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}.

Acknowledgment. We thank the National Institutes of Health (Grant GM 32027) for partial support of this work.

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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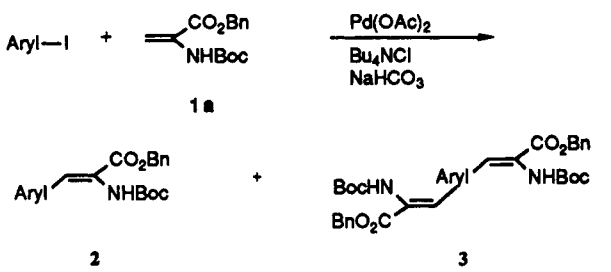
The Heck arylation reaction[1] has been widely used for alkenylation of aromatic rings but is rarely used to make one-pot di- or polyfunctionalizations. A recent publication describes the palladium-catalyzed reaction between polyhalobenzenes and methyl acrylate or styrene, resulting in di-, tri-, and 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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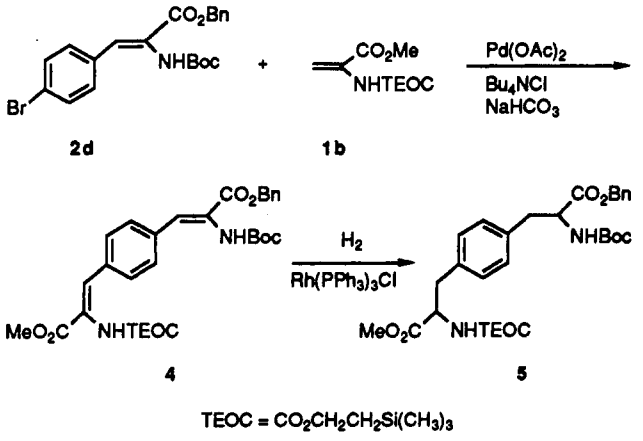
Table I. Yields and Conditions of the Palladium-Catalyzed Coupling Reaction of Aromatic Halides and 1a

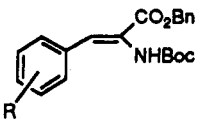
entry	starting material	conditions[a]	products	% isol yield[b]
1	2-bromoiodobenzene	A	**2a**	28 (60)
2	2-bromoiodobenzene	B	**2a**	41
3	1,2-diiodobenzene	A	-	(>95)
4	1,2-diiodobenzene	B	-	(>95)
5	3-bromoiodobenzene	A	**2b/3a**	63/0
6	3-bromoiodobenzene	B	**2b/3a**	0/57
7	1,3-diiodobenzene	A	**2c/3a**	38/20 (41)
8	1,3-diiodobenzene	B	**2c/3a**	1/52
9	4-bromoiodobenzene	A	**2d/3b**	52/2
10	4-bromoiodobenzene	B	**2d/3b**	0/71
11	1,4-diiodobenzene	A	**2e/3b**	21/22 (36)
12	1,4-diiodobenzene	B	**2e/3b**	0/55
13	4,4'-diiodobiphenyl	B	**3c**	59
14	3,3'-diiodo-4,4'-dimethoxybiphenyl	A	**2j/3d**	43/16
15	3,3'-diiodo-4,4'-dimethoxybiphenyl	B	**2j/3d**	0/55
16	4-bromoacetophenone	A	**2f**	76
17	2-fluoroiodobenzene	A	**2g**	81
18	2-chloroiodobenzene	A	**2h**	83
19	2-iodotoluene	A	**2i**	84
20	1-iodo-2-methylnaphthalene	A	**2k**	67
21	**2d**	A	**3b**	67

[a] For conditions A and B see the Experimental Section. [b] Unreacted starting material in parentheses.

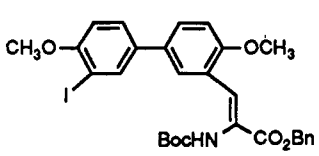
Scheme II



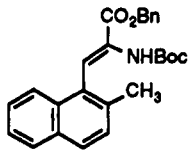
the two side arms. A stepwise coupling of two differently protected amidoacrylates would thus be preferable. Diiodoaromatics are, however, less suited as starting materials for such stepwise couplings; when 1,3- and 1,4-diiodobenzene and 3,3'-diiodo-4,4'-dimethoxybiphenyl were treated with 1 equiv of olefin **1a**, a mixture of the mono- and the bis-coupling products were obtained (Entries 7, 11, and 14). Heck et al. have earlier reported that *iodo* aromatics coupled with olefins in the absence of a phosphine ligand, while *bromo* aromatics needed phosphine for reaction. Stepwise couplings between bromoiodo aromatics and two different olefins were thus realized.[3a] However, this procedure is not applicable in our system, since the addition of phosphine markedly decreases the yield of coupling product.[16] Fortunately, we were able to take advantage of the fact that electron-withdrawing substituents in the aromatic ring seem to be beneficial for coupling. It is known from a kinetic study that the oxidative addition of Pd(0) to iodobenzenes is facilitated by electron-withdrawing substituents.[17] Indeed, we found that although bromobenzene itself reacts poorly (24%), 4-bromoacetophenone gave a good yield of **2f** (entry 16). It also turned out that the 4-bromo compound **2d** reacted readily to give the bis-coupling product **3b** when treated with 1 equiv of **1a** (entry 21). In addition, the bis-coupling products **3a** and **3b** were obtained in good yields when 3-bromoiodobenzene and 4-bromoiodobenzene, respectively, were treated with double equivalents of **1a** (entries 6 and 10). 2-Bromoiodobenzene gave, however, only the mono-coupling product (entry 2). In this case the yield of **2a** improved on increasing the amount of olefin from 1 to 2 equiv.



