-position are located on the same side of the ring and, thus, can be assigned as *cis*-**7**. The major diastereoisomer of **5o** should therefore be *trans*-**5o**. In fact, *trans*-**6** and *cis*-**6** can be converted into (±)-manzacidin A and C, respectively, in three steps, as reported by Ohfune previously.[4a] The catalytic ability of DBU to tolerate the structural change of nitroalkanes, enables the analogues of (±)-manzacidin A and C to be successfully prepared by this route.

Table 2 Scope of the DBU-Catalyzed Three-Component Cascade Reaction[a]



3 **4** **2** **5**

3a: R^1 = Bn
3b: R^1 = *n*-pentyl
3c: R^1 = *n*-Pr
3d: R^1 = *i*-Pr
3e: R^1 = PhthNCH$_2$
3f: R^1 = BnO
3g: R^1 = BocNH

4a: R^2 = H
4b: R^2 = Me
4c: R^2 = Ph
4d: R^2 = 4-FC_6H_4
4e: R^2 = 4-MeOC_6H_4

4f: R^2 = 2,4-$Cl_2C_6H_3$
4g: R^2 = 3,4-(OCH$_2$O)C_6H_3
4h: R^2 = $CH_2CH_2CO_2Me$
4i: R^2 = OH

R^3 = H, O

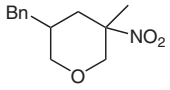
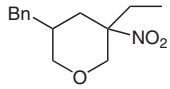
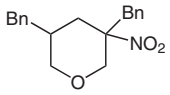
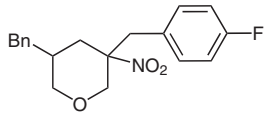
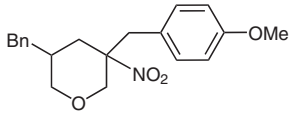
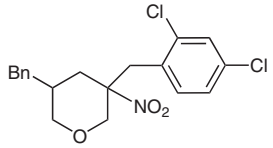
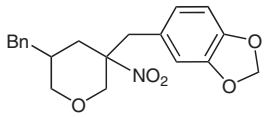
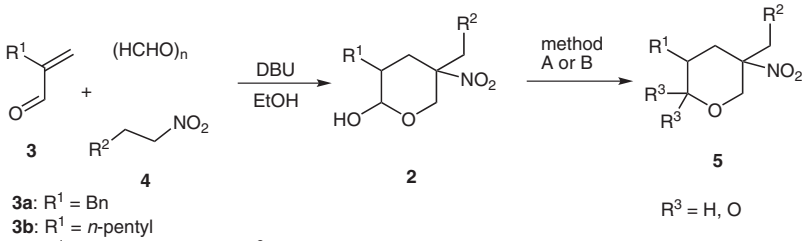
Entry	Products	Yield (%)[b]	dr[c]
1	 **5a**	84	78:22
2	 **5b**	82	75:25
3	 **5c**	85	84:16
4	 **5d**	83	85:15
5	 **5e**	80	84:16
6	 **5f**	79	84:16
7	 **5g**	86	84:16

Table 2 Scope of the DBU-Catalyzed Three-Component Cascade Reaction[a] (continued)

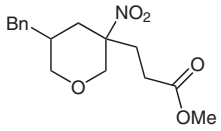
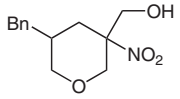
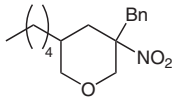
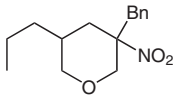
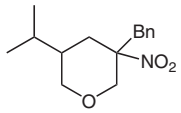
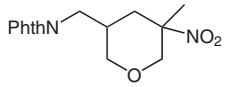
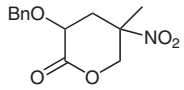
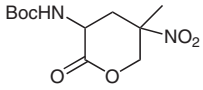


3a: R^1 = Bn
3b: R^1 = *n*-pentyl
3c: R^1 = *n*-Pr
3d: R^1 = *i*-Pr
3e: R^1 = PhthNCH$_2$
3f: R^1 = BnO
3g: R^1 = BocNH

4a: R^2 = H
4b: R^2 = Me
4c: R^2 = Ph
4d: R^2 = 4-FC_6H_4
4e: R^2 = 4-$MeOC_6H_4$

