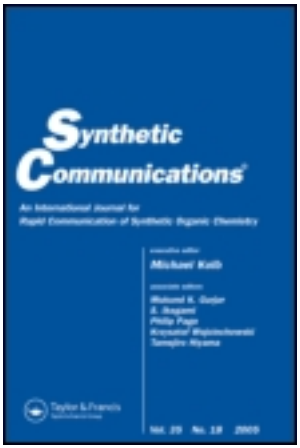


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Pd(0)-Catalyzed Heck-Type Arylation of Didehydropeptides

Shital K. Chattopadhyay [a], Benoy K. Pal [a] & Suman Biswas [a]

[a] Department of Chemistry, University of Kalyani, Kalyani, West Bengal, India

Version of record first published: 16 Aug 2006.

To cite this article: Shital K. Chattopadhyay, Benoy K. Pal & Suman Biswas (2005): Pd(0)-Catalyzed Heck-Type Arylation of Didehydropeptides, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 35:9, 1167-1175

To link to this article: http://dx.doi.org/10.1081/SCC-200054757

Synthetic Communications®, 35: 1167–1175, 2005

ISSN 0039-7911 print/1532-2432 online
DOI: 10.1081/SCC-200054757

Pd(0)-Catalyzed Heck-Type Arylation of Didehydropeptides

Shital K. Chattopadhyay, Benoy K. Pal, and Suman Biswas
Department of Chemistry, University of Kalyani, Kalyani,
West Bengal, India

Abstract: Pd(0)-catalyzed Heck-type arylation of several didehydropeptides has been studied and the process has been found to be a viable method for the synthesis of the corresponding arylated products stereoselectively but in moderate yields.

Keywords: Heck reaction, Pd(0)-catalysis, didehydropeptides, stereoselectivity

INTRODUCTION

Dehydroalanine residues are known[1] to introduce both side-chain and backbone conformational constraints within peptides. Their importance [2] as precursors for various modified peptides are also well documented. For this and other reasons, the synthesis[3] and synthetic modification[4] of dehydropeptides has proved to be an interesting area of research. Although Mizoroki–Heck type inter-[5–7] and intra-molecular[8] arylation of didehydroalanine derivatives has been extensively studied, to the best of our knowledge, a similar type of arylation of dehydropeptides has been less documented.[9] Herein, we report the results of a systematic investigation on the palladium(0)-catalyzed arylation of dehydropeptides.

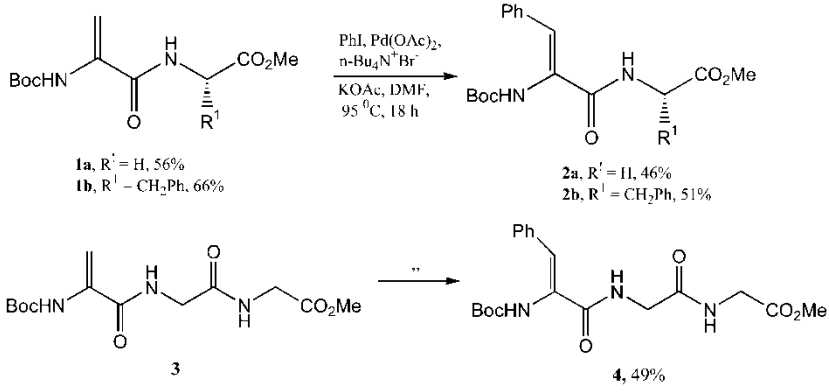
Received in India December 20, 2004
Address correspondence to Shital K. Chattopadhyay, Department of Chemistry, University of Kalyani, Kalyani, 741235, West Bengal, India. E-mail: skchatto@yahoo.com

