analyses. Helpful discussions with Dr. A. G. Schultz are gratefully acknowledged.

Registry No. (±)-**2**, 88304-40-9; (±)-**2**·HCl, 88335-59-5; **3**, 64982-52-1; **4**, 88304-27-2; **5**, 88304-28-3; (±)-**6**, 88304-29-4; **7**, 88304-30-7; (±)-**8**, 88304-31-8; (±)-**9**, 88304-32-9; (±)-**10**, 88304-33-0; (±)-**11** (isomer 1), 88304-34-1; (±)-**11** (isomer 2), 88304-41-0; (±)-**12**, 88304-35-2; (±)-**14**, 88304-36-3; (±)-**15**, 88304-37-4; (±)-**16**, 88335-56-2; (±)-**17**, 88304-38-5; (±)-**18**, 88335-58-4; (±)-**19**, 88304-39-6; (±)-**19**·$^1/_2C_2H_2O_4$, 88335-84-6; 2-methoxy-5-chlorobenzaldehyde, 7035-09-8; 2-methoxy-5-chlorophenol, 3743-23-5; 2,3,4,5,6,6a-hexahydro-3-methyl-6-hydroxy-8-methoxy-1*H*-4,11b-methanobenzofuro[3,2-*d*]azocine hydrochloride, 88335-57-3.

Supplementary Material Available: Tables of atomic parameters for the heavier atoms and bond angles (3 pages). Ordering information is given on any current masthead page.

Electroorganic Chemistry. 82. β-Amino Acid Esters from α-Methoxycarbamates and Ketene Silyl Acetals; Cyclization to β-Lactams

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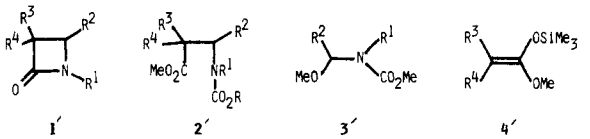
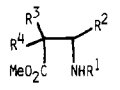
A new synthetic method of β-lactams 1′ is described. The key intermediates, *N*-carbomethoxy-β-amino acid esters 2′, were synthesized by the reaction of α-methoxylated carbamates 3′ with ketene methyl trimethylsilyl acetals 4′ catalyzed by titanium tetrachloride in 66–93% yields. 2′ were deprotected to 5′ by 25% HBr in HOAc (R = Me) or hydrogenolysis (R = CH_2Ph) in 42–78% yields. 1′ were prepared by treating 5′ with Grignard reagents (PhMgBr or EtMgBr) in 38–95% yields.

β-Lactams are some of the most important antibiotics, as exemplified by penicillins and cephalosporins, and hence preparation of new compounds containing a β-lactam moiety has always attracted much attention. We report herein a new synthetic method of β-lactams[1] utilizing the reaction of α-methoxylated carbamates[2] with ketene methyl trimethylsilyl acetals[3] as the key reaction.



1′ 2′ 3′ 4′



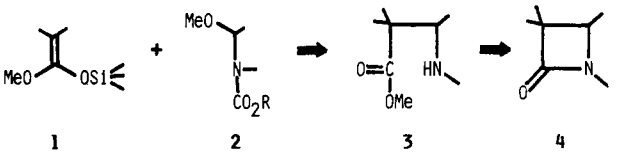
5′

R^1 = H, Me, iso-Bu. R^2 = H, Me, iso-Pr.

R^1-R^2 = $(CH_2)_3$, $(CH_2)_4$, $(CH_2)_5$. R^3,R^4 = Me,Me; H,Ph; H,Et; H,n-C_6H_{13}. R = Me, CH_2Ph.

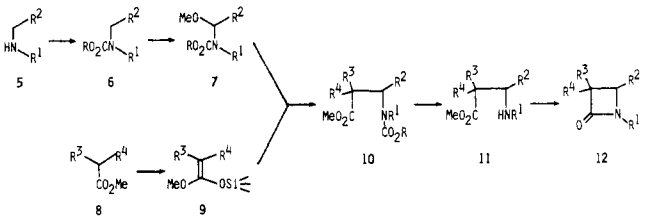
As shown in Scheme I, the cyclization step comprises the formation of a nitrogen–carbon bond between amino and methoxycarbonyl groups in β-amino acid esters **3** synthesized from **1** and **2**. Since **1** and **2** are prepared from esters and amines respectively, the 2-azetidinone skeleton **4** is constructed by a formal [2 + 2] addition of an ester and an amine. The overall procedure is shown in Scheme II, which suggests that a variety of substituents R^1–R^4 can be introduced to β-lactams **12** through the proper choice of the starting materials (**5** and **8**).

