Article

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Development of the Ireland–Claisen Rearrangement of Allyl-2-alkoxyacetate Bearing an Allylic Amine and the Transformation to 3-Hydroxy-4-hydroxymethylpyrrolidine

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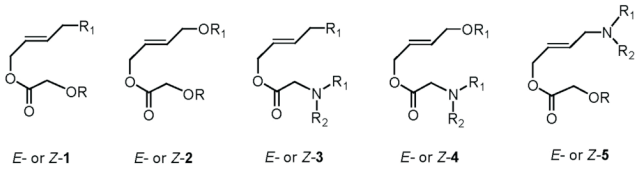
An unprecedented Ireland–Claisen rearrangement of allylglycolate bearing an allylic amine was realized, affording the corresponding product with excellent diastereoselectivity and in high yield. The product was analyzed by X-ray crystallography, and demonstrated the transformation to the 4-hydroxymethylpyrrolidin-3-ol.

Keywords: Ireland–Claisen rearrangement; Synthesis; Allylglycolate; Allylic amine.

INTRODUCTION

For nearly a century, the Claisen Rearrangement[1] has played a pivotal role in organic synthesis, and a variety of modifications have been discovered for different purposes. Among the variant rearrangements, the Ireland–Claisen rearrangement[2] is one of the most interesting protocols, efficiently providing γ,δ-unsaturated carbonyl compounds with high stereoselectivity.[3] Recently, the observation of Claisen rearrangements in biological systems has further attracted scientists' interests,[4] resulting in the development of the organocatalysis Claisen rearrangements.[5] Traditionally, the Ireland–Claisen rearrangements of the corresponding allylglycolate (*e.g.*, **1**–**4**) have received much attention,[6] and the reactions of the variants bearing oxygen or nitrogen at different positions of the starting substrates have been reported (Scheme I).[7] Nevertheless, the Ireland–Claisen rearrangement of an allylglycolate bearing an allylic amine (*e.g.*, **5**),[8] as depicted in Scheme I, has received little attention. It would be interesting to explore the reaction of such substrates, to reveal the stereoselectivity of the transformation, and to identify synthetic applications. Herein we report such observations and an application toward the synthesis of 4-hydroxymethylpyrrolidin-3-ol, an important intermediate in the synthesis of nucleotides or sodium channel blockers.[9]

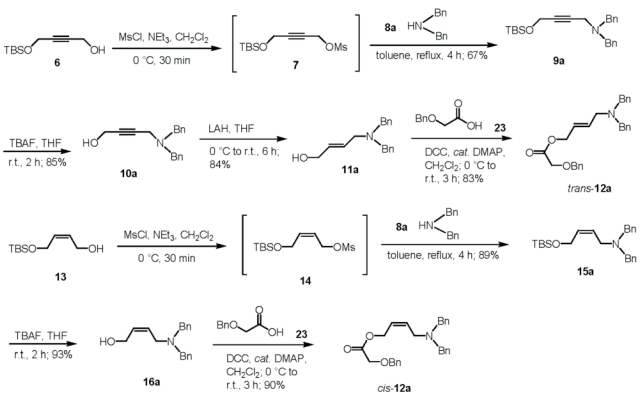
Scheme I Selected allylglycolate variants for the Ireland–Claisen rearrangement



RESULTS AND DISCUSSION

Initially, the *trans*-glycolate **12a** was prepared through a sequence of reactions starting from 1-(*tert*-butyldimethylsilyloxy)but-2-yn-4-ol (**6**)[10] by mesylation and amination (MsCl, Et_3N, CH_2Cl_2, 0 °C, 30 min; Bn_2NH, toluene, reflux, 4 h; 89%) to give the propargyl amine **9a**. Deprotection of **9a** followed by reduction afforded the allylic amine **11a**, which was reacted with 2-(benzyloxy)acetic acid to provide the *trans*-glycolate **12a** (Scheme II). On the other hand, the *cis*-glycolate **12a**[11] was prepared starting from the allylether **13** by a similar reaction sequence (Scheme II).

Scheme II Preparation of the allylglycolate **12a**



At the outset of the study, the rearrangement of *cis*-glycolate **12a** was carried out using various Lewis acids, Lewis bases, and solvents, see Table 1. The series of screenings revealed that the best yield was obtained by the

Dedicated to the memory of Professor Yung-Son Hon (1955–2011).

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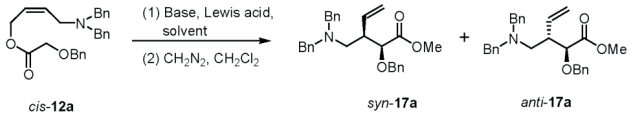
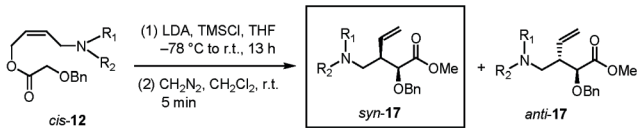
Table 1. Reaction condition screening for the rearrangement



Entry	Base	Solvent	Lewis acid	Time (h)	Yield [b] (%)
1	LDA	THF	TMSCl	13	90
2	LiHMDS	THF	TMSCl	13	82
3	NaHMDS	THF	TMSCl	13	54
4	KHMDS	THF	TMSCl	12	73
5	LDA	toluene	TMSCl	12	69
6	LDA	Ether	TMSCl	12	79
7	LDA	THF	TBSCl	13	76
8	LDA	THF	TMSOTf	12	65
9	NEt_3	CH_2Cl_2	TMSOTf	14	76 [c]

[b] Isolated yields; unless otherwise noted, dr (*cis*:*trans*) >95:5. [c] dr (*cis*:*trans*) = 75:25.

Table 2. Scope of the rearrangement of *cis*-glycolate **12**



Entry	Product	Yield (%)[a]	dr[b]
1	**17a** $R_1 = R_2 =$ Bn	90	>95:5
2	**17b** $R_1 =$ allyl, $R_2 =$ Bn	81	>95:5
3	**17c** $R_1 =$ Ph, $R_2 =$ Me	82	16:1
4	**17d** $R_1 = c\text{-}C_6H_{11}$, $R_2 =$ Bn	63	>95:5
5	**17e** $R_1 = R_2 = i\text{-}C_3H_7$	71	>95:5
6	**17f** $R_1 = R_2 =$ pyrrolidine	79	>95:5
7	**17g** $R_1 = R_2 =$ piperidine	57	>95:5
8	**17h** $R_1 =$ Me, $R_2 =$ Bn	90	>95:5
9	**17i** $R_1 =$ allyl, $R_2 = c\text{-}C_6H_{11}$	58	>95:5
10	**17j** $R_1 =$ PMB, $R_2 =$ Bn	67	>95:5
11	**17k** $R_1 = R_2 = N_3$	60	4:1

[a] Isolated yield. [b] Determined by ^1H NMR of the crude products.

reaction conditions involving LDA–TMSCl in THF at ambient temperature for 13 h, followed by in situ treatment of diazomethane to give a 90% yield of the *trans*-**17** as the only observable diastereomer (Table 1, entries 1). Replacement of LDA by LiHMDS, NaHMDS, or KHMDS under the same reaction conditions afforded a lower yield of the products, 54–82%, (Table 1, entries 2–4). The reaction under LDA–TMSCl condition in other solvents, *e.g.*, toluene, Et_2O, provided lower yields, 69–79% (Table 1, entries 5–6). Replacement of TMSCl by other acids, such as TBSCl or TMSOTf, also gave lower yields, (Table 1, entries 7–8). It is noteworthy that the reaction with Et_3N-TMSOTf in CH_2Cl_2 yielded a 3:1 ratio of the *cis*/*trans* mixture of **17** (Table 1, entry 9). The structure of the product *syn*–**17** was unambiguously confirmed based on the X-ray analysis (Figure 1).

