A Practical Preparation of the Indolizidine Nucleus: Synthesis of (±)-Elaeokanine A

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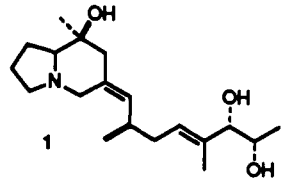
Reduction of **3** followed by acid-catalyzed cyclization provides α,β-unsaturated ester **5**. As **3** can be prepared in two steps from succinimide, acrolein, and trimethyl phosphonoacetate, this is a practical method for the assembly of the indolizidine nucleus. The structure of **5** was secured by conversion to elaeokanine A, **7**.

Synthesis of (±)-Elaeokanine A

In conjunction with a project directed toward the synthesis of pumiliotoxin B, **1**,[1,2] we needed a practical preparation of indolizidine ester **2**. Among the several methods for indolizine synthesis that have been introduced, iminium ion cyclization as developed by Speckamp[3] and others[4] seemed most straightforward.



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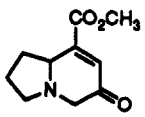


2

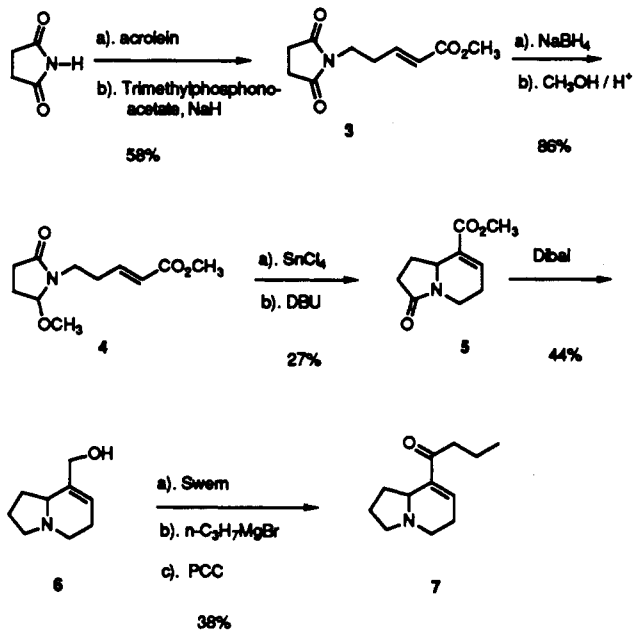
The first challenge was the preparation of the requisite α,β-unsaturated ester **3** (Scheme I). After some exploration, we found that addition of trimethyl phosphonoacetate to the (sticky, poorly characterized) product resulting from addition of succinimide to acrolein gave the nicely crystalline ester **3** in 58% overall yield.

Reduction of **3** by the method of Chamberlin[4a] proceeded smoothly. The propensity of the crude amido alcohol to add in a Michael sense to the unsaturated ester dictated conversion to the corresponding methyl ether prior to cyclization.

The early work of Eschenmoser[5] suggested that use of an α,β-unsaturated ester as a terminator for the carbocationic cyclization should enforce the desired six-membered ring formation. Indeed, exposure of methyl ether **4** to stannic chloride, followed by dehydrochlorination, gave the crystalline ester **5** in 27% yield. While the overall yield from succinimide is modest,[6] this procedure is simple enough to allow ready preparation of gram quantities of **5**.

To confirm the structure of **5**, it was carried on to the indolizidine alkaloid elaeokanine A.[7,8] Thus, reduction

Scheme I



gave alcohol **6**. Oxidation,[9] addition of *n*-propylmagnesium bromide, and oxidation[10] again then gave **7**, identical[8k-m] (^{1}H, ^{13}C NMR) with authentic elaeokanine A.