RESULTS AND DISCUSSION

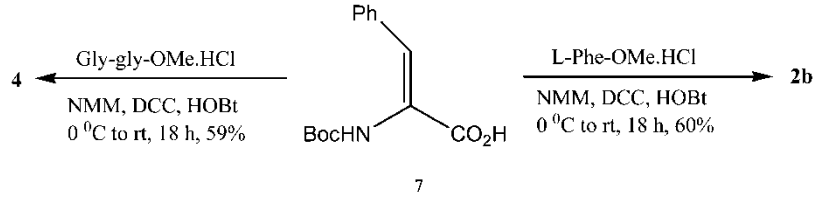
The N-terminal dehydrodipeptides **1a, b** were prepared following literature procedure [10,11] as outlined in Scheme 1. Arylation of the dehydropeptides **1a, b** was then examined under a range of conditions.[12] The reaction proceeded best under Jeffery's two-phase protocol [13] using potassium acetate as base. The arylated products **2a, b** were obtained in geometrically pure form but in moderate yield. The N-terminal dehydrotripeptide **3** (prepared by condensation of Gly-Gly-OMe.HCl with **1**) also underwent arylation reaction to provide diastereomerically pure **4**.

Z-configuration[14] of **2b** and **4** were established by their alternate syntheses. Thus, Pd(0)-catalyzed arylation of methyl 2-(*tert*-butoxycarbonylamino)acrylate (**5**) with iodobenzene under reported[15] conditions provided the cinnamate **6** of known configuration (Scheme 2). Hydrolysis of the latter followed by coupling of the resulting acid **7** with L-phenylalanine methyl ester hydrochloride (L-Phe-OMe.HCl) or glycylglycine methyl ester hydrochloride (Gly-Gly-OMe.HCl) provided products that were identical in all respects with **2b** and **4**, respectively.

We next turned our attention on the arylation of C-terminal dehydropeptides. Starting from N-Boc-Phe-Ser-OMe (**8**), the C-terminal dehydrodipeptide **9** was prepared by a two-step, one-pot protocol involving mesylation and elimination sequence (Scheme 3). It was pleasing to observe that the dehydrodipeptide **9** underwent smooth arylation with iodobenzene to provide the arylated product **10**. Assignment of *Z*-configurtion of **10**. was based[16] on the $^3J_{CH}$-coupling contant of 5.2 Hz between the vinyl proton and ester carbonyl carbon. Selective decoupling after exchange with D_2O allowed unambiguous determination.



Scheme 1.



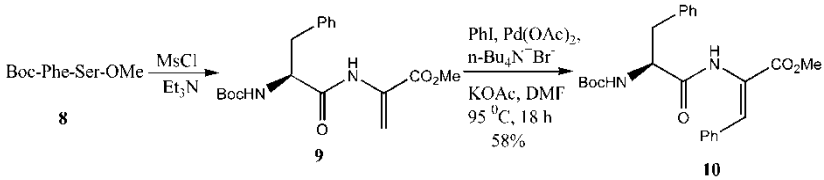
Scheme 2.

Similarly, the tri-peptide olefin N-Boc-Phe-Phe-Δ.-Ala-OMe (**11**) was prepared from the dipeptide **9** (Scheme 4). The tri-peptide olefin **11**, upon coupling with methyl 4-iodobenzoate, provided the diastereomerically pure arylated product **12**. Assignment of the configuration of the newly formed double bond in **12** proved to be difficult in view of the fact that the required signals were not sufficiently separated in the ^{13}C-NMR. We have tentatively assigned Z-configuration to it based on the trend we have observed.

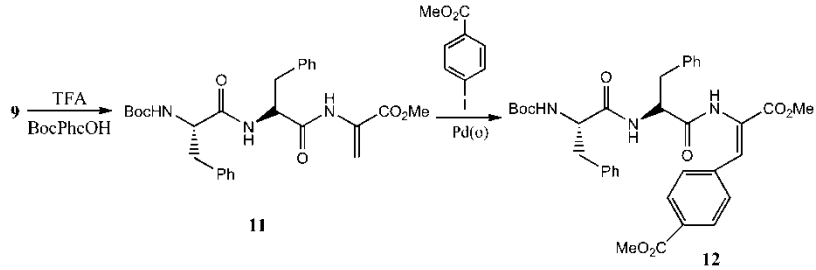
In short, we have demonstrated that Pd(0)-catalyzed Mizoroki–Heck-type arylation of both N-terminal and C-terminal dehydropeptides stereoselectively leads to the corresponding thermodynamically more stable Z-olefins. The process appears to be racemization-free and therefore may find application in the synthesis of modified peptides.

