Organocatalytic Asymmetric α-Aminomethylation of Cyclohexanones

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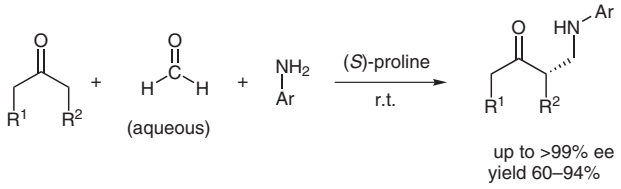
Abstract: The amino acid catalyzed direct asymmetric Mannich reaction between aminomethyl ether **1** and cyclohexanones is presented. The unprecedented reaction proceeds via an ionic transition state and gives the corresponding Mannich bases in moderate to high yields with 75–99% ee.

Key words: organocatalysis, Mannich reactions, aminomethylation, amino acids, asymmetric catalysis

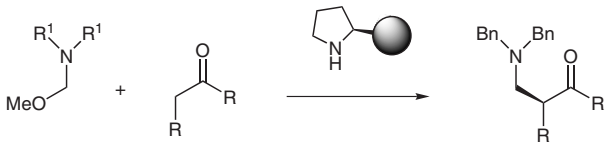
The classical Mannich reaction,[1] in which an aminomethyl group is introduced in the α-position to a carbonyl compound, has found a multitude of applications in organic chemistry.[2] The resulting Mannich bases are of particular interest due to their biological activities, such as analgesics, antioplastics, and antibiotics, and as synthetic building blocks and precursors for pharmaceutically valuable γ-amino alcohols.[2] However, only a few stereoselective α-aminomethylation reactions have been developed.[3,4]

Several stoichiometrically indirect stereoselective Mannich transformations that utilize preformed enol equivalents or imines are known.[5] More recently, the first successful examples of catalytic asymmetric additions of enolates to imines were reported.[6] This has led to an intense research of catalytic indirect Mannich reactions.[7] The first direct asymmetric Mannich reaction was catalyzed by Shibasaki's heterodimetallic complexes.[8] Recently, dinuclear zinc organometallic complexes were reported that catalyze highly enantioselective Mannich-type reactions between hydroxyaryl ketones and preformed imines.[9] Moreover, chiral copper(II) bisoxazoline (BOX) complexes catalyze direct asymmetric Mannich reactions involving activated ketones as donors.[10] Recently, direct organocatalytic Mannich reactions that are catalyzed by chiral Brønsted acids,[11] chincona alkaloids,[12] proline and its derivatives,[13] peptide derivatives[14] and amino acids[15] were developed. In this context, we reported the amino acid catalyzed α-aminomethylation of ketones (Equation 1).[16] More recently, Gellman[17] and we independently reported the direct α-aminomethylation of aldehydes (Equation 2).[18]



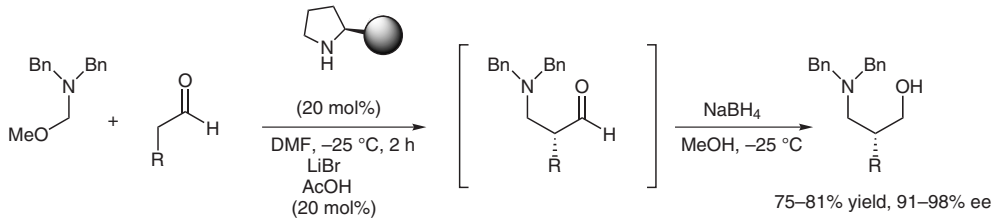
Equation 1

Encouraged by these findings, we envisioned the possibility of developing a direct organocatalytic asymmetric Mannich reaction between aminomethyl ethers and ketones (Equation 3).



Equation 3

If successful, the reaction would give access to Mannich products with protective groups that can be readily removed by hydrogenolysis. Herein, we report the unprecedented organocatalytic enantioselective Mannich reaction between dibenzyl aminomethyl ether **1** and ketones **2**, which furnish the corresponding Mannich bases in moderate to high yields with 75–99% ee. In initial experi-



