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The *homo*-PADAM Protocol: Stereoselective and Operationally Simple Synthesis of α-Oxo- or α-Hydroxy-γ-acylaminoamides and Chromanes**

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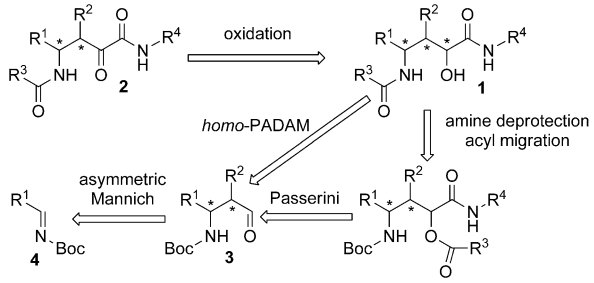
Abstract: A straightforward and fully stereoselective synthesis of a new class of peptidomimetics, that is α-oxo-γ-acylaminoamides, was achieved starting from various benzaldehydes by a sequence of 1) an asymmetric organocatalytic Mannich reaction, 2) a Passerini multicomponent reaction, 3) an amine deprotection–acyl migration protocol, and 4) a final oxidation. The whole sequence can be performed without purification of the intermediates and represents the first example of a *homo*-Passerini–amine deprotection–acyl migration (PADAM) strategy. Highly stereoselective reduction of the α-oxo-γ-acylaminoamides afforded α-hydroxy-γ-acylaminoamides as well. In some cases both diastereomers were obtained by simply changing the reducing agent. Finally, starting from protected salicylaldehyde, the same sequence, followed by a Mitsunobu cyclization, afforded highly substituted chromanes.

Keywords: asymmetric synthesis · ketones · multicomponent reactions · organocatalysis · peptidomimetics

Introduction

In 2000, inspired by the work on the Ugi reaction of α-amino aldehydes carried out by Hulme and co-workers,[1] we introduced the PADAM protocol (Passerini–amine deprotection–acyl migration)[2] as a step- and atom-economical approach to the synthesis of α-hydroxy- or α-oxo-β-acylaminoamides. The PADAM procedure starts from protected enantiomerically pure α-amino aldehydes and represents the most efficient access to these peptidomimetics, which are very important protease inhibitors.[3] An attractive extension of this methodology would be the "*homo*-PADAM" protocol, involving instead the use of β-aminoaldehydes, and leading to a different, poorly explored,[4] class of peptidomimetics, represented by α-hydroxy- or α-oxo-γ-acylaminoamides of the general formula **1** and **2** (see Scheme 1). However, although α-aminoaldehydes can be easily prepared from a huge variety of commercially available enantiomerically pure α-amino acids, β-amino acids are less accessible and their conversion into aldehydes **3** could be troublesome, especially when an α stereogenic center is present.[5]

In 2007, List and co-workers reported that proline is able to efficiently catalyze the asymmetric Mannich reaction of *N*-Boc imines (Boc = *tert*-butyloxycarbonyl) to afford aldehydes **3**.[6] Since then this methodology has been widely applied[7] but, to our knowledge, the aldehyde functional group of the Mannich adducts has never been directly exploited in C–C bond formation reactions. In all cases this group was either reduced to a primary alcohol[7a,b] or oxidized to a carboxylic acid[6a,7a–d] or to a ketone[7g] in the early steps of the synthesis, probably because of the stereochemical instability of adducts **3**.[5] Despite this instability, we reasoned that the mild, neutral conditions of the Passerini reaction would be ideal for an epimerization-free addition to these aldehydes. The combination of an organocatalytic asymmetric process with an ensuing multicomponent reaction has been seldom exploited so far[8] but we anticipate a great utility in it. Our retrosynthetic approach is depicted in Scheme 1 and entails the sequence of an asymmetric Mannich reaction followed by the *homo*-PADAM protocol and by a final oxidation.



Scheme 1. Retrosynthetic approach.

Results and Discussion

In an exploratory study, ureidosulfone **5a** (R^1 = Ph) was converted by using cesium carbonate,[9] into Boc-imine **4a**, which was reacted, under the conditions of List et al.,[6b]

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[**] PADAM = Passerini–amine deprotection–acyl migration.

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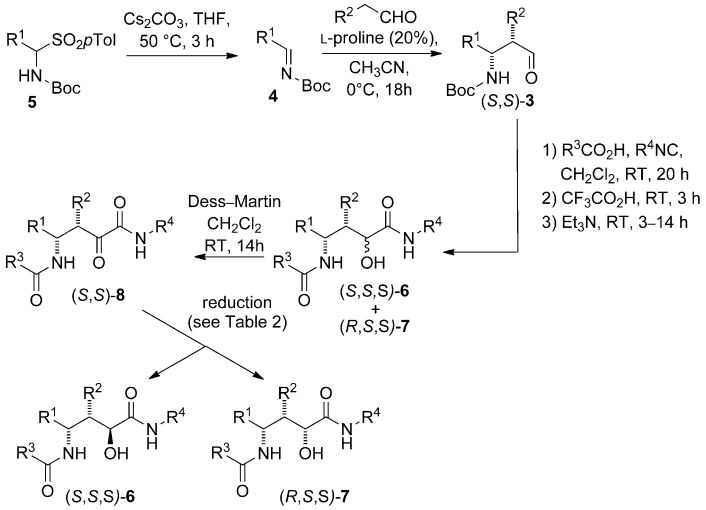


Scheme 2. Synthesis of peptidomimetics **6**–**8**. *p*Tol = *para*-methylphenyl.

with propanal to afford (*S*,*S*)-**3a**, with high diastereo- and enantioselectivity (Scheme 2). The crude aldehyde **3a** was directly subjected to a one-pot sequence involving: 1) the Passerini reaction[10] with cyclohexyl isocyanide and methoxyacetic acid, 2) treatment with trifluoroacetic acid (TFA) to remove the *tert*-butyl urethane, 3) treatment with Et_3N to promote *N*,*O* acyl migration[11] affording a diastereomeric mixture of alcohols **6** and **7**, and d) a Dess–Martin oxidation. The diastereomerically pure ketone (*S*,*S*)-**8a** was obtained in an excellent overall yield of 68% from ureidosulfone **5a** (six steps).

