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Synthesis of Constrained Phenylalanine Derivatives Via a [2 + 2 + 2] Cycloaddition Strategy

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Abstract—A simple synthesis of dialkyne building blocks (**6**, **7**, **8** and **9**) embodying amino acid moiety is described. The dialkyne **6** participated in a [2 + 2 + 2] cycloaddition reaction with various monoalkynes in presence of Wilkinson's catalyst to give 5- and 5,6-disubstituted indan-based α-amino acid derivatives. Cobalt catalyst [e.g., $CpCo(CO)_2$] has also been employed in the synthesis of various 2-indanyl glycine derivatives via co-trimerization reaction of the diyne building blocks **6** and **7** with several monoalkynes.

Introduction

Synthetic α-amino acids (AAAs) bearing unusual side chains have gained a widespread use in peptide design.[1] In particular, α,α-disubstituted and/or cyclic α,α-amino acids are used as a means of controlling the secondary structure of a peptide.[2] On several occasions incorporation of the unusual AAAs into peptides has led to a unique analogues which are biologically more active and resistant to enzymatic degradation.[3] Accessibility of the unusual AAA where only one of the properties such as steric/electronic or hydrophobic properties varies, while the other remain approximately constant makes the QSAR studies more meaningful.

As part of a general program towards the synthesis of unusual AAAs,[4] we conceived a novel 'building block approach', involving a [2 + 2 + 2] cycloaddition reaction as a key step for the synthesis of 2-indanyl glycine (Ind) **1** (R_1, R_2 = H). Compound **1** has been utilized in the synthesis of peptides with angiotensin II receptor with agonistic and antagonistic activity.[5] In addition, Ind derivatives play an important role in the design of chemotactic peptides [6] and are also used for analyzing the binding pockets of substance P.[7] The documented difficulties involving the most commonly used Bucherer–Berg[8a] and Schiff's base[8b] methods for the synthesis of functionalized Ind derivatives have encouraged us to search for new synthetic methods.

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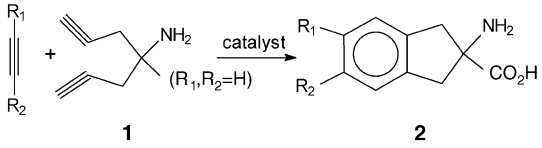
Strategy

The [2 + 2 + 2] cycloaddition approach to AAA derivatives such as **1** involves the partially intermolecular trimerization reaction in which the dialkyne containing an amino acid moiety **2** reacts with a mono alkyne leading to the formation of an Ind **1** in a single-step process (eq 1). Although the alkyne co-trimerization reaction has been known in the literature for several years,[9] it was not utilized in the synthesis of unusual AAAs. The cycloaddition approach to unusual AAAs is strategically different from the other known routes because it involves generation of the benzenoid ring system while the other routes[4a,8] involve manipulation of the preformed benzene derivatives. Herein, we describe the full details for the preparation of indan-based AAA derivatives via a [2 + 2 + 2] cycloaddition reaction as a key step.[10]



1 **2** eq 1

Results and Discussion

The dialkyne building block **6** containing AAA moiety may be readily prepared from a suitable AAA synthon. In this regard, initially the benzylidene glycine ester was chosen as a possible AAA synthon and the dialkylation reaction under different conditions with propargyl bromide was found to be unsuccessful.[11] Later on, it was found that the ethyl isocyanoacetate **3**[12] with two

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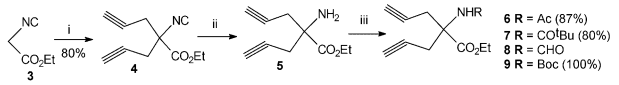
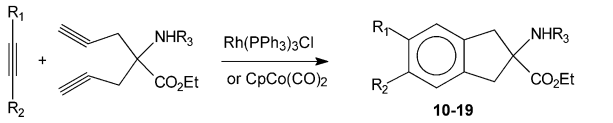


Scheme 1. (1) $HC{\equiv}CCH_2Br$, K_2CO_3, TBAHS CH_3CN 80 °C; (ii) HCl, EtOH, rt; (iii) protecting reagents.