Scheme I



1 2 3 4

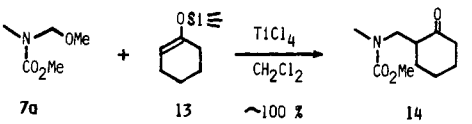
Scheme II



5 6 7 8 9 10 11 12

Results and Discussion

Reaction of α-Methoxylated Carbamates 7 with Ketene Methyl Trimethylsilyl Acetals 9. As we have already reported, α-methoxylated carbamates (**7**) react with various nucleophiles under acidic conditions.[4] For example, the reaction of **7a** with silyl enol ether **13** afforded *N*-(carbomethoxyamino)methylated cyclohexanone **14** (eq 1).[4a] In order to prepare β-alanine derivatives **10**, the



7a 13 ~100 % 14 (1)

reaction of **7** with ketene methyl trimethylsilyl acetals **9** was investigated. The reaction of **7a** with **9a** gave **10a** in satisfactory yield under similar reaction conditions to those

(1) Interesting methods recently developed, for example: (a) Miller, M. J.; Mattingly, P. G.; Morrison, M. A.; Kerwin, J. F., Jr. *J. Am. Chem. Soc.* **1980**, *102*, 7026. (b) Floyd, D. M.; Fritz, A. W.; Cimarusti, C. M. *J. Org. Chem.* **1982**, *47*, 176.

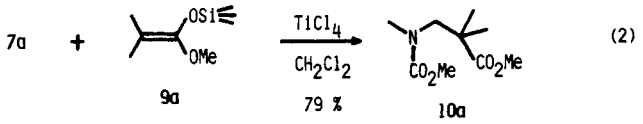
(2) Shono, T.; Hamaguchi, H.; Matsumura, Y. *J. Am. Chem. Soc.* **1975**, *97*, 4264.

(3) Ainsworth, C.; Chen, F.; Kuo, Y.-N. *J. Organomet. Chem.* **1972**, *46*, 59.

(4) (a) Shono, T.; Matsumura, Y.; Tsubata, K. *J. Am. Chem. Soc.* **1981**, *103*, 1172. (b) Shono, T.; Matsumura, Y.; Tsubata, K.; Takata, J. *Chem. Lett.* **1981**, 1121. (c) Shono, T.; Matsumura, Y.; Tsubata, K. *Tetrahedron Lett.* **1981**, *22*, 2411. (d) Shono, T.; Matsumura, Y.; Tsubata, K. *Ibid.* **1981**, *22*, 3249.

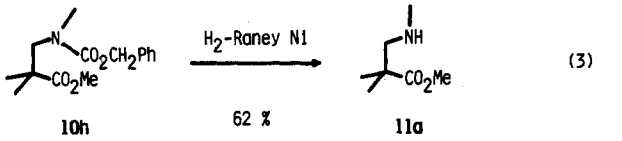
0022-3263/84/1949-1056$01.50/0

in eq 1 (eq 2). All the results are summarized in Table I. Although the reaction of ketene alkyl trimethylsilyl acetals with imines[5] or carbamates[6] has already been reported, the types of amines in the imines or carbamates are rather limited. On the other hand, a variety of primary, secondary, and cyclic amines can be used in our method as shown in Table I. Benzyl carbamate (**7d**) is also usable in place of methyl carbamates (Table I, entry 8). Stereoselectivity was not always observed in the reaction of **7** with **9** under the reaction conditions used in the present study (see footnotes b, e, f, and g of Table I).



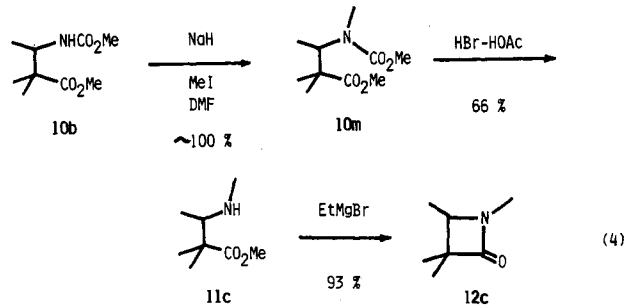
(2)

Deprotection of Carbamates. Selective removal of the carbomethoxyl group of carbamates from **10** without hydrolyzing the methyl ester is necessary to obtain β-amino acid esters **11**. This process was carried out by treating **10** with excess of 25% hydrogen bromide solution in acetic acid[7] followed by working up with alkali. Results are summarized in Table II. An alternative synthetic method of **11** is hydrogenolysis of a benzyl carbamate. Namely, **11a**, obtainable by the hydrogen bromide method in 52% yield, was prepared by hydrogenolysis of **10h** in 62% yield (eq 3).



