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Synthesis of Modified Phenylalanine Peptides by Cross Enyne Metathesis and a Diels–Alder Reaction as Key Steps

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Modified phenylalanine-based di- and tripeptides have been efficiently assembled by cross enyne metathesis and a Diels–Alder reaction as key steps under mild conditions. In all cases, peptide integrity was preserved, no racemisation was observed, and good yields of modified peptides were obtained.

Introduction

With the advances in combinatorial chemistry, the diversity of peptide-based drugs has steadily increased.[1] These methods provide access to peptides with improved bioavailability and resistance to cellular peptidases.[2] Among the different strategies available to modify a preformed peptide sequence, manipulation of either the backbone[1c,3] or various side-chains[4] have been investigated. Such procedures can provide a multitude of peptide analogs, which cannot be prepared from the component amino acids; these peptides are useful for structure–activity relationship (SAR) studies.[5] Therefore, such approaches for drug discovery, which can generate a large number of peptides with diverse structural, electronic and stereochemical variations from a single presynthesised peptide sequence by the application of various chemical transformations, are useful to generate lead compounds in a combinatorial fashion.

Peptide modifications can be carried out by various chemical reactions such as C–C bond-forming reactions (Suzuki–Miyaura cross-coupling),[6] metathesis (ring-closing metathesis),[7] oxidation,[8] cycloaddition ([2+2+2] cycloaddition)[9] and biotransformations.[10] However, there is still a pressing need to devise mild procedures to modify preassembled peptides that are compatible with a wide range of functional groups and well suited to library generation. Perhaps the most powerful method to generate modified peptides is by restructuring the available amino acid equivalents by chemical transformations. As Grubbs catalysts are both selective and tolerate a wide range of functional groups, an innovative methodology that employs cross enyne metathesis (CEM)[11] and a Diels–Alder (DA) reaction[12] (Figure 1) to modify preformed peptides is worthy of systematic investigation. Such a methodology is the first of its kind to be used in the posttranslational modification of peptides. This diversity-oriented[13] approach would

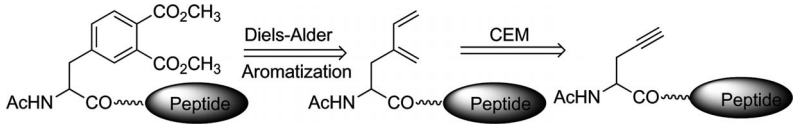

Figure 1. Retrosynthesis for modified phenylalanine-based peptides.

generate a library of peptides by simply varying one of the reaction partners during the CEM or DA sequence.

One can also visualise that this strategy could be extended to assemble a library of modified commercially available HIV-inhibiting drugs[14] such as Kaletra (**I**), Reyataz (**II**) and Norvir (**III**) (Figure 2) to generate new drugs.

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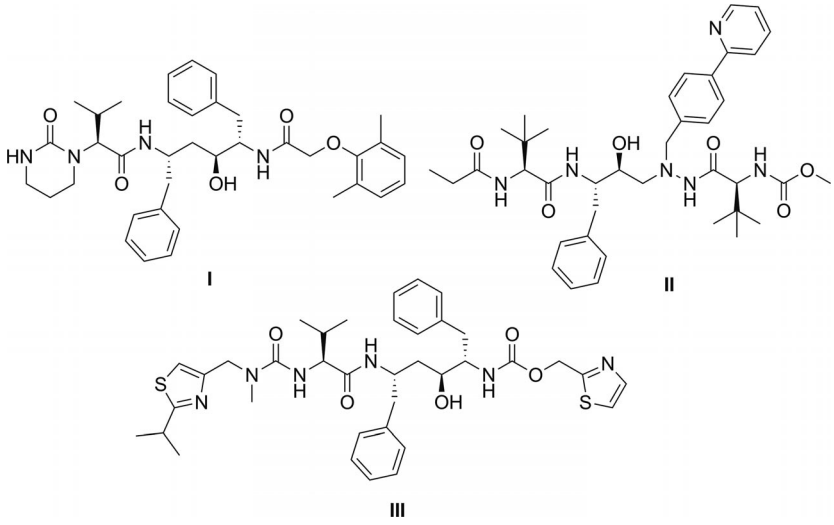
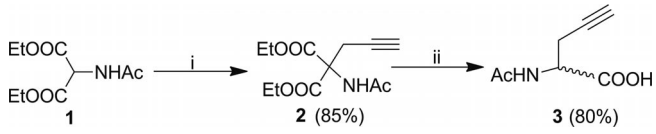


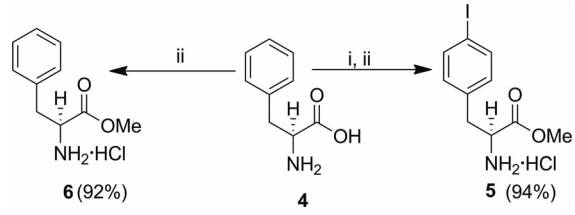
Figure 2. Structures of HIV-inhibiting drugs.

Results and Discussion

Our journey to realise the synthesis of the phenylalanine (Phe) based peptides depicted in Figure 1 began with the readily accessible and inexpensive starting material diethyl acetamidomalonate (**1**). Propargylation of **1** with Cs_2CO_3 delivered the acetylene derivative **2**.[15] Decarboxylation of **2** with KOH afforded the key building block **3** as a racemic mixture (Scheme 1). The other key building block **5** required for peptide coupling was prepared by iodination of L-phenylalanine (**4**) with $AcOH/H_2SO_4$ in the presence of $I_2/NaIO_3$ followed by treatment with thionyl chloride in methanol (Scheme 2).[16] Along similar lines, **6** was prepared by treating **4** with thionyl chloride in methanol.[16]