10 R_1,R_2 = CH_2OH, R_3 = Ac (68%)
11 R_1 = H, R_2 = CH_2OH, R_3 = Ac (81%)
12 R_1 = H, R_2 = $(CH_2)_2OH$, R_3 = Ac (97%)
13 R_1 = H,R_2= $(CH_2)_3OH$, R_3 = Ac (50%)
14 R_1 = H, R_2= $(CH_3)_2COH$, R_3 = Ac (95%)
10-14 prepared by $Rh(PPh_3)_3Cl$
15-19 prepared by $CpCo(CO)_2$
15 R_1, R_2 = Ph, R_3 = Ac (22%)
16 R_1, R_2 = Ph, R_3 = COtBu (33%)
17 R_1 = H, R_2 = Ph, R_3 = Ac (27%)
18 R_1 = H, R_2 = Ph, R_3 = COtBu (38%)
19 R_1, R_2 = CO_2Me, R_3 = Ac (27%)

Scheme 2.

equivalents of propargyl bromide in presence of potassium carbonate and tetrabutylammonium hydrogensulfate (TBAHS) in dry acetonitrile gave the required product **4** in 80% isolated yield (Scheme 1). The structure of the isonitrile **4** was confirmed on the basis of mass spectral data (*m*/*e* 189) and also by its 8-line ^{13}C NMR spectral data (δ 13.8, 28.2, 63.4, 64.5, 73.4, 75.8, 161.5 and 165.8).

Reaction of isonitrile derivative **4** with one equivalent of mono alkyne such as 2-butyne-1,4-diol in presence of Wilkinson's catalyst (WC) gave several products as judged by TLC. So, it was necessary to hydrolyze the isonitrile group and protect the resulting amino group present in **5** as an acetyl derivative. The diyne **6** was found to react with the excess amount of 2-butyne-1,4-diol (5–8 equivalents) under Wilkinson's catalyst conditions,[13] to give the required co-trimerized product **10** in 68% isolated yield (Scheme 2).

The molecular ion peak at *m*/*e* 307.1432 ($C_{16}H_{21}NO_5$) in the high-resolution mass spectrum supported its molecular formulation of compound **10**. Various other mono alkynols that underwent a [2+2+2] cycloaddition reaction with the diyne **6** delivering Ind derivatives **10-14** are summarized in Scheme 2. The monoynes that don't contain a hydroxy functionality failed to give the co-trimerized products under WC conditions. Hydroxy group in the mono alkyne may be necessary for the co-trimerization reaction because of its coordination to Rh during the co-trimerization reaction. In this regard we explored other catalyst systems such as η^5-cyclopentadienyl cobalt dicarbonyl [$CpCo(CO)_2$] [Vollhardt catalyst (VC)].[14] Initial attempts to use acetyl derivative **6** under VC conditions gave lower yields of the products. The typical experimental procedure for the VC conditions involves the slow addition of a solution of the diyne in *n*-octane containing catalyst to a refluxing solution of the monoyne in *n*-octane containing a small amount of catalyst.

Probably due to poor solubility of the diyne **6** in *n*-octane the yield of the co-trimerized product was very low. To improve the solubility of the diyne the pivaloyl derivative **7** and Boc derivative **9** were prepared. These derivatives have better solubilities in *n*-octane and the addition of diyne mixed with catalyst in *n*-octane to monoyne became more practical. However, Boc derivative **9** resulted in no products as the diyne found to decompose under high temperature conditions. While the pivaloyl derivative was stable and provided imporved yields of the co-trimerized products. Various Ind derivatives prepared by this methodology (**15**–**19**) are also included in Scheme 2.

Conclusions

In summary, for the first time we have shown that the 'building block approach' is useful for the synthesis of several indan-based AAA derivatives via a [2+2+2] cycloaddition reaction mediated by Wilkinson's and Vollhardt catalysts.

Experimental

General experimental details are identical with those reported earlier.[4a] Razel A-99 syringe pump was used in all the high dilution reactions.

Ethyl 2-isocyano-2-propargyl-4-pentynoate (4). A solution of ethyl isocyanoacetate **3** (750 mg, 6.6 mmol), propargyl bromide (1.88 g, 15.8 mmol), potassium carbonate (7.29 g, 52.8 mmol) and tetrabutylammonium hydrogensulfate (TBAHS) (447 mg, 1.31 mmol) in acetonitrile (100 mL) was refluxed for 9 h. Then, the reaction mixture was cooled and filtered off the inorganic salts using a G4 glass crucible. The filtrate was evaporated under reduced pressure. The resulting brown residue taken in diethyl ether was washed with water, and brine, and then dried. Evaporation of the solvent gave the crude product, which was charged on a silica gel column. Elution of the column with ethyl acetate–hexane (1:19) mixture gave **4** as a light yellow liquid (901 mg, 80%). Due to the unstable nature of this compound at rt the satisfactory analytical data was not obtained. IR (neat): ν 3305, 2147, 1754 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.35 (t, J=7.1 Hz, 3H), 2.21 (t, J=2.5 Hz, 2H), 2.94 (d, J=2.5 Hz, 4H), 4.34 (q, J=7.1 Hz, 2H). ^{13}C NMR (75.43 MHz, $CDCl_3$): δ 13.8, 28.2, 63.4, 64.5, 73.4, 75.8, 161.6, 165.8. Mass: *m*/*e* 189 (M^+).

