Isosteviol–Proline Conjugates as Highly Efficient Amphiphilic Organocatalysts for Asymmetric Three-Component *Mannich* Reactions in the Presence of Water

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In this work, six isosteviol–amino acid conjugates were designed and synthesized through simple condensation on a large scale without protecting group (*Scheme*). These amphiphilic organocatalysts mediated asymmetric three-component *Mannich* reactions of cyclohexanone and anilines with aromatic aldehydes in the presence of H_2O. Meanwhile, the isosteviol–proline conjugate **3b** has been established as a highly efficient catalyst (*Table 1*), and afforded *syn-Mannich* products with excellent diastereoselectivities (*syn*/*anti* up to 98 : 2) and enantioselectivities (up to > 99% ee; *Table 3*). The transition state of the reaction in the presence of H_2O is proposed (*Fig. 2*).

Introduction. – The asymmetric *Mannich* reaction is one of the most important C–C bond forming reactions for the production of optically enriched β-amino carbonyl motifs [1]. It has been considered as a crucial synthetic methodology in the synthesis of pharmaceutically valuable compounds and natural products [2]. The first organocatalyst-mediated direct asymmetric *Mannich* reaction was reported by *List* [3], followed by excellent contributions from several groups [4]. Then, the amino acid derivatives have been utilized as efficient catalysts. However, most of these reactions proceed in polar organic solvents [5].

Water is the most friendly medium, which avoids the problems of pollution that are inherent with organic solvents [6]. There is an endeavor to develop highly enantioselective *Mannich* reaction in the presence of H_2O. *Ibrahem* and *Córdova* [7] have reported that L-proline catalyzes the three-component *Mannich* reaction in DMSO/H_2O. Then, the application of amino acid derivatives in asymmetric *Mannich* reactions in aqueous media was further extended by excellent work by *Córdova* and co-workers [8], and *Wang* and co-workers [9]. Although these reactions proceeded in an aqueous solution, the polar organic solvents were dominant. The first finding that the direct asymmetric *Mannich* reaction is promoted by a primary amino acid derivative in a purely aqueous system was reported by *Lu* and co-workers [10]. Then, the application of L-serine and L-proline derivatives in H_2O were reported by *Teo et al.* [11], and *Hayashi et al.* [12], respectively; however, only moderate yields were obtained using cyclohexanone as the ketone part.

Results and Discussion. – As mentioned above, the reports about direct asymmetric *Mannich* reactions in a purely aqueous system is rather sparse. We have previously

disclosed direct aldol reactions [13] and α-aminoxylation reactions [14] in aqueous media promoted by isosteviol–proline conjugates. In the work presented here, we designed and synthesized the amphiphilic isosteviol–amino acid conjugates **1**–**3** by a simple condensation without protecting group (*Scheme*), and evaluated their catalytic properties in asymmetric three-component *Mannich* reactions in the presence of H_2O. Meanwhile, the amphiphilic proline derivatives **4** [15] and **5** [16] with long alkyl chains were also tested under these reaction conditions, to compare them with the catalysts **1**–**3** (see *Fig. 1*).

Scheme. *Preparation of Amphiphilic Catalysts* **1**–**3**

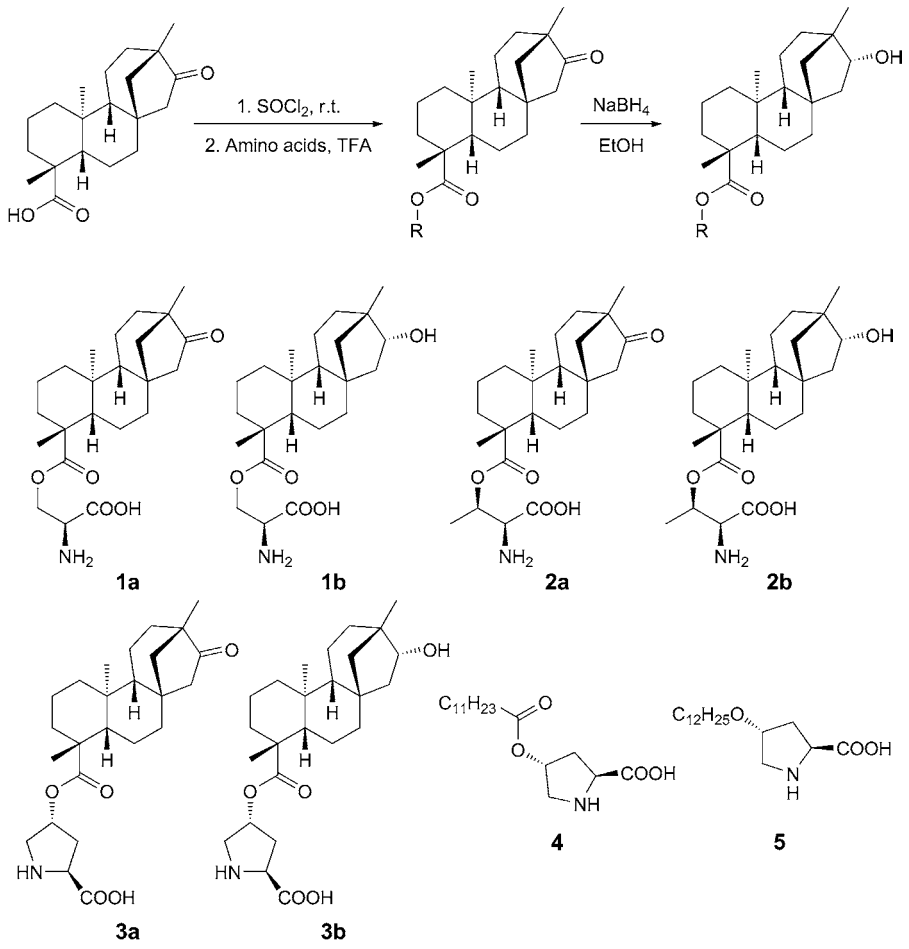
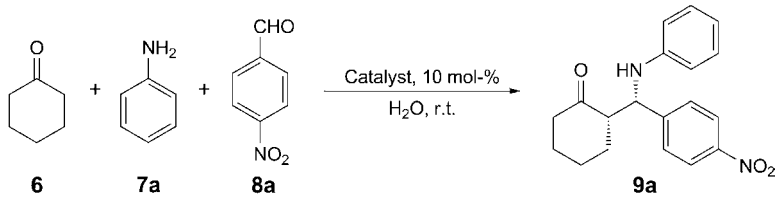


