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Helical-Peptide-Catalyzed Enantioselective Michael Addition Reactions and Their Mechanistic Insights

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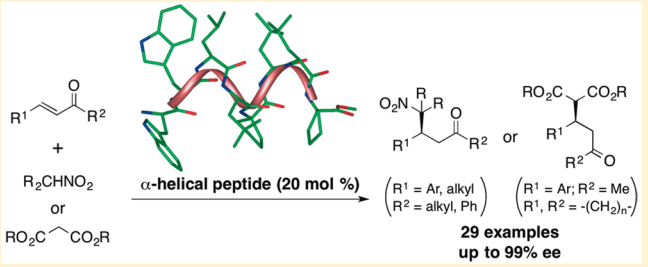
Supporting Information

ABSTRACT: Helical peptide foldamer catalyzed Michael addition reactions of nitroalkane or dialkyl malonate to α,β-unsaturated ketones are reported along with the mechanistic considerations of the enantio-induction. A wide variety of α,β-unsaturated ketones, including β-aryl, β-alkyl enones, and cyclic enones, were found to be catalyzed by the helical peptide to give Michael adducts with high enantioselectivities (up to 99%). On the basis of X-ray crystallographic analysis and depsipeptide study, the amide protons, N(2)−H and N(3)−H, at the N terminus in the α-helical peptide catalyst were crucial for activating Michael donors, while the N-terminal primary amine activated Michael acceptors through the formation of iminium ion intermediates.



INTRODUCTION

Due to their broad variety, chiral aminocatalysts have attracted increased attention in recent years.[1] Peptides are also potential aminocatalysts because of the amino group on the N terminus. One of the advantages of a peptide catalyst is its tunability and diversity, which are achieved by exchanging amino acid components with readily available coded amino acids as well as nonproteinogenic amino acids. Most of these peptide catalysts possess a specific secondary structure, such as an α-helix or a β-turn.[2] We and other groups recently reported the highly enantioselective Juliá−Colonna epoxidation of α,β-unsaturated ketones using an L-Leu-based peptide foldamers[3] stabilized by α,α-disubstituted α-amino acid (dAA) components.[4−9] We previously showed a positive correlation between the enantioselectivities and α-helicities of peptides. Moreover, asymmetric Michael additions catalyzed by a resin-supported peptide were recently described.[10] We herein describe helical-peptide-catalyzed enantioselective Michael addition reactions and performed mechanistic considerations into the origin of enantioselection based on an X-ray crystallographic analysis and the use of depsipeptides.[11]

RESULTS AND DISCUSSION

We initially examined the dAA moieties of peptide catalysts because we previously demonstrated that the structures of dAAs strongly influenced enantioselectivities in our study on peptide-catalyzed Juliá−Colonna epoxidation.[4] We selected three different dAAs, as described in Figure 1: α-aminoisobutyric acid (Aib, **a**), 1-aminocyclopentane-1-carboxylic acid (Ac_5c, **b**), and chiral dAA [(1*S*,3*S*)-Ac_5c^{OM}, **c**]. Nine dAA-containing L-Leu-based heteropeptides, H-(L-Leu-L-Leu-dAA)$_n$-OMe [dAA = Aib, Ac_5c, (1*S*,3*S*)-Ac_5c^{OMe}; n = 1, 2, 3], were prepared as a tripeptide (**1**), hexapeptide (**2**), and nonapeptide (**3**). The results of the Michael addition reaction of nitromethane with the α,β-unsaturated ketone **4a** are summarized in Table 1. It is important to note that the helical secondary structure was necessary for this peptide catalysis because all of the tripeptides examined, namely, **1a**, **1b**, and **1c**, showed poor selectivities as well as low conversions (entries 1, 4, and 7). The lengths of tripeptides were insufficient to form helical structures. The best result was obtained when the nonapeptide **3c** was used as a catalyst (73% ee, entry 9). This preference in % ee value over Aib-containing peptide such as nonapeptide **3a** (62% ee, entry 3) may be explained hypothetically based on our previous findings that the chiral cyclic dAA (1*S*,3*S*)-Ac_5c^{OM} induced the α-helical structure of its peptides, while Aib-containing peptides preferred the 3_{10}-helix.[4,12,13]

We then optimized reaction conditions using a readily accessible, excellent catalyst, hexapeptide **2b**. No reaction proceeded without the use of a peptide catalyst (Table 2, entry 1). When the reaction was performed in the absence of benzoic acid, it was very sluggish, while enantiomeric excess was of a moderate level (61% ee, entry 2).[14] We conducted the reaction in a more concentrated solution (0.2 M) in THF with excess

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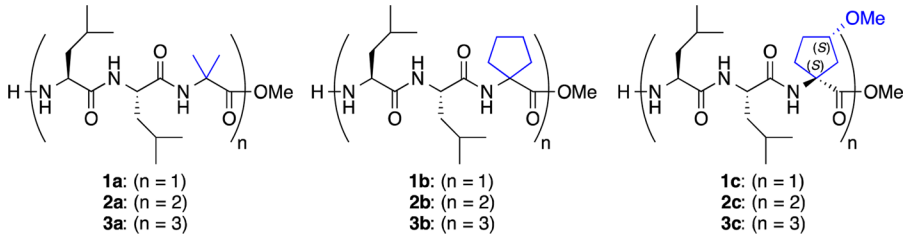
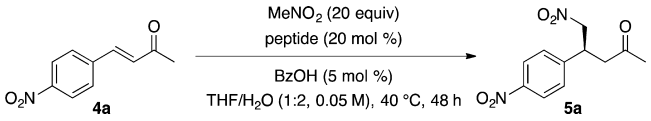


Figure 1. Chemical structures of peptides having α,α-disubstituted α-amino acids.

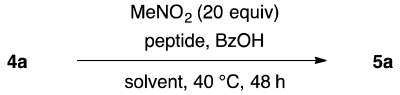
Table 1. Screening of Peptides



entry	peptide	conv[a] (%)	ee[b] (%)
1	**1a**: Aib, trimer	25	−17
2	**2a**: Aib, hexamer	48	50
3	**3a**: Aib, nonamer	70	62
4	**1b**: Ac_5c, trimer	16	−9
5	**2b**: Ac_5c, hexamer	63	65
6	**3b**: Ac_5c, nonamer	69	65
7	**1c**: (1*S*,3*S*)-Ac_5c^{OM}, trimer	27	−12
8	**2c**: (1*S*,3*S*)-Ac_5c^{OM}, hexamer	50	59
9	**3c**: (1*S*,3*S*)-Ac_5c^{OM}, nonamer	57	73

[a]Conversion was determined by ^{1}H NMR analysis. [b]Ee was determined by chiral HPLC analysis.

Table 2. Optimization of Reaction Conditions



entry	peptide (mol %)	BzOH (mol %)	solvent (M)	conv[a] (%)	ee[b] (%)
1	none	5	THF/H_2O[c](0.05)	0	–
2	**2b** (20)	0	THF/H_2O[c] (0.05)	7	61
3	**2b** (20)	5	TFE (0.05)	4	46
4	**2b** (20)	5	DMSO (0.05)	11	11
5	**2b** (20)	5	toluene (0.05)	46	57
6	**2b** (20)	5	THF (0.05)	31	68
7	**2b** (20)	100	THF (0.2)	>99	79
8[d]	**2b** (20)	100	THF (0.2)	54	85
9	**3c** (20)	100	THF (0.2)	89	84
10	**6** (20)	100	THF (0.2)	>99	91
11	**7** (20)	100	THF (0.2)	96	97
12	**7** (10)	50	THF (0.4)	88 (95)[e]	95 (95)[e]
13	**7** (5)	25	THF (0.4)	40 (58)[e]	95 (94)[e]

[a]Conversion was determined by ^{1}H NMR analysis. [b]Ee was determined by chiral HPLC analysis. [c]THF/H_2O = 1:2. [d]The reaction was performed at 0 °C. [e]The values in parentheses are results obtained after 120 h.

benzoic acid (100 mol %) and achieved increases in the conversion to >99% along with 79% ee (entry 7). When the α-helical peptide **3c** was employed, enantioselectivity increased to 84% ee (entry 9). The best reaction was achieved by using the tryptophan-containing octapeptide **7** possessing a sterically demanding indole side chain (Figure 2) as a catalyst (97% ee, 96% conversion, entry 11). Furthermore, lowering catalyst loading to 5 and 10 mol % was also successful, yielding excellent enantioselectivities (94−95% ee), albeit with the prolongation of the reaction time (entries 12 and 13).

We then explored the scope of Michael acceptors under the optimized condition (Scheme 1). Substituent groups at the *p*-position of the phenyl group (i.e., electron withdrawing, electron donating, bulky, etc.) did not affect enantioselectivities (94−96% ee, **5b**−**5e**). Different *o*-, *m*-, and *p*-substitution patterns on the phenyl ring also afforded the products **5f**−**5h** with good yields and high enantiomeric excess. Substrates possessing an aromatic group (R^1) other than a phenyl group, for example, 2-furyl, 2-naphtyl, and 9-anthracenyl, were also suitable for the reaction (**5i**−**5k**). When conjugated $\alpha,\beta,\gamma,\delta$-unsaturated dienone and enynone were used as substrates, complete 1,4-addition was observed, rather than 1,6-addition, along with slightly decreased enantioselectivities (**5l** and **5m**). Substrates having an aliphatic group (R^1) at the β-position were also applicable (**5n** and **5o**). We also explored other substrates by replacing a methyl group with alkyl substituents (R^2). As a result, the linear alkyl groups (e.g., ethyl and *n*-propyl, **5p** and **5q**) showed good yields, and bulky substituent groups (e.g., isopropyl and phenyl, **5r** and **5s**) caused sluggish reaction rates; however, all these compounds afforded excellent enantioselectivities (94−99% ee).

Scheme 2 summarizes the scope of the substrates on Michael donors and acceptors. Other nitroalkanes, such as nitroethane and 2-nitropropane, worked well (**9a** and **9b**). The poor diastereoselectivity of compound **9a** is possibly due to the epimerization under the reaction conditions via deprotonation of the acidic proton at the γ-position catalyzed by the peptide, because when we treated the pure major diastereomer of **9a** under the same reaction conditions, the compound *anti*-**9a** epimerized to 1.4:1 dr after 48 h. On the other hand, no epimerization was observed in the absence of peptide catalyst under the reaction conditions. Dimethyl malonate was also a good substrate for this peptide-catalyzed reaction (**9c** and **9d**). However, a bulkier nucleophile (e.g., diisopropyl malonate, dimedone, and 4-hydroxycoumarin) resulted in decreases in enantioselectivities, albeit with acceptable reactivities (**9e**−**9g**). Cyclic enones were also used for this reaction, and they provided the desired adducts **9h**−**9j** with excellent enantioselectivities (89−98% ee), regardless of the ring sizes of the enones. It is important to note that the cyclic ketone products **9h**−**9j** were also obtained by other amino acid catalysis, as described in the literature.[15−18] However, the substrate scope of those reported catalysts is limited, since enantioselectivities were significantly affected by the ring sizes of the cyclic enones. Thus, the wide substrate scope is an advantage of peptide foldamer catalysts compared to simple amino acid catalysts.

The secondary structure of peptide foldamer **7** in the crystal state was confirmed using X-ray crystallographic analysis. Figure 3 shows that peptide **7** formed a right-handed α-helical secondary structure, in which $i \leftarrow i + 4$ type hydrogen bonds

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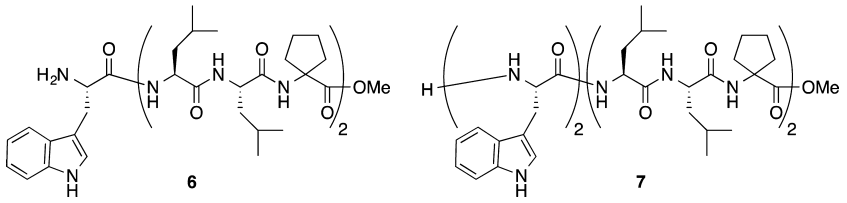
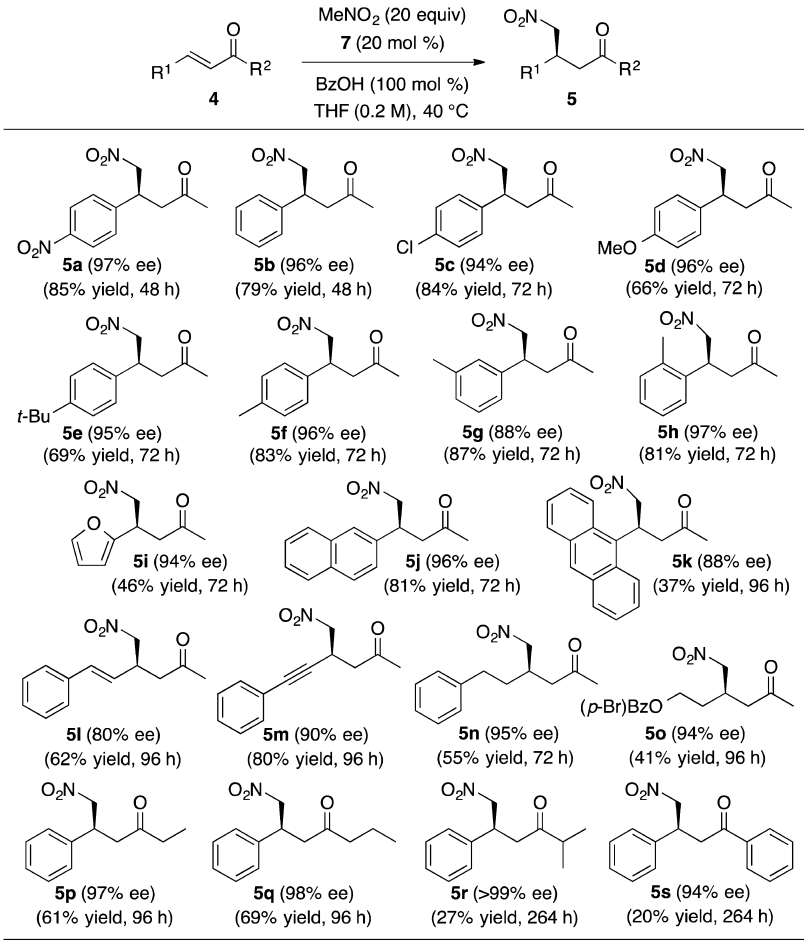


Figure 2. Structures of peptides **6** and **7**.

Scheme 1. Scope of Michael Acceptors



were observed.[19] Regarding helical structures, it should be noted that the N-terminal tetrapeptide stretch of **7** being devoid of any strongly helicogenic α,α-disubstituted α-amino acid is indeed a remarkable event. We also studied the secondary structure of peptide **7** in solution. The NOESY spectrum of peptide **7** revealed that a helical structure was formed due to the observed correlation between each NH amide proton.[19−22] However, it was unclear whether the helical structure was an α- or 3_{10}-helix from the NOESY spectrum due to the complexity of the spectrum.[23]

Figure 4 illustrates plausible mechanisms for the helical-peptide-catalyzed Michael addition of nitromethane or dibenzyl malonate to an α,β-unsaturated ketone based on X-ray crystallographic analysis. The primary amino group of the α-helical peptide reacts with an α,β-unsaturated ketone to form the iminium intermediate with the minimized allylic 1,3- and 1,2-strain,[24−26] and this process is promoted by benzoic acid. Meanwhile, the Michael donor is activated by the exposed amide protons, N(2)−H and N(3)−H, on the N terminus. Two tryptophan units possibly regulate the rotation of the iminium intermediate. Consequently, the Michael donor attacks from the *si*-face of the α,β-unsaturated iminium to provide the product.