Hydrolysis of compound (4). To a solution of the isonitrile derivative **4** (708 mg, 3.74 mmol), in absolute ethanol (8 mL) were added six drops of con. HCl. The mixture was stirred at rt for 1 h. The solvent was evaporated under reduced pressure, and the resulting white salt was dissolved in water and extracted with diethyl ether to remove other organic residues. The combined ether extract was washed with water, and brine, and then dried. The aqueous layer was basified with NH_4OH solution (pH = 10) and then extracted with ethyl acetate. The combined ethyl acetate extracts were washed with water, and brine, and then dried. Evaporation of ethyl acetate under reduced pressure on a

rotary evaporator gave amino ester **5** as a light yellow oil (641 mg, 95%). IR (neat): ν 3450, 2140, 1740 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.30 (t, $J=7.1$ Hz, 3H), 2.01 (s, 2H), 2.09 (t, $J=2.5$ Hz, 2H), 2.64 (d q, $J=16.5$, 2.5 Hz, 2H), 4.24 (q, $J=7.1$ Hz, 2H). ^{13}C NMR (75.43 MHz, $CDCl_3$): δ 14.1, 29.0, 59.7, 61.6, 71.8, 78.8, 173.6. Evaporation of the diethyl ether layer gave the formyl derivative, ethyl 2-formamido-2-propargyl-4-pentynoate **8** as a white crystalline solid (23 mg, 3%). Mp 96–97 °C. IR (KBr): ν 3365, 3265, 2120, 1749, 1635 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.33 (t, $J=7.1$ Hz, 3H), 2.02 (t, $J=2.5$ Hz, 2H), 2.77 (d 1/2 ABq, $J=16.7$, 2.5 Hz, 2H), 3.38 (d 1/2 ABq, $J=16.7$, 2.5 Hz, 2H), 4.33 (q, $J=7.1$ Hz, 2H), 6.67 (s, 1H), 8.23 (s, 1H). ^{13}C NMR (75.43 MHz, $CDCl_3$): δ 14.1, 25.4, 62.0, 62.8, 71.6, 78.1, 160.4, 170.3. Mass: *m/e* 208 (M + 1). Anal. for $C_{11}H_{13}NO_3$: calcd 63.75 (C), 6.32 (H), 6.75 (N); found 63.89 (C), 6.34 (H), 6.51 (N).

Ethyl 2-acetamido-2-propargyl-4-pentynoate (6). To a solution of amino ester **5** (640 mg, 3.5 mmol) in dry CH_2Cl_2 (8 mL) was added a solution of acetic anhydride (918 mg, 9 mmol) in dry CH_2Cl_2 (1 mL) at rt and the mixture was stirred for 2 h. The reaction mixture was washed with water, brine and then dried. Evaporation of the solvent and purification by a silica gel column using ethyl acetate-hexane (1:4) gave the acetyl derivative **6** as colorless needles (677 mg, 87%). Mp 116–118 °C. IR (KBr): ν 3295, 3262, 2124, 1739, 1645 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.32 (t, $J=7.1$ Hz, 3H), 2.0 (t, $J=2.6$ Hz, 2H), 2.06 (s, 3H), 2.75 (d, ABq, $J=16.6$, 2.6 Hz, 2H), 3.36 (d, ABq, $J=16.6$, 2.7 Hz, 2H), 4.31 (q, $J=7.1$ Hz, 2H), 6.52 (s, 1H). ^{13}C NMR (75.43 MHz, $CDCl_3$): δ 14.1, 23.7, 25.1, 61.7, 62.5, 71.4, 78.4, 169.9, 170.7. Mass: *m/e* 222 (M + 1). Anal. for $C_{12}H_{15}NO_3$: calcd 65.14 (C), 6.83 (H), 6.33 (N); found 65.43 (C), 6.85 (H), 6.33 (N).

Ethyl 2-trimethylacetamido-2-propargyl-4-pentynoate (7). To a stirred solution of amino ester **5** (300 mg, 1.8 mmol) and triethylamine (910 mg, 9 mmol) in dry THF (5 mL) was added a solution of pivaloyl chloride (1.1 g, 9 mmol) in dry THF (2 mL) at 0 °C. The reaction mixture was stirred for 5 h at rt. Solvent was evaporated under reduced pressure and the white solid obtained was dissolved in water and extracted with diethyl ether. The combined organic extracts were washed with water, brine and then dried. Evaporation of the solvent and purification of the crude product by silica gel column chromatography using ethyl acetate–hexane (1:9) as an eluent furnished **7** as a white flaky solid (407 mg, 80%). Mp 80–81 °C. IR (KBr): ν 3348, 3265, 2344, 1737, 1640 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.24 (s, 9H), 1.32 (t, $J=7.1$ Hz, 3H), 1.99 (t, $J=2.5$ Hz, 2H), 2.73 (d, ABq, $J=16.6$, 2.5 Hz, 2H), 3.35 (d, ABq, $J=16.6$, 2.5 Hz, 2H), 4.30 (q, $J=7.1$ Hz, 2H), 6.72 (s, 1H, NH). ^{13}C NMR (75.43 MHz, $CDCl_3$): δ 14.0, 24.8, 27.4, 39.1, 61.2, 62.1, 71.1, 78.4, 170.7, 177.6. Mass: *m/e* 263 (M^+). Anal. for $C_{15}H_{21}NO_3$: calcd 68.42 (C), 8.04 (H), 5.32 (N); found 67.96 (C), 7.90 (H), 4.95 (N).

