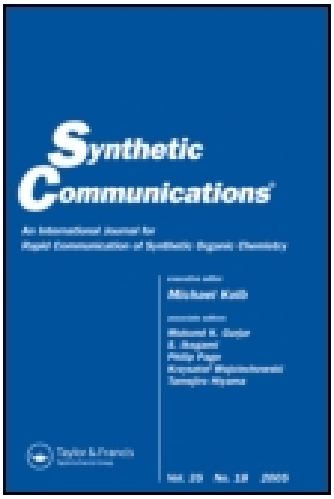

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# Unified Approach to the Asymmetric Synthesis of Higher Homologues of (3-Quinolyl)-alanine

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# UNIFIED APPROACH TO THE ASYMMETRIC SYNTHESIS OF HIGHER HOMOLOGUES OF (3-QUINOLYL)-ALANINE

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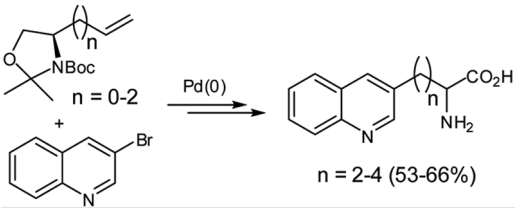
## GRAPHICAL ABSTRACT




**Abstract** *A new protocol based on a palladium-catalyzed Heck reaction of an amino acid–derived vinyl unit with 3-bromoquinoline has been developed to access the title compounds in good yield and optical purity.*

**Keywords** α-Amino acids; Heck reaction; quinoline

## INTRODUCTION

Synthesis of noncoded amino acids has remained an important activity over the decades because of amino acids' known importance in chemistry and biology.[1] A class of such nonproteinogenic amino acids are the heterocycle appended α-amino acids, which are important because of their wide range of chemical and biological applications as components of natural products and peptide nucleic acids, building blocks in therapeutic lead generation, and conformational control elements in the design and synthesis of modified peptides.[2] Thus, synthesis of α-amino acids accommodating a side-chain heterocyclic units such as pyrrole,[3] furan,[4] pyridine,[5] pyrimidine,[6] purine,[7] pyrrazole,[8] thiophene,[9] indole,[10] quinolone,[11] and quinoxaline[12] have been described. Although superb catalytic methods are being continuously developed,[13] conversion of simple coded amino acids into desired targets have remained important. Thus, several amino-acid-based building blocks have emerged.[14] One such type of building block is the α, β-, or γ-vinylic oxazolidines

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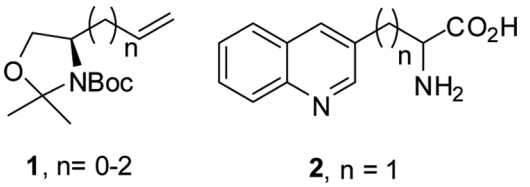


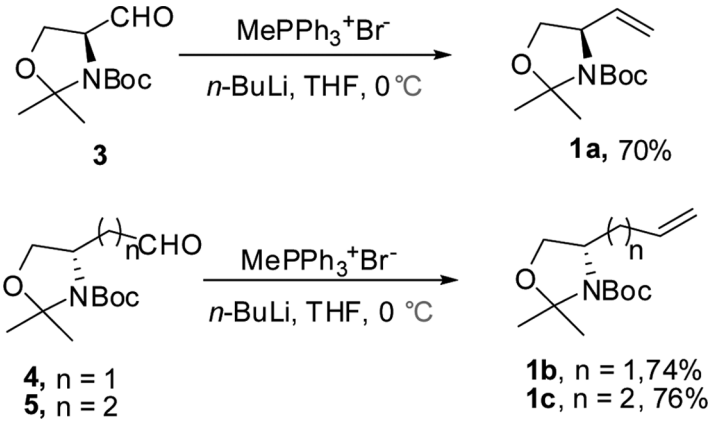

**Figure 1.** Background of the work.

of the general structure **1** (Fig. 1). Heck-type arylation of **1** and derivatives thereof continue to be useful in the synthesis of aryl amino acids.[15] However, its utility for the preparation of heteroaromatic amino acids has remained comparatively less explored.