The plausible mechanism described above was supported by a comparative study of peptides and depsipeptides, as shown in Table 3. We prepared the octapeptide **10** and its depsipeptide analogs **11a**, **11b**, and **11c**. This peptide and the depsipeptides were subjected to the Michael addition of nitromethane to enone **4a** in order to reveal which NH of amides is crucial for the reaction through hydrogen-bonding activation. When the octapeptide **10** was employed as a catalyst, we obtained the 1,4-adduct with 100% conversion and 81% ee (entry 1). On the other hand, the depsipeptides **11a** and **11b** showed low conversions and poor enantioselectivities (entries 2 and 3). These results indicated that amide N(2)−H and N(3)−H both play a key role in the activation of Michael donors, as well as asymmetric induction through hydrogen bonding. Since the depsipeptide **11c** showed good conversion (89%) with

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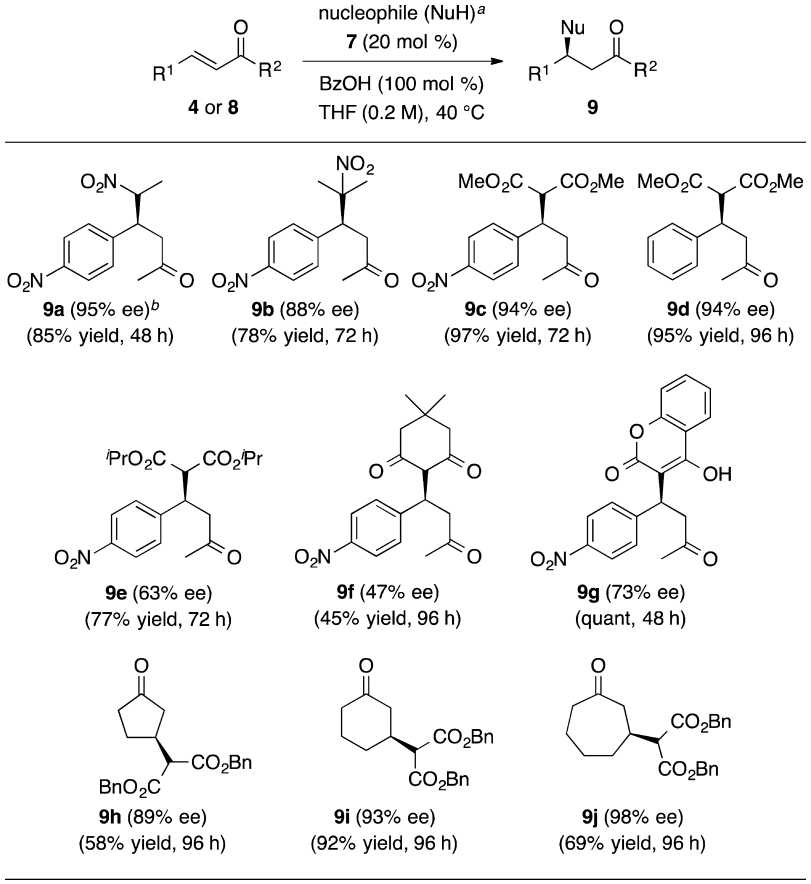
Scheme 2. Scope of Substrates



[a]Twenty equivalents of Michael donors (nucleophiles) were used for **9a** and **9b**, and 3 equiv of nucleophiles were used for **9c**–**9j** against enones. [b]Ee for the major anti-isomer (dr = 1.1:1).

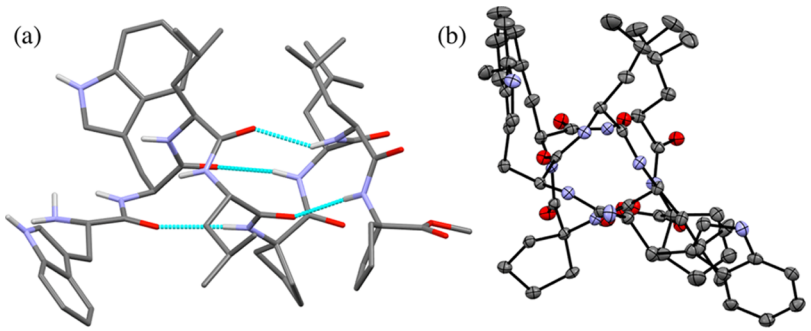


Figure 3. X-ray crystallographic structure of octapeptide **7**: (a) A view perpendicular to the α-helical axis and (b) an ORTEP drawing as viewed along the helical axis from the N terminus (ellipsoids at 50% probability).

moderate enantiomeric excess (54% ee), it is reasonable to assume that the amide N(4)–H may not affect the activation of the Michael donor. For the reaction of 2-cyclohexen-1-one (**8i**) with dibenzyl malonate, depsipeptides **11a**–**11c** provided low conversion in all cases (28–38% conversion, entries 6–8), although complete conversion and excellent enantioselectivity (98% ee, entry 5) were achieved by the regular peptide **10**. Therefore, the amide protons, N(2)–H, N(3)–H, and N(4)–H, contributed greatly to activation of Michael donors for the reaction of cyclic enones and malonates.

As shown in Scheme 3, we synthesized a 2,4,5-trisubstituted tetrahydropyran ring system from the ketone **9d**, which was obtained by the peptide-catalyzed Michael addition reaction. The ketone **9d** was protected as an acetal, followed by the reduction of the ester moieties, providing the diol **12**. Compound **12** was diastereoselectively cyclized by the Kishi reduction[27–29] to give the 2,4,5-trisubstituted tetrahydropyran **13** as a single diastereomer with two newly formed chiral centers and without any loss of ee value (94% ee). The prochiral diol in compound **12** was successfully differentiated during the course of cyclization. This stereoselectivity may be derived from the phenyl substituent oriented in the equatorial direction in the reaction intermediate. Since substituted tetrahydropyran rings are common motifs that are frequently observed in biologically active compounds,[30–32] this de novo

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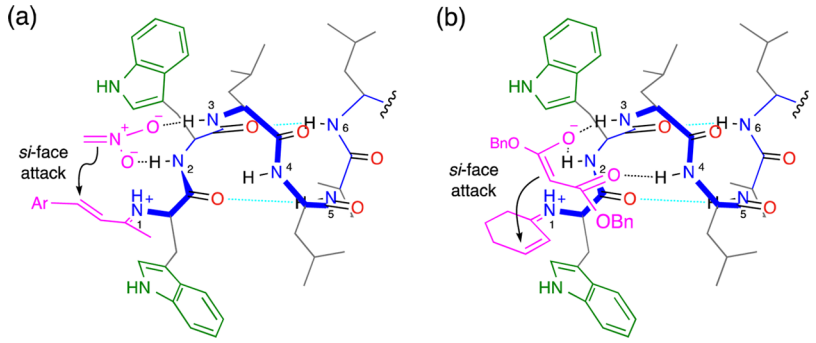
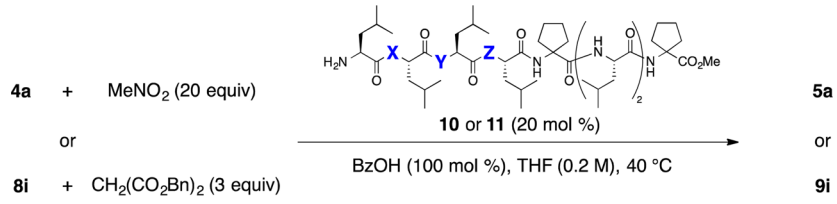


Figure 4. Plausible mechanisms for the reaction catalyzed by peptide **7**: (a) The reaction of acyclic enone **4** with nitromethane and (b) the reaction of cyclic enone **8** with dibenzyl malonate.

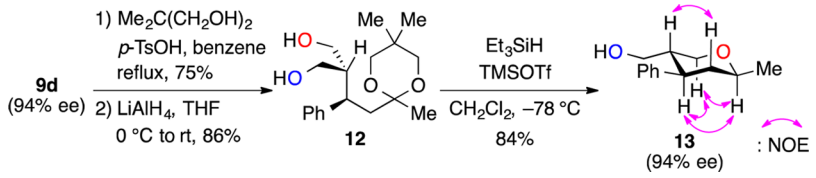
Table 3. Reactions Catalyzed by Depsipeptides



entry	SM	catalyst	X	Y	Z	time (h)	product	conv[a] (%)	ee[b] (%)
1	**4a**	**10**	NH	NH	NH	48	**5a**	100	82
2	**4a**	**11a**	O	NH	NH	48	**5a**	15	−6
3	**4a**	**11b**	NH	O	NH	48	**5a**	11	20
4	**4a**	**11c**	NH	NH	O	48	**5a**	89	54
5	**8i**	**10**	NH	NH	NH	96	**9i**	100	98
6	**8i**	**11a**	O	NH	NH	96	**9i**	28	75
7	**8i**	**11b**	NH	O	NH	96	**9i**	26	33
8	**8i**	**11c**	NH	NH	O	96	**9i**	38	63

[a]Conversion was determined by ^{1}H NMR analysis. [b]Ee was determined by chiral HPLC analysis.

Scheme 3. Synthesis of the 2,4,5-Trisubstituted THP Ring



synthetic pathway may provide a facile access to these compounds.

CONCLUSION

In summary, we herein demonstrated the α-helical peptide foldamer catalyzed Michael addition of nitroalkanes and dialkyl malonates to α,β-unsaturated ketones. The α-helical chirality and N-terminal amide protons of peptide catalysts seemed to be crucial for the enantio-induction of this catalysis, on the basis of the experimental results. These results will be helpful for design of new peptide catalysts and their application to other organocatalytic reaction. On the basis of these results, further studies on the modification of peptide catalysts and expansion of the substrate scope, including applications to bulkier nucleophiles, are currently ongoing in our laboratories.

EXPERIMENTAL SECTION

General Experimental Methods. Optical rotations were measured using $CHCl_3$ or MeOH as a solvent. ^{1}H NMR and ^{13}C NMR spectra were recorded on a 500 MHz (500 MHz for ^{1}H and 125 MHz for ^{13}C), 400 MHz (400 MHz for ^{1}H and 100 MHz for ^{13}C), or 300 MHz (300 MHz for ^{1}H) spectrometer. Chemical shifts (δ) are reported in parts per million (ppm). For ^{1}H NMR spectra ($CDCl_3$), tetramethylsilane was used as the internal reference (0.00 ppm), while the central solvent peak was the reference (77.0 ppm in $CDCl_3$) for ^{13}C NMR spectra. IR spectra were measured with KBr or as a thin film. High-resolution mass spectra (HRMS) were obtained using electrospray ionization (ESI) or direct analysis in real time (DART) ionization in TOF mode or using fast atom bombardment (FAB) ionization in the dual focusing sector field mode. Circular dichroism (CD) spectra were measured using a 1.0 mm path length cell. Analytical and semipreparative thin layer chromatography (TLC) was performed with precoated TLC plates (silica gel 60 F_{254}, layer thickness 0.25 and 0.50 mm, respectively). Compounds were observed under UV-light at 254 nm and then visualized by staining with iodine, *p*-anisaldehyde, or phosphomolybdic acid stain. Flash and gravity column chromatography separations were performed on silica gel (spherical neutral, particle size 40−50 and 63−210 μm, respectively). Analytical high-performance liquid chromatography (HPLC) was carried out with a UV spectrophotometric detector (254 nm) to which

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a 4.6 × 250 mm size chiral column (Daicel Chiralpak AD-H or AS-H) was attached. All moisture-sensitive reactions were conducted under an inert atmosphere. Reagents and solvents were commercial grade and were used as supplied, unless otherwise noted.

General Procedure A (Peptide Coupling). To a solution of carboxylic acid (1.00 equiv) in CH_2Cl_2 (0.15 M) were added *N*-(3-(dimethylamino)propyl)-*N*′-ethylcarbodiimide hydrochloride (EDCI·HCl, 1.00 equiv) and 1-hydroxybenzotriazole hydrate (HOBt·H_2O, 1.20 equiv) at 0 °C, and the reaction mixture was stirred at 0 °C for 30 min. A solution of amine (1.00 equiv) in CH_2Cl_2 (0.3 M) was added to the reaction mixture dropwise at 0 °C. The resultant solution was gradually warmed to room temperature and stirred at room temperature overnight. After removal of CH_2Cl_2, the residue was diluted with EtOAc and washed successively with 1 M HCl, water, sat. aq $NaHCO_3$, and brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo to give crude product, which was purified by flash column chromatography on silica gel eluted with EtOAc in *n*-hexane to give the desired peptide.

General Procedure B (Boc Deprotection). To a solution of Boc-protected amine in CH_2Cl_2 (0.1 M) was added trifluoroacetic acid (1 M) dropwise at room temperature, and the reaction mixture was stirred overnight at the same temperature. The reaction mixture was neutralized by adding sat. aq $NaHCO_3$, and the aqueous phase was extracted with $CHCl_3$ four times. The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under vacuum to give crude product, which was used for the next step without further purification.

General Procedure C (Cbz Deprotection). To a solution of Cbz-protected amine in MeOH (0.1 M) was added 10% palladium on carbon (25−50 wt %) at room temperature, and the reaction mixture was vigorously stirred under a hydrogen atmosphere overnight at the same temperature. The reaction mixture was passed through a short plug of Celite, and the filtrate was concentrated under vacuum to give crude product, which was used for the next step without further purification.

General Procedure D (Preparation of α,β-Unsaturated Ketone).[33] To a solution of aldehyde (1.00 equiv) in ketone (0.4 M) was added morpholinium trifluoroacetate (0.400 equiv) at room temperature, and the resultant mixture was heated at 75 °C for 2−6 days. The reaction solution was cooled to room temperature and poured into sat. aq $NaHCO_3$. The aqueous phase was extracted with EtOAc three times, and the combined organics were dried over anhydrous $MgSO_4$ and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (EtOAc in *n*-hexane) to afford desired α,β-unsaturated ketone.

General Procedure E (Peptide-Catalyzed Michael Addition). To a solution of α,β-unsaturated ketone (0.100 mmol), peptide catalyst (0.0200 mmol, 20 mol %), and benzoic acid (12.2 mg, 0.100 mmol, 1 equiv) in THF (0.5 mL) in a screw vial equipped with a magnetic stirring bar was added Michael donor (2.00 mmol, 20 equiv for nitroalkanes and 0.300 mmol, 3 equiv for malonates, dimedone, and 4-hydroxycoumarin) at room temperature, and the reaction mixture was stirred at 40 °C for the given time. The reaction mixture was diluted with EtOAc and washed with sat. aq $NaHCO_3$. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under vacuum to afford crude product, which was purified by flash column chromatography on silica gel to give the desired product.