(3)

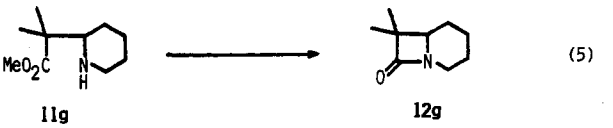
Cyclization of β-Amino Acid Esters 11 to β-Lactams 12. (i) Monocyclic β-Lactams. β-Amino acid esters **11a–e**, prepared from primary and acyclic secondary amines, were transformed to monocyclic β-lactams by treating with Grignard reagents.[9] When the starting amines are primary, further alkylation of the nitrogen atom is achievable after the reaction of α-methoxylated carbamates and ketene methyl trimethylsilyl acetals was carried out. Thus, **10b** was methylated to give **10m**, which was then transformed to β-lactam **12c** (eq 4).



(4)

This stepwise alkylation of the amino moiety is important, since the anodic α-methoxylation always takes place at the less-substituted α-position of the starting dialkylamine carbamates.[2] Thus, compound **10m** cannot be prepared directly from *N*-methylethylamine, since the first α-methoxylation takes place at the methyl group rather than ethyl group. All the results are summarized in Table II.

(ii) Bicyclic β-Lactams. When cyclic amines such as pyrrolidine, piperidine, and hexamethyleneimine were used as the starting amines, bicyclic β-lactams were obtained. However, since these bicyclic β-lactams have much more ring strain than monocyclic ones, low yields of the products were anticipated. With use of an amino ester **11g** as the typical compound, a variety of reaction conditions were investigated to find out the best conditions (eq 5). The results (Tables III and IV) show that the phenylmagnesium bromide–THF system gave the best result among the reaction conditions investigated, though ethylmagnesium bromide or LDA as a base and ether or benzene as a solvent also gave fairly good results. All the results are shown in Table II.



(5)

Experimental Section

All the products gave satisfactory analyses; infrared and ^1H NMR spectra were consistent with structures. Complete analytical and spectral data, which were submitted for review are given in supplemental material. (See paragraph at end of paper.)

Melting points were taken with a Yanako micro melting point apparatus and are uncorrected as are boiling points. GLC analyses were performed on a Shimadzu GC-4BIT gas chromatograph. Solvents (THF, ether, benzene, CH_2Cl_2, and hexane) were dried and distilled under an atmosphere of nitrogen. Grignard reagents (EtMgBr,[10] PhMgBr,[11] and *t*-BuMgCl[12]) were prepared according to the reported methods, and the concentration was determined by titration.

Preparation of α-Methoxylated Carbamates. α-Methoxylated Carbamates were obtained by anodic oxidation of the corresponding carbamates in methanol according to the reported procedure.[2,4a] The data of the new compounds are as follows.

***N*-(Benzyloxycarbonyl)-α-methoxydimethylamine (7d)**: 82% yield at 3.9 F/mol; bp 105–110 °C (2 mm).

1-Carbomethoxy-2-methoxyhexamethylenimine (7h): 89% yield at 2 F/mol; bp 72–75 °C (3 mm).

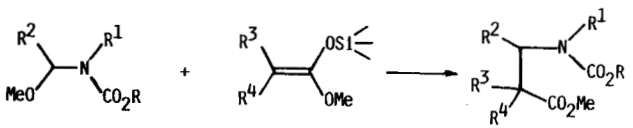
Preparation of Ketene Methyl Trimethylsilyl Acetals. Ketene methyl trimethylsilyl acetals were synthesized from the corresponding methyl esters according to the reported procedure.[3] The data of a new compound **9d** is as follows.