Experimental Section

General. ^{1}H and ^{13}C NMR spectra were obtained on a Brucker AM-250 spectrometer as solutions in $CDCl_3$. Carbon signals were assigned by an INEPT pulse sequence, u = methylene or quaternary carbon, d = methyl or methine. The infrared (IR) spectra were obtained as solutions in CCl_4 and are reported in cm^{-1}. Substances for which C, H analysis are not reported were purified as specified and gave spectroscopic data consistent with being >95% of the assigned structure. Organic chemicals were pur-

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(2) For syntheses in the pumiliotoxin B series, see: (a) Overman, L. E.; Bell, K. L.; Ito, F. *J. Am. Chem. Soc.* **1984**, *106*, 4192. (b) Overman, L. E.; Goldstein, S. W. *J. Am. Chem. Soc.* **1984**, *106*, 5360. (c) Trost, B. M.; Scanlan, T. S. *J. Am. Chem. Soc.* **1989**, *111*, 4988.

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(4) For leading references to other approaches to iminium ion mediated cyclization, see: (a) Chamberlin, A. R.; Nguyen, H. D.; Chung, J. Y. L. *J. Org. Chem.* **1984**, *49*, 1682. (b) Speckamp, W. N.; Hiemstra, H. *Tetrahedron* **1985**, *41*, 4367.

(5) Stadler, P. A.; Nechvatal, A.; Frey, A. J.; Eschenmoser, A. *Helv. Chim. Acta* **1957**, *40*, 1373.

(6) The crude cyclization product contained β-chloro ester epimers, along with **5**. We have not been able to identify the other products from the cyclization. Alternative Lewis acids gave **5** in lower overall yield.

(7) For the isolation and structure of elaeokanine A, see: Hart, N. K.; Johns, S. R.; Lamberton, J. A. *Aust. J. Chem.* **1972**, *25*, 817.

(8) Elaeokanine A has been prepared a number of times. For leading references, see ref 4a and the following: (a) Tufariello, J. J.; Ali, S. A. *Tetrahedron Lett.* **1979**, 4445. (b) Howard, A. S.; Gerrans, G. C.; Meerholz, C. A. *Tetrahedron Lett.* **1980**, *21*, 1373. (c) Watanabe, T.; Nakashita, Y.; Katayama, S.; Yamauchi, M. *Heterocycles* **1980**, *14*, 1433. (d) Khatri, N. A.; Schmitthenner, H. F.; Shringarpure, J.; Weinreb, S. M. *J. Am. Chem. Soc.* **1981**, *103*, 6387. (e) Wijnberg, B. P.; Speckamp, W. N. *Tetrahedron Lett.* **1981**, *22*, 5079. (f) Otomasu, H.; Takatsu, N.; Honda, T. Kametani, T. *Tetrahedron* **1982**, *38*, 2627. (g) Otomasu, H.; Takatsu, N.; Honda, T.; Kametani, T. *Heterocycles* **1982**, *19*, 511. (h) Overman, L. E.; Malone, T. C.; Meier, G. P. *J. Am. Chem. Soc.* **1983**, *105*, 6993. (i) Shono, T.; Matsumura, Y.; Uchida, K.; Tsubata, K.; Makino, A. *J. Org. Chem.* **1984**, *49*, 300. (j) Fann, C.; Malone, M. C.; Overman, L. E. *J. Am. Chem. Soc.* **1987**, *109*, 6097. (k) Gribble, G. W.; Switzer, F. L.; Soll, R. M. *J. Org. Chem.* **1988**, *53*, 3164. (l) Comins, D. L.; Myoung, Y. C. *J. Org. Chem.* **1990**, *55*, 292. (m) Hua, D. Y.; Bharathi, S. N.; Robinson, P. D.; Tsujimoto, A. *J. Org. Chem.* **1990**, *55*, 2128.

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chased from Aldrich Chemical Co. THF and Et_2O were distilled from sodium/benzophenone. The solvent mixtures used for chromatography are volume/volume mixtures. R_f values indicated refer to thin-layer chromatography on Analtech 2.5 × 10 cm, 250 μm analytical plates coated with silica gel GF. Et_2O* refers to anhydrous ether further prepared by shaking with one-quarter volume pH = 10 sodium carbonate buffer containing 10% by volume diethylamine. The organic phase was dried over Na_2SO_4 before use. Column chromatography was carried out with TLC-mesh silica gel, using the procedure we have described.[11] Unless otherwise specified, all reactions were carried out in flame-dried glassware under an atmosphere of N_2.