*Synthesis of Peptides **1b, 2b, 3b, 6, and 7**.* Peptides **1a**, **2a**, **3a**, **1c**, **2c**, and **3c** were prepared by the literature procedure.[4]

*Boc-(L-Leu)$_2$-Ac$_5$c-OMe (**S-1**).* According to general procedure A, the coupling of 1-aminocyclopentanecarboxylic acid methyl ester (1.55 g, 10.8 mmol) with Boc-(L-Leu)$_2$-OH (3.73 g, 10.8 mmol) gave the title compound **S-1** (4.36 g, 86%) as a white solid after purification by flash column chromatography on silica gel (40% EtOAc in *n*-hexane). Mp: 158−160 °C. $[\alpha]_D^{20}$: −67.0 (*c* 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.04 (br s, 1H), 6.71 (d, *J* = 7.3 Hz, 1H), 5.11 (d, *J* = 6.3 Hz, 1H), 4.51−4.36 (m, 1H), 4.18−4.05 (m, 1H), 3.68 (s, 3H), 2.28−2.13 (m, 2H), 2.04−1.86 (m, 2H), 1.83−1.59 (m, 8H), 1.59−1.46 (m, 2H), 1.44 (s, 9H), 1.03−0.84 (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 174.5, 172.8, 171.4, 155.8, 80.2, 65.7, 53.3, 52.2, 51.4, 40.8, 40.1, 37.0, 36.9, 28.1 (3C), 24.6, 24.5, 24.4 (2C), 22.8 (2C), 21.9, 21.8. IR (KBr): 3329, 2959, 1744, 1700, 1528, 1172 cm^{-1}. HRMS (DART) *m*/*z*: $[M + H]^+$ calcd for $C_{24}H_{44}N_3O_6$, 470.3230; found, 470.3221.

*H-(L-Leu)$_2$-Ac$_5$c-OMe (**1b**).* According to general procedure B, Boc deprotection of peptide **S-1** (2.50 g, 5.33 mmol) afforded the desired product **1b** (1.95 g, 99%) as a white solid after purification by flash column chromatography on silica gel (5% MeOH in $CHCl_3$). Mp: 137−139 °C. $[\alpha]_D^{21}$: −64.0 (*c* 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.72 (d, *J* = 8.8 Hz, 1H), 7.20 (s, 1H), 4.44 (dt, *J* = 8.8, 5.9 Hz, 1H), 3.69 (s, 3H), 3.41 (dd, *J* = 9.8, 3.9 Hz, 1H), 2.31−2.10 (m, 2H), 2.05−1.86 (m, 2H), 1.82−1.62 (m, 8H), 1.61−1.44 (m, 3H), 1.40−1.30 (m, 1H), 1.04−0.83 (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 176.2, 174.5, 171.7, 65.7, 53.3, 52.3, 50.9, 43.8, 40.0, 37.2, 37.1, 24.7, 24.6, 24.52, 24.50, 23.3, 22.8, 22.0, 21.2. IR (KBr): 3283, 2955, 1747, 1632, 1539 cm^{-1}. HRMS (DART) *m*/*z*: $[M + H]^+$ calcd for $C_{19}H_{36}N_3O_4$, 370.2706; found, 370.2693.

*Boc-[(L-Leu)$_2$-Ac$_5$c]$_2$-OMe (**S-3**).* To a solution of tripeptide **S-1** (4.00 g, 8.53 mmol) in MeOH (85 mL) was added 0.5 M aq NaOH (68 mL, 34 mmol) dropwise at 0 °C, and the resultant white suspension was stirred at room temperature for 2 d. The reaction mixture was acidified with 1 M HCl at 0 °C and was evaporated to remove MeOH. The aqueous solution was extracted with EtOAc four times and the combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, and concentrated under vacuum. The residue was passed through a short plug of silica gel (5% MeOH in $CHCl_3$) to give acid **S-2** (3.76 g, 97%), which was used for the next step without further purification. According to general procedure A, the coupling of acid **S-2** (2.42 g, 5.30 mmol) with amine **1b** (1.96 g, 5.30 mmol) gave the title compound **S-3** (3.95 g, 92%) as a white solid after purification by flash column chromatography on silica gel (60% EtOAc in *n*-hexane). Mp: 218−220 °C. $[\alpha]_D^{22}$: −4.1 (*c* 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.56 (br s, 1H), 7.49−7.41 (m, 2H), 7.29 (s, 1H), 6.90 (d, *J* = 4.0 Hz, 1H), 5.79 (d, *J* = 2.4 Hz, 1H), 4.37−4.29 (m, 1H), 4.25−4.17 (m, 1H), 3.99−3.93 (m, 1H), 3.92−3.85 (m, 1H), 3.66 (s, 3H), 2.69−2.57 (m, 1H), 2.37−2.24 (m, 1H), 2.21−2.05 (m, 4H), 1.96−1.66 (m, 17H), 1.65−1.55 (m, 5H), 1.49 (s, 9H), 1.01−0.84 (m, 24H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 175.6, 175.3, 174.8, 173.22, 173.20, 173.18, 157.1, 81.3, 66.9, 65.7, 55.3, 54.6, 54.0, 52.2, 52.0, 40.3, 39.9, 39.6, 39.3, 37.7, 37.2, 36.5, 35.7, 28.1 (3C), 25.1, 24.83, 24.75, 24.73, 24.68, 24.44, 24.38, 24.3, 23.32, 23.26, 22.8, 22.6, 21.9, 21.4, 21.0, 20.7. IR (KBr): 3325, 2953, 1734 cm^{-1}. HRMS (ESI) *m*/*z*: $[M + Na]^+$ calcd for $C_{42}H_{74}N_6O_9Na$, 829.5415; found, 829.5403.

*H-[(L-Leu)$_2$-Ac$_5$c]$_2$-OMe (**2b**).* According to general procedure B, Boc deprotection of peptide **S-3** (800 mg, 0.991 mmol) afforded the desired product **2b** (668 mg, 95%) as a white solid after purification by flash column chromatography on silica gel (5% MeOH in $CHCl_3$). Mp: 207−209 °C. $[\alpha]_D^{20}$: −27.7 (*c* 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.08 (d, *J* = 2.9 Hz, 1H), 7.50−7.38 (m, 2H), 7.20 (s, 1H), 6.81 (s, 1H), 4.41−4.30 (m, 1H), 4.28−4.18 (m, 1H), 3.98−3.88 (m, 1H), 3.67 (s, 3H), 3.41 (dd, *J* = 9.8, 3.4 Hz, 1H), 2.67−2.57 (m, 1H), 2.34−2.22 (m, 1H), 2.19−1.95 (m, 4H), 1.90−1.56 (m, 23H), 1.36 (t, *J* = 9.5 Hz, 1H), 1.04−0.83 (m, 24H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 178.5, 175.2, 175.0, 173.8, 173.3, 173.2, 66.6, 65.8, 54.8, 53.9, 53.1, 52.3, 52.0, 43.6, 39.9, 39.8, 39.2, 38.8, 37.3, 36.4, 35.9, 25.2, 24.9, 24.7, 24.6, 24.5, 24.4 (3C), 23.30 (2C), 23.25, 22.5, 21.7, 21.2, 21.0, 20.7. IR (KBr): 3314, 2959, 1651, 1532 cm^{-1}. HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{37}H_{67}N_6O_7$, 707.5071; found, 707.5057.

*H-[(L-Leu)$_2$-Ac$_5$c]$_3$-OMe (**3b**).* According to general procedure B, Boc deprotection of peptide **S-4**[13] (108 mg, 0.0944 mmol) afforded the desired product **3b** (91.7 mg, 93%) as a white solid after purification by flash column chromatography on silica gel (5% MeOH in $CHCl_3$). Mp: 255−257 °C. $[\alpha]_D^{21}$: −0.1 (*c* 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.37 (br s, 1H), 7.91 (br s, 1H), 7.75−7.57 (m, 3H), 7.54 (br s, 2H), 7.38 (d, *J* = 5.9 Hz, 1H), 4.31 (t, *J* = 11.0 Hz, 1H), 4.25−4.16 (m, 1H), 4.06 (dt, *J* = 10.0, 5.2 Hz, 1H), 3.97−3.85 (m, 2H), 3.66 (s, 3H), 3.44 (d, *J* = 6.3 Hz, 1H), 2.63 (td, *J* = 13.8, 8.5 Hz, 2H), 2.45−2.22 (m, 2H), 2.20−2.06 (m, 3H), 1.99−1.53 (m, 36H), 1.38 (t, *J* = 9.3 Hz, 1H), 1.05−0.80 (m, 36H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 176.3, 175.9 (2C), 175.8, 175.1 (2C), 174.2, 173.8, 173.7, 66.9, 66.4, 65.8, 55.3, 55.1, 54.8, 54.0, 53.2, 52.6, 52.0 (2C),

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43.5, 40.1, 39.9, 39.4, 39.2 (2C), 38.5, 37.7, 37.2, 36.5, 36.0, 35.2, 25.0, 24.93, 24.85, 24.8, 24.7, 24.6, 24.4 (4C), 24.3, 23.32 (2C), 23.28, 23.1, 23.0, 22.4, 21.8, 21.2, 21.14, 21.12, 20.9, 20.8. IR (KBr): 3310, 2959, 1651, 1539 cm^{-1}. HRMS (FAB) m/z: $[M]^+$ calcd for $C_{55}H_{97}N_9O_{10}$, 1043.7358; found, 1043.7367.

*Cbz-L-Trp-[(L-Leu)$_2$-Ac$_5$c]$_2$-OMe (**S-5**).* According to general procedure A, the coupling of Cbz-L-Trp-OH (629 mg, 1.86 mmol) with amine **2b** (1.31 g, 1.86 mmol) gave the title compound **S-5** (1.74 g, 91%) as a white solid after purification by flash column chromatography on silica gel (2% MeOH in chloroform). Mp: 188–190 °C. $[\alpha]_D^{22}$: −0.7 (c 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.38 (br s, 1H), 7.61–7.50 (m, 3H), 7.48–7.42 (m, 2H), 7.42–7.24 (m, 7H), 7.20 (t, J = 7.6 Hz, 1H), 7.10 (t, J = 7.3 Hz, 1H), 6.53 (d, J = 3.4 Hz, 1H), 6.12 (br s, 1H), 5.07 (s, 2H), 4.50–4.33 (m, 1H), 4.33–4.20 (m, 2H), 4.01–3.88 (m, 2H), 3.59 (s, 3H), 3.39 (dd, J = 14.6, 3.4 Hz, 1H), 3.28–3.14 (m, 1H), 2.68 (dt, J = 13.4, 8.2 Hz, 1H), 2.47–2.36 (m, 1H), 2.34–2.22 (m, 1H), 2.21–2.06 (m, 3H), 2.03–1.57 (m, 20H), 1.53–1.44 (m, 1H), 1.40 (dt, J = 13.2, 6.6 Hz, 1H), 1.32–1.22 (m, 1H), 1.04–0.75 (m, 24H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 175.8, 175.3, 174.3, 174.2, 174.1, 173.7, 173.6, 157.9, 136.8, 135.6, 128.7 (2C), 128.5, 127.7 (2C), 126.9, 124.5, 122.3, 119.6, 118.1, 111.9, 108.3, 67.3, 66.9, 65.8, 57.4, 54.7, 54.4, 54.0, 52.6, 52.0, 39.9, 39.8, 39.5, 39.3, 38.0, 37.2, 36.7, 35.2, 27.1, 25.2, 24.8, 24.7, 24.53, 24.45, 24.4, 24.30, 24.27, 23.3 (2C), 22.9, 22.6, 21.7, 21.00, 20.98, 20.94. IR (KBr): 3337, 2959, 1655, 1531, 1269 cm^{-1}. HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{56}H_{82}N_8O_{10}Na$, 1049.6052; found, 1049.6069.

*H-L-Trp-[(L-Leu)$_2$-Ac$_5$c]$_2$-OMe (**6**).* According to general procedure C (using THF as solvent instead of MeOH), Cbz deprotection of peptide **S-5** (680 mg, 0.662 mmol) afforded the desired product **6** (593 mg, quant) as a white amorphous material that was used for the next step without further purification. An aliquot of the crude product was purified by column chromatography on silica gel (10% MeOH in chloroform) for analytical data collection. $[\alpha]_D^{21}$: −21.9 (c 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.63 (br s, 1H), 7.93 (br s, 1H), 7.68–7.54 (m, 2H), 7.52–7.38 (m, 2H), 7.31 (d, J = 5.9 Hz, 1H), 7.25–7.19 (m, 2H), 7.16–7.08 (m, 2H), 6.50 (br s, 1H), 4.45–4.31 (m, 1H), 4.30–4.19 (m, 1H), 4.02–3.89 (m, 2H), 3.85–3.75 (m, 1H), 3.65 (s, 3H), 3.35 (dd, J = 14.6, 4.1 Hz, 1H), 3.08 (dd, J = 14.6, 7.8 Hz, 1H), 2.66 (dt, J = 13.4, 8.4 Hz, 1H), 2.32–2.03 (m, 5H), 2.03–1.58 (m, 21H), 1.58–1.44 (m, 3H), 1.03–0.74 (m, 24H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 177.9, 175.8, 175.2, 174.2, 173.7, 173.6, 173.5, 136.7, 127.2, 123.8, 121.9, 119.0, 118.4, 111.7, 110.0, 66.9, 65.7, 54.6 (2C), 54.5, 53.9, 52.5, 52.0, 39.9, 39.8, 39.5, 39.4, 38.0, 37.1, 36.5, 35.2, 30.4, 25.1, 24.8, 24.7, 24.5, 24.3 (2C), 24.2 (2C), 23.22, 23.20, 22.5 (2C), 21.6, 21.3, 21.0, 20.8. IR (KBr): 3321, 2959, 1670, 1528 cm^{-1}. HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{48}H_{76}N_8O_8Na$, 915.5684; found, 915.5662.

*Boc-(L-Trp)$_2$-[(L-Leu)$_2$-Ac$_5$c]$_2$-OMe (**S-6**).* According to general procedure A, the coupling of Boc-L-Trp-OH (250 mg, 0.821 mmol) with amine **6** (734 mg, 0.822 mmol) gave the title compound **S-6** (930 mg, 96%) as a white solid after purification by flash column chromatography on silica gel (50% EtOAc in chloroform). Mp: 243–245 °C dec. $[\alpha]_D^{22}$: −14.1 (c 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.79 (br s, 1H), 9.63 (br s, 1H), 7.70 (d, J = 6.8 Hz, 1H), 7.64 (s, 1H), 7.54 (s, 1H), 7.52 (s, 1H), 7.45 (d, J = 7.8 Hz, 1H), 7.40 (d, J = 8.3 Hz, 1H), 7.36–7.29 (m, 2H), 7.25–7.20 (m, 1H), 7.17–7.07 (m, 4H), 7.00–6.93 (m, 1H), 6.91 (d, J = 6.3 Hz, 1H), 6.54 (d, J = 2.0 Hz, 1H), 6.35 (d, J = 3.9 Hz, 1H), 5.22 (br s, 1H), 4.50–4.39 (m, 1H), 4.38–4.28 (m, 1H), 4.23–4.14 (m, 1H), 4.12–4.01 (m, 2H), 4.00–3.93 (m, 1H), 3.64 (s, 3H), 3.36–3.24 (m, 1H), 3.19–3.09 (m, 1H), 3.08–2.99 (m, 1H), 2.81–2.67 (m, 1H), 2.50–2.26 (m, 3H), 2.25–2.12 (m, 3H), 2.07–1.61 (m, 19H), 1.57–1.47 (m, 1H), 1.46–1.37 (m, 1H), 1.32–1.21 (m, 1H), 1.14 (s, 9H), 1.08–0.79 (m, 24H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 175.9, 175.5, 175.1, 174.7, 174.1, 174.0 (2C), 173.8, 156.8, 136.8, 136.7, 127.4, 127.0, 124.0, 123.7, 122.4, 122.1, 119.5, 119.4, 118.0, 117.9, 112.2, 112.0, 108.0, 107.9, 81.2, 66.8, 65.9, 56.5, 55.1, 55.0, 54.3, 54.1, 53.1, 52.2, 40.1, 39.84, 39.81, 39.2, 38.2, 37.1, 36.8, 35.1, 27.7 (3C), 26.7, 25.6, 24.99, 24.96, 24.6 (2C), 24.5, 24.4, 24.33, 24.28, 23.33, 23.26, 22.9, 22.4, 21.6, 21.3, 21.2, 21.1. IR (KBr): 3329, 2959, 1659, 1528 cm^{-1}. HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{64}H_{94}N_{10}O_{11}Na$, 1201.7001; found, 1201.6981.