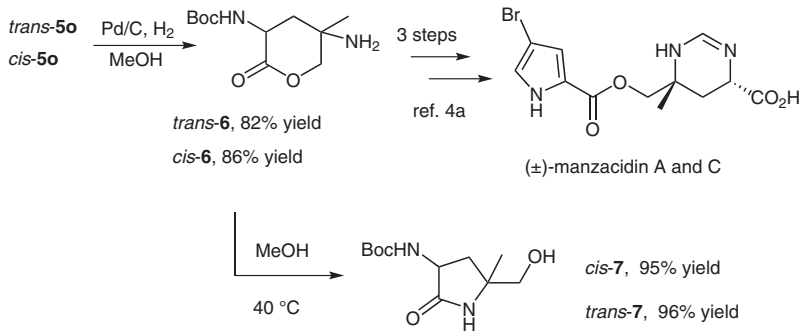
4f: R^2 = 2,4-$Cl_2C_6H_3$
4g: R^2 = 3,4-$(OCH_2O)C_6H_3$
4h: R^2 = $CH_2CH_2CO_2Me$
4i: R^2 = OH

R^3 = H, O

Entry	Products	Yield (%)[b]	dr[c]
8	 **5h**	75	64:36
9	 **5i**	84	78:22
10	 **5j**	80	77:23
11	 **5k**	76	78:22
12	 **5l**	84	82:18
13	 **5m**	79	77:23
14	 **5n**	74	78:22
15	 **5o**	71	80:20

[a] Reaction conditions: acrolein (0.5 mmol), nitroalkane (0.55 mmol), paraformaldehyde (0.6 mmol), DBU (0.05 mmol), EtOH (1 mL) at r.t.
[b] Isolated yield of **5**.
[c] Diastereoselectivities determined by ^{1}H NMR analysis of crude **5**.

In summary, we have developed a novel organocatalytic, multicomponent cascade reaction between various nitroalkanes, α-substituted acroleins, and paraformaldehyde by employing DBU as the catalyst. This versatile and efficient domino reaction affords functionalized δ-lactols and their derivatives such as δ-lactones and tetrahydropyrans in good yields. Furthermore, this method provides a facile approach to the natural products (±)-manzacidin A



Scheme 3 Formal semisynthesis of (±)-manzacidin A and C

and C from easily accessible reagents under mild conditions.

Solvents were purified by standard procedures and distilled before use. Reagents and starting materials obtained from commercial suppliers were used without further purification unless otherwise noted. For thin-layer chromatography (TLC), silica gel plates GF254 were used and compounds were visualized by irradiation with UV light, I_2, or by treatment with basic $KMnO_4$. NMR spectra were obtained with a Bruker AV-400 NMR spectrometer with TMS as the internal standard. Chemical shifts were reported in parts per million (ppm), and the residual solvent peak was used as an internal reference: ^1H (δ = 7.26 ppm), ^{13}C (δ = 77.0 ppm). Multiplicity is indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublet), br s (broad singlet). Coupling constants are reported in hertz (Hz). High-resolution mass spectra were obtained on a Bruker Apex IV FTMS using electrospray ionization (ESI). Flash chromatography was carried out on silica gel 60 A (10–40 μm, purchased from Qingdao Haiyang).

Multicomponent Cascade Reaction; General Procedure

To a mixture of α-substituted acrolein (0.5 mmol), nitroalkane (0.55 mmol), and paraformaldehyde (0.6 mmol) in EtOH (800 μL), was added a solution of DBU in EtOH (0.25 M, 200 μL). The reaction mixture was stirred at r.t. until complete consumption of the α-substituted acrolein was observed. The reaction mixture was filtered through a silica gel pad, washed with 5% MeOH–CH_2Cl_2, and concentrated in vacuo.

Method A

The resulting crude δ-lactol **2a**–**m** was dissolved in CH_2Cl_2 (10.0 mL), and triethylsilane (5.0 mmol) and TFA (5.0 mmol) were added at –78 °C. After stirring at –78 °C for 1 h, the temperature of reaction mixture was gradually raised to r.t. The reaction was quenched with aq $NaHCO_3$ (10.0 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The organic phase was combined, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The diastereoisomeric ratio was determined by ^1H NMR analysis of crude product **5** (based on the different chemical shift of $OCH_aH_bCNO_2$). The residue was purified by flash chromatography (CH_2Cl_2) to give the corresponding tetrahydropyran **5a**–**m** (major).

5-Benzyltetrahydro-3-methyl-3-nitro-2*H*-pyran (5a)

Yield: 84%; diastereomeric ratio: 78:22 (determined by ^1H NMR).

