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Diastereoselective Michael addition of (*S*)-mandelic acid enolate to nitroalkenes. Enantioselective synthesis of α-hydroxy-α,β-diaryl-γ-lactams

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Abstract—The reaction of the lithium enolate of the (*S*,*S*)-*cis*-1,3-dioxolan-4-one derived from optically active (*S*)-mandelic acid and pivalaldehyde with several aromatic nitroalkenes in the presence of HMPA proceeds readily to give the corresponding Michael adducts in good yields and diastereoselectivities. Reduction of the nitro group with Zn/HCl/EtOH/H_2O with concomitant intramolecular aminolysis of the acetal moiety leads directly to enantiomerically pure α-hydroxy-α,β-diaryl-γ-lactams.

1. Introduction

Recently, we have reported a highly diastereoselective Michael reaction of the (*S*)-mandelic acid enolate with α,β-unsaturated carbonyl compounds and the transformation of the corresponding adducts into highly enantioenriched 2-substituted 1,4-dicarbonyl compounds.[1] In that synthesis the strategy employed to exert stereochemical control in the newly created stereogenic centers involved the use of (*S*)-mandelic acid (**1**) as source of chiral information through its previous conversion into (*S*,*S*)-*cis*-1,3-dioxolan-4-one **2** derived from pivalaldehyde (Seebach principle of self-regeneration of stereocenters).[2] We have now extended this methodology to diastereoselective Michael additions using aromatic nitroalkenes as acceptors. The reactions of **2** and related dioxolanones with nitroalkenes have been previously reported, although with low yields and diastereoselectivities.[3] The only described example of such a reaction with **2** has involved nitropropene as Michael acceptor, but no examples with aromatic nitroalkenes have been reported so far.

By reduction of the nitro group in the resulting adducts with concomitant intramolecular aminolysis of the acetal moiety in a further step we have prepared enantiomerically pure α-hydroxy-α,β-diaryl-γ-lactams. γ-Lactams and γ-amino acids are important pharmacologically active compounds, as several neurological diseases have been associated with the deficiency of γ-aminobutyric acid (GABA). In fact several unnatural γ-amino acids have found pharmaceutical application as GABA analogues.[4] Although the molecule of GABA is achiral, the prochiral hydrogen atoms at each carbon atom of the GABA framework become mutually different during the interaction of GABA with the chiral biomolecules of the different GABA synaptic mechanisms.[4a,5] Consequently the synthesis of GABA model compounds containing chiral centers with established absolute stereochemistry and in which the conformational and electronic effects can be modified is an important and current target in organic synthesis.[6]

2. Results and discussion

Herein we report on the diastereoselective Michael addition of (*S*,*S*)-*cis*-1,3-dioxolan-4-one **2** to aromatic nitroalkenes as the key step for a stereoselective synthesis of α-hydroxy-α,β-diaryl-γ-lactams. Nitroalkenes are easily obtained via the Henry reaction[7] and subsequent dehydration, besides they are excellent Michael acceptors due to the strong anion-stabilising effect of the nitro group and in addition the nitro group can be converted into a broad range of functionalities such as the carbonyl group via Nef reaction or an amino group by reduction.[8] However, despite the recent advances in this area,[9] there are very few examples of diastereoselective Michael reactions with nitroalkenes.[10]

At first, the enolate of (*S*,*S*)-*cis*-1,3-dioxolan-4-one **2** was reacted with nitrostyrene (Scheme 1, Table 1) using an inverse addition protocol,[1] that is to say, a mixture of both compounds in THF was treated at −78 °C with a solution of LDA (1.5 equiv.). After the reaction mixture reached

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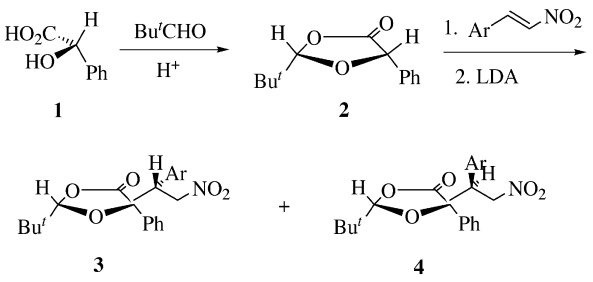


a Ar = Ph; **b** Ar = 4-MeO-Ph; **c** Ar = 3,4-$(MeO)_2$-Ph; **d** Ar = 2,4-$(MeO)_2$-Ph
e Ar = 4-OH, 3-MeO-Ph; **f** Ar = 4-Br-Ph; **g** Ar = 4-CF_3O-Ph; **h** 4-CF_3-Ph

Scheme 1.

Table 1. Michael reaction of (*S*,*S*)-*cis*-1,3-dioxolan-4-one **2** with nitrostyrene

Entry	Additive (eq.)	Product	Yield[a] (%)	dr[b] **3a/4a**
1	None	**3a**+**4a**	36	63/37
2	HMPA (1.5)	**3a**+**4a**	53	84/16
3	HMPA (3.0)	**3a**+**4a**	70	85/15
4	HMPA (6.0)	**3a**+**4a**	71	80/20
5	DMPU (3.0)	**3a**+**4a**	66	89/11
6	TMEDA (3.0)	**3a**+**4a**	25	37/63

[a] Yield refer to isolated diastereoisomeric product mixture.
[b] Ratios determined by ^{1}H NMR.