^{1}H NMR analysis of crude **8a** before chromatography showed a *syn*/*anti* ratio of 96:4, corresponding to the ratio determined at the level of aldehyde **3a**. The minor *anti* isomer was completely removed by chromatography.[12] The purified **8a** had an enantiomeric excess (*ee*) of 99%. It is worth noting that the whole sequence from **5a** to **8a** required minimal operations: 1) filtration and evaporation of the filtrate after generation of the Boc-imine,[13] 2) an aqueous washing after the Mannich reaction, 3) a series of three evaporations during the one-pot sequence from **3a** to **8a**. Only a single chromatography was needed at the end of the sequence. The reaction conditions are simple (0–50 °C), do not require strict exclusion of moisture or oxygen, and do not use any metal. The overall protocol generates four new bonds, allows the introduction of four diversity points, and is fully stereoselective.

The scope of the methodology is displayed in Table 1. All four diversity points were varied. When protected amino acids were employed, extended peptidomimetics were obtained. Analogous results were achieved when α-isocyano esters were used as the isonitrile moiety. The enantioselectivity and the diastereoselectivity are excellent in all studied cases and both enantiomers can be accessed by using L- or D-proline. The overall yields were good to excellent, with few exceptions; the most critical step appears to be the Mannich reaction, which was slightly less efficient for the *N*-Boc imine of 3-bromobenzaldehyde.

Obviously, the sequence can be terminated at the level the of α-hydroxy-γ-acylamino amides **6** and **7** as well. However, due to the typical poor diastereoselectivity of the Passerini reaction,[14] an approximately 1:1 mixture of the epimers **6** and **7** was obtained. Even if the epimers can be separated in all cases by chromatography, the use of a stereoselective protocol in the synthesis of these peptidomimetics would be more elegant. For this reason we submitted the ketones **8a 8b**, **8j**, and **8m** to reduction with various borohydrides. The most selective one turned out to be L-selectride (lithium tri-*sec*-butyl(hydrido)borate) (Table 2, entries 1–4). Surprisingly, the prevailing isomer depended on the nature of the R^2 group. With R^2 = Me (Table 2, entries 1 and 4), **6**

Table 1. Scope of the Mannich–*homo*-PADAM–oxidation to give α-oxo-γ-acylaminoamides.[a]

Entry	Final product	R^1	R^2	R^3	R^4	Proline used[b]	Yield [%][c]	*syn*/*anti*[d]	*ee* [%][e]
1	**8a**	Ph	Me	$MeOCH_2$	cyHex[f]	L, D	68	96:4	>99
2	**8b**	Ph	*i*Pr	$MeOCH_2$	cyHex	L, D	64	98:2	96
3[g]	**8c**	Ph	*i*Pr	Ph	cyHex	L	59	96:4	96
4	**8d**	Ph	*i*Pr	$ZNHCH_2$[h]	Bn[i]	L	66	98:2	96
5[g]	**8e**	4-$MeOC_6H_4$	*i*Pr	L-ZNHCH(*i*Pr)	Me	L, D	58	98:2	96[j]
6[g]	**8f**	4-$MeOC_6H_4$	*i*Pr	Et	4-$BnOC_6H_4CH_2CH_2$	L	46	96:4	96
7	**8g**	3-BrC_6H_4	*i*Pr	5-Cl-2-thienyl	*i*Pr	L, D	15	99:1	99
8	**8h**	3-BrC_6H_4	*i*Pr	L-ZNHCH(Bn)	2,6-$Me_2C_6H_4$	L	38	86:14	99[j]
9	**8i**	3-BrC_6H_4	*i*Pr	*n*Pr-C≡C	4-$(BnO_2C)C_6H_4$	L	18	88:12	99
10[g]	**8j**	4-MeC_6H_4	*i*Pr	Et	*n*Bu	L, D	57	99:1	92
11[g]	**8k**	4-MeC_6H_4	*i*Pr	Ph	EtO_2C-CH_2	L	35	99:1	92
12	**8l**	2-$BnOC_6H_4$	*i*Pr	$PhCH_2$	*n*Pent	L, D	58	89:11	96
13	**8m**	2-$BnOC_6H_4$	Me	$MeOCH_2$	cyHex	L, D	35	93:7	99[k]

[a] For the reaction conditions, see the typical procedure given in the Experimental Section. [b] With L-proline, (*S*,*S*)-**8** was obtained; with D-proline, (*R*,*R*)-**8** was obtained. [c] Yield of pure *syn*-**8** after chromatography (calculated from the starting ureidosulfone **5**). The yields obtained from L- or D-proline were quite similar. Only the best one is reported. [d] Determined by ^{1}H NMR spectroscopic analysis of crude **8** before chromatography [e] Determined by HPLC on a chiral stationary phase. The *ee* obtained from L- or D-proline were identical or very close. Only the best one is reported. [f] cyHex = cyclo-hexyl. [g] In this case the reaction time for the *N*,*O*-acyl migration step was 14 h. [h] Z = benzyloxycarbonyl. [i] Bn = benzyl. [j] In this case it is actually a diastereomeric excess (*de*). [k] Determined through the method using the Mosher's ester, after reduction to **6m**.

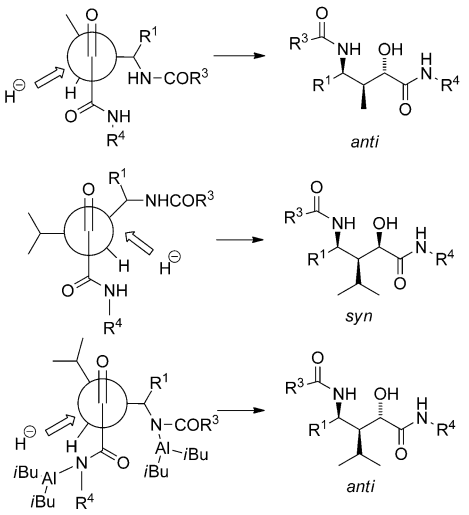
Table 2. Stereoselective reduction of ketones **8**.