Fig. 1. *Structures of the Catalysts*

First, the catalytic effect of the amphiphilic catalysts **1**–**5** for the asymmetric three-component *Mannich* reaction in the presence of H_2O was investigated, by performing the reaction of 4-nitrobenzaldehyde, aniline, and cyclohexanone as a model, and the results are compiled in *Table 1*. All of the isosteviol–amino acid conjugates **1**–**3** afford

Table 1. *Catalyst Screening*[a])[b])



6 **7a** **8a** **9a**

Entry	Catalyst	Yield [%][c])	*syn/anti*[d])	ee [%][d])[e])
1	**1a**	97	71 : 29	74
2	**2a**	61	77 : 23	81
3	**3a**	46	81 : 19	88
4	**1b**	77	84 : 16	84
5	**2b**	69	83 : 17	82
6	**3b**	90	91 : 9	98
7	**4**	36	57 : 43	48
8	**5**	95	45 : 55	2

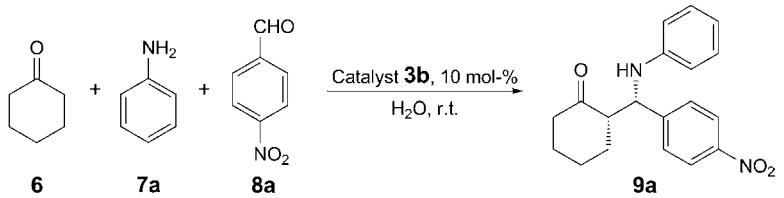
[a]) For the screened catalysts, see *Fig. 1.* [b]) Reaction conditions: cyclohexanone (**6**; 0.75 mmol, 3 equiv.), aniline (**7**; 0.25 mmol, 1 equiv.), 4-nitrobenzaldehyde (**8**; 0.25 mmol, 1 equiv.), and catalyst (10 mol-%) in H_2O (0.1 ml) for 23 h. [c]) Yield of isolated product. [d]) Determined by HPLC analysis on a *Chiralpak AD-H column.* [e]) Value for the *syn*-product.

higher activities than long-chain alkyl-substituted proline derivatives **4** and **5**, and gave the *syn*-configured products (*Entries 1–6 vs. 8* and *9*). The configurations of the *Mannich* products were determined by their NMR data (^{1}H-NMR coupling constants) and their behavior on HPLC analysis in comparison with the literature [7–9]. These observations hint at the different effect of aggregation of catalysts on the surface of H_2O molecules. By application of the isosteviol–amino acid conjugates, it turned out that the L-proline derivatives **3a** and **3b** were more suitable for the asymmetric three-component *Mannich* reaction in the presence of H_2O, due to the rational matching of L-proline and the chiral cavity of isosteviol. Catalyst **3b** led to the highest yield and stereoselectivities in the presence of H_2O (*Entry 6*).

The optimum condition was investigated, therefore, with catalyst **3b**. The results are collected in *Table 2*. The reaction, when carried out in the absence of H_2O, led to significantly lower dr and ee values (*Entry 1*). Addition of different amounts of H_2O to the reaction mixture was beneficial for the diastereo- and enantioselectivities. The optimum amount of H_2O was determined as 22 equiv. (0.1 ml) relative to the substrate, thereby affording the product with high yield and stereoselectivity (*Entry 6*). The addition of excess amount of H_2O (44 equiv. or 110 equiv.) to the mixture did not lead to any significant improvement in the activity and stereoselectivity (*Entries 7* and *8*). The yield and ee value decreased when brine was used as reaction medium (*Entry 9*). Then, excellent stereoselectivity was achieved by using PBS (phosphate buffered saline) solutions (pH, 7.7) as solvent; however, the yield was poor (*Entry 12*). The diastereoselectivity decreased with a reduced amount of cyclohexanone (*Entry 13*).

Then, the optimized reaction conditions were applied to *Mannich* reactions with various aromatic aldehydes and amines (*Table 3*). Among the reactions of cyclo-

Table 2. *Optimization of Reaction Conditions*[a])



6 **7a** **8a** **9a**

Entry	H_2O	Yield [%][b])	*syn*/*anti*[c])	ee [%][c])[d])
1	–	74	67 : 33	85
2	1 equiv.	82	91 : 9	95
3	2 equiv.	79	91 : 9	96
4	5 equiv.	78	89 : 11	96
5	10 equiv.	83	90 : 10	96
6	0.1 ml	90	91 : 9	98
7	0.2 ml	78	88 : 12	96
8	0.5 ml	73	88 : 12	97
9[e])	brine	78	90 : 10	96
10[f])	PBS, 4.5	64	89 : 11	95
11[g])	PBS, 7.7	49	94 : 6	98
12[h])	PBS, 9.1	48	91 : 9	98
13[g])	0.1 ml	61	87 : 13	96