***n*-Hexyl ketene methyl trimethylsilyl acetal (9d)**: 72% yield; bp 98–102 °C (13 mm).

Reaction of α-Methoxylated Carbamates with Ketene Methyl Trimethylsilyl Acetals. General Procedure. To a stirred solution of titanium tetrachloride (20 mmol) in CH_2Cl_2 (20 mL) was added a solution of **7** (20 mmol) in CH_2Cl_2 (2 mL) at −70 °C under an atmosphere of nitrogen. After the solution was stirred for 5 min, a solution of **9** (22 mmol) in CH_2Cl_2 (2 mL) was added to the reaction mixture, which was then stirred under the reaction conditions (temperature and time) shown in Table I. The mixture was poured into cold brine (50 mL), and the resulting solution was stirred for 20–30 min. The organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). After the combined organic layer was dried ($MgSO_4$), filtered, and concentrated, the residue was purified by distillation or column chromatography on silica gel (*n*-hexane–AcOEt) to give **10**.

(5) Ojima, I.; Inaba, S.; Yoshida, K. *Tetrahedron Lett.* **1977**, *3643*.
(6) Ikeda, K.; Terao, Y.; Sekiya, M. *Chem. Pharm. Bull.* **1981**, *29*, 1747.
(7) This reagent is generally applied to the deprotection of the benzyloxycarbonyl group.[8]
(8) (a) Ben-Isai, D.; Berger, A. *J. Org. Chem.* **1952**, *17*, 1564. (b) Ben-Ishai, D. *Ibid.* **1954**, *19*, 62.
(9) Grignard reagents are often used as bases in cyclization of β-amino acid esters. For example: (a) Holley, R. W.; Holley, A. D. *J. Am. Chem. Soc.* **1949**, *71*, 2124. (b) Shibuya, M.; Kubota, S. *Heterocycles* **1980**, *14*, 601. (c) Kametani, T.; Huang, S. P.; Yokohama, S.; Suzuki, Y.; Ihara, M. *J. Am. Chem. Soc.* **1980**, *102*, 2060.
(10) Fisher, H. "Organic Syntheses"; Wiley: New York, 1943; Collect. Vol. 2, p 198.
(11) Allen, C. F.; Converse, S. "Organic Syntheses", 2nd ed.; Wiley: New York, 1941; Collect. Vol. 1, p 226.
(12) Puntambeker, S. V.; Zoellner, E. A. "Organic Syntheses", 2nd ed.; Wiley: New York, 1941; Collect. Vol. 1, p 524.

Table I. Reaction of 7 with 9

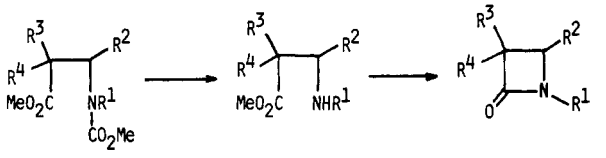


7 9 10

entry	7[a]	9	reaction temp, °C	reaction time, h	10[a]	bp or mp, °C (mm)	yield, %
1	**7a**	**9a**	−70 → rt[j]	2	**10a**	73-74 (1.4)	79
2	**7b**, R^1 = H; R^2 = Me	**9a**	−70 → rt	2	**10b**, R^1 = H; R^2 = R^3 = R^4 = Me	86-89 (2)	71
3	**7b**	**9b**, R^3 = H; R^4 = Ph	−70 → rt	17	**10c**,[b] R^1 = R^3 = Ph; R^2 = Me, R^4 = Ph	95-102 (0.55)[c,d]	81
4	**7b**	**9c**, R^3 = H; R^4 = Me	−70 → rt	5.5	**10d**,[e] R^1 = R^3 = H; R^2 = R^4 = Me	85-93 (1.5)[d]	78
5	**7b**	**9d**, R^3 = H; R^4 = n-C_6H_{13}	−70 → rt	2	**10e**,[f] R^1 = R^3 = H; R^2 = Me; R^4 = n-C_6H_{13}	118-122 (2)[d]	67
6	**7c**, R^1 = H; R^2 = i-Pr	**9a**	−60	1	**10f**, R^1 = H; R^2 = i-Pr; R^3 = R^4 = Me	65-70 (0.65)[c]	93
7	**7c**	**9b**	−70 → rt	15	**10g**,[g] R^1 = R^3 = H; R^2 = i-Pr; R^4 = Ph	**10g-A**, 165-166[h] **10g-B**, 132-133[h]	66
8	**7d**, R^1 = Me; R^2 = H; R = CH_2Ph	**9b**	−70 → rt	5	**10h**, R^1 = R^3 = R^4 = Me; R^2 = H; R = CH_2Ph	*i*	91
9	**7e**, R^1 = i-Bu; R^2 = i-Pr	**9a**	−60	0.7	**10i**, R^1 = i-Bu; R^2 = i-Pr; R^3 = R^4 = Me	*i*	85
10	**7f**, R^1,R^2 = $(CH_2)_3$	**9a**	−70 → rt	4.5	**10j**, R^1,R^2 = $(CH_2)_3$; R^3 = R^4 = Me	75-80 (0.55)[c]	68
11	**7g**, R^1,R^2 = $(CH_2)_4$	**9a**	−70 → rt	2	**10k**, R^1,R^2 = $(CH_2)_4$; R^3 = R^4 = Me	120-123 (4)	66
12	**7h**, R^1,R^2 = $(CH_2)_5$	**9a**	−70 → rt	15	**10l**, R^1,R^2 = $(CH_2)_5$; R^3 = R^4 = Me	108-109 (1.2)	73