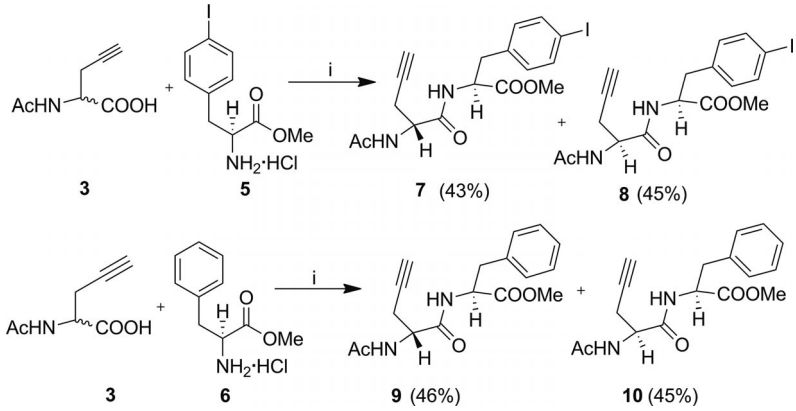
Scheme 1. Synthesis of **3**. Reagents and conditions: (i) propargyl bromide, Cs_2CO_3, CH_3CN, r.t., 18 h; (ii) KOH, $MeOH/H_2O$ (5:1), reflux, 4 h.



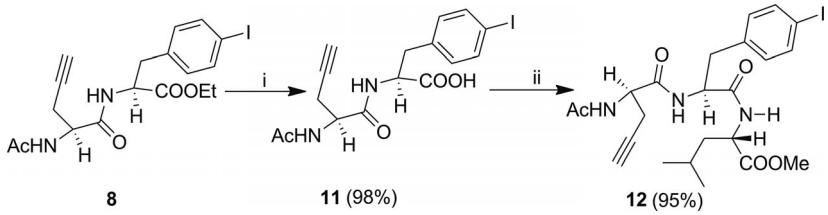
Scheme 2. Synthesis of **5** and **6**. Reagents and conditions: (i) AcOH, H_2SO_4, I_2, $NaIO_3$, 70 °C, 21 h; (ii) $SOCl_2$, MeOH, 0 °C to r.t., 24 h.

Next, the condensation of **3** with **5** in the presence of *N*-[3-(dimethylamino)propyl]-*N*′-ethylcarbodiimide hydrochloride (EDCl) gave a diasteromeric mixture of peptides **7** and **8** (Scheme 3), whose absolute configuration was established unequivocally.[17]

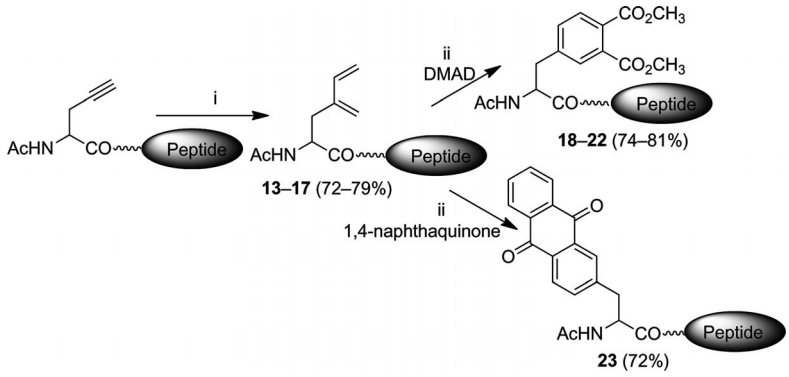
Furthermore, we synthesised tripeptide **12** from **8**. To this end, **8** was subjected to hydrolysis to generate the acid **11**, which was coupled with L-isoleucine methyl ester hydrochloride to furnish the alkyne-based building block **12** (Scheme 4).



Scheme 3. Peptide coupling between **3** and **5** or **6**. Reagents and conditions: (i) EDCl, HOBt, Et_3N, dry tetrahydrofuran (THF), 0 °C to r.t., 24 h.



Scheme 4. Synthesis of **12**. Reagents and conditions: (i) 1 N NaOH, MeOH, r.t., 24 h; (ii) L-isoleucine methyl ester hydrochloride, EDCl, HOBt, Et_3N, dry THF, 0 °C to r.t., 24 h.



Scheme 5. General method for the synthesis of **18**–**23**. Reagents and conditions: (i) ethylene, (dihydrolMes)(Cy_3P)Cl_2Ru=CHPh (G-II) (10 mol-%), CH_2Cl_2, r.t., 20–24 h; (ii) (a) toluene, 90 °C, 18–20 h, (b) MnO_2, dioxane, reflux, 20–24 h.

We initially chose **7** as a model to carry out CEM with ethylene as the cross-coupling partner. To this end, cross-metathesis with Grubbs first-generation catalyst (G-I) under different solvent and temperature conditions (CH_2Cl_2 r.t., CH_2Cl_2 45 °C, toluene r.t., toluene 90 °C) was attempted, but the desired diene **13** was not obtained in an acceptable yield. However, Grubbs second-generation catalyst (G-II) gave **13** in good yield (Scheme 5). Compound **13** was characterised by various spectroscopic methods. The disappearance of peaks that corresponded to the acetylenic protons and the appearance of new peaks at δ = 5.02–5.34 and 6.33 ppm in the ^{1}H NMR spectrum indicated the formation of **13**.