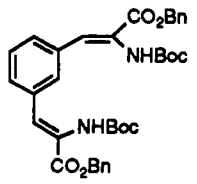
2a R = 2-Br **2b** R = 3-Br **2c** R = 3-I **2d** R = 4-Br **2e** R = 4-I **2f** R = 4-COCH3 **2g** R = 2-F **2h** R = 2-Cl **2i** R = 2-CH3



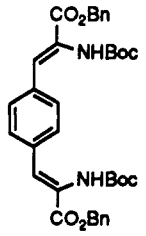
2j



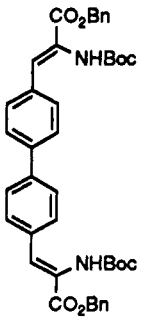
2k



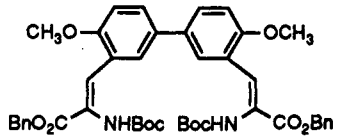
3a



3b



3c



3d

Using these results, we were able to synthesize the bis(amino acid) derivative **5**, possessing different sets of protecting groups in the two side arms. The synthesis started with the coupling of 4-bromoiodobenzene with **1a** to give the mono-substituted bromobenzene **2d** (52%), which then was reacted with olefin **1b** to give the bis(didehydroamino acid) derivative **4** (62%, Scheme II). Subsequent hydrogenation of the double bonds using the Wilkinson catalyst ($Rh(PPh_3)_3Cl$) gave **5** (50%). The low yield in the hydrogenation step may be due to instability

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of the amino protecting group 2-(trimethylsilyl)ethoxycarbonyl (TEOC)[18] during the prolonged reaction time required. Olefin **1b** is readily polymerized, and all reactions involving this olefinic system should be performed in the presence of a radical scavenger, e.g. hydroquinone.

In an attempted coupling of 1,2-diiodobenzene with **1a** (and with the sterically less demanding methyl 2-acetamidoacrylate) neither the bis- nor the mono-coupling products were obtained (entries 3 and 4); the starting diiodide was left unreacted. 2-Fluoroiodobenzene and 2-chloroiodobenzene reacted in the iodo position in high yields (entries 17 and 18), while 2-bromoiodobenzene gave considerably lower yield (entry 1). Thus, the yields decrease with increasing steric bulk and decreasing electronegativity of the halogens. However, this tendency does not extend to other systems, since good yields are obtained in the couplings of 2-iodotoluene (entry 19) and 1-iodo-2-methylnaphthalene (entry 20). +M–I substituents other than Br and I placed in the ortho position to iodine give good to high yields of coupling products. Besides the examples mentioned, we earlier showed that 2-iodoanisol and 2-iodophenol gave fair yield of coupling products (57% and 50%, respectively).[5] The possibility that a contaminant inhibited the reaction of 1,2-diiodobenzene is unlikely, since two different preparations of 1,2-diiodobenzene (one commercial product and one home-made preparation) both gave negative results. Surprisingly, the coupling between iodobenzene and **1a** (normally proceeding in about 80% yield) was almost completely inhibited by the presence of 1 equiv of 1,2-diiodobenzene. The unreactivity of 1,2-diiodobenzene contrasts to Heck's successful bis-couplings of 1,2-diiodobenzene with methyl acrylate[2] and styrene,[3b] as well as of 1,2-dibromobenzene with ethylene.[3c] At present we are studying the influence of different factors on this type of reaction.[16]

Experimental Section

NMR spectra were recorded with a Varian XL-300 NMR spectrometer. NOE experiments were performed as described previously.[5] Melting points were determined with a Reichert microscope and are uncorrected. Thin-layer chromatography (TLC) was performed on Merck precoated silica gel F-254 plates, and spots were visualized by UV light (254 and 366 nm). Rapid column chromatography[19] was performed using Merck SiO_2 60 (0.040–0.063 mm). The gas chromatographic determinations of unreacted starting material were performed on a Shimadzu GC-9 chromatograph using a medium polarity capillary column (DB-17t, J&W Scientific), with 2-methylnaphthalene as internal standard. 1,2-Diiodobenzene,[20] 1,3-diiodobenzene,[21] 4,4′-dimethoxybiphenyl,[22] benzyl 2-[(*tert*-butoxycarbonyl)amino]acrylate (**1a**),[5] and methyl 2-acetamidoacrylate[23] were prepared by literature procedures.