^1H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.31–7.27 (m, 2 H), 7.23–7.19 (m, 1 H), 7.14–7.11 (m, 2 H), 4.61 (dd, *J* = 12.4, 2.8 Hz, 1 H), 3.97 (dd, *J* = 11.2, 2.4 Hz, 1 H, minor isomer), 3.87 (ddd, *J* = 11.2, 4.3, 1.8 Hz, 1 H), 3.26 (d, *J* = 12.8 Hz, 1 H), 3.03 (d, *J* = 11.2 Hz, 1 H), 2.75–2.69 (m, 1 H), 2.50–2.48 (m, 2 H), 2.22–2.12 (m, 1 H), 1.41 (s, 3 H), 1.30 (dd, *J* = 14.8, 12.4 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 138.2, 128.8, 128.6, 126.5, 86.1, 73.1, 72.6, 38.7, 38.4, 33.6, 24.3.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{13}H_{17}NNaO_3$: 258.11006; found: 258.11009.

5-Benzyl-3-ethyltetrahydro-3-nitro-2*H*-pyran (5b)

Yield: 82%; diastereomeric ratio: 75:25 (determined by ^1H NMR).

^1H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.31–7.28 (m, 2 H), 7.22–7.20 (m, 1 H), 7.14–7.13 (m, 2 H), 4.63 (dd, *J* = 12.8, 2.8 Hz, 1 H), 4.11 (dd, *J* = 11.2, 2.4 Hz, 1 H, minor isomer), 3.87 (ddd, *J* = 11.2, 4.4, 2.0 Hz, 1 H), 3.28 (d, *J* = 12.8 Hz, 1 H), 3.03 (d, *J* = 11.2 Hz, 1 H), 2.79–2.73 (m, 1 H), 2.56–2.45 (m, 2 H), 2.19–2.10 (m, 1 H), 1.86–1.76 (m, 1 H), 1.68–1.59 (m, 1 H), 1.25 (dd, *J* = 14.4, 12.0 Hz, 1 H), 0.85 (t, *J* = 7.6 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 138.3, 128.8, 128.6, 126.4, 89.7, 72.9, 72.6, 38.5, 36.6, 33.5, 30.8, 7.3.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{14}H_{19}NNaO_3$: 272.12571; found: 272.12564.

3,5-Dibenzyltetrahydro-3-nitro-2*H*-pyran (5c)

Yield: 85%; diastereomeric ratio: 84:16 (determined by ^1H NMR).

^1H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.29–7.24 (m, 5 H), 7.21–7.17 (m, 1 H), 7.09–7.07 (m, 2 H), 7.02–7.00 (m, 2 H), 4.63 (dd, *J* = 12.8, 2.8 Hz, 1 H), 4.18 (dd, *J* = 11.2, 1.6 Hz, 1 H, minor isomer), 3.87 (ddd, *J* = 11.2, 4.4, 2.0 Hz, 1 H), 3.38 (d, *J* = 12.4 Hz, 1 H), 3.07–2.90 (m, 3 H), 2.65–2.60 (m, 1 H), 2.53 (dd, *J* = 13.6, 6.4 Hz, 1 H), 2.40 (dd, *J* = 14.0, 8.0 Hz, 1 H), 2.13–2.07 (m, 1 H), 1.43–1.36 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 138.3, 132.9, 129.7, 128.8, 128.7, 128.5, 127.9, 126.5, 89.8, 72.7, 72.4, 43.9, 38.6, 37.0, 33.6.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{19}H_{21}NNaO_3$: 334.14136; found: 334.14142.

3-(4-Fluorobenzyl)-5-benzyltetrahydro-3-nitro-2*H*-pyran (5d)

Yield: 83%; diastereomeric ratio: 85:15 (determined by ^1H NMR).

^1H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.29–7.25 (m, 2 H), 7.22–7.18 (m, 1 H), 7.09 (d, *J* = 7.2 Hz, 2 H), 7.00–6.97 (m, 4 H), 4.62 (dd, *J* = 12.4, 2.8 Hz, 1 H), 4.09 (dd, *J* = 11.6, 2.0 Hz, 1 H, minor isomer), 3.83 (ddd, *J* = 11.2, 4.4, 1.6 Hz, 1 H), 3.37 (d, *J* = 12.4 Hz, 1 H), 3.06–2.98 (m, 2 H), 2.88 (d, *J* = 14.4 Hz, 1 H), 2.62–2.58 (m, 1 H), 2.54 (dd, *J* = 14.0, 6.4 Hz, 1 H), 2.42 (dd, *J* = 14.0, 8.0 Hz, 1 H), 2.15–2.06 (m, 1 H), 1.44–1.34 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 162.5 (d, *J* = 245.3 Hz), 138.1, 131.2 (d, *J* = 8.0 Hz), 128.8, 128.6 (d, *J* = 2.6 Hz), 128.5, 126.5, 115.7 (d, *J* = 21.4 Hz), 89.7, 72.7, 72.4, 43.0, 38.6, 37.0, 33.6.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{19}H_{20}FNNaO_3$: 352.13194; found: 352.13199.

