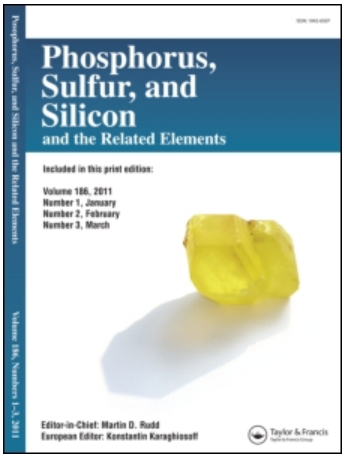

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2-HALOVINYL ARYL SULFONES: NEW COUPLING REAGENTS FOR CARBOXAMIDE FORMATION[1]

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2-HALOVINYL ARYL SULFONES: NEW COUPLING REAGENTS FOR CARBOXAMIDE FORMATION[1]

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E-2-Chlorovinyl *p*-nitrophenyl sulfone **6** and 2-bromo-2-trifluoromethylvinyl phenyl sulfone **7a** reacted with carboxylic acids in the presence of a molar equiv of Et_3N affording the corresponding 2-acyloxyvinyl sulfones **8**, **11**, **17**, **18**, **22**, **25**, **28** and **29**. The latter, on treatment with amines, gave amides **9**, **13**, **19**, **23** and **26** and peptides **30** and **32**. These reagents **6** and **7a** were also used for the formation of *N*-methylanilides **13d**, **13e**, **19d**, **23** and **26**. Particularly, **6** was successfully used for synthesis of a macrocyclic lactam **23** involving a *N*-methylanilide moiety. The amidation reactions proceeded under essentially neutral conditions. Therefore, base-sensitive β-hydroxycarboxy-*N*-methylanilides such as **26**, whose structural unit was involved in maytansine **5**, could be prepared by the present method. The reagent **6** was also effective for the preparation of peptides such as Val-*N*-MeVal derivatives (e.g. **32**), which were difficult to prepare by other methods.

INTRODUCTION

2-Halovinyl sulfoxides or sulfones **1** are known to react with various nucleophiles such as amines,[2] thiols,[2b,3] sulfinate anions,[2b,4] alkoxides,[2b,5] copper reagents[6] and carbanions[7] producing the corresponding β-sulfinyl- or β-sulfonylvinyl derivatives. Based on these observations we considered that these reagents might react even with carboxylate anions. If so, the resulting products **2** involving a vinylogous mixed anhydride structure can serve as effective acylating reagents. Moreover, when **2** is allowed to react with amines, for example, the developing carbanions are nicely oriented to assist the proton abstraction from amines through a six-membered transition state like **3a** or **3b**, thereby liberating neutral aldehydes **4** in contrast to the usual mixed anhydrides that produce acids on amidation. This suggests that the reaction of **2** with amines would be much more facilitated and should proceed under essentially neutral conditions without adding any additional bases. From these considerations, the aforementioned reagents **1** were expected to be mild amidation reagents useful for peptide synthesis.

We have developed an efficient method for the construction of medium-ring ketones by cyclization of large-membered lactam sulfoxides or sulfones.[8] In that study we prepared these intermediary lactam sulfides (cf. **23**) by C—S bond formation. All attempts to construct a large ring by a lactam-forming process gave only unsatisfactory results, although a wide variety of known methods[9] was employed. Nevertheless, we have continued an effort to develop a new method for cyclic *N*-methylanilide formation, because this particular lactam is involved in the framework of maytansine **5**,[10] a typical ansamitosin antibiotic having remarkable

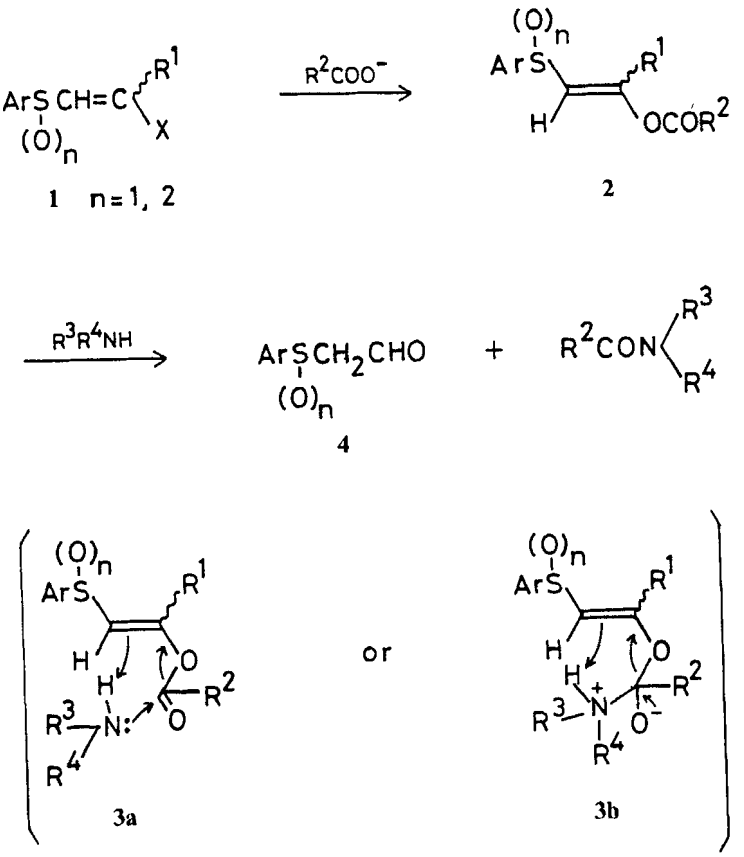

FIGURE 1

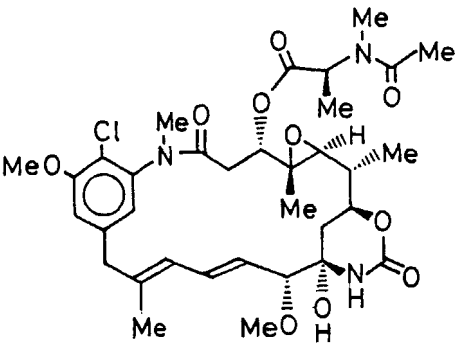

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FIGURE 2

bioactivity. Thus, we examined whether the reagents **1** were applicable to this type of cyclic *N*-methylanilide formation.

Among various 2-halovinyl sulfoxides and sulfones **1** examined, *E*-2-chlorovinyl *p*-nitrophenyl sulfone **6** and 2-bromo-2-trifluoromethylvinyl phenyl sulfone **7a** were found to be effective for coupling carboxylic acids with amines, particularly with weakly nucleophilic *N*-methylanilines and bulky *N*-methylamino acid esters.