EXPERIMENTAL

Melting points were determined in a sulphuric acid bath and are uncorrected. IR spectra were recorded on a Perkin Elmer 1330 apparatus purchased in a DST-FIST grant. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker 300 MHz instrument at the Indian Institute of Chemical Biology, Kolkata. Mass spectra and elemental analyses were obtained as a paid service from CDRI, Lucknow and I. I. C. B., Kolkata. Silica gel (60–120 mesh) was obtained from Spectrochem, India. Peteroleum ether refers to the fraction boiling in the range 60–80°C.



Scheme 3.



Scheme 4.

General Procedure for the Preparation of N-Terminal Dehydropeptides

4-Methylmorpholine (270 mg, 2.67 mmol) was added dropwise to a stirred solution of appropriate amino acid methyl ester hydrochloride (2.67 mmol) in dry dichloromethane (3 ml) at 0 °C under nitrogen and the mixture was stirred for 15 min. Then, a solution of 2-(*tert*-butoxycarbonylamino)acrylic acid (500 mg, 2.67 mmol) in dry dichloromethane (1.5 ml) and solid 1-hydroxybenzotriazole (361 mg, 2.67 mmol) were added sequentially. After stirring for another 15 min, dicyclohexyl carbodiimide (DCC) (579 mg, 2.8 mmol) was added in one portion and the resulting mixture was stirred for 1 h. It was then allowed to come to room temperature and stirred for 18 h. The precipitated urea was filtered off and the filtrate was concentrated under reduced pressure. It was then diluted with ethyl acetate (25 ml) and washed sequentially with saturated sodium bicarbonate solutuion (2×20 ml), HCl (2%, 1×20 ml), and water (20 ml) and then dried (Na_2SO_4). It was then filtered and the filtrate was concentrated under reduced pressure to leave the crude product, which was purified by chromatography using an appropriate eluent.

Methyl 2-{[2-({2-[*tert*-butoxycarbonyl)amino]acryloyl)amino}acetyl] amino}acetate (3): Eluted with a mixture of 20% ethyl acetate in petroleum ether and the product was obtained as a colorless viscous liquid. Yield: 56%. IR (neat, cm^{-1}): 3391, 2980, 1729, 1666, 1629, 1439, 1394, 1245, 1109. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.41 (1H, br s), 7.07 (1H, br s), 6.85 (1H, br s), 6.08 (1H, s), 5.16 (1H, s), 4.09 (2H, d, J = 5.6 Hz), 3.79 (3H, s), 3.77 (2 H, d, J = 5.8 Hz), 1.46 (9H, s). Anal. found: C, 49.68%; H, 6.94%; N, 13.11%; $C_{13}H_{21}N_3O_6$ requires C, 49.52%: H, 6.71%; N, 13.33%.

(*S*)-Methyl 2-((2S)-2-[(tert-butoxycarbonyl)-3-phenylpropanamido)-3-hydroxy-propanoate (8): 4-Methylmorpholine (0.2 ml, 1.84 mmol) was added dropwise to a stirred solution of L-Ser-OMe.HCl (286 mg, 1.84 mmol) in dry dichloromethane (3 ml) at 0 °C under nitrogen. Then,

Boc-Phe-OH (487 mg, 1.84 mmol), HOBt (284 mg), and DCC (398 mg, 1.92 mmol) were sequentially added and stirring continued for 1.5 h. It was then allowed to come to room temperature and stirred for 6 h. The precipitated urea was filtered and the filtrate was diluted with ethyl acetate (30 ml). The organic extract was washed sequentially with saturated $NaHCO_3$ solution (2×20 ml), HCl (2%, 2×20 ml), water (2×20 ml), and brine (20 ml). It was then dried (Na_2SO_4) and filtered, and the filtrate was concentrated under reduced pressure to leave the crude product as a pale yellow viscous liquid, which was purified by chromatography (SiO_2) (petroleum ether–ethyl acetate 3:2) to give the product as a colorless viscous liquid. Yield: 552 mg (82 %). $[\alpha]_D$ +5.0 (c, 0.09 in MeOH). IR (neat, cm^{-1}): 3344, 3291, 1740, 1689, 1647, 1521, 1367, 1242, 1168. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.27–7.16 (6H, m), 5.35 (1H, d, J = 6.9 Hz), 4.64–4.61 (1H, m), 4.43 (1H, d, J = 5.8 Hz), 3.90 (2H, s), 3.74 (3H, s), 3.20 (1H, br s), 3.14 (1H, dd, J = 13.6, 5.3 Hz), 3.02–2.95 (1H, m), 1.37 (9H, s). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 171.9, 170.6, 155.8, 136.4, 129.3, 128.4, 126.8, 80.3, 62.5, 55.7, 54.7, 52.6, 38.3, 28.1. Anal. found: C, 59.33%; H, 7.31%; N, 7.42%; $C_{18}H_{26}N_2O_6$ requires C, 59.00%: H, 7.15%; N, 7.65%.