Entry	Ketone	R^2	Reducing agent[a]	Yield [%][b]	**6**/**7**[c]
1	**8a**	Me	L-selectride	88	89:11
2	**8b**	*i*Pr	L-selectride	86	6:94
3	**8j**	*i*Pr	L-selectride	90	<1:99
4	**8m**	Me	L-selectride	77	96:4
5	**8a**	Me	$MgBr_2$–DIBALH	94	93:7
6	*ent*-**8b**	*i*Pr	$MgBr_2$–DIBALH	98	95:5
7	**8j**	*i*Pr	$MgBr_2$–DIBALH	99	93:7
8	**8m**	Me	$MgBr_2$–DIBALH	90	83:17

[a] Reductions with L-selectride were carried out in THF at −78 °C; reductions with $MgBr_2$–diisobuylaluminium hydride (DIBALH) were carried out in CH_2Cl_2/Et_2O (1:2) at −45 °C. [b] Overall yield of both isolated diastereomers after chromatography. [c] Determined by ^{1}H NMR spectroscopic analysis of crude **6** and **7** before chromatography.

was obtained,[4b] whereas the other epimer **7** was the major one when $R^2 = i$Pr (Table 2, entries 2 and 3). In all cases the diastereoselectivity was excellent. The absolute configuration of the newly formed stereogenic center, and hence the relative configurations of **6** and **7** was determined by the Mosher's method[15] as detailed in the Supporting Information.

Both results can be explained by alternative Felkin–Anh models where either the ArCH(NHCOR^3) (Ar = aryl) or the *i*Pr groups play the role of the "large" group (Scheme 3).



Scheme 3. Models for the rationalization of the diastereoselective reduction of **8**.

In an attempt to find a stereoselective access to the minor products of the reduction with L-selectride, we screened a series of alternative reducing reagents. We were pleased to find that, when $R^2 = i$Pr (Table 2, entries 5 and 6), the $MgBr_2$–DIBALH system,[16] leads to alcohol **6** with excellent stereoselection, making this method fully complementary with the reduction by L-selectride. Usually, the combination of DIBALH with Lewis acids is expected to promote a chelation-controlled reaction.[16,17] In our case, if chelation control occurred, product **7**, not **6** should be obtained. So the explanation for this puzzling reversed stereoselectivity must be different. The observation of an intense gas evolution after addition of DIBALH and the fact that more than three equivalents of DIBALH are needed in order to achieve full conversion, suggest that DIBALH, in the presence of $MgBr_2$, gives an acid–base reaction with the two secondary amides. Interestingly, when using DIBALH alone, that is, without $MgBr_2$, no gas evolution is observed, and 1.5 equivalents of the reagent are enough to give full conversion even at −78 °C, although with poor stereoselection (**6j**/**7j** = 60:40). Therefore, $MgBr_2$ is essential in order to promote the acid–base reaction of DIBALH with the two amides to give a covalent adduct that renders the main chain more encumbered than the isopropyl group (Scheme 3, bottom).

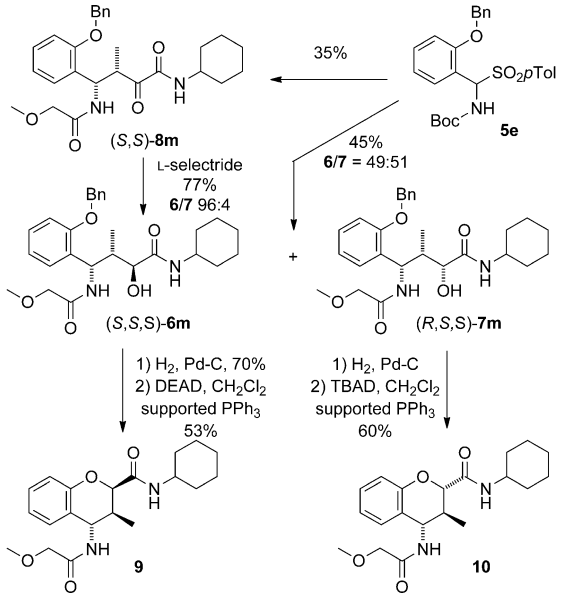
Thanks to this stereodivergent reduction, four of the eight possible stereoisomers of the alcohols **6b** and **6j** as well as **7b** and **7j** can be obtained with high stereochemical control. A full exploration of the stereochemical diversity, obtaining all eight possible stereoisomers, seems feasible, by implementing *anti*-selective Mannich reactions.[7b,c,e,f] Studies towards this goal are in progress.

On the other hand, when R^2 = Me the $MgBr_2$–DIBALH system again affords alcohol **6** as the major product (Table 2, entries 5 and 8), and thus, in this case the methodology is not complementary to L-selectride. This outcome confirms the model proposed in Scheme 3.

When an additional functional group is placed into one of the diversity points, the alcoholic moiety in **6** and **7** can be exploited for a further cyclization step,[18] opening the way to various drug-like heterocyclic structures. As a first example, we report here the synthesis of dihydrobenzopyrans (chromans). These are "privileged structures", quite often employed in medicinal chemistry.[19,20]

The two epimeric alcohols **6m** and **7m** were obtained in 45% overall yield as a nearly 1:1 mixture from ureidosulfone **5e**. In this case, the Mannich–*homo*-PADAM sequence was stopped before the final oxidation, and the epimers were separated by chromatography (Scheme 4). Alcohol **6m** could also be obtained stereoselectively by reduction with L-selectride of ketone (*S*,*S*)-**8m**. These alcohols were independently hydrogenolized and then cyclized under Mitsunobu conditions to the chromanes **9** and **10**. Their relative configuration was established by ^{1}H NMR spectroscopy, on the basis of the vicinal coupling constants (see the Supporting Information for details). The cyclization was therefore demonstrated to be completely stereospecific (proceeding with inversion of the configuration).

The enantiomers of **9** and **10** have also been prepared by simply using D-proline instead of L-proline as a catalyst in the Mannich reaction. Thus, four of the eight possible stereoisomers of these chromanes have been synthesized.



Scheme 4. Cyclization of **6m** and **7m** to chromanes **9** and **10**. DEAD = diethyl azodicarboxylate. TBAD = di-*tert*-butyl azodicarboxylate.