Methyl 5-(2,5-Dioxo-1-pyrrolidino)-2-pentenoate (3). Following a modification of the method of Moe and Warner,[12] succinimide (50.00 g, 505 mmol) was added to a solution of sodium (0.10 g, 4.3 mmol) in absolute ethanol (100 mL) to give a white suspension. Acrolein (33.7 mL, 505 mmol) was then added at a rate such that the internal temperature was maintained at 30 °C (air bath). After an additional 2 h at room temperature, glacial acetic acid (2 mL, 35 mmol) was added, followed by silica gel (50 g, 60–200 mesh), and the reaction mixture was concentrated in vacuo. The resulting solid was added to the top of a silica gel column (100 g), and the column was eluted with 5% acetone/$CHCl_3$ to give 55 g of the semipure aldehyde as a viscous oil. This was used directly: R_f (20% acetate/chloroform) = 0.39; ^1H NMR ($CDCl_3$) δ 2.74 (s, 4 H), 2.77 (dt, J = 1.4 Hz, 6.9 Hz, 2 H), 3.83 (t, J = 6.9 Hz, 2 H), 9.74 (t, J = 1.4 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 28.0, 32.3, 41.3, 177.0, 199.5; IR (CCl_4) 1728, 1704, 1692, 1403, 1173 cm^{-1}.

Trimethyl phosphonoacetate (60.0 mL, 370 mmol) was added dropwise to sodium hydride (17.0 g, 354 mmol) in dry THF (400 mL) at −10 °C. After an additional 30 min, the above aldehyde (55.0 g, 355 mmol) in THF (100 mL) was added. The ice/salt bath was removed, and the reaction mixture was stirred for 16 h at room temperature. The reaction mixture was acidified with 10% aqueous HCl (150 mL) and then partioned between water and EtOAc. The combined organic extract was washed with H_2O and then brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was distilled bulb-to-bulb (bp 110–130 °C, 1 mmHg) and then crystallized from methanol (80 mL) to afford 60.4 g (58% from succinimide) of ester **3** as colorless needles: mp 64–65 °C; R_f (20% acetone/chloroform) = 0.65; ^1H NMR (CCl_4) δ 2.51 (dq, J = 1.5, 7.1 Hz, 2 H), 2.73 (s, 4 H), 3.65 (t, J = 7.1 Hz, 2 H), 3.71 (s, 3 H), 5.86 (dt, J = 1.5, 15.7 Hz, 1 H), 6.85 (dt, J = 7.1, 15.7 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 27.8, 29.9, 36.6, 51.2, 122.9, 144.1, 166.0, 176.8; IR (CCl_4) 1708, 1700, 1438, 1403, 1331, 1284, 1203, 1159 cm^{-1}; mass calcd for $C_{10}H_{13}NO_4$ 211.0844, found 211.0846; MS 211 (M^+, 11), 180 (56), 179 (92), 152 (31), 151 (79), 123 (10), 113 (25), 112 (100). Anal. Calcd for $C_{10}H_{13}NO_4$: C, 56.87; H, 6.20. Found: C, 56.53; H, 6.09.

Methyl 5-(2-Methoxy-5-oxo-1-pyrrolidino)-2-pentenoate (4). Sodium borohydride (5.0 g, 131.6 mmol) was added in small portions to a solution of ester **3** (13.71 g, 65 mmol) in methanol (80 mL) at 0 °C. When the reduction was complete by TLC [R_f (20% acetone/$CHCl_3$) = 0.33], the reaction mixture was acidified by the dropwise addition of concentrated aqueous HCl (50 mL). The mixture was diluted with H_2O (200 mL) and extracted with CH_2Cl_2 (5 × 100 mL). The combined organic extract was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The crude hydroxylactam (12.4 g) was obtained as a colorless oil: ^1H NMR ($CDCl_3$) δ 1.92–2.60 (m, 6 H), 3.67 (t, J = 7.1 Hz, 2 H), 3.74 (s, 3 H), 4.91 (br s, 1 H), 5.89 (d, J = 15.7 Hz, 1 H), 6.92 (dt, J = 7, 15.7 Hz, 1 H).