Ethyl 2-*N*-*t*-butyloxycarbonylamino-2-propargyl-4-pentynoate (9). A solution of amino ester **5** (150 mg, 0.84 mmol), and $(Boc)_2O$ (218 mg, 1 mmol) in dry $CHCl_3$ (10 mL) was refluxed for 3 days. Then, the solvent was evaporated and crude product obtained was purified by silica gel column chromatography using ethyl acetate-hexane (1:19) mixture as an eluent to give **9** as light yellow liquid (234 mg, 100%). IR (KBr): ν 3428, 3295, 2150, 1741, 1713 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.30 (t, $J=7.1$ Hz, 3H), 1.45 (s, 9H), 2.03 (t, $J=2.7$ Hz, 2H), 2.81 (d 1/2 ABq, $J=16.7$, 2.7 Hz, 2H), 3.13 (1/2 ABq, $J=16.7$ Hz, 2H), 4.28 (q, $J=7.9$ Hz, 2H), 5.53 (s, 1H). ^{13}C NMR (75.43 MHz, $CDCl_3$): δ. 14.1, 25.5, 28.3, 61.1, 62.3, 71.6, 78.5, 154.2, 170.8. Mass: *m/e* 280 (M + 1).

General procedure for a [2 + 2 + 2] cycloaddition reaction using Wilkinson's catalyst

To a solution of the diyne building block **6** (1 mmol) and monoyne (5–8 mmol) in absolute ethanol (20 mL) was degassed for 30 min by bubbling nitrogen gas through the solution. Wilkinson's catalyst (2–3 mol%) was added and then the resulting clear red colored solution was refluxed under nitrogen atmosphere until all the diyne was consumed (TLC monitoring). Then, the solvent was evaporated under reduced pressure on a rotary evaporator. The brown colour residue obtained was purified by silica gel column chromatography using ethyl acetate–hexane mixture as an eluent to give co-trimerized product.

Ethyl 2-acetamido-5,6-bis(hydroxymethyl) indan-2-carboxylate (10). The diyne **6** (140 mg, 0.63 mmol), 2-butyne-1,4-diol (272 mg, 3.15 mmol) in absolute ethanol (14 mL) were reacted according to the general procedure for 48 h. Purification of the crude product by silica gel column chromatography using ethyl acetate–hexane (1:1 to 2:1) as an eluent furnished **10** as a light yellow solid (170 mg, 68%). Mp 122–124 °C. IR (KBr): ν 3375, 3227, 1740, 1650 cm^{-1}. UV ($CHCl_3$): λ_{max} nm (∈ M^{-1} cm^{-1}) 285 (2245), 277 (1265). ^1H NMR (300 MHz, $CDCl_3$): δ 1.24 (t, $J=6.9$ Hz, 3H), 1.89 (s, 3H), 3.24 (1/2 ABq, $J=16.5$ Hz, 4H), 3.56 (1/2 ABq, $J=16.5$ Hz, 2H), 4.21 (q, $J=7.3$ Hz, 2H), 4.68 (q, $J=14.3$ Hz, 4H), 6.25 (s, 1H), 7.18 (s, 2H). ^{13}C NMR (75.43 MHz, $CDCl_3$): δ 14.1, 22.6, 43.1, 61.8, 63.6, 66.0, 125.7, 138.5, 140.1, 170.9, 173.1; HRMS: *m/e* for $C_{16}H_{21}NO_5$: calcd 307.1419; found 307.1432.