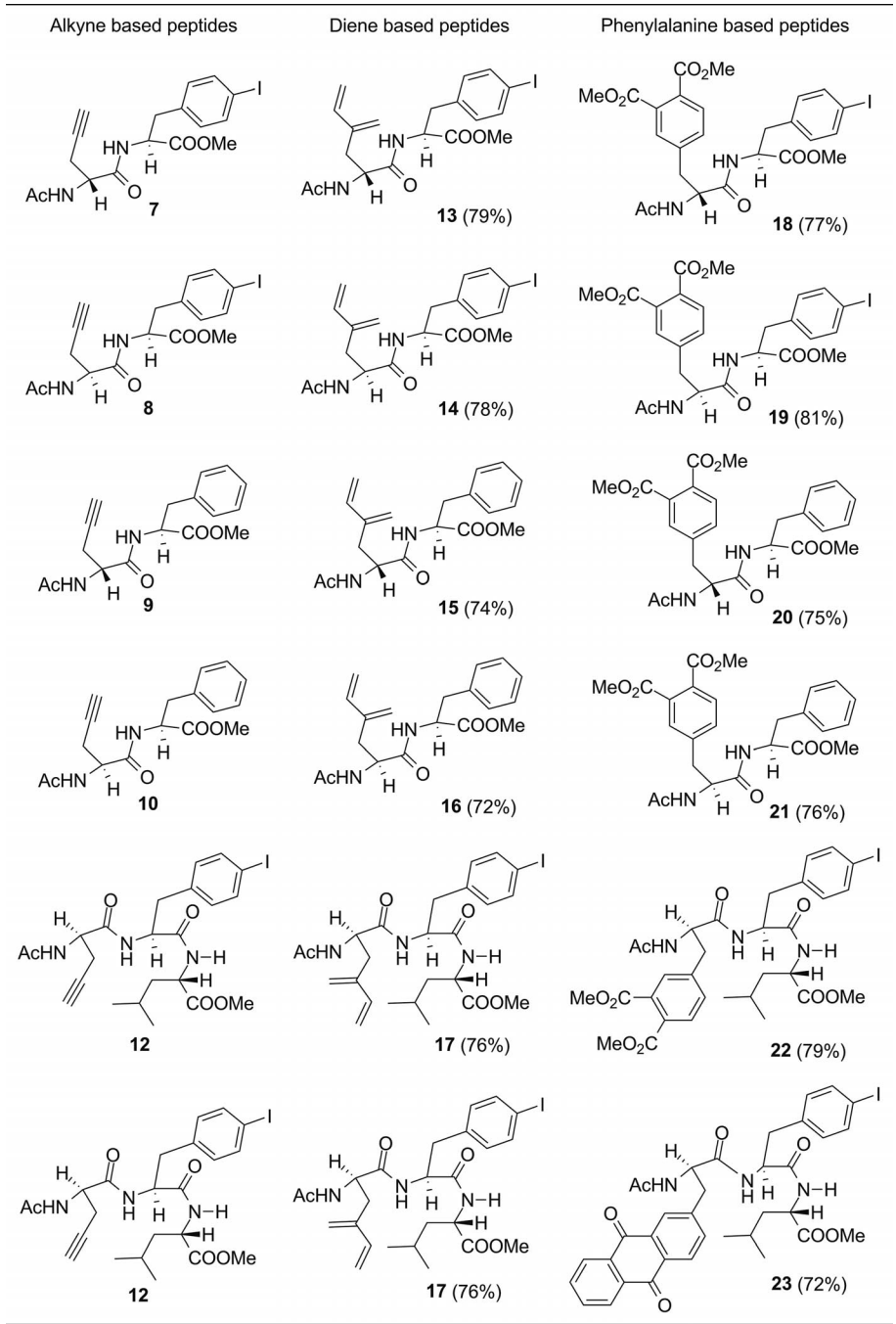
Furthermore, treatment of **13** with a dienophile, such as dimethyl acetylenedicarboxylate, delivered the DA adduct. It was necessary to perform the DA reaction at 90 °C; at higher temperatures, a retro-DA reaction was observed. Initially, the DA adduct was subjected to 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) mediated aromatisation; however, separation of the desired product **18** from the DDQ byproduct was cumbersome. As an alternative, the aromatisation sequence was carried out by using activated MnO_2 in boiling dioxane to deliver the desired modified Phe-based peptide **18** in good yield (Table 1). The structure of **18** was confirmed by the presence of seven peaks between δ = 129 and 140 ppm in the ^{13}C NMR spectrum, which was supported by the presence of peaks between δ = 7.00 and 8.00 ppm in the ^{1}H NMR spectrum. A peak at *m*/*z* = 611.0918 in the HRMS gave additional support for the formation of **18**.

Having optimised the reaction conditions with **13**, the next task was to extend this methodology to other alkyne-based dipeptides such as **8**–**10** (Table 1). Compounds **8**–**10** were subjected to the optimised reaction conditions for the CEM and DA reaction sequence. Along similar lines, this methodology was extended to tripeptide **12**, which was subjected to the CEM and DA reaction sequence to furnish the desired tripeptides **22** and **23** with dienophiles dimethyl acetylenedicarboxylate and 1,4-naphthoquinone, respectively (Table 1). It is gratifying to note that the results observed with the tripeptide proceed along the expected lines. In all cases, peptide integrity was preserved, and good yields of modified peptides were obtained.

Conclusions

We have demonstrated an exceptionally simple and versatile method for the synthesis of modified Phe-based peptides in high overall yields from the inexpensive starting material diethyl acetamidomalonate (**1**). As Phe-based peptides are useful for the treatment of several disorders, our methodology is likely to find application in medicinal chemistry and peptide-based drug design. Our approach has combined several diverse points (CEM coupling partners, dienophiles and Suzuki–Miyaura cross-coupling). Consequently, our approach can provide access to a library of Phe peptides, which may be suitable for SAR studies.

Table 1. Various Phe-based peptides synthesised by the CEM and DA strategy.



Experimental Section

General: All reactions were monitored by TLC using an appropriate solvent system for development. Reactions involving air/oxygen-sensitive reagents or catalysts were performed in degassed solvents. The transfer of moisture-sensitive materials was carried out in a glovebox by using standard syringe–septum techniques and the reaction mixtures were maintained under nitrogen until workup. Yields reported are isolated yields. Ruthenium catalysts were purchased from Aldrich and Strem chemicals. All the commercial reagents were used without further purification. IR spectra were recorded with a Nicolet Impact-400 FT IR spectrometer as KBr discs. ^{1}H (400 MHz) and ^{13}C NMR (100.6 MHz) spectra were recorded with Bruker/Varian spectrometers. HRMS data were recorded with a Micromass Q-Tof spectrometer. Melting points were recorded with a Büchi B-545 apparatus.