(3-Quinolyl)-alanine (**2**) has been extensively utilized as a replacement of histidine residue in important peptides for the preparation of somatostatin analogs,[16] gonadotropin-releasing-hormone-receptor antagonists,[17] and gramicidin channel receptor agonists.[18] However, higher homologues of (3-quinolyl)-alanine are less known. Herein, we report synthesis of three homologues of **2** having variation in the chain length (n = 2–4), involving Heck-type arylation of 3-bromoquinoline with the olefins **1** as the key step.

## RESULTS AND DISCUSSION

Our synthesis started with the preparation of the olefins **1a–c** (Scheme 1). Wittig-type methylenation of Garner's aldehyde **3**[19] has been found to be problematic and prone to racemization as well as poor yielding when KH or *n*-BuLi was used as base.[20] However, use of potassium hexamethyldisilazide (KHMDS) as base circumvented both the problems.[21] Other conditions such as use of $Me_3Al/Zn/CH_2I_2$ combination for racemization-free olefination of **1a** are also known.[20a,21] However, we have found that a good yield conversion of **3** to **1a** could simply be achieved if the reaction is carried out at 0 °C instead of −78 °C in the presence of

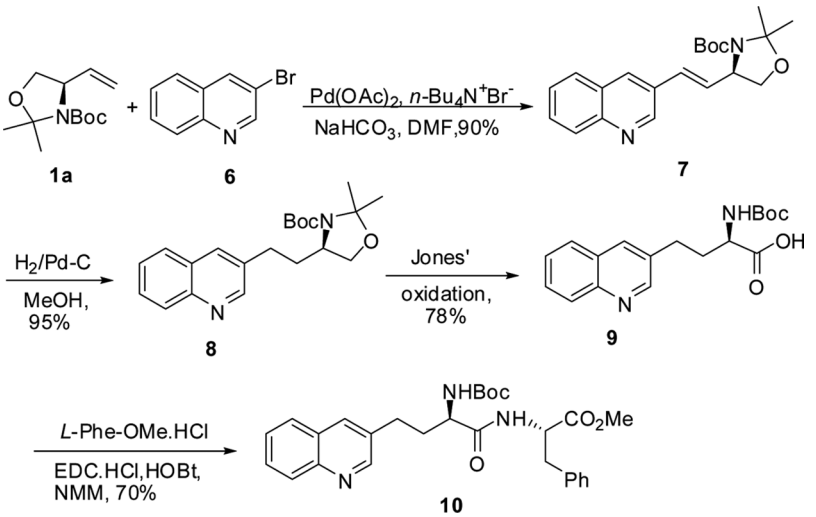



**Scheme 1.** Preparation of starting materials.

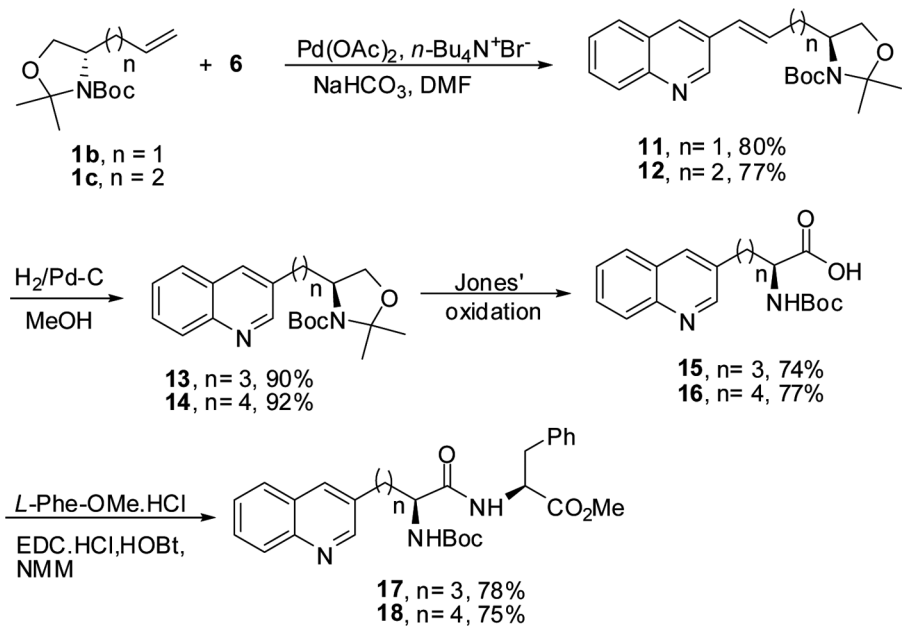
*n*-BuLi as base. Moreover, the optical purity of the product also proved to be unaffected because the product **1a** displayed a specific rotation value, $[\alpha]_D + 17.2$ (*c* 1.20, $CHCl_3$), in close agreement to those reported [$[\alpha]_D + 15.6$ (c 2.0, $CHCl_3$)]; [$[\alpha]_D + 15$ (*c* 2.5, $CHCl_3$)] for optically pure compound.[19,20] The aspartic-acid-derived aldehyde **4**[22,4e] and the glutamic acid-derived aldehyde **5** [23] were similarly methylenated under the developed conditions to yield the corresponding olefins **1b** and **1c** respectively, in good yields.