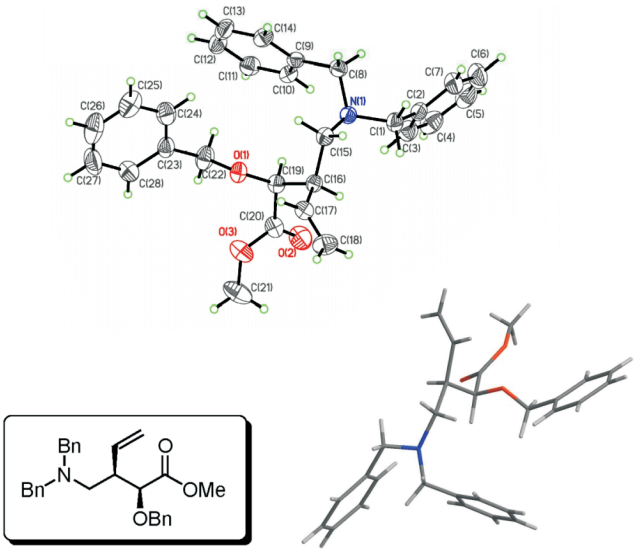


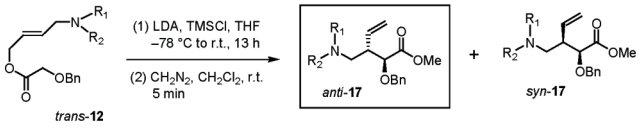
Fig. 1. Stereo plots of the X-ray crystal structures of *syn*-**17a**: C, gray; N, blue; O, red, and the ORTEP diagram.

With the optimized conditions in hand, a series of *cis*-glycolates **12** was prepared according the aforementioned protocol and subjected to the rearrangement conditions. The results are summarized in Table 2, and, for most cases, the reaction gave *syn*-**17** in good yields (57–90%) with excellent diastereoselectivities, except for two examples. For the case of **17c**, the diastereomeric ratio dropped to 16:1, then decreased to 4:1, for the case of **17k** in which the two substituents on the nitrogen were azide, Table 2, entries 3 and 11.

The reaction conditions of the Ireland-Claisen rearrangement were alternatively applied to the *trans*-glycolate **12**, prepared according the aforementioned protocol, followed by esterification, to afford the *anti*-**17** as the major isomers (Table 3). For most cases, the *anti*-isomers were the only observable products (dr: >95:5). In a few cases, the diastereomeric ratio dropped to 3:1 or 7:1 (Table 3, entries 2, 3, 8, and 11).

Finally, we explored the possibility of extending the product to 4-(hydroxymethyl)pyrrolidin-3-ol (Scheme III). The *syn*-**17** was converted to the *anti*-lactam **18** by deprotection of the allyl group and spontaneous lactamization (Pd–C, MeOH–HOAc, 100 °C, 3d), followed oxidative

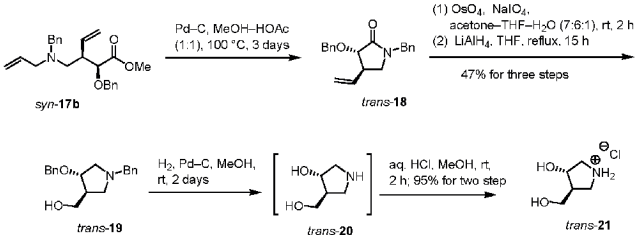
Table 3. Scope of the rearrangement of *trans*-glycolate **12**



Entry	Product	Yield (%)	dr
1	**17a** $R_1 = R_2 =$ Bn	82	>95:5
2	**17b** R_1 = allyl, R_2 = Bn	76	7:1
3	**17c** R_1 = Ph, R_2 = Me	72	3:1
4	**17d** $R_1 = c\text{-}C_6H_{11}$, R_2 = Bn	63	>95:5
5	**17e** $R_1 = R_2 = i\text{-}C_3H_7$	54	>95:5
6	**17f** $R_1 = R_2$ = pyrrolidine	58	>95:5
7	**17g** $R_1 = R_2$ = piperidine	82	>95:5
8	**17h** R_1 = Me, R_2 = Bn	86	8:1
9	**17i** R_1 = allyl, $R_2 = c\text{-}C_6H_{11}$	62	>95:5
10	**17j** R_1 = PMB, R_2 = Bn	61	>95:5
11	**17k** $R_1 = R_2 = N_3$	61	7:1

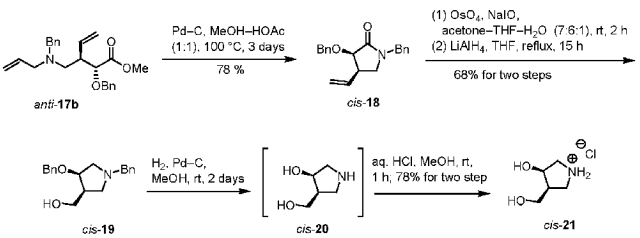
cleavage (OsO_4, $NaIO_4$, acetone–THF–H_2O (7:6:1) and reduction with $LiAlH_4$ to give 47% yield of **19** in three consecutive steps without purification of the intermediates (Scheme III). Deprotection of **19** (Pd–C, H_2, MeOH) afforded the pyrrolidine **20**, which was further treated with an aqueous HCl solution to give 4-(hydroxymethyl)pyrrolidin-3-ol.[12]

Scheme III



The same reaction sequence was alternatively applied in the *anti*-**17b** to give the *cis*-4-(hydroxymethyl)pyrrolidin-3-ol (Scheme IV).

Scheme IV



In summary, an unprecedented Ireland–Claisen rearrangement of an allylglycolate bearing an allylic amine was realized, affording the corresponding methyl 2-alkoxy-3-aminomethylpent-4-enoate with excellent yields and diastereoselectivity. The structure of the product was confirmed unambiguously by X-ray analysis of the appropriate product. Transformations of the products to the *cis*- and *trans*-4-hydroxymethylpyrrolidin-3-ol were achieved.

EXPERIMENTAL

Reactions were normally carried out under nitrogen atmosphere in glassware. Merck silica gel 60 (particle size 0.04-0.063 mm) was employed for flash chromatography. ^{1}H NMR spectra were obtained in $CDCl_3$ unless otherwise noted at 400 MHz (Bruker DPX-400) or 500 MHz (Varian-Unity INOVA-500). ^{13}C NMR spectra were obtained at 100 MHz or 125 MHz. The *melting point was recorded* on a melting point apparatus (MPA100 – Automated melting point system, Stanford Research Systems, Inc.) and is uncorrected.

Typical experimental procedure for the preparation of *trans*-glycolate 12a

To a solution of **11a** (492 mg, 1.84 mmol), N,N-dicyclohexylcarbodiimide (493 mg, 2.39 mmol) and N,N-4-dimethylaminopyridine (22 mg, 0.18 mmol) in CH_2Cl_2 (18 mL) was added benzyloxyacetic acid (398 mg, 2.39 mmol) at 0 °C. The solution was stirred at ambient temperature for 3 h until the completion of reaction, as monitored by TLC. The solution was filtered to remove the precipitate, and the filtrate was concentrated *in vacuo* to give the crude product. The residue was purified by flash column chromatography with 10% EtOAc-hexane (R_f = 0.57 in 20% EtOAc-hexane) to afford product *trans*-glycolate **12a** as a yellow oil (625 mg, 83% yield). Selected spectroscopic data: IR (CH_2Cl_2): 3027, 2924, 2797, 1753, 1454, 1193, 1125, 970, 736, 698 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.36-7.23 (m, 15 H), 5.90-5.83 (m, 1 H), 5.79-5.72 (m, 1 H), 4.64 (d, J = 6.4 Hz, 2 H), 4.62 (s, 2 H), 4.10 (s, 2 H), 3.56 (s, 4 H), 3.07 (d, J = 5.6 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.0 (C), 139.2 (two C), 137.1 (C), 133.4 (CH), 128.8 (four CH), 128.5 (two CH), 128.2 (four CH), 128.04 (two CH), 127.99 (CH), 126.9 (two CH), 126.3 (CH), 73.3 (CH_2), 67.2 (CH_2), 65.0 (CH_2), 57.9 (two CH_2), 54.7 (CH_2); MS (*m/z*, relative intensity): 415 (M^+, 75), 338 (7), 324 (5), 250 (14), 249 (20), 210 (8), 158 (11), 106 (6), 92 (11), 91 (100), 65 (6); exact mass calculate for $C_{27}H_{29}NO_3$ (M^+): 415.2147; found 415.2155.