3-(4-Methoxybenzyl)-5-benzyltetrahydro-3-nitro-2*H*-pyran (5e)

Yield: 80%; diastereomeric ratio: 84:16 (determined by ^{1}H NMR).

^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.29–7.25 (m, 2 H), 7.21–7.18 (m, 1 H), 7.10–7.08 (m, 2 H), 6.94–6.91 (m, 2 H), 6.84–6.81 (m, 2 H), 4.62 (dd, *J* = 12.4, 2.8 Hz, 1 H), 4.12 (dd, *J* = 11.2, 2.0 Hz, 1 H, minor isomer), 3.81 (ddd, *J* = 11.2, 4.4, 1.6 Hz, 1 H), 3.78 (s, 3 H), 3.36 (d, *J* = 12.4 Hz, 1 H), 3.01–2.96 (m, 2 H), 2.86 (d, *J* = 14.0 Hz, 1 H), 2.64–2.60 (m, 1 H), 2.54 (dd, *J* = 14.0, 6.4 Hz, 1 H), 2.41 (dd, *J* = 14.0, 8.0 Hz, 1 H), 2.13–2.06 (m, 1 H), 1.37 (dd, *J* = 14.4, 12.4 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 159.3, 138.3, 130.8, 128.8, 128.5, 126.5, 124.8, 114.1, 89.9, 72.6, 72.3, 55.3, 43.1, 38.6, 37.0, 33.6.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{23}NNaO_4$: 364.15193; found: 364.15185.

3-(2,4-Dichlorobenzyl)-5-benzyltetrahydro-3-nitro-2*H*-pyran (5f)

Yield: 79%; diastereomeric ratio: 82:18 (determined by ^{1}H NMR).

^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.40 (d, *J* = 2.0 Hz, 1 H), 7.29–7.25 (m, 2 H), 7.22–7.20 (m, 1 H), 7.17 (dd, *J* = 8.4, 2.0 Hz, 1 H), 7.10–7.08 (m, 2 H), 6.90 (d, *J* = 8.4 Hz, 1 H), 4.61 (dd, *J* = 12.8, 2.8 Hz, 1 H), 4.18 (dd, *J* = 11.6, 2.0 Hz, 1 H, minor isomer), 3.83 (ddd, *J* = 11.2, 4.4, 1.6 Hz, 1 H), 3.45 (d, *J* = 12.4 Hz, 1 H), 3.20–3.12 (m, 2 H), 3.02 (d, *J* = 8.4 Hz, 1 H), 2.62–2.57 (m, 1 H), 2.52 (dd, *J* = 14.0, 6.8 Hz, 1 H), 2.44 (dd, *J* = 14.0, 8.0 Hz, 1 H), 2.11–2.05 (m, 1 H), 1.52 (dd, *J* = 14.4, 12.4 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 138.1, 135.4, 134.6, 132.2, 129.9, 129.7, 128.8, 128.6, 127.7, 126.5, 90.3, 72.6, 72.1, 39.3, 38.5, 36.8, 33.7.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{19}H_{19}Cl_2NNaO_3$: 402.06342; found: 402.06348.

5-[(5-Benzyltetrahydro-3-nitro-2*H*-pyran-3-yl)methyl]benzo[*d*][1,3]dioxole (5g)

Yield: 86%; diastereomeric ratio: 84:16 (determined by ^{1}H NMR).