RESULTS AND DISCUSSION

The reaction of **6**[11] with benzoic acid was performed in the presence of Et_3N in dry THF at 25.5°C. Although the yield of **8** was excellent (95.6%), 4 hours were required for the completion of the reaction. When the solvent was changed from THF to DMF, the rate of the reaction was much enhanced and **6** disappeared within 15 minutes to give **8** in 91.4% yield. The resulting vinylogous mixed anhydride **8** was subjected to the reaction with amines to give the corresponding amides **9**. When the amidation was carried out without isolating intermediary active esters **8**, the yields of **9** were much improved. Therefore, the subsequent amidation was always carried out by a one-pot reaction. The results are shown in Table I. However, an appreciable amount of by-product of type **10** was always obtained. The particular feature of the present method is that reaction of the active ester **8** with amines proceeded even at −20°C, which suggests that weak amines such as aniline derivatives should be acylated by **8**. In fact, when the active ester **11** prepared from **6** and *n*-butyric acid at room temperature with Et_3N was treated with an excess of aniline **12a** (3 equiv) for 20 hours at room temperature, the anilide **13** (R = H, X = H) was obtained in 98%

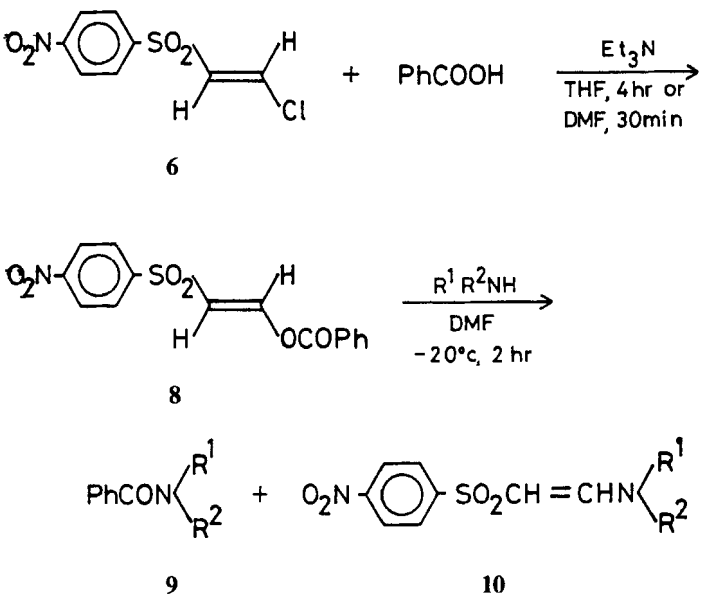

FIGURE 3

TABLE I

One-pot condensation of benzoic acid with amines by means of **6**

Entry		R^1R^2NH R^1	R^2	Products (Yield %) **9**	**10**
1	**a**	n-C_6H_{13}	H	83.1	[a]
2	**b**	$PhCH_2$	H	75.0	23.9
3	**c**	c-C_6H_{11}	H	90.0	[a]
4	**d**	$-(CH_2)_4-$		80.6	7.7
5	**e**	$-(CH_2)_5-$		86.7	[a]

[a] The corresponding enamines **10** were produced but not isolated.

yield. The enamine **15** was also obtained in 42% yield, which clearly shows that **15** was not formed by the reaction of aniline with **11** but was produced from aniline and the aldehyde **14**.[12] On the other hand, in the reactions of **11** with *o*-chloroaniline **12b** (Entry 2) and *N*-methylanilines (**12d** and **e**) (Entries 3 and 4), yields were unsatisfactory. However, when the reaction was carried out under forcing conditions (95–100°C, 2 hr), the yields were much improved (see Table II). Here, enamines of type **15** were not detected, possibly because of the ready polymerization of the liberated aldehyde under these conditions.

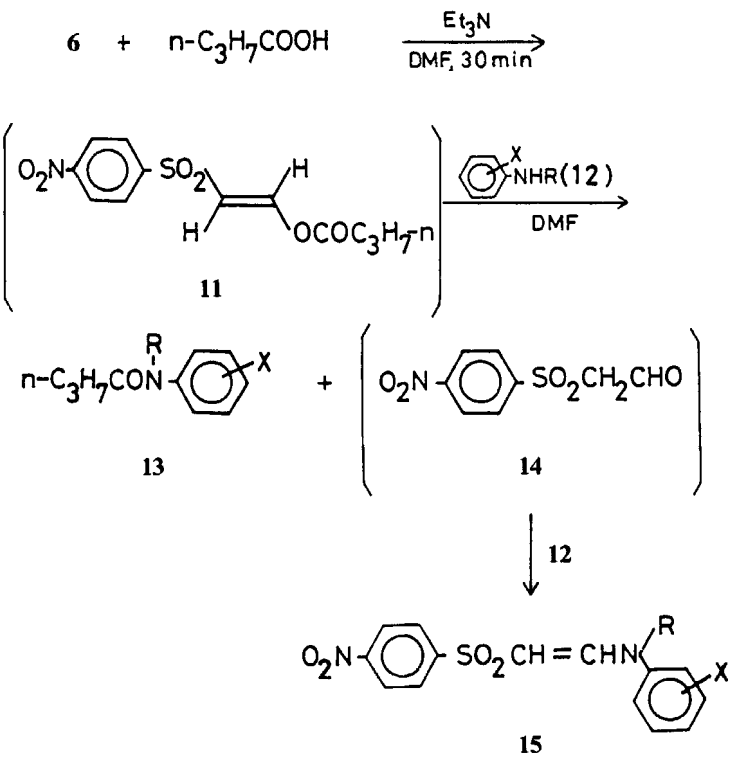

FIGURE 4

TABLE II

Condensation of butyric acid with anilines **12** by means of **6**

Entry	Aniline	X	R	Products (Yield %) Conditions A[a] 13	Conditions A[a] 15	Conditions B[b] 13	Conditions B[b] 15
1	**12a**	H	H	98.0	42	—	—
2	**12b**	*o*-Cl	H	46.0	[c]	48.7	nil
3	**12d**	H	Me	29.0	34	72.2	nil
4	**12e**	*o*-Cl	Me	nil		68.5	nil

[a]At room temp for 15 hr in DMF.
[b]At 95–100°C for 2 hr in DMF.
[c]Unidentified products were produced.