Conclusion

In conclusion, we have developed a straightforward and efficient entry to α-hydroxy-γ-acylaminoamides, α-oxo-γ-acylaminoamides, and dihydrobenzopyrans (chromanes) by coupling an asymmetric organocatalytic Mannich reaction with a Passerini multicomponent reaction (MCR) and a series of post-MCR transformations. Although these complex sequences involve six to seven steps, most of them may be carried out in a one-pot manner and the final products are obtained in pure form performing just one or two chromatographic purifications. This is, to our knowledge, the first application of a *homo*-PADAM protocol. Four diversity inputs may be varied at will, four to five new bonds are formed, up to three stereogenic centers are fully controlled, and four different stereoisomers may be independently obtained. Therefore, we think that this methodology can find wide application in diversity-oriented synthesis and in medicinal chemistry.

Experimental Section

General conditions: NMR spectra were taken at room temperature in $CDCl_3$ at 300 MHz (^1H) and 75 MHz (^{13}C) by using as internal standards: trimethylsilane (TMS) for ^1H NMR spectroscopy and the central peak of $CDCl_3$ (at $\delta = 77.02$ ppm) for ^{13}C NMR spectroscopy. Chemical shifts are reported in ppm (δ scale), coupling constants are reported in Hertz. Peak assignments were also made with the aid of gCOSY gHSQC, and gHMBC experiments. In an ABX system, the proton A is considered upfield and the B proton is considered downfield. HRMS was performed by employing an ESI+ ionization method. IR spectra were recorded as $CHCl_3$ solutions or directly on solid, oil, or foamy samples, with the ATR (attenuated total reflectance) technique. TLC analyses were carried out on silica gel plates and viewed at UV ($\lambda = 254$ nm) and developed with Hanessian stain (dipping into a solution of $(NH_4)_4MoO_4{\cdot}4H_2O$ (21 g) and $Ce(SO_4)_2{\cdot}4H_2O$ (1 g) in H_2SO_4 (31 mL) and H_2O (469 mL) and warming) or, only to detect free amines after Boc deprotection, with ninhydrin (ninhydrin (900 mg) in *n*BuOH (300 mL) and AcOH (9 mL, Ac = acyl), followed by warming). R_f values were measured after an elution of 7–9 cm. In $[\alpha]_D$ the units are: $^\circ cm^3 g^{-1} dm^{-1}$ for $[\alpha]$ and $100\,g\,cm^{-3}$ for *c*. HPLC analyses were performed (unless otherwise stated) on a Daicel Chiral Pak AD 250×4.6 mm column, at 25–28 °C with a flow of 1 mL min^{-1} (UV detection at $\lambda = 220$ nm). Column chromatography was done with the "flash" methodology by using 220–400 mesh silica. Petroleum ether (40–60 °C) is abbreviated as PE. In an extractive workup, aqueous solutions were always re-extracted three times with the appropriate organic solvent. Organic extracts were always dried over Na_2SO_4 and filtered, before evaporation of the solvent under reduced pressure. All reactions employing dry solvents were carried out under a nitrogen atmosphere.

Ureidosulfones **5a** (R^1 = Ph),[6b,21] **5b** (R^1 = *p*-MeOC$_6$H$_4$),[22] and **5d** (R^1 = *p*-tolyl)[22a] were already previously reported. The preparation and characterization of **5c** and **5e** is reported in the Supporting Information.

Typical procedure for the synthesis of ketones 8

*(3S,4S)-N-Cyclohexyl-4-(2-methoxyacetamido)-3-methyl-2-oxo-4-phenylbutanamide (**8a**)*: Ureidosulfone **5a** (R^1 = Ph) (300 mg, 0.83 mmol) was dissolved in dry THF (9 mL), treated with Cs_2CO_3 (540 mg, 1.66 mmol), and heated at 50 °C for 3 h. After cooling, the white suspension was filtered through a celite cake and the residue was washed with THF. The filtrate was evaporated, dissolved in dry CH_3CN (7.5 mL), cooled to 0 °C, and treated with L-proline (19 mg, 0.166 mmol) and with freshly distilled propanal (120 μL, 1.67 mmol). The mixture was stirred at 0 °C for 18 H; and then quenched with water (5 mL). The mixture was extracted with CH_2Cl_2 (3×10 mL) and the organic extract was dried (Na_2SO_4), evaporated to dryness, and dissolved in CH_2Cl_2 (3.5 mL). Methoxyacetic acid (83 μL, 1.08 mmol) and cyclohexyl isocyanide (135 μL, 1.08 mmol) were added and the solution was stirred for 20 h at room temperature. Trifluoroacetic acid (0.85 mL) was added and the solution was stirred for 3 h at room temperature and then evaporated to dryness (with the aid of *n*-heptane for azeotropical removal of all TFA). The residue was dissolved in CH_2Cl_2 (3.5 mL) and treated with Et_3N (480 μL). After 3 h the solution was evaporated to dryness, the residue was dissolved in dry CH_2Cl_2 (9 mL) and treated with Dess–Martin periodinane (1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3-(1*H*)-one) (385 mg, 0.91 mmol). The reaction mixture was stirred overnight at room temperature, and then the reaction was quenched with solid $Na_2S_2O_3$ (288 mg, 1.82 mmol) and saturated aqueous $NaHCO_3$ (5 mL). After stirring for 10 min, the mixture was extracted with AcOEt (3×15 mL), dried (Na_2SO_4), evaporated, and purified by chromatography through 220–400 mesh silica gel (PE/AcOEt 50:50) to afford pure **8a** as a foamy white solid (202 mg, 68%). R_f = 0.45 (PE/AcOEt 1:1); $[\alpha]_D = +19.8$ ($c = 2$, $CHCl_3$); HPLC: hexane/*i*PrOH 90:10. R_t = 15.38 min. (R_t of *ent*-**8a**: 14.03); *ee* > 99%; ^1H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 7.35$–7.22 (m, 5H), 7.17 (d, $^3J(H,H) = 9.3$ Hz, 1H; $H_2C(C{=}O)$-N*H*), 6.72 (d, $^3J(H,H) = 8.1$ Hz, 1H; NH-cyHex), 5.61 (dd, $^3J(H,H) = 9.3$, 5.7 Hz, 1H; H-4), 4.13 (dq, $^3J(H,H) = 6.9$ (q), 5.7 Hz (d), 1H; H-3), 3.92, 3.87 (AB syst., $^2J(H,H) = 15.1$ Hz, 2H; C*H*$_2$OMe), 3.79–3.65 (m, 1H; C*H*NH cyHex), 3.44 (s, 3H; OCH_3), 1.95–1.85 (m, 2H), 1.77–1.50 (m, 2H), 1.45–1.08 (m, 5H), 1.12 (d, $^3J(H,H) = 6.9$ Hz, 3H; CH_3), 0.95–0.82 ppm (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 200.1$, 169.6, 159.5 (C=O), 139.8 (quat.), 129.0 (2×), 128.0, 126.9 (aromatic CH), 71.8 (*C*H$_2$OMe), 59.2 (OCH_3), 52.8 (C-4), 48.4 (CHNH cyHex), 44.5 (C-3), 32.3, 32.2, 25.0, 24.4, 24.3 (CH_2 cyHex), 10.7 ppm (*C*H$_3$CH); IR (ATR): $\tilde{\nu} = 3326$, 3287, 2991, 2928, 2854, 1673, 1651, 1526, 1449, 1296, 1193, 1113, 1024, 762, 695 cm^{-1}; HRMS (ESI+): *m*/*z* calcd for $C_{20}H_{29}N_2O_4$: 361.2127 $[M+H]^+$; found: 361.2127.