Typical experimental procedure for the preparation of *cis*-glycolate 12a

To a solution of **16a** (1.24 g, 4.66 mmol), N,N-dicyclohexylcarbodiimide (1.25 g, 6.05 mmol) and N,N-4-dimethylaminopyridine (56 mg, 0.46 mmol) in CH_2Cl_2 (46 mL) was added benzyloxyacetic acid (1.00 g, 6.05 mmol) at 0 °C. The solution was stirred at ambient temperature for 3 h until the completion of reaction, as monitored by TLC. The solution was filtered to remove the precipitate, and the filtrate was concentrated *in vacuo* to give the crude product. The residue was purified by flash column chromatography with 10% EtOAc-hexane (R_f = 0.77 in 25% EtOAc-hexane) to afford product *cis*-glycolate **12a** as a yellow oil (1.74 g, 90% yield). Selected spectroscopic data: IR (CH_2Cl_2): 3028, 2922, 1750, 1455, 1193, 1126, 737, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.36-7.20 (m, 15 H), 5.88-5.76 (m, 1 H), 5.69-5.63 (m, 1 H), 4.64 (d, *J* = 6.8 Hz, 2 H), 4.60 (s, 2 H), 4.06 (s, 2 H), 3.55 (s, 4 H), 3.10 (d, *J* = 6.4 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.0 (C), 139.2 (two C), 137.0 (C), 132.8 (CH), 128.7 (four CH), 128.4 (two CH), 128.2 (four CH), 128.0 (two CH), 127.9 (CH), 126.9 (two CH), 125.7 (CH), 73.3 (CH_2), 67.1 (CH_2), 60.6 (CH_2), 58.1 (two CH_2), 50.0 (CH_2); MS (*m/z*, relative intensity): 415 (M^+, 32), 250 (14), 249 (43), 197 (8), 196 (5), 158 (27), 106 (21), 92 (11), 91 (100), 65 (5); exact mass calculate for $C_{27}H_{29}NO_3$ (M^+): 415.2147; found 415.2153.

Typical experimental procedure for the Ireland-Claisen rearrangement of glycolate 12a, preparation of *syn*-17a

To a solution of *cis*-glycolate **12a** (110 mg, 0.26 mmol) in dry THF (4 mL) was added a solution of lithium diisopropylamide in THF (2.0 M in THF, 0.26 mL, 0.52 mmol) at -78 °C. The solution was stirred for 15 h, followed by the addition of chloro trimethylsilane (TMSCl, 0.10 mL, 0.78 mmol). The solution was gradually warm up to room temperature and stirred for 13 h, followed by the addition of saturated aqueous NH_4Cl (3 mL). The solution was extracted with EtOAc (5 mL × 3), dried over $MgSO_4$, and concentrated in vacuo to give the crude product as yellow oil. The residue was dissolved in CH_2Cl_2, followed by the slow addition of a solution of diazomethane in ether, monitored by TLC. The solution was concentrated *in vacuo* to give the crude product. The residue was purified by flash column chromatography with 10% EtOAc-hexane (R_f = 0.68 in 20% EtOAc-hexane) to afford product *syn*-**17a** as a yellow oil (104 mg, 90% yield).

Spectroscopic data for *syn*-**17a**: IR (CH_2Cl_2): 3028, 2923, 2851, 1749, 1455, 1266, 1204, 1136, 737, 699 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.33-7.13 (m, 15 H), 5.79-5.71 (m, 1 H), 5.08-4.99 (m, 2 H), 4.54 (d, *J* = 11.2 Hz, 1 H), 4.29 (d, *J* = 2.0 Hz, 1 H), 3.99 (d, *J* = 11.2 Hz, 1 H), 3.69 (s, 3 H), 3.63 (d, *J* = 13.6 Hz, 2 H), 3.45 (d, *J* = 13.6 Hz, 2 H), 2.81-2.73 (m, 2 H) 2.47-2.40 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 173.0 (C), 139.2 (two C), 137.8 (C), 135.9 (CH), 129.1 (four CH), 128.2 (four CH), 128.1 (two CH), 127.8 (two CH), 127.4 (CH), 126.9 (two CH), 117.3 (CH_2), 78.7 (CH), 72.5 (CH_2), 58.5 (two CH_2), 55.0 (CH_2), 51.6 (CH_3), 46.3 (CH); MS (*m/z*, relative intensity): 429 (M^+, 49), 211 (17), 210 (100), 181 (4), 92 (8), 91 (87), 65 (5); exact mass calculate for $C_{28}H_{31}NO_3$ (M^+): 429.2304; found 429.2298.

For *anti*-**17a**: 91 mg, 82% yield; R_f = 0.74 (Hexane/EtOAc = 4 : 1), yellow oil.

Spectroscopic data for *anti*-**17a**: IR (CH_2Cl_2): 3027, 2923, 2851, 2797, 1748, 1494, 1453, 1201, 1128, 916, 745, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.32-7.18 (m, 15 H), 5.68-5.59 (m, 1 H), 5.12-5.08 (m, 2 H), 4.64 (d, *J* = 12.0 Hz, 1 H), 4.32 (d, *J* = 12.0 Hz, 1 H), 3.91 (d, *J* = 5.6 Hz, 1 H), 3.64 (d, *J* = 13.6 Hz, 2 H), 3.60 (s, 3 H), 3.40 (d, *J* = 13.6 Hz, 2 H), 2.86-2.81 (m, 1 H) 2.67 (dd, *J* = 12.8, 5.6 Hz, 1 H), 2.54 (dd, *J* = 12.8, 8.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.9 (C), 139.3 (two C), 137.40 (CH), 137.39 (C), 129.0 (four CH), 128.2 (two CH), 128.0 (four CH), 127.8 (two CH), 127.7 (CH), 126.7 (two CH), 117.1 (CH_2), 80.4 (CH), 72.5 (CH_2), 58.3 (two CH_2), 54.0 (CH_2), 51.4 (CH_3), 45.9 (CH); MS (*m/z*, relative intensity): 429 (M^+, 29), 211 (10), 210 (100), 181 (4), 92 (7), 91 (79), 65 (4); exact mass calculate for $C_{28}H_{31}NO_3$ (M^+): 429.2304; found 429.2296.

For *syn*-**17b**: 516 mg, 81% yield; R_f = 0.63 (Hexane/EtOAc = 5 : 1); yellow oil.

Spectroscopic data for *syn*-**17b**: IR (CH_2Cl_2): 3065, 3028, 2949, 2925, 2803, 1752, 1455, 1260, 1202, 1136, 918, 740, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.30-7.21 (m, 10 H), 5.85-5.74 (m, 2 H), 5.15-5.00 (m, 4 H), 4.69 (d, *J* = 11.2 Hz, 1 H), 4.37 (d, *J* = 2.0 Hz, 1 H), 4.26 (d, *J* = 11.2 Hz, 1 H), 3.71 (s, 3 H), 3.68 (d, *J* = 13.6 Hz, 1 H), 3.46 (d, *J* = 13.6 Hz, 1 H), 3.10 (dd, *J* = 14.0, 6.0 Hz, 1 H), 2.96 (dd, *J* = 14.0, 6.8 Hz, 1 H), 2.79-2.73 (m, 2 H), 2.41 (dd, *J* = 17.2, 10.4 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 173.2 (C), 139.3 (C), 137.8 (C), 135.8 (CH), 135.4 (CH), 129.0 (two CH), 128.2 (four CH), 127.9 (two CH), 127.6 (CH), 126.9 (CH), 117.6 (CH_2), 117.4 (CH_2), 78.5 (CH),

72.8 (CH_2), 58.3 (CH_2), 56.8 (CH_2), 54.7 (CH_2), 51.6 (CH_3), 46.1 (CH); MS (*m/z*, relative intensity): 379 (M^+, 49), 161 (11), 160 (100), 92 (5), 91 (73); exact mass calculate for $C_{24}H_{29}NO_3$ (M^+): 379.2147; found 379.2138.