Equation 2

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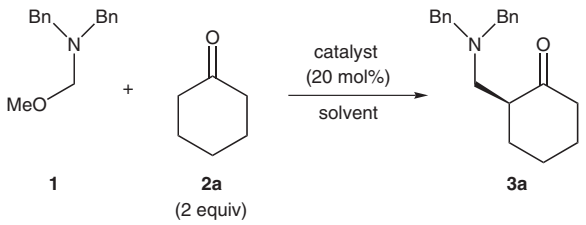
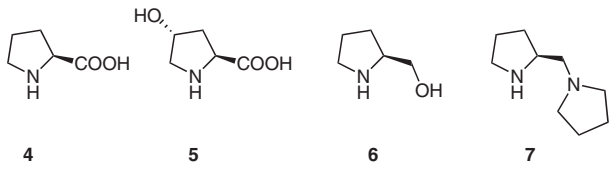
ments, we screened different chiral pyrrolidines (20 mol%) for their ability to catalyze the asymmetric reaction between α-aminomethyl ether **1** (1 mmol) and cyclohexanone (**2a**) (2 mmol) in DMSO (2 mL) at room temperature (Table 1).

We found that all the tested chiral amines **4**–**7** catalyze the asymmetric formation of **3a** with high efficiency but low to moderate enantioselectivity. (*S*)-Proline gave the highest asymmetric induction and was selected as the catalyst to be further investigated. The efficiency and enantioselectivity of the (*S*)-proline-catalyzed reaction was significantly increased by heating or microwave irradiation.[13j,19] For instance, Mannich base **3a** was obtained in 53% yield with 99% ee at 40 °C (entry 5). We also found that the reaction was highly enantioselective in DMF. Notably, the use of ten equivalents of **2a** gave the Mannich product **3a** in 75% yield with 99% ee after three hours (entry 10). Encouraged by this excellent result, we decided to investigate the scope of the reaction for different cyclohexanones (Table 2). We found that the reactions with ketones **2a**–**e** gave the corresponding α-aminomethylated ketones **3a**–**e** in good to high yields with high enantioselectivity (75–99% ee). We also investigated the reaction for cycloheptanone but the major product was the corresponding 2-methylenecycloheptanone. The use of hydroxyacetone as the donor enabled the asymmetric formation of Mannich base **3f** as the only regioisomer in 32% yield with 83% ee. However, octan-2-one did only give trace amounts of products. The Mannich bases **3** can also be converted in one-pot to the corresponding amino alcohols (Scheme 1). For instance, a one-pot tandem organocatalytic α-aminomethylation/reduction sequence gave amino alcohol **8** (*cis*/*trans* = 1:1) in 74% yield with 99% ee. After that, a *Pseuomonas cepacia* lipase-catalyzed kinetic resolution gave acetylated *trans*-**9** and remaining *cis*-**8**. The utilization of dehydrogenation and acetylation sequences provided the corresponding diacetate **10**.

Comparison with the literature revealed that the absolute configuration at C2 of **3a** was *S*.[4b] Based on this result, we

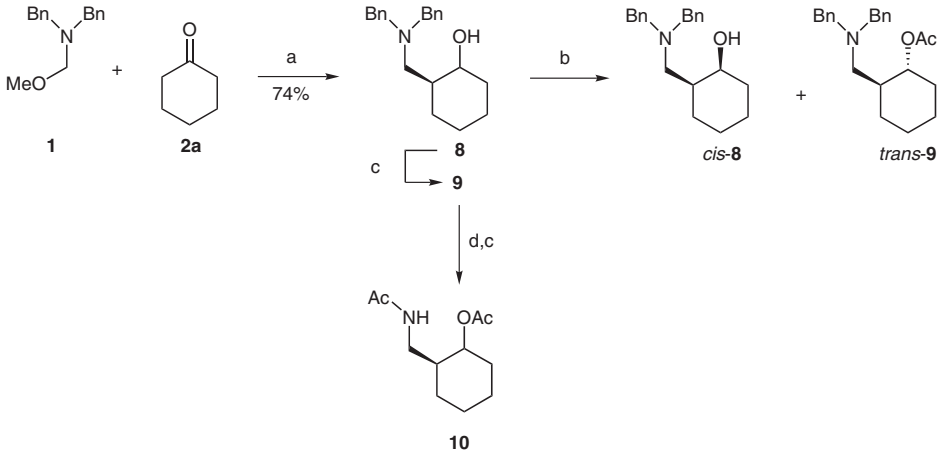
Table 1 Screening of Catalysts for Enantioselective Mannich Reactions