Methyl 2-({(2S)-2-[(tert-butoxycarbonyl)amino]-3-phenylpropanoyl} -amino)-acrylate (9): Methanesulfonyl chloride (940 mg, 1.96 mmol) was added in one portion to a stirred solution of Boc-Phe-Ser-OMe (**8**) (240 mg, 0.66 mmol) in dry dichloromethane (5 ml) at 0°C under nitrogen. Then, a solution of triethylamine (198 mg, 1.96 mmol) in dry dichloromethane (3 ml) was added dropwise over 10 min and the resulting solution was allowed to come to room temperature over 3 h. It was then diluted with dichloromethane (25 ml) and washed sequentially with HCl (5%, 2×20 ml), water (2×20 ml), and brine (20 ml). The organic phase was dried (Na_2SO_4) and filtered, and the filtrate was concentrated under reduced presuure to leave the crude product as a pale yellow viscous liquid, which was purified by chromatography (SiO_2) (petroleum ether–ethyl acetate 5:1) to give the product as a colorless viscous liquid. Yield: 180 mg (78%). $[\alpha]_D$ − 6.3 (c, 0.19 in MeOH). IR (neat, cm^{-1}): 3390, 3355, 2983, 1720, 1699, 1508, 1440, 1329, 1166. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.15 (1H, br s), 7.31–7.19 (5H, m), 6.61 (1H, s), 5.90 (1H, s), 5.02–4.96 (1H, m), 4.41 (1H, br s), 3.79 (3H, s), 3.17–3.10 (2H, m), 1.41 (9H, s). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 170.2, 163.9, 155.3, 136.2, 130.5, 129.1, 128.7, 127.0, 109.3, 80.4, 56.4, 52.8, 38.1, 28.1. Anal. found: C, 62.24%; H, 7.13%; N, 8.21%; $C_{18}H_{24}N_2O_5$ requires C, 62.05%; H, 6.94% N, 8.04%.

Methyl 2-((S)-2-((S)-2-(tert-butoxycarbonyl)-3-phenylpropanamido)-3-phenylpropanamido) acrylate: Trifluoroacetic acid (0.8 ml) was added in one portion to a stirred solution of the peptide **9** (174 mg, 0.5 mmol) in dry dichloromethane (4 ml) under nitrogen and the resulting solution was stirred for 2 h at room temperature. It was then concentrated in vacuo to leave the crude product as a foam, which was used as such in the next step.

4-Methylmorpholine (51 mg, 0.5 mmol), 1-hydroxybenzotriazole (68 mg, 0.5 mmol), and Boc-Phe-OH (132 mg, 0.52 mmol) were added sequentially to a solution of the amine salt in dichloromethane (2 ml) at 0 °C under nitrogen and the resulting mixture was stirred at the same temperature for 15 min. Solid DCC (110 mg, 0.55 mmol) was added in one portion and the mixture was stirred for 1 h. It was then allowed to come to room temperature and stirred for 18 h. It was then filtered to remove the precipitated urea and the filtrate was diluted with ethyl acetate (25 ml). The organic extract was washed sequentially with saturated sodium bicarbonate (2 × 25 ml), HCl (2%, 20 ml), water (20 ml) and brine (20 ml), and then dried (Na_2SO_4). It was then filtered and the filtrate was concentrated in vacuo to leave the crude product as a viscous liquid, which was purified by chromatography over silica gel using a mixture of petroleum ether–ethyl acetate (3:2) as eluent. Yield: 186 mg (76%). $[\alpha]_D$+19 (c 0.29 in $CHCl_3$). IR (neat, cm^{-1}): 3399, 3339, 1721, 1673, 1526, 1441, 1368, 1318, 1227, 1251. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.98 (1H, brs), 7.45–7.38 (10H, m), 6.51 (2H, br s, olefinic + NH), 5.88 (1H, s), 4.93 (1H, br s), 4.69–4.62 (1H, m), 4.35–4.33 (1H, m), 3.79 (3H, s), 3.02 (4H, d, J = 6.5 Hz), 1.38 (9H, s). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 171.5, 169.3, 163.7, 155.3, 136.4, 135.9, 130.7, 129.2, 129.1, 128.5, 128.4, 126.9, 126.8, 109.8, 80.0, 55.5, 55.0, 52.8, 38.3, 37.9, 28.1. Anal. found: C, 65.67%; H, 6.88%; N, 8.57%; $C_{27}H_{33}N_3O_6$ requires C, 65.44%; H, 6.71%; N, 8.48%.