For *anti*-**17b**: 78 mg, 76% yield; R_f = 0.69 (Hexane/EtOAc = 4 : 1); yellow oil.

Spectroscopic data for *anti*-**17b**: IR (CH_2Cl_2): 3065, 3028, 2948, 2838, 2801, 1750, 1454, 1258, 1202, 1132, 917, 739, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.33-7.21 (m, 10 H), 5.87-5.69 (m, 2 H), 5.14-5.05 (m, 4 H), 4.72 (d, *J* = 12.0 Hz, 1 H), 4.37 (d, *J* = 12.0 Hz, 1 H), 3.98 (d, *J* = 4.4 Hz, 1 H), 3.67 (s, 3 H), 3.61 (d, *J* = 13.6 Hz, 1 H), 3.50 (d, *J* = 13.6 Hz, 1 H), 3.07-2.96 (m, 2 H), 2.87-2.79 (m, 1 H), 2.72 (dd, *J* = 12.8, 6.8 Hz, 1 H), 2.50 (dd, *J* = 12.8, 7.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.1 (C), 139.2 (C), 137.6 (C), 137.5 (CH), 135.6 (CH), 129.1 (two CH), 128.3 (two CH), 128.0 (two CH), 127.8 (two CH), 127.7 (CH), 126.7 (CH), 117.3 (CH_2), 116.9 (CH_2), 80.1 (CH), 72.6 (CH_2), 58.2 (CH_2), 56.7 (CH_2), 53.7 (CH_2), 51.5 (CH_3), 45.8 (CH); MS (*m/z*, relative intensity): 379 (M^+, 63), 161 (11), 160 (93), 92 (8), 91 (100), 65 (5); exact mass calculate for $C_{24}H_{29}NO_3$ (M^+): 379.2147; found 379.2144.

For *syn*-**17c**: 97 mg, 82% yield; R_f = 0.68 (Hexane/EtOAc = 5 : 1); yellow oil.

Spectroscopic data for *syn*-**17c**: IR (CH_2Cl_2): 2950, 2870, 1752, 1599, 1507, 1203, 1133, 748, 694 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.39-7.30 (m, 5 H), 7.23-7.17 (m, 2 H), 6.74-6.64 (m, 3 H), 5.95-5.85 (m, 1 H), 5.13-5.07 (m, 2 H), 4.75 (d, *J* = 11.2 Hz, 1 H), 4.25 (d, *J* = 11.2 Hz, 1 H), 4.10 (d, *J* = 2.8 Hz, 1 H), 3.70 (s, 3 H), 3.61 (dd, *J* = 14.8, 8.8 Hz, 1 H), 3.26 (dd, *J* = 14.8, 6.0 Hz, 1 H), 2.99-2.93 (m, 1 H), 2.89 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.3 (C), 149.3 (C), 137.6 (C), 134.7 (CH), 129.1 (two CH), 128.3 (two CH), 127.9 (two CH), 127.8 (CH), 118.4 (CH_2), 116.4 (CH), 112.3 (two CH), 78.3 (CH), 72.4 (CH_2), 54.2 (CH_2), 51.7 (CH_3), 46.3 (CH), 38.9 (CH_3); MS (*m/z*, relative intensity): 339 (M^+, 100), 121 (8), 120 (100), 91 (6); exact mass calculate for $C_{21}H_{25}NO_3$ (M^+): 339.1834; found 339.1840.

For *anti*-**17c**: 73 mg, 72% yield; R_f = 0.74 (Hexane/EtOAc = 4 : 1); yellow oil.

Spectroscopic data for *anti*-**17c**: IR (CH_2Cl_2): 2948, 2871, 1747, 1599, 1507, 1346, 1204, 1132, 993, 749, 695 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.39-7.29 (m, 5 H), 7.22-7.18 (m, 2 H), 6.69-6.66 (m, 3 H), 5.85-5.76 (m, 1 H), 5.15-5.08 (m, 2 H), 4.83 (d, *J* = 11.6 Hz, 1 H), 4.40 (d, *J* = 11.6 Hz, 1 H), 3.93 (d, *J* = 4.8 Hz, 1 H), 3.60 (dd, *J* = 14.4, 7.6 Hz, 1 H), 3.49 (s, 3 H), 3.28 (dd, *J* = 14.4, 7.2 Hz, 1 H), 3.17-3.12 (m, 1 H), 2.86 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.4 (C), 149.1 (C), 137.5 (C), 136.4 (CH), 128.9 (two CH), 128.3 (two CH), 127.9 (two CH), 127.8 (CH), 117.8 (CH_2), 116.1 (CH), 112.2 (two CH), 79.3 (CH), 72.8 (CH_2), 53.6 (CH_2), 51.2 (CH_3), 45.7 (CH), 39.8 (CH_3); MS (*m/z*, relative intensity): 339 (M^+, 100), 121 (9), 120 (100), 105 (7), 91 (11), 77(5); exact mass calculate for $C_{21}H_{25}NO_3$ (M^+): 339.1834; found 339.1831.

For *syn*-**17d**: 98 mg, 63% yield; R_f = 0.50 (Hexane/EtOAc = 8 : 1); yellow oil.

Spectroscopic data for *syn*-**17d**: IR (CH_2Cl_2): 2927, 2853, 1751, 1454, 1248, 1203, 1137, 915, 838, 737, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.35-7.20 (m, 10 H), 5.82-5.73 (m, 1 H), 5.04 (dd, *J* = 10.4, 2 Hz, 1H), 4.96 (dd, *J* = 17.6, 2 Hz, 1H), 4.68 (d, *J* = 11.2 Hz, 1 H), 4.40 (d, *J* = 2.0 Hz, 1 H), 4.19 (d, *J* = 11.2 Hz, 1 H), 3.67 (s, 3 H), 3.64 (s, 2 H), 2.80 (dd, *J* = 12.8, 9.6 Hz, 1 H), 2.54-2.49 (m, 1 H), 2.45 (dd, *J* = 12.8, 5.2 Hz, 1 H), 2.41-2.17 (m, 1 H), 1.87-1.80 (m, 1 H), 1.76-1.64 (m, 3 H), 1.58-0.98 (m, 6 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 173.4 (C), 141.3 (C), 138.0 (C), 136.0 (CH), 128.6 (two CH), 128.2 (two CH), 128.1 (two CH), 127.8 (two CH), 127.5 (CH), 126.5 (CH), 117.1 (CH_2), 78.4 (CH), 72.6 (CH_2), 59.6 (CH), 55.2 (CH_2), 52.0 (CH_2), 51.5 (CH_3), 47.2 (CH), 29.8 (CH_2), 27.7 (CH_2), 26.3 (CH_2), 26.2 (CH_2), 26.1 (CH_2); MS (*m/z*, relative intensity): 421 (M^+, 44), 203 (13), 202 (100), 120 (11), 92 (4), 91 (54), 55 (5); exact mass calculate for $C_{27}H_{35}NO_3$ (M^+): 421.2617; found 421.2624.

For *anti*-**17d**: 79 mg, 63% yield; R_f = 0.49 (Hexane/EtOAc = 9 : 1); yellow oil.

Spectroscopic data for *anti*-**17d**: IR (CH_2Cl_2): 2927, 2853, 1748, 1452, 1265, 1203, 1131, 736, 699 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.33-7.19 (m, 10 H), 5.71-5.62 (m, 1 H), 5.06-5.01 (m, 2 H), 4.67 (d, *J* = 11.6 Hz, 1 H), 4.34 (d, *J* = 11.6 Hz, 1 H), 3.99 (d, *J* = 4.8 Hz, 1 H), 3.66 (s, 3 H), 3.66-3.55 (m, 2 H), 2.74 (dd, *J* = 12.4, 5.2 Hz, 1 H), 2.66-2.59 (m, 1 H), 2.55 (dd, *J* = 12.4, 8.0 Hz, 1 H), 2.41-2.35 (m, 1 H), 1.78-1.71 (m, 4 H), 1.24-0.96 (m, 6 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.2 (C), 141.3 (C), 137.58 (C), 137.56 (CH), 128.5 (two CH), 128.2 (two CH), 127.92 (two CH), 127.89 (two CH), 127.7 (CH), 126.4 (CH), 116.8 (CH_2), 80.2 (CH), 72.6 (CH_2), 59.2 (CH), 54.9 (CH_2), 51.4 (CH_3), 50.9 (CH_2), 46.9 (CH), 29.2 (CH_2), 28.0 (CH_2), 26.4 (CH_2), 26.21 (CH_2), 26.15 (CH_2); MS (*m/z*, relative intensity): 421 (M^+, 27), 203 (15), 202 (100), 120 (15), 92 (6), 91 (83), 55 (8); exact mass calculate for

$C_{27}H_{35}NO_3$ (M^+): 421.2617; found 421.2613.