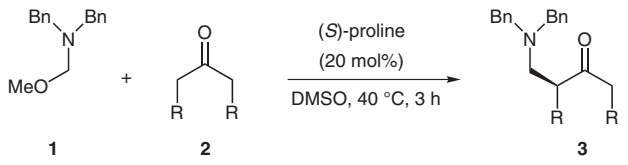
Entry	Catalyst	Solvent	Temp (°C)	Time (h)	Yield (%)[a]	ee (%)[b]
1	**4**	DMSO	r.t.	4	45	41
2	**5**	DMSO	r.t.	4	60	24
3	**6**	DMSO	r.t.	4	70	20
4	**7**	DMSO	r.t.	4	40	27
5	**4**	DMSO	40	3	53	99
6	**4**	DMSO	60	2	70	60
7	**4**	DMSO	100	0.3	30	80
8	**4**	DMF	40	3	60	86
9	**4**	NMP	40	3	40	49
10	**4**	DMSO	40	3	75[c]	99[c]

[a] Yield of pure compound after silica gel column chromatography.
[b] Determined by chiral-phase HPLC analyses.
[c] Ten equivalents of cyclohexanone (**2a**) were used.

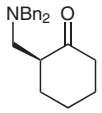
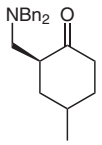
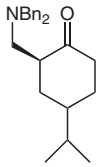
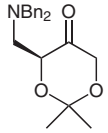
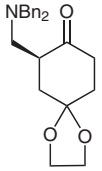
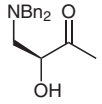


Scheme 1 *Reagents and conditions*: (a) (*S*)-proline (20 mol%), DMSO, 40 °C, 3 h; (b) *P. cepacia* lipase, isopropenyl acetate, $CHCl_3$, 50 °C, 4 h; (c) Ac_2O, cat. DMAP, CH_2Cl_2, r.t., 8 h; (d) Pd/C (10 mol%), MeOH, r.t., 16 h.

Table 2 Organocatalytic Asymmetric α-Aminomethylation of Ketones



1 2 3

Entry	Ketone	Product	Yield (%)[a]	dr[b]	ee (%)[c]
1	**2a**	 **3a**	75[d]	–	99
2	**2b**	 **3b**	73[d]	1:1	98
3	**2c**	 **3c**	70[d]	1:1	n.d.[e]
4	**2d**	 **3d**	43[f]	–	84
5	**2e**	 **3e**	50[f]	–	75
6	**2f**	 **3f**	32[d]	–	83

[a] Yield of pure compound after silica gel column chromatography.
[b] *Anti*/*syn* ratio determined by NMR analysis.
[c] Determined by chiral-phase HPLC analyses.
[d] Ten equivalents of the corresponding ketone **2** were used.
[e] n.d. = not determined.
[f] Two equivalents of the corresponding ketone **2** were used.

propose that the (*S*)-proline-catalyzed reaction proceed via an ionic transition state where the *Si* face of the chiral enamine is approached by the in situ generated iminium ion (Figure 1). This is in accordance with previous (*S*)-proline-catalyzed α-aminomethylation of aldehydes with aminomethyl ether **1** as the electrophile.[17,18]

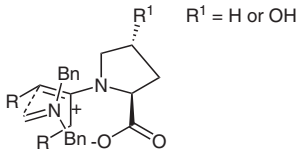


Figure 1 Possible transition state for (*S*)-proline-catalyzed Mannich reaction.

In summary, we have described a highly regio- and enantioselective organocatalytic Mannich-type reaction between α-aminomethyl ethers and cyclohexanones as well as hydroxyacetone. Further development of this reaction to the use of other acyclic ketones and molecular modeling studies are in progress.

Chemicals and solvents were either purchased puriss p.A. from commercial suppliers or purified by standard techniques. Aminomethyl ether **1** was synthesized according to literature procedures.[20] For TLC, silica gel plates Merck 60 F254 were used and compounds were visualized by irradiation with UV light and/or by treatment with a solution of phosphomolybdic acid (25 g), $Ce(SO_4)_2 \cdot H_2O$ (10 g), concd H_2SO_4 (60 mL), and H_2O (940 mL) followed by heating or by treatment with a solution of *p*-anisaldehyde (23 mL), concd H_2SO_4 (35 mL), AcOH (10 mL), and EtOH (900 mL) followed by heating. Flash chromatography was performed using silica gel Merck 60 (particle size 0.040–0.063 mm). ^{1}H NMR and ^{13}C NMR spectra were recorded on Varian AS 400. Chemical shifts are given in δ relative to TMS, and the coupling constants *J* in Hz. The NMR spectra were recorded at r.t. in $CDCl_3$ as solvent; TMS served as internal standard (δ = 0) for ^{1}H NMR, and $CDCl_3$ was used as internal standard (δ = 77.0) for ^{13}C NMR. HPLC was carried out using a Waters 2690 Millennium with photodiode array detector. Optical rotations were recorded on a Perkin-Elmer 241 Polarimeter (λ = 589 nm, 1 dm cell) at 23 °C.