In order to avoid the formation of these unfavorable by-products, 2-bromo-2-trifluoromethylvinyl phenyl sulfones **7a** and **b**, which produce the ketone **16** after amidation, were prepared as follows. Phenylsulfenyl carbanion liberated from thioanisole by the aid of *n*-BuLi-DABCO was acylated with ethyl trifluoroacetate in THF at room temperature to phenyl trifluoroacetylmethyl sulfide **16**. Direct conversion of the sulfide or its derivatives to halovinyl compounds was unsuccessful even though the sulfide **16** was present in enolized form. Therefore, **16** was converted to **7a** and **b** by indirect method: ((i) $NaBH_4$ (ii) MsCl—Py (iii) DBU (iv) Br_2 (v) DBU (vi) mCPBA). The sulfones **7a** and **b** were separated by Lober column chromatography and the product having higher R_f value was shown to be **7a** and the lower one **7b**. The reaction of **7a** with carboxylate anions was very fast and complete within 30 minutes at −20°C to give **17** and **18**. In contrast to **7a**, isomer **7b** did not react with the anion. The mixed anhydride **17** was subjected to the reaction with amines, namely, anilines **12a–e** were added to **17** or **18** at −20°C and the mixture was then allowed to stand overnight at room temperature to give the corresponding anilides **19b–d** and **13a, b, d, e** (Table III). It is noteworthy that no enamines **20** were obtained as expected. Even a condensation of **17** with *p*-nitroaniline **12c**, an extremely weak nucleophile, gave good results when 3 molar equiv of **12c** was used in THF. However, **17** did not react with *o*-chloro-*N*-methylaniline **12e**. The active ester **18**, on the other hand, reacted with an equimolar amount of **12e** to give the anilide **13e** in 37.6% yield. The yield was increased to 48.7% when 3 molar equiv of **12e** was used and much improved to 62.8% when MeI was added. It is interesting that such difference of reactivity was observed in the reaction of **17** and **18** with **12c** and **e**. Here again, no enamines **20** were produced.

Since the new coupling reagents **6** and **7a** were thus found to be effective enough for *N*-methylanilide formation, we then examined whether these reagents could be used for large-membered cyclic *N*-methylanilide formation. The active ester **22** was prepared in a syringe by treating **6** (1.2 equiv) with **21** (1.0 equiv) in DMF at room temperature for 30 minutes in the presence of Et_3N (1.0 equiv). The syringe was then directly attached to the reaction vessel and **22** in DMF thus prepared was slowly added (12 hr) to a well-stirred toluene solution at 95–100°C using a microfeeder under nitrogen without adding any base. After the usual work up, the desired 15-membered cyclic lactam sulfide **23** was obtained in 66.2% yield. Quite

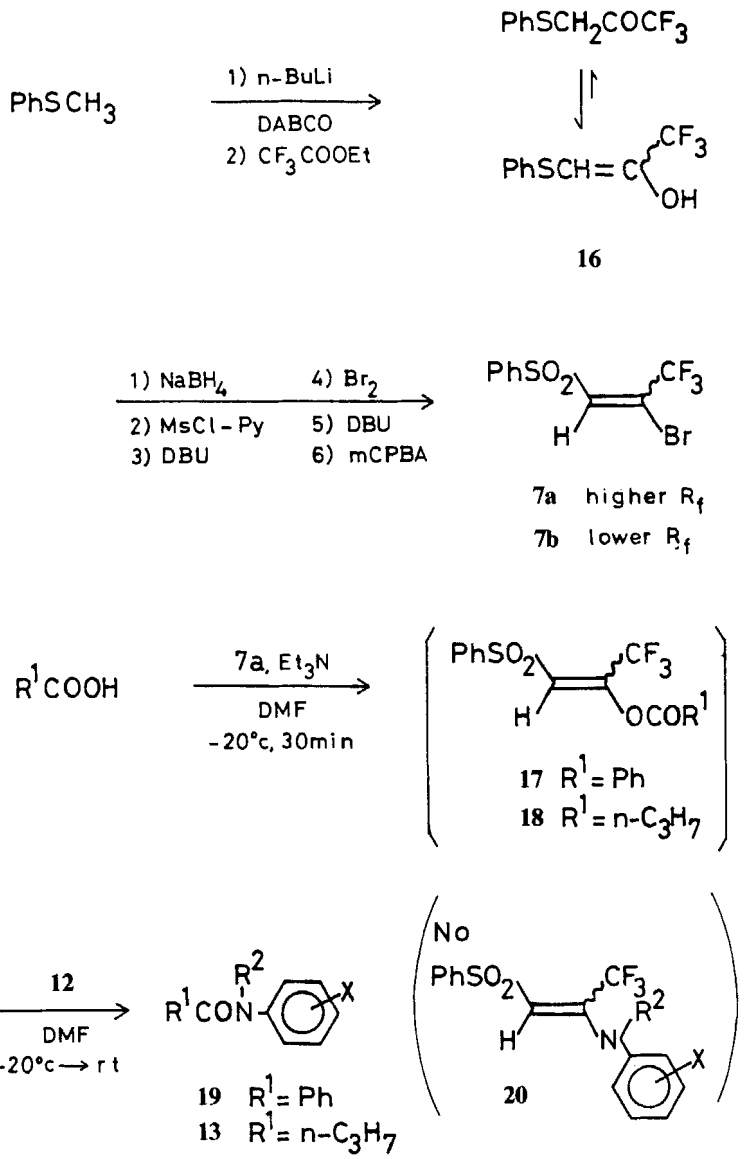

FIGURE 5

unexpectedly, **7a** did not give **23**, although various reaction conditions were examined.

As mentioned above, the coupling proceeds under essentially neutral conditions. Therefore, even if a hydroxyl group is present at the β-position of a carboxylic acid, the amidation can occur without producing β-elimination products. In fact, when the active ester **25**, prepared from 4,4-dimethyl-3-hydroxypentanoic acid **24** and **6** in DMF at room temperature, was treated with *N*-methylaniline **12d** at 95–100°C for 12 hours, β-hydroxy-*N*-methylanilide **26** was obtained in 55% yield. Although the

TABLE III

Condensation of benzoic or butyric acid with anilines **12** by means of **7a**

Entry	Aniline			Products (Yield %)	
		X	R	**19**	**13**
1	**12a**	H	H	—	69.2
2	**12b**	*o*-Cl	H	52.9	73.8
3	**12c**	*p*-NO_2	H	19.8[a] / 71.1[b]	nil
4	**12d**	H	Me	78.1	65.5
5	**12e**	*o*-Cl	Me	nil	37.6 / 48.7[c] / 62.8[d]

[a]The amidation was carried out at room temp for 9 days.
[b]The whole reaction was carried out in THF. The amidation was carried out by adding 3 molar equiv of **12c** at room temp for 2.5 days.
[c]The amidation was carried out by adding 3 molar equiv of **12e**.
[d]The amidation was carried out by adding 3 molar equiv of **12e** and 1.2 molar equiv of MeI.

yield was not exceptional, as expected, no α,β-unsaturated anilide was detected in the reaction mixture.