*H-(L-Trp)$_2$-[(L-Leu)$_2$-Ac$_5$c]$_2$-OMe (**7**).* Peptide **S-6** (188 mg, 0.159 mmol) was dissolved in 2 M HCl in MeOH (3.2 mL) at room temperature, and the solution was stirred overnight at 30 °C. The reaction mixture was neutralized by adding sat. aq $NaHCO_3$, and the aqueous phase was extracted with $CHCl_3$ four times. The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under vacuum to give crude product, which was purified by column chromatography on silica gel eluted with 10% MeOH in chloroform to afford desired amine **7** (165 mg, 96%) as a white solid. Single crystals for the X-ray crystallographic analysis were obtained by recrystallization from EtOAc/MeOH/n-hexane (ca. 8:1:1) by slow evaporation of the solvents at room temperature. Mp: 232–234 °C. $[\alpha]_D^{17}$: −15.4 (c 1.00, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.57 (br s, 1H), 9.19 (br s, 1H), 7.97 (br s, 1H), 7.74 (s, 1H), 7.66 (d, J = 5.9 Hz, 1H), 7.59 (d, J = 11.2 Hz, 2H), 7.50 (d, J = 7.8 Hz, 1H), 7.47–7.35 (m, 4H), 7.23–7.13 (m, 2H), 7.11–7.02 (m, 2H), 6.92 (s, 1H), 6.73 (s, 1H), 6.32 (br s, 1H), 4.48–4.36 (m, 1H), 4.35–4.24 (m, 1H), 4.19–4.09 (m, 1H), 4.06–3.94 (m, 2H), 3.75–3.65 (m, 1H), 3.58 (s, 3H), 3.25–2.98 (m, 4H), 2.79–2.64 (m, 1H), 2.48–2.35 (m, 1H), 2.33–2.23 (m, 1H), 2.22–2.07 (m, 3H), 2.03–1.57 (m, 21H), 1.51–1.35 (m, 2H), 1.33–1.19 (m, 1H), 1.09–0.75 (m, 24H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 178.2, 176.0, 175.5, 174.7, 174.5, 174.0, 173.9, 173.8, 136.7, 136.6, 127.3, 127.0, 123.64, 123.62, 122.2, 122.1, 119.5, 119.2, 118.4, 118.1, 111.9, 111.8, 109.5, 108.5, 66.9, 65.9, 56.1, 55.0, 54.6, 54.3, 54.2, 53.0, 52.1, 40.0, 39.8, 39.6, 39.2, 38.1, 37.1, 36.7, 35.1, 30.4, 26.7, 25.1, 25.0, 24.7, 24.6, 24.5 (2C), 24.31, 24.28, 23.3, 23.2, 23.0, 22.6, 21.7, 21.2, 21.04, 21.00. IR (KBr): 3325, 2959, 1655, 1531 cm^{-1}. HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{59}H_{86}N_{10}O_9Na$, 1101.6477; found, 1101.6468.

*Preparation of α,β-Unsaturated Ketones **4**.* Compounds **4a**, **4b**, **4h**, **4j**, **4k**, **4l**, and **4n** were prepared according to the literature procedure reported by List and co-workers.[33] Preparation of compounds **4c** and **4d** by the above procedure is also known in the literature.[34] Compounds **4e**, **4f**, **4g**, **4i**, **4p**, **4q**, and **4r** were synthesized by List's procedure[33] this time, and all these compounds are known compounds. Compound **4m** was prepared by the known procedure reported by Kuroda et al.[35] Compound **4o** was synthesized from 1,3-propanediol. Compound **4s** is commercially available.

*(E)-4-(4′-tert-Butylphenyl)-3-buten-2-one (**4e**).*[36] According to general procedure D, the reaction of 4-*tert*-butylbenzaldehyde (1.62 g, 10.0 mmol) in acetone (25 mL) gave the title compound **4e** (1.96 g, 97%) as a colorless oil after purification by flash column chromatography on silica gel (5% EtOAc in n-hexane). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.50 (d, J = 16.3 Hz, 1H), 7.50–7.47 (m, 2H), 7.46–7.40 (m, 2H), 6.69 (d, J = 16.3 Hz, 1H), 2.38 (s, 3H), 1.33 (s, 9H).

*(E)-4-(4′-Tolyl)-3-buten-2-one (**4f**).*[37] According to general procedure D, the reaction of p-tolualdehyde (1.20 g, 10.0 mmol) in acetone (25 mL) gave the title compound **4f** (1.56 g, 98%) as an off-white solid after purification by flash column chromatography on silica gel (7% EtOAc in n-hexane). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.49 (d, J = 16.3 Hz, 1H), 7.45 (d, J = 7.9 Hz, 2H), 7.21 (d, J = 7.9 Hz, 2H), 6.68 (d, J = 16.3 Hz, 1H), 2.38 (s, 3H), 2.37 (s, 3H).

*(E)-4-(3′-Tolyl)-3-buten-2-one (**4g**).*[37] According to general procedure D, the reaction of m-tolualdehyde (1.20 g, 10.0 mmol) in acetone (25 mL) gave the title compound **4g** (1.54 g, 97%) as a colorless oil after purification by flash column chromatography on silica gel (5% EtOAc in n-hexane). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.49 (d, J = 16.3 Hz, 1H), 7.40–7.16 (m, 4H), 6.71 (d, J = 16.3 Hz, 1H), 2.38 (s, 3H), 2.38 (s, 3H).

*(E)-4-Furyl-3-buten-2-one (**4i**).*[37] According to general procedure D, the reaction of furfural (961 mg, 10.0 mmol) in acetone (25 mL) gave the title compound **4i** (1.20 g, 88%) as a light brown solid after purification by flash column chromatography on silica gel (7% EtOAc in n-hexane). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.51 (d, J = 1.7 Hz, 1H), 7.28 (d, J = 16.0 Hz, 1H), 6.67 (d, J = 3.4 Hz, 1H), 6.62 (d, J = 16.0 Hz, 1H), 6.49 (dd, J = 3.4, 1.7 Hz, 1H), 2.33 (s, 3H).

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(E)-1-Phenyl-1-penten-3-one (**4p**).[37] According to general procedure D, the reaction of benzaldehyde (530 mg, 5.00 mmol) in 2-butanone (12.5 mL) gave the title compound **4p** (703 mg, 88%) as an off-white solid after purification by flash column chromatography on silica gel (4% EtOAc in *n*-hexane). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.61−7.51 (m, 3H), 7.45−7.36 (m, 3H), 6.75 (d, J = 16.3 Hz, 1H), 2.70 (q, J = 7.3 Hz, 2H), 1.17 (t, J = 7.3 Hz, 3H).

(E)-1-Phenyl-1-hexen-3-one (**4q**).[38] According to general procedure D, the reaction of benzaldehyde (530 mg, 5.00 mmol) in 2-pentanone (12.5 mL) gave the title compound **4q** (796 mg, 91%) as a pale yellow oil after purification by flash column chromatography on silica gel (5% EtOAc in *n*-hexane). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.62−7.51 (m, 3H), 7.45−7.34 (m, 3H), 6.75 (d, J = 16.2 Hz, 1H), 2.65 (t, J = 7.3 Hz, 2H), 1.72 (qt, J = 7.4, 7.3 Hz, 2H), 0.99 (t, J = 7.4 Hz, 3H).

(E)-4-Methyl-1-phenyl-1-penten-3-one (**4r**).[37] According to general procedure D, the reaction of benzaldehyde (530 mg, 5.00 mmol) in methyl isopropyl ketone (12.5 mL) gave the title compound **4r** (392 mg, 45%) as a yellow oil after purification by flash column chromatography on silica gel (5% EtOAc in *n*-hexane). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.61 (d, J = 16.0 Hz, 1H), 7.59−7.53 (m, 2H), 7.43−7.37 (m, 3H), 6.82 (d, J = 16.0 Hz, 1H), 2.94 (hept, J = 6.9 Hz, 1H), 1.19 (d, J = 6.9 Hz, 6H).

3-Hydroxypropyl 4-Bromobenzoate (**S-7**). To a mixture of 1,3-propanediol (500 mg, 6.58 mmol), pyridine (1.06 mL, 13.2 mmol), and 4-(dimethylamino)pyridine (DMAP; 80.3 mg, 0.658 mmol) in CH_2Cl_2 (20 mL) was added 4-bromobenzoyl chloride (1.44 g, 6.58 mmol) at −40 °C. The reaction mixture was stirred at −40 °C for 40 min and then gradually warmed to 0 °C over 2 h before addition of MeOH (0.5 mL). The reaction mixture was diluted with EtOAc and washed twice with 1 M HCl and once each with water, sat. aq $NaHCO_3$, and brine. After drying (anhydrous Na_2SO_4) and removal of the solvent, the residue was purified by flash column chromatography on silica gel (20% then 30% EtOAc in *n*-hexane) to give alcohol **S-7** (1.15 g, 68%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.94−7.86 (m, 2H), 7.64−7.55 (m, 2H), 4.48 (t, J = 6.2 Hz, 2H), 3.77 (t, J = 6.1 Hz, 2H), 2.11 (br s, 1H), 2.01 (tt, J = 6.2, 6.1 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 166.2, 131.7 (2C), 131.1 (2C), 128.9, 128.1, 62.0, 59.1, 31.8. IR (film): 3418, 1721 cm^{-1}. HRMS (DART) m/z: $[M + H]^+$ calcd for $C_{10}H_{12}BrO_3$, 258.9964; found, 258.9952.

3-Oxopropyl 4-Bromobenzoate (**S-8**). A solution of potassium bromide (23.0 mg, 0.193 mmol) in sat. aq $NaHCO_3$ (1.9 mL) was added to a solution of the alcohol **S-7** (500 mg, 1.93 mmol) and 2-hydroxy-2-azaadamantane[39,40] (AZADOL; 3.0 mg, 0.0193 mmol) in CH_2Cl_2 (5.2 mL) at 0 °C. To the above solution was added dropwise a solution of sodium hypochlorite pentahydrate (382 mg, 2.32 mmol) in sat. aq $NaHCO_3$ (4.7 mL) over 5 min at 0 °C with vigorous stirring. After additional stirring for 15 min at 0 °C, the reaction was quenched by adding 10 wt % aq $Na_2S_2O_3$. The aqueous phase was extracted with CH_2Cl_2 twice, and the combined organic phases were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash column chromatography on silica gel (20% EtOAc in *n*-hexane) to give aldehyde **S-8** (433 mg, 87%) as a white semisolid. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.86 (t, J = 1.4 Hz, 1H), 7.92−7.82 (m, 2H), 7.63−7.51 (m, 2H), 4.66 (t, J = 6.1 Hz, 2H), 2.92 (td, J = 6.1, 1.4 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 199.1, 165.6, 131.7 (2C), 131.1 (2C), 128.6, 128.3, 58.7, 42.7. IR (KBr): 1721, 1686 cm^{-1}. HRMS (DART) m/z: $[M + H]^+$ calcd for $C_{10}H_{10}BrO_3$, 256.9808; found, 256.9818.

(E)-5-Oxo-3-hexen-1-yl 4-Bromobenzoate (**4o**). To a solution of aldehyde **S-8** (350 mg, 1.36 mmol) in CH_2Cl_2 (14 mL) was added (acetylmethylene)triphenylphosphorane (476 mg, 1.50 mmol) at room temperature. After 17 h, another portion of (acetylmethylene)-triphenylphosphorane (216 mg, 0.680 mmol) was added to the reaction mixture. After 17 h, the resultant mixture was concentrated under vacuum and the residue was purified by flash column chromatography on silica gel (10% EtOAc in *n*-hexane) to give enone **4o** (238 mg, 59%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.90−7.84 (m, 2H), 7.62−7.55 (m, 2H), 6.82 (dt, J = 16.0, 6.9 Hz, 1H), 6.20 (dt, J = 16.0, 1.5 Hz, 1H), 4.46 (t, J = 6.4 Hz, 2H), 2.70 (dtd, J = 6.9, 6.4, 1.5 Hz, 2H), 2.26 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 198.0, 165.6, 142.6, 133.2, 131.8 (2C), 131.0 (2C), 128.7, 128.2, 62.9, 31.7, 27.1. IR (film): 1721, 1679 cm^{-1}. HRMS (DART) m/z: $[M + H]^+$ calcd for $C_{13}H_{14}BrO_3$, 297.0121; found, 297.0123.

Synthesis of Nitromethane Adducts 5. According to general procedure E, the reaction of α,β-unsaturated ketone and nitromethane gave the desired product.

(S)-5-Nitro-4-(4-nitrophenyl)pentan-2-one (**5a**).[41] Reaction of **4a** and nitromethane gave **5a** as a pale yellow solid in 85% yield. $[\alpha]_D^{23}$: +3.2 (*c* 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.20 (d, J = 8.3 Hz, 2H), 7.44 (d, J = 8.3 Hz, 2H), 4.76 (dd, J = 12.8, 6.4 Hz, 1H), 4.65 (dd, J = 12.8, 8.4 Hz, 1H), 4.15 (quin, J = 6.8 Hz, 1H), 2.97 (dd, J = 6.6, 2.7 Hz, 2H), 2.16 (s, 3H). HPLC (Chiralpak AD-H, 2-propanol/*n*-hexane = 20/80, flow rate = 1.0 mL/min): t_R = 14.9 min (major), t_R = 20.5 min (minor), ee = 97%.

(S)-5-Nitro-4-phenylpentan-2-one (**5b**).[41] Reaction of **4b** and nitromethane gave **5b** as a white solid in 79% yield. $[\alpha]_D^{24}$: +2.7 (*c* 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.45−7.15 (m, 5H), 4.70 (dd, J = 12.8, 6.8 Hz, 1H), 4.60 (dd, J = 12.8, 7.6 Hz, 1H), 4.01 (quin, J = 7.2 Hz, 1H), 2.92 (d, J = 6.8 Hz, 2H), 2.12 (s, 3H). HPLC (Chiralpak AD-H, 2-propanol/*n*-hexane = 10/90, flow rate = 1.0 mL/min): t_R = 10.3 min (major), t_R = 11.0 min (minor), ee = 96%.