General Procedure for the Heck-Type Arylation of the Didehydropeptides

To a mixture of appropriate iodobenzene (0.225 mmol), appropriate dehydropeptide (0.34 mmol), n-$Bu_4N^+Br^-$ (73 mg, 0.225 mmol), and KOAc (53 mg, 0.54 mmol) in dry and degassed N,N-DMF (3 ml) in a screw-cap-sealed tube was added $Pd(OAc)_2$ (3 mg, 6 mol%) under argon and the sealed tube was placed in a preheated oil bath at 95°C. The mixture was heated with stirring for 18 h and then allowed to come to room temperature. It was then diluted with water (30 ml) and extracted with ethyl acetate (2 × 30 ml). The organic extract was washed with hydrochloric acid (1 N, 10 ml), water (20 ml), and brine (20 ml). It was then dried (Na_2SO_4) and filtered, and the filtrate was concentrated in vacuo. The residual brownish mass was chromatographed over silica using an appropriate eluent.

Methyl 2-({(*Z*)-2-[(*tert*-butoxycarbonyl)amino]-3-phenyl-2-propanoyl} amino)acetate (2a): Eluted with 30% ethyl acetate in petroleum ether. Yield: 52%. Mp 143°C. IR (KBr, cm^{-1}): 3291, 2979, 2929, 1740, 1708, 1665, 1527, 1368, 1205, 1164. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.40–7.26 (5H, m), 7.15 (1H, s), 6.90 (1H, br s), 6.16 (1H, s), 4.18 (2H, d, J = 5.1 Hz), 3.78 (3H, s), 1.42 (9H, s). ^{13}C-NMR (75 MHz, $CDCl_3$): δ

170.3, 165.7, 153.7, 133.8, 129.3, 128.9, 128.7, 128.4, 128.1, 81.4, 52.3, 41.6, 28.1. Anal. found: C, 61.22%; H, 6.69%; N, 8.49%; $C_{17}H_{22}N_2O_5$ requires C, 61.07%; H, 6.63%; N, 8.38%.

Methyl (2S)-2-({(*Z*)-2-[(*tert*-butoxycarbonyl)amino]-3-phenyl-2-propenoyl}-amino)-3-phenylpropanoate (2b): Eluted with 20% ethyl acetate in petroleum ether. Yield: 61%. Mp 118°C. $[\alpha]_D + 52$ (c 0.14 in $CHCl_3$). IR (KBr, cm^{-1}): 3316, 2913, 1721, 1668, 1512, 1367, 1246, 1163. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.45–7.14 (10H, m), 7.10 (1H, s), 6.80 (1H, d, J = 7.5 Hz), 5.99 (1H, br s), 5.01–4.95 (1H, m), 3.72 (3H, s), 3.20 (2H, d, J = 5.6 Hz), 1.40 (9H, s). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 171.7, 165.0, 153.5, 135.8, 133.7, 129.3, 129.0, 128.9, 128.7, 128.5, 128.2, 127.0, 81.3, 53.6, 52.2, 37.9, 28.0. m/z (FAB): 446 ($M^+ + Na$). Anal. found: C, 68.11%; H, 6.74%; N, 6.48%; $C_{24}H_{28}N_2O_5$ requires C, 67.91%; H, 6.65%; N, 6.60%.