−40 °C, it was quenched with aqueous NH_4Cl and extracted with ethyl ether. This procedure provided the Michael adducts with poor yield (36%) and moderate diastereoselectivity (**3a**–**4a** ratio 63:37) (entry 1). However the use of HMPA as an additive increased the yield and the diastereoselectivity.[11] Thus the addition of 1.5 equiv. of HMPA (entry 2) improved the reaction yield up to 53% which was much more increased up to 70% with the addition of 3 equiv.. of HMPA (entry 3). In both cases, the reaction took place with a notable increasing of the diastereoselectivity (85:15). Addition of more HMPA (6 equiv.) (entry 4) did not further enhance the yield of the reaction nor modified the diastereoselectivity. The use of DMPU (entry 5) as substitute for HMPA increased slightly the diastereoselectivity but gave a lower yield, while the use of TMEDA decreased both yield and diastereoselectivity.

In order to investigate the effect of the substituents on the aromatic ring of the nitroalkenes and the generality of the method, the reaction was carried out with a range of different substrates (Table 2). The reaction with aromatic nitroalkenes bearing electron-donating groups (entries 2–5) gave products **3**–**4** in good to excellent yields (79–96%) while with aromatic nitroalkenes having electron-withdrawing groups (entries 6–8) gave products **3**–**4** in poor yields. In regard to the diastereoselectivity, the diastereoisomeric ratios range from 85:15 to 90:10 in the case of electron-donating substituted nitroalkenes, while somewhat lower, but still good diastereoisomeric ratios (ranging from 73:27 to 84:16) were observed with electron-withdrawing substituted nitroalkenes.

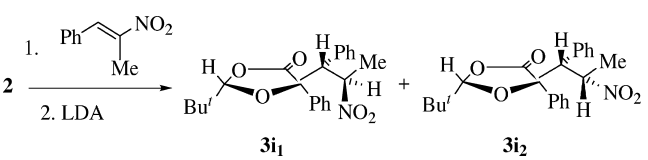
Table 2. Michael reaction of (*S*,*S*)-*cis*-1,3-dioxolan-4-one **2** with nitroalkenes

Entry	Nitroalkene	Product	Yield[a] (%)	dr[b] **3/4**
1	Nitrostyrene	**3a**+**4a**	70	85/15
2	*p*-Methoxynitrostyrene	**3b**+**4b**	79	90/10
3	3,4-Dimethoxy nitrostyrene	**3c**+**4c**	96	87/13
4	2,4-Dimethoxy nitrostyrene	**3d**+**4d**	94	85/15
5	4-Hydroxy-3-methoxynitrostyrene	**3e**+**4e**	79	85/15
6	*p*-Bromonitrostyrene	**3f**+**4f**	43	84/16
7	*p*-Trifluoromethoxy nitrostyrene	**3g**+**4g**	39	80/20
8	*p*-Trifluoromethyl nitrostyrene	**3h**+**4h**	16	73/27
9	α-Methylnitrostyrene	**3i**+**4i**[c]	66	93/7

[a] Yield refer to isolated diastereoisomeric product mixture.
[b] Ratios determined by ^{1}H NMR.
[c] Compound **3i** is a 50:43 epimer mixture. Compound **4i** is a 4:3 epimers mixture.

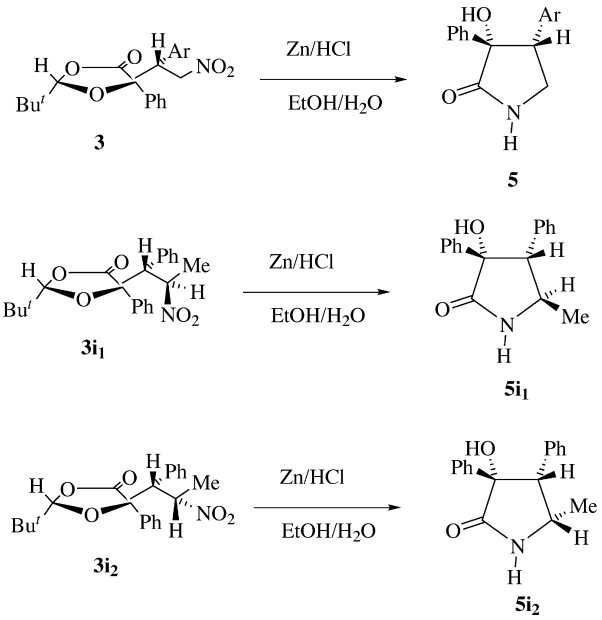
It is important to note that the Michael adducts were obtained as only two diastereoisomers out of the four possible ones for the two newly created stereogenic centers. The stereochemical structures of the Michael adducts **3** and **4** were elucidated by NOEs. These experiments showed in all of the cases the *cis*-relationship between the *t*-Bu group and the phenyl group from the original mandelic acid. The absolute configuration of the newly formed quaternary carbon atom was then assigned to be *S*, upon the consideration that the absolute configuration of the acetal carbon bearing the *t*-Bu group in **2** is *S* and it keeps unaltered from **2** to **3** or **4**.[1,2] The assignment of the stereochemistry at the tertiary stereocenter in the side chain was established later, after cyclisation to γ-lactams **5** (see below). These results are compatible with the assumption that the lithium enolate of **2** reacts exclusively from its *Re*-face, the major stereoisomer **3** resulting from the attack to the *Re*-face of the nitroalkenes (relative topicity like) and the minor stereoisomer **4** from the attack to the *Si*-face (relative topicity unlike)