Mannich Bases 3; (–)-(*S*)-2-[(Dibenzylamino)methyl]cyclohexan-1-one [(*S*)-3a]: Typical Procedure

To a mixture of (*S*)-proline [(23 mg, 0.2 mmol (20 mol%)] and aminomethyl ether **1** (241 mg, 1 mmol) in DMSO (2 mL), was added cyclohexanone (**2a**; 980 mg, 10 mmol) at 40 °C. After stirring vigorously for 3 h at this temperature, the mixture was directly loaded onto a neutral aluminum oxide[21] column and eluted with EtOAc–toluene mixtures to furnish the pure Mannich base **3a**; $[\alpha]_D$ –20.2 (*c* = 1.0, $CHCl_3$). The enantiomeric excess was determined by HPLC with an AD column. Conditions: *n*-hexane–*i*-PrOH (99.5:0.5), 0.5 mL/min; major isomer: t_R = 26.5 min, minor isomer: t_R = 29.6 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.31 (m, 1 H), 1.52 (m, 1 H), 1.63 (m, 1 H), 1.72 (m, 1 H), 1.87 (m, 1 H), 2.20 (m, 1 H), 2.28 (m, 1 H), 2.34 (m, 1 H), 2.45 (m, 1 H), 2.55 (m, 1 H), 2.80 (dd, *J* = 5.4, 12.8 Hz, 1 H), 3.42 (d, *J* = 13.6 Hz, 2 H), 3.64 (d, *J* = 13.6 Hz, 2 H), 7.21–7.37 (m, 10 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.2, 28.0, 32.1, 41.8, 49.1, 53.2, 59.2, 127.1, 128.4, 129.1, 140.0, 213.4.

3b

$[\alpha]_D$ –10.8 (*c* = 1.0, $CHCl_3$). The enantiomeric excess was determined by HPLC with an ODH column. Conditions: *n*-hexane–*i*-PrOH (99.0:1.0), 0.5 mL/min; major isomer: t_R = 17.6 min, minor isomer: t_R = 21.0 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ (mixture of two diastereomers) = 0.89 (d, *J* = 6.2 Hz, 3 H), 0.99 (d, *J* = 6.5 Hz, 3 H), 1.32 (m, 2 H), 1.60 (m, 2 H), 1.80 (m, 2 H), 2.0 (m, 2 H), 2.12 (m, 2 H), 2.29

(m, 2 H), 2.50 (m, 2 H), 2.75 (m, 2 H), 2.82 (m, 2 H), 3.34 (d, *J* = 13.5 Hz, 2 H), 3.44 (d, *J* = 13.3 Hz, 2 H), 3.63 (d, *J* = 13.3 Hz, 2 H), 3.74 (d, *J* = 13.5 Hz, 2 H), 7.20–7.38 (m, 20 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.0, 21.6, 26.6, 32.1, 35.0, 36.0, 38.0, 38.4, 41.0, 42.0, 47.5, 48.1, 53.7, 54.4, 58.6, 59.5, 127.0, 127.2, 128.3, 128.4, 129.0, 129.4, 139.6, 140.0, 213.2, 214.4.

3c

$[\alpha]_D$ –12.4 (*c* = 1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.86 (dd, *J* = 6.7–8.8 Hz, 6 H), 0.92 (dd, *J* = 1.24, 6.7 Hz, 6 H), 1.35 (m, 2 H), 1.47 (m, 2 H), 1.55 (m, 2 H), 1.64 (m, 2 H), 1.75 (m, 2 H), 1.83 (m, 2 H), 1.96 (m, 2 H), 2.13 (m, 2 H), 2.27 (m, 2 H), 2.42 (m, 2 H), 2.83 (m, 2 H), 3.35 (d, *J* = 13.6 Hz, 2 H), 3.48 (d, *J* = 13.3 Hz, 2 H), 3.58 (d, *J* = 13.3 Hz, 2 H), 3.73 (d, *J* = 13.6 Hz, 2 H), 7.37–7.23 (m, 20 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.9, 20.1, 20.2, 20.4, 29.6, 31.0, 31.5, 32.3, 33.0, 35.7, 37.6, 38.5, 42.0, 43.1, 47.5, 48.2, 54.0, 54.5, 58.6, 59.7, 127.1, 127.2, 128.3, 128.4, 129.1, 129.3, 139.6, 140.0, 213.4, 214.7.