(S)-5-Nitro-4-(4-chlorophenyl)pentan-2-one (**5c**).[41] Reaction of **4c** and nitromethane gave **5c** as a white solid in 84% yield. $[\alpha]_D^{23}$: +2.4 (*c* 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.31 (d, J = 8.3 Hz, 2H), 7.16 (d, J = 8.3 Hz, 2H), 4.68 (dd, J = 12.8, 6.8 Hz, 1H), 4.57 (dd, J = 12.8, 7.6 Hz, 1H), 3.99 (quin, J = 7.2 Hz, 1H), 2.90 (d, J = 7.3 Hz, 2H), 2.13 (s, 3H). HPLC (Chiralpak AD-H, 2-propanol/*n*-hexane = 10/90, flow rate = 1.0 mL/min): t_R = 12.2 min (major), t_R = 14.0 min (minor), ee = 94%.

(S)-5-Nitro-4-(4-methoxyphenyl)pentan-2-one (**5d**).[41] Reaction of **4d** and nitromethane gave **5d** as a white solid in 66% yield. $[\alpha]_D^{24}$: −0.1 (*c* 0.87, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.14 (d, J = 8.8 Hz, 2H), 6.86 (d, J = 8.8 Hz, 2H), 4.66 (dd, J = 12.4, 6.8 Hz, 1H), 4.56 (dd, J = 12.4, 8.0 Hz, 1H), 3.96 (quin, J = 7.2 Hz, 1H), 3.78 (s, 3H), 2.89 (d, J = 6.8 Hz, 2H), 2.12 (s, 3H). HPLC (Chiralpak AD-H, 2-propanol/*n*-hexane = 10/90, flow rate = 1.0 mL/min): t_R = 15.3 min (major), t_R = 17.1 min (minor), ee = 96%.

(S)-5-Nitro-4-(4-tert-butylphenyl)pentan-2-one (**5e**). Reaction of **4e** and nitromethane gave **5e** as a colorless oil in 69% yield. $[\alpha]_D^{19}$: +2.7 (*c* 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.33 (d, J = 8.3 Hz, 2H), 7.14 (d, J = 8.3 Hz, 2H), 4.68 (dd, J = 12.4, 8.0 Hz, 1H), 4.59 (dd, J = 12.4, 8.0 Hz, 1H), 3.99 (quin, J = 7.3 Hz, 1H), 2.91 (d, J = 7.3 Hz, 2H), 2.12 (s, 3H), 1.29 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 205.7, 150.8, 135.7, 127.0 (2C), 126.0 (2C), 79.5, 46.2, 38.5, 34.4, 31.2 (3C), 30.3. IR (KBr): 2963, 1717, 1549 cm^{-1}. HRMS (DART) m/z: $[M + H]^+$ calcd for $C_{15}H_{22}NO_3$, 264.1600; found, 264.1601. HPLC (Chiralpak AD-H, 2-propanol/*n*-hexane = 20/80, flow rate = 0.8 mL/min): t_R = 7.4 min (major), t_R = 8.0 min (minor), ee = 95%.

(S)-5-Nitro-4-(4-methylphenyl)pentan-2-one (**5f**).[42] Reaction of **4f** and nitromethane gave **5f** as clear crystals in 83% yield. $[\alpha]_D^{22}$: +1.3 (*c* 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.23−7.01 (m, 4H), 4.67 (dd, J = 12.4, 8.0 Hz, 1H), 4.58 (dd, J = 12.4, 8.0 Hz, 1H), 3.97 (quin, J = 7.1 Hz, 1H), 2.89 (d, J = 6.8 Hz, 2H), 2.31 (s, 3H), 2.11 (s, 3H). HPLC (Chiralpak AD-H, 2-propanol/*n*-hexane = 10/90, flow rate = 1.0 mL/min): t_R = 9.7 min (major), t_R = 10.7 min (minor), ee = 96%.

(S)-5-Nitro-4-(3-methylphenyl)pentan-2-one (**5g**).[43] Reaction of **4g** and nitromethane gave **5g** as a pale yellow oil in 87% yield. $[\alpha]_D^{22}$: +1.9 (*c* 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.25−7.18 (m, 1H), 7.08 (d, J = 7.8 Hz, 1H), 7.02 (s, 1H), 7.01 (d, J = 8.0 Hz, 1H), 4.68 (dd, J = 12.4, 8.0 Hz, 1H), 4.59 (dd, J = 12.4, 8.0 Hz, 1H), 3.97 (quin, J = 7.2 Hz, 1H), 2.90 (d, J = 6.8 Hz, 2H), 2.33 (s, 3H), 2.12 (s, 3H). HPLC (Chiralpak AD-H, 2-propanol/*n*-hexane = 10/90, flow rate = 1.0 mL/min): t_R = 8.5 min (major), t_R = 9.1 min (minor), ee = 88%.

(S)-5-Nitro-4-(2-methylphenyl)pentan-2-one (**5h**).[44] Reaction of **4h** and nitromethane gave **5h** as a pale yellow oil in 81% yield. $[\alpha]_D^{21}$: +1.2 (*c* 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.22−7.07 (m, 4H), 4.64 (dd, J = 12.4, 7.2 Hz, 1H), 4.56 (dd, J = 12.4, 7.2 Hz, 1H),

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4.31 (quin, J = 7.2 Hz, 1H), 2.90 (dd, J = 7.2, 2.7 Hz, 2H), 2.44 (s, 3H), 2.11 (s, 3H). HPLC (Chiralpak AD-H, 2-propanol/*n*-hexane = 4/96, flow rate = 0.8 mL/min): t_R = 16.5 min (major), t_R = 17.7 min (minor), ee = 97%.

*(R)-5-Nitro-4-furan-2-ylpentan-2-one (**5i**).*[41] Reaction of **4i** and nitromethane gave **5i** as a brown solid in 46% yield. $[\alpha]_D^{24}$: +4.1 (c 0.51, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.34 (d, J = 2.0 Hz, 1H), 6.30 (dd, J = 2.9, 2.0 Hz, 1H), 6.15 (d, J = 2.9 Hz, 1H), 4.79−4.60 (m, 2H), 4.11 (quin, J = 6.7 Hz, 1H), 3.05−2.84 (m, 2H), 2.18 (s, 3H). HPLC (Chiralpak AD-H, 2-propanol/*n*-hexane = 10/90, flow rate = 1.0 mL/min): t_R = 10.3 min (major), t_R = 11.6 min (minor), ee = 94%.

*(S)-4-(Naphthalen-2-yl)-5-nitropentan-2-one (**5j**).*[43] Reaction of **4j** and nitromethane gave **5j** as clear crystals in 81% yield. $[\alpha]_D^{19}$: +4.8 (c 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.87−7.77 (m, 3H), 7.67 (s, 1H), 7.54−7.43 (m, 2H), 7.38−7.31 (m, 1H), 4.77 (dd, J = 12.4, 6.8 Hz, 1H), 4.70 (dd, J = 12.4, 7.6 Hz, 1H), 4.18 (quin, J = 7.1 Hz, 1H), 3.00 (d, J = 6.8 Hz, 2H), 2.12 (s, 3H). HPLC (Chiralpak AD-H, 2-propanol/*n*-hexane = 20/80, flow rate = 1.0 mL/min): t_R = 10.5 min (major), t_R = 11.6 min (minor), ee = 96%.

*(S)-4-(Anthracen-9-yl)-5-nitropentan-2-one (**5k**).*[45] Reaction of **4k** and nitromethane gave **5k** as an orange solid in 37% yield. $[\alpha]_D^{23}$: +25.5 (c 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.66 (d, J = 8.8 Hz, 1H), 8.44 (s, 1H), 8.07 (d, J = 8.3 Hz, 1H), 8.04−7.96 (m, 2H), 7.73−7.60 (m, 1H), 7.59−7.53 (m, 1H), 7.52−7.45 (m, 2H), 6.05−5.84 (m, 1H), 5.21 (dd, J = 12.4, 8.5 Hz, 1H), 4.94 (dd, J = 12.4, 6.3 Hz, 1H), 3.56 (dd, J = 18.5, 6.8 Hz, 1H), 3.35 (dd, J = 18.5, 5.1 Hz, 1H), 2.12 (s, 3H). HPLC (Chiralpak AS-H, 2-propanol/*n*-hexane = 10/90, flow rate = 1.0 mL/min): t_R = 42.4 min (major), t_R = 67.7 min (minor), ee = 88%.

*(S)-(E)-4-(Nitromethyl)-6-phenyl-5-hexen-2-one (**5l**).*[41] Reaction of **4l** and nitromethane gave **5l** as clear crystals in 62% yield. $[\alpha]_D^{24}$: +6.1 (c 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.50−7.12 (m, 5 H), 6.53 (d, J = 15.6 Hz, 1H), 6.08 (dd, J = 15.6, 8.5 Hz, 1H), 4.60 (dd, J = 12.4, 6.3 Hz, 1H), 4.52 (dd, J = 12.4, 8.5 Hz, 1H), 3.71−3.42 (m, 1H), 2.75 (d, J = 6.3 Hz, 2H), 2.19 (s, 3H). HPLC (Chiralpak AS-H, 2-propanol/*n*-hexane = 20/80, flow rate = 1.0 mL/min): t_R = 16.7 min (major), t_R = 19.6 min (minor), ee = 80%.

*(S)-4-(Nitromethyl)-6-phenylhex-5-yn-2-one (**5m**).*[46] Reaction of **4m** and nitromethane gave **5m** as a white solid in 80% yield. $[\alpha]_D^{22}$: +28.2 (c 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.44−7.34 (m, 2H), 7.34−7.24 (m, 3H), 4.65 (dd, J = 12.8, 6.4 Hz, 1H), 4.59 (dd, J = 12.8, 6.4 Hz, 1H), 3.87 (quin, J = 6.6 Hz, 1H), 2.93 (d, J = 6.6 Hz, 2H), 2.24 (s, 3H). HPLC (Chiralpak AS-H, 2-propanol/*n*-hexane = 10/90, flow rate = 1.0 mL/min): t_R = 26.1 min (major), t_R = 38.5 min (minor), ee = 89%.

*(R)-4-(Nitromethyl)-6-phenylhexan-2-one (**5n**).*[41] Reaction of **4n** and nitromethane gave **5n** as a pale yellow oil in 55% yield. $[\alpha]_D^{24}$: +5.2 (c 0.66, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.35−7.27 (m, 2H), 7.26−7.14 (m, 3H), 4.57−4.43 (m, 2H), 2.89−2.46 (m, 5H), 2.16 (s, 3H), 1.81−1.68 (m, 2H). HPLC (Chiralpak AS-H, 2-propanol/*n*-hexane = 20/80, flow rate = 1.0 mL/min): t_R = 15.6 min (major), t_R = 19.3 min (minor), ee = 95%.

*(R)-4-(Nitromethyl)-6-(4-bromophenyloxy)hexan-2-one (**5o**).* Reaction of **4o** and nitromethane gave **5o** as a white solid in 41% yield. Mp: 63−65 °C. $[\alpha]_D^{18}$: −2.2 (c 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.89 (d, J = 8.8 Hz, 2H), 7.60 (d, J = 8.8 Hz, 2H), 4.56 (d, J = 5.9 Hz, 2H), 4.50−4.32 (m, 2H), 2.93−2.78 (m, 1H), 2.77−2.59 (m, 2H), 2.19 (s, 3H), 2.04−1.84 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 206.2, 165.8, 131.9 (2C), 131.2 (2C), 128.7, 128.5, 77.8, 62.1, 44.1, 30.4, 30.2, 30.1. IR (KBr): 1717, 1549 cm^{-1}. HRMS (DART) m/z: $[M + H]^+$ calcd for $C_{14}H_{17}BrNO_5$, 358.0290; found, 358.0288. HPLC (Chiralpak AD-H, 2-propanol/*n*-hexane = 10/90, flow rate = 1.0 mL/min): t_R = 24.2 min (major), t_R = 25.8 min (minor), ee = 94%.

*(S)-6-Nitro-5-phenylhexan-3-one (**5p**).*[47] Reaction of **4p** and nitromethane gave **5p** as a white solid in 61% yield. $[\alpha]_D^{19}$: +12.2 (c 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.45−7.15 (m, 5H), 4.71 (dd, J = 12.4, 6.8 Hz, 1H), 4.61 (dd, J = 12.4, 8.0 Hz, 1H), 4.03 (quin, J = 7.2 Hz, 1H), 2.89 (d, J = 7.2 Hz, 2H), 2.49−2.26 (m, 2H), 1.00 (t, J = 7.3 Hz, 3H). HPLC (Chiralpak AS-H, 2-propanol/*n*-hexane = 20/80, flow rate = 1.0 mL/min): t_R = 15.9 min (major), t_R = 20.6 min (minor), ee = 97%.

*(S)-1-Nitro-2-phenylheptan-4-one (**5q**).*[47] Reaction of **4q** and nitromethane gave **5q** as a pale yellow oil in 69% yield. $[\alpha]_D^{23}$: +8.4 (c 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.45−7.11 (m, 5H), 4.70 (dd, J = 12.4, 6.8 Hz, 1H), 4.60 (dd, J = 12.4, 8.0 Hz, 1H), 4.02 (quin, J = 7.2 Hz, 1H), 2.87 (d, J = 7.2 Hz, 2H), 2.42−2.23 (m, 2H), 1.64−1.54 (m, 2H), 0.85 (t, J = 7.3 Hz, 3H). HPLC (Chiralpak AD-H, 2-propanol/*n*-hexane = 10/90, flow rate = 1.0 mL/min): t_R = 8.5 min (major), t_R = 9.8 min (minor), ee = 98%.

*(S)-2-Methyl-6-nitro-5-phenylhexan-3-one (**5r**).*[48] Reaction of **4r** and nitromethane gave **5r** as a pale yellow oil in 27% yield. $[\alpha]_D^{27}$: +12.0 (c 0.64, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.45−7.13 (m, 5H), 4.71 (dd, J = 12.4, 6.8 Hz, 1H), 4.62 (dd, J = 12.4, 8.0 Hz, 1H), 4.03 (quin, J = 7.2 Hz, 1H), 2.99−2.93 (m, 2H), 2.63−2.43 (m, 1H), 1.06 (d, J = 6.8 Hz, 3H), 1.00 (d, J = 6.8 Hz, 3H). HPLC (Chiralpak AS-H, 2-propanol/*n*-hexane = 20/80, flow rate = 1.0 mL/min): t_R = 8.7 min (major), t_R = 12.5 min (minor), ee > 99%.

*(S)-4-Nitro-1,3-diphenylbutan-1-one (**5s**).*[43] Reaction of **4s** and nitromethane gave **5s** as a white solid in 20% yield. $[\alpha]_D^{24}$: −17.4 (c 0.52, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.05−7.88 (m, 2H), 7.68−7.55 (m, 1H), 7.55−7.42 (m, 2H), 7.42−7.22 (m, 5H), 4.84 (dd, J = 12.4, 8.0 Hz, 1H), 4.70 (dd, J = 12.4, 8.0 Hz, 1H), 4.24 (quin, J = 7.1 Hz, 1H), 3.57−3.38 (m, 2H). HPLC (Chiralpak AD-H, 2-propanol/*n*-hexane = 10/90, flow rate = 1.0 mL/min): t_R = 15.9 min (major), t_R = 22.3 min (minor), ee = 94%.

Synthesis of Michael Adducts 9. According to general procedure E, the reaction of α,β-unsaturated ketone and Michael donor gave the desired product.