To a solution of the crude hydroxylactam (12.4 g) in MeOH (100 mL) was added a solution of acetyl chloride (3 drops) in MeOH (1 mL). After being stirred for 18 h at room temperature, the reaction mixture was neutralized with solid $NaHCO_3$ (0.5 g). Silica gel (20 g, 60–200 mesh) was then added, and the reaction mixture was concentrated in vacuo. The residue was chromatographed on silica gel (50 g) with 5% acetone/$CHCl_3$ to give 12.72 g (86% from ester **3**) of methoxylactam **4** as a colorless oil: R_f (20% acetone/$CHCl_3$) = 0.55; ^1H NMR ($CDCl_3$) δ 2.00–2.59 (m, 6 H), 3.26, 3.27 (s, s, 3 H), 3.53–3.62 (m, 2 H), 3.67, 3.73 (s, s, 3 H), 4.93 (dt, J = 1.3, 6.4 Hz, 1 H), 5.89 (dt, J = 1.4, 15.7 Hz, 1 H), 6.92 (dt, J = 7.1, 15.7 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ (major) 23.6, 28.7, 30.5, 39.1, 51.4, 52.5, 90.2, 122.6, 145.4, 166.5, 174.9; (minor) 22.1, 26.9, 33.4, 39.9, 51.4, 52.6, 89.8, 122.6, 145.4, 166.5, 173.7; IR (CCl_4) 1720, 1709, 1690, 1454, 1438, 1422, 1284, 1201, 1082 cm^{-1}. Anal. Calcd for $C_{11}H_{17}NO_4$: C, 58.11; H, 7.54. Found: C, 58.03; H, 7.77.

Methyl 1,2,3,5,6,8a-Hexahydro-3-oxoindolizine-8-carboxylate (5). Stannic chloride (16.0 mL, 137 mmol) was added dropwise to a solution of methoxylactam **4** (12.00 g, 52.9 mmol) in dichloroethane (200 mL) at 0 °C. The reaction mixture was stirred for 30 min at 0 °C, warmed to 70 °C, and then stirred for 18 h. The reaction mixture was then cooled to 0 °C and quenched with 15% aqueous NaOH (200 mL). The aqueous phase was extracted with CH_2Cl_2 (4 × 100 mL). The combined organic extract was washed with brine (200 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue was filtered through silica gel (50 g) with 5% acetone/$CHCl_3$ and then distilled bulb-to-bulb (110–140 °C (bath), 1 mmHg) to afford 3.41 g of a mixture of esters: R_f (20% acetone/$CHCl_3$) = 0.50 and 0.41; ^1H NMR ($CDCl_3$) δ 1.63–1.94 (m, 3 H), 2.10–2.53 (m, 4 H), 2.78 (t, J = 12 Hz, 1 H), 3.50–3.68 (m, 1 H), 3.77 (s, 3 H), 4.09–4.28 (m, 2 H); IR (CCl_4) 1739, 1732, 1702, 1686, 1674, 1437, 1271, 1166 cm^{-1}.

To a solution of the above esters (3.41 g) in THF (30 mL) at room temperature was added DBU (2.90 mL, 19.4 mmol). The reaction mixture was warmed to 60 °C and then stirred for 14 h. The resulting suspension was cooled to room temperature and diluted with CH_2Cl_2 (100 mL). The organic phase was extracted with 10% aqueous HCl (50 mL), H_2O (50 mL), and brine (50 mL). The aqueous washings were back-extracted with CH_2Cl_2 (100 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo, and the residue was distilled bulb-to-bulb (100–115 °C (bath), 1 mmHg) to afford 2.73 g (27% from methoxylactam **4**) of ester **5**: R_f (20% acetone/$CHCl_3$) = 0.50; ^1H NMR ($CDCl_3$) δ 1.61 (quintet, J = 10.8 Hz, 1 H), 2.30–2.83 (m, 6 H), 3.8 (s, 3 H), 4.24 (m, 1 H), 4.43 (m, 1 H), 7.14 (br s, 1 H); ^{13}C NMR δ 24.7, 26.2, 26.2, 26.3, 31.0, 34.6, 51.1, 54.1, 131.5, 137.3, 164.7, 172.5; IR (CCl_4) 1706, 1685, 1674, 1439, 1423, 1275, 1265 cm^{-1}; MS 195 (M^+, 58), 180 (46), 164 (24), 136 (100), 108 (19), 106 (13).