General Procedures for the Coupling Reactions. A mixture of the aryl halide, benzyl 2-[(*tert*-butoxycarbonyl)amino]acrylate, $Pd(OAc)_2$, Bu_4NCl, and $NaHCO_3$ in DMF (the amounts are given below) was stirred under a nitrogen atmosphere in a screw-cap sealed tube at 85 °C for 16 h. After cooling, the mixture was diluted with water (25 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic phase was washed with water (2 × 15 mL) and dried (Na_2SO_4), and the solvent was evaporated. The products were isolated by chromatography using heptane–EtOAc, 7.5:1 (for products **2**), or heptane–EtOAc, 3:1 (for products **3**), as eluent.

The amounts of reactants and reagents were as follows.

Conditions A: aryl halide (0.38 mmol), benzyl 2-[(*tert*-butoxycarbonyl)amino]acrylate (150 mg, 0.54 mmol), $Pd(OAc)_2$ (2.6 mg, 0.011 mmol), Bu_4NCl (110 mg, 0.38 mmol), and $NaHCO_3$ (80 mg, 0.95 mmol) in DMF (5 mL).

Conditions B: aryl halide (0.38 mmol), benzyl 2-[(*tert*-butoxycarbonyl)amino]acrylate (300 mg, 1.1 mmol), $Pd(OAc)_2$ (5.2 mg, 0.023 mmol), Bu_4NCl (220 mg, 0.76 mmol), and $NaHCO_3$ (160 mg, 1.9 mmol) in DMF (7.5 mL).

Compounds **2a–k** and **3a–d** were prepared by these conditions in yields according to Table I.

1-[2-(Benzyloxycarbonyl)-2-[(*tert*-butoxycarbonyl)amino]ethenyl]-2-bromobenzene (2a): mp 81–84 °C (EtOAc/hexane); ^1H NMR ($CDCl_3$) δ 1.32 (s, 9 H, $C(CH_3)_3$), 5.32 (s, 2 H, $PhCH_2$), 6.23 (br s, 1 H, NH), 7.15 (dt, 1 H, J = 7.5, 1.7 Hz, Ar-H), 7.25–7.46 (m, 7 H, Ar-H, HC=), 7.59 (dt, 2 H, J = 8.0, 1.2 Hz, Ar-H). Anal. Calcd for $C_{21}H_{22}BrNO_4$: C, 58.34; H, 5.13; N, 3.24. Found: C, 58.48; H, 4.94; N, 3.23.

1-[2-(Benzyloxycarbonyl)-2-[(*tert*-butoxycarbonyl)amino]ethenyl]-3-bromobenzene (2b): mp 82–84 °C (EtOAc/hexane); ^1H NMR ($CDCl_3$) δ 1.40 (s, 9 H, $C(CH_3)_3$), 5.29 (s, 2 H, $PhCH_2$), 6.35 (br s, 1 H, NH), 7.22 (t, 2 H, J = 7.9 Hz, Ar-H, HC=), 7.41 (m, 7 H, Ar-H), 7.67 (t, 1 H, J = 1.5 Hz, Ar-H). Anal. Calcd for $C_{21}H_{22}BrNO_4$: C, 58.34; H, 5.13; N, 3.24. Found: C, 58.63; H, 5.31; N, 3.28.

1-[2-(Benzyloxycarbonyl)-2-[(*tert*-butoxycarbonyl)amino]ethenyl]-3-iodobenzene (2c): mp 81–84 °C (EtOAc/hexane); ^1H NMR ($CDCl_3$) δ 1.41 (s, 9 H, $C(CH_3)_3$), 5.28 (s, 2 H, $PhCH_2$), 6.35 (br s, 1 H, NH), 7.08 (t, 1 H, J = 7.8 Hz, Ar-H), 7.18 (s, 1 H, HC=), 7.40 (m, 6 H, Ar-H), 7.62 (dt, 1 H, J = 7.9, 1.8 Hz, Ar-H), 7.87 (t, 1 H, J = 1.7 Hz, Ar-H). Anal. Calcd for $C_{21}H_{22}INO_4$: C, 52.62; H, 4.63; N, 2.92. Found: C, 52.53; H, 4.65; N, 2.92.

1-[2-(Benzyloxycarbonyl)-2-[(*tert*-butoxycarbonyl)amino]ethenyl]-4-bromobenzene (2d): mp 111–113 °C (EtOAc/hexane); ^1H NMR ($CDCl_3$) δ 1.39 (s, 9 H, $C(CH_3)_3$), 5.28 (s, 2 H, $PhCH_2$), 6.28 (br s, 1 H, NH), 7.22 (s, 1 H, HC=), 7.37–7.49 (m, 9 H, Ar-H). Anal. Calcd for $C_{21}H_{22}BrNO_4$: C, 58.34; H, 5.13; N, 3.24. Found: C, 58.41; H, 5.04; N, 3.22.