These results show that **6** is a promising coupling reagent for construction of macrocyclic lactams having a hydroxyl group at the β-position of the lactam carboxyl such as **5**.

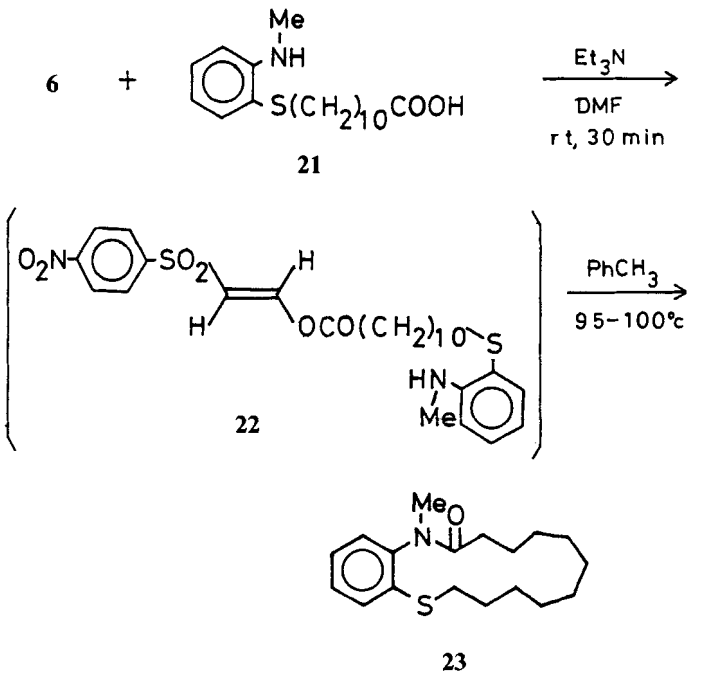

FIGURE 6

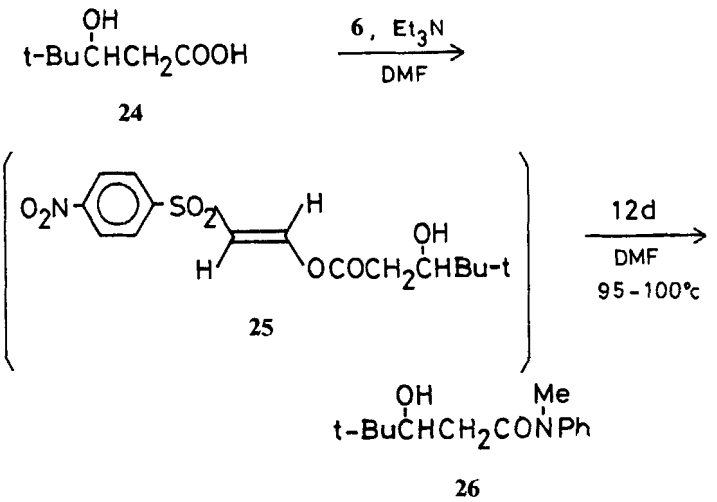

FIGURE 7

Next, we examined the suitability of **6** and **7a** for peptide formation. When *Boc*- and *Z*-amino acids **27** were treated with **6** in DMF at room temperature for an hour in the presence of Et_3N, the active esters **28** were obtained. On the other hand, when **7a** was used in place of **6**, the reaction was complete at $-20°C$ within 15 minutes to an hour yielding **29**. The esters **28** and **29** were used for the subsequent reaction without isolation.

The reaction of **28** in DMF with amino acid esters was performed at -40 to $-60°C$. Condensation was complete in a few minutes to give dipeptides **30b**, **d**–**h** in 45.5–80.8% yields. Yields were low particularly when GlyOEt was used as an amino acid ester. Enamines **31** were always obtained as by-products. On the other hand, much better results were obtained when **29** prepared from **7a** was used (Table IV). Enamines were not formed. Furthermore, in all cases examined here where the amino acids were protected by urethane formation (*Boc*- and *Z*-amino acids), no appreciable racemization occurred. Moreover, the value of the present reagent was evident in the formation of bulky *N*-methyldipeptide.

It has been reported that the coupling reaction is quite sluggish when *N*-methyl amino acids are used as a counterpart.[13] Although acid chlorides are known to react with *N*-methylamino acid,[13,14] a selective acid chloride formation cannot be achieved when amino acids carry hydroxyl, mercapto or ω-amino groups in the same molecule. Thus, it is desirable to explore a new coupling reagent that can satisfy this requirement. The reagents **6** or **7a** are expected to serve for this purpose, because the active esters prepared by means of **6** and **7a** were found to react even with *N*-methylaniline derivatives as mentioned above (see Table II and Table III).

As a model case, synthesis of *Boc*Val-*N*-MeValOMe **32**, one of the most hindered *N*-methyldipeptides was undertaken. *Boc*Val was treated with **6** to give the corresponding active ester, to which was added *N*-MeValOMe · HBr[15] and a molar equiv of Et_3N at $-20°C$. The temperature was raised gradually to room temperature over 18 hours. The usual work up gave *Boc*Val-*N*-MeValOMe **32** in 56.1% yield. Although

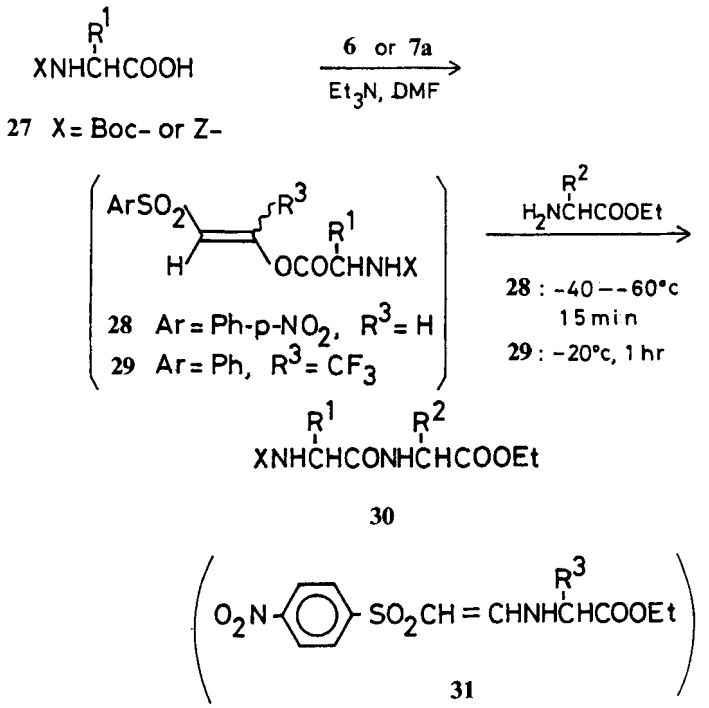

FIGURE 8

TABLE IV

Condensation of *Boc*- or *Z*-amino acids **27** with amino acid esters by means of **6** or **7a**