Having access to the required olefins **1a–c**, we then focused on their projected Heck-type coupling with 3-bromoquinoline. Palladium-catalyzed Mizoroki–Heck olefination[24] is usually more regio- and stereoselective with electron-deficient olefins and often been found to be problematic with nonactivated olefins, with poor regioselectivity and stereoselectivity being major concerns. After some experimentation, we have found that olefination of 3-bromoquinoline (**6**) with olefin **1a** proceeds better under Jeffery's two-phase protocol[25] involving use of $n\text{-}Bu_4N^+Br^-$ as an additive, and the coupled product **7** (Scheme 2) is obtained as the only isolable product in good yield.

The *E*-geometry of the newly formed double bond was easily secured from its $^1$H NMR spectrum, a 16-Hz coupling between the olefinic protons being diagnostic. Moreover, characteristic rotamerism[26] of the oxazolidine moiety was reflected in doubling of some signals in its $^{13}$C NMR spectrum. Rerecording the $^{13}$C NMR spectrum at higher temperature removed this commonly observed complexity and a single set of signals was observed. We also observed signal broadening in the $^1$H NMR spectrum recorded in $CDCl_3$. A better resolution of the peaks was observed when the spectrum was recorded in DMSO-$d_6$[see Supporting Information]. Catalytic hydrogenation of the compound **7** led to the corresponding saturated compound **8** and a one-pot deprotection of the oxazolidine unit in the latter followed by in situ oxidation of the resulting primary alcohol using Jones's oxidation reaction proceeded smoothly to provide the α-amino acid derivative **9** in an overall yield of 66% over three steps. Compound **9** was then subjected to peptide bond formation with *L*-Phe-OMe.HCl




**Scheme 2.** Preparation of (3-quinolyl)-homoalanine.




**Scheme 3.** Synthesis of higher homologues of (3-quinolyl)-alanine.

and the resulting dipeptide **10** was analyzed by NMR and high-performance liquid chromatography (HPLC) for its stereochemical purity. Pleasingly, compound **10** was found to be homogeneous, thereby indicating little racemization during the sequence of reactions depicted in Scheme 2.

We then focused on the projected arylation of the olefins **1b** and **1c**. Separate treatment of each of these olefins with 3-bromoquinoline under the developed conditions furnished the corresponding coupled products **11** and **12** (Scheme 3) in good yields in a regio- and stereoselective manner. Saturation of the olefinic unit in each of these compounds proceeded uneventfully to provide the compounds **13** and **14** respectively. Repetition of the one-pot deprotection–oxidation sequence on these compounds as detailed for the conversion **8** → **9** then led to the desired α-amino acid derivatives **15** and **16** in good overall yields of 53–55% over three steps. Each of these α-amino acids were then converted to the corresponding dipeptides **17** and **18** under conventional conditions. The latter were also found to be optically homogeneous.