1-[2-(Benzyloxycarbonyl)-2-[(*tert*-butoxycarbonyl)amino]ethenyl]-4-iodobenzene (2e): mp 132–135 °C (EtOAc/hexane); ^1H NMR ($CDCl_3$) δ 1.39 (s, 9 H, $C(CH_3)_3$), 5.28 (s, 2 H, $PhCH_2$), 6.27 (br s, 1 H, NH), 7.21, 7.68 (AB q with further couplings, 4 H, J_{AB} = 8.8 Hz, Ar-H), 7.26 (s, 1 H, HC=), 7.39 (m, 5 H, Ar-H). Anal. Calcd for $C_{21}H_{22}INO_4$: C, 52.62; H, 4.63; N, 2.92. Found: C, 52.72; H, 4.65; N, 2.79.

4-[2-(Benzyloxycarbonyl)-2-[(*tert*-butoxycarbonyl)amino]ethenyl]acetophenone (2f): mp 105–108 °C (EtOAc/hexane); ^1H NMR ($CDCl_3$) δ 1.38 (s, 9 H, $C(CH_3)_3$), 2.60 (s, 3 H, $COCH_3$), 5.30 (s, 2 H, $PhCH_2$), 6.40 (br s, 1 H, NH), 7.28 (s, 1 H, HC=), 7.40 (m, 5 H, Ar-H), 7.59, 7.93 (AB q with further couplings, 4 H, J_{AB} = 8.3 Hz, Ar-H). Anal. Calcd for $C_{23}H_{25}NO_5$: C, 69.86; H, 6.37; N, 3.54. Found: C, 69.51; H, 6.39; N, 3.63.

1-[2-(Benzyloxycarbonyl)-2-[(*tert*-butoxycarbonyl)amino]ethenyl]-2-fluorobenzene (2g): mp 80–82 °C (EtOAc/hexane); ^1H NMR ($CDCl_3$) δ 1.36 (s, 9 H, $C(CH_3)_3$), 5.30 (s, 2 H, $PhCH_2$), 6.35 (br s, 1 H, NH), 7.10 (m, 2 H, Ar-H), 7.27-7.45 (m, 7 H, Ar-H, HC=), 7.59 (t, 1 H, J = 7.8 Hz, Ar-H). Anal. Calcd for $C_{21}H_{22}FNO_4$: C, 67.91; H, 5.97; N, 3.77. Found: C, 67.82; H, 5.86; N, 3.68.

1-[2-(Benzyloxycarbonyl)-2-[(*tert*-butoxycarbonyl)amino]ethenyl]-2-chlorobenzene (2h): mp 71–74 °C (hexane); ^1H NMR ($CDCl_3$) δ 1.32 (s, 9 H, $C(CH_3)_3$), 5.31 (s, 2 H, $PhCH_2$), 6.25 (br s, 1 H, NH), 7.24 (m, 2 H, Ar-H), 7.34–7.45 (m, 7 H, Ar-H, HC=), 7.60 (m, 1 H, Ar-H) Anal. Calcd for $C_{21}H_{22}ClNO_4$: C, 65.03; H, 5.72; N, 3.61. Found: C, 64.99; H, 5.76; N, 3.58.

2-[2-(Benzyloxycarbonyl)-2-[(*tert*-butoxycarbonyl)amino]ethenyl]toluene (2i): mp 78–80 °C (EtOAc/hexane); ^1H NMR ($CDCl_3$) δ 1.34 (s, 9 H, $C(CH_3)_3$), 2.32 (s, 3 H, CH_3), 5.30 (s, 2 H, $PhCH_2$), 6.08 (br s, 1 H, NH), 7.16–7.48 (m, 10 H, Ar-H, HC=). Anal. Calcd for $C_{22}H_{25}NO_4$: C, 71.91; H, 6.86; N, 3.81. Found: C, 71.93; H, 6.76; N, 3.77.

3-[2-(Benzyloxycarbonyl)-2-[(*tert*-butoxycarbonyl)amino]ethenyl]-3′-iodo-4,4′-dimethoxybiphenyl (2j): mp

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123–125 °C (EtOAc/hexane); ^{1}H NMR ($CDCl_3$) δ 1.35 (s, 9 H, $C(CH_3)_3$), 3.90 (s, 3 H, OCH_3), 3.91 (s, 3 H, OCH_3), 5.30 (s, 2 H, $PhCH_2$), 6.44 (br s, 1 H, NH), 6.85 (d, 1 H, J = 8.6 Hz, Ar-H), 6.96 (d, 1 H, J = 8.6 Hz, Ar-H), 7.41 (m, 8 H, Ar-H, HC=), 7.67 (d, 1 H, J = 2.2 Hz, Ar-H), 7.93 (d, 1 H, J = 2.3 Hz, Ar-H). Anal. Calcd for $C_{29}H_{30}INO_6$: C, 56.59; H, 4.91; N, 2.28. Found: C, 56.61; H, 4.96; N, 2.28.