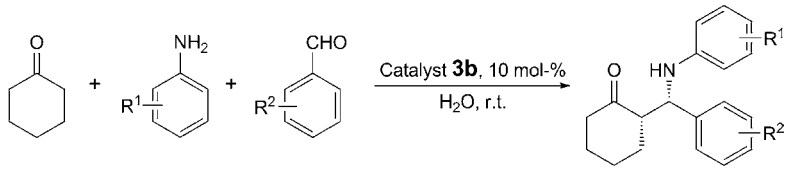
[a]) Reaction conditions: cyclohexanone (**6**; 0.75 mmol, 3 equiv.), aniline (**7**; 0.25 mmol, 1 equiv.), 4-nitrobenzaldehyde (**8**; 0.25 mmol, 1 equiv.), and catalyst **3b** (10 mol %) in aqueous solvent for 23 h. [b]) Yield of isolated product. [c]) Determined by HPLC analysis on a *Chiralpak AD-H* column. [d]) Value for the *syn*-product. [e]) 0.1 ml of sat. NaCl soln. [f]) 0.1 ml of phosphate buffered saline (PBS) soln. [g]) 2 Equiv. of cyclohexanone were used.

hexanone, aniline, and substituted benzaldehydes, nitrobenzaldehydes gave the best diastereoselectivities (up to >99 : 1 dr) and enantioselectivities (up to 99% ee), although the yield was unsatisfactory with 2-nitrobenzaldehyde (*Entry 2*). It was rather strange that the 4-fluorobenzaldehyde gave the *anti*-configured product with poor stereoselectivity (*Entry 3*). The optimized conditions were extended to a series of aromatic amines with 4-nitrobenzaldehyde as acceptor (*Entries 5–10*). The electronic effect of the substituent of aniline **7** was the important factor for the stereoselectivity. The halogenated anilines afforded high yields and excellent stereoselectivities in a short time (*Entries 8* and *9*). Meanwhile, good yield and high enantiostereoselectivity were obtained with 3-methylaniline (*Entry 10*). However, the alkoxy-substituted anilines, afforded poor stereoselectivities with this catalytic system (*Entries 6* and *7*).

The configurations of the *Mannich* products were determined by their NMR data and their behavior on HPLC analysis in comparison with the literature [7–9]. Although the mechanism of the actual *Mannich* reaction has yet to be elucidated, the stereochemical course catalyzed by the amphiphilic catalyst **3b** with cyclohexanone as the donor molecule can be explained by a plausible transition state as depicted in *Fig. 2*.

With the mediation of the amphiphilic catalyst *via* H-bond formation, the aqueous media and the organic reactants generate a biphase system. In the H_2O-surrounded

Table 3. *Direct Asymmetric Mannich Reactions of Cyclohexanone*[a])



6 **7** **8** **9**

Entry	R^1	R^2	Product	Time [h]	Yield [%][b])	*syn*/*anti*[c])	ee [%][c])[d])
1	H	4-NO_2	**9a**	23	90	91 : 9	98
2	H	2-NO_2	**9b**	23	38	> 99 : 1	> 99
3	H	4-F	**9c**	23	46	44 : 56	62
4	H	4-Br	**9d**	23	70	61 : 39	82
5	4-Me	4-NO_2	**9e**	4	56	76 : 24	89
6	4-MeO	4-NO_2	**9f**	4	48	49 : 51	48
7	4-EtO	4-NO_2	**9g**	4	75	46 : 54	37
8	4-Cl	4-NO_2	**9h**	4	> 99	94 : 6	> 99
9	3-Br	4-NO_2	**9i**	4	90	95 : 5	> 99
10	3-Me	4-NO_2	**9j**	4	98	90 : 10	97

[a]) Reaction conditions: cyclohexanone (**6**; 0.75 mmol, 3 equiv.), aromatic amines **7** (0.25 mmol, 1 equiv.), aromatic aldehydes **8** (0.25 mmol, 1 equiv.), and catalyst **3b** (10 mol-%) in H_2O (0.1 ml). [b]) Yield of isolated product. [c]) Determined by HPLC analysis on a *Chiralpak AD-H* column. [d]) Value for the *syn*-product.

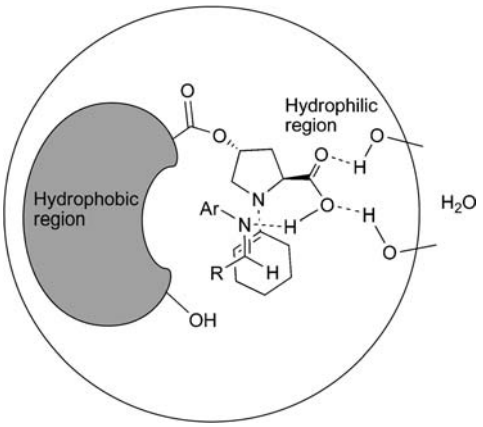


Fig. 2. *Proposed transition state of the reaction*

organic microphase, the substrates and the catalyst assemble in a special order, and the transition state can be stabilized by H-bonding between the N-atom of the (*Z*)-configured imine and the COO group of the proline moiety of the catalyst. In the transition state, the *Si*-face of the *in situ* generated acceptor imine is selectively attacked by the catalytically generated enamine. Thus, the asymmetric *Mannich* reaction catalyzed by **3b** affords *syn*-configured products.