The reaction of the enolate of **2** with α-methylnitrostyrene (entry 9) provides three new stereogenic centers (Scheme 2). Only four out of the eight possible stereoisomers were formed. As in the other cases, the stereogenic centers at β and γ positions with respect to the nitro group are formed during the carbon–carbon bond-forming step, which took place with relative topicity like between the *Re* faces of the enolate and nitroalkene, in the major product **3** and with relative topicity unlike between the *Re* and *Si* faces of the enolate and nitroalkene, respectively, in the minor product **4** (ratio **3i**–**4i** 93:7). The third stereogenic center (α to the nitro group) is formed by a non-diastereoselective protonation of the nitronate intermediate, so that the major adduct is a mixture of epimers at the nitro α position $\mathbf{3i_1}$ and $\mathbf{3i_2}$ (ratio 50:43), which could be separated by HPLC.[12] We would like to remark that the reactions described in this paper are the first examples of addition of **2** to aromatic nitroalkenes, as well as the advantages of our modifications with respect to other procedures,[3] i.e. the inverse addition protocol[1] and the use of HMPA, which allow to obtain good yields (70–96%) and stereoselectivities with nitrostyrenes substituted with electron-donating groups.



Scheme 2.

With the major Michael adducts **3a**-**3f** and **3i$_1$** and **3i$_2$** in hand, we carried out the reduction of the nitro group with Zn/HCl/EtOH/H_2O (Scheme 3). The reaction took place with concomitant intramolecular aminolysis of the acetal moiety leading directly to enantiomerically pure α-hydroxy-α,β-diaryl-γ-lactams **5**.[13]



Scheme 3.

The stereochemical structures of the γ-lactams **5** were established by NOEs. The choice of DMSO-d_6 for these experiments was crucial since it is known that this solvent slows down the exchange of the hydroxyl proton which in our case provided a good starting point for NOE experiments.[14] For instance, in compound **5b** irradiation at δ 5.98 (s) enhanced the signal at δ 7.24 (d) of the phenyl group and the signal at δ 6.96 (d) of the *p*-methoxyphenyl group indicating the *cis*-relationship between the hydroxyl and the *p*-methoxyphenyl groups. In the reverse direction, irradiation at δ 6.96 (d) enhanced the signal at δ 5.98 (s) corresponding to the hydroxyl group and, furthermore gave NOEs with signals at δ 6.74 (d) corresponding to the *meta*-aromatic protons and δ 3.44 (t) of the CH group and δ 3.59 (t) of the *cis*-proton on the CH_2 group (see Figure 1). According to these experiments the absolute configuration of the tertiary carbon atom bearing the aryl group was then assigned to be *R*, upon the consideration that the absolute configuration of the quaternary carbon bearing the phenyl group was *S* in all the cases as explained earlier. These experiments also allowed the assignment of the absolute stereochemistry of the tertiary stereocenter of compounds **3**, i.e. the *R* configuration of this stereocenter in compound **5** was assigned to this carbon in its Michael adduct precursor **3**. The opposite configuration *S* was therefore assigned in adduct **4** since both **3** and **4** are epimers at this position.

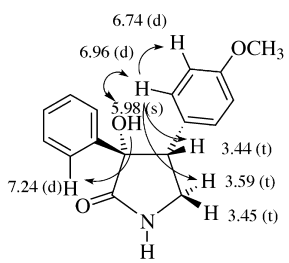


Figure 1. Significative NOEs in compound **5b**.

In summary, we have developed a diastereoselective Michael reaction of a mandelic acid enolate equivalent with aromatic nitroalkenes based on the Seebach principle of self-regeneration of stereocenters.[2] The reaction provides the corresponding adducts with good yields and diastereoisomeric excesses specially with aromatic nitroalkenes bearing electron-donating groups. By reduction with Zn/HCl/EtOH/H_2O, the Michael adducts were converted in the title compounds which constitute interesting enantiomerically pure GABA analogues.

3. Experimental

3.1. General

All melting points are uncorrected. Column chromatography was performed on silica gel (Merck, silica gel 60, 230–400 mesh). Optical rotations were determined on a Perkin–Elmer 243 polarimeter. NMR spectra were recorded on a Bruker Advance 300 DPX spectrometer (^{1}H at 300 MHz and ^{13}C at 75 MHz) or a Varian Unity 400 (^{1}H at 400 MHz and ^{13}C at 100 MHz) as indicated, and referenced to the residual non-deuterated solvent as internal standard. The carbon type was determined by DEPT experiments. In the case of 3d the ^{13}C NMR was registered in DMSO-d_6 at 70 °C in order to observe all the expected signals. Mass spectra were run by electron impact at 70 eV or by chemical ionisation using methane as ionising gas on a Fisons Instruments VG Autospec GC 8000 series spectrometer. (*S*,*S*)-*cis*-1,3-dioxolan-4-one 2 was prepared according to the literature.[15]

3.2. Michael reaction of nitroalkenes to (*S*,*S*)-*cis*-1,3-dioxolan-4-one 2

A solution of freshly prepared LDA (1.25 mmol) in dry THF (1.3 mL) was slowly added to a solution of (*S*,*S*)-*cis*-1,3-dioxolan-4-one **2** (220 mg, 1 mmol) and the nitroalkene (1.25 mmol) in dry THF–HMPA (5 mL:0.53 mL) at −78 °C. After 1 h, the reaction mixture was quenched with a saturated aqueous solution of NH_4Cl at this temperature, and extracted with diethyl ether (3×30 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. The residue was chromatographed on silica gel to afford Michael adducts **3** and **4**, which were analysed by ^{1}H NMR in order to determine the ratio of both compounds (yields and diastereoisomeric ratios are included in Table 2). Careful flash chromatography (silica gel, hexane–diethyl ether or hexane–dichloromethane) gave pure adducts **3** and adducts **4** slightly contaminated with minor amounts of **3**. Adducts **3g/4g** and **3h/4h** were not separated.