Typical procedure for the reduction of ketones 8 to alcohols 6 or 7 with L-selectride

*(2R,3S,4S)-N-Cyclohexyl-3-isopropyl-2-hydroxy-4-(2-methoxyacetamido)-4-phenylbutanamide **7b***: A solution of ketone **8b** (124 mg, 0.319 mmol) in dry THF (1 mL) was cooled to −78 °C and treated with a solution of L-selectride (lithium tri(*sec*-butoxy)borohydride) (1.0 M, 960 μL, 0.960 mmol). After 3 h, the reaction was quenched with a saturated aqueous solution of NH_4Cl (5 mL) and extracted with AcOEt. Evaporation

gave a pure solid, corresponding to a 94:6 mixture of **7b** and **6b**. Chromatographic purification gave the pure diastereomer **7b** as a white solid (101 mg, 83%). Overall yield: 88%. M.p. 238.6–240.0°C; R_f = 0.50 (PE/AcOEt 4:7 + 0.5% MeOH); $[\alpha]_D = -10.8$ ($c = 2$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25°C, TMS): δ = 7.40–7.22 (m, 5H), 7.13 (d, ^3J(H,H) = 9.1 Hz, 1H; H_2C(C=O)-NH), 6.99 (d, ^3J(H,H) = 8.1 Hz, 1H; NH-cyHex), 5.36 (dd, ^3J(H,H) = 7.3, 9.1 Hz, 1H; H-4), 3.95 (dd, ^3J(H,H) = 3.9, 5.7 Hz, 1H; H-2), 3.92, 3.87 (AB syst., ^2J(H,H) = 15.3 Hz, 2H; CH_2OMe), 3.82–3.66 (m, 1H; C*H*NH cyHex), 3.44 (s, 3H; OCH_3), 3.07 (d, ^3J(H,H) = 5.7 Hz, 1H; OH), 2.51 (dt, ^3J(H,H) = 3.9 (t), 7.3 Hz (d), 1H; H-3), 1.92 (d of heptuplet, ^3J(H,H) = 5.1 (d), 6.9 Hz (hept), 1H; C*H*(CH_3)$_2$), 1.93–1.75 (m, 2H), 1.75–1.52 (m, 2H), 1.43–1.00 (m, 6H), 1.07 (d, ^3J(H,H) = 6.9 Hz, 3H; CH_3), 1.06 ppm (d, ^3J(H,H) = 6.9 Hz, 3H; CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C, TMS): δ = 172.8, 169.7 (C=O), 141.5 (quat.), 129.2 (2×), 127.8, 127.2 (2×) (aromatic CH), 73.0 (C-2), 71.8 (*C*H_2OMe), 59.2 (OCH_3), 53.1 (C-4), 50.4 (C-3), 47.8 (CHNH cyHex), 32.6, 32.5, 25.2, 24.5, 24.4 (CH_2 cyHex), 26.7 (*C*H(CH_3)$_2$), 21.6, 21.2 ppm (*C*H_3CH); IR (ATR): $\tilde{\nu}$ = 3390, 3216, 3060, 2930, 2856, 1666, 1647, 1520, 1451, 1259, 1245, 1196, 1118, 1011, 765, 702, 631, 557 cm^{-1}; HRMS (ESI+): *m*/*z* calcd for $C_{22}H_{35}N_2O_4$ [*M*+H]$^+$: 391.2597; found: 391.2594.

Typical procedure for the reduction of ketones 8 to alcohols 6 by using $MgBr_2$–DIBALH