Ethyl 2-acetamido-5-hydroxymethylindan-2-carboxylate (11). The diyne **6** (50 mg, 0.22 mmol), propargyl alcohol (56 mg, 0.9 mmol) were reacted as described in the general procedure for 6 h. Purification by silica gel column chromatography using ethyl acetate–hexane (1:1) mixture as an eluent furnished the co-trimerization product **11** as a white solid (50 mg, 81%). Mp 135–137 °C. IR (KBr): ν 3380, 3228, 1740, 1650 cm^{-1}. UV ($CHCl_3$): λ_{max} nm (∈ M^{-1} cm^{-1}) 277 (1206), 270 (1194). ^1H NMR (300 MHz, $CDCl_3$): δ 1.25 (t, $J=7.1$ Hz, 3H), 1.58 (s, 1H), 1.94 (s, 3H) 3.24 (1/2 ABq, $J=16.6$ Hz, 2H), 3.63 (1/2 ABq, $J=16.6$ Hz, 2H), 4.22 (q, $J=7.1$ Hz, 2H), 4.67 (s, 2H), 5.99 (s, 1H), 7.19 (d, $J=10.5$ Hz, 2H), 7.23 (s, 1H). ^{13}C NMR (75.43 MHz, $CDCl_3$): δ 14.1, 23.1, 43.2, 43.4, 61.7, 65.2, 66.1, 123.5, 124.7,

126.1, 139.4, 140.0, 140.4, 170.3, 172.9. Mass: *m/e* 277 (M^+). HRMS: *m/e* for $C_{15}H_{19}NO_4$: calcd 277.1308; found 277.1297.

Ethyl 2-acetamido-5-(2′-hydroxyethyl)indan-2-carboxylate (12). The diyne **6** (75 mg, 0.34 mmol) and 3-butyn-1-ol (120 mg, 1.7 mmol) in absolute ethanol (8 mL) were reacted according to the general procedure for 2.5 h. Product was purified by silica gel column chromatography using ethyl acetate–hexane (2:1) as an eluent to afford compound **12** as a white solid (96 mg, 97%). Mp 108–110 °C. IR (KBr): ν 3375, 3227, 1737, 1651 cm^{-1}. UV ($CHCl_3$): λ_{max} nm ($\in$ M^{-1} cm^{-1}) 278 (2010), 270 (2130). ^1H NMR (300 MHz, $CDCl_3$): δ 1.25 (t, $J=7.1$ Hz, 3H), 1.69 (s, 1H), 1.94 (s, 3H), 2.85 (t, $J=6.6$ Hz, 2H), 3.21 (d, 1/2 ABq, $J=16.6$, 3.3 Hz, 2H), 3.61 (d 1/2 ABq, $J=16.6$, 7.8 Hz, 2H), 3.84 (t, $J=6.4$ Hz, 2H), 4.22 (q, $J=7.1$ Hz, 2H), 6.09 (s, 1H), 7.06 (1/2 ABq, $J=7.6$ Hz, 1H), 7.07 (s, 1H), 7.11 (1/2 ABq, $J=7.6$ Hz, 1H). ^{13}C NMR (75.43 MHz, $CDCl_3$): δ 14.1, 22.9, 38.9, 43.1, 43.3, 61.6, 63.6, 66.0, 124.6, 125.2, 127.8, 137.6, 138.0, 140.3, 170.5, 173.0. Mass: *m/e* 291 (M^+). HRMS: *m/e* for $C_{16}H_{21}NO_4$, calcd 291.1464; found 291.1460.

Ethyl 2-acetamido-5-(3′-hydroxypropyl)indan-2-carboxylate (13). The diyne **6** (50 mg, 0.22 mmol) and 4-pentyn-1-ol (94 mg, 1.13 mmol) in absolute ethanol (10 mL) were reacted according to the general procedure for 6 h. Product was purified by silica gel column chromatography using ethyl acetate-hexane (4:1) to furnish **13** as a white solid (25 mg, 50%; based on starting material recovered, 12 mg). Mp. 132–134 °C. IR (KBr): ν 3378, 3230, 1735, 1653 cm^{-1}. UV ($CHCl_3$): λ_{max} nm ($\in$ M^{-1} cm^{-1}) 278 (2218), 270 (2508); 237 (3482); ^1H NMR (300 MHz, $CDCl_3$): δ 1.25 (t, $J=7.1$ Hz, 3H), 1.68 (s, 1H), 1.82–1.92 (m, 2H), 1.93 (s, 3H), 2.68 (t, $J=8.0$ Hz, 2H), 3.19 (d 1/2 ABq, $J=16.5$, 4.4 Hz, 2H), 3.59 (d, 1/2 ABq, $J=9.5$, 8.2 Hz, 2H), 3.67 (t, $J=3.6$ Hz, 2H), 4.21 (q, $J=7.1$ Hz, 2H), 6.07 (s, 1H), 7.03 (1/2 ABq, $J=7.1$ Hz, 1H), 7.04 (s, 1H), 7.12 (1/2 ABq, $J=7.1$ Hz, 1H). ^{13}C NMR (75.43 MHz, $CDCl_3$): δ 14.1, 23.2, 31.9, 34.4, 43.3, 43.4, 61.7, 62.2, 66.1, 124.5, 124.7, 127.3, 137.3, 140.2, 140.9, 170.3, 172.9. Mass: *m/e* 305 (M^+). HRMS: *m/e* for $C_{17}H_{23}NO_4$; calcd 305.1625; found 305.1705.