*5-Nitro-4-(S)-(4-nitrophenyl)hexan-2-one (**9a**).* Reaction of **4a** and nitroethane gave **9a** in 85% yield, dr = 1.1:1. The major isomer was partially separated by column chromatography. The absolute stereochemistry of the major isomer was assigned as (4*S*,5*S*) by analogy to the literature compound (4*S*,5*S*)-5-nitro-4-phenylhexan-2-one,[41] on the basis of the chemical shifts and the coupling constant values. Major isomer *anti*-**9a**: yellow oil. $[\alpha]_D^{20}$: +1.7 (c 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.18 (d, J = 8.8 Hz, 2H), 7.35 (d, J = 8.8 Hz, 2H), 4.92 (quin, J = 6.8 Hz, 1H), 3.85 (q, J = 7.2 Hz, 1H), 3.09 (dd, J = 18.0, 6.0 Hz, 1H), 2.93 (dd, J = 18.0, 8.0 Hz, 1H), 2.16 (s, 3H), 1.53 (d, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 204.7, 147.6, 145.5, 129.3 (2C), 124.0 (2C), 85.4, 44.6, 44.2, 30.4, 17.0. IR (KBr): 1717, 1558, 1541, 1522, 1348 cm^{-1}. HRMS (DART) m/z: $[M + H]^+$ calcd for $C_{12}H_{15}N_2O_5$, 267.0981; found, 267.0984. HPLC (Chiralpak AD-H, 2-propanol/*n*-hexane = 2/98, flow rate = 1.0 mL/min): t_R = 76.3 min (major), t_R = 105.3 min (minor), ee = 95%.

*(S)-5-Methyl-5-nitro-4-(4-nitrophenyl)hexan-2-one (**9b**).*[49] Reaction of **4a** and 2-nitropropane gave **9b** as a colorless oil in 78% yield. $[\alpha]_D^{23}$: −39.4 (c 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.18 (d, J = 8.3 Hz, 2H), 7.38 (d, J = 8.3 Hz, 2H), 4.04 (dd, J = 10.5, 3.2 Hz, 1H), 3.12 (dd, J = 17.6, 10.5 Hz, 1H), 2.88 (dd, J = 3.2, 17.6 Hz, 1H), 2.09 (s, 3H), 1.58 (s, 3H), 1.53 (s, 3H). HPLC (Chiralpak AD-H, 2-propanol/*n*-hexane = 20/80, flow rate = 1.0 mL/min): t_R = 23.1 min (major), t_R = 15.3 min (minor), ee = 88%.

*(R)-2-[1-(4-Nitrophenyl)-3-oxobutyl] 1,3-Dimethyl Ester **9c**.*[50] Reaction of **4a** and dimethyl malonate gave **9c** as a yellow oil in 97% yield. $[\alpha]_D^{24}$: −14.8 (c 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.15 (d, J = 8.8 Hz, 2H), 7.45 (d, J = 8.8 Hz, 2H), 4.10 (td, J = 9.0, 4.9 Hz, 1H), 3.77 (d, J = 9.0 Hz, 1H), 3.75 (s, 3H), 3.55 (s, 3H), 3.15−2.88 (m, 2H), 2.08 (s, 3H). HPLC (Chiralpak AD-H, 2-propanol/*n*-hexane = 20/80, flow rate = 1.0 mL/min): t_R = 15.8 min (major), t_R = 24.5 min (minor), ee = 94%.

*(R)-2-(1-Phenyl-3-oxobutyl) 1,3-Dimethyl Ester **9d**.* Reaction of **4b** and dimethyl malonate gave **9d** as a white solid in 95% yield. $[\alpha]_D^{27}$: −13.6 (c 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.39−7.11 (m, 5H), 3.98 (td, J = 9.0, 5.4 Hz, 1H), 3.74 (d, J = 9.0 Hz, 1H), 3.73 (s, 3H), 3.50 (s, 3H), 3.05−2.86 (m, 2H), 2.03 (s, 3H). HPLC (Chiralpak AD-H, 2-propanol/*n*-hexane = 10/90, flow rate = 1.0 mL/min): t_R = 12.5 min (major), t_R = 14.7 min (minor), ee = 94%.

*(R)-2-[1-(4-Nitrophenyl)-3-oxobutyl] 1,3-Diisopropyl Ester **9e**.*[51] Reaction of **4a** and diisopropyl malonate gave **9e** as a pale yellow oil in

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77% yield. $[\alpha]_D^{24}$: −13.2 (*c* 1.00, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ: 8.14 (d, *J* = 8.8 Hz, 2H), 7.47 (d, *J* = 8.8 Hz, 2H), 5.06 (dt, *J* = 12.7, 6.3 Hz, 1H), 4.81 (dt, *J* = 12.3, 6.3 Hz, 1H), 4.07 (td, *J* = 9.8, 4.4 Hz, 1H), 3.67 (d, *J* = 9.8 Hz, 1H), 3.14−2.87 (m, 2H), 2.06 (s, 3H), 1.24 (dd, *J* = 6.3, 4.4 Hz, 6H), 1.05 (dd, *J* = 18.0, 6.3 Hz, 6H). HPLC (Chiralpak AD-H, 2-propanol/*n*-hexane = 20/80, flow rate = 1.0 mL/min): t_R = 14.3 min (major), t_R = 41.1 min (minor), ee = 63%.

*(R)-2-[1-(Nitrophenyl)-3-oxobutyl]-5,5-dimethyl-1,3-cyclohexanedione (**9f**).*[52] Reaction of **4a** and 5,5-dimethyl-1,3-cyclohexanedione gave **9f** as a pale yellow oil in 45% yield. $[\alpha]_D^{27}$: +19.0 (*c* 1.00, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ: 8.17−8.08 (m, 2H), 7.35−7.28 (m, 2H), 4.01 (t, *J* = 5.6 Hz, 0.4H), 3.94 (dd, *J* = 11.7, 6.8 Hz, 0.6H), 3.10 (br s, 0.6H), 2.83 (br s, 0.4H), 2.54−2.06 (m, 6H), 1.58 (s, 2H), 1.54 (s, 1H), 1.19 (s, 1H), 1.16 (s, 2H), 1.11 (s, 1H), 1.09 (s, 2H). HPLC (Chiralpak AD-H, 2-propanol/*n*-hexane = 20/80, flow rate = 1.0 mL/min): t_R = 31.3 min (major), t_R = 12.4 min (minor), ee = 47%.

*(S)-4-Hydroxy-3-[1-(4-nitrophenyl)-3-oxobutyl]-2H-1-benzopyran-2-one (**9g**).*[53] Reaction of **4a** and 4-hydroxycoumarin gave **9g** as a white solid in quantitative yield. $[\alpha]_D^{27}$: +21.4 (*c* 1.00, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ: 8.16 (d, *J* = 8.3 Hz, 2H), 7.97−7.77 (m, 1H), 7.67−7.49 (m, 1H), 7.46−7.28 (m, 4H), 4.27 (br s, 1H), 3.44 (br s, 0.7H), 3.08 (br s, 0.3H), 2.44 (d, *J* = 11.7 Hz, 1.3H), 2.04−1.88 (m, 0.7H), 1.78 (br s, 2H), 1.73 (br s, 1H). HPLC (Chiralpak AD-H, 2-propanol/*n*-hexane = 20/80, flow rate = 1.0 mL/min): t_R = 40.7 min (major), t_R = 11.8 min (minor), ee = 73%.

*(S)-2-(3-Oxocyclopentyl) 1,3-Dibenzyl Ester **9h**.*[17] Reaction of 2-cyclopenten-1-one (**8h**) and dibenzyl malonate gave **9h** as a colorless oil in 58% yield. $[\alpha]_D^{19}$: −42.2 (*c* 1.00, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.44−7.21 (m, 10H), 5.26−5.08 (m, 4H), 3.45 (d, *J* = 9.3 Hz, 1H), 2.99−2.79 (m, 1H), 2.46 (dd, *J* = 7.3, 18.5 Hz, 1H), 2.37−2.25 (m, 1H), 2.25−2.10 (m, 2H), 1.99 (dd, *J* = 10.7, 18.5 Hz, 1H), 1.70−1.55 (m, 1H). HPLC (Chiralpak AD-H, 2-propanol/*n*-hexane = 5/95, flow rate = 0.5 mL/min): t_R = 98.3 min (major), t_R = 102.5 min (minor), ee = 89%.

*(S)-2-(3-Oxocyclohexyl) 1,3-Dibenzyl Ester **9i**.*[17] Reaction of 2-cyclohexen-1-one (**8i**) and dibenzyl malonate gave **9i** as a colorless oil in 92% yield. $[\alpha]_D^{20}$: +0.2 (*c* 1.00, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.47−7.16 (m, 10H), 5.15 (d, *J* = 2.9 Hz, 4H), 3.41 (d, *J* = 7.8 Hz, 1H), 2.66−2.50 (m, 1H), 2.49−2.32 (m, 2H), 2.30−2.13 (m, 2H), 2.02 (ddd, *J* = 13.4, 6.3, 3.2 Hz, 1H), 1.96−1.83 (m, 1H), 1.72−1.55 (m, 1H), 1.54−1.38 (m, 1H). HPLC (Chiralpak AS-H, 2-propanol/*n*-hexane = 10/90, flow rate = 1.0 mL/min): t_R = 49.8 min (major), t_R = 40.5 min (minor), ee = 93%.

*(S)-2-(3-Oxocycloheptyl) 1,3-Dibenzyl Ester **9j**.*[17] Reaction of 2-cyclohepten-1-one (**8j**) and dibenzyl malonate gave **9j** as a colorless oil in 69% yield. $[\alpha]_D^{20}$: −22.3 (*c* 1.00, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.49−7.21 (m, 10H), 5.27−5.04 (m, 4H), 3.42 (d, *J* = 6.3 Hz, 1H), 2.67−2.39 (m, 5H), 2.00−1.76 (m, 3H), 1.60−1.28 (m, 3H). HPLC (Chiralpak AD-H, 2-propanol/*n*-hexane = 5/95, flow rate = 0.5 mL/min): t_R = 88.1 min (major), t_R = 94.9 min (minor), ee = 98%.

Synthesis of Peptide 10 and Depsipeptides 11a, 11b, and 11c. *Cbz-(L-Leu)$_4$-Ac$_5$c-(L-Leu)$_2$-Ac$_5$c-OMe (**S-9**).* According to general procedure A, the coupling of Cbz-(L-Leu)$_2$-OH (39.7 mg, 0.105 mmol) with amine **2b** (70.7 mg, 0.100 mmol) gave the title compound **S-9** (99.2 mg, 93%) as a white solid after purification by flash column chromatography on silica gel (80% EtOAc in *n*-hexane). Mp: 237−240 °C. $[\alpha]_D^{22}$: −8.6 (*c* 1.00, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ: 7.57−7.46 (m, 2H), 7.45−7.31 (m, 7H), 7.31−7.23 (m, 3H), 6.21 (s, 1H), 5.19 (d, *J* = 12.4 Hz, 1H), 5.12 (d, *J* = 12.4 Hz, 1H), 4.27−4.14 (m, 2H), 4.14−4.00 (m, 2H), 4.00−3.90 (m, 2H), 3.63 (s, 3H), 2.62 (dt, *J* = 13.5, 8.3 Hz, 1H), 2.39−2.23 (m, 2H), 2.16−2.04 (m, 3H), 1.99−1.51 (m, 28H), 1.02−0.81 (m, 36H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 175.7, 175.3, 175.2, 175.0, 174.6, 174.4, 173.9, 173.8, 158.0, 136.0, 128.6 (2C), 128.1, 127.4 (2C), 67.0, 66.9, 65.7, 56.3, 55.1, 54.9, 54.4, 54.0, 53.1, 52.0, 40.2, 40.0, 39.7, 39.5, 39.4, 39.2, 37.7, 37.5, 36.6, 34.8, 25.0, 24.90, 24.86, 24.81 (2C), 24.77, 24.49, 24.45, 24.2, 24.1, 23.4, 23.1, 23.0, 22.9, 22.5, 22.3, 22.1, 21.8, 21.5, 21.4, 21.2, 20.9. IR (KBr): 3383, 1744, 1655 cm^{-1}. HRMS (ESI) *m*/*z*: $[M + Na]^+$ calcd for $C_{57}H_{94}N_8O_{11}Na$, 1089.6934; found, 1089.6920.

*H-(L-Leu)$_4$-Ac$_5$c-(L-Leu)$_2$-Ac$_5$c-OMe (**10**).* According to general procedure C (by using THF as solvent instead of MeOH), Cbz deprotection of peptide **S-9** (52.7 mg, 0.0494 mmol) afforded the desired product **10** (44.0 mg, 95%) as a white amorphous material after purification by flash column chromatography on silica gel (5% MeOH in $CHCl_3$). $[\alpha]_D^{22}$: −15.5 (*c* 1.00, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ: 8.32 (br s, 1H), 7.57 (s, 2H), 7.52 (d, *J* = 7.9 Hz, 1H), 7.41 (s, 1H), 7.31 (d, *J* = 6.1 Hz, 1H), 7.07 (d, *J* = 4.6 Hz, 1H), 4.31 (ddd, *J* = 11.6, 7.9, 3.7 Hz, 1H), 4.19 (ddd, *J* = 11.6, 6.0, 3.2 Hz, 1H), 4.07 (dt, *J* = 9.8, 5.2 Hz, 1H), 4.02−3.92 (m, 2H), 3.66 (s, 3H), 3.44 (dd, *J* = 9.8, 4.0 Hz, 1H), 2.63 (dt, *J* = 13.2, 8.0 Hz, 1H), 2.32−2.21 (m, 2H), 2.18−2.06 (m, 3H), 2.03−1.54 (m, 29H), 1.38 (ddd, *J* = 14.0, 9.8, 4.6 Hz, 1H), 1.08−0.76 (m, 36H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 178.8, 175.6, 175.1, 174.4, 174.29, 174.27, 173.39, 173.37, 66.8, 65.8, 54.9 (2C), 54.3, 54.0, 53.2, 52.6, 52.1, 43.8, 40.0, 39.9, 39.6, 39.5, 39.1, 38.0, 37.2, 36.7, 35.2, 25.1 (2C), 25.03, 24.99, 24.7, 24.6, 24.54, 24.53, 24.4, 24.3, 23.43, 23.38, 23.36, 23.1, 22.8, 22.5, 21.9, 21.5, 21.3, 21.14, 21.11, 20.9. IR (KBr): 3341, 1655 cm^{-1}. HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{49}H_{89}N_8O_9$, 933.6747; found, 933.6736.