Conclusions. – In summary, the organocatalyst-mediated asymmetric three-component *Mannich* reaction in the presence of H_2O has been described. Among the synthesized isosteviol–amino acid conjugates, the proline-derived amphiphilic catalyst **3b** exhibited good activity and stereoselectivity for the reaction of cyclohexanone, substituted anilines and aromatic aldehydes, and led to high enantioselectivities of the *syn*-products with H_2O as the reaction medium. Further investigations on the application of the amphiphilic isosteviol–proline conjugates in different asymmetrically catalyzed processes are in progress and will be reported in due course.

Experimental Part

General. All chemicals were used as received unless otherwise noted. Reagent-grade solvents were distilled prior to use. Chromatography was performed on silica gel (SiO_2; 200–300 mesh). Enantiomeric excess (ee) was determined by HPLC at r.t. with a *Labtech 2006* pump equipped with *Labtech UV600* ultradetector and *Chiralpak AD-H* (4.6 mm × 250 mm). M.p.: *XT5A* apparatus; uncorrected. Optical rotations: *Perkin Elmer 341* polarimeter. IR Spectra: *Thermo Nicolet IR200* unit. ^{1}H- and ^{13}C-NMR spectra: *Bruker DPX 400* NMR spectrometer with TMS as an internal reference. HR-MS: *Waters Micromass Q-Tof Micro*™ instrument using the ESI technique.

General Procedure for Preparation of Chiral Catalysts **1a**–**3a** (*GP1*). Isosteviol (6.36 g, 20 mmol) was dissolved in $SOCl_2$ (20 ml), and the mixture was stirred at r.t. for 1 h. After evaporating the solvent under vacuum, amino acid (20 mmol) and CF_3COOH (20 ml) were added. The resulting soln. was stirred at r.t. for 2 h. Under cooling with an ice/water bath, Et_2O (40 ml) was added carefully to give a fine white precipitate that was vacuum-filtered, washed with Et_2O (5 ml × 2), and dried at r.t. for 2 h to give the hydrochloride as a fine white powder. The white powder was dissolved in 40 ml of warm 95% EtOH, and propylene oxide (10 ml) was then added. Stirring was discontinued, and the soln. was left for crystallization at r.t. for 7 h. The crystalline product was vacuum-filtered and dried at r.t. *in vacuo* to give product **1a**–**3a**.

*(2*S*)*-O-*(*ent*-16-Oxobeyerane-19-carbonyl)serine* (= O-*(16,18-Dioxobeyeran-18-yl)*-L-*serine*; **1a**) was prepared according to the *GP1* using L-serine. Yield 6.73 g (83%). White solid. M.p. 125–126°. $[\alpha]_D^{20} = -50.6$ ($c = 0.25$, MeOH). IR: 3418, 2949, 2848, 1735, 1651, 1149, 1128. ^{1}H-NMR (400 MHz, DMSO): 7.95 (br. *s*, 1 H); 2.89 (*s*, 1 H); 2.73 (*s*, 1 H); 2.01 (*d*, $J = 13.0$, 1 H); 1.89–1.85 (*m*, 1 H); 1.78–1.73 (*m*, 2 H); 1.69–1.62 (*m*, 4 H); 1.53–1.50 (*m*, 1 H); 1.40–1.32 (*m*, 5 H); 1.23–1.11 (*m*, 4 H); 1.16 (*s*, 3 H); 1.02–0.87 (*m*, 3 H); 0.92 (*s*, 3 H); 0.73 (*s*, 3 H). ^{13}C-NMR (100 MHz, DMSO): 221.3; 179.2; 162.9; 67.8; 56.6; 54.4; 53.9; 48.4; 48.3; 43.4; 41.2; 39.9; 38.2; 37.2; 36.3; 31.3; 29.3; 22.1; 20.4; 20.3; 19.2; 13.7. HR-ESI-MS: 428.2413 ($[M + Na]^+$, $C_{23}H_{35}NNaO_5^+$; calc. 428.2407).

*(2*S*,3*R*)*-O-*(*ent*-16-Oxobeyerane-19-carbonyl)threonine* (= O-*(16,18-Dioxobeyeran-18-yl)*-L-*threonine*; **2a**) was prepared according to the *GP1* using L-threonine. Yield 7.17 g (86%). White solid. M.p. 122–123°. $[\alpha]_D^{20} = -50.3$ ($c = 0.50$, MeOH). IR: 3412, 2948, 2847, 1734, 1638, 1165, 1129. ^{1}H-NMR (400 MHz, DMSO): 5.19 (*q*, $J = 2.8$, 1 H); 3.36 (br. *s*, 2 H); 3.33 (*d*, $J = 2.2$, 1 H); 2.11 (*d*, $J = 12.7$, 1 H); 1.83–1.75 (*m*, 2 H); 1.69–1.59 (*m*, 5 H); 1.51–1.33 (*m*, 6 H); 1.23 (*d*, $J = 6.4$, 3 H); 1.16–1.05 (*m*, 4 H); 1.11 (*s*, 3 H); 0.95–0.81 (*m*, 2 H); 0.86 (*s*, 3 H); 0.61 (*s*, 3 H). ^{13}C-NMR (100 MHz, DMSO): 221.7; 175.9; 168.8; 70.1; 57.8; 56.8; 54.3; 53.8; 48.5; 48.4; 44.0; 41.5; 39.7; 38.0; 37.8; 37.2; 29.0; 21.6; 20.5; 20.3; 19.3; 17.2; 13.8. HR-ESI-MS: 420.2750 ($[M + H]^+$, $C_{24}H_{38}NO_5^+$; calc. 420.2745).