Preparation of 2: To a solution of diethyl acetamidomalonate (**1**, 2.0 g, 9.22 mmol) in CH_3CN (25 mL) was added propargyl bromide (1.65 g, 13.82 mmol) and Cs_2CO_3 (3.0 g, 9.22 mmol). The resulting heterogeneous mixture was stirred at r.t. for 18 h. The reaction mixture was filtered and concentrated, the residue was dissolved in ethyl acetate (30 mL), washed with water and brine and dried with Na_2SO_4. Evaporation of the solvent gave the crude prod-

uct as a yellowish white solid, which was purified by column chromatography (30% ethyl acetate/petroleum ether) to give **2** as a white solid (2.01 g, 85%). We have slightly modified the literature procedure. ^{1}H and ^{13}C NMR spectroscopic data are consistent with those in the literature reports. M.p. 90 °C (ref.[15] 91–92 °C).

Preparation of 3: KOH (966.3 mg, 17.25 mmol) was added portionwise to a well-stirred suspension of **2** (2 g, 7.84 mmol) in MeOH (160 mL) and H_2O (32 mL). The mixture was heated at reflux for 4 h, allowed to cool, and the solvents were evaporated to dryness. The residue was treated with ethyl acetate and 2 N HCl to pH = 1 (decarboxylation). After separation, the aqueous phase was extracted with ethyl acetate (3 × 20 mL), the combined organic layers were dried with Na_2SO_4 and the solvents evaporated to yield **3** (971 mg, 80%). We have modified the literature procedure. ^{1}H and ^{13}C NMR spectroscopic data are consistent with those in the literature reports. M.p. 137 °C (ref.[15] 137–139 °C).

Preparation of 5: To a stirred solution of L-phenylalanine (**4**, 2.0 g, 12.12 mmol) in AcOH (11 mL) and concd. H_2SO_4 (1.44 mL) was added powdered I_2 (1.22 g, 4.79 mmol) and $NaIO_3$ (507 mg, 2.55 mmol). The mixture was heated at 70 °C until TLC showed the reaction to be complete, which took 21 h and the addition of two further portions of $NaIO_4$ (50 mg) at this 2 g scale reaction. Completion was indicated by the I_2 colour fading to orange. AcOH was removed by rotary evaporation, and the residual viscous oil was diluted with water (40 mL) and washed twice with Et_2O (20 mL) and CH_2Cl_2 (20 mL). The aqueous solution was neutralised with NaOH to precipitate the crude product, which, after chilling, was collected by filtration and rinsed with water (20 mL) and ethanol (20 mL). The precipitate was dried in a vacuum desiccator for 1 h to yield 4-iodo-L-phenylalanine (2.45 g, 75%). M.p. 259 °C (ref.[16] 261–262 °C). To a suspension of 4-iodo-L-phenylalanine (1.0 g, 3.43 mmol) in methanol (10 mL) was added thionyl chloride (0.4 mL, 5.15 mmol) dropwise at 0 °C. The reaction mixture was stirred at r.t. for 24 h. Evaporation of the methanol gave hydrochloride **5** as a white solid (1.1 g, 94%). We have slightly modified the literature procedure for the hydrochloride formation reaction. ^{1}H and ^{13}C NMR spectroscopic data are consistent with those in the literature reports. M.p. 198 °C (ref.[16] 199–200 °C). The same procedure was used to synthesise **6**. M.p. 160 °C (ref.[16] 158–160 °C).

General Procedure for Peptide Coupling: To a solution of **3** (1.94 mmol) and HOBt (1.83 mmol) in dry THF (10 mL) was added EDCl (1.83 mmol) at 0 °C. Then, **5** or **6** (1.83 mmol) and Et_3N (0.3 mL, the pH of the reaction mixture was 9) in THF (10 mL) were added at 0 °C. The reaction mixture was stirred at r.t. for 24 h. The solvent was evaporated, and the residue was diluted with water. The aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with water and brine and dried with Na_2SO_4. Evaporation of the solvent gave the crude product, which was purified by column chromatography (ethyl acetate/petroleum ether) to give the diasteromeric dipeptides.

Compound 7: R_f = 0.44 (80% ethyl acetate/petroleum ether). M.p. 178–179 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.02 (s, 3 H), 2.06 (t, J = 2.7 Hz, 1 H), 2.50–2.59 (m, 1 H), 2.72–2.81 (m, 1 H), 2.98–3.05 (m, 1 H), 3.11–3.18 (m, 1 H), 3.74 (s, 3 H), 4.49–4.56 (m, 1 H), 4.79–4.86 (m, 1 H), 6.18 (d, J = 7.8 Hz, 1 H), 6.75 (d, J = 7.8 Hz, 1 H), 6.86 (d, J = 8.4 Hz, 2 H), 7.61 (d, J = 8.4 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.0, 23.3, 37.4, 51.5 52.7, 53.5, 72.1, 79.3, 92.9, 131.4, 135.5, 137.8, 169.7, 170.5, 171.3 ppm. HRMS (QTOF): calcd. for $C_{17}H_{20}N_2O_4I$ [M + H]$^+$ 443.0468; found 443.0453. IR (KBr): $\tilde{\nu}$ = 1644, 1736, 2306 cm^{-1}. HPLC: t_R = 3.087 min (100% acetonitrile, flow rate 1 mL/min, detector wavelength 254 nm, reverse-phase C18 column). $[\alpha]_D^{25}$ = 27.63 (c = 0.08, $CHCl_3$).