Ethyl 2-acetamido-5-(1′-methyl-1′-hydroxyethyl) indan-2-carboxylate (14). The diyne **6** (50 mg, 0.22 mmol) and 2-methyl-3-butyn-2-ol (94 mg, 1.13 mmol) in absolute ethanol (8 mL) were reacted according to the general procedure for 5 h. Product was purified by silica gel column chromatography using ethyl acetate–hexane (3:2) as an eluent to obtain **14** as a white solid (65 mg, 95%). Mp 142–143 °C. IR (KBr): ν 3388, 3240, 1737, 1643 cm^{-1}. UV ($CHCl_3$): λ_{max} nm ($\in$ M^{-1} cm^{-1}) 277 (1566), 270 (1578); ^1H NMR (300 MHz, $CDCl_3$): δ 1.23 (t, $J=7.1$ Hz, 3H), 1.55 (s, 6H), 1.88 (s, 3H), 2.28 (s, 1H), 3.21 (1/2 ABq, $J=16.4$ Hz, 2H), 3.61 (1/2 ABq, $J=16.4$ Hz, 2H), 4.19 (q, $J=7.1$ Hz, 2H), 6.37 (s, 1H), 7.14 (d, $J=7.7$ Hz, 1H), 7.30 (d, $J=8.0$ Hz, 1H), 7.34 (s, 1H). ^{13}C NMR (75.43 MHz, $CDCl_3$): δ 14.0, 22.9, 31.8, 31.9, 43.1, 43.5, 61.5, 66.0, 72.4, 120.7, 123.3, 124.1, 138.1, 139.9, 148.4, 170.2, 172.9. Mass: *m/e* 305 (M^+). HRMS: *m/e* for $C_{17}H_{23}NO_4$; calcd 305.1625; found 305.1629

Ethyl 2-acetamido-5,6-diphenylindan-2-carboxylate (15). To a refluxing solution of diyne **6** (25 mg, 0.11 mmol), diphenylacetylene (40.2 mg, 0.22 mmol) and $CpCo(CO)_2$ (1.2 μL) in dry *n*-octane (1.5 mL) were added (syringe pump) a solution of $CpCo(CO)_2$ (1.5 μL) in *n*-octane (1.5 mL) under N_2 over a period of 14 h. All the volatiles were distilled off under reduced pressure to leave crude product as a dark oil. Purification of the crude product by a silica gel column using ethyl acetate-hexane (1:3) as an eluent gave **15** as a white flaky solid (10 mg, 22%). Mp 204–206 °C. IR (KBr): ν 3240, 1742, 1655 cm^{-1}. UV ($CHCl_3$): λ_{max} nm ($\in$ M^{-1} cm^{-1}) 273 (7220). ^1H NMR (300 MHz, $CDCl_3$): δ 1.28 (t, $J=7.1$ Hz, 3H), 1.99 (s, 3H), 3.32 (1/2 ABq, $J=16.6$ Hz, 2H), 3.73 (1/2 ABq, $J=16.6$ Hz, 2H), 4.25 (q, $J=7.1$ Hz, 2H), 6.06 (s, 1H), 7.08–7.21 (m, 10H), 7.27 (s, 2H). ^{13}C NMR (75.43 MHz, $CDCl_3$): δ 14.2, 23.3, 43.4, 61.8, 65.1, 126.4, 126.7, 127.9, 129.9, 139.3, 139.9, 141.5, 170.2, 172.9. Mass: *m/e* 399 (M^+). Anal: for $C_{26}H_{25}NO_3$; calcd 78.17 (C), 6.30 (H), 3.50 (N); found 78.23 (C), 6.51 (H), 3.51 (N).