1-[2-(Benzyloxycarbonyl)-2-[(*tert*-butoxycarbonyl)amino]ethenyl]-2-methylnaphthalene (2k): mp 115–118 °C (EtOAc/hexane); ^{1}H NMR ($CDCl_3$) δ 1.28 (s, 9 H, $C(CH_3)_3$), 2.42 (s, 3 H, CH_3), 5.36 (s, 2 H, $PhCH_2$), 5.69 (br s, 1 H, NH), 7.35–7.49 (m, 9 H, Ar-H, HC=), 7.79 (m, 3 H, Ar-H). Anal. Calcd for $C_{26}H_{27}NO_4$: C, 74.80; H, 6.52; N, 3.35. Found: C, 74.89; H, 6.58; N, 3.40.

1,3-Bis[2-(benzyloxycarbonyl)-2-[(*tert*-butoxycarbonyl)amino]ethenyl]benzene (3a): mp 115–118 °C (EtOAc/hexane); ^{1}H NMR ($CDCl_3$) δ 1.36 (s, 18 H, $C(CH_3)_3$), 5.28 (s, 4 H, $PhCH_2$), 6.26 (br s, 2 H, NH), 7.25 (s, 2 H, HC=), 7.32–7.44 (m, 11 H, Ar-H), 7.49, 7.51, 7.61 (br singlets, each 1 H, Ar-H). Anal. Calcd for $C_{36}H_{40}N_2O_8$: C, 68.77; H, 6.41; N, 4.46. Found: C, 68.62; H, 6.39; N, 4.42.

1,4-Bis[2-(benzyloxycarbonyl)-2-[(*tert*-butoxycarbonyl)amino]ethenyl]benzene (3b): mp 195–199 °C (EtOAc/hexane); ^{1}H NMR ($CDCl_3$) δ 1.38 (s, 18 H, $C(CH_3)_3$), 5.28 (s, 4 H, $PhCH_2$), 6.27 (br s, 2 H, NH), 7.24 (s, 2 H, HC=), 7.39 (m, 10 H, Ar-H), 7.51 (s, 4 H, Ar-H). Anal. Calcd for $C_{36}H_{40}N_2O_8$: C, 68.77; H, 6.41; N, 4.46. Found: C, 68.85; H, 6.45; N, 4.42.

4,4′-Bis[2-(benzyloxycarbonyl)-2-[(*tert*-butoxycarbonyl)amino]ethenyl]biphenyl (3c): mp 193–197 °C (EtOAc/hexane); ^{1}H NMR ($CDCl_3$) δ 1.40 (s, 18 H, $C(CH_3)_3$), 5.30 (s, 4 H, $PhCH_2$), 6.27 (br s, 2 H, NH), 7.33–7.45, (m, 12 H, Ar-H, HC=), 7.61 (s, 8 H, Ar-H). Anal. Calcd for $C_{42}H_{44}N_2O_8$: C, 71.57; H, 6.29; N, 3.97. Found: C, 71.53; H, 6.38; N, 3.77.

3,3′-Bis[2-(benzyloxycarbonyl)-2-[(*tert*-butoxycarbonyl)amino]ethenyl]-4,4′-dimethoxybiphenyl (3d): mp 174–177 °C (EtOAc/hexane); ^{1}H NMR ($CDCl_3$) δ 1.26 (s, 18 H, $C(CH_3)_3$), 3.90 (s, 6 H, OCH_3), 5.30 (s, 4 H, $PhCH_2$), 6.95 (d, 2 H, Ar-H), 7.42 (m, 16 H, Ar-H, HC=), 7.80 (br s, 2 H, NH). Anal. Calcd for $C_{44}H_{48}N_2O_{10}$: C, 69.09; H, 6.32; N, 3.66. Found: C, 68.84; H, 6.41; N, 3.64.

3,3′-Diiodo-4,4′-dimethoxybiphenyl was prepared by treating a solution of 4,4′-dimethoxybiphenyl (0.48 g, 2.2 mmol) in diethyl ether (50 mL) with butyllithium (17 mL of a 1.4 M solution in hexane, 24 mmol) during 15 h at room temperature. The temperature was lowered to −70 °C, and a solution of iodine (7.4 g, 29 mmol) in diethyl ether (100 mL) was added dropwise. The mixture was allowed to reach room temperature and was then poured into ice water (100 mL). Extraction with CH_2Cl_2, washing of the organic phase with a 2% aqueous solution of $Na_2S_2O_3$ followed by water, drying (Na_2SO_4), and evaporation of the solvent gave a crude product that was chromatographed in toluene–CH_2Cl_2–heptane, 5:1:15. The yield was 0.57 g (1.2 mmol, 55%): mp 156–157 °C (EtOAc); ^{1}H NMR ($CDCl_3$) δ 3.92 (s, 6 H), 6.86 (d, 2 H, J = 8.6 Hz), 7.45 (dd, 2 H, J = 8.5, 2.3 Hz), 7.93 (d, 2 H, J = 2.3 Hz). Anal. Calcd for $C_{14}H_{12}I_2O_2$: C, 36.1; H, 2.6. Found: C, 36.2; H, 2.5.