[a] R = Me except for **7d** and **10h** (R = CH_2Ph). [b] Two stereoisomers were not able to be separated by GLC or TLC. The ratio of the isomers was determined from NMR to be ~1:1. [c] Bulb-to-bulb distillation. [d] Boiling point of the mixture of the stereoisomers. [e] Analytical samples of two stereoisomers [**10d-A** (the former peak) and **10d-B** (the latter peak)] were separated by GLC. The ratio of **10d-A**/**10d-B** was determined from GLC to be 9:5. [f] Analytical samples of two stereoisomers (**10e-A** and **10e-B**) were separated by preparative TLC (silica, *n*-hexane–AcOEt; 5:1, R_f **10e-A** = 0.27; **10e-B** = 0.20). The ratio of **10e-A**/**10e-B** was determined from GLC to be 9:5. [g] Analytical samples of two stereoisomers (**10g-A** and **10g-B**) were separated by preparative TLC (silica, *n*-hexane–AcOEt; 5:1, R_f **10g-A** = 0.43, **10g-B** = 0.37). The ratio of **10g-A**/**10g-B** was determined from NMR to be 1:1. [h] Recrystallized from *n*-hexane. [i] These liquids were isolated by column chromatography on silica gel (*n*-hexane–AcOEt). [j] rt = room temperature.

Table II. Deprotection of Carbamates and Cyclization of Amino Acid Esters to β-Lactams



10 11 12

					deprotection of carbamates			cyclization of amino acid esters[a]				
entry	R^1	R^2	R^3	R^4	11	bp,[b] °C (mm)	yield of 11, %	R in RMgBr	reaction temp, °C	reaction time, h	12	yield of 12, %
1	Me	H	Me	Me	**11a**	53-58 (14)	52	Et	0	2	**12a**	91
2	H	Me	Me	Me	**11b**	80-88 (13.5)	66	Et	0	3	**12b**	87
3	Me	Me	Me	Me	**11c**	85-90 (13.5)	66	Et	0 → rt[f]	15	**12c**	93
									0 → 5	4		92[c]
4	H	Me	H	n-C_6H_{13}	**11d**	85-90 (5)[d]	78	Et	0	2	**12d**[e]	38
								Ph	0	1		51
5	i-Bu	i-Pr	Me	Me	**11e**	40-45 (0.5)	42	Et	0 → rt	24	**12e**	42
6	$(CH_2)_3$		Me	Me	**11f**	90-93 (0.5)	61	Ph	0	1	**12f**	79
7	$(CH_2)_4$		Me	Me	**11g**	90-95 (0.3)	75	Ph	0	1	**12g**	95
8	$(CH_2)_5$		Me	Me	**11h**	93-95 (1.9)	78	Ph	0	1	**12h**	83

[a] THF was used as solvent unless otherwise noted. [b] Bulb-to-bulb distillation except for **11h**. [c] Ether was used as solvent. [d] Boiling point of two stereoisomers, which were not able to be separated. [e] A mixture of two stereoisomers [**12d-A** (the former peak) and **12d-B** (the latter peak)], of which analytical samples were separated by GLC. The ratio of **12d-A**/**12d-B** was determined from GLC and NMR to be ~2:1. [f] rt = room temperature.

Table III. Cyclization of 11g (Solvent = THF)

base	yield of 12g, %	base	yield of 12g, %
EtMgBr	75	t-BuMgCl	49
PhMgBr	95	LDA	91

Table IV. Cyclization of 11g (Base = PhMgBr)

solvent	yield of 12g, %	solvent	yield of 12g, %
ether	75	benzene	78
THF	95	hexane	22
CH_2Cl_2	49		

Deprotection of Carbamates. (A) HBr–HOAc Method. General Procedure. A mixture of **10** (10 mmol) and 25% HBr in HOAc (10 mL) was stirred at room temperature overnight. After HBr and HOAc were evaporated with heating under reduced pressure, the residue was made basic with 10% sodium hydroxide in ice–water bath. The product was extracted with ether (4 × 10 mL), and the combined organic layer was dried ($MgSO_4$), filtered, and concentrated. The residue was purified by bulb-to-bulb distillation to give **11**.