In short, we have developed a three-step synthetic protocol for the access of three homologues of the important α-amino acid (3-quinolyl)-alanine (*viz.* compounds **9**, **15**, and **16**) in good overall yields and optical purity. Easy access to the starting olefins **1a–c** has also been developed. The synthetic protocols may allow access to related compounds of interest and hence may find application.

## EXPERIMENTAL

Melting points were recorded in open capillaries and are uncorrected. Infrared (IR) spectra were recorded on a Perkin-Elmer Spectrum-1 spectrophotometer. Proton and carbon NMR spectra were recorded on a Bruker Avance-400 spectrometer

(purchased through DST-FIST Grant). Chemical shifts are recorded relative to residual solvent peak. Data for rotamers are given within parentheses. Mass spectra were recorded on a Jeol-JMS 600 instrument from I.I.C.B., Kolkata or IACS, Kolkata. Petroleum ether refers to the fraction boiling in the range 60–80 °C. Silica gel (60–120, 200–230 mesh) for column chromatography was purchased from Spectrochem, India.

### General Procedure for the Synthesis of the Olefins 1a–c

**(*R*)-*tert*-Butyl 2,2-dimethyl-4-vinyl-oxazolidine-3-carboxylate (1a).** n-BuLi (2 M in hexane, 1.7 mL, 3.45 mmol, 1.5 eqv.) was added to a stirred suspension of methyltriphenylphosphonium bromide (1.23 g, 3.45 mmol, 1.5 eqv.) in dry THF (10 mL) under argon at 0 °C dropwise over 5 min, and the resulting solution was allowed to stir for 20 min at 0 °C. A solution of the aldehyde **3** (528 mg, 2.30 mmol) in THF (5 mL) was then added dropwise over 5 min with stirring at the same temperature. After 20 min, the solution was allowed to come to room temperature and was stirred for another 4 h. The reaction mixture was quenched by addition of aqueous $NH_4Cl$ solution (3 mL) and then extracted with ethyl acetate ($2 \times 50$ mL). The combined organic extract was washed successively with $H_2O$ (40 mL) and brine solution (40 mL) and then dried over $MgSO_4$. It was then filtered, and the filtrate was concentrated under reduced pressure to leave the crude product, which was purified by column chromatography over silica gel (EtOAc–PE, 1:19) to give the olefin **1a** as a colorless liquid; yield: 366 mg (70%); $[\alpha]_D + 17.2$ (*c* 1.20, $CHCl_3$); Lit.[21a] [$[\alpha]_D +$ 15.6 (*c* 2.0, $CHCl_3$)]; lit.[20a] [$[\alpha]_D + 15$ (*c* 2.5, $CHCl_3$)].

IR ($CHCl_3$): 2981, 1699, 1479, 1456, 1385, 1366, 1254 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 400 MHz): δ 5.76 (s, 1H), 5.20–5.09 (m, 2H), 4.35–4.22 (br m, 1H), 3.99 (td, $J = 6.4$, 2.8 Hz, 1H), 3.70 (dd, $J = 9.2$, 2.4 Hz, 1H), 1.56 (s, 3H), 1.46–1.38 (m, 12H). $^1H$ NMR (DMSO-$d_6$, 400 MHz): δ 5.78 (ddd, $J = 6.8$, 10.0, 16.8 Hz, 1H), 5.20–5.09 (m, 2H), 4.35–4.22 (br m, 1H), 4.00 (dd, $J = 6.4$, 8.8 Hz, 1H), 3.70 (dd, $J = 9.2$, 2.0 Hz, 1H), 1.56 (s, 3H), 1.46–1.38 (two singlets, 12H). $^{13}C$ NMR ($CDCl_3$, 100 MHz): δ 151.9, 137.3, 115.7, 93.9, 79.5, 68.1, 59.6, 28.3, 26.5, 23.6. MS (TOF, ES+): $m/z$ (%) = 250 (100) [M +Na].