(2S,3S,4S)-N-*Butyl-2-hydroxy-3-isopropyl-4-(4-methylphenyl)-4-(propanamido)butanamide* ***6j***: Ketone **8j** (72 mg, 0.2 mmol) was dissolved in dry CH_2Cl_2 (4 mL) and diluted with dry diethyl ether (8 mL). $MgBr_2$·Et_2O (310 mg, 1.2 mmol) was added and the resulting suspension was stirred at room temperature for 30 min. Complete dissolution was observed. The temperature was lowered to −45°C and diisobutylaluminum hydride (DIBALH) (1.0 M in toluene, 1.2 mL, 1.2 mmol) was added. Intense gas evolution was observed. After stirring for 2 h, the reaction was quenched by adding a saturated aqueous solution of $NaHCO_3$ (10 mL) and a 20% solution of sodium potassium tartrate (10 mL). Extraction with AcOEt and evaporation of the solvent afforded the crude 93:7 mixture of alcohols **6j** and **7j** as a solid, which was rather pure as confirmed by ^{1}H NMR spectroscopy. Chromatography (PE/AcOEt 30:70 + 0.5% MeOH) afforded the pure major diastereomer **6j** (66 mg, 92%) as a white solid. Overall yield: 99%. M.p.: 241.1–242.7°C; R_f = 0.45 (PE/AcOEt 37 + 0.5% MeOH); $[\alpha]_D = -72.4$ (c = 0.25, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25°C, TMS): δ = 7.22, 7.13 (AB syst., ^3J(H,H) = 8.0 Hz, 4H), 6.80 (t, ^3J(H,H) = 8.6 Hz, 1H; H_2CN*H*), 6.10 (d, ^3J(H,H) = 8.7 Hz, 1H; N*H*CH), 5.00 (dd, ^3J(H,H) = 4.2, 8.7 Hz, 1H; H-4), 4.24 (dd, ^3J(H,H) = 2.2, 9.0 Hz, 1H; H-2), 4.16 (d, ^3J(H,H) = 9.0 Hz, 1H; OH), 3.21 (dq, ^3J(H,H) = 7.0 (q), ^2J(H,H) = 14.0 Hz (d), 1H; NHC*H*H), 3.04 (dq, ^3J-(H,H) = 7.0 (q), ^2J(H,H) = 14.0 Hz (d), 1H; NHC*H*H), 2.65 (ddd, ^3J-(H,H) = 2.2, 4.2, 7.8 Hz, 1H; H-3), 2.31 (s, 3H; $ArCH_3$), 2.30 (q, ^3J-(H,H) = 7.5 Hz, 2H; CH_2CO), 1.92 (octuplet, ^3J(H,H) = 6.9, 1H; C*H*-(CH_3)$_2$), 1.48–1.25 (m, 2H), 1.40–1.24 (m, 2H), 1.19 (t, ^3J(H,H) = 7.6 Hz, 2H; C*H*$_3$$CH_2CO$), 1.06 (d, ^3J(H,H) = 6.9 Hz, 3H; CH_3), 1.00 (d, ^3J-(H,H) = 6.6 Hz, 3H; CH_3), 0.89 ppm (t, ^3J(H,H) = 7.2 Hz, C*H*$_3$$CH_2CH_2$); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C, TMS): δ = 175.0, 174.6 (C=O), 138.9, 137.6 (quat.), 129.8, 127.0 (aromatic CH), 72.5 (C-2), 51.9, 51.0 (C-3, C-4), 38.8 (CH_2NH), 31.2 (*C*H_2CH$_2$NH), 29.6 (*C*H_2CO), 26.3 (*C*H(CH_3)$_2$), 22.9, 20.7, 19.9, 19.7, 13.4, 9.4 ppm (CH_3); IR (ATR): $\tilde{\nu}$ = 3292, 2959, 2874, 1642, 1533, 1465, 1371, 1261, 1238, 1214, 1096, 1070, 862, 837, 816, 755, 696 cm^{-1}; HRMS (ESI+): *m*/*z* calcd for $C_{21}H_{35}N_2O_3$ [*M*+H]$^+$: 363.2648; found: 363.2650.

(2S,3S,4S)- and (2R,3S,4S)-4-(2-Benzyloxyphenyl)-N-*cyclohexyl-2-hydroxy-4-(2-methoxyacetamido)-3-methylbutanamide (****6m****) and (****7m****)*: Compound **6m** could be obtained stereoselectively by reduction of **8m** with L-selectride (see the typical procedure described above for **8b**). However, because the reduction with both L-selectride and the $MgBr_2$–DIBALH system afforded **6m** as the major product, compound **7m** was prepared from ureidosulfone **5e** following the usual Mannich–PADAM procedure (see the synthesis of **8a**), stopping it before the final oxidation. The crude mixture, containing a 49:51 mixture of **6m** and **7m**, was purified by chromatography (PE/AcOEt 2:8 + 0.5% MeOH) to give pure **6m** (lower R_f) and **7m** (higher R_f) in 45% overall yield from **5e**.

Analytical data for ***6m***: White foam; R_f = 0.39 (PE/AcOEt 10:90); $[\alpha]_D = -53.5$ (c = 1, $CHCl_3$); *ee* = 99%, determined by transformation into Mosher's ester by using either the (*R*)- or (*S*)-acyl chloride. Reverse-phase HPLC analysis (column: Synergi Hydro RP 150×3 mm 4 μm; isocratic elution with H_2O/CH_3CN 35:65; flow: 0.5 mL min^{-1}; detection: λ = 220 nm) showed a diastereomeric ratio of 99.3:0.7 ((*S*) Mosher ester: R_t = 20.94; (*R*) Mosher ester: R_t = 22.43 min); ^{1}H NMR (300 MHz, $CDCl_3$, 25°C, TMS): δ = 8.19 (d, ^3J(H,H) = 9.3 Hz., 1H; MeOCH_2CON*H*), 7.55–7.35 (m, 5H), 7.30–7.19 (m, 2H), 7.04–6.95 (m, 2H), 6.61 (d, ^3J(H,H) = 8.1 Hz, 1H; NH cyHex), 5.53 (dd, ^3J(H,H) = 3.6, 9.3 Hz, 1H; H-4), 5.29 (d, ^3J(H,H) = 5.4 Hz, 1H; OH), 5.13 (s, 2H; CH_2Ph), 3.85 (s, 2H; CH_2OMe), 3.70 (dd, ^3J(H,H) = 5.4, 7.6 Hz., 1H; H-2), 3.78–3.60 (m, 1H; HNC*H* cyHex), 3.18 (s, 3H; OCH_3), 2.25 (dquint, ^3J(H,H) = 7.2 (q), 3.6 Hz (d), 1H; H-3), 1.96–1.75 (m, 2H), 1.75–1.53 (m, 3H), 1.42–1.00 (m, 5H), 1.02 ppm (d, ^3J(H,H) = 7.2 Hz, 3H; CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C, TMS): δ = 171.7, 170.7 (C=O), 156.2 (*C*-OBn), 136.2, 127.66 (quat.), 129.5, 128.70, 128.68 (2×), 128.2, 127.69 (2×), 121.4, 112.4 (aromatic CH), 74.3 (CHOH), 71.5 (CH_2O), 70.5 (*C*H_2Ph), 59.0 (OCH_3), 51.9 (C-4), 47.6 (cyHex CHNH), 44.6 (C-3), 33.1, 32.8, 25.5, 24.8 (2×) (cyHex CH), 11.5 ppm (CH_3); IR ($CHCl_3$): $\tilde{\nu}$ = 3677, 3613, 3408, 3008, 2971, 2931, 2853, 1655, 1519, 1476, 1421, 1382, 1332, 1198, 1114, 1042, 926 cm^{-1}; HRMS (ESI+): *m*/*z* calcd for $C_{27}H_{37}N_2O_5$ [*M*+H]$^+$: 469.2702; found: 469.2695.