1-Iodo-2-methylnaphthalene was prepared by lithiating 1-bromo-2-methylnaphthalene (10 g, 45 mmol) with butyllithium (175 mmol), and treating the resulting lithium compound with iodine (49 g, 190 mmol), following the experimental procedure described for the synthesis of 3,3′-diiodo-4,4′-dimethoxybiphenyl. The crude product was distilled to give 6.2 g (23 mmol, 51%) of 1-iodo-2-methylnaphthalene: $bp_{0.5}$ 128–130 °C (lit.[24] bp_3 155 °C).

Methyl 2-[[[2-(Trimethylsilyl)ethoxy]carbonyl]amino]acrylate (1b). A 0.5 M solution of NaOH was added to a solution of *d,l*-serine methyl ester hydrochloride (1.3 g, 8.4 mmol) in water (5 mL) until pH reached ~7.5. The water was coevaporated with toluene. The residue was dissolved in pyridine (20 mL) and 2-(trimethylsilyl)ethyl *p*-nitrophenyl carbonate (2.6 g, 9.2 mmol) was added. The mixture was stirred at 55 °C for 5 h and then at room temperature overnight. EtOAc (30 mL) was added, and the organic phase was washed several times with a $NaHCO_3$ solution at pH 8, to remove most of the *p*-nitrophenolate ions formed. Drying (Na_2SO_4) and evaporation of the solvent gave a crude product that was chromatographed in heptane–EtOAc, 2:1. The product, ***N*-[[2-(trimethylsilyl)ethoxy]carbonyl]-serine methyl ester**, was isolated as an oil (1.8 g, 7.0 mmol, 83%): ^{1}H NMR ($CDCl_3$) δ 0.04 (m, 9 H, $Si(CH_3)_3$), 1.00 (m, 2 H, $SiCH_2$), 2.27 (br s, 1 H, OH), 3.79 (s, 3 H, CO_2CH_3), 3.96 (m, 2 H, CH_2CH), 4.18 (m, 2 H, $SiCH_2CH_2$), 4.42 (br s, 1 H, CH_2CH), 5.55 (br s, 1 H, NH). Anal. Calcd for $C_{10}H_{21}NO_5Si$: C, 45.60; H, 8.04; N, 5.32. Found: C, 45.46; H, 7.95; N, 5.26.

A cold (0 °C) solution of this compound (380 mg, 1.4 mmol) was treated with methanesulfonyl chloride (210 mg, 1.8 mmol) and triethylamine (460 mg, 4.6 mmol) as previously described.[5] The reaction and the following evaporations were performed in the presence of a trace of hydroquinone (3 mg) in order to prevent polymerization of the olefin. After 15 min at 0 °C and 1 h at room temperature, the mixture was washed with 0.3% $KHSO_4$(aq) until neutral and dried, and the solvent was evaporated. The residue was chromatographed in heptane–EtOAc, 10:1, to give 330 mg (1.3 mmol, 96%) of **1b** as an oil: ^{1}H NMR ($CDCl_3$) δ 0.04 (m, 9 H, $Si(CH_3)_3$), 1.02 (m, 2 H, $SiCH_2$), 3.83 (s, 3 H, CO_2CH_3), 4.23 (m, 2 H, $SiCH_2CH_2$), 5.75 (d, 1 H, J = 1.5 Hz, HC=), 6.21 (s, 1 H, HC=), 7.11 (br s, 1 H, NH). Anal. Calcd for $C_{10}H_{19}NO_4Si$: C, 48.95; H, 7.80; N, 5.71. Found: C, 49.08; H, 7.89; N, 5.82.

1-[2-(Benzyloxycarbonyl)-2-[(*tert*-butoxycarbonyl)amino]ethyl]-4-[2-(methoxycarbonyl)-2-[[[2-(trimethylsilyl)ethoxy]carbonyl]amino]ethyl]benzene (5). Compound **2d** (230 mg, 0.53 mmol) was treated with olefin **1b** (170 mg, 0.69 mmol) in the presence of $Pd(OAc)_2$ (3.4 mg, 0.015 mmol), Bu_4NCl (160 mg, 0.54 mmol), $NaHCO_3$ (110 mg, 1.3 mmol), and hydroquinone (3 mg) according to the general procedure for the coupling reactions. After chromatography of the crude product in heptane–EtOAc, 5:2, 200 mg (0.33 mmol, 62%) of **1-[2-(benzyloxycarbonyl)-2-[(*tert*-butoxycarbonyl)amino]ethenyl]-4-[2-(methoxycarbonyl)-2-[[[2-(trimethylsilyl)ethoxy]carbonyl]amino]ethenyl]benzene (4)** was isolated: mp 139–142 °C (EtOAc/hexane); ^{1}H NMR ($CDCl_3$) δ 0.02 (m, 9 H, $Si(CH_3)_3$), 0.96 (m, 2 H, $SiCH_2$), 1.38 (s, 9 H, $C(CH_3)_3$), 3.86 (s, 3 H, CO_2CH_3), 4.17 (m, 2 H, $SiCH_2CH_2$), 5.29 (s, 2 H, $PhCH_2$), 6.28 (br s, 2 H, NH), 7.24 (s, 1 H, HC=), 7.27 (s, 1 H, HC=), 7.39 (m, 5 H, Ar-H), 7.52 (s, 4 H, Ar-H); ^{13}C NMR ($CDCl_3$) δ −1.5 ($Si(CH_3)_3$), 17.6 ($SiCH_2$), 28.1 ($C(CH_3)_3$), 52.7 ($SiCH_2CH_2$), 64.3 (CO_2CH_3), 67.5 ($PhCH_2$), 81.2 ($C(CH_3)_3$), 125.0–135.5 (14 signals, aromatic and vinylic C), 152.6, 154.0 (C=O carbamate), 165.3, 165.7 (C=O ester). Anal. Calcd for $C_{31}H_{40}N_2O_8Si$: C, 62.39; H, 6.76; N, 4.69. Found: C, 62.47; H, 6.78; N, 4.77. NOE experiments on compounds **2d** and **4** indicated *Z* configuration of the double bonds (irradiation of the amide proton signal resulted in no NOE effect for the vinyl proton signals).