Ethyl 2-trimethylacetamido-5,6-diphenylindan-2-carboxylate (16). A solution of diyne **7** (50 mg, 0.19 mmol) in *n*-octane (1 mL) containing $CpCo(CO)_2$ (2 μL) were added (syringe pump) to a refluxing (oil bath 140 °C) solution of diphenyl acetylene (67.7 mg, 0.38 mmol) in *n*-octane (1.5 mL) containing $CpCo(CO)_2$ (1 μL) under N_2 over a period of 8 h. Then the reaction mixture was stirred at 140 °C for an additional 1 h. The flask was cooled and the solvent was distilled out under vacuum. The remaining dark residue was purified by silica gel column chromatography using ethyl acetate–hexane (1:4) mixture as an eluent to obtain **16** as a white crystalline solid (28 mg, 33%). Mp 179–180 °C. IR (KBr): ν 3355, 1740, 1636 cm^{-1}. UV ($CHCl_3$): λ_{max} nm ($\in$ M^{-1} cm^{-1}) 269 (6270). ^1H NMR (300 MHz, $CDCl_3$): δ 1.27 (s, 9H), 1.32 (t, $J=7.2$ Hz, 3H), 3.37 (1/2 ABq, $J=16.8$ Hz, 2H), 3.82 (1/2 ABq, $J=16.8$ Hz, 2H), 4.29 (q, $J=6.9$ Hz, 2H), 6.36 (s, 1H), 7.16–7.31 (m, 10H), 7.57 (s, 2H). ^{13}C NMR (75.43 MHz, $CDCl_3$): δ 14.0, 27.3, 38.4, 43.7, 61.5, 65.3, 126.2, 126.4, 127.7, 129.8, 139.3, 139.6, 141.5, 173.2, 178.4. Mass: *m/e* 441 (M^+). Anal: for $C_{29}H_{31}NO_3$; calcd 78.88 (C), 7.07 (H), 3.17 (N); found 78.68 (C), 7.08 (H), 3.22 (N).

Ethyl 2-acetamido-5-phenylindan-2-carboxylate (17). To a solution of diyne building block **6** (25 mg, 0.11 mmol) in *n*-octane (2 mL) were slowly added (syringe pump) a mixture of phenylacetylene (23 mg, 0.22 mmol), $CpCo(CO)_2$ (3 μL) in dry *n*-octane under a stream of N_2 over a period of 7 h. Distillation of all volatiles under reduced pressure to leave a dark oil which was purified by silica gel column chromatography using ethyl acetate–hexane (1:4) as an eluent to furnish compound **17** as a light yellow sticky solid (10 mg, 27%). Mp. 145–147 °C; IR (KBr): ν 3243, 1745, 1651 cm^{-1}. UV ($CHCl_3$): λ_{max} nm ($\in$ M^{-1} cm^{-1}) 267 (5960). ^1H NMR (300 MHz, $CDCl_3$): δ 1.26 (t, $J=7.1$ Hz, 3H), 1.96 (s,

3H), 3.29 (d, 1/2 ABq, $J = 16.7$, 6.0 Hz, 2H), 3.68 (d, 1/2 ABq, $J = 16.7$, 6.7 Hz, 2H), 4.24 (q, $J = 7.1$ Hz, 2H), 6.03 (s, 1H), 7.28 (s, 1H), 7.33–7.48 (m, 5H), 7.56 (m, 2H). HRMS: for $C_{20}H_{21}NO_3$; calcd 323.1515; found 323.1521.

Ethyl 2-trimethylacetamido-5-phenylindan-2-carboxylate (18). A solution of diyne **7** (50 mg, 0.19 mmol), phenyl acetylene (30 mg, 0.2 mmol) in *n*-octane (2 mL) containing $CpCo(CO)_2$ (2 μL) were added (syringe pump) to a refluxing (oil bath 140 °C) solution of *n*-octane (1.5 mL) containing $CpCo(CO)_2$ (2 μL) under N_2 over a period of 8 h. Then, the reaction mixture was stirred at 140 °C for an additional 1 h. The flask was cooled and the solvent was distilled out under vacuum. The remaining dark residue was purified by silica gel column chromatography using ethyl acetate–hexane (1:4) mixture as an eluent to obtain compound **18** as a white crystalline solid (26 mg, 38%). Mp 116–118 °C. IR (KBr): ν 3326, 1750, 1629 cm^{-1}. UV ($CHCl_3$): λ_{max} nm ($\in M^{-1} cm^{-1}$) 270 (6560). ^1H NMR (300 MHz, $CDCl_3$): δ 1.18 (s, 9H), 1.24 (t, $J = 6.9$ Hz, 3H), 3.24 (d, 1/2 ABq, $J = 16.8$, 6.0 Hz, 2H), 3.71 (d, 1/2 ABq, $J = 16.8$, 7.2 Hz, 2H), 4.21 (q, $J = 6.9$ Hz, 2H), 6.22 (s, 1H), 7.26 (s, 1H), 7.30–7.45 (m, 5H), 7.56 (d, $J = 1.5$ Hz, 2H). ^{13}C NMR (75.43 MHz, $CDCl_3$): δ 14.1, 27.3, 38.5, 43.5, 43.8, 61.5, 65.3, 123.2, 124.7, 126.1, 127.1, 128.7, 139.1, 140.3, 140.6, 141.2, 173.2, 178.4. HRMS: for $C_{23}H_{27}NO_3$; calcd 365.1990; found 365.1974.