Entry		Product	Yield %		$[\alpha]_D$ (Temp in EtOH)		By-Product **31** %
			Method A[a]	Method B[b]	Method A[a]	Method B[b]	Method A[a]
1	**30a**	ZPheGlyOEt	—	73.6	—	−16.5° (21.5°C)[c,e]	—
2	**30b**	ZLeuGlyOEt	48.4	—	−26.6° (23°C)[d]	—	12.5
3	**30c**	ZAlaAlaOEt	—	83.1	—	−41.3° (19°C)	—
4	**30d**	ZPheAlaOEt	80.8	89.8	−20.7° (23°C)	−19.7° (18°C)	7.3
5	**30e**	*Boc*PheGlyOEt	45.5	76.8	−4.8° (20.5°C)	−4.5° (20°C)	23.0
6	**30f**	*Boc*ValGlyOEt	48.5	71.3	−26.7° (20.5°C)	−26.7° (20°C)	25.2
7	**30g**	*Boc*PheAlaOEt	63.4	72.7	−12.8° (20.5°C)[f]	−13.5° (21.5°C)	12.3
8	**30h**	*Boc*ValAlaOEt	67.9	67.7	−43.8° (23°C)[g]	−43.5° (21.5°C)	8.4

[a]The sulfone **6** was used for the coupling reagent.
[b]The sulfone **7a** was used for the coupling reagent.
[c]Reported $[\alpha]_D$: −16.6° (25°C).
[d]Reported $[\alpha]_D$: −26.3° (20°C).
[e]DCC-HOSu method: $[\alpha]_D^{25}$ −15.9°.
[f]DCC-HOSu method: $[\alpha]_D^{25}$ −11.1°.
[g]DCC-HOSu method: $[\alpha]_D^{25}$ −42.9°.

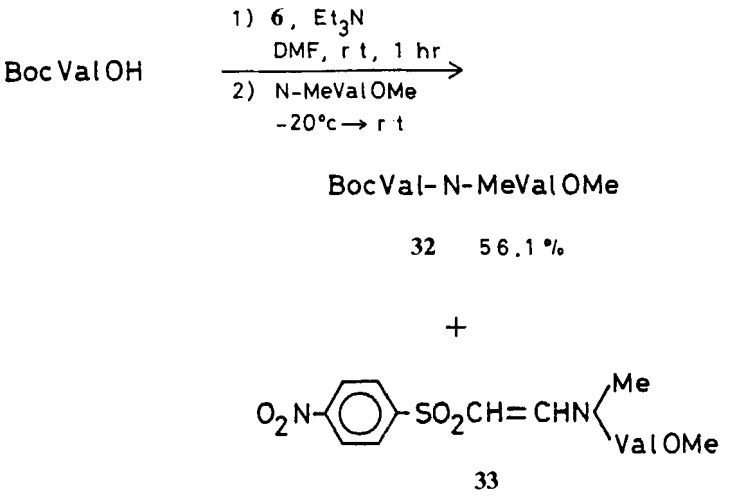

FIGURE 9

enamine **33** was also isolated in 83.7% yield, this can be readily separated by simple chromatography. The same coupling reaction did not take place when DCC-HOSu (in DMF) or DCC (in CH_2Cl_2, CH_3CN or DMF) were used. The reagent **7a** failed to give **32**.

Thus, **6** proved to be an effective coupling reagent for the formation of peptides such as Val-*N*-MeVal containing bulky *N*-methyl moieties.

EXPERIMENTAL

Boiling and melting points are uncorrected. Melting points were taken on a Kofler-type block. IR spectra were measured on a JASCO A-3 spectrophotometer, NMR spectra on JEOL MH-60 instrument in $CDCl_3$, MS spectrum on a HITACHI RMU-6MG mass spectrometer and $[\alpha]_D$ on a PERKIN-ELMER 241MC polarimeter. Lober column chromatography was subjected to MERCK Lober Größe B (310–25) LiChroprep Si 60 (40–63 μm).

E-2-Chlorovinyl p-nitrophenyl sulfone **6**. *E*-2-Chlorovinyl *p*-nitrophenyl sulfide was prepared in one pot by modification of Montanari's method.[11] Chlorine gas was introduced into a solution of *p*-nitrodiphenyl disulfide (15.00 g, 48.6 mmole) in CCl_4 (150 ml) for 3.5 hr at room temperature and the mixture was stirred overnight. Excess Cl_2 and CCl_4 were evaporated, first at room temperature and then at 50°C. The residue was dissolved in ethyl acetate (150 ml) and acetylene was introduced for 4 hr at room temperature. After the solution was stirred for 4.5 hr, acetylene was re-introduced for an hour. The mixture was then stirred for 12.5 hr at room temperature. The solvent was evaporated and the residue was chromatographed on silica gel (150 g) with *n*-hexane–ether (2 : 1–1 : 1) as an eluent to give the sulfide (14.89 g, 70.9%). Mp 101–103°C (CCl_4) (lit.[11] 108–109°C). IR ν_{max}^{neat} cm^{-1}: 1500, 1340. NMR δ: 6.61 (s, vinyl-H), 7.34 (d, J = 9.5 Hz, arom.-H), 8.17 (d, J = 9.5 Hz, arom.-H). *Anal.* Calcd.: C, 44.55; H, 2.80; N, 6.50. Found: C, 44.47; H, 2.76; N, 6.38.

m-Chloroperbenzoic acid (7.59 g, 44.0 mmole) was added to a solution of the above sulfide (4.31 g, 20.0 mmole) in CH_2Cl_2 (75 ml) under ice cooling and the mixture was stirred for 20 hr at room temperature. The resulting mixture was filtered and the filtrate was washed successively with 10% $Na_2S_2O_3$ solution, 10% Na_2CO_3 solution and brine and dried over Na_2SO_4. The solvent was evaporated and the residue was recrystallized from CCl_4 to give **6** (4.33 g, 87.4%). Mp 149–150°C (CCl_4) (lit.[11] mp. 158°C). IR ν_{max}^{neat} cm^{-1}: 1520, 1310, 1145. NMR δ: 6.75 (d, J = 13 Hz, vinyl-H), 7.57 (d, J = 13 Hz, vinyl-H), 8.07 (d, J = 9 Hz, arom.-H), 8.41 (d, J = 9 Hz, arom.-H). *Anal.* Calcd.: C, 38.80; H, 2.44; N, 5.66. Found: C, 38.70; H, 2.36; N; 5.48.