3.2.1. Michael adduct 3a. Mp 112–114 °C (CH_2Cl_2); $[\alpha]_D^{25}=-64.9$ (*c* 0.8, $CHCl_3$); HRMS *m*/*z* (EI) 369.1571 (M^+, 2.7, $C_{21}H_{23}NO_5$ required 369.1576), 219 (27.7), 191

(6.2), 105 (100.0); ^{1}H NMR ($CDCl_3$) δ 0.70 (9H, s), 4.16 (1H, dd, J=10.9, 4.7 Hz), 4.35 (1H, s), 4.53 (1H, dd, J=13.7, 4.7 Hz), 5.12 (1H, dd, J=13.7, 10.9 Hz), 7.3–7.4 (8H, m), 7.63 (2H, dd, J=8.1, 2.3 Hz); ^{13}C NMR ($CDCl_3$) δ 23.1 (q), 35.0 (s), 53.0 (d), 74.9 (t), 83.5 (s), 110.6 (d), 125.5 (d), 128.7 (d), 128.8 (d), 128.9 (d), 129.0 (d), 129.1 (d), 133.4 (s), 136.0 (s), 171.2 (s).

3.2.2. Michael adduct 4a. ^{1}H NMR ($CDCl_3$) δ 0.83 (9H, s), 4.23 (1H, dd, J=15.1, 4.5 Hz), 4.24 (1H, dd, J=13.2, 4.5 Hz), 4.56 (1H, s), 4.93 (1H, dd, J=15.1, 13.2 Hz), 7.3–7.5 (8H, m), 7.82 (2H, dd, J=8.5, 1.5 Hz); ^{13}C NMR ($CDCl_3$) δ 23.4 (q), 35.3 (s), 52.3 (d), 74.4 (t), 83.9 (s), 110.9 (d), 125.0 (d), 128.7 (d), 128.8 (d), 128.9 (d), 129.0 (d), 129.1 (d), 132.8 (s), 135.8 (s), 171.3 (s).

3.2.3. Michael adduct 3b. Mp 96–98 °C (CH_2Cl_2); $[\alpha]_D^{25}$=−54.2 (c 1.5, $CHCl_3$); HRMS m/z (EI) 399.1677 (M^+, 1.7, $C_{22}H_{25}NO_6$ required 399.1682), 219 (18.8), 180 (26.3), 134 (63.3), 105 (100.0); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.71 (9H, s), 3.81 (3H, s), 4.10 (1H, dd, J=11.1, 4.8 Hz), 4.44 (1H, s), 4.48 (1H, dd, J=13.6, 4.8 Hz), 5.06 (1H, dd, J=13.6, 11.1 Hz), 6.87 (2H, d, J=8.9 Hz), 7.20 (2H, d, J=8.9 Hz), 7.40 (3H, m), 7.62 (2H, dd, J=7.9, 2.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.1 (q), 35.0 (s), 52.3 (d), 55.2 (q), 75.0 (t), 83.6 (s), 110.6 (d), 114.2 (d), 125.1 (s), 125.5 (d), 128.7 (d), 129.0 (d), 130.2 (d), 136.1 (s), 159.8 (s), 171.3 (s).

3.2.4. Michael adduct 4b. ^{1}H NMR ($CDCl_3$) δ 0.84 (9H, s), 3.82 (3H, s), 4.18 (1H, dd, J=12.8, 4.5 Hz), 4.19 (1H, dd, J=14.1, 4.5 Hz), 4.65 (1H, s), 4.87 (1H, dd, J=14.1, 12.8 Hz), 6.92 (2H, d, J=8.7 Hz), 7.35 (2H, d, J=8.7 Hz), 7.4–7.5 (3H, m), 7.81 (2H, dd, J=7.9, 2.0 Hz).

3.2.5. Michael adduct 3c. Mp 169–171 °C (CH_2Cl_2); $[\alpha]_D^{25}$=−56.0 (c 0.6, $CHCl_3$); HRMS m/z (EI) 429.1784 (M^+, 4.5, $C_{23}H_{27}NO_7$ required 429.1788), 210 (17.4), 164 (100), 105 (67.0); ^{1}H NMR ($CDCl_3$) δ 0.71 (9H, s), 3.86 (3H, s), 3.89 (3H, s), 4.09 (1H, dd, J=11.1, 4.7 Hz), 4.47 (1H, s), 4.48 (1H, dd, J=13.6, 4.7 Hz), 5.09 (1H, dd, J=13.6, 11.1 Hz), 6.76 (1H, d, J=1.7 Hz), 6.85 (1H, m), 6.87 (1H, dd, J=8.3, 1.7 Hz), 7.3–7.4 (3H, m), 7.63 (2H, dd, J=7.7, 1.7 Hz); ^{13}C NMR ($CDCl_3$) δ 23.1 (q), 35.0 (s), 52.7 (d), 55.8 (q), 55.9 (q), 75.0 (t), 83.6 (s), 110.6 (d), 111.1 (d), 112.5 (d), 121.0 (d), 125.5 (d and s, overlaped signals), 128.7 (d), 129.0 (d), 136.1 (s), 148.9 (s), 149.3 (s), 171.3 (s); ^{13}C NMR (acetone-d_6) δ 22.6 (q), 34.8 (s), 52.5 (d), 55.0 (q), 55.2 (q), 75.5 (t), 83.3 (s), 110.0 (d), 111.3 (d), 113.5 (d), 121.4 (d), 125.6 (d), 125.9 (s), 128.2 (d), 128.5 (d), 136.6 (s), 149.1 (s), 149.6 (s), 171.4 (s)

3.2.6. Michael adduct 4c. ^{1}H NMR ($CDCl_3$) δ 0.84 (9H, s), 3.90 (3H, s), 3.91 (3H, s), 4.20 (2H, m), 4.63 (1H, s), 4.88 (1H, dd, J=14.5, 13.2 Hz), 6.8–7.0 (3H, m), 7.4–7.5 (3H, m), 7.81 (2H, dd, J=8.1, 1.1 Hz).