### General Procedure for Heck-Type Olefination with 1a–c: (*R,E*)-*tert*-Butyl 2,2-Dimethyl-4-(2-(quinolin-3-yl)vinyl)oxazolidine-3-carboxylate (7)

A solution of the olefin **1a** (170 mg, 0.75 mmol), 3-bromoquinoline (171 mg, 0.82 mmol, 1.1 eqv.), palladium acetate (8 mg, 0.04 mmol, 5 mol %), $NaHCO_3$ (94 mg, 1.12 mmol, 1.5 eqv.), and $n$-$Bu_4N^+Br^-$ (723 mg, 2.24 mmol, 3 eqv.) in DMF (5 mL) was taken in a sealed tube and stirred at 90 °C for 18 h. The reaction mixture was allowed to come to rt and then diluted with $H_2O$ (60 mL). It was then extracted with EtOAc ($2 \times 50$ mL). The combined organic extract was washed successively with $H_2O$ ($2 \times 50$ mL) and brine (50 mL), and then dried ($MgSO_4$). It was filtered and then concentrated in vacuo to leave a residue, which was purified over silica gel (EtOAc–PE, 3:7) to provide the coupled product **7** as a colorless solid (238 mg, 90%). Mp 120–121 °C. $[\alpha]_D - 98.7$ (*c* 0.42, $CHCl_3$). IR ($CHCl_3$): 2991, 2869, 1680,

1494, 1390, 1361, 1255 $cm^{-1}$.$^1$H NMR (400 MHz, $CDCl_3$): δ 8.98 (s, 1H), 8.08–8.05 (m, 2H), 7.78 (s, 1H), 7.66 (s, 1H), 7.52 (s, 1H), 6.75–6.61 (br m, 1H), 6.41 (s, 1H), 4.64–4.92 (br m, 1H), 4.16 (dd, $J = 8.8$, 6.4 Hz, 1H), 3.89 (dd, $J = 8.8$, 1.2 Hz, 1H), 1.71 (s, 3H), 1.57 (1.49) (s, 3H), 1.42 (s, 9H).$^1$H NMR (400 MHz, DMSO-$d_6$): δ 9.06 (s, 1H), 8.38 (s, 1H), 8.00–7.95 (m, 2H), 7.72 (t, $J = 7.6$ Hz, 1H), 7.60 (dd, $J = 8.4$, 6.8 Hz, 1H), 6.66 (d, $J = 16$ Hz, 1H), 6.55 (dd, $J = 7.2$, 15.6 Hz, 1H), 4.56–4.48 (br m, 1H), 4.13 (dd, $J = 8.8$, 6.4 Hz, 1H), 3.84 (dd, $J = 8.8$, 1.2 Hz, 1H), 1.48–1.35 (overlapping singlets, 15H).$^{13}$C NMR (100 MHz, $CDCl_3$): δ 151.9, 149.2, 147.5, 132.7, 132.4, 131.2, 129.5, 129.2, 128.3, 128.0, 127.8, 127.0, 94.3 (93.8), 80.5 (79.9), 68.2, 59.5, 28.5, 27.6 (26.7), 24.7 (23.7). $^{13}$C NMR (100 MHz, DMSO-$d_6$, 70 °C): δ 152.0, 149.8, 147.6, 132.7, 132.5, 130.2, 129.8, 129.3, 128.7, 128.3, 128.1, 127.5, 94.0, 79.7, 68.3, 59.6, 28.7, 26.4, 23.2. Anal. Calcd. for $C_{21}H_{26}N_2O_3$: C, 71.16; H, 7.39; N, 7.90; found: C, 71.31, H, 7.46; N, 7.85. MS (TOF, ES+): $m/z$ (%) = 355 (100) [M +H].