^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.29–7.25 (m, 2 H), 7.22–7.20 (m, 1 H), 7.10–7.09 (m, 2 H), 6.72 (d, *J* = 7.6 Hz, 1 H), 6.49–6.46 (m, 2 H), 5.94 (s, 2 H), 4.62 (dd, *J* = 12.8, 2.8 Hz, 1 H), 4.12 (dd, *J* = 11.2, 2.0 Hz, 1 H, minor isomer), 3.82 (ddd, *J* = 11.2, 4.4, 1.6 Hz, 1 H), 3.36 (d, *J* = 12.4 Hz, 1 H), 3.02–2.96 (m, 2 H), 2.83 (d, *J* = 14.4 Hz, 1 H), 2.66–2.61 (m, 1 H), 2.55 (dd, *J* = 13.6, 6.4 Hz, 1 H), 2.41 (dd, *J* = 14.0, 8.0 Hz, 1 H), 2.13–2.08 (m, 1 H), 1.37 (dd, *J* = 14.4, 12.0 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 147.9, 147.3, 138.2, 128.8, 128.5, 126.5, 126.3, 123.0, 109.9, 108.4, 101.2, 89.8, 72.6, 72.4, 43.6, 38.6, 37.0, 33.6.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{21}NNaO_5$: 378.13119; found: 378.13126.

Methyl 3-(5-Benzyltetrahydro-3-nitro-2*H*-pyran-3-yl)propanoate (5h)

Yield: 75%; diastereomeric ratio: 64:36 (determined by ^{1}H NMR).

^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ (major) = 7.32–7.28 (m, 2 H), 7.26–7.21 (m, 1 H), 7.13–7.11 (m, 2 H), 4.60 (dd, *J* = 12.4, 2.8 Hz, 1 H), 3.89–3.85 (m, 1 H), 3.64 (s, 3 H), 3.31 (d, *J* = 12.8 Hz, 1 H), 3.04 (dd, *J* = 11.6, 11.2 Hz, 1 H), 2.70–2.66 (m, 1 H), 2.55–2.45 (m, 2 H), 2.42–2.38 (m, 1 H), 2.24–2.07 (m, 3 H), 2.00–1.92 (m, 1 H), 1.28 (dd, *J* = 14.4, 12.4 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ (major) = 172.2, 138.1, 128.8, 128.6, 126.5, 88.5, 72.8, 72.5, 52.0, 38.4, 36.6, 33.4, 32.1, 27.6.

^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ (minor) = 7.32–7.28 (m, 2 H), 7.26–7.21 (m, 1 H), 7.13–7.11 (m, 2 H), 4.07 (dd, *J* = 11.2, 2.4 Hz, 1 H), 3.89–3.85 (m, 1 H), 3.64 (s, 3 H), 3.61 (d, *J* = 11.2 Hz, 1 H), 3.04 (dd, *J* = 11.6, 11.2 Hz, 1 H), 2.55–2.45 (m, 2 H), 2.42–2.38 (m, 1 H), 2.36–2.27 (m, 2 H), 2.24–2.07 (m, 3 H), 1.77 (dd, *J* = 12.8, 12.4 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ (minor) = 172.3, 138.2, 128.8, 128.7, 126.6, 86.2, 72.8, 70.9, 52.0, 38.4, 37.7, 32.1, 29.1, 28.1.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{16}H_{21}NNaO_5$: 330.13119; found: 330.13112.

(5-Benzyltetrahydro-3-nitro-2*H*-pyran-3-yl)methanol (5i)

Yield: 84%; diastereomeric ratio: 78:22 (determined by ^{1}H NMR).

^{1}H NMR (400 MHz, DMSO-d_6, 25 °C, TMS): δ = 7.20–7.16 (m, 2 H), 7.10–7.04 (m, 3 H), 5.42 (t, *J* = 6.0 Hz, 1 H), 4.43 (dd, *J* = 12.4, 2.8 Hz, 1 H), 4.13 (dd, *J* = 11.2, 1.6 Hz, 1 H, minor isomer), 3.75 (dd, *J* = 11.2, 2.8 Hz, 1 H), 3.62 (dd, *J* = 11.6, 6.0 Hz, 1 H), 3.53 (dd, *J* = 11.6, 6.0 Hz, 1 H), 3.44 (d, *J* = 12.4 Hz, 1 H), 3.07 (t, *J* = 11.2 Hz, 1 H), 2.54 (dd, *J* = 13.6, 6.4 Hz, 1 H), 2.44 (dd, *J* = 14.4, 2.0 Hz, 1 H), 2.36 (dd, *J* = 13.6, 8.0 Hz, 1 H), 1.88–1.86 (m, 1 H), 1.46 (dd, *J* = 14.4, 12.4 Hz, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6, 25 °C, TMS): δ = 139.3, 129.3, 128.8, 126.6, 91.2, 72.2, 69.7, 66.1, 33.9, 33.6.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{13}H_{17}NNaO_4$: 274.10498; found: 274.10491.

3-Benzyltetrahydro-3-nitro-5-pentyl-2*H*-pyran (5j)

Yield: 80%; diastereomeric ratio: 77:23 (determined by ^{1}H NMR).