Compound 8: R_f = 0.40 (80% ethyl acetate/petroleum ether). M.p. 179–180 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.04 (s, 3 H), 2.06 (t, J = 2.7 Hz, 1 H), 2.52–2.61 (m, 1 H), 2.68–2.76 (m, 1 H), 2.99–3.15 (m, 2 H), 3.74 (s, 3 H), 4.53–4.59 (m, 1 H), 4.82–4.88 (m, 1 H), 6.28 (d, J = 7.5 Hz, 1 H), 6.67 (d, J = 7.8 Hz, 1 H), 6.99 (d, J = 8.0 Hz, 2 H), 7.62 (d, J = 8.0 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.4, 23.3, 37.6, 51.5, 52.7, 53.3, 72.1, 79.2, 92.9, 131.5, 135.5, 137.8, 169.6, 170.5, 171.5 ppm. HRMS (QTOF): calcd. for $C_{17}H_{20}N_2O_4I$ [M + H]$^+$ 443.0468; found 443.0484. IR (KBr): $\tilde{\nu}$ = 1647, 1741, 2353 cm^{-1}. HPLC: t_R = 3.108 min (100% acetonitrile, flow rate 1 mL/min, detector wavelength 254 nm, reverse-phase C18 column). $[\alpha]_D^{25}$ = 21.15 (c = 0.08, $CHCl_3$).

Compound 9: R_f = 0.49 (80% ethyl acetate/petroleum ether). M.p. 129–130 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.01 (br. s, 4 H), 2.51–2.76 (m, 2 H), 3.07–3.19 (m, 2 H), 3.73 (s, 3 H), 4.53–4.58 (m, 1 H), 4.82–4.87 (m, 1 H), 6.36 (d, J = 7.6 Hz, 1 H), 6.82 (d, J = 7.6 Hz, 1 H), 7.09–7.11 (m, 2 H), 7.23–7.28 (m, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.2, 23.2, 37.8, 51.5, 52.6, 53.7, 71.9, 79.4, 127.3, 128.8, 129.4, 135.8, 169.7, 170.5, 171.6 ppm. HRMS (QTOF): calcd. for $C_{17}H_{21}N_2O_4$ [M + H]$^+$ 317.1501; found 317.1490. IR (KBr): $\tilde{\nu}$ = 1665, 1746, 2306 cm^{-1}. HPLC: t_R = 3.252 min (100% acetonitrile, flow rate 1 mL/min, detector wavelength 254 nm, reverse-phase C18 column). $[\alpha]_D^{25}$ = 31.94 (c = 0.2, $CHCl_3$).

Compound 10: R_f = 0.45 (80% ethyl acetate/petroleum ether). M.p. 150–151 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.01 (t, J = 2.8 Hz, 1 H), 2.02 (s, 3 H), 2.53–2.67 (m, 2 H), 3.11–3.15 (m, 2 H), 3.73 (s, 3 H), 4.57–4.59 (m, 1 H), 4.86–4.88 (m, 1 H), 6.44 (d, J = 7.2 Hz, 1 H), 6.76 (d, J = 8.0 Hz, 1 H), 7.13–7.15 (m, 2 H), 7.25–7.31 (m, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.5, 23.2, 38.0, 51.5, 52.6, 53.5, 71.9, 79.3, 127.4, 128.8, 129.5, 135.8, 169.6, 170.5, 171.8 ppm. HRMS (QTOF): calcd. for $C_{17}H_{21}N_2O_4$ [M + H]$^+$ 317.1501; found 317.1492. IR (KBr): $\tilde{\nu}$ = 1647, 1742, 2300 cm^{-1}. HPLC: t_R = 3.329 min (100% acetonitrile, flow rate 1 mL/min, detector wavelength 254 nm, reverse-phase C18 column). $[\alpha]_D^{25}$ = 36.42 (c = 0.2, $CHCl_3$).

Compound 11: R_f = 0.12 (100% ethyl acetate). M.p. 176–177 °C. ^{1}H NMR (400 MHz, CD_3OD): δ = 1.96–1.99 (br. s, 4 H), 2.40–2.57 (m, 2 H), 2.93–3.19 (m, 2 H), 4.48–4.63 (m, 1 H), 4.64–4.89 (m, 1 H), 7.01 (d, J = 8.4 Hz, 2 H), 7.62 (d, J = 8.4 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ = 22.5, 22.8, 37.9, 53.4, 54.7, 72.3, 80.2, 92.9, 132.7, 138.1, 138.7, 172.1, 173.4, 174.0 ppm. HRMS (QTOF): calcd. for $C_{16}H_{18}N_2O_4I$ [M + H]$^+$ 429.0311; found 429.0298. IR (KBr): $\tilde{\nu}$ = 1658, 1745, 2320, 3460 cm^{-1}. $[\alpha]_D^{25}$ = 150.03 (c = 0.1, CH_3OH).

Compound 12: R_f = 0.41 (80% ethyl acetate/petroleum ether). M.p. 200–202 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.87–0.89 (m, 6 H), 1.48–1.59 (m, 3 H), 2.00–2.03 (br. s, 4 H), 2.53–2.69 (m, 2 H), 3.05 (d, J = 6.8 Hz, 2 H), 3.71 (s, 3 H), 4.49–4.56 (m, 2 H), 4.67–4.72 (m, 1 H), 6.53–6.57 (m, 2 H), 6.98 (d, J = 8.2 Hz, 2 H), 7.05 (d, J = 8.0 Hz, 1 H), 7.60 (d, J = 8.2 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.0, 22.2, 22.9, 23.2, 24.9, 37.7, 41.4, 51.1, 51.9, 52.6, 54.5, 72.1, 79.0, 92.7, 131.6, 136.1, 137.9, 170.0, 170.2, 170.9, 173.0 ppm. HRMS (QTOF): calcd. for $C_{23}H_{31}N_3O_5I$ [M + H]$^+$ 556.1308; found 556.1288. IR (KBr): $\tilde{\nu}$ = 1650, 1731, 2251 cm^{-1}. $[\alpha]_D^{25}$ = 7.28 (c = 0.6, $CHCl_3$).