### General Procedure for Hydrogenation of the Coupled Olefins: (*R*)-*tert*-Butyl 2,2-Dimethyl-4-(2-(quinolin-3-yl)ethyl)oxazolidine-3-carboxylate (8)

Pd–C (10 mol%; 14 mg) was added to a solution of the coupled product **7** (200 mg, 0.56 mmol) in MeOH (6 mL) at rt and the heterogeneous mixture was vigorously stirred under hydrogen atmosphere for 2 h. It was then filtered through celite, and the filter cake was thoroughly washed with MeOH (10 mL). The combined filtrate was concentrated in vacuo to leave a crude mass, which was purified by chromatography over silica gel (EtOAc–PE, 3:7) to furnish the product **8** as a colorless solid (189 mg, 95%). Mp 80–81 °C. $[\alpha]_D - 41.8$ (*c* 0.61, $CHCl_3$). IR ($CHCl_3$): 2979, 2870, 1676, 1496, 1392, 1251 $cm^{-1}$.$^1$H NMR (400 MHz, $CDCl_3$): δ 8.78 (s, 1H), 8.08 (d, $J = 8.4$ Hz, 1H), 7.98–7.92 (br m, 1H), 7.77 (d, $J = 8.0$ Hz, 1H), 7.66 (s, 1H), 7.53 (s, 1H), 4.06–3.86 (m, 3H), 2.90–2.70 (m, 2H), 2.30–1.97 (m, 2H), 1.66 (1.63) (s, 3H), 1.50 (s, 9H), 1.41 (s, 3H).$^{13}$C NMR (100 MHz, $CDCl_3$): δ 151.9, 151.7, 146.9, 134.1, 129.2, 128.6, 128.1, 127.3, 126.6, 93.4, 80.2 (79.7), 66.8, 57.4 (56.8), 35.1 (34.4), 29.9, 28.5, 27.6 (26.8), 24.5 (23.2). Anal. calcd. for $C_{21}H_{28}N_2O_3$: C, 70.76; H, 7.92; N, 7.86. Found: C, 70.91, H, 7.84; N, 7.95. MS (TOF, ES+): $m/z$ (%) = 357(100) [M +H].

### General Procedure for Jones's Oxidation: (*R*)-2-(*tert*-Butoxycarbonylamino)-4-(quinolin-3-yl)butanoic Acid (9)

Jones's reagent (2.67 M, 366 μL, 0.66 mmol) was added to a solution of the appropriate oxazolidine derivative **8** (90 mg, 0.25 mmol) in acetone (3 mL) at 0 °C. The reaction mixture was stirred for 5 h and then quenched by addition of 2-propanol (2.5 mL). The resulting reaction mixture was stirred for 10 min and then neutralized with saturated aqueous $NaHCO_3$ solution (pH = 4–5). It was then extracted with ethyl acetate (2 × 25 mL), and the combined organic extract was washed successively with $H_2O$ (20 mL) and brine solution (15 mL) and then dried over $MgSO_4$. It was then filtered, and the filtrate was concentrated under reduced pressure to leave the crude product, which was purified by column chromatography over silica gel (EtOAc–PE, 7:3) to obtain compound **9** as a colorless solid (64 mg, 78%); Mp 176–178 °C; $[\alpha]_D$– 51.5

($c$ 0.13, $CHCl_3$). IR ($CHCl_3$): 3402, 2976, 2479, 1716, 1584, 1521, 1364, 1282 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): δ 13.28 (s, 1H), 8.84 (s, 1H), 8.14 (s, 1H), 8.01 (d, $J = 8.0$ Hz, 1H), 7.76 (d, $J = 8.0$ Hz, 1H), 7.59 (t, $J = 6.8$ Hz, 1H), 7.50 (t, $J = 7.6$ Hz, 1H), 5.67 (d, $J = 7.2$ Hz, 1H), 4.48 (d, $J = 5.2$ Hz, 1H), 2.98 (d, $J = 6.8$ Hz, 2H), 2.43 (d, $J = 6.4$ Hz, 1H), 2.24 (d, $J = 6.4$ Hz, 1H), 1.47 (s, 9H).$^{13}C$ NMR (100 MHz, $CDCl_3$): δ 175.3, 155.6, 149.8, 143.8, 137.2, 134.6, 129.8, 128.2, 127.5, 127.4, 126.2, 79.7, 53.3, 33.9, 28.7, 28.4. HRMS (TOF, ES+): $m/z$ [$M^+$ +H] calcd. for $C_{18}H_{23}N_2O_4$: 331.1658; found: 331.1651.