For *syn*-**17e**: 124 mg, 71% yield; R_f = 0.44 (Hexane/EtOAc = 4 : 1); yellow oil.

Spectroscopic data for *syn*-**17e**: IR (CH_2Cl_2): 2965, 1751, 1455, 1382, 1254, 1207, 1174, 1133, 916, 843, 736, 698, 668, 595 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.39-7.27 (m, 5 H), 5.88-5.79 (m, 1 H), 5.07-4.99 (m, 2 H), 4.74 (d, *J* = 11.2 Hz, 1 H), 4.42 (d, *J* = 1.6 Hz, 1 H), 4.35 (d, *J* = 11.2 Hz, 1 H), 3.73 (s, 3 H), 3.03-2.96 (m, 2 H), 2.68-2.58 (m, 2 H), 2.51-2.45 (m, 1 H), 1.00-0.96 (m, 12 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 173.8 (C), 138.1 (C), 136.2 (CH), 128.2 (two CH), 127.7 (two CH), 127.5 (CH), 117.0 (CH_2), 78.1 (CH), 72.4 (CH_2), 51.5 (CH_3), 47.8 (two CH), 47.5 (CH), 46.4 (CH_2), 21.7 (two CH_3), 20.1 (two CH_3); MS (*m/z*, relative intensity): 333 (M^+, 26), 304 (4), 115 (7), 114 (100), 91 (18), 72 (13); exact mass calculate for $C_{20}H_{31}NO_3$ (M^+): 333.2304; found 333.2309.

For *anti*-**17e**: 71 mg, 54% yield; R_f = 0.50 (Hexane/EtOAc = 1 : 1); yellow oil.

Spectroscopic data for *anti*-**17e**: IR (CH_2Cl_2): 2964, 2928, 2869, 1752, 1455, 1386, 1361, 1253, 1206, 1118, 915, 735, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.37-7.28 (m, 5 H), 5.75-5.66 (m, 1 H), 5.09-5.04 (m, 2 H), 4.75 (d, *J* = 12.0 Hz, 1 H), 4.40 (d, *J* = 12.0 Hz, 1 H), 4.03 (d, *J* = 4.4 Hz, 1 H), 3.72 (s, 3 H), 2.98-2.91 (m, 2 H), 2.74-2.64 (m, 1 H), 2.44 (dd, *J* = 12.8, 7.2 Hz, 1 H), 0.93 (d, *J* = 6.4 Hz, 12 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.4 (C), 137.75 (C), 137.73 (CH), 128.3 (two CH), 128.0 (two CH), 127.7 (CH), 116.6 (CH_2), 80.0 (CH), 72.7 (CH_2), 51.4 (CH_3), 47.6 (two CH), 47.2 (CH), 45.5 (CH_2), 20.8 (two CH_3), 20.7 (two CH_3); MS (*m/z*, relative intensity): 333 (M^+, 5), 115 (8), 114 (100), 91 (22), 72 (15), 70 (4); exact mass calculate for $C_{20}H_{31}NO_3$ (M^+): 333.2304; found 333.2304.

For *syn*-**17f**: 90 mg, 79% yield; R_f = 0.61 (CH_2Cl_2/MeOH = 10 : 1); yellow oil.

Spectroscopic data for *syn*-**17f**: IR (CH_2Cl_2): 2951, 2929, 2788, 1752, 1455, 1278, 1202, 1132, 916 737, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.37-7.28 (m, 5 H), 5.86-5.77 (m, 1 H), 5.10-5.04 (m, 2 H), 4.77 (d, *J* = 11.6 Hz, 1 H), 4.40 (d, *J* = 11.6 Hz, 1 H), 4.28 (d, *J* = 2.8 Hz, 1 H), 3.72 (s, 3 H), 2.76-2.69 (m, 2 H), 2.54-2.51 (m, 2 H), 2.38-2.32 (m, 3 H), 1.75-1.68 (m, 4 H)); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 173.0 (C), 137.9 (C), 136.1 (CH), 128.2 (two CH), 128.0 (two CH), 127.7 (CH), 117.3 (CH_2), 79.0 (CH), 72.9 (CH_2), 57.0 (CH_2), 54.0 (two CH_2), 51.6 (CH_3), 46.8 (CH), 23.6 (two CH_2); MS (*m/z*, relative intensity): 303 (M^+, 15), 91 (9), 85 (4), 84 (100); exact mass calculate for $C_{18}H_{25}NO_3$ (M^+): 303.1834; found 303.1839.

For *anti*-**17f**: 70 mg, 58% yield; R_f = 0.55 (CH_2Cl_2/MeOH = 10 : 1); yellow oil.

Spectroscopic data for *anti*-**17f**: IR (CH_2Cl_2): 2951, 2925, 2788, 1750, 1455, 1258, 1201, 1132, 916, 736, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.36-7.28 (m, 5 H), 5.84-5.75 (m, 1 H), 5.16-5.08 (m, 2 H), 4.75 (d, *J* = 11.6 Hz, 1 H), 4.39 (d, *J* = 11.6 Hz, 1 H), 3.96 (d, *J* = 4.8 Hz, 1 H), 3.71 (s, 3 H), 2.84-2.77 (m, 1 H), 2.73-2.70 (m, 1 H), 2.58-2.42 (m, 5 H), 1.71-1.66 (m, 4 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.2 (C), 137.6 (C), 137.4 (CH), 128.3 (two CH), 127.9 (two CH), 127.7 (CH), 117.0 (CH_2), 80.2 (CH), 72.8 (CH_2), 56.2 (CH_2), 54.2 (two CH_2), 51.5 (CH_3), 46.5 (CH), 23.5 (two CH_2); MS (*m/z*, relative intensity): 303 (M^+, 10), 91 (18), 85 (6), 84 (100), 55 (6); exact mass calculate for $C_{18}H_{25}NO_3$ (M^+): 303.1834; found 303.1836.

For *syn*-**17g**: 65 mg, 57% yield; R_f = 0.21 (Hexane/EtOAc = 5 : 1); yellow oil.

Spectroscopic data for *syn*-**17g**: IR (CH_2Cl_2): 2930, 2852, 1752, 1600, 1455, 1267, 1197, 1132, 750, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.37-7.27 (m, 5 H), 5.83-5.74 (m, 1 H), 5.07-5.01 (m, 2 H), 4.76 (d, *J* = 11.6 Hz, 1 H), 4.41 (d, *J* = 11.6 Hz, 1 H), 4.35 (d, *J* = 3.2 Hz, 1 H), 3.72 (s, 3 H), 2.80-2.73 (m, 1 H), 2.52 (dd, *J* = 12.4, 10.4 Hz, 1 H), 2.45-2.43 (m, 2 H) 2.20-2.13 (m, 3 H), 1.53-1.47 (m, 4 H), 1.42-1.39 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 173.4 (C), 138.0 (C), 136.0 (CH), 128.2 (two CH), 128.1 (two CH), 127.6 (CH), 117.3 (CH_2), 78.7 (CH), 73.1 (CH_2), 59.5 (CH_2), 54.7 (two CH_2), 51.6 (CH_3), 45.0 (CH), 26.2 (two CH_2), 24.5 (CH_2); MS (*m/z*, relative intensity): 317 (M^+, 46), 99 (6), 98 (100), 91 (8); exact mass calculate for $C_{19}H_{27}NO_3$ (M^+): 317.1991; found 317.1981.