3.2.7. Michael adduct 3d. An oil; $[\alpha]_D^{25}$=+31.2 (c 0.7, $CHCl_3$); HRMS m/z (EI) 429.1776 (M^+, 1.1, $C_{23}H_{27}NO_7$ required 429.1788) 210 (56.8), 164 (100), 105 (21.8); ^{1}H NMR ($CDCl_3$) δ 0.84 (9H, s), 3.76 (3H, s), 3.80 (3H, s), 4.67 (2H, br s), 4.85 (1H, br s), 5.00 (1H, s), 6.40 (2H, m), 6.74 (1H, d, J=7.5 Hz), 7.35 (3H, m), 7.49 (2H, m); ^{1}H NMR (DMSO-d_6, 70 °C) δ 0.83 (9H, s), 3.57 (3H, s), 3.74 (3H, s), 4.70 (1H, dd, J=9.8, 5.4 Hz), 4.87 (1H, dd, J=13.4, 5.4 Hz), 4.96 (1H, dd, J=13.4, 9.8 Hz), 5.34 (1H, s), 6.41 (1H, d, J=2.4 Hz), 6,47 (1H, dd, J=8.7, 2.4 Hz), 6.74 (1H, d, J=7.5 Hz), 7.00 (1H, d, J=8.7 Hz), 7.35 (3H, m), 7.40 (2H, m); ^{13}C NMR (DMSO-d_6, 70 °C) δ 22.8 (q), 34.4 (s), 43.2 (d), 55.1 (q), 55.4 (q), 75.3 (t), 82.0 (s), 98.4 (d), 105.0 (d), 108.7 (d), 114.0 (s), 125.3 (d), 127.5 (d), 128.1 (d), 129.3(d), 135.5 (s), 158.6 (s), 160.4 (s), 170.8 (s).

3.2.8. Michael adduct 4d. ^{1}H NMR ($CDCl_3$) δ 0.86 (9H, s), 3.80–3.90 (2H, m), 3.81 (3H, s), 3.86 (3H, s), 4.32 (1H, dd, J=12.6, 4.2 Hz), 4.90 (1H, s), 6.46 (2H, m), 7.18 (1H, d, J=9.1 Hz), 7.3–7.4 (3H, m), 7.78 (2H, dd, J=8.1, 1.3 Hz).

3.2.9. Michael adduct 3e. Mp 129–131 °C (CH_2Cl_2); $[\alpha]_D^{25}$=−51.8 (c 0.7, $CHCl_3$); HRMS m/z (EI) 415.1611 (M^+, 3.4, $C_{22}H_{25}NO_7$ required 415.1631), 220 (12.0), 196 (19.7), 150 (74.8), 105 (100.0); ^{1}H NMR ($CDCl_3$) δ 0.72 (9H, s), 3.86 (3H, s), 4.08 (1H, dd, J=10.9, 4.7 Hz), 4.48 (1H, dd, J=13.4, 4.7 Hz), 4.49 (1H, s), 5.06 (1H, dd, J=13.4, 10.9 Hz), 5.65 (1H, s), 6.73 (1H, d, J=1.9 Hz), 6.80 (1H, dd, J=8.1, 1.9 Hz), 6.87 (1H, d, J=8.1 Hz), 7.3–7.4 (3H, m), 7.61 (2H, dd, J=7.9, 1.7 Hz); ^{13}C NMR ($CDCl_3$) δ 23.1 (q), 35.0 (s), 52.7 (d), 56.0 (q), 75.0 (t), 83.6 (s), 110.6 (d), 111.5 (d), 114.7 (d), 122.2 (d), 124.2 (s), 125.5 (d), 128.7 (d), 129.0 (d), 136.0 (s), 146.0 (s), 146.5 (s), 171.4 (s).

3.2.10. Michael adduct 4e. ^{1}H NMR ($CDCl_3$) δ 0.84 (9H, s), 3.92 (3H, s), 4.17 (1H, dd, J=12.6, 4.5 Hz), 4.18 (1H, dd, J=14.1, 4.5 Hz), 4.65 (1H, s), 4.87 (1H, dd, J=14.1, 12.6 Hz), 5.69 (1H, s), 6.8–7.0 (3H, m), 7.3–7.5 (3H, m), 7.81 (2H, dd, J=8.1, 1.1 Hz).