3d

Two equivalents of ketone **2d** were used in the reaction.

$[\alpha]_D$ –23.0 (*c* = 1.0, $CHCl_3$). The enantiomeric excess was determined by HPLC with an AD column. Conditions: *n*-hexane–*i*-PrOH (98.0:2.0), 0.5 mL/min; major isomer: t_R 10.8 min, minor isomer: t_R = 12.8 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.44 (s, 3 H), 1.51 (s, 3 H), 2.74 (q, *J* = 8.0, 14.4 Hz, 1 H), 3.18 (dd, *J* = 2.7, 14.5 Hz, 1 H), 3.67 (d, *J* = 13.7 Hz, 2 H), 3.77 (d, *J* = 13.7 Hz, 2 H), 3.96 (d, *J* = 16.9 Hz, 1 H), 4.24 (dd, *J* = 1.5, 16.9, 1 H), 4.51 (m, 1 H), 7.40–7.30 (m, 10 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.9, 24.3, 52.1, 59.0, 67.0, 75.1, 101.0, 127.2, 128.4, 129.0, 140.0, 208.9.

3e

Two equivalents of ketone **2e** were used in the reaction.

$[\alpha]_D$ –18.0 (*c* = 1.0, $CHCl_3$). The enantiomeric excess was determined by HPLC with an ODH column. Conditions: *n*-hexane–*i*-PrOH (97.0:3.0), 0.5 mL/min; major isomer: t_R 38.5 min, minor isomer: t_R 42.3 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.90 (m, 1 H), 1.98 (m, 1 H), 2.30 (m, 1 H), 2.41 (m, 1 H), 2.49 (m, 1 H), 2.56 (m, 1 H), 2.61 (m, 1 H), 2.82 (d, *J* = 4.2 Hz, 1 H), 2.9 (m, 1 H), 3.31 (d, *J* = 13.6 Hz, 2 H), 3.72 (d, *J* = 13.6 Hz, 2 H), 3.99 (m, 4 H), 7.23–7.35 (m, 10 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 35.0, 38.5, 39.0, 45.0, 53.1, 59.0, 64.7, 65.0, 107.7, 127.1, 128.4, 129.1, 140.0, 211.5.

3f

$[\alpha]_D$ –4.6 (*c* = 1.0, $CHCl_3$). The enantiomeric excess was determined by HPLC with an ODH column. Conditions: *n*-hexane–*i*-PrOH (97.0:3.0), 0.5 mL/min; major isomer: t_R 23.0 min, minor isomer: t_R 29.4 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.92 (s, 3 H), 2.75–2.88 (m, 1 H), 3.45 (d, *J* = 13.4 Hz, 2 H), 3.84 (d, *J* = 13.4 Hz, 2 H), 4.2 (dd, *J* = 2.6, 4.1 Hz, 1 H), 7.35–7.23 (m, 10 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.0, 55.3, 59.2, 76.1, 127.6, 128.6, 129.5, 139.0, 210.2.

***Cis*-8 and *trans*-8**

One-Pot Preparation: To a mixture of (*S*)-proline [23 mg, 0.2 mmol (20 mol%)] and aminomethyl ether **1** (241 mg, 1 mmol) in DMSO (2 mL), was added cyclohexanone (**2a**; 980 mg, 10 mmol) at 40 °C. After stirring vigorously for 3 h at this temperature, the temperature was decreased to 0 °C, and MeOH (2 mL) and then excess $NaBH_4$ (757 mg, 20 mmol) were added. After stirring for 5 min at this temperature, the mixture was poured into a cold stirred mixture of EtOAc (20 mL) and aq 1 M HCl (2 mL). The mixture was dried (Na_2SO_4), evaporated and the residue was purified by column chromatography to afford the corresponding reduced alcohols **8** (*cis*/*trans* = 1:1); yield: 229 mg (74%). The enantiomeric excess was determined by HPLC with an ODH column. Conditions: *n*-hexane–*i*-PrOH (99.5:0.5), 0.5 mL/min; major *syn*-isomer: t_R 46.3 min, minor *syn*-isomer: t_R 33.0 min, major *anti*-isomer: t_R 46.3 min, minor *anti*-isomer: t_R 77.7 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ (mixture of two diastereomers) = 0.77 (m, 1 H), 1.12–1.53 (m, 10 H), 1.61–1.78 (m, 4 H), 1.94 (m, 2 H), 2.10 (m, 1 H), 2.22 (dd, *J* = 13.0, 4.2 Hz, 1 H), 2.30 (dd, *J* = 13.0, 2.8 Hz, 1 H), 2.62 (dd, *J* = 13.0, 11.6 Hz, 1 H), 2.85 (dd, *J* = 13.0, 19.9 Hz, 1 H), 3.11 (d, *J* = 13.2 Hz, 2 H), 3.21 (d, *J* = 13.2 Hz, 2 H), 3.90 (d, *J* = 13.2 Hz, 2 H), 4.09 (d, *J* = 13.3 Hz, 2 H), 7.33–7.38 (m, 20 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.3, 25.8, 27.4, 29.0, 31.7, 34.4, 37.0, 40.6, 59.2 (2 C), 59.3, 61.3, 70.3 (2 C), 127.5, 127.6, 18.7, 129.0, 130.0 (2 C), 138.0, 139.0.