For *anti*-**17g**: 93 mg, 82% yield; R_f = 0.26 (Hexane/EtOAc = 2 : 1); yellow oil.

Spectroscopic data for *anti*-**17g**: IR (CH_2Cl_2): 2931, 2853, 1752, 1455, 1260, 1207, 1121, 1027, 916, 736, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.36-7.28 (m, 5 H), 5.79-5.73 (m, 1 H), 5.12-5.05 (m, 2 H), 4.78 (d, *J* = 11.6 Hz, 1 H), 4.39 (d, *J* = 11.6 Hz, 1 H), 3.97 (d, *J* = 4.4 Hz, 1 H), 3.74 (s, 3 H), 2.88-2.81 (m, 1 H), 2.59 (dd, *J* = 12.8, 8.4 Hz, 1 H), 2.34-2.21 (m, 5 H), 1.49-1.45 (m, 4 H), 1.39-1.35 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.3 (C), 137.82 (C), 137.75 (CH), 128.2 (two CH), 127.9 (two CH), 127.7 (CH), 116.5 (CH_2), 79.9 (CH), 72.8 (CH_2), 58.8 (CH_2), 54.8 (two CH_2), 51.5 (CH_3), 44.8 (CH), 25.9 (two CH_2), 24.4 (CH_2); MS (*m/z*, relative intensity): 317 (M^+, 80), 302

(30), 138 (80), 137 (84), 124 (13), 122 (16), 98 (53), 91 (100), 86 (10), 85 (65), 84 (45), 83 (10), 65 (11), 55 (26); exact mass calculate for $C_{19}H_{27}NO_3$ (M^+): 317.1991; found 317.1999.

For *syn*-**17h**: 104 mg, 90% yield; R_f = 0.26 (Hexane/EtOAc = 2 : 1); yellow oil.

Spectroscopic data for *syn*-**17h**: IR (CH_2Cl_2): 2949, 2845, 2790, 1751, 1455, 1266, 1202, 1137, 1025, 917, 740, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.31-7.21 (m, 10 H), 5.85-5.76 (m, 1 H), 5.11-5.04 (m, 2 H), 4.74 (d, *J* = 11.2 Hz, 1 H), 4.39 (d, *J* = 2.8 Hz, 1 H), 4.34 (d, *J* = 11.2 Hz, 1 H), 3.72 (s, 3 H), 3.52 (d, *J* = 12.8 Hz, 1 H), 3.42 (d, *J* = 12.8 Hz, 1 H), 2.83-2.77 (m, 1 H), 2.70 (dd, *J* = 12.0, 10.0 Hz, 1 H), 2.29 (dd, *J* = 12.0, 5.6 Hz, 1 H), 2.14 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 173.1 (C), 137.8 (two C), 135.7 (CH), 129.0 (two CH), 128.22 (two CH), 128.15 (two CH), 128.0 (two CH), 127.7 (CH), 126.9 (CH), 117.5 (CH_2), 78.5 (CH), 73.0 (CH_2), 62.5 (CH_2), 58.4 (CH_2), 51.6 (CH_3), 45.8 (CH), 42.2 (CH_3); MS (*m/z*, relative intensity): 353 (M^+, 7), 135 (9), 134 (100), 92 (4), 91 (64), 65 (3); exact mass calculate for $C_{22}H_{27}NO_3$ (M^+): 353.1991; found 353.1998.

For *anti*-**17h**: 94 mg, 86% yield; R_f = 0.55 (Hexane/EtOAc = 3 : 1); yellow oil.

Spectroscopic data for *anti*-**17h**: IR (CH_2Cl_2): 2949, 2924, 2844, 2791, 1749, 1454, 1265, 1206, 1135, 1025, 917, 737, 699 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.34-7.22 (m, 10 H), 5.82-5.72 (m, 1 H), 5.16-5.10 (m, 2 H), 4.76 (d, *J* = 11.6 Hz, 1 H), 4.39 (d, *J* = 11.6 Hz, 1 H), 4.00 (d, *J* = 4.4 Hz, 1 H), 3.68 (s, 3 H), 3.57 (d, *J* = 13.2 Hz, 1 H), 3.36 (d, *J* = 13.2 Hz, 1 H), 2.91-2.84 (m, 1 H), 2.67 (dd, *J* = 12.8, 7.2 Hz, 1 H), 2.41 (dd, *J* = 12.8, 7.6 Hz, 1 H), 2.11 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.2 (C), 138.9 (C), 137.6 (C), 137.4 (CH), 129.2 (two CH), 128.3 (two CH), 128.0 (two CH), 127.9 (two CH), 127.7 (CH), 126.8 (CH), 116.9 (CH_2), 79.9 (CH), 72.7 (CH_2), 62.5 (CH_2), 57.6 (CH_2), 51.5 (CH_3), 45.5 (CH), 42.2 (CH_3); MS (*m/z*, relative intensity): 353 (M^+, 84), 135 (9), 134 (100), 92 (6), 91 (65), 65 (4); exact mass calculate for $C_{22}H_{27}NO_3$ (M^+): 353.1991; found 353.1997.

For *syn*-**17i**: 78 mg, 58% yield; R_f = 0.46 (Hexane/EtOAc = 8 : 1); yellow oil.

Spectroscopic data for *syn*-**17i**: IR (CH_2Cl_2): 2928, 2853, 1752, 1453, 1258, 1201, 1135, 1051, 995, 916, 735, 697 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.39-7.27 (m, 5 H), 5.84-5.75 (m, 2 H), 5.15-4.99 (m, 4 H), 4.75 (d, *J* = 11.2 Hz, 1 H), 4.41 (d, *J* = 2.4 Hz, 1 H), 4.35 (d, *J* = 11.2 Hz, 1 H), 3.72 (s, 3 H), 3.13 (d, *J* = 6.4 Hz, 2 H), 2.74-2.61 (m, 2 H), 2.45-2.37 (m, 2 H), 1.76-1.56 (m, 6 H), 1.25-0.99 (m, 4 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 173.5 (C), 138.2 (CH), 138.0 (C), 136.0 (CH), 128.2 (two CH), 127.8 (two CH), 127.5 (CH), 117.1 (CH_2), 115.7 (CH_2), 78.5 (CH), 72.7 (CH_2), 60.3 (CH), 54.0 (CH_2), 51.61 (CH_2), 51.55 (CH), 47.1 (CH), 30.0 (CH_2), 28.3 (CH_2), 26.3 (CH_2), 26.21 (CH_2), 26.17 (CH_2); MS (*m/z*, relative intensity): 371 (M^+, 57), 153 (9), 152 (100), 91 (12), 70 (16), 55 (5); exact mass calculate for $C_{23}H_{33}NO_3$ (M^+): 371.2460; found 371.2465.

For *anti*-**17i**: 82 mg, 62% yield; R_f = 0.27 (Hexane/EtOAc = 9 : 1); yellow oil.

Spectroscopic data for *anti*-**17i**: IR (CH_2Cl_2): 2927, 2854, 1751, 1453, 1257, 1202, 1131, 1027, 995, 915, 735, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.40-7.28 (m, 5 H), 5.81-5.68 (m, 2 H), 5.15-4.94 (m, 4 H), 4.76 (d, *J* = 11.6 Hz, 1 H), 4.39 (d, *J* = 11.6 Hz, 1 H), 3.99 (d, *J* = 3.6 Hz, 1 H), 3.71 (s, 3 H), 3.15-3.01 (m, 2 H), 2.75-2.69 (m, 2 H), 2.47-2.40 (m, 2 H), 1.74-1.64 (m, 5 H), 1.26-1.11 (m, 5 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.3 (C), 138.1 (CH), 137.8 (C), 137.7 (CH), 128.2 (two CH), 127.9 (two CH), 127.6 (CH), 116.6 (CH_2), 115.6 (CH_2), 79.9 (CH), 72.7 (CH_2), 59.9 (CH), 53.9 (CH_2), 51.4 (CH_3), 50.5 (CH_2), 46.6 (CH), 28.87 (CH_2), 28.85 (CH_2), 26.4 (CH_2), 26.24 (CH_2), 26.22 (CH_2); MS (*m/z*, relative intensity): 371 (M^+, 25), 153 (12), 152 (100), 91 (15), 70 (25), 55 (9); exact mass calculate for $C_{23}H_{33}NO_3$ (M^+): 371.2460; found 371.2453.