3.2.11. Michael adduct 3f. An oil; $[\alpha]_D^{25}$=−58.7 (c 0.6, $CHCl_3$); HRMS m/z (CI) 450.0751 and 448.0740 (M^++1, 11.40 and 12.75, $C_{21}H_{23}NO_5Br$ required 450.0739 and 448.0760 respectively), 364 (98), 362 (100), 317 (52.4), 315 (54), 261 (19.1), 259 (19.6), 219 (57.6); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.73 (9H, s), 4.13 (1H, dd, J=11.2, 4.4 Hz), 4.52 (1H, dd, J=13.6, 4.4 Hz), 4.58 (1H, s), 5.04 (1H, dd, J=13.6, 11.2 Hz), 7.13 (2H, d, J=8.5 Hz), 7.39 (3H, m), 7.47 (2H, d, J=8.5 Hz), 7.58 (2H, dd, J=8.1, 1.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.1 (q), 35.2 (s), 52.5 (d), 74.7 (t), 83.2 (s), 110.8 (d), 123.1 (s), 125.4 (d), 128.8 (d), 129.2 (d), 130.7 (d), 132.0 (d), 132.4 (s), 135.7 (s), 170.9 (s).

3.2.12. Michael adduct 4f. ^{1}H NMR ($CDCl_3$) δ 0.84 (9H, s), 4.2–4.3 (2H, m), 4.67 (1H, s), 4.87 (1H, dd, J=14.7, 13.0 Hz), 7.3–7.6 (7H, m), 7.79 (2H, dd, J=8.1, 1.9 Hz).

3.2.13. Michael adduct 3g. ^{1}H NMR ($CDCl_3$) δ 0.72 (9H, s), 4.18 (1H, dd, J=10.9, 4.7 Hz), 4.49 (1H, s), 4.56 (1H, dd, J=13.7, 4.7 Hz), 5.07 (1H, dd, J=13.7, 10.9 Hz), 7.1–7.5 (7H, m), 7.58 (2H, m); ^{13}C NMR ($CDCl_3$) δ 23.1 (q), 35.1 (s), 52.4 (d), 74.7 (t), 83.2 (s), 110.8 (d), 121.0 (d), 125.4 (d), 128.7 (d), 129.2 (d), 130.7 (d), 132.1 (s), 135.6 (s), 149.5 (s), 171.0 (s).

3.2.14. Michael adduct 4g. ^{1}H NMR ($CDCl_3$) δ 0.83 (9H, s), 4.1–4.3 (2H, m), 4.58 (1H, s), 4.88 (1H, dd, J=14.7, 13.0 Hz), 7.1–7.5 (7H, m), 7.80 (2H, d, J=7.2 Hz); ^{13}C

NMR ($CDCl_3$) δ 23.4 (q), 35.3 (s), 51.7 (d), 74.3 (t), 83.7 (s), 111.1 (d), 121.3 (d), 125.0 (d), 129.0 (d), 129.2 (d), 130.8 (d), 131.5 (s), 135.4 (s), 150.5 (s), 171.0 (s).

3.2.15. Michael adduct 3h. ^{1}H NMR ($CDCl_3$) δ 0.73 (9H, s), 4.24 (1H, dd, *J*=10.9, 4.7 Hz), 4.57 (1H, s), 4.58 (1H, dd, *J*=13.7, 4.7 Hz), 5.10 (1H, dd, *J*=13.7, 10.9 Hz), 7.3–7.6 (7H, m), 7.58 (2H, m); ^{13}C NMR ($CDCl_3$) δ 23.1 (q), 35.2 (s), 52.7 (d), 74.6 (t), 83.1 (s), 110.8 (d), 125.4 (d), 125.6 (d, J_{C-F}(q)=3.9 Hz), 128,8 (d), 129.2 (d), 129.6 (d), 129.4 (s, J_{C-F}(q)=34.2 Hz), 135,5 (s), 137.6 (s), 170.8 (s).

3.2.16. Michael adduct 4h. ^{1}H NMR ($CDCl_3$) δ 0.83 (9H, s), 4.30 (2H, m), 4.63 (1H, s), 4.93 (1H, dd, *J*=14.5, 12.6 Hz), 7.3–7.8 (9H, m).

3.2.17. Michael adduct 3i$_1$. Mp 133–135 °C (CH_2Cl_2); $[\alpha]_D^{25}$=+35.2 (*c* 0.7, $CHCl_3$); HRMS *m/z* (EI) 383.1737 (M^+, 1.3, $C_{22}H_{25}NO_5$ required 383.1733), 219 (32.2), 191 (5.2), 105 (100.0); ^{1}H NMR ($CDCl_3$) δ 0.84 (9H, s), 1.25 (3H, d, *J*=6.8 Hz), 4.12 (1H, d, *J*=10.4 Hz), 5.06 (1H, s), 5.15 (1H, m), 6.77 (2H, br d, *J*=7.0 Hz), 7.2–7.4 (6H, m), 7.45 (2H, dd, *J*=8.0, 2.1 Hz); ^{13}C NMR ($CDCl_3$) δ 20.3 (q), 23.1 (q), 34.5 (s), 55.2 (d), 81.9 (d), 82.5 (s), 108.8 (d), 127.0 (d), 127.6 (d), 128.0 (d), 128.4 (d), 128.6 (d), 130.9 (d), 132.6 (s), 133.9 (s), 170.6 (s).

3.2.18. Michael adduct 3i$_2$. Mp 110–112 °C (CH_2Cl_2); $[\alpha]_D^{25}$=−98.7 (*c* 0.5, $CHCl_3$); HRMS *m/z* (EI) 383.1737 (M^+, 1.7, $C_{22}H_{25}NO_5$ required 383.1733), 219 (31.5), 191 (5.3), 105 (100.0); ^{1}H NMR ($CDCl_3$) δ 0.78 (9H, s), 1.48 (3H, d, *J*=6.6 Hz), 3.87 (1H, d, *J*=10.2 Hz), 4.76 (1H, s), 5.40 (1H, m), 7.1–7.3 (8H, m), 7.47 (2H, m); ^{13}C NMR ($CDCl_3$) δ 20.1 (q), 23.3 (q), 35.1 (s), 58.6 (d), 83.1 (s), 84.7 (d), 110.7 (d), 125.7 (d), 128.18 (d), 128.21 (d), 128.24 (d), 128.5 (d), 130.0 (d), 134.3 (s), 137.4 (s), 172.0 (s).