*Depsi-dipeptide **S-10**.* To a mixture of carboxylic acid Cbz-L-Leu-OH (935 mg, 3.53 mmol) and L-leucic acid *tert*-butyl ester[54] (664 mg, 3.53 mmol) in CH_2Cl_2 (35 mL) were added *N*,*N*′-diisopropylcarbodiimide (DIC, 0.546 mL, 3.53 mmol) and DMAP (431 mg, 3.53 mmol) at 0 °C, and the resultant mixture was gradually warmed to room temperature. After stirring for 18 h, the reaction mixture was diluted with EtOAc and washed with sat. aq $NaHCO_3$ and brine. Then, the organic phase was dried over anhydrous Na_2SO_4 and concentrated in vacuo to give crude product, which was purified by flash column chromatography on silica gel. The fraction eluted with 8% EtOAc in *n*-hexane afforded the title compound **S-10** (1.44 g, 94%) as a colorless oil. $[\alpha]_D^{19}$: −27.3 (*c* 1.01, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ: 7.40−7.28 (m, 5H), 5.18 (d, *J* = 8.9 Hz, 1H), 5.10 (s, 2H), 4.92 (dd, *J* = 9.0, 4.3 Hz, 1H), 4.44 (ddd, *J* = 9.8, 8.9, 4.0 Hz, 1H), 1.85−1.68 (m, 4H), 1.67−1.59 (m, 1H), 1.59−1.50 (m, 1H), 1.45 (s, 9H), 1.04−0.82 (m, 12H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 172.7, 169.2, 155.9, 136.2, 128.4 (2C), 128.1, 128.0 (2C), 82.0, 72.3, 66.9, 52.2, 41.7, 39.6, 27.9 (3C), 24.7, 24.6, 23.0, 22.9, 21.7, 21.5. IR (film): 3345, 1740 cm^{-1}. HRMS (ESI) *m*/*z*: $[M + Na]^+$ calcd for $C_{24}H_{37}NO_6Na$, 458.2513; found, 458.2514.

*Depsi-octapeptide **S-12**.* To a solution of depsi-dipeptide **S-10** (353 mg, 0.786 mmol) in CH_2Cl_2 (8 mL) was added trifluoroacetic acid (0.8 mL) at room temperature, and the reaction mixture was stirred at the same temperature for 2 d. After evaporation of the solvent and coevaporation with toluene, the residue was purified by flash column chromatography on silica gel (60% EtOAc in *n*-hexane) to give acid **S-11** (300 mg, 97%). According to general procedure A, the coupling of acid **S-11** (62.5 mg, 0.165 mmol) with amine **2b** (106 mg, 0.150 mmol) gave the title compound **S-12** (111 mg, 69%) as a white amorphous material after purification by flash column chromatography on silica gel (40% EtOAc in *n*-hexane). $[\alpha]_D^{20}$: −18.8 (*c* 1.00, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ: 7.48−7.43 (m, 2H), 7.40−7.34 (m, 3H), 7.33−7.29 (m, 2H), 7.27−7.23 (m, 2H), 7.21 (s, 1H), 6.81 (d, *J* = 4.6 Hz, 1H), 6.08 (d, *J* = 3.7 Hz, 1H), 5.22 (d, *J* = 12.7 Hz, 1H), 5.15 (d, *J* = 12.7 Hz, 1H), 4.78 (dd, *J* = 9.1, 4.6 Hz, 1H), 4.35 (ddd, *J* = 11.4, 7.9, 2.9 Hz, 1H), 4.20 (ddd, *J* = 11.7, 6.1, 3.0 Hz, 1H), 4.12 (ddd, *J* = 8.2, 6.5, 4.0 Hz, 1H), 4.06 (dt, *J* = 6.4, 5.6 Hz, 1H), 3.91 (dt, *J* = 9.9, 4.6 Hz, 1H), 3.64 (s, 3H), 2.62 (dt, *J* = 13.3, 8.2 Hz, 1H), 2.32−2.23 (m, 1H), 2.23−2.04 (m, 4H), 1.95−1.60 (m, 28H), 1.02−0.82 (m, 36H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 175.4, 175.2, 174.2, 174.1, 173.6, 173.1, 173.0, 172.2, 157.7, 135.7, 128.7 (2C), 128.4, 127.0 (2C), 76.2, 67.1, 66.8, 65.7, 54.7, 54.3, 54.1, 54.0, 52.2, 52.0, 39.82, 39.77, 39.6, 39.43, 39.37, 39.26, 38.1, 37.3, 36.6, 35.2, 25.1, 24.9, 24.81, 24.80, 24.78, 24.67, 24.5 (2C), 24.3, 24.2, 23.5, 23.4, 23.0, 22.9, 22.8, 22.4, 21.7, 21.5, 21.1, 21.0, 20.9, 20.8. IR (KBr): 3379, 1736, 1669 cm^{-1}. HRMS (ESI) *m*/*z*: $[M + Na]^+$ calcd for $C_{57}H_{93}N_7O_{12}Na$, 1090.6774; found, 1090.6753.

*Depsi-octapeptide **11a**.* According to general procedure C (by using THF as solvent instead of MeOH), Cbz deprotection of peptide **S-12** (61.8 mg, 0.0579 mmol) afforded the desired product **11a** (51.5 mg, 95%) as a white amorphous material after purification by flash

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column chromatography on silica gel (5% MeOH in $CHCl_3$). $[\alpha]_D^{23}$: −7.1 (*c* 1.00, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ: 8.39 (br s, 1H), 7.94 (br s, 1H), 7.80 (s, 1H), 7.64 (s, 1H), 7.30 (s, 1H), 7.14 (s, 1H), 4.85−4.71 (m, 1H), 4.23−4.05 (m, 4H), 3.91−3.81 (m, 1H), 3.74 (s, 3H), 2.66−2.48 (m, 1H), 2.32−2.07 (m, 5H), 2.08−1.44 (m, 30H), 1.16−0.65 (m, 36H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 175.7, 175.39, 175.35, 175.2, 174.7, 174.2, 173.9, 171.5, 77.2, 66.6, 66.0, 55.5, 55.1, 54.4, 53.6, 53.2, 52.6, 40.4, 40.0, 39.7, 39.6, 38.5, 37.6, 36.9, 36.8, 34.5, 34.2, 25.0, 24.7 (2C), 24.64, 24.56, 24.40, 24.38, 24.3, 24.0, 23.8, 23.1 (2C), 22.8, 22.5, 22.4, 22.3, 22.2, 21.8, 21.7, 21.6, 21.3, 21.2. IR (KBr): 3368, 1669 cm^{-1}. HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{49}H_{88}N_7O_{10}$, 934.6587; found, 934.6580.

Cbz-Ac$_5$c-(L-Leu)$_2$-Ac$_5$c-OMe (**S-13**). According to general procedure A, the coupling of Cbz-Ac$_5$c-OH (171 mg, 0.650 mmol) with amine **1b** (218 mg, 0.591 mmol) gave the title compound **S-13** (309 mg, 85%) as a white solid after purification by flash column chromatography on silica gel (50% EtOAc in *n*-hexane). Mp: 172−174 °C. $[\alpha]_D^{22}$: −7.2 (*c* 1.02, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ: 7.44−7.28 (m, 6H), 7.14 (s, 1H), 6.65 (d, *J* = 5.6 Hz, 1H), 5.98 (s, 1H), 5.14 (d, *J* = 12.3 Hz, 1H), 5.08 (d, *J* = 12.3 Hz, 1H), 4.40 (ddd, *J* = 11.1, 8.2, 4.1 Hz, 1H), 4.26 (ddd, *J* = 10.1, 5.6, 4.1 Hz, 1H), 3.62 (s, 3H), 2.63−2.53 (m, 1H), 2.32−2.24 (m, 1H), 2.17−1.95 (m, 4H), 1.91−1.57 (m, 15H), 1.53 (ddd, *J* = 13.9, 10.4, 5.1 Hz, 1H), 0.96 (d, *J* = 6.6 Hz, 3H), 0.91 (d, *J* = 6.5 Hz, 3H), 0.91 (d, *J* = 6.6 Hz, 3H), 0.85 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 174.9, 174.8, 172.4, 171.8, 156.5, 135.6, 128.6 (2C), 128.4, 127.7 (2C), 67.3, 67.2, 65.8, 53.7, 52.1, 51.9, 39.8, 39.6, 38.3, 37.3, 36.5, 35.8, 25.2, 24.9, 24.5, 24.4, 24.1, 24.0, 23.3, 23.1, 21.3, 20.9. IR (film): 3329, 1740, 1655 cm^{-1}. HRMS (ESI) *m*/*z*: $[M + Na]^+$ calcd for $C_{33}H_{50}N_4O_7Na$, 637.3572; found, 637.3573.

Cbz-L-Leu-Ac$_5$c-(L-Leu)$_2$-Ac$_5$c-OMe (**S-15**). According to general procedure C, Cbz deprotection of peptide **S-13** (299 mg, 0.487 mmol) gave crude amine **S-14** (236 mg) as a white solid, which was used for the next step without further purification. According to general procedure A, the coupling of Cbz-L-Leu-OH (82.5 mg, 0.311 mmol) with the crude amine **S-14** (136 mg, 0.283 mmol) gave the title compound **S-15** (147 mg, 71% in two steps) as a white solid after purification by flash column chromatography on silica gel (60% EtOAc in *n*-hexane). Mp: 171−181 °C. $[\alpha]_D^{20}$: −13.7 (*c* 1.01, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ: 7.74 (s, 1H), 7.59 (d, *J* = 7.7 Hz, 1H), 7.42−7.27 (m, 7H), 6.78 (s, 1H), 5.19 (d, *J* = 12.4 Hz, 1H), 5.03 (d, *J* = 12.4 Hz, 1H), 4.37−4.22 (m, 2H), 3.88 (ddd, *J* = 9.0, 6.5, 3.1 Hz, 1H), 3.59 (s, 3H), 2.66 (ddd, *J* = 13.0, 7.8, 7.8 Hz, 1H), 2.34 (ddd, *J* = 13.3, 7.8, 7.8 Hz, 1H), 2.12−1.96 (m, 4H), 1.97−1.47 (m, 19H), 0.97 (d, *J* = 6.5 Hz, 3H), 0.94 (d, *J* = 6.4 Hz, 3H), 0.93 (d, *J* = 6.5 Hz, 3H), 0.86 (d, *J* = 6.4 Hz, 3H), 0.85 (d, *J* = 5.6 Hz, 3H), 0.82 (d, *J* = 5.4 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 175.1, 175.0, 174.6, 173.4, 173.2, 157.8, 135.9, 128.5 (2C), 128.1, 127.7 (2C), 67.0, 66.8, 65.7, 56.3, 53.6, 52.8, 52.0, 40.0, 39.9, 39.5, 38.4, 37.5, 36.4, 35.8, 25.2, 24.7, 24.61, 24.59, 24.57, 24.40, 24.37, 23.4, 23.1, 22.5, 21.9, 21.4, 20.6. IR (KBr): 3333, 1744, 1665 cm^{-1}. HRMS (ESI) *m*/*z*: $[M + Na]^+$ calcd for $C_{39}H_{61}N_5O_8Na$, 750.4412; found, 750.4406.

Depsi-heptapeptide **S-17**. According to general procedure C, Cbz deprotection of peptide **S-15** (147 mg, 0.202 mmol) gave crude amine **S-16** (124 mg) as a white solid, which was used for the next step without further purification. According to general procedure A, the coupling of acid **S-11** (99.5 mg, 0.263 mmol) with the crude amine **S-16** (124 mg) gave the title compound **S-17** (179 mg, 93% in two steps) as a white amorphous material after purification by flash column chromatography on silica gel (50% EtOAc in *n*-hexane). $[\alpha]_D^{21}$: −17.5 (*c* 1.02, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ: 7.41 (d, *J* = 4.9 Hz, 1H), 7.40−7.33 (m, 4H), 7.33−7.29 (m, 2H), 7.19 (s, 1H), 7.09 (d, *J* = 6.1 Hz, 1H), 6.78 (s, 1H), 5.81 (d, *J* = 3.9 Hz, 1H), 5.21 (d, *J* = 12.6 Hz, 1H), 5.14 (d, *J* = 12.6 Hz, 1H), 4.76 (dd, *J* = 9.4, 4.2 Hz, 1H), 4.36 (ddd, *J* = 11.7, 7.9, 3.6 Hz, 1H), 4.25−4.12 (m, 2H), 3.95 (ddd, *J* = 7.5, 7.0, 4.9 Hz, 1H), 3.65 (s, 3H), 2.63 (dt, *J* = 13.6, 8.2 Hz, 1H), 2.32−2.23 (m, 1H), 2.19−1.99 (m, 4H), 1.95−1.86 (m, 2H), 1.84−1.59 (m, 23H), 1.02−0.88 (m, 24H), 0.85 (d, *J* = 6.1 Hz, 3H × 2). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 175.1, 175.0, 173.7, 173.3, 173.0, 172.7, 172.1, 157.6, 135.6, 128.7 (2C), 128.4, 127.1 (2C), 75.8, 67.2, 66.8, 65.7, 54.6, 54.2, 54.0, 52.1, 52.0, 39.8 (2C), 39.5, 39.4, 39.3, 38.2, 37.3, 36.6, 35.1, 25.2, 24.83, 24.77, 24.73 (2C), 24.5 (2C), 24.2, 24.1, 23.5, 23.3, 23.0, 22.9, 22.4, 21.7, 21.3, 21.1, 21.0, 20.8. IR (KBr): 3379, 1736, 1659 cm^{-1}. HRMS (ESI) *m*/*z*: $[M + Na]^+$ calcd for $C_{51}H_{82}N_6O_{11}Na$, 977.5934; found, 977.5928.

Depsi-octapeptide **S-19**. According to general procedure C (by using THF as solvent instead of MeOH), Cbz deprotection of peptide **S-17** (179 mg, 0.187 mmol) gave crude amine **S-18** (171 mg) as a white amorphous material, which was used for the next step without further purification. According to general procedure A, the coupling of Cbz-L-Leu-OH (54.5 mg, 0.206 mmol) with the crude amine **S-18** (171 mg) gave the title compound **S-19** (71.7 mg, 36% in two steps) as a white amorphous material after purification by flash column chromatography on silica gel (40% EtOAc in $CHCl_3$). Mp: 232−234 °C. $[\alpha]_D^{20}$: −6.2 (*c* 0.74, MeOH). ^1H NMR (500 MHz, $CDCl_3$/CD_3OD = 1:1) δ: 8.09 (d, *J* = 4.3 Hz, 1H), 7.93 (s, 1H), 7.74 (d, *J* = 4.1 Hz, 1H), 7.68 (d, *J* = 7.7 Hz, 1H), 7.65 (s, 1H), 7.42−7.31 (m, 5H), 7.07 (d, *J* = 6.5 Hz, 1H), 5.23 (d, *J* = 12.4 Hz, 1H), 5.12 (d, *J* = 12.4 Hz, 1H), 4.75 (dd, *J* = 9.4, 4.9 Hz, 1H), 4.29 (ddd, *J* = 11.3, 7.7, 4.0 Hz, 1H), 4.22 (ddd, *J* = 10.3, 6.4, 3.1 Hz, 1H), 4.18−4.12 (m, 1H), 4.08−4.01 (m, 1H), 4.01−3.94 (m, 1H), 3.67 (s, 3H), 2.54 (dt, *J* = 13.2, 8.6 Hz, 1H), 2.32−2.16 (m, 2H), 2.15−2.06 (m, 3H), 1.93−1.55 (m, 28H), 1.05−0.84 (m, 36H). ^{13}C NMR (125 MHz, $CDCl_3$/CD_3OD = 1:1) δ: 175.2, 175.1, 174.9, 174.0, 173.9, 173.5, 172.4, 172.1, 156.3, 135.6, 128.0 (2C), 127.7, 127.1 (2C), 75.3, 66.5, 66.3, 65.5, 55.2, 54.8, 53.42, 53.36, 52.3, 51.4, 40.1, 39.7, 39.4, 39.0, 38.9, 38.4, 36.9, 36.6, 36.1, 34.3, 24.5, 24.3, 24.12, 24.11, 24.0, 23.90, 23.88, 23.7, 23.5, 23.3, 22.6 (2C), 21.8, 21.6, 21.52, 21.46 (2C), 21.43, 21.2, 20.9, 20.1, 19.9. IR (KBr): 3321, 1740, 1655 cm^{-1}. HRMS (ESI) *m*/*z*: $[M + Na]^+$ calcd for $C_{57}H_{93}N_7O_{12}Na$, 1090.6774; found, 1090.6785.