Enzyme-Catalyzed Kinetic Resolution of Amino Alcohol 8

To a solution of amino alcohol **8** [*cis*/*trans* (1:1), 278 mg, 0.9 mmol] and isopropenyl acetate (135 mg, 1.35 mmol) in toluene was added *P. cepacia* lipase (PS-C Amano II, 90 mg) at 50 °C. After 5.5 h, 50% conversion was reached and the enzyme was removed by filtration. Purification by silica gel column chromatography (EtOAc–pentane mixtures) gave *cis*-**8** and *trans*-**9** quantitatively.

(+)-(1*S*,2*S*)-*cis*-8

$[\alpha]_D$ +8.1 (*c* = 1.0, MeOH).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.86 (m, 1 H), 1.10–1.41 (m, 3 H), 1.63 (m, 2 H), 1.83–1.90 (m, 2 H), 2.18 (m, 2 H), 2.83 (dd, *J* = 16.9, 4.9 Hz, 1 H), 3.14 (t, *J* = 15.4 Hz, 1 H), 3.40 (d, *J* = 13.6 Hz, 2 H), 3.63 (d, *J* = 13.6 Hz, 2 H), 7.28–7.38 (m, 10 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.8, 23.4, 27.4, 31.7, 37.0, 55.2, 59.3, 70.3, 127.5, 128.6, 129.4, 138.9.

(–)-(1*R*,2*S*)-*trans*-9

$[\alpha]_D$ –5.1 (*c* = 1.0, MeOH).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.78 (m, 1 H), 1.13–1.32 (m, 4 H), 1.62–1.87 (m, 3 H), 2.02 (s, 3 H), 2.19 (m, 2 H), 2.42 (dd, *J* = 12.7, 3.6 Hz, 1 H), 3.27 (d, *J* = 13.9 Hz, 2 H), 3.77 (d, *J* = 13.9 Hz, 2 H), 4.44 (m, 1 H), 7.29–7.40 (m, 10 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.6, 24.3, 24.9, 29.4, 31.2, 31.6, 40.1, 56.1, 59.1, 75.6, 127.1, 128.4, 129.1, 140.0, 171.0.

Diacetate 10[22]

To a solution of acetate **9** (*cis*/*trans*-1:1, 0.9 mmol) in MeOH (2.0 mL) was added a catalytic amount of Pd/C. After hydrogenolysis (90 MPa) for 17 h, the catalyst was filtered off on a pad of Celite and the solvent was removed under reduced pressure. After that, the intermediate amino alcohol was N-acetylated by addition of CH_2Cl_2 (2 mL), Et_3N (101 mg, 1.0 mmol), Ac_2O (102 mg, 1.0 mmol) and DMAP (12.2. mg, 0.1 mmol). After stirring for 16 h, the mixture was directly loaded onto a silica gel column and eluted with pentane–EtOAc mixtures to give the pure known diacetate **10** (*cis*/*trans* = 1:1)[22] as a clear oil; yield: 171 mg (89%).

^{1}H NMR (400 MHz, $CDCl_3$): δ (mixture of two diastereomers) = 0.76–1.00 (m, 2 H), 1.10–1.35 (m, 4 H), 1.40–1.54 (m, 4 H), 1.62–1.74 (m, 4 H), 1.80–1.96 (m, 4 H), 2.01 (s, 3 H), 2.02 (s, 3 H), 2.04 (s, 3 H), 2.05 (s, 3 H), 4.36–4.48 (m, 4 H), 4.93 (m, 2 H).[22]

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