3.3. Reduction of Michael adducts 3

To a solution of compound **3** (0.49 mmol) in EtOH–H_2O (3.80:0.95 mL) was added Zn dust (361 mg, 5.5 mmol) and conc. HCl (0.75 mL). The reaction mixture was refluxed during 1 hour up to consumption of the starting material (in some cases additional Zn dust and prolonged reaction times until 5–6 h were required). After this time the reaction mixture was filtered, diluted with water and extracted with ethyl acetate (3×20 mL). The organic extracts were combined, washed with brine and then dried over anhydrous $MgSO_4$. After filtration, the solvent was removed under vacuum to give γ-lactam **5**. Yields are included in Table 3.

Table 3. Reduction of Michael adducts **3**

Entry	Michael adduct	γ-Lactam product	Yield (%)
1	**3a**	**5a**	88
2	**3b**	**5b**	93
3	**3c**	**5c**	92
4	**3d**	**5d**	84
5	**3e**	**5e**	76
6	**3f**	**5f**	87
7	**3i$_1$**	**5i$_1$**	99
8	**3i$_2$**	**5i$_2$**	86

3.3.1. γ-lactam 5a. Mp 188–190 °C (AcOEt); $[\alpha]_D^{25}$=+7,3 (*c* 0.9, $CHCl_3$); HRMS *m/z* (EI) 253.1105 (M^+, 3.0, $C_{16}H_{15}NO_2$ required 253.1103), 193 (6.7), 181 (24.8), 169 (38.3), 131 (60.0), 119 (31.3), 69 (100.0); ^{1}H NMR (DMSO-d_6) δ 3.46 (1H, t, *J*=8.4 Hz), 3.54 (1H, t, *J*=8.4 Hz), 3.64 (1H, t, *J*=8.4 Hz), 6.00 (1H, s), 7.03 (2H, m), 7.1–7.3 (8H, m), 8.23 (1H, s); ^{13}C NMR ($CDCl_3$) δ 44.9 (t), 54.5 (d), 79.5 (s), 125.9 (d), 127.5 (d), 127.7 (d), 128.0 (d), 128.2 (d), 129.3 (d), 134.9 (s), 141.1 (s), 177.9 (s).

3.3.2. γ-Lactam 5b. Mp 220–222 °C (AcOEt); $[\alpha]_D^{25}$=−37.9 (*c* 0.5, CH_3OH); HRMS *m/z* (EI) 283.1213 (M^+, 11.8, $C_{17}H_{17}NO_3$ required 283.1208), 265 (40.6), 236 (13.9), 165 (5.6), 134 (100.0); ^{1}H NMR (DMSO-d_6) δ 3.44 (1H, t, *J*=7.5 Hz), 3.45 (1H, t, *J*=7.5 Hz), 3.59 (1H, t, *J*=7.5 Hz), 3.67 (3H, s), 5.98 (1H, s), 6,74 (2H, d, *J*=8.7 Hz), 6.96 (2H, d, *J*=8.7 Hz), 7.15–7.35 (5H, m), 8.22 (1H, s); ^{13}C NMR (DMSO-d_6) δ 44.4 (t), 53.8 (d), 55.2 (q), 79.1 (s), 113.3 (d), 126.8 (d), 127.0 (d), 127.7 (d), 128.3 (s), 130.8 (d), 142.8 (s), 158.5 (s), 176.5 (s).

3.3.3. γ-Lactam 5c. $[\alpha]_D^{25}$=−21.5 (*c* 0.6, $CHCl_3$); HRMS *m/z* (EI) 313.1306 (M^+, 41.0, $C_{18}H_{19}NO_4$ required 313.1314), 295 (24.7), 256 (5.4), 164 (100), 148 (9.4), 105 (14.5); ^{1}H NMR (DMSO-d_6) δ 3.45 (2H, m), 3.54 (3H, s), 3.63 (1H, t, *J*=7.0 Hz), 3.66 (3H, s), 5.90 (1H, s), 6.56 (1H, dd, *J*=8.0, 1.9 Hz), 6.59 (1H, d, *J*=1.9 Hz), 6.75 (1H, d, *J*=8,0 Hz), 7.2–7.3 (5H, m), 8.20 (1H, s); ^{13}C NMR ($CDCl_3$) δ 44.7 (t), 54.2 (d), 55.6 (q), 55.7 (q), 79.4 (s), 110.6 (d), 112.6 (d), 121.1 (d), 125.9 (d), 127.0 (s), 127.7 (d), 128.1 (d), 141.1 (s), 148.3 (s), 148.4 (s), 177.8 (s).