General Procedure for CEM: A solution of the alkyne dipeptide (0.11 mmol) in CH_2Cl_2 (15 mL) was degassed with nitrogen for 10 min and degassed with ethylene for 10 min. G-II (0.011 mmol,

10 mol-%) was added, and the reaction vessel was kept under 1 atm pressure of ethylene (balloon pressure). The reaction mixture was stirred at r.t. for 20–24 h. After completion of the reaction (TLC monitoring), the solvent was evaporated, and the crude product was purified by flash silica gel column chromatography (ethyl acetate/petroleum ether) to give the dipeptide-based diene.

Compound 13: R_f = 0.46 (80% ethyl acetate/petroleum ether). M.p. 126–128 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.97 (s, 3 H), 2.62 (d, J = 7.6 Hz, 2 H), 2.95–3.11 (m, 2 H), 3.72 (s, 3 H), 4.51–4.57 (m, 1 H), 4.75–4.80 (m, 1 H), 5.02 (s, 1 H), 5.09 (s, 1 H), 5.15 (d, J = 10.8 Hz, 1 H), 5.39 (d, J = 18 Hz, 1 H), 6.07 (d, J = 7.2 Hz, 1 H), 6.33 (dd, J = 17.6, 10.8 Hz, 1 H), 6.56 (d, J = 8.0 Hz, 1 H), 6.86 (d, J = 8.0 Hz, 2 H), 7.59 (d, J = 8.0 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.1, 34.1, 37.4, 52.0, 52.4, 53.0, 92.6, 114.9, 119.1, 131.3, 135.3, 137.6, 137.7, 141.3, 170.0, 170.7, 171.2 ppm. HRMS (QTOF): calcd. for $C_{19}H_{24}N_2O_4I$ [M + H]$^+$ 471.0781; found 471.0783. IR (KBr): $\tilde{\nu}$ = 1621.9, 1681.7, 1743.2, 3052.9 cm^{-1}. $[\alpha]_D^{25}$ = 28.98 (c = 0.07, $CHCl_3$).

Compound 14: R_f = 0.42 (80% ethyl acetate/petroleum ether). M.p. 128–130 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.96 (s, 3 H), 2.57–2.62 (m, 2 H), 2.98–3.03 (m, 2 H), 3.69 (s, 3 H), 4.56–4.57 (m, 1 H), 4.75–4.77 (m, 1 H), 4.95 (s, 1 H), 5.01 (s, 1 H), 5.14 (d, J = 10.8 Hz, 1 H), 5.37 (d, J = 17.6 Hz, 1 H), 6.05 (d, J = 6.8 Hz, 1 H), 6.29 (dd, J = 18.0, 11.2 Hz, 1 H), 6.59 (d, J = 7.6 Hz, 1 H), 6.86 (d, J = 8.4 Hz, 2 H), 7.60 (d, J = 8.4 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.3, 34.3, 37.6, 52.2, 52.6, 53.2, 92.8, 115.2, 119.1, 131.4, 135.6, 137.9, 141.6, 170.4, 171.1, 171.6 ppm. HRMS (QTOF): calcd. for $C_{19}H_{24}N_2O_4I$ [M + H]$^+$ 472.0859; found 472.0841. IR (KBr): $\tilde{\nu}$ = 1622, 1662, 1748, 3055 cm^{-1}. $[\alpha]_D^{25}$ = 26.51 (c = 0.4, $CHCl_3$).

Compound 15: R_f = 0.50 (80% ethyl acetate/petroleum ether). M.p. 123–125 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.97 (s, 3 H), 2.56–2.65 (m, 2 H), 3.02–3.16 (m, 2 H), 3.72 (s, 3 H), 4.50–4.56 (m, 1 H), 4.77–4.82 (m, 1 H), 5.01 (s, 1 H), 5.06 (s, 1 H), 5.14 (d, J = 10.8 Hz, 1 H), 5.43 (d, J = 18.0 Hz, 1 H), 5.99 (d, J = 7.2 Hz, 1 H), 6.28–6.39 (m, 2 H), 7.08–7.09 (m, 2 H), 7.24–7.30 (m, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.3, 34.5, 38.1, 52.2, 52.6, 53.5, 115.3, 119.5, 127.4, 128.8, 129.5, 135.8, 137.8, 141.6, 170.1, 170.8, 171.6 ppm. HRMS (QTOF): calcd. for $C_{19}H_{25}N_2O_4$ [M + H]$^+$ 345.1814; found 345.1808. IR (KBr): $\tilde{\nu}$ = 1543, 1650, 1743, 3062 cm^{-1}. $[\alpha]_D^{25}$ = 6.179 (c = 0.34, $CHCl_3$).

Compound 16: R_f = 0.46 (80% ethyl acetate/petroleum ether). M.p. 125–127 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.97 (s, 3 H), 2.59 (d, J = 7.2 Hz, 2 H), 3.11–3.15 (m, 2 H), 3.71 (s, 3 H), 4.57–4.59 (m, 1 H), 4.77–4.79 (m, 1 H), 4.94 (s, 1 H), 5.01 (s, 1 H), 5.14 (d, J = 11.2 Hz, 1 H), 5.39 (d, J = 17.6 Hz, 1 H), 6.11 (d, J = 7.2 Hz, 1 H), 6.35 (dd, J = 18.0, 11.2 Hz, 1 H), 6.49 (d, J = 7.6 Hz, 1 H), 7.11–7.13 (m, 2 H), 7.24–7.33 (m, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.3, 34.6, 38.0, 52.3, 52.6, 53.5, 115.2, 119.2, 127.4, 128.9, 129.4, 135.8, 137.8, 141.6, 170.2, 171.0, 171.8 ppm. HRMS (QTOF): calcd. for $C_{19}H_{25}N_2O_4$ [M + H]$^+$ 345.1814; found 345.1812. IR (KBr): $\tilde{\nu}$ = 1540, 1658, 1745, 3060 cm^{-1}. $[\alpha]_D^{25}$ = 37.04 (c = 0.6, $CHCl_3$).