Analytical data for ***7m***: White foam; R_f = 0.56 (PE/AcOEt 10:90); $[\alpha]_D = -14.8$ (c = 0.6, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25°C, TMS): δ = 7.65 (d, ^3J(H,H) = 9.6 Hz., 1H; MeOCH_2CON*H*), 7.55–7.32 (m, 5H), 7.28–7.19 (m, 2H), 7.02–6.90 (m, 2H), 6.81 (d, ^3J(H,H) = 8.7 Hz, 1H; cyHex NH), 5.26 (t, ^3J(H,H) = 9.1 Hz, 1H; H-4), 5.16 (s, 2H; CH_2Ph), 3.87, 3.84 (AB syst., ^2J(H,H) = 15.2 Hz, 2H; CH_2OMe), 3.83 (dd, ^3J(H,H) = 3.0, 4.8 Hz., 1H; H-2), 3.78–3.67 (m, 1H; HNC*H* cyHex), 3.63 (br s, 1H; OH), 3.28 (s, 3H; OCH_3), 2.62 (ddq, ^3J(H,H) = 6.9 (q), 3.0, 9.0 Hz (d), 1H; H-3), 1.96–1.75 (m, 2H), 1.75–1.53 (m, 3H), 1.42–1.00 (m, 5H), 0.89 ppm (d, ^3J(H,H) = 6.9 Hz, 3H; CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, 25°C, TMS): δ = 171.5, 169.5 (C=O), 156.0 (*C*-OBn), 136.2, 127.3 (quat.), 129.0, 128.9, 128.8 (2×), 128.3, 127.8 (2×), 121.7, 113.0 (aromatic CH), 73.0 (CHOH), 71.8 (CH_2O), 71.0 (*C*H_2Ph), 59.1 (OCH_3), 52.8 (C-4), 47.7 (cyHex CHNH), 41.8 (C-3), 33.1, 32.9, 25.5, 24.8 (2×) (cyHex CH), 9.6 ppm (CH_3); IR ($CHCl_3$): $\tilde{\nu}$ = 3668, 3602, 3401, 3034, 2984, 2931, 2852, 1649, 1601, 1508, 1450, 1374, 1350, 1313, 1287, 1247, 1111, 1009, 918 cm^{-1}; HRMS (ESI+): *m*/*z* calcd for $C_{27}H_{37}N_2O_5$ [*M*+H]$^+$: 469.2702; found: 469.2704.

(2*R*,3*S*,4*S*)-*N*-Cyclohexyl-4-(2-methoxyacetamido)-3-methylchroman-2-carboxamide (9): A solution of alcohol **6m** (185 mg, 0.395 mmol) in 96% EtOH (7 mL) was treated with 10% Pd/C (30 mg) and hydrogenated at room temperature under the slight overpressure of an inflated balloon. After stirring for 18 h, the suspension was filtered and evaporated. The crude product was purified by chromatography (PE/AcOEt 2:8 + 0.5% MeOH) to give analytically pure (2*S*,3*S*,4*S*)-*N*-cyclohexyl-2-hydroxy-4-(2-hydroxyphenyl)-4-(2-methoxyacetamido)-3-methylbutanamide (**11m**) as a white foam (106 mg, 70%). R_f = 0.48 (PE/AcOEt 10:90); $[\alpha]_D = -32.1$ (c = 1.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25°C, TMS): δ = 8.78 (s, 1H; phenolic OH), 7.56 (d, ^3J(H,H) = 8.6 Hz., 1H; MeOCH_2CON*H*), 7.16–7.08 (m, 2H), 6.92–6.83 (m, 2H), 6.82 (d, ^3J(H,H) = 8.4 Hz, 1H; cyHex NH), 5.23 (dd, ^3J(H,H) = 6.0, 8.6 Hz, 1H; H-4), 4.53 (d, ^3J(H,H) = 7.0 Hz, 1H; OH), 3.96, 3.86 (AB syst., ^2J(H,H) = 15.3 Hz., 2H; CH_2OMe), 3.88 (dd, ^3J(H,H) = 4.2, 7.0 Hz., 1H; C*H*OH), 3.81–3.68 (m, 1H; HNC*H* cyHex), 3.42 (s, 3H; OCH_3), 2.50 (ddq, ^3J(H,H) = 7.2 (q), 6.0, 4.2 Hz (d), 1H; H-3), 1.98–1.84 (m, 2H), 1.79–1.55 (m, 3H), 1.42–1.11 (m, 5H), 1.07 ppm (d, ^3J(H,H) = 7.2 Hz, 3H; CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C, TMS): δ = 172.5, 170.5 (C=O), 154.0 (C-OH), 128.9, 126.5, 120.5, 118.1 (aromatic CH), 127.1 (quat.), 73.7 (CHOH), 71.5 (CH_2O), 59.3 (OCH_3), 49.2 (C-4), 48.4 (cyHex CHNH), 42.6 (C-3), 32.9, 32.7, 25.4, 24.8 (2×) (cyHex CH), 11.5 ppm (CH_3); IR ($CHCl_3$): $\tilde{\nu}$ = 3401, 3250 (broad), 3008, 2931, 2853, 1648, 1510, 1451, 1382, 1350, 1249, 1216, 1151, 1094, 1009, 918 cm^{-1}; HRMS (ESI+): *m*/*z* calcd for $C_{20}H_{31}N_2O_5$ [*M*+H]$^+$: 379.2233; found: 379.227. A solution of alcohol **11m** (89 mg, 236 μmol) in dry CH_2Cl_2 (10 mL) was treated with polystyrene-supported PPh_3 (Polymer Laboratories, 150–300 μm, 1.52 mmol g^{-1}) (388 mg, 590 μmol) and with 40% diethyl azodicarboxylate (DEAD) in