3.3.4. γ-Lactam 5d. Mp 171–173 °C (AcOEt); $[\alpha]_D^{25}$=+20.4 (*c* 0.3, CH_3OH); HRMS *m/z* (EI) 313.1317 (M^+, 24.0, $C_{18}H_{19}NO_4$ required 313.1314) 295 (15.1), 256 (5.0), 164 (100),149 (18.9), 121 (17.5), 105 (14.8); ^{1}H NMR (DMSO-d_6) δ 3.23 (3H, s), 3.32 (1H, t, *J*=9.2 Hz), 3.47 (1H, t, *J*=9.2 Hz), 3.70 (3H, s), 3.90 (1H, t, *J*=9.2 Hz), 5.85 (1H, s), 6.33 (1H, d, *J*=2,4 Hz), 6.46 (1H, dd, *J*=8.5, 2.4 Hz), 7.21 (5H, m), 7.41 (1H, d, *J*=8.5 Hz), 8.18 (1H, s); ^{13}C NMR (DMSO-d_6) δ 44.1 (t), 45.8 (d), 55.4 (q), 55.6 (q), 78.9 (s), 98.4 (d), 104.7 (d), 117.0 (s), 126.5 (d), 126.7 (d), 127.4 (d), 131.0 (d), 143.2 (s), 158.7 (s), 159.5 (s), 176.5 (s).

3.3.5. γ-Lactam 5e. Mp 232–235 °C (AcOEt); $[\alpha]_D^{25}$=−16,3 (*c* 0.9, CH_3OH); HRMS *m/z* (EI) 299.1168 (M^+, 10.8, $C_{17}H_{17}NO_4$ required 299.1158), 281 (7.7), 150 (100.0), 135 (7.8), 105 (12.8); ^{1}H NMR (DMSO-d_6) δ 3.41 (2H, m), 3.56 (3H, s), 3.62 (1H, dd, *J*=11.8, 12.0 Hz), 5.88 (1H, s), 6.43 (1H, dd, *J*=8.1, 1.9 Hz), 6.55 (1H, d, *J*=1.9 Hz), 6.56 (1H, d, *J*=8.1 Hz), 7.2–7.3 (5H, m), 8.20 (1H, s), 8.74 (1H, s); ^{13}C NMR (DMSO-d_6) δ 44.1 (t), 54.1 (q), 55.7 (d), 79.2 (s), 114.1 (d), 115.0 (d), 122.1 (d), 126.9 (d), 127.0 (d), 127.1 (s), 127.6 (d), 142.9 (s), 145.7 (s), 146.9 (s), 176.5 (s).

3.3.6. γ-Lactam 5f. Mp 261–263 °C (AcOEt); $[\alpha]_D^{25}$=−53.2 (*c* 0.8, CH_3OH); HRMS *m/z* (EI) 333.0164 and 331.0207 (M^+, 31.4 and 28.3, $C_{16}H_{14}NO_2Br$ required 333.0187 and 331.0208 respectively), 315 (16.3), 313 (13.2), 276 (7.8), 274 (7.9), 184 (100), 182 (93.8),105 (53.7); ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.40–3.65 (3H, m), 6.10 (1H, s), 7.00 (2H, d, *J*=8.5 Hz), 7.2–7.3 (5H, m),

7.38 (2H, d, J=8.5 Hz), 8.24 (1H, s); ^{13}C NMR (100 MHz, DMSO-d_6) δ 44.0 (t), 53.8 (d), 79.0 (s), 120.4 (s), 126.7 (d), 127.2 (d), 127.8 (d), 130.7 (d), 132.0 (d), 136.0 (s), 142.5 (s), 176.1 (s).

3.3.7. γ-Lactam 5i$_1$. Mp 223–225 °C (AcOEt); $[\alpha]_D^{25}$= +38.3 (c 0.7, CH_3OH); HRMS m/z (EI) 267.1252 (M^+, 23.5, $C_{17}H_{17}NO_2$ required 267.1259), 249 (3.6), 196 (13.8), 118 (100) 105 (19.5); ^{1}H NMR (DMSO-d_6) δ 1.08 (3H, d, J=6.0 Hz), 2.92 (1H, d, J=9.2 Hz), 4.05 (1H, m), 6.06 (1H, s), 7.01 (2H, m), 7.1–7.3 (8H, m), 8.29 (1H, s); ^{13}C NMR (DMSO-d_6) δ 19.3 (q), 51.2 (d), 63.8 (d), 80.5 (s), 126.7 (d), 127.0 (d), 127.2 (d), 127.6 (d), 127.8 (d), 130.2 (d), 135.1 (s), 142.6 (s), 175.4 (s).

3.3.8. γ-Lactam 5i$_2$. Mp 187–189 °C (AcOEt); $[\alpha]_D^{25}$= −121.2 (c 0.4, $CHCl_3$); HRMS m/z (EI) 267.1264 (M^+, 31.4, $C_{17}H_{17}NO_2$ required 267.1259), 249 (43.8), 234 (29.3), 220 (13.9), 196 (22.1), 178 (15.2), 118 (100), 105 (34.0); ^{1}H NMR (DMSO-d_6) δ 0.89 (3H, d, J=6.8 Hz), 3.54 (1H, d, J=6.4 Hz), 3.74 (1H, m), 6.03 (1H, s), 7.1–7.4 (10H, m), 8.33 (1H, s); ^{13}C NMR (DMSO-d_6) δ 18.4 (q), 50.5 (d), 57.5 (d), 80.2 (s), 126.5 (d), 126.8 (d), 127.4 (d), 127.8 (d), 128.1 (d), 130.9 (d), 137.0 (s), 143.8 (s), 176.6 (s).

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12. In the case of **3i$_1$** and **3i$_2$** which have an additional stereogenic center the absolute stereochemistry was assigned also by NOEs experiments in compounds **5i$_1$** and **5i$_2$** following a similar reasoning as in compounds **5a**–**5f**.
13. Enantiomeric excesses (>98%) were proven by ^{1}H NMR experiments using the chiral lanthanide shift reagent Eu(hfc)$_3$ under conditions previously optimized for racemic mixtures prepared from (±)-mandelic acid.
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