E-2-Benzoyloxyvinyl p-nitrophenyl sulfone **8**. (a) Triethylamine (45.1 μl, 0.323 mmole) was added to a solution of **6** (80.0 mg, 0.323 mmole) and benzoic acid (39.5 mg, 0.323 mmole) in THF (1.5 ml) at 25.5°C and the mixture was stirred for 4 hr. The resulting mixture was diluted with CH_2Cl_2–ether (1 : 4) and the organic layer was washed with water and dried over Na_2SO_4. The solvent was evaporated and the residue was recrystallized from CCl_4 to give **8** (93.7 mg, 87.0%). The mother liquor was concentrated and the residue was recrystallized from CCl_4 to give more **8** (9.3 mg, 8.6%).

(b) When the solvent was changed from THF to DMF in the above reaction, condensation was completed within 15 min to give **8**. The first crop: 93.2 mg (86.6%). The second crop: 5.2 mg (4.8%). Mp 185–187°C (CCl_4). IR ν_{max}^{neat} cm^{-1}: 1745. NMR δ: 6.49 (d, J = 12 Hz, vinyl-H), 8.13 (d, J = 9 Hz, arom.-H), 8.42 (d, J = 9 Hz, arom.-H), 8.71 (d, J = 12 Hz, vinyl-H). *Anal.* Calcd.: C, 54.05; H, 3.33; N, 4.20; S, 9.62. Found: C, 53.99; H, 3.33; N, 4.21; S, 9.54.

n-Hexylbenzamide **9a** *from* **8** *and n-hexylamine*. The mixed anhydride **8** (53.9 mg, 0.16 mmole) was dissolved in DMF (0.75 ml) at 50°C. *n*-Hexylamine (21.3 μl, 0.16 mmole) was added after the solution had been cooled to room temperature and the mixture was stirred for 2 hr. The resulting mixture was diluted with CH_2Cl_2–ether and the organic layer was washed with water and dried over Na_2SO_4. The solvent was evaporated and the residue was chromatographed on silica gel (5 g) using *n*-hexane–ether (5 : 1) as an eluent to give **9a** (24.3 mg, 73.2%).

n-Hexylbenzamide **9a** *from benzoyl chloride and n-hexylamine*. *n*-Hexylamine (202 mg, 2.00 mmole) in CCl_4 (2 ml) was added to a stirred solution of benzoyl chloride (281 mg, 2.00 mmole) in CCl_4 (1 ml) at −10°C over 15 min and the mixture was stirred for 2 hr. After addition of ice, the mixture was extracted with CCl_4. The extract was washed successively with 10% HCl solution, 10% Na_2CO_3 solution and brine and dried over Na_2SO_4. The solvent was evaporated and the residue was chromatographed on silica gel (30 g) using *n*-hexane–ether (3 : 1) as an eluent to give **9a** (181 mg, 44%). The IR and NMR spectra were identical with those obtained from *n*-hexylamine and benzoic acid by means of **6**.

Direct preparation of benzamides **9** *by means of* **6** *as a coupling reagent*

General procedure: Triethylamine (45.1 μl, 0.323 mmole) was added to a solution of **6** (80.0 mg, 0.323 mmole) and benzoic acid (39.5 mg, 0.323 mmole) in DMF (1.5 ml) at room temperature and the mixture was stirred for 15 min. Amines (0.323 mmole) were added after the solution had been cooled to −20°C and the mixture was stirred for 2 hr. The resulting mixture was diluted with CH_2Cl_2–ether (1 : 4) and the organic layer was washed with water and dried over Na_2SO_4. The solvent was evaporated and the residue was chromatographed on silica gel (5 g) using *n*-hexane–ether (5 : 1–1 : 1) as an eluent to give corresponding amides **9**. Further elution with *n*-hexane–ether (1 : 1) and ether gave the corresponding enamines **10** (see Table I for yields).

E-2-Pyrrolidinovinyl p-nitrophenyl sulfone **10d** *from* **6** *and pyrrolidine*.[2a] Pyrrolidine (59.3 μl, 0.711 mmole) was added to a solution of **6** (80.0 mg, 0.323 mmole) in DMF (1.5 ml) under ice cooling and the mixture was stirred for 30 min. The resulting mixture was diluted with CH_2Cl_2–ether (1 : 4) and the organic layer was washed with water and dried over Na_2SO_4. The solvent was evaporated and the residue was recrystallized from CCl_4 to give **10d**. The IR and NMR spectra were identical with those of the by-product obtained in preparation of **9d** from the active ester **8** and pyrrolidine.

Preparation of butyranilides **13** *by means of* **6** *as a coupling reagent*

General procedure: (a) *Reaction at room temperature*. Triethylamine (16.7 μl, 0.12 mmole) was added to a solution of **6** (24.8 mg, 0.10 mmole) and butyric acid (11.0 μl, 0.12 mmole) in DMF (0.5 ml) under ice cooling and the mixture was stirred for 30 min at room temperature. Anilines (0.30 mmole) were then added and the solution was stirred for 20 hr at room temperature. The mixture was diluted with CH_2Cl_2–ether (1 : 4) and the organic layer was washed with water and dried over Na_2SO_4. The solvent was evaporated and the residue was subjected to preparative TLC (silica gel, 1 mm × 20 cm × 20 cm) using *n*-hexane–ethyl acetate (3 : 1) as a developing solvent to give the corresponding amides **13** and enamines **15** (see Table II for yields).

(b) *Reaction on heating*. In amidation step, DMF (0.5 ml) was added and the solution was stirred for 12 hr at 95–100°C under argon atmosphere. Other procedures were the same as those described in (a) (see Table II for yields).

Phenyl trifluoroacetyl sulfide **16**. *n*-Butyllithium (1.54 N, 27.1 ml, 41.6 mmole) was added to a stirred solution of thioanisole (2.44 ml, 20.8 mmole) and DABCO (4.67 g, 41.6 mmole) in THF (40 ml) under nitrogen at −20°C and the mixture was stirred for 10 min at this temperature and then for 30 min at 0°C. The solution was cooled again at −20°C and ethyl trifluoroacetate (2.98 ml, 25.0 mmole) was added.