For *syn*-**17j**: 104 mg, 67% yield; 0.54 (Hexane/EtOAc = 5 : 1); mp. 56-58 °C; yellow solid.

Spectroscopic data for *syn*-**17j**: IR (CH_2Cl_2): 2926, 2834, 1751, 1611, 1509, 1455, 1249, 1203, 1136, 1030, 741, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.31-7.13 (m, 12 H), 6.81 (d, *J* = 8.0 Hz, 2 H) 5.79-5.71 (m, 1 H), 5.08-5.04 (m, 2 H), 4.54 (d, *J* = 11.2 Hz, 1 H), 4.30 (d, *J* = 1.6 Hz, 1 H), 3.98 (d, *J* = 11.2 Hz, 1 H), 3.73 (s, 3 H), 3.69 (s, 3 H), 3.64 (d, *J* = 13.6 Hz, 1 H), 3.58 (d, *J* = 13.2 Hz, 1 H), 3.42 (d, *J* = 13.6 Hz, 1 H), 3.36 (d, *J* = 13.2 Hz, 1 H), 2.82-2.74 (m, 2 H), 2.45-2.37 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 173.3 (C), 158.8 (C), 139.6 (C), 138.0 (C), 136.1 (CH), 131.4 (C), 130.5 (two CH), 129.3 (two CH), 128.4 (two CH), 128.3 (two CH), 127.9 (two CH), 127.6 (CH), 127.1 (CH), 117.5 (CH_2), 113.8 (two CH), 78.8 (CH), 72.7 (CH_2), 58.5 (CH_2), 57.9 (CH_2), 55.4 (CH_3), 54.9 (CH_2), 51.9 (CH_3), 46.5 (CH); MS (*m/z*, relative intensity): 459 (M^+, 47), 241 (7), 240 (43), 122 (7), 121 (100), 91 (15); exact mass calculate for $C_{29}H_{33}NO_4$ (M^+): 459.2410; found 459.2415.

For *anti*-**17j**: 70 mg, 61% yield; 0.36 (Hexane/EtOAc = 8 : 1); yellow oil.

Spectroscopic data for *anti*-**17j**: IR (CH_2Cl_2): 2923, 1748, 1540, 1508, 1456, 1247, 739, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.32-7.14 (m, 12 H), 6.81 (d, *J* = 8.4 Hz, 2 H) 5.67-5.58 (m, 1 H), 5.16-5.04 (m, 2 H), 4.65 (d, *J* = 11.6 Hz, 1 H), 4.32 (d, *J* = 11.6 Hz, 1 H), 3.91 (d, *J* = 5.6 Hz, 1 H), 3.78 (s, 3 H), 3.65 (d, *J* = 6.4 Hz, 1 H), 3.62-3.59 (m, 4 H), 3.38 (d, *J* = 13.6 Hz, 1 H), 3.34 (d, *J* = 13.6 Hz, 1 H), 2.87-2.80 (m, 1 H), 2.66 (dd, *J* = 12.8, 5.6 Hz, 1 H), 2.52 (dd, *J* = 12.8, 8.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.0 (C), 158.5 (C), 139.6 (C), 137.50 (CH), 137.46 (C), 131.3 (C), 130.2 (two CH), 129.0 (two CH), 128.3 (two CH), 128.0 (two CH), 127.8 (two CH), 127.7 (CH), 126.7 (CH), 117.1 (CH_2), 113.4 (two CH), 80.5 (CH), 72.5 (CH_2), 58.2 (CH_2), 57.6 (CH_2), 55.2 (CH_3), 53.9 (CH_2), 51.5 (CH_3), 45.9 (CH); MS (*m/z*, relative intensity): 459 (M^+, 45), 241 (7), 240 (39), 122 (4), 121 (100), 91 (13); exact mass calculate for $C_{29}H_{33}NO_4$ (M^+): 459.2410; found 459.2415.

For *syn*-**17k**: 71 mg, 60% yield; 0.58 (Hexane/EtOAc = 4 : 1); yellow oil.

Spectroscopic data for *syn*-**17k**: IR (CH_2Cl_2): 2924, 2869, 2100, 1751, 1455, 1203, 1127, 738, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.36-7.31 (m, 5 H), 5.82-5.73 (m, 1 H), 5.19-5.14 (m, 2 H), 4.80 (d, *J* = 11.6 Hz, 1 H), 4.39 (d, *J* = 11.6 Hz, 1 H), 4.17 (d, *J* = 3.2 Hz, 1 H), 3.75 (s, 3 H), 3.44 (dd, *J* = 12.0, 8.4 Hz, 1 H), 3.35 (dd, *J* = 12.0, 6.4 Hz, 1 H), 2.77-2.75 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.7 (C), 137.2 (C), 133.3 (CH), 128.4 (two CH), 128.2 (two CH), 128.0 (CH), 119.5 (CH_2), 77.6 (CH), 72.9 (CH_2), 52.0 (CH_2), 51.9 (CH_3), 47.1(CH); MS (*m/z*, relative intensity): 275 (M^+, 3), 149 (6), 113 (14), 105 (5), 92 (9), 91 (100), 83 (4), 82 (4), 81 (5), 71 (5), 69 (4), 65 (8), 57 (7), 55 (6); exact mass calculate for $C_{14}H_{17}N_3O_3$ (M^+): 275.1270; found 275.1275.

For *anti*-**17k**: 72 mg, 61% yield; 0.55 (Hexane/EtOAc = 4 : 1); yellow oil.

Spectroscopic data for *anti*-**17k**: IR (CH_2Cl_2): 2924., 2869, 2100, 1749, 1455, 1266, 1200, 1119, 739, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.36-7.30 (m, 5 H), 5.78-5.69 (m, 1 H), 5.21-5.17 (m, 2 H), 4.70 (d, *J* = 11.2 Hz, 1 H), 4.41 (d, *J* = 11.2 Hz, 1 H), 3.96 (d, *J* = 6.8 Hz, 1 H), 3.73 (s, 3 H), 3.49 (d, *J* = 5.6 Hz, 2 H), 2.80-2.74 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.7 (C), 137.0 (C), 134.5 (CH), 128.4 (two CH), 128.14 (two CH), 128.07 (CH), 119.1 (CH_2), 78.8 (CH), 72.9 (CH_2), 51.8 (CH_3), 51.6 (CH_2), 47.0 (CH); MS (*m/z*, relative intensity): 275 (M^+, 12), 113 (11), 112 (4), 92 (8), 91 (100), 82 (4), 65 (7); exact mass calculate for $C_{14}H_{17}N_3O_3$ (M^+): 275.1270; found 275.1276.

Typical experimental procedure for the preparation of 18

To a solution of *syn*-**17b** (548 mg, 1.45 mmol) and acetic acid (7.5 mL) in MeOH (7.5 mL) was added Pd/C (31 mg, 0.29 mmol) at room temperature. The solution was stirred under H_2 atmosphere (1 atm) for 3 days, followed by filtrating through Celite and concentrated *in vacuo* to give the crude product as brown oil. The residue was purified by flash column chromatography with 10% EtOAc-hexane (R_f = 0.46 in 20% EtOAc-hexane) to afford product *anti*-**18** as a yellow oil (383 mg, 86% yield).

Spectroscopic data for *anti*-**18**: IR (CH_2Cl_2): 2925, 2856, 2360, 2337, 1697, 1492, 1440, 1253, 1130, 1081, 919, 738, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.42-7.23 (m, 10 H), 5.77-5.69 (m, 1 H), 5.16-5.08 (m, 3 H), 4.87 (d, *J* = 12.0 Hz, 1 H), 4.51 (d, *J* = 14.4 Hz, 1 H), 4.40 (d, *J* = 14.4 Hz, 1 H), 3.98 (d, *J* = 8.0 Hz, 1 H), 3.34-3.28 (m, 1 H), 2.97-2.89 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.3 (C), 137.9 (C), 136.1 (CH), 135.9 (C), 128.8 (two CH), 128.3 (two CH), 128.2 (two CH), 128.1 (two CH), 127.8 (CH), 127.7 (CH), 117.6 (CH_2), 80.1 (CH), 72.3 (CH_2), 47.5 (CH_2), 46.7 (CH_2), 44.3 (CH); MS (*m/z*, relative intensity): 307 (M^+, 15), 202 (5), 201 (34), 200 (6), 174 (4), 92 (9), 91 (100), 77 (4), 65 (12); exact mass calculate for $C_{20}H_{21}NO_2$ (M^+): 307.1572; found 307.1575.