^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ (major) = 7.30–7.26 (m, 3 H), 7.07–7.01 (m, 2 H), 4.63 (dd, *J* = 12.8, 2.8 Hz, 1 H), 3.90 (ddd, *J* = 11.2, 4.4, 1.6 Hz, 1 H), 3.38 (d, *J* = 12.4 Hz, 1 H), 3.05 (d, *J* = 14.0 Hz, 1 H), 2.97–2.88 (m, 2 H), 2.63–2.59 (m, 1 H), 1.75–1.70 (m, 1 H), 1.32–1.23 (m, 7 H), 1.14–1.09 (m, 2 H), 0.86 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ (major) = 133.0, 129.7, 128.7, 127.8, 89.8, 73.1, 72.5, 43.9, 37.1, 32.2, 32.0, 31.9, 26.0, 22.5, 14.1.

^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ (minor) = 7.30–7.26 (m, 3 H), 7.07–7.01 (m, 2 H), 4.12 (dd, *J* = 11.2, 2.4 Hz, 1 H), 3.98 (ddd, *J* = 11.2, 4.4, 0.8 Hz, 1 H), 3.49 (d, *J* = 11.2 Hz, 1 H), 3.44 (d, *J* = 14.4 Hz, 1 H), 2.97–2.88 (m, 2 H), 2.39–2.35 (m, 1 H), 2.04–1.96 (m, 1 H), 1.32–1.23 (m, 7 H), 1.14–1.09 (m, 2 H), 0.90 (t, *J* = 6.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ (minor) = 134.2, 129.8, 128.7, 127.7, 87.4, 73.3, 70.5, 40.4, 37.9, 33.6, 32.0, 31.9, 26.2, 22.6, 14.1.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{25}NNaO_3$: 314.17266; found: 314.17260.

3-Benzyltetrahydro-3-nitro-5-propyl-2*H*-pyran (5k)

Yield: 76%; diastereomeric ratio: 78:22 (determined by ^{1}H NMR).

^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.31–7.26 (m, 3 H), 7.04–7.02 (m, 2 H), 4.65 (dd, *J* = 12.8, 2.8 Hz, 1 H), 4.15 (dd, *J* = 11.2, 2.4 Hz, 1 H, minor isomer), 3.92 (ddd, *J* = 11.2, 4.4, 1.6 Hz, 1 H), 3.39 (d, *J* = 12.8 Hz, 1 H), 3.08 (d, *J* = 14.0 Hz, 1 H), 2.96–2.90 (m, 2 H), 2.66–2.60 (m, 1 H), 1.80–1.73 (m, 1 H), 1.33–1.23 (m, 3 H), 1.15–1.09 (m, 2 H), 0.87 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 133.0, 129.7, 128.7, 127.9, 89.7, 73.1, 72.5, 43.9, 37.1, 34.2, 31.8, 19.5, 14.2.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{21}NNaO_3$: 286.14136; found: 286.14140.

3-Benzyltetrahydro-5-isopropyl-3-nitro-2*H*-pyran (5l)
Yield: 84%; diastereomeric ratio: 82:18 (determined by ^{1}H NMR).

^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.30–7.28 (m, 3 H), 7.04–7.02 (m, 2 H), 4.62 (dd, *J* = 12.4, 2.8 Hz, 1 H), 4.12 (dd, *J* = 11.2, 2.0 Hz, 1 H, minor isomer), 3.97 (ddd, *J* = 11.2, 4.4, 2.0 Hz, 1 H), 3.36 (d, *J* = 12.4 Hz, 1 H), 3.07 (d, *J* = 13.6 Hz, 1 H), 3.02 (t, *J* = 14.4 Hz, 1 H), 2.94 (d, *J* = 13.6 Hz, 1 H), 2.68–2.63 (m, 1 H), 1.56–1.47 (m, 1 H), 1.41–1.33 (m, 2 H), 0.89 (d, *J* = 4.9 Hz, 3 H), 0.86 (d, *J* = 4.9 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 133.0, 129.7, 128.7, 127.9, 89.9, 72.2, 71.4, 44.1, 38.2, 24.7, 29.7, 19.8, 19.7.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{21}NNaO_3$: 286.14136; found: 286.14131.

2-[(Tetrahydro-5-methyl-5-nitro-2*H*-pyran-3-yl)methyl]isoindoline-1,3-dione (5m)
Yield: 79%; diastereomeric ratio: 77:23 (determined by ^{1}H NMR).