The temperature was gradually raised to 22°C over 4 hr. The resulting mixture was poured into ice-water and extracted with CH_2Cl_2–ether (1 : 4). The extract was washed with brine and dried over Na_2SO_4. The solvent was evaporated and the residue was distilled to give **16** (3.88 g, 84.7%). Bp 124–125°C (3 mmHg). IR ν_{max}^{neat} cm^{-1}: 3170 (b) (no C=O band). NMR δ: 3.42, 3.97 (each s, vinyl-H), 4.04 (s, OH). *Anal.* Calcd.: C, 49.10: H, 3.21. Found: C, 49.18; H, 3.18.

2-Bromo-2-trifluoromethylvinyl phenyl sulfone **7a** *and* **b**. Sodium borohydride (1.88 g, 49.8 mmole) was added to a solution of **16** (9.13 g, 47.4 mmole) in ethanol (95 ml) under ice cooling and the mixture was stirred for 15 min at 0°C and then for 2 hr at room temperature. The resulting mixture was diluted with CH_2Cl_2–ether (1 : 3) and the organic layer was washed with water and dried over Na_2SO_4. The solvent was evaporated to give crude alcohol (7.52 g).

Methanesulfonyl chloride (5.17 ml, 67.6 mmole) was added to a solution of the alcohol (7.52 g) in pyridine (75 ml) under ice cooling and the mixture was stirred for 12 hr. The resulting mixture was poured into ice and extracted with CH_2Cl_2–ether (1 : 4). The extract was washed with water and dried over Na_2SO_4. The solvent was evaporated to give crude methanesulfonate (9.76 g). NMR δ: 3.18 (s, OMs), 3.25 (d, J = 7 Hz, CH_2), 4.75–5.26 (m, CH).

A solution of DBU (5.66 g, 37.1 mmole) in dry benzene (30 ml) was added to a solution of the sulfonate (9.76 g) in benzene (200 ml) under ice cooling and the mixture was heated at gentle reflux for 4 hr. The resulting mixture was diluted with CCl_4 (375 ml) and the organic layer was washed with water and dried over Na_2SO_4. The filtrate was used for the following reactions without evaporation of the solvent.

A solution of ice-salt cooled Br_2 (5.4 g, 33.8 mmole) in CCl_4 (28 ml) was added to the above stirred solution below −15°C over 5 min and the mixture was stirred for 5.5 hr at −20°C. The solvent was evaporated to give crude dibromide (11.92 g).

A solution of DBU (5.66 g, 37.1 mmole) in dry benzene (30 ml) was added to a solution of the dibromide (11.92 g) in dry benzene (185 ml) under ice cooling and the mixture was heated at gentle reflux for 4.5 hr. The resulting mixture was diluted with CH_2Cl_2 (280 ml) and the organic layer was washed with water and dried over Na_2SO_4. The filtrate was used for the following reaction without evaporation of the solvent.

m-Chloroperbenzoic acid (14.63 g, 65.5 mmole) was added portionwise to the above stirred solution under ice-salt cooling. The temperature was gradually raised to 25°C over 8 hr and the suspension was stirred for another 4 hr. The resulting mixture was filtered and the filtrate was washed successively with 10% Na_2CO_3 solution and brine and dried over Na_2SO_4. The solvent was evaporated and the residue was chromatographed on a Lober column using *n*-hexane–ethyl acetate (3 : 1) as an eluent to give **7a** (3.39 g, 26.1% from **16**), a mixture of **7a** and **b** (0.23 g, 1.7% from **16**) and **7b** (2.24 g, 17.2% from **16**), successively. The sulfone **7a** shows higher R_f value than **7b**. **7a**: bp 80°C (0.05 mmHg). IR ν_{max}^{neat} cm^{-1}: 1335, 1155. NMR δ: 7.58 (s, vinyl-H). *Anal.* Calcd.: C, 34.31; H, 1.92; S, 10.18. Found: C, 34.66; H, 1.95; S, 10.31. **7b**: mp 58–60°C (ethanol–water). IR ν_{max}^{neat} cm^{-1}: 1320, 1130 (b). NMR δ: 7.23 (s, vinyl-H). *Anal.* Calcd.: C, 34.31; H, 1.92; S, 10.18. Found: C, 34.28; H, 1.94; S, 10.24.

Preparation of anilides **19b–d** *and* **13a, b, d, e** *by means of* **7a** *as a coupling reagent*

General procedure: Triethylamine (16.7 μl, 0.12 mmole) was added to a solution of **7a** (31.5 mg, 0.12 mmole) and benzoic acid (14.7 mg, 0.12 mmole) or *n*-butyric acid (11.0 μl, 0.12 mmole) in DMF (0.5 ml) at −20°C and the mixture was stirred for 30 min. Anilines (0.12 mmole) were added to the stirred solution and the temperature was gradually raised to room temperature over 20 hr. The resulting mixture was diluted with CH_2Cl_2–ether (1 : 3) and the organic layer was washed with water and dried over Na_2SO_4. The solvent was evaporated and the residue was subjected to preparative TLC (silica gel, 1 mm × 20 cm × 20 cm) using *n*-hexane–ethyl acetate (3 : 1–1 : 1) as a developing solvent to give the corresponding anilides **19** and **13** (see Table III for yields). In these reactions no enamines **20** could be obtained.

Preparation of lactam sulfide **23** *from* **21** *by means of* **6** *as a coupling reagent.* (a) Triethylamine (14.0 μl, 0.10 mmole) was added to a solution of **6** (29.7 mg, 0.12 mmole) and **21** (32.3 mg, 0.10 mmole) in DMF (0.5 ml) under ice cooling in 10 ml syringe and the mixture was stirred for 30 min at room temperature. After dilution with DMF (1.5 ml), the mixture was injected to vigorous stirred DMF (10 ml) at 95–100°C by using a microfeeder over 12 hr under nitrogen atmosphere (the syringe was cooled with running water). The solution was heated for another 4 hr. The solvent was evaporated at 40°C and the residue was filtered through silica gel (3 g) with CH_2Cl_2 as an eluent to give an oil. The oil was subjected to preparative TLC (silica gel, 1 mm × 20 cm × 20 cm) using *n*-hexane–ethyl acetate (5 : 1 and then 4 : 1) as a developing solvent to give **23** (17.3 mg, 56.7%). The IR and NMR spectra were identical with those of authentic sample.[8]

(b) The reaction was conducted in the same manner as described above except for changing the solvent from DMF to toluene in lactamization step and raising the reaction temperature to reflux temperature of toluene. The lactam **22** was obtained in 66.2% yield after purification on preparative TLC (20.2 mg).