*(2*S*,4*R*)-4-[(*ent*-16-Oxobeyerane-19-carbonyl)oxy]proline* (= *(4*R*)-4-[(16,18-Dioxobeyeran-18-yl)oxy]*-L-*proline*; **3a**) was prepared according to the *GP1* using L-proline. Yield 7.42 g (86%). White solid. M.p. 176–178°. $[\alpha]_D^{20} = -56.7$ ($c = 0.13$, $CHCl_3$). IR: 3601, 3448, 2955, 2849, 1733, 1654, 1149, 1130. ^{1}H-NMR (400 MHz, $CDCl_3$): 5.23 (*s*, 1 H); 4.13 (*d*, $J = 1.68$, 1 H); 3.60 (*s*, 1 H); 3.38 (*s*, 1 H); 2.62 (*d*, $J = 20$, 1 H); 2.44 (*s*, 1 H); 2.29 (*s*, 1 H); 2.18 (*d*, $J = 12$, 3 H); 1.88–1.78 (*m*, 2 H); 1.66–1.38 (*m*, 10 H); 1.18 (*s*, 3 H); 1.12–1.09 (*m*, 2 H); 0.95 (*s*, 3 H); 0.98–0.85 (*m*, 2 H); 0.69 (*s*, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 222.5; 176.5; 173.1; 72.3; 59.7; 57.0; 54.5; 54.1; 49.8; 48.6; 48.4; 43.8; 41.4; 39.6; 39.4; 38.0; 37.5; 37.2; 35.4; 28.9; 21.5; 20.3; 19.8; 19.0; 13.8. HR-ESI-MS: 454.2569 ($[M + Na]^+$, $C_{25}H_{37}NNaO_5^+$; calc. 454.2570).

General Procedure for Preparation of Chiral Catalysts **1b**–**3b** (*GP2*). A soln. of compound **1a**–**3a** (20 mmol) and $NaBH_4$ (1.71 g; 30 mmol) in dry EtOH (100 ml) was stirred at 0° for 2 h. The mixture was then concentrated under vacuum, and treated with $CHCl_3$ and H_2O. The org. layer was separated and washed with sat. aq. NaCl soln. Then, the solvent was dried (anh. $MgSO_4$) and evaporated under vacuum to afford crude product. After recrystallization from MeOH, the catalyst **1b**–**3b** was obtained as a white powder.

*(2*S*)*-O-*(*ent-*16-Hydroxybeyerane-19-carbonyl)serine* (=O-*[(16α)-16-Hydroxy-18-oxobeyeran-18-yl]*-L-*serine*; **1b**) was prepared according to *GP2* using L-serine. Yield 7.82 g (96%). White solid. M.p. 148–149°. $[\alpha]_D^{20} = -43.3$ ($c = 0.64$ in MeOH). IR: 3404, 2938, 2845, 1716, 1637, 1455, 1231, 1175, 1147. ^{1}H-NMR (400 MHz, DMSO): 4.36–4.34 (*m*, 1 H); 4.09–4.05 (*m*, 1 H); 3.66–3.64 (*m*, 1 H); 3.53–3.52 (*m*, 1 H); 2.13 (*d*, *J* = 11.6, 1 H); 1.72–1.48 (*m*, 8 H); 1.43–1.39 (*m*, 2 H); 1.32–1.22 (*m*, 2 H); 1.19–1.16 (*m*, 1 H); 1.12 (*s*, 3 H); 1.09–0.91 (*m*, 6 H); 0.81 (*s*, 3 H); 0.65 (*s*, 3 H). ^{13}C-NMR (100 MHz, DMSO): 176.9; 169.4; 78.8; 64.9; 57.1; 56.4; 56.0; 55.5; 53.7; 49.0; 43.7; 43.1; 42.1; 38.0; 37.7; 34.2; 29.0; 25.5; 21.6; 20.3; 19.2; 19.0; 13.6. HR-ESI-MS: 430.2569 ($[M+Na]^+$, $C_{23}H_{37}NNaO_5^+$; calc. 430.2564).

*(2*S*,3*R*)*-O-*(*ent-*16-Hydroxybeyerane-19-carbonyl)threonine* (=O-*[(16α)-16-Hydroxy-18-oxobeyeran-18-yl]*-L-*threonine*; **2b**) was prepared according to *GP2* using L-threonine. Yield 8.00 g (95%). White solid. M.p. 145–146°. $[\alpha]_D^{20} = -36.1$ ($c = 0.7$ in MeOH). IR: 3417, 2940, 2844, 1713, 1635, 1453, 1406, 1228, 1147, 1026. ^{1}H-NMR (400 MHz, DMSO): 5.26 (*q*, *J* = 3.4, 1 H); 3.73–3.69 (*dd*, *J* = 4.0, 1 H); 3.40–3.38 (*m*, 1 H); 2.20 (*d*, *J* = 12.6, 1 H); 1.96 (br. *s*, 1 H); 1.78–1.58 (*m*, 8 H); 1.50–1.44 (*m*, 2 H); 1.38–1.22 (*m*, 3 H); 1.31 (*d*, *J* = 6.4, 3 H); 1.14 (*s*, 3 H); 1.11–0.96 (*m*, 5 H); 0.87 (*s*, 3 H); 0.93–0.83 (*m*, 1 H); 0.71 (*s*, 3 H). ^{13}C-NMR (100 MHz, DMSO): 175.7; 170.9; 78.8; 69.5; 60.2; 57.8; 57.0; 55.9; 49.0; 43.9; 43.0; 42.1; 38.1; 37.6; 34.2; 29.2; 25.5; 21.5; 21.2; 20.3; 19.3; 17.1; 14.5; 14.1. HR-ESI-MS: 444.2726 ($[M+Na]^+$, $C_{24}H_{39}NNaO_5^+$; calc. 444.2721).