Compound 17: R_f = 0.45 (80% ethyl acetate/petroleum ether). M.p. 197–198 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88–0.90 (m, 6 H), 1.52–1.55 (m, 3 H), 1.97 (s, 3 H), 2.57–2.61 (m, 2 H), 3.00–3.02 (m, 2 H), 3.69 (s, 3 H), 4.35–4.41 (m, 1 H), 4.46–4.51 (m, 1 H), 4.61–4.66 (m, 1 H), 4.96 (s, 1 H), 5.03 (s, 1 H), 5.15 (d, J = 10.8 Hz, 1 H), 5.31 (d, J = 17.7 Hz, 1 H), 6.05 (br. s, 1 H), 6.29 (dd, J = 17.6 Hz, J = 10.9 Hz, 1 H), 6.44 (d, J = 7.5 Hz, 1 H), 6.58 (d, J = 7.6 Hz, 1 H), 6.95 (d, J = 8.2 Hz, 2 H), 7.61 (d, J = 8.0 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, CD_3Cl_3): δ = 21.9, 22.9, 23.1, 24.9, 34.2, 37.5, 41.2, 51.1, 52.4, 52.9, 54.2, 92.6, 114.9, 119.3, 126.8, 128.9, 131.6, 136.3, 137.7, 137.8, 141.2, 170.3, 170.9, 171.4, 172.9 ppm. HRMS (QTOF): calcd. for $C_{25}H_{35}N_3O_5I$ [M + H]$^+$ 584.1621; found 584.1628. IR (KBr): $\tilde{\nu}$ = 1540, 1641, 1738, 2958 cm^{-1}. $[\alpha]_D^{25}$ = –14.25 (c = 0.3, $CHCl_3$).

General Procedure for DA Reaction: To a solution of dipeptide-based diene (0.07 mmol) was added dimethyl acetylenedicarboxylate (0.16 mmol) in dry toluene (10 mL), and the reaction mixture was heated at 90 °C for 18–20 h. The solvent was evaporated under reduced pressure, and the crude product obtained was purified by flash silica gel column chromatography (ethyl acetate/petroleum ether) to afford the DA adduct. Oxidation of the DA adduct (0.03 mmol) was carried out with MnO_2 (0.33 mmol) in dioxane (10 mL) at reflux for 20–24 h. The solvent was removed under reduced pressure, and the crude product was purified by flash silica gel column chromatography using (ethyl acetate/petroleum ether) to afford the aromatised product.

Compound 18: R_f = 0.33 (80% ethyl acetate/petroleum ether). M.p. 144–146 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.95 (s, 3 H), 2.92–2.94 (m, 1 H), 3.03–3.08 (m, 3 H), 3.68 (s, 3 H), 3.88 (s, 6 H), 4.61–4.63 (m, 1 H), 4.71–4.73 (m, 1 H), 6.14 (d, J = 7.6 Hz, 1 H), 6.39 (d, J = 7.6 Hz, 1 H), 6.79 (d, J = 8.0 Hz, 2 H), 7.36 (d, J = 8.0 Hz, 1 H), 7.49 (s, 1 H), 7.57 (d, J = 8.4 Hz, 2 H), 7.67 (d, J = 8.0 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.3, 37.5, 37.8, 52.7, 52.8, 52.9, 53.3, 54.1, 92.9, 129.6, 129.9, 130.5, 131.4, 131.9, 132.8, 135.4, 137.8, 140.3, 167.7, 168.1, 170.1, 171.7 ppm. HRMS (QTOF): calcd. for $C_{25}H_{28}N_2O_8I$ [M + H]$^+$ 611.0890; found 611.0918. IR (KBr): $\tilde{\nu}$ = 1652, 1731, 3055 cm^{-1}. $[\alpha]_D^{25}$ = 4.10 (c = 0.29, $CHCl_3$).

Compound 19: R_f = 0.31 (80% ethyl acetate/petroleum ether). M.p. 143–144 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.94 (s, 3 H), 2.87–2.89 (m, 2 H), 2.91–2.98 (m, 1 H), 3.00–3.15 (m, 1 H), 3.67 (s, 3 H), 3.89 (s, 3 H), 3.90 (s, 3 H), 4.69–4.76 (m, 2 H), 6.17 (d, J = 8.4 Hz, 1 H), 6.66 (d, J = 8.0 Hz, 2 H), 6.69 (d, J = 8.0 Hz, 1 H), 7.28 (d, J = 8.0 Hz, 1 H), 7.52 (s, 1 H), 7.56 (d, J = 8.0 Hz, 2 H), 7.67 (d, J = 7.6 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.2, 37.5, 37.8, 52.7, 52.9, 53.0, 53.2, 54.1, 92.9, 129.6, 129.9, 130.5, 131.3, 132.0, 132.9, 135.4, 137.9, 140.5, 167.7, 168.2, 170.3, 170.4, 171.4 ppm. HRMS (QTOF): calcd. for $C_{25}H_{28}N_2O_8I$ [M + H]$^+$ 611.0890; found 611.0881. IR (KBr): $\tilde{\nu}$ = 1652, 1731, 3064 cm^{-1}. $[\alpha]_D^{25}$ = 29.07 (c = 0.26, $CHCl_3$).

Compound 20: R_f = 0.26 (80% ethyl acetate/petroleum ether). M.p. 124–125 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.93 (s, 3 H), 2.98–3.13 (m, 4 H), 3.69 (s, 3 H), 3.88 (s, 6 H), 4.73–4.78 (m, 2 H), 6.19 (d, J = 8.0 Hz, 1 H), 6.41 (d, J = 7.3 Hz, 1 H), 7.01–7.05 (m, 2 H), 7.21–7.37 (m, 4 H), 7.49 (d, J = 1.6 Hz, 1 H), 7.64 (d, J = 7.9 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.2, 37.9, 52.6, 52.7, 52.8, 53.5, 54.0, 127.4, 128.8, 129.3, 129.5, 129.9, 130.5, 132.0, 132.8, 135.7, 140.4, 167.8, 168.1, 170.1, 170.2, 171.4 ppm. HRMS (QTOF): calcd. for $C_{25}H_{29}N_2O_8$ [M + H]$^+$ 485.1936; found 485.1924. IR (KBr): $\tilde{\nu}$ = 1660, 1741, 2926 cm^{-1}. $[\alpha]_D^{25}$ = 16.69 (c = 0.38, $CHCl_3$).