Methyl 2-{[2-({(*Z*)-2-[(*tert*-butoxycarbonyl)amino]-3-phenyl-2-propenoyl}-amino}acetyl]amino}acetate (4): Eluted with 40% ethyl acetate in petroleum ether. Yield: 49%. Mp 142°C. IR (KBr, cm^{-1}): 3323, 2979, 1744, 1665, 1527, 1368, 1248, 1162.^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.41–7.33 (5H, m), 7.27 (1H, br s), 7.10 (1H, br s), 6.90 (1H, br s), 6.37 (1H, s), 4.14 (2H, d, J = 5.9 Hz), 4.04 (2H, d, J = 5.7 Hz), 3.72 (3H, s), 1.44 (9H, s). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 170.1, 169.6, 165.9, 154.2, 133.5, 129.1, 128.9, 82.0, 52.2, 43.3, 41.0, 28.1. m/z (FAB): 414 ($M^+ + Na$). Anal. found: C, 58.56%; H, 6.52%; N, 10.71%; $C_{19}H_{25}N_3O_6$ requires C, 58.30%; H, 6.44%; N, 10.74%.

Methyl (Z)-2-({(*2S*)-2-[(*tert*-butoxycarbonyl)amino]-3-phenylpropanoyl}-amino)-3-phenyl-2-propenoate (10): Eluted with 30% ethyl acetate in petroleum ether. Yield: 58%. Mp 110°C. $[\alpha]_D - 50$ (c 0.27 in $CHCl_3$). IR (KBr, cm^{-1}): 3293, 2928, 2850, 1716, 1675, 1497, 1437, 1267, 1169. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.69 (1H, s), 7.36–7.12 (11H, m), 4.99 (1H, d, J = 6.6 Hz), 4.51–4.49 (1H, m), 3.81 (3H, s), 3.20 (1H, dd, J = 13.9, 7.1 Hz), 3.06 (1H, dd, J = 14.0, 7.3 Hz), 1.39 (9H, s). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 170.2, 165.3, 155.6, 136.4, 133.4, 132.6, 129.7, 129.4, 129.3, 128.6, 128.5, 126.9, 123.8, 80.5, 55.9, 52.6, 37.4, 28.2. m/z (EI, 70 eV): 424 (M^+, 10.8%), 368 (16.7%), 177 (100%). Anal. found: C, 68.06%; H, 6.72%; N, 6.56%; $C_{24}H_{28}N_2O_5$ requires C, 67.91%; H, 6.65%; N, 6.60%.

Methyl 4- ((Z)-2-{[(*2S*)-2- ({(2S)-2-[(*tert*-butoxycarbonyl)amino]-3-phenylpropanoyl}-amino)-3-phenylpropanoyl]amino}-3-methoxy-3-oxo-1-propenyl)benzoate (12): Eluted with 30% ethyl acetate in petroleum ether. Yield: 55%. $[\alpha]_D$ +36 (c, 0.04 in $CHCl_3$). IR (neat, cm^{-1}): 3278, 2984, 1663, 1649, 1523, 1497, 1438, 1367, 1283, 1164. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.00 (2H, d, J = 8.1Hz), 7.90 (1H, br s), 7.45 (2H, d, J = 8.0 Hz), 7.37 (1H, s), 7.30–7.26 (6H, m), 7.14–7.11 (4H, m), 6.33 (1H, d, J = 7.8 Hz), 4.82–4.79 (2H, m), 4.21–4.19 (1H, m), 3.91 (3H, s), 3.82 (3H, s), 3.08–2.93 (4H, m), 1.27 (9H, s). ^{13}C-NMR (75 MHz, $CDCl_3$):

δ 170.9, 170.6, 169.6, 155.1, 136.3, 136.0, 134.1, 130.5, 130.0, 129.7, 129.6, 129.3, 128.9, 128.8, 128.2, 127.3, 80.6, 59.9, 52.9, 52.6, 38.3, 28.3. m/z (FAB): 652 ($M^+ + Na$). Anal. found: C, 66.81%; H, 6.28%; N, 6.67%; $C_{35}H_{39}N_3O_8$ requires C, 66.76%; H, 6.24%; N, 6.67%.

ACKNOWLEDGMENT

The authors are thankful to C. S. I. R., New Delhi for grants and fellowship.