A solution of **4** (200 mg, 0.34 mmol) in ethanol (25 mL) was hydrogenated at 4 atm and 50 °C for 5 days using $Rh(PPh_3)_3Cl$ (42 mg) as catalyst. The solvent was evaporated, and the crude product was chromatographed in heptane–EtOAc, 3:1, to give 100 mg (0.17 mmol, 50%) of **5**: ^{1}H NMR ($CDCl_3$) δ 0.02 (m, 9 H, $Si(CH_3)_3$), 0.96 (m, 2 H, $SiCH_2$), 1.41 (s, 9 H, $C(CH_3)_3$), 3.05 (m, 4 H, Ar-CH_2), 3.69 (s, 3 H, CO_2CH_3), 4.14 (m, 2 H, $SiCH_2CH_2$), 4.60 (m, 2 H, Ar-CH_2CH), 4.96 (br d, 1 H, J = 8.5 Hz, NH), 5.04 (br d, 1 H, J = 8.7 Hz, NH), 5.13 (AB q, 2 H, J_{AB} = 12.2 Hz, $PhCH_2$), 6.98 (s, 4 H, Ar-H), 7.35 (m, 5 H, Ar-H). ^{13}C NMR ($CDCl_3$) δ −1.5 ($Si(CH_3)_3$), 17.7 ($SiCH_2$), 28.3 ($C(CH_3)_3$), 37.8, 37.9 (Ar-CH_2CH), 52.2 (CO_2CH_3), 54.4, 54.6 (Ar-CH_2CH), 63.5 ($SiCH_2CH_2$), 67.1 ($PhCH_2$), 80.0 ($C(CH_3)_3$), 128.5, 128.6, 129.4, 129.6 (aromatic CH), 134.5, 134.7, 135.2 (aromatic C), 155.1, 156.0 (C=O carbamate), 171.6, 172.1 (C=O ester). Anal. Calcd for $C_{31}H_{44}N_2O_8Si$: C, 61.98; H, 7.38; N, 4.66. Found: C, 61.78; H, 7.32; N, 4.73.

Acknowledgment. We are grateful to The Swedish Natural Science Research Council for financial support.

Registry No. **1a**, 94882-75-4; **1b**, 130247-01-7; **2a**, 130247-02-8; **2b**, 130247-03-9; **2c**, 130247-04-0; **2d**, 130274-20-3; **2e**, 130247-05-1; **2f**, 130247-06-2; **2g**, 130247-07-3; **2h**, 130247-08-4; **2i**, 130247-09-5;

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2j, 130247-10-8; 2k, 130247-11-9; 3a, 130247-12-0; 3b, 130247-13-1; 3c, 130247-14-2; 3d, 130247-15-3; 4, 130247-16-4; 5, 130247-17-5; 2-BrC_6H_4I, 583-55-1; 1,2-$I_2C_6H_4$, 615-42-9; 3-BrC_6H_4I, 591-18-4; 1,3-$I_2C_6H_4$, 626-00-6; 4-BrC_6H_4I, 589-87-7; 1,4-$I_2C_6H_4$, 624-38-4; 4-BrC_6H_4Ac, 99-90-1; 2-FC_6H_4I, 348-52-7; 2-ClC_6H_4I, 615-41-8; 2-IC_6H_4Me, 615-37-2; H-DL-Ser-OMe·HCl, 5619-04-5; TEOC-DL-Ser-OMe, 130247-18-6; 4,4′-diiodobiphenyl, 3001-15-8; 3,3′-diiodo-4,4′-dimethoxybiphenyl, 130247-00-6; 1-iodo-2-methylnaphthalene, 36374-82-0; 4,4′-dimethoxybiphenyl, 2132-80-1; 1-bromo-2-methylnaphthalene, 2586-62-1.