^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.86 (dd, *J* = 5.6, 3.2 Hz, 2 H), 7.75 (dd, *J* = 5.2, 2.8 Hz, 2 H), 4.61 (dd, *J* = 12.8, 2.8 Hz, 1 H), 4.01 (dd, *J* = 10.8, 2.0 Hz, 1 H, minor isomer), 3.97 (ddd, *J* = 11.2, 4.4, 2.0 Hz, 1 H), 3.57 (d, *J* = 6.8 Hz, 1 H), 3.29 (d, *J* = 12.8 Hz, 1 H), 3.14 (dd, *J* = 11.6, 11.2 Hz, 1 H), 2.81–2.77 (m, 1 H), 2.34–2.28 (m, 1 H), 1.46 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 168.4, 134.3, 131.8, 123.5, 85.6, 73.0, 70.6, 39.2, 36.5, 32.7, 24.3.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{16}N_2NaO_5$: 327.09514; found: 327.09508.

Method B
To a solution of the crude δ-lactol **2n** or **2o** generated above in CH_2Cl_2 (10.0 mL), 4 Å molecular sieves and pyridinium dichromate (PDC; 376 mg, 1.0 mmol) were added at r.t. The reaction mixture was stirred for 24 h, diluted with EtOAc (20.0 mL), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (CH_2Cl_2 then CH_2Cl_2–MeOH, 100:1) to give the corresponding δ-lactone.

3-(Benzyloxy)tetrahydro-5-methyl-5-nitropyran-2-one (5n)
Yield: 74%; diastereomeric ratio: 78:22 (determined by ^{1}H NMR).

^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.38–7.26 (m, 5 H), 4.94 (dd, *J* = 12.0, 11.6 Hz, 2 H), 4.82 (dd, *J* = 12.4, 1.6 Hz, 1 H, minor isomer), 4.62 (d, *J* = 11.6 Hz, 1 H), 4.20 (d, *J* = 12.8 Hz, 1 H), 4.09 (dd, *J* = 9.2, 7.2 Hz, 1 H), 3.14 (dd, *J* = 15.6, 9.2 Hz, 1 H), 2.43 (dd, *J* = 15.6, 7.2 Hz, 1 H), 1.69 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 169.3, 136.6, 128.7, 128.3, 128.0, 84.5, 72.6, 70.6, 69.7, 36.3, 25.0.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{13}H_{15}NNaO_5$: 288.08424; found: 288.08419.

***tert*-Butyl Tetrahydro-5-methyl-5-nitro-2-oxo-2*H*-pyran-3-ylcarbamate (5o)**
Yield: 71%; *trans*-**5o** and *cis*-**5o** were isolated by flash chromatography.

***trans*-5o (major)**
^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 5.45 (d, *J* = 4.4 Hz, 1 H), 4.87 (dd, *J* = 12.4, 1.6 Hz, 1 H), 4.50 (d, *J* = 12.0 Hz, 1 H), 4.32 (dt, *J* = 11.6, 6.8 Hz, 1 H), 3.25 (dd, *J* = 14.4, 7.2 Hz, 1 H), 2.18 (t, *J* = 12.8 Hz, 1 H), 1.72 (s, 3 H), 1.45 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 169.5, 155.3, 84.3, 81.0, 71.7, 47.4, 37.0, 28.3, 24.7.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{11}H_{18}N_2NaO_6$: 297.10571; found: 297.10579.

***cis*-5o (minor)**
^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 5.57 (d, *J* = 6.4 Hz, 1 H), 4.95 (d, *J* = 13.2 Hz, 1 H), 4.50 (dt, *J* = 10.4, 8.0 Hz, 1 H), 4.31 (d, *J* = 13.2 Hz, 1 H), 2.86–2.73 (m, 2 H), 1.75 (s, 3 H), 1.46 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 170.4, 155.2, 85.8, 80.9, 70.8, 46.9, 36.4, 28.3, 23.9.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{11}H_{18}N_2NaO_6$: 297.10571; found: 297.10576.

Transformations of 5o; Typical Procedure
To a solution of *trans*-**5o** (0.3 mmol, 82 mg) in MeOH (5 mL), was added Pd/C (20 mg, 10% w/w). The resulting suspension was stirred under H_2 (1 atm) at r.t. overnight. When the reaction was complete, the reaction mixture was filtered through a pad of Celite and washed with MeOH. The filtrate was concentrated under reduced pressure, and the residue was purified by column chromatography (CH_2Cl_2 then CH_2Cl_2–MeOH, 100:1) to afford δ-lactone *trans*-**6**. A solution of *trans*-**6** in MeOH (10 mL) was stirred overnight at 40 °C and concentrated in vacuo to give the corresponding γ-lactam *cis*-**7**. Similar transformation was also applied to *cis*-**5o**, which provided *cis*-**6** and *trans*-**7**.