1,2,3,5,6,8a-Hexahydroindolizine-8-methanol (6). A solution of amide-ester **5** (100 mg, 0.513 mmol) in THF (1.7 mL, 0.3 M) was cooled to 0 °C in an ice/salt bath. Dibal (1.86 mL, 2.82 mmol, 1.5 M in toluene) was added dropwise over 10 min. The reaction mixture was stirred at 0 °C for 30 min and then let warm to room temperature and stirred for 5 h. Ether (5 mL) was added, followed by NaF (0.473 g, 11.28 mmol, in portions). Water (0.152 mL, 8.46 mmol) was added dropwise, and then the resulting gelatinous mixture was stirred for 10 min. The mixture was diluted with acetone and filtered. The filtrate was concentrated in vacuo, and the residue was chromatographed on 1 g of silica gel with Et_2O* to give the amino alcohol **6** as an oil (0.035 g, 44%): R_f (Et_2O*) = 0.15; ^1H NMR ($CDCl_3$) δ 1.40–1.60 (m, 1 H), 1.60–2.08 (m, 4 H), 2.20 (br s, 1 H), 2.49 (q, 2 H), 2.71 (m, 2 H), 2.90 (m, 1 H), 3.15 (br t, 1 H), 4.02 (s, 2 H), 5.63 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 22.6 u, 25.4 u, 28.7 u, 47.0 u, 53.4 u, 60.8 d, 65.0 u, 120.9 d, 139.9 u; IR (CCl_4) 3561–3059, 2939, 2891, 2844, 1470, 1315, 1039 cm^{-1}; mass calcd for $C_9H_{15}NO$ 153.1154, found 153.1157; MS 153 (M^+ 20), 152 (37), 134 (22), 125 (30), 122 (100), 120 (18).

Elaeokanine A (7). The above alcohol was oxidized by the procedure of Swern[12] and worked up in the usual way to leave a residue. This was chromatographed on 5 g of silica gel with Et_2O* to give the aldehyde (0.142 g, 72%) as a brown oil: R_f (100% Et_2O*) = 0.30; ^1H NMR ($CDCl_3$) δ 1.43 (m, 1 H), 1.84 (m, 2 H), 2.26–2.79 (m, 5 H), 2.93 (m, 2 H), 3.37 (br t, 1 H), 6.86 (m, 1 H), 9.42 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 23.0 u, 26.1 u, 29.1 u, 45.7 u, 52.4 u, 57.9 d, 144.1 u, 148.9 d, 193.2 u; IR (CCl_4) 2959, 2878, 2808, 2720, 1692, 1640, 1580, 1419, 1233.

Propylmagnesium bromide (0.33 mL, 0.98 mmol, 3 M in Et_2O) was added dropwise to the above aldehyde (74 mg, 0.490 mmol) in THF (0.5 mL) at −10 °C. After 10 min the cooling bath was removed, and stirring was continued for an additional 45 min. The reaction mixture was partitioned between Et_2O and water. The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was chromatographed on 1 g of silica gel with 50% Et_2O*/petroleum ether to give the homologated alcohol (elaeokanine B and its diaste-

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reomer) as an oil (74.5 mg, 78%): R_f (100% Et_2O*) = 0.27; ^1H NMR ($CDCl_3$) δ 0.80–1.02 (m, 3 H), 1.18–3.12 (m, 16 H), 3.95 (dt, 1 H), 5.61 (m, 1 H); IR (CCl_4) 3620–3021, 2961, 2934, 2874, 1551, 1217, 1118 cm^{-1}.