*(2*S*,4*R*)-4-[(*ent-*16-Hydroxybeyerane-19-carbonyl)oxy]proline* (=*(4*R*)-4-{[(16α)-16-Hydroxy-18-oxobeyeran-18-yl]oxy}*-L-*proline*; **3b**) was prepared according to *GP2* method using L-proline. Yield 8.15 g (94%). White solid. M.p. 167–170°. $[\alpha]_D^{20} = -50.0$ ($c = 0.12$, MeOH). IR: 3422, 2926, 2847, 1719, 1596, 1438, 1384, 1176, 1150. ^{1}H-NMR (400 MHz, $CDCl_3$): 5.26 (*s*, 1 H); 4.20 (*s*, 1 H); 3.81 (*d*, *J* = 5.6, 2 H); 3.30 (*d*, *J* = 16.4, 1 H); 2.39–2.30 (*m*, 2 H); 2.14 (*d*, *J* = 16.4, 1 H); 1.74–1.70 (*m*, 6 H); 1.53–1.38 (*m*, 5 H); 1.29–1.23 (*m*, 2 H); 1.17 (*s*, 3 H); 1.07–0.73 (*m*, 9 H); 0.89 (*s*, 3 H); 0.73 (*s*, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 177.0; 80.1; 72.7; 60.6; 57.0; 55.7; 55.0; 50.2; 43.8; 42.5; 42.0; 41.9; 41.6; 40.3; 39.7; 38.1; 37.7; 35.0; 33.7; 28.9; 24.9; 21.7; 20.4; 18.8; 13.8. HR-ESI-MS: 456.2726 ($[M+Na]^+$, $C_{25}H_{39}NNaO_5^+$; calc. 456.2726).

General Procedure for the Asymmetric Mannich *Reactions of Cyclohexanone* (*Table 3*). The mixture of aldehyde (0.25 mmol, 1 equiv.), catalyst **3b** (10 mmol-%), and aniline (0.25 mmol, 1 equiv.) in H_2O (0.1 ml) were stirred for 1 h at r.t. followed by addition of cyclohexanone (0.75 mmol, 3 equiv.). After stirring for the corresponding reaction time at r.t., the resulting mixture was purified by TLC on SiO_2 (petroleum ether (PE)/AcOEt) to provide the product.

2-[(4-Nitrophenyl)(phenylamino)methyl]cyclohexanone (**9a**). HPLC (for *syn*): *Daicel Chiralpak AD-H*; hexane/i-PrOH 85:15; flow rate, 1.0 ml/min, UV 254 nm; t_R(major) 22.4, t_R(minor) 16.0 min. IR: 3416, 3045, 2923, 2853, 1706, 1598, 1515, 1342, 1258. ^{1}H-NMR (400 MHz, $CDCl_3$; *syn*-isomer): 8.14 (*dd*, *J* = 1.7, 8.7, 2 H); 7.56 (*d*, *J* = 8.7, 2 H); 7.18 (*t*, *J* = 8.2, 2 H); 6.68 (*t*, *J* = 7.3, 1 H); 6.49 (*d*, *J* = 7.7, 2 H); 4.85 (*d*, *J* = 4.4, 1 H); 4.71 (*d*, *J* = 5.3, 1 H); 2.86–2.83 (*m*, 1 H); 2.43–2.32 (*m*, 2 H); 2.08–1.92 (*m*, 2 H); 1.65–1.60 (*m*, 4 H). ^{13}C-NMR (100 MHz, $CDCl_3$, *syn*-isomer): 210.6; 149.5; 147.0; 146.5; 129.2; 128.5; 123.6; 118.3; 113.9; 57.31; 56.1; 42.4; 29.0; 27.0; 24.9.

2-[(2-Nitrophenyl)(phenylamino)methyl]cyclohexanone (**9b**). HPLC (for *syn*): *Daicel Chiralpak OD-H*; hexane/i-PrOH 85:15, flow rate, 0.8 ml/min; UV 254 nm; t_R(major) 30.0, t_R(minor) 55.8 min. IR: 3378, 3056, 2934, 2857, 1698, 1586, 1515, 1353. ^{1}H-NMR (400 MHz, $CDCl_3$, *syn*-isomer): 7.96 (*d*, *J* = 8.0, 1 H); 7.77 (*d*, *J* = 7.8, 2 H), 7.53 (*t*, *J* = 7.3, 1 H); 7.49 (*t*, *J* = 8.0, 1 H); 7.10 (*t*, *J* = 7.8, 2 H); 6.70 (*t*, *J* = 7.3, 1 H); 6.57 (*d*, *J* = 8.0, 2 H); 5.63 (*d*, *J* = 4.3, 1 H); 5.47 (*d*, *J* = 7.0, 1 H); 3.01–2.96 (*m*, 1 H); 2.48–2.31 (*m*, 2 H); 2.11–2.02 (*m*, 2 H); 1.72–1.57 (*m*, 4 H). ^{13}C-NMR (100 MHz, $CDCl_3$; *syn*-isomer): 210.2; 149.2; 146.6; 137.2; 133.1; 130.3; 129.2; 128.0; 125.1; 118.4; 114.0; 55.4; 52.2; 42.4; 29.7; 28.4; 27.3; 25.0.