(B) Hydrogenolysis of Benzyl Carbamate. A mixture of **10h** (5 mmol) and Raney nickel[13] (0.5 g) in methanol (20 mL) was shaken under an atmosphere of hydrogen (10 kg/cm^2) for 5 h. The mixture was filtered, concentrated, and distilled (bulb to bulb) to yield **11a** in 62% yield.

Preparation of Methyl 3-(Carbomethoxymethylamino)-2,2-dimethylbutyrate (10m). To a stirred suspension of sodium hydride (7.5 mmol) in dry DMF (15 mL) was added dropwise a solution of **10b** (5 mmol) in dry DMF (5 mL) at 0 °C under an atmosphere of nitrogen. After the solution was stirred at 0 °C for 1 h, methyl iodide (7.5 mmol) was added to the reaction mixture, which was then stirred at 0 °C for 2 h and at room temperature for 6 h. The mixture was poured into brine (50 mL) and was extracted with ether (5 × 15 mL). After the combined ethereal solution was dried ($MgSO_4$), filtered, and concentrated, the residue was distilled to afford **10m** in a quantitative yield; bp 86–88 °C (2 mm).

Preparation of β-Lactams. General Procedure. To a stirred solution of **11** (2 mmol) in THF (5 mL) was added dropwise a Grignard reagent (2 mmol for secondary amines and 4 mmol for primary amines) at 0 °C under an atmosphere of nitrogen. After the reaction was completed, the mixture was poured into cold aqueous ammonium chloride (20 mL). The solution was extracted with ether (20 mL) and CH_2Cl_2 (2 × 20 mL). The combined organic layer was dried ($MgSO_4$), filtered, concentrated, and purified by silica gel column or preparative TLC to afford **12**.

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Registry No. **6** (R = CH_2Ph, R^1 = Me, R^2 = H), 10507-52-5; **6** (R = Me, R^1R^2 = $(CH_2)_5$), 50396-38-8; **7a**, 76469-93-7; **7b**, 13592-48-8; **7c**, 78999-66-3; **7d**, 88413-58-5; **7e**, 83486-96-8; **7f**, 56475-88-8; **7g**, 56475-86-6; **7h**, 84839-66-7; **8** (R^3 = H, R^4 = n-C_6H_{13}), 111-11-5; **9a**, 31469-15-5; **9b**, 32346-06-8; **9c**, 72658-09-4; **9d**, 88413-59-6; **10a**, 88413-60-9; **10b**, 88413-61-0; (*R**,*R**)-**10c**, 88413-62-1; (*R**,*S**)-**10c**, 88413-63-2; (*R**,*R**)-**10d**, 88413-64-3; (*R**,*S**)-**10d**, 88413-65-4; (*R**,*R**)-**10e**, 88413-66-5; (*R**,*S**)-**10e**, 88413-67-6; **10f**, 88413-68-7; (*R**,*R**)-**10g**, 88413-69-8; (*R**,*S**)-**10g**, 88413-70-1; **10h**, 79380-11-3; **10i**, 88413-71-2; **10j**, 88413-72-3; **10k**, 88413-73-4; **10l**, 88413-74-5; **10m**, 88413-75-6; **11a**, 21640-84-6; **11b**, 88413-76-7; **11c**, 88413-77-8; (*R**,*R**)-**11d**, 88413-78-9; (*R**,*S**)-**11d**, 88413-79-0; **11e**, 88413-80-3; **11f**, 86000-16-0; **11g**, 88413-81-4; **11h**, 88413-82-5; **12a**, 27983-92-2; **12b**, 13423-21-7; **12c**, 88413-83-6; *cis*-**12d**, 88413-84-7; *trans*-**12d**, 88413-85-8; **12e**, 88413-86-9; **12f**, 88413-87-0; **12g**, 88413-88-1; **12h**, 88413-89-2.

Supplementary Material Available: Full spectral and analytical data for all compounds in the tables (9 pages). Ordering information is given on any current masthead page.

(13) Mozingo, R. "Organic Syntheses", Wiley: New York, 1955; Collect. Vol. 3, p 181.