For *syn*-**18**: 325 mg, 78% yield; 0.38 (Hexane/EtOAc = 4 : 1); yellow oil.

Spectroscopic data for *syn*-**18**: IR (CH_2Cl_2): 2923, 2854, 1695, 1434, 1253, 1124, 738, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.39-7.22 (m, 10 H), 6.00-5.91 (m, 1 H), 5.16-5.09 (m, 2 H), 4.91 (d, *J* = 12.0 Hz, 1 H), 4.78 (d, *J* = 12.0 Hz, 1 H), 4.49 (d, *J* = 14.8 Hz, 1 H), 4.45 (d, *J* = 14.8 Hz, 1 H), 4.06 (d, *J* = 6.4 Hz, 1 H), 3.28-3.18 (m, 2 H), 3.01-2.94 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.9 (C), 137.8 (C), 136.0 (C), 133.8 (CH), 128.7 (two CH), 128.3 (two CH), 128.1 (two CH), 127.8 (two CH), 127.7 (CH), 127.6 (CH), 117.8 (CH_2), 77.8 (CH), 72.0 (CH_2), 49.3 (CH_2), 46.5 (CH_2), 41.9 (CH); MS (*m/z*, relative intensity): 307 (M^+, 25), 202 (13), 201 (84), 200 (13), 174 (27), 110 (5), 92 (9), 91 (100), 65 (11); exact mass calculate for $C_{20}H_{21}NO_2$ (M^+): 307.1572; found 307.1576.

Typical experimental procedure for the preparation of 19

To a solution of *anti*-**18** (264 mg, 0.84 mmol) in acetone (12.6 mL), H_2O (1.8 mL), and THF (10.8 mL) was added $NaIO_4$ (901 mg, 4.22 mmol) and a solution of OsO_4 in H_2O (0.4 M, 54 μL). The solution was stirred at room temperature for 2 h until the completion of reaction, as monitored by TLC. To the reaction mixture was added saturated aqueous Na_2SO_3 solution (5 mL), and removed the organic solvent under vacuum. The solution was extracted with EtOAc (5 mL × 3), dried over $MgSO_4$, and concentrated in vacuo to give the crude aldehyde product as yellow oil. To the solution of this crude product in dry THF (24 mL) was added $LiAlH_4$ (352 mg, 9.24 mmol) at 0 °C. The solution was heated to reflux for 15 h, followed by the addition of saturated aqueous NaOH solution (0.5 mL). The solution was filtered to remove the precipitate, and the filtrate was dried over $MgSO_4$, concentrated *in vacuo* to give the crude product. The residue was purified by flash column chromatography with 20% EtOAc-hexane (R_f = 0.22 in 20% EtOAc-hexane) to afford product *anti*-**19** as a yellow oil (135 mg, 55% yield).

Spectroscopic data for *anti*-**19**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.35-7.23 (m, 10 H), 4.48 (s, 2 H), 4.08-4.04 (m, 1 H), 3.72 (dd, *J* = 10.0, 4.4 Hz, 1 H), 3.64 (dd, *J* = 10.0, 4.0 Hz, 1 H), 3.61 (s, 2 H), 3.16 (dd, *J* = 10.0, 6.8 Hz, 1 H), 2.75 (dd, *J* = 9.2, 6.8 Hz, 1 H), 2.67 (dd, *J* = 9.2, 2.8 Hz, 1 H), 2.40 (dd, *J* = 10.0, 4.4 Hz, 1 H), 2.32-2.30 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 138.23 (C), 138.16 (C), 128.7 (two CH), 128.40 (two CH), 128.36 (two CH), 127.68 (two CH), 127.65 (CH), 127.2 (CH), 81.3 (CH), 71.4 (CH_2), 66.1 (CH_2), 60.5 (CH_2), 60.0 (CH_2), 56.5 (CH_2), 46.3 (CH); IR (CH_2Cl_2): 3351, 3062, 3029, 2923, 2861, 2798, 1454, 1093, 1068, 738, 698 cm^{-1}; MS (*m/z*, relative intensity): 297 (M^+, 26), 206 (5), 191 (10), 160 (6), 120 (28), 92 (9), 91 (100), 65 (5); exact mass calculate for $C_{19}H_{23}NO_2$ (M^+): 297.1729; found 297.1723.

For *syn*-**19**: 214 mg, 68% yield; 0.29 (Hexane/EtOAc = 1 : 4); yellow oil.

Spectroscopic data for *syn*-**19**: IR (CH_2Cl_2): 3396, 3028, 2917, 2795, 1494, 1454, 1092, 739, 702, 666, 604 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.36-7.27 (m, 10 H), 4.57 (d, *J* = 12.0 Hz, 1 H), 4.42 (d, *J* = 12.0 Hz, 1 H), 4.29-4.24 (m, 1 H), 3.78-3.77 (m, 2 H), 3.64 (d, *J* = 12.8 Hz, 1 H), 3.60 (d, *J* = 12.8 Hz, 1 H), 3.03 (dd, *J* = 9.6, 6.4 Hz, 1 H), 2.82-2.77 (m, 1 H), 2.54-2.48 (m, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 138.6 (C), 137.9 (C), 128.7 (two CH), 128.5 (two CH), 128.3 (two CH), 127.8 (CH), 127.5 (two CH), 127.0 (CH), 79.7 (CH), 72.0 (CH_2), 61.7 (CH_2), 60.5 (CH_2), 59.5 (CH_2), 55.1 (CH_2), 43.0 (CH).

Typical experimental procedure for the preparation of 21

To a solution of *anti*-**19** (253 mg, 0.85 mmol) in MeOH (9 mL) was added Pd/C (18 mg, 0.17 mmol) at room temperature. The solution was stirred under H_2 atmosphere (1 atm) for 2 days, followed by filtrating through Celite and concentrated *in vacuo* to give the crude product as brown oil. To a solution of the residue in MeOH (8 mL) was slowly added a solution of aqueous HCl solution (12 M, 0.4 mL) at room temperature. The solution was stirred for 2 h and concentrated in vacuo to give *anti*-**21** as brown oil. (124 mg, 95% yield). Brown oil.

Spectroscopic data for *anti*-**21**: ^{1}H NMR (hydrochloride, D_2O, 400 MHz): δ 4.49-4.46 (m, 1 H), 3.73-3.63 (m, 3 H), 3.50 (dd, *J* = 12.4, 4.8 Hz, 1 H), 3.33 (d, *J* = 11.5 Hz, 1 H), 3.23 (dd, *J* = 12.4, 5.6 Hz, 1 H), 2.49-2.57 (m, 1 H); ^{13}C NMR (hydrochloride, D_2O, 100 MHz): δ 71.9 (CH), 60.9 (CH_2), 52.1 (CH_2), 47.9 (CH), 46.6 (CH_2).

For *syn*-**21**: 86 mg, 78% yield; yellow oil.

Spectroscopic data for *syn*-**21**: ^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.32 (br s, 1 H), 9.12 (br s, 1 H), 5.37 (br s, 1 H), 4.29-4.26 (m, 1 H), 3.62 (dd, *J* = 10.8, 7.2 Hz, 1 H), 3.45 (dd, *J* = 11.2, 7.2 Hz, 1 H), 3.29-3.18 (m, 2 H), 3.08-3.04 (m, 1 H), 2.91-2.85 (m, 1 H), 2.26-2.19 (m, 1 H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 68.8 (CH), 58.2 (CH_2), 53.0 (CH_2), 46.1 (CH), 45.5 (CH_2).

Supporting Information Available

Spectra data for the new compounds.

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