2-[(4-Fluorophenyl)(phenylamino)methyl]cyclohexanone (**9c**). HPLC (for *syn*): *Daicel Chiralpak AD-H*; hexane/i-PrOH 85:15; flow rate, 1.0 ml/min; UV 254 nm; t_R(major) 24.2, t_R(minor) 15.6 min. IR:

3399, 3051, 2937, 2862, 1705, 1602, 1505, 1316, 1221, 837, 750, 692. ^{1}H-NMR (400 MHz, $CDCl_3$; *syn*-isomer): 7.47 (*dd*, *J* = 7.3, 2 H); 7.10 – 7.08 (*m*, 2 H); 7.00 – 6.97 (*m*, 2 H); 6.77 (*q*, *J* = 6.8, 1 H); 6.58 – 6.55 (*m*, 2 H); 4.80 (*d*, *J* = 4.4, 1 H); 4.67 (*d*, *J* = 6.6, 1 H); 2.81 – 2.76 (*m*, 1 H); 2.44 – 2.30 (*m*, 2 H); 1.94 – 1.62 (*m*, 6 H). ^{13}C-NMR (100 MHz, $CDCl_3$; *syn*-isomer): 212.5; 163.0; 160.6; 147.1; 137.5; 129.1; 117.6; 115.3; 113.6; 57.3; 56.7; 41.9; 31.3; 27.8; 23.8.

2-[(4-Bromophenyl)(phenylamino)methyl]cyclohexanone (**9d**). HPLC (for *syn*): *Daicel Chiralpak AD-H*; hexane/i-PrOH 85 : 15, flow rate, 1.0 ml/min; UV 254 nm; t_R(major) 21.0; t_R(minor) 15.6 min. IR: 3396, 3050, 2935, 2861, 1704, 1601, 1502, 1315, 1070, 1008, 825, 750, 692. ^{1}H-NMR (400 MHz, $CDCl_3$; *syn*-isomer): 7.43 – 7.41 (*m*, 2 H); 7.29 – 7.25 (*m*, 2 H); 7.10 – 7.06 (*m*, 2 H); 6.69 – 6.63 (*m*, 1 H); 6.54 – 6.52 (*m*, 2 H); 4.76 (*d*, *J* = 4.0, 1 H); 4.63 (*d*, *J* = 6.3, 1 H); 2.79 – 2.75 (*m*, 1 H); 2.43 – 2.28 (*m*, 2 H); 1.99 – 1.89 (*m*, 2 H); 1.78 – 1.57 (*m*, 4 H). ^{13}C-NMR (100 MHz, $CDCl_3$, *syn*-isomer): 212.3; 147.1; 141.0; 131.5; 129.2; 129.1; 120.8; 117.7; 113.6; 57.2; 56.4; 42.0; 31.5; 27.9; 24.0.

2-{[(4-Methylphenyl)amino](4-nitrophenyl)methyl}cyclohexanone (**9e**). HPLC (for *syn*): *Daicel Chiralpak AD-H*, hexane/i-PrOH 80 : 20; flow rate, 0.8 ml/min; UV 254 nm, t_R(major) 26.6; t_R(minor) 24.9 min. IR: 3388, 3021, 235, 2861, 1706, 1616, 1517, 1448, 1344, 1127, 855, 810, 702. ^{1}H-NMR (400 MHz, $CDCl_3$; *syn*-isomer): 8.14 (*d*, *J* = 8.5, 2 H); 7.59 – 7.55 (*m*, 2 H); 6.89 (*d*, *J* = 8.0, 2 H); 6.44 (*d*, *J* = 8.4, 2 H); 4.86 (*d*, *J* = 4.4, 1 H); 4.72 (*d*, *J* = 7.6, 1 H); 2.88 – 2.82 (*m*, 1 H); 2.42 – 2.30 (*m*, 2 H); 2.17 (*s*, 3 H); 2.05 – 1.89 (*m*, 3 H); 1.74 – 1.70 (*m*, 2 H); 1.62 – 1.56 (*m*, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$; *syn*-isomer): 211.8; 150.1; 146.9; 130.7; 128.3; 127.2; 123.6; 113.6; 57.9; 57.0; 42.3; 31.9; 27.8; 24.4; 20.3.

2-{[(4-Methoxyphenyl)amino)(4-nitrophenyl)methyl}cyclohexanone (**9f**). HPLC (for *syn*): *Daicel Chiralpak AD-H*; hexane/i-PrOH 80 : 20; flow rate, 0.8 ml/min; UV 254 nm; t_R(major) 35.7; t_R(minor) 38.1 min. IR: 3394, 3027, 2935, 2861, 1705, 1600, 1513, 1463, 1344, 1245, 1036, 854, 822. ^{1}H-NMR (400 MHz, $CDCl_3$; *syn*-isomer): 8.15 (*d*, *J* = 8.6, 2 H); 7.58 – 7.54 (*m*, 2 H); 6.69 – 6.64 (*m*, 2 H); 6.46 (*d*, *J* = 8.8, 2 H); 4.80 (*d*, *J* = 4.2, 1 H); 4.65 (*d*, *J* = 5.6, 1 H); 3.68 (*s*, 3 H); 2.84 – 2.80 (*m*, 1 H); 2.42 – 2.30 (*m*, 2 H); 1.98 – 1.89 (*m*, 2 H); 1.78 – 1.62 (*m*, 4 H). ^{13}C-NMR (100 MHz, $CDCl_3$; *syn*-isomer): 211.8; 152.4; 150.0; 147.0; 140.7; 128.3; 123.6; 115.6; 114.8; 58.7; 57.0; 55.6; 43.4; 31.8; 27.7; 24.4.