Hemiketal Formation and Subsequent Intramolecular Acylation of an *N*-Hydroxy β-Lactam

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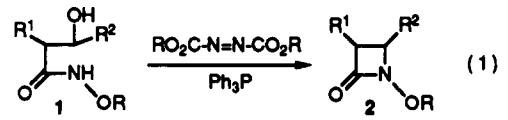
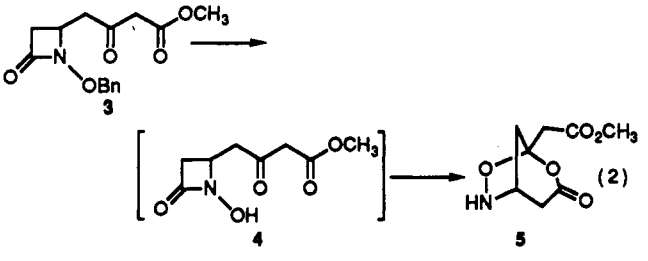
Since our initial efforts in the area of hydroxamate-mediated β-lactam synthesis,[1] we and others have been interested in exploring further the reactivity and synthetic utility of the resulting *N*-oxy β-lactams **2** (eq 1).



(1)

Previously, we reported an intramolecular rearrangement of *N*-hydroxy β-lactams when alkylated with bromomalonates[2] and the rearrangement of 4-carbalkoxy-*N*-hydroxy-2-azetidinones upon treatment with diisopropyl carbodiimide.[3] The facile intramolecular O-acylation of *N*-hydroxy β-lactams to give the corresponding isoxazolidinones has also been reported.[4] Herein, we report a unique intramolecular rearrangement of the *N*-hydroxy β-lactam **4** to provide the bicyclic system **5** (eq 2). This rearrangement appears to be the favored process, in a competive manner, over intramolecular isoxazolidinone formation.



(2)

The preparation of the protected rearrangement precursor **3**,[5] which incorporates a protected *N*-hydroxy β-lactam with a β-keto ester side chain appended to the C-4 position, is shown in Scheme I. Of notable importance in the synthesis of **3** was the use of a silyl-protected hydroxy group as the ketone precursor, since it has been shown that the Mitsunobu cyclization of the corresponding β-hydroxy hydroxamate **6** was somewhat problematic, resulting in a mixture of the β-lactam and the β,γ-unsaturated hydroxamate (eq 3).[6] Thus, it was essential to mask

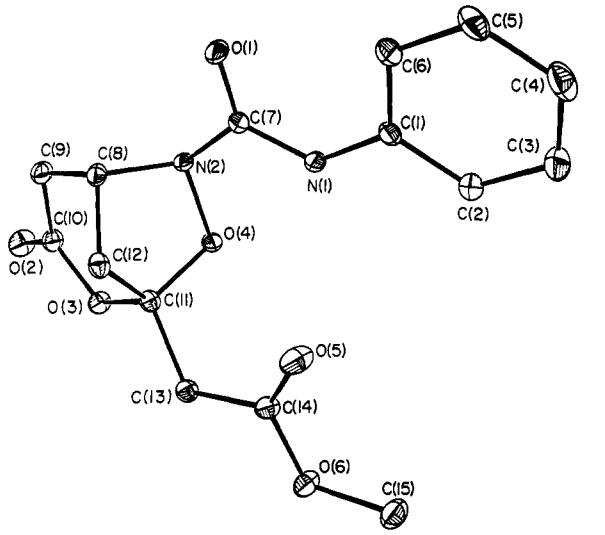
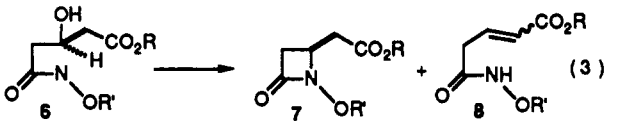


Figure 1. ORTEP representation of **18**.

the carbonyl group of the β-keto ester side chain prior to the Mitsunobu cyclization.



(3)

The mono acid–ester **9** was prepared according to literature precedent.[7] This acid was transformed to the corresponding acylimidazole and treated with the magnesium salt of monobenzyl malonate **10**, to provide the β-keto ester **11** in 86% yield using the procedure of Masamune.[8] This homologation provided the entire required carbon framework of the protected rearrangement precursor. Reduction of the ketone with $NaBH_4$ gave the secondary alcohol **12** in 84% yield as a mixture of diastereomers (ca. 2:1). Subsequent hydrogenolysis of the benzyl ester and, without isolation, direct DCC-mediated coupling with *O*-benzylhydroxylamine produced the β-hydroxy hydroxamate **13**, typically in 50–60% yields for the two steps. The hydroxamate was cyclized under Mitsunobu conditions[9] (diethyl azodicarboxylate, triphenylphosphine) to give the β-lactam **14** (66%) as a mixture of diastereomers. Deprotection of the silyl ether with tetrabutylammonium fluoride in the presence of 1.0 equiv of acetic acid provided the alcohol **15** in 86% yield. Oxidation of the resulting secondary alcohol, using a modified procedure for preparation of CrO_3–pyridine complex,[10] provided the labile ketone **3** in 72% isolated yield. Use of other oxidizing agents, such as PCC, followed by silica gel chromatography promoted cleavage of the *N*-benzyloxy β-lactam ring. The β,γ-unsaturated hy-

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