4,4-Dimethyl-3-hydroxypentanoic acid **24**. Acetic acid (0.34 ml, 6.00 mmole) was added to a stirred solution of LDA in THF (10 ml) prepared from di-*i*-propylamine (1.80 ml, 13.00 mmole) and 1.33 N *n*-BuLi in *n*-hexane (9.00 ml, 12.0 mmole) at −65°C under nitrogen atmosphere and the mixture was stirred for 10 min. Pivalaldehyde (0.54 ml, 5.00 mmole) was added to the above solution at the same temperature. The temperature was then gradually raised to −18°C over 3 hr. Water was added and the reaction mixture was acidified with oxalic acid to pH 4 and extracted with ether. The extract was washed with brine and dried over Na_2SO_4. The solvent was evaporated and the residue was recrystallized from benzene–*n*-hexane to give **24** (292.8 mg, 40%). Mp 75–78°C (benzene–*n*-hexane). IR ν_{max}^{neat} cm^{-1}: 3400 (b), 1715 (b). NMR δ: 0.92 (s, Me), 2.39–2.54 (m, CH_2), 3.71, 3.78 (each d, J = 8.5 Hz, CH), 6.89 (b.s. OH). *Anal.* Calcd.: C, 57.57; H, 9.58. Found: C, 57.47; H, 9.66.

N-Methyl-4,4-dimethyl-3-hydroxypentananilide **26**. Triethylamine (16.7 μl, 0.12 mmole) was added to a solution of **6** (24.8 mg, 0.10 mmole) and **24** (17.5 mg, 0.12 mmole) in DMF (0.5 ml) under ice cooling and the mixture was stirred for an hour at room temperature. The solution was diluted with DMF (0.5 ml) and then *N*-methylaniline **12d** (32.6 μl, 0.30 mmole) was added. The mixture was heated for 12 hr at 95–100°C with stirring under argon atmosphere. The resulting mixture was diluted with CH_2Cl_2–ether (1 : 3) and the organic layer was washed with brine and dried over Na_2SO_4. The solvent was evaporated and the residue was subjected to preparative TLC (silica gel, 1 mm × 20 cm × 20 cm) using *n*-hexane–ethyl acetate (3 : 1) as a developing solvent to give **26** (13.0 mg, 55%). IR ν_{max}^{neat} cm^{-1}: 3440 (b), 1645. NMR δ: 0.76 (s, Me), 2.00–2.57 (m, CH_2), 3.28 (s, N—Me), 3.50–3.73 (m, CH). MS: m/e 235 (M^+).

Preparation of dipeptides **30b, d–h** *by means of* **6** *as a coupling reagent.* Triethylamine (41.9 μl, 0.300 mmole) was added to a solution of **6** (74.3 mg, 0.300 mmole) and *Boc*- or *Z*-amino acid (0.300 mmole) in DMF (1.2 ml) under ice cooling and the mixture was stirred for 5 min under ice cooling and for an hour at room temperature. Amino acid ethyl ester hydrochlorides (0.300 mmole) and Et_3N (41.9 μl, 0.300 mmole) were added after the solution had been cooled to −40 to −60°C and the mixture was stirred for 15 min. Water was added and the resulting mixture was extracted with CH_2Cl_2–ether (1 : 4). The extract was washed with water and dried over Na_2SO_4. The solvent was evaporated and the residue was passed through a silica gel short column and chromatographed on a Lober column using *n*-hexane–ethyl acetate (3 : 2–1 : 1) as an eluent to give the corresponding dipeptides **30** (see Table IV for yields and $[\alpha]_D$ values).

Preparation of dipeptides **30a, c–h** *by means of* **7a** *as a coupling reagent.* Triethylamine (30.7 μl, 0.220 mmole) was added to a solution of **7a** (63.0 mg, 0.200 mmole) and *Boc*- or *Z*-amino acid (0.220 mmole) in DMF (0.4 ml) at −20°C and the mixture was stirred for 15 min to an hour. Amino acid ethyl ester hydrochloride (0.220 mmole) and Et_3N (30.7 μl, 0.220 mmole) were then added to the solution at −20°C and the mixture was stirred for an hour. Water was added and the resulting mixture was extracted with CH_2Cl_2–ether (1 : 4). The extract was washed with water and dried over Na_2SO_4. The solvent was evaporated and the residue was passed through a silica gel short column and chromatographed on a Lober column using *n*-hexane–ethyl acetate (3 : 2–1 : 1) as an eluent to give the corresponding dipeptides **30** (see Table IV for yields and $[\alpha]_D$ values).

BocVal-N-MeValOMe **32**. Triethylamine (15.3 μl, 0.110 mmole) was added to a solution of **6** (24.8 mg, 0.100 mmole) and BocVal (21.9 mg, 0.120 mmole) in DMF (0.5 ml) under ice cooling and the mixture was stirred for an hour at room temperature. *N*-MeValOMe · HBr[15] (54.0 mg, 0.240 mmole) and Et_3N (27.9 μl, 0.200 mmole) were added after the stirred solution had been cooled to −20°C. The temperature was then gradually raised to 23°C over 18 hr. The mixture was stirred for another 9 hr at room temperature. The resulting mixture was diluted with CH_2Cl_2–ether (1 : 3) and the organic layer was washed with water and dried over Na_2SO_4. The solvent was evaporated and the residue was subjected to preparative TLC (silica gel, 1 mm × 20 cm × 20 cm) using *n*-hexane–ethyl acetate (3 : 1) as an eluent to give **32** (19.3 mg, 56.1%) and **33** (29.8 mg, 83.7%). **32**: bp 135° (0.05 mmHg). IR ν_{max}^{neat} cm^{-1}: 3325, 1740, 1705, 1645. NMR δ: 0.85, 0.97, 0.97, 1.03 (each d, J = 6 Hz, *i*-propyl–Me), 1.46 (s, *t*-butyl–Me), 3.12 (s, N—Me), 3.75 (s, COOMe). *Anal.* Calcd.: C, 59.10; H, 9.63. Found: C, 59.47; H, 9.47. **33**: IR ν_{max}^{neat} cm^{-1}: 1740, 1610, 1530, 1350, 1135. NMR δ: 0.92, 0.98 (each d, J = 7 and 6.5 Hz, *i*-propyl–Me), 2.84 (s, N—Me), 3.79 (s, COOMe), 5.06 (d, J = 13 Hz, vinyl-H), 7.45 (d, J = 13 Hz, vinyl-H), 8.00 (d, J = 9 Hz, arom.-H), 8.31 (d, J = 9 Hz, arom.-H).

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