Depsi-octapeptide **11b**. According to general procedure C (using THF as a solvent instead of MeOH), Cbz deprotection of peptide **S-19** (51.7 mg, 0.0484 mmol) afforded the desired product **11b** (44.0 mg, 97%) as a white amorphous material after purification by flash column chromatography on silica gel (5% MeOH in $CHCl_3$). $[\alpha]_D^{22}$: −21.1 (*c* 1.00, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ: 8.35 (br s, 1H), 7.75−7.57 (m, 1H), 7.44 (d, *J* = 7.6 Hz, 1H), 7.28 (s, 1H), 7.16−6.90 (m, 2H), 4.82−4.68 (m, 1H), 4.30 (ddd, *J* = 10.8, 7.7, 3.2 Hz, 1H), 4.24−4.08 (m, 2H), 4.00 (dt, *J* = 10.4, 5.0 Hz, 1H), 3.67 (s, 3H), 3.52 (s, 1H), 2.89−2.71 (m, 1H), 2.62 (dt, *J* = 13.2, 8.1 Hz, 1H), 2.29−1.97 (m, 5H), 1.97−1.50 (m, 29H), 1.12−0.75 (m, 36H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 175.2, 175.1, 173.8, 173.24, 173.22, 173.19, 173.12, 172.2, 75.7, 66.7, 65.8, 54.7, 54.0, 53.4, 53.0, 52.5, 52.1, 39.8, 39.6, 39.54, 39.49, 39.3, 39.0, 38.2, 37.2, 36.7, 35.0, 25.1, 25.0, 24.9, 24.73, 24.71, 24.68, 24.51, 24.50, 24.2, 24.1, 23.4, 23.3, 23.02, 23.01, 22.6, 22.3, 21.9, 21.5, 21.24, 21.18, 21.0, 20.9. IR (KBr): 3345, 1655 cm^{-1}. HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{49}H_{88}N_7O_{10}$, 934.6587; found, 934.6573.

Depsi-hexapeptide **S-20**. According to general procedure A, the coupling of acid **S-11** (86.7 mg, 0.229 mmol) with the crude amine **S-14** (100 mg, 0.208 mmol) gave the title compound **S-20** (71.4 mg, 41% in two steps from tetrapeptide **S-13**) as a white amorphous material after purification by flash column chromatography on silica gel (40% EtOAc in *n*-hexane). $[\alpha]_D^{20}$: −11.2 (*c* 1.00, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ: 7.54 (s, 1H), 7.41−7.31 (m, 5H), 7.28 (s, 1H), 7.12 (s, 1H), 6.60 (d, *J* = 5.9 Hz, 1H), 5.70 (d, *J* = 4.3 Hz, 1H), 5.26 (d, *J* = 12.6 Hz, 1H), 5.09 (d, *J* = 12.6 Hz, 1H), 4.62 (dd, *J* = 7.9, 5.9 Hz, 1H), 4.39−4.32 (m, 1H), 4.20−4.09 (m, 2H), 3.65 (s, 3H), 2.62 (dt, *J* = 13.2, 7.9 Hz, 1H), 2.30−2.23 (m, 1H), 2.20−2.01 (m, 5H), 1.93−1.86 (m, 1H), 1.82−1.51 (m, 20H), 1.00 (d, *J* = 6.5 Hz, 3H), 0.97 (d, *J* = 6.4 Hz, 3H × 2), 0.95 (d, *J* = 6.6 Hz, 3H), 0.91 (d, *J* = 6.7 Hz, 3H), 0.90 (d, *J* = 6.6 Hz, 3H × 2), 0.85 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 175.0, 174.8, 173.8, 172.7, 172.4, 171.4, 157.5, 135.9, 128.6 (2C), 128.4, 127.3 (2C), 75.9, 67.2, 67.0, 65.7, 54.0, 53.8, 52.03, 52.01, 39.8, 39.6, 39.5, 39.4, 37.7, 37.3, 36.6, 35.4, 25.3, 24.9, 24.8, 24.7, 24.5 (2C), 24.4, 24.3, 23.4, 23.2, 22.9, 22.6, 21.43, 21.40, 20.9, 20.8. IR (KBr): 3395, 1736, 1659 cm^{-1}. HRMS (ESI) *m*/*z*: $[M + Na]^+$ calcd for $C_{45}H_{71}N_5O_{10}Na$, 864.5093; found, 864.5080.

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Depsi-octapeptide ***S-22***. According to general procedure C (by using THF as solvent instead of MeOH), Cbz deprotection of peptide **S-20** (71.4 mg, 0.0848 mmol) gave the crude amine **S-21** (63.3 mg) as a colorless oil, which was used for the next step without further purification. According to general procedure A, the coupling of Cbz-(L-Leu)$_2$-OH (32.1 mg, 0.0848 mmol) with the crude amine **S-21** (63.3 mg) gave the title compound **S-22** (70.8 mg, 78% in two steps) as a white solid after purification by flash column chromatography on silica gel (40% EtOAc in $CHCl_3$). Mp: 229−230 °C. $[\alpha]_D^{20}$: −13.3 (*c* 1.01, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3/CD_3OD$ = 1:1) δ: 8.16 (s, 1H), 7.60 (s, 1H), 7.49 (s, 1H), 7.42−7.33 (m, 6H), 7.21 (d, *J* = 5.1 Hz, 1H), 5.16 (s, 2H), 4.37−4.22 (m, 2H), 4.22−4.00 (m, 4H), 3.67 (s, 3H), 2.59 (dt, *J* = 13.3, 8.1 Hz, 1H), 2.39−2.20 (m, 2H), 2.20−2.02 (m, 3H), 1.94−1.54 (m, 28H), 1.03−0.84 (m, 36H). ^{13}C NMR (125 MHz, $CDCl_3/CD_3OD$ = 1:1) δ: 175.3, 174.8, 174.4, 173.5, 173.27, 173.26, 172.8, 171.9, 157.0, 135.9, 127.9 (2C), 127.6, 126.9 (2C), 75.2, 66.4, 66.3, 65.4, 53.9, 53.6, 53.0, 52.9, 52.0, 51.3, 39.9, 39.7, 39.38, 39.35, 38.8, 38.2, 36.6, 36.5, 36.1, 34.3, 24.21, 24.16, 24.15, 24.0, 23.90 (2C), 23.85, 23.76, 23.4, 23.2, 22.50, 22.49, 21.9 (2C), 21.5, 21.4 (2C), 21.0, 20.9, 20.7, 19.92, 19.86. IR (KBr): 3321, 1744, 1655 cm^{-1}. HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{57}H_{94}N_7O_{12}$, 1068.6955; found, 1068.6957.

Depsi-octapeptide ***11c***. According to general procedure C (by using THF as solvent instead of MeOH), Cbz deprotection of peptide **S-22** (50.8 mg, 0.0476 mmol) afforded the desired product **11c** (32.3 mg, 73%) as a white amorphous material after purification by flash column chromatography on silica gel (5% MeOH in $CHCl_3$). $[\alpha]_D^{23}$: −16.3 (*c* 1.00, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.40 (br s, 1H), 8.01 (s, 1H), 7.80 (br s, 1H), 7.39 (s, 1H), 7.33 (d, *J* = 7.7 Hz, 1H), 7.18 (s, 1H), 4.69−4.52 (m, 1H), 4.38−4.16 (m, 3H), 4.16−4.02 (m, 2H), 3.70 (s, 3H), 2.67−2.51 (m, 1H), 2.39−1.94 (m, 5H), 1.94−1.35 (m, 30H), 1.21−0.62 (m, 36H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 175.44, 175.42, 175.4, 174.3, 173.7, 173.4, 173.2, 171.7, 75.9, 66.9, 65.9, 54.3, 53.8, 53.5, 53.2, 52.8, 52.4, 42.4, 40.0, 39.9, 39.8, 39.5, 39.0, 37.1, 37.0, 36.8, 34.8, 24.9 (2C), 24.8, 24.7, 24.6, 24.51 (2C), 24.48, 24.1, 23.9, 23.28, 23.25, 22.9, 22.7, 22.4, 22.2 (2C), 22.0, 21.7, 21.6, 21.1, 21.0. IR (KBr): 3368, 1655 cm^{-1}. HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{49}H_{88}N_7O_{10}$, 934.6587; found, 934.6583.

Synthesis of 2,4,5-Trisubstituted Tetrahydropyran 13. *Acetal* ***S-23***. A solution of ketone **9d** (38.6 mg, 0.139 mmol), 2,2-dimethyl-1,3-propanediol (144 mg, 1.39 mmol), and *p*-toluenesulfonic acid monohydrate (1.3 mg, 7.0 μmol) in benzene (5 mL) was heated at reflux overnight with a Dean−Stark apparatus. After cooling to room temperature, the reaction mixture was quenched by adding sat. aq $NaHCO_3$ and extracted with EtOAc three times. The combined organic extracts were dried over anhydrous Na_2SO_4 and the solvents were removed in vacuo. The residue was purified by flash column chromatography on silica gel (10% EtOAc in *n*-hexane) to give acetal **S-23** (37.9 mg, 75%) as a colorless oil. $[\alpha]_D^{24}$: −4.6 (*c* 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.36−7.23 (m, 4H), 7.22−7.12 (m, 1H), 3.75 (d, *J* = 9.8 Hz, 1H), 3.75 (s, 3H), 3.67 (ddd, *J* = 9.8, 9.3, 3.4 Hz, 1H), 3.53 (d, *J* = 11.7 Hz, 1H), 3.42 (s, 3H), 3.43 (d, *J* = 11.7 Hz, 1H), 3.25 (d, *J* = 11.7 Hz, 1H), 3.21 (d, *J* = 11.7 Hz, 1H), 2.25 (dd, *J* = 14.1, 3.4 Hz, 1H), 2.17 (dd, *J* = 14.1, 9.3 Hz, 1H), 1.11 (s, 3H), 0.92 (s, 3H), 0.88 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.9, 168.2, 141.7, 128.6 (2C), 128.2 (2C), 126.9, 98.6, 70.3, 70.0, 58.7, 52.4, 52.1, 41.0, 39.2, 29.6, 23.0, 22.6, 22.5. IR (film): 2955, 1751, 1736 cm^{-1}. HRMS (DART) *m*/*z*: $[M + H]^+$ calcd for $C_{20}H_{29}O_6$, 365.1964; found, 365.1961.

Diol ***12***. To a stirred solution of acetal **S-23** (37.9 mg, 0.104 mmol) in THF (1 mL) was added $LiAlH_4$ (19.8 mg, 0.520 mmol) at 0 °C, and the resultant white suspension was gradually warmed to room temperature overnight. After complete consumption of starting material, as checked by TLC, the reaction mixture was diluted with THF (2 mL) and carefully quenched by successively adding water (20 μL), 15% aq NaOH (20 μL), and water (60 μL) dropwise at 0 °C. The resultant suspension was passed through a Celite pad (EtOAc), dried over anhydrous $MgSO_4$, and concentrated under vacuum. The crude product was purified by flash column chromatography on silica gel (50% EtOAc in *n*-hexane) to give diol **12** (27.6 mg, 86%) as a colorless oil. $[\alpha]_D^{28}$: +26.4 (*c* 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.33−7.14 (m, 5H), 4.05 (dd, *J* = 11.2, 3.9 Hz, 1H), 3.93 (d, *J* = 11.2 Hz, 1H), 3.66−3.54 (m, 3H), 3.50−3.29 (m, 4H), 3.24 (ddd, *J* = 10.0, 6.3, 2.7 Hz, 1H), 2.67 (br s, 1H), 2.33 (dd, *J* = 14.9, 2.7 Hz, 1H), 2.09 (dd, *J* = 14.9, 6.3 Hz, 1H), 1.79−1.69 (m, 1H), 1.28 (s, 3H), 1.19 (s, 3H), 0.80 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 146.3, 128.5 (2C), 128.2 (2C), 126.1, 100.0, 70.4 (2C), 64.6, 63.5, 47.8, 44.1, 36.7, 29.8, 23.0, 22.1, 18.6. IR (film): 3406, 2955 cm^{-1}. HRMS (ESI) *m*/*z*: $[M + Na]^+$ calcd for $C_{18}H_{28}O_4Na$, 331.1885; found, 331.1887.

2,4,5-Trisubstituted Tetrahydropyran ***13***. To a mixture of diol **12** (26.5 mg, 0.0859 mmol) and triethylsilane (0.137 mL, 0.859 mmol) in CH_2Cl_2 (1.7 mL) at −78 °C was added trimethylsilyl trifluoromethanesulfonate (31.1 μL, 0.172 mmol) dropwise and the reaction mixture was stirred at the same temperature for 30 min. After quenching with sat. aq $NaHCO_3$, the aqueous phase was extracted with $CHCl_3$ three times and dried over anhydrous Na_2SO_4. After removal of the solvents, the residue was purified by flash column chromatography on silica gel (30% EtOAc in *n*-hexane) to give diol **13** (14.9 mg, 84%) as a white solid. Mp: 119−122 °C. $[\alpha]_D^{20}$: −22.4 (*c* 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.40−7.27 (m, 2H), 7.26−7.15 (m, 3H), 4.24 (dd, *J* = 11.5, 4.1 Hz, 1H), 3.56 (dqd, *J* = 10.7, 5.9, 2.0 Hz, 1H), 3.44 (dd, *J* = 11.2, 3.4 Hz, 2H), 3.45 (dd, *J* = 11.5, 11.2 Hz, 1H), 3.27 (dd, *J* = 11.2, 6.8 Hz, 1H), 2.62 (ddd, *J* = 12.2, 11.7, 3.9 Hz, 1H), 2.00 (ddddd, *J* = 11.7, 11.2, 6.8, 4.1, 3.4 Hz, 1H), 1.79 (ddd, *J* = 13.2, 3.9, 2.0 Hz, 1H), 1.53 (ddd, *J* = 13.2, 12.2, 10.7 Hz, 1H), 1.22 (d, *J* = 5.9 Hz, 3H), 1.13 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 143.8, 128.8 (2C), 127.4 (2C), 126.7, 73.9, 70.8, 62.4, 44.3, 43.5, 41.8, 21.7. IR (KBr): 3406, 2932 cm^{-1}. HRMS (DART) *m*/*z*: $[M + H]^+$ calcd for $C_{13}H_{19}O_2$, 207.1385; found, 207.1384. HPLC (Chiralpak AD-H, 2-propanol/*n*-hexane = 10/90, flow rate = 1.0 mL/min): t_R = 9.0 min (major), t_R = 7.3 min (minor), ee = 94%.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00982.

X-ray crystallographic analysis of **7**, and CD spectra, NMR spectra, and HPLC charts for various compounds (PDF)

Crystallographic data of **7** in CIF format (CIF)

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Notes

The authors declare no competing financial interest.

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