Compound 21: R_f = 0.24 (80% ethyl acetate/petroleum ether). M.p. 129–131 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.94 (s, 3 H), 2.95–3.13 (m, 4 H), 3.68 (s, 3 H), 3.88 (s, 6 H), 4.68–4.80 (m, 2 H), 6.13 (d, J = 7.9 Hz, 1 H), 6.54 (d, J = 7.8 Hz, 1 H), 6.95–6.97 (m, 2 H), 7.00–7.29 (m, 4 H), 7.48 (d, J = 1.56 Hz, 1 H), 7.64 (d, J = 7.9 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.2, 37.9, 52.6, 52.8, 52.9, 53.4, 54.0, 127.5, 128.9, 129.3, 129.6, 129.9, 130.5, 131.9, 132.8, 135.7, 140.5, 167.8, 168.2, 170.2, 170.3, 171.7 ppm. HRMS (QTOF): calcd. for $C_{25}H_{29}N_2O_8$ [M + H]$^+$ 485.1924; found

485.1909. IR (KBr): $\tilde{\nu}$ = 1665, 1739, 2928 cm^{-1}. $[a]_D^{25}$ = 26.26 (c = 0.19, $CHCl_3$).

Compound 22: R_f = 0.30 (80% ethyl acetate/petroleum ether). M.p. 102–103 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.86–0.88 (m, 6 H), 1.41–1.54 (m, 3 H), 1.95 (s, 3 H), 2.76–3.15 (m, 4 H), 3.69 (s, 3 H), 3.89 (s, 3 H), 3.90 (s, 3 H), 4.43–4.62 (m, 2 H), 4.63–4.72 (m, 1 H), 6.34 (d, J = 7.4 Hz, 1 H), 6.55 (d, J = 8.0 Hz, 1 H), 6.62 (d, J = 8.4 Hz, 1 H), 6.78 (d, J = 8.2 Hz, 2 H), 7.28–7.29 (m, 1 H), 7.50 (s, 1 H), 7.56 (d, J = 8.28 Hz, 2 H), 7.68 (d, J = 7.96 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.9, 22.9, 23.1, 24.9, 37.3, 37.5, 41.2, 51.2, 52.5, 52.8, 52.9, 54.1, 54.8, 92.8, 128.7, 129.7, 129.8, 130.6, 131.5, 131.9, 132.9, 135.9, 137.9, 140.3, 167.6, 168.2, 169.9, 170.5, 170.9, 172.9 ppm. HRMS (QTOF): calcd. for $C_{31}H_{39}N_3O_9I$ $[M + H]^+$ 724.1731; found 724.1760. IR (KBr): $\tilde{\nu}$ = 1637, 1734, 2926 cm^{-1}. $[a]_D^{25}$ = –9.4 (c = 0.18, $CHCl_3$).

Compound 23: R_f = 0.30 (60% ethyl acetate/petroleum ether). M.p. 158–161 °C. ^{1}H NMR (400 MHz, CD_3OD): δ = 0.85–0.95 (m, 6 H), 1.59–1.87 (m, 3 H), 1.89 (s, 3 H), 2.75–3.11 (m, 4 H), 3.68 (s, 3 H), 4.41–4.45 (m, 3 H), 6.95 (d, J = 8.3 Hz, 2 H), 7.51 (d, J = 8.3 Hz, 2 H), 7.56–7.58 (m, 1 H), 7.87–7.89 (m, 2 H), 8.10 (d, J = 1.6 Hz, 1 H), 8.17 (d, J = 8.0 Hz, 1 H), 8.28–8.31 (m, 2 H) ppm. HRMS (QTOF): calcd. for $C_{35}H_{37}N_3O_7I$ $[M + H]^+$ 738.1676; found 738.1674. IR (KBr): $\tilde{\nu}$ = 1458, 1654, 1936 3002 cm^{-1}. $[a]_D^{25}$ = –11.5(c = 0.12, CH_3OH).

Supporting Information (see footnote on the first page of this article): Copies of ^{1}H/^{13}C NMR spectra of all new products.

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[17] The diasteromeric nature of the products was confirmed by the presence of two singlets of almost equal intensity at δ = 3.725 and 3.736 ppm (–OCH_3 protons) in the ^{1}H NMR spectrum of

the crude reaction mixture. Percolation of the reaction mixture through a silica gel column with ethyl acetate/petroleum ether (3:7) resulted in the separation of the diasteromeric dipeptides **7** and **8**. The structures of these two dipeptides were established by IR, ^{1}H NMR, and ^{13}C NMR spectroscopy and MS. The presence of singlets at δ = 3.736 and 3.725 ppm in the ^{1}H NMR spectra of **7** and **8**, respectively, indicate the successful separation of the two diasteromers by column chromatography. HPLC further supports the purity of the two diasteromers. The 2D NMR spectra (COSY and NOESY) of **7** and **8** were not of much help in the assignment of their stereochemistry, and therefore, we undertook an independent synthesis of these two diasteromers to establish their absolute stereochemistry. In this regard, we acetylated commercially available (*S*)-propargylglycine and (*R*)-propargylglycine according to a literature procedure.[18] (*S*)-Ac-propargylglycine and (*R*)-Ac-propargylglycine were treated with the *p*-iodomethyl ester hydrochloride of (*S*)-phenylalanine **5**. These dipeptides were characterised and compared with **7** and **8** by inspection of the R_f, ^{1}H NMR and $[\alpha]_D$ values. Based on this data, it was concluded that **7** is the (*R*,*S*)-dipeptide, and **8** is an (*S*,*S*)-dipeptide. The configurations of **9** and **10** were established along similar lines.

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