### General Procedure for Peptide Coupling: (*S*)-Methyl 2-((*R*)-2-(*tert*-Butoxycarbonylamino)-4-(quinolin-3-yl)butanamido)-3-phenylpropanoate (10)

*N*-Methylmorpholine (75 μL, 0.75 mmol) was added dropwise to a stirred suspension of *L*-Phe-OMe.HCl (50 mg, 0.3 mmol, 1 eqv.) in dry $CH_2Cl_2$ (4 mL) at 0 °C under argon. After 10 min, a solution of the carboxylic acid **9** (100 mg, 0.3 mmol, 1 eqv) in dry $CH_2Cl_2$ (4 mL) was added dropwise and stirred for 10 min. Then N-(3-dimethylaminopropyl)-N′-ethylcarbodiimide hydrochloride (EDC · HCl) (64 mg, 0.34 mmol, 1.1 eqv.) and 1-hydroxybenzotriazole (HOBT) (46 mg, 0.34 mmol, 1.1 eqv.) were added successively in 10-min intervals at the same temperature. The reaction mixture was allowed to come to room temperature and stirred for 18 h. It was then diluted with water (25 mL) and extracted with EtOAc (2 × 25 mL). The combined organic layer was washed successively with $H_2O$ (2 × 20 mL) and brine (15 mL). It was then dried over $Na_2SO_4$ and filtered, and the filtrate was concentrated in vacuo to leave a pale yellow liquid, which was purified by chromatography over silica gel (EtOAc–PE, 1:1) as eluent to give the product **10** as a colorless solid (104 mg, 70%). Mp 124–126 °C. $[\alpha]_D + 36.7$ ($c$ 0.12, $CHCl_3$). IR ($CHCl_3$): 3337, 2991, 2858, 1736, 1681, 1661, 1537, 1522, 1435, 1281 $cm^{-1}$.$^1H$ NMR (400 MHz, $CDCl_3$): δ 8.71 (s, 1H), 8.08 (d, $J = 8.4$ Hz, 1H), 7.87 (s, 1H), 7.75 (d, $J = 8.0$ Hz, 1H), 7.67 (dt, $J = 7.2$, 1.2 Hz, 1H), 7.53 (t, $J = 7.6$ Hz, 1H), 7.23 (d, $J = 7.6$ Hz, 2H), 7.19 (d, $J = 6.8$ Hz, 1H), 7.11 (d, $J = 7.6$ Hz, 2H), 6.67 (d, $J = 7.2$ Hz, 1H), 5.13 (d, $J = 7.6$ Hz, 1H), 4.89 (dd, $J = 13.2$, 6.8 Hz, 1H), 4.20 (d, $J = 4.4$ Hz, 1H), 3.73 (s, 3H), 3.18 (dd, $J = 14.0$, 5.6 Hz, 1H), 3.05 (dd, $J = 14.0$, 6.8 Hz, 1H), 2.74 (t, $J = 7.6$ Hz, 1H), 2.20–2.15 (m, 1H), 1.94–1.87 (m, 2H), 1.43 (s, 9H).$^{13}C$ NMR (100 MHz, $CDCl_3$): δ 171.9, 171.5, 155.7, 151.6, 146.7, 135.8, 134.5, 133.7, 129.2, 129.0, 128.9, 128.6, 128.0, 127.4, 127.2, 126.7, 80.2, 53.8, 53.1, 52.4, 37.8, 33.8, 28.9, 28.3. Anal. calcd for $C_{28}H_{33}N_3O_5$: C, 68.41; H, 6.77; N, 8.55. Found: C, 68.64, H, 6.67; N, 8.61.MS (TOF, ES+): $m/z$ (%) = 492 (100) [M +H].

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This article is respectfully dedicated to the late Professor Alexander McKillop in admiration of his immense contribution to organic chemistry.

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## SUPPLEMENTARY CONTENT

Full experimental detail and $^{1}H$ and $^{13}C$ NMR spectra are included in the Supplementary Content. This material can be can be accessed on the publisher's website.

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