Ethyl 2-acetamido-5,6-dicarbomethoxyindan-2-carboxylate (19). A solution of diyne **6** (25 mg, 0.11 mmol), dimethyl acetylenedicarboxylate (32 mg, 0.22 mmol) in dry toluene (2 mL) containing $CpCo(CO)_2$ (2 μL) were added (syringe pump) to a refluxing solution of dry toluene (1.5 mL) containing $CpCo(CO)_2$ (2 μL) under N_2 over a period of 10 h. Then, the reaction mixture was stirred at 140 °C for an additional 1 h. The flask was cooled and the solvent was distilled out under vacuum. The remaining dark residue was purified by silica gel column chromatography using ethyl acetate–hexane (1:4) mixture as an eluent to obtain compound **19** as a white crystalline solid (11 mg, 27%). Mp 145–146 °C. IR (KBr): ν 3326, 1750, 1629 cm^{-1}. UV ($CHCl_3$): λ_{max} nm ($\in M^{-1} cm^{-1}$) 248 (2096). ^1H NMR (300 MHz, $CDCl_3$): δ 1.23 (t, $J = 7.1$ Hz, 3H), 1.96 (s, 3H), 3.36 (1/2 ABq, $J = 17.1$ Hz, 2H), 3.62 (1/2 ABq, $J = 17.1$ Hz, 2H), 3.89 (s, 6H), 4.21 (q, $J = 7.1$ Hz, 2H), 6.14 (s, 1H), 7.54 (s, 2H). ^{13}C NMR (75.43 MHz, $CDCl_3$): δ 14.0, 23.2, 43.1, 52.6, 62.0, 65.7, 125.0, 131.2, 143.8, 168.1, 170.1, 172.5. Mass: *m/e* 363 (M^+). Anal. for $C_{18}H_{21}NO_7$; calcd 59.49 (C), 5.82 (H), 3.85 (N); found 59.33 (C), 5.64 (H), 3.73 (N).

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References and Notes

1. Cativala, C.; Diaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **2000**, *11*, 645. Gibson, S. E.; Guillo, N.; Tozer, M. J. *Tetrahedron* **1999**, *55*, 585. Giannis, A.; Kolter, T. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1244. Duthaler, R. O. *Tetrahedron* **1997**, *50*, 1539. Williams, R. M.; *Synthesis of Optically Active α-Amino Acids*; Pergamon: Oxford, 1989.
2. Balaram, P. *Curr. Opin. Struct. Biol.* **1992**, *2*, 845.
3. Gante, J. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1699. Liskamp, R. M. J. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 305.
4. (a) Kotha, S.; Brahmachary, E. *J. Org. Chem.* **2000**, *65*, 1359. (b) Kotha, S.; Sreenivasachary, N. *J. Chem. Soc., Chem. Comm.* **2000**, 503. (c) Kotha, S.; Brahmachary, E.; Sreenivasachary, N. *Tetrahedron Lett.* **1998**, *39*, 4095. (d) Kotha, S.; Sreenivasachary, N.; Brahmachary, E. *Tetrahedron Lett.* **1998**, *39*, 2805.
5. Hsieh, K.-H.; LaHann, T. R.; Speth, R. C. *J. Med. Chem.* **1989**, *32*, 898. For reviews related to indan chemistry, see: Ganellin, C. R. *Adv. Drug Res.* **1967**, *4*, 163. Hong, B. C.; Sarshar, S. *Org. Prep. Proc. Int.* **1999**, *31*, 1.
6. Torrini, I.; Zecchini, G. P.; Paradisi, M. P.; Lucente, G.; Gavuzzo, E.; Mazza, F.; Pochetti, G.; Spisani, S.; Giuliani, A. L. *Int. J. Peptide Protein Res.* **1991**, *38*, 495.
7. Josien, H.; Lavielle, S.; Brunissen, A.; Saffroy, M.; Torrens, Y.; Beaujouan, J-C.; Glowinski, J.; Chassaing, G. *J. Med. Chem.* **1994**, *37*, 1586.
8. (a) Trigalo, F.; Buisson, D.; Azerad, R. *Tetrahedron Lett.* **1988**, *29*, 6109. (b) Kotha, S.; Kuki, A. *Tetrahedron Lett.* **1992**, *33*, 1565.
9. Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49.
10. Kotha, S.; Brahmachary, E. *Tetrahedron Lett.* **1997**, *38*, 3561.
11. (a) Stork, G.; Leong, A. Y. W.; Touzin, A. M. *J. Org. Chem.* **1976**, *41*, 3491. (b) O'Donnell, M. J.; Polt, R. L. *J. Org. Chem.* **1982**, *47*, 2663.
12. Schollkopf, U. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 339. Schollkopf, U.; Deng, C. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 798.
13. Grigg, R.; Scott, R.; Stevenson, P. *J. Chem. Soc., Perkin Trans 1* **1988**, 1357.
14. Hillard, R. L.III; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1977**, *99*, 4058.