Finely ground PCC (0.095 g, 0.442 mmol) and sodium acetate (0.036 g, 0.442 mmol) were suspended in CH_2Cl_2 (1.5 mL). The above alcohol mixture (0.043 g, 0.221 mmol) in CH_2Cl_2 (0.5 mL) was added dropwise at room temperature. After 3 h TLC showed the absence of starting material. The solution was diluted with Et_2O (10 mL) and filtered through a pipet column of Florisil. The crude product was concentrated in vacuo and chromatographed on a silica gel column (2 g) with 20% Et_2O*/petroleum ether to give (±)-elaeokanine A (7) (29 mg, 68%, 38% from alcohol 6) as an oil: R_f (100% Et_2O*) = 0.36; ^1H NMR ($CDCl_3$) δ 0.92 (t, 3 H, J = 7.4 Hz), 1.18–1.97, 2.20–2.98 (m, 14 H), 3.44 (br t, 1 H), 6.88 (dt, 1 H, J = 4.2, 1.4 Hz); ^{13}C NMR ($CDCl_3$) δ 14.3 d, 18.6 u, 22.8 u, 25.9 u, 29.9 u, 39.7 u, 45.5 u, 53.1 u, 59.1 d, 137.3 d, 142.4 u, 201.2 u; IR (CCl_4) 2963, 2934, 2878, 1671, 1459, 1046 cm^{-1}.

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Supplementary Material Available: ^1H and ^{13}C NMR spectra for 5–7 (8 pages). Ordering information is given on any current masthead page.

Notes

Palladium-Catalyzed Bis-coupling of Dihaloaromatics with 2-Amidoacrylates

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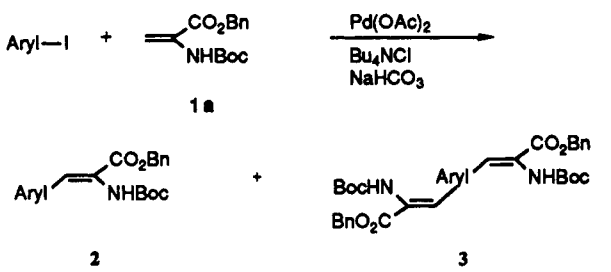
The Heck arylation reaction[1] has been widely used for alkenylation of aromatic rings but is rarely used to make one-pot di- or polyfunctionalizations. A recent publication describes the palladium-catalyzed reaction between polyhalobenzenes and methyl acrylate or styrene, resulting in di-, tri-, and tetracoupling.[2] Earlier, bis-alkenylations of aromatics using palladium catalysis were studied in just a few cases.[3] Recently we synthesized 1,1′-ferrocenylbis(alanine)[4] via the palladium-catalyzed reaction between 1,1′-diiodoferrocene and protected 2-aminoacrylate derivatives, followed by catalytic hydrogenation. We then became interested in using this reaction[5] for the synthesis of various bis(amino acids), which are similar to the ones present in the peptide antibiotics vancomycin,[6] bouvardin,[7] biphenomycin,[8] K-13,[9] and OF4949 I-IV[10] (a number of synthetic efforts toward these peptides have been published[11]). Bis(amino acids) may also be used as β-turn mimetics[12] or as cross-links for restricting the internal mobility of peptides. The bis(amino acids) *o*-, *m*-, and *p*-phenylenebis(alanine) were synthesized already in 1961,[13] and the synthesis of optically active *o*-phenylenebis(alanine) has also been reported.[14]

Scheme I



We now present some aspects of the structural requirements of the aromatic component in the palladium-catalyzed bis-coupling of aromatic dihalides with 2-amidoacrylates (Scheme I).

Results and Discussion

The results of the coupling reactions are shown in Table I, and the reactions were performed using the modified Heck conditions as described by Cacchi et al. (arylhalide, olefin, $Pd(OAc)_2$, Bu_4NCl, and $NaHCO_3$ in DMF).[15] With 2 equiv of olefin **1a** the reaction of 1,3- and 1,4-diiodobenzene, 4,4′-diiodobiphenyl, and 3,3′-diiodo-4,4′-dimethoxybiphenyl gave the bis-coupling products **3a–d** in about 50% yields (entries 8, 12, 13, and 15). The bis(amino acid) derivatives obtainable after reduction of these compounds are of limited value in peptide synthesis, since they have identical sets of carboxyl and amino protecting groups on

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