toluene (163 μL, 356 μmol). The suspension was shaken in an orbit shaker for 20 h at room temperature. Filtration and chromatography (PE/AcOEt 20:80) afforded pure **9** as a white foam (64 mg, 75%). Compound **9** has also been obtained in 55% overall yield (from **6m**) without intermediate purification of alcohol **11m**. R_f=0.42 (PE/AcOEt 20:80); $[\alpha]_D$=−50.90 (c=1.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25°C, TMS): δ=7.30–7.23 (m, 2H; H-6 and H-8), 7.00 (dt, ^3J(H,H)=7.5 (t), 1.2 Hz (d), 1H; H-7), 6.96 (dd, ^3J(H,H)=8.4, 1.2 Hz, 1H; H-9), 6.83 (d, ^3J-(H,H)=7.7 Hz, 1H; C-4-NH), 6.61 (d, ^3J(H,H)=8.1 Hz, 1H; cyHex NH), 4.83 (dd, ^3J(H,H)=7.7, 1.5 Hz, 1H; H-4), 4.41 (d, ^3J(H,H)=2.4 Hz, 1H; H-2), 3.94, 3.91 (AB syst., ^2J(H,H)=15.0 Hz, 2H; CH_2OMe), 3.97–3.84 (m, 1H; cyHex CH), 3.35 (s, 3H; CH_3O), 2.69 (tq, ^3J(H,H)=7.2 Hz (q), 1.9 Hz (t), 1H; H-3), 2.04–1.85 (m, 2H), 1.82–1.56 (m, 4H), 1.50–1.10 (m, 4H), 0.88 ppm (d, ^3J(H,H)=7.2 Hz, 3H; CH_3CH); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C, TMS): δ=168.9, 168.6 (C=O), 153.0 (C-10), 131.9 (C-8), 130.0 (C-6), 122.5 (C-7), 120.2 (C-5), 117.2 (C-9), 74.2 (C-2), 71.8 (CH_2O), 58.9 (OCH_3), 48.7 (C-4), 47.8 (CHNH cyHex), 34.6 (C-3), 33.0, 32.7, 25.2, 24.6, 24.5 (cyHex CH_2), 10.8 ppm (CH_3CH); IR (ATR): $\tilde{\nu}$=3286, 2930, 2854, 1647, 1520, 1486, 1451, 1382, 1350, 1316, 1259, 1233, 1198, 1151, 1119, 1103, 1065, 1015, 990, 942, 891, 873, 798, 755, 730 cm^{-1}; HRMS (ESI+): m/z calcd for $C_{20}H_{29}N_2O_4$ $[M+H]^+$: 361.2127; found: 361.2130.

(2*S*,3*S*,4*S*)-*N*-Cyclohexyl-4-(2-methoxyacetamido)-3-methylchroman-2-carboxamide (10): Alcohol **7m** (225 μmol) was hydrogenated as described above to give crude (*2R,3S,4S*)-*N*-cyclohexyl-2-hydroxy-4-(2-hydroxyphenyl)-4-(2-methoxyacetamido)-3-methylbutanamide **(12m)**. This crude alcohol was not purified but directly taken up in dry CH_2Cl_2 (10 mL) and treated with polystyrene-supported PPh_3 (Polymer Laboratories, 150–300 μm, 1.52 mmol g^{-1}) (222 mg, 338 μmol) and with di-*tert*-butyl azodicarboxylate (TBAD) (78 mg, 338 μmol). The suspension was shaken in an orbit shaker for 20 h at room temperature. Filtration and chromatography (PE/AcOEt 20:80) afforded pure **10** as a white foam (49 mg, 60% overall yield from **7m**). R_f=0.50 (PE/AcOEt 20:80); $[\alpha]_D$=−68.5 (c=1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25°C, TMS): δ=7.32–7.19 (m, 2H; H-6 and H-8), 6.98 (dt, ^3J(H,H)=7.5 (t), 1.2 Hz (d), 1H; H-7), 6.93 (dd, ^3J(H,H)=8.4, 0.9 Hz, 1H; H-9), 6.85 (d, ^3J(H,H)=8.9 Hz, 1H; C-4-NH), 6.25 (d, ^3J(H,H)=8.1 Hz, 1H; cyHex NH), 4.95 (dd, ^3J-(H,H)=8.9, 5.0 Hz, 1H; H-4), 4.43 (d, ^3J(H,H)=5.1 Hz, 1H; H-2), 3.94 (s, 2H; CH_2OMe), 3.85–3.70 (m, 1H; cyHex CH), 3.38 (s, 3H; CH_3O), 2.61 (tq, ^3J(H,H)=7.2 (q), 5.1 Hz (t), 1H; H-3), 1.99–1.88 (m, 1H), 1.80–1.63 (m, 2H), 1.63–1.00 (m, 7H), 1.17 ppm (d, ^3J(H,H)=7.2 Hz, 3H; CH_3CH); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C, TMS): δ=169.4 (O=*C*–CH_2OMe), 168.7 (OC-NH cyHex), 151.8 (C-10), 130.3 (C-8), 129.4 (C-6), 122.1 (C-7), 121.9 (C-5), 116.5 (C-9), 78.8 (C-2), 71.9 (CH_2O), 59.1 (OCH_3), 47.9 (C-4), 47.7 (CHNH cyHex), 34.7 (C-3), 32.72, 32.69, 25.4, 24.6 (2×) (cyHex CH_2), 16.4 ppm (CH_3CH); IR ($CHCl_3$): $\tilde{\nu}$=3675, 3612, 3419, 3008, 2971, 2932, 2855, 1667, 1512, 1477, 1421, 1202, 1099, 1030, 927, 909, 874 cm^{-1}; HRMS (ESI+): m/z calcd for $C_{20}H_{29}N_2O_4$ $[M+H]^+$: 361.2127; found: 361.2130.

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[12] Although compounds **8** have some tendency to epimerize upon prologed standing in solution at room temperature, during chromatography, epimerization was negligible and the *syn*/*anti* ratio determined by weight corresponded to the one mesaured on the crude product.

[13] In order to further simplify the protocol, we attempted the one-pot, proline-catalyzed, Mannich reaction starting from ureidosulfone **5a**. However, under the reported conditions (in situ elimination with KF),[7d] we obtained a rather poor *syn*/*anti* ratio.

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