(*trans*)-*tert*-Butyl 5-Aminotetrahydro-5-methyl-2-oxo-2*H*-pyran-3-ylcarbamate (*trans*-6)
Yield: 86%.

^{1}H NMR (400 MHz, CD_3OD, 25 °C, TMS): δ = 4.35 (t, *J* = 8.0 Hz, 1 H), 3.70 (d, *J* = 11.2 Hz, 1 H), 3.32 (d, *J* = 11.2 Hz, 1 H), 2.21 (dd, *J* = 12.8, 10.0 Hz, 1 H), 1.99 (dd, *J* = 12.8, 6.4 Hz, 1 H), 1.46 (s, 9 H), 1.22 (s, 3 H).

^{13}C NMR (100 MHz, CD_3OD, 25 °C, TMS): δ = 168.4, 156.4, 79.3, 63.8, 62.6, 34.0, 27.3, 18.8.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{11}H_{20}N_2NaO_4$: 267.13153; found: 267.13158.

(*cis*)-*tert*-Butyl 5-Aminotetrahydro-5-methyl-2-oxo-2*H*-pyran-3-ylcarbamate (*cis*-6)
Yield: 82%.

^{1}H NMR (400 MHz, CD_3OD, 25 °C, TMS): δ = 4.37 (t, *J* = 9.2 Hz, 1 H), 3.68 (d, *J* = 11.6 Hz, 1 H), 3.32 (d, *J* = 11.6 Hz, 1 H), 2.55 (dd, *J* = 12.4, 10.0 Hz, 1 H), 1.72 (dd, *J* = 11.6, 10.0 Hz, 1 H), 1.44 (s, 9 H), 1.23 (s, 3 H).

^{13}C NMR (100 MHz, CD_3OD, 25 °C, TMS): δ = 169.0, 156.4, 79.1, 64.3, 62.7, 35.7, 27.3, 20.1.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{11}H_{20}N_2NaO_4$: 267.13153; found: 267.13147.

(*cis*)-*tert*-Butyl 5-(Hydroxymethyl)-5-methyl-2-oxopyrrolidin-3-ylcarbamate (*cis*-7)
Yield: 95%.

^{1}H NMR (400 MHz, DMSO-d_6, 25 °C, TMS): δ = 9.33 (s, 1 H), 6.85 (d, *J* = 9.2 Hz, 1 H), 4.85 (t, *J* = 5.6 Hz, 1 H), 4.11 (q, *J* = 8.8 Hz, 1 H), 3.41 (dd, *J* = 10.8, 4.8 Hz, 1 H), 3.20 (dd, *J* = 10.8, 5.6 Hz, 1 H), 2.00 (dd, *J* = 12.8, 9.6 Hz, 1 H), 1.85 (dd, *J* = 12.8, 8.0 Hz, 1 H), 1.39 (s, 9 H), 1.07 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6, 25 °C, TMS): δ = 167.3, 155.6, 78.6, 64.9, 61.6, 47.7, 34.2, 28.7, 19.9.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{11}H_{20}N_2NaO_4$: 267.13153; found: 267.13160.

(*trans*)-*tert*-Butyl 5-(Hydroxymethyl)-5-methyl-2-oxopyrrolidin-3-ylcarbamate (*trans*-7)
Yield: 96%.

^{1}H NMR (400 MHz, DMSO-d_6, 25 °C, TMS): δ = 9.34 (s, 1 H), 7.07 (d, *J* = 8.8 Hz, 1 H), 4.97 (t, *J* = 4.8 Hz, 1 H), 4.17 (t, *J* = 9.6 Hz, 1 H), 3.43 (dd, *J* = 10.8, 5.6 Hz, 1 H), 3.15 (dd, *J* = 10.8, 5.6 Hz, 1 H), 2.34 (dd, *J* = 12.0, 9.6 Hz, 1 H), 1.58 (dd, *J* = 12.0, 10.0 Hz, 1 H), 1.38 (s, 9 H), 1.07 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6, 25 °C, TMS): δ = 167.8, 155.6, 78.3, 64.4, 61.6, 48.4, 35.7, 28.7, 22.0.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{11}H_{20}N_2NaO_4$: 267.13153; found: 267.13155.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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