2-{[(4-Ethoxyphenyl)amino](4-nitrophenyl)methyl}cyclohexanone (**9g**). HPLC: *Daicel Chiralpak AD-H*; hexane/i-PrOH 80 : 20; flow rate, 0.8 ml/min; UV 254 nm: t_R(major) 30.1; t_R(minor) 25.8 min. IR: 3395, 3067, 2934, 2865, 1706, 1597, 1512, 1478, 1344, 1235, 854, 820. ^{1}H-NMR (400 MHz, $CDCl_3$; *syn*-isomer): 8.13 (*d*, *J* = 8.6, 2 H); 7.57 – 7.53 (*m*, 2 H); 6.66 (*d*, *J* = 8.8, 2 H); 6.44 (*d*, *J* = 8.8, 2 H); 4.79 (*d*, *J* = 4.2, 1 H); 4.65 (*d*, *J* = 5.6, 1 H); 3.88 (*q*, *J* = 6.9, 2 H); 2.83 – 2.79 (*m*, 1 H); 2.44 – 2.29 (*m*, 2 H); 1.94 – 1.86 (*m*, 2 H); 1.76 – 1.58 (*m*, 4 H); 1.32 (*t*, *J* = 6.9, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$; *syn*-isomer): 211.8; 151.8; 150.1; 147.0; 140.7; 128.4; 123.6; 115.6; 115.1; 63.9; 58.7; 57.0; 42.3; 31.8; 27.8; 24.4; 14.9.

2-{[(4-Chlorophenyl)amino](4-nitrophenyl)methyl}cyclohexanone (**9h**). HPLC (for *syn*): *Daicel Chiralpak AD-H*; hexane/i-PrOH 80 : 20; flow rate, 0.8 ml/min, UV 254 nm; t_R(major) 29.9, t_R(minor) 24.3 min. IR: 3428, 3024, 2943, 2858, 1702, 1600, 1512, 1346, 1108, 729, 708. ^{1}H-NMR (400 MHz, $CDCl_3$; *syn*-isomer): 8.13 (*d*, *J* = 8.4, 2 H); 7.55 – 7.51 (*m*, 2 H); 6.99 (*d*, *J* = 8.7, 2 H); 6.41 (*d*, *J* = 8.7, 2 H); 4.81 (*d*, *J* = 4.3, 1 H); 4.65 (*d*, *J* = 5.3, 1 H); 2.85 – 2.83 (*m*, 1 H); 2.44 – 2.28 (*m*, 2 H); 1.91 – 1.58 (*m*, 6 H). ^{13}C-NMR (100 MHz, $CDCl_3$; *syn*-isomer): 211.9; 149.4; 147.0; 145.4; 129.0; 128.3; 123.7; 122.6; 114.6; 57.9; 56.9; 42.4; 32.1; 27.8; 24.5.

2-{[(3-Bromophenyl)amino](4-nitrophenyl)methyl}cyclohexanone (**9i**). HPLC (for *syn*): *Daicel Chiralpak AD-H*; hexane/i-PrOH 80 : 20; flow rate, 0.8 ml/min, UV 254 nm; t_R(major) 26.8, t_R(minor) 17.9 min. IR: 3397, 3070, 2937, 2861, 1705, 1677, 1594, 1518, 1479, 1344, 853, 763, 702. ^{1}H-NMR (400 MHz, $CDCl_3$; *syn*-isomer): 8.08 (*d*, *J* = 8.5, 2 H); 7.53 – 7.49 (*m*, 2 H); 6.87 – 6.83 (*m*, 1 H); 6.71 – 6.69 (*m*, 1 H); 6.63 – 6.62 (*m*, 1 H); 6.37 – 6.35 (*m*, 1 H); 4.82 (*d*, *J* = 4.1, 1 H); 4.66 (*d*, *J* = 5.1, 1 H); 2.85 – 2.80 (*m*, 1 H); 2.35 – 2.24 (*m*, 2 H); 1.86 – 1.83 (*m*, 2 H); 1.67 – 1.55 (*m*, 4 H). ^{13}C-NMR (100 MHz, $CDCl_3$; *syn*-isomer): 211.6; 149.2; 148.2; 147.0; 130.4; 128.5; 123.6; 120.8; 116.6; 112.3; 56.7; 42.3; 32.1; 28.8; 27.0; 24.8.

2-{[(3-Methylphenyl)amino](4-nitrophenyl)methyl}cyclohexanone (**9j**). HPLC (for *syn*): *Daicel Chiralpak AD-H*, hexane/i-PrOH 80 : 20; flow rate, 0.8 ml/min, UV 254 nm; t_R(major) 23.7, t_R(minor) 17.8 min. IR: 3380, 3038, 2921, 2855, 1706, 1604, 1518, 1489, 1344, 854, 772, 694. ^{1}H-NMR (400 MHz, $CDCl_3$; *syn*-isomer): 8.14 (*d*, *J* = 8.6, 2 H); 7.57 (*t*, *J* = 8.4, 2 H); 6.96 (*t*, *J* = 7.7, 1 H); 6.51 – 6.48 (*m*, 1 H); 6.36 (*s*, 1 H); 6.28 (*d*, *J* = 7.9, 1 H); 4.87 (*d*, *J* = 4.5, 1 H); 4.73 (*d*, *J* = 5.2, 1 H); 2.88 – 2.84 (*m*, 1 H); 2.42 –

2.32 (*m*, 2 H); 2.19 (*s*, 3 H); 1.96 – 1.60 (*m*, 6 H). ^{13}C-NMR (100 MHz, $CDCl_3$; *syn*-isomer): 211.8; 150.1; 139.0; 128.6; 123.6; 119.0; 114.9; 114.4; 110.9; 110.4; 57.0; 56.3; 42.4; 32.0; 29.0; 27.8; 24.4.

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