REFERENCES

1. Padmanavan, B.; Dey, S.; Khandelwal, B.; Subbarao, G.; Singh, T. P. Design of peptides: Synthesis, crystal structure, molecular conformation, and conformational calculations of N-Boc-L-Phe-dehydro-Ala-OCH_3. *Biopolymers* **1992**, *32*, 1271–1276.
2. Ojima, I. Homogeneous asymmetric catalysis by means of chiral rhodium complexes. *Pure Appl. Chem.* **1984**, *56*, 99–110.
3. Schmidt, A.; Lieberknecht, A.; Wild, J. Didehydroamino acids (DDAA) and didehydropeptides (DDP). *Synthesis* **1988**, 159–171.
4. Burkett, B. A.; Chai, C. L.L. N-Fmoc-dehydroalanine: A versatile molecular scaffold for the rapid solid-phase synthesis of cycloaliphatic amino acid. *Tetrahedron Lett.* **2000**, *41*, 6661–6664.
5. Harrington, P. J.; Hegedus, L. S.; McDaniel, K. F. Palladium-catalyzed reactions in the synthesis of 3- and 4-substituted indoles. *J. Am. Chem. Soc.* **1987**, *109*, 4335–4338.
6. Basu, B.; Chattopadhyay, S. K.; Ritzen, A.; Frejd, T. Synthesis of optically active arylene bis-alanine derivatives carrying orthogonal protecting groups. *Tetrahedron: Asymmetry* **1998**, *9*, 503–512.
7. Cutolo, M.; Fiandanese, V.; Naso, F.; Sciacovelli, O. Synthesis of dehydrophenylalanine derivatives by palladium-catalyzed arylation of 2-acetamidoacrylic acid. *Tetrahedron Lett.* **1983**, *24*, 4603–4606.
8. Gibson, S. E.; Middleton, R. J. Synthesis of 7-, 8-, and 9-membered rings via endo heck cyclisations of amino acid derived substrates. *J. Chem. Soc., Chem. Commun.* **1995**, 1743–1744.
9. While this work was in progress, a similar work has been published: Doi, T.; Fujimoto, T.; Fujimoto, N.; Watanabe, J.; Takahasi, T. Palladium(0)-catalyzed Mizoroki–Heck reaction and Rh(I)-catalyzed asymmetric hydrogenation of polymer-supported dehydroalanine system. *Tetrahedron Lett.* **2003**, *44*, 2161–2165.
10. Shin, C.-G.; Yonezawa, Y.; Takahasi, M.; Yoshimura, J. Dehydrooligopeptides. II. The synthesis of dehydrodipeptides by direct coupling and base-catalyzed β-elimination. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 1132–1136.
11. Shin, C.-G.; Yonezawa, Y.; Yamada, T. Dehydrooligopeptides. IV. Synthesis of various types of dehydrodi- and tripeptides by fragment condensation and base-catalyzed β -elimination. *Chem. Pharm. Bull.* **1984**, *32*, 2825–2831.

12. Beletskaya, I.; Cheprakov, A. V. The Heck reaction as a sharpening stone of palladium catalysis. *Chem. Rev.* **2000**, *100*, 3009–3066.
13. Jeffery, T. Highly stereospecific palladium-catalyzed vinylation of vinylic halides under solid–liquid phase transfer conditions. *Tetrahedron Lett.* **1985**, *26*, 2667–2670.
14. Shimohigashi, Y.; -Nitz, T. J.; Stammer, C. H. E/Z-configuration assignment of dehydropeptides: Differential NOE enhancement between the vinyl and amide protons of an α,β-dehydroamino acid derivative. *Tetrahedron Lett.* **1982**, *23*, 3235–3236.
15. Carlstrom, A. -S.; Frejd, T. Palladium-catalyzed synthesis of didehydroamino acid derivatives. *Synthesis.* **1989**, 414–418.
16. Prokofev, E. P.; Karpeiskaya, E. I. The proton coupled 13C NMR direct determination of Z, E-configuration of 4-benzylidene-Z-phenyl(methyl)-Δ^2-oxazolin-5-ones and products of their solvolysis. *Tetrahedron Lett.* **1979**, 737–741.