H); ^{19}F NMR (CD_3CN) δ −78.61 (s, $CF_3SO_3^-$); ^{13}C NMR (CD_3CN) δ 136.35, 133.28 (d, J_{C-P} = 12.8 Hz), 131.13 (d, J_{C-P} = 13.7 Hz) (all Ph), 125.20 (d, J_{C-P} = 31.2 Hz, C≡CP$^+$), 121.82 (q, J = 320 Hz, $CF_3SO_3^-$), 119.4 (d, J_{C-P} = 100.1 Hz, ipso), 61.97 (d, J_{C-P} = 189.6 Hz, C≡CP$^+$), 26.77 (CH_2), 20.63 (d, J_{C-P} = 3.8 Hz, CH_2); ^{31}P NMR (CD_3CN) δ 6.80 (s, Ph_3P^+); FAB HRMS m/z 777.197 02 (M − $CF_3SO_3^-$)$^+$, calcd for $C_{45}H_{38}F_3O_3P_2S$ 777.196 89.

1,9-Bis[triphenyl[(trifluoromethanesulfonyl)oxy]-phosphoranyl]-1,8-nonadiyne (12c). Reaction of **9c** (0.20 g, 0.24 mmol) with Ph_3P (0.13 g, 0.50 mmol) gave 0.176 g (78%) of **12c** as a yellow oil: IR (CCl_4) 3084, 3064, 2935, 2202 (C≡C), 1224, 1188, 1031 cm^{-1}; ^{1}H NMR (CD_3CN) δ 7.9–7.6 (m, 30 H), 2.77 (m, 4 H), 1.80 (m, 4 H), 1.59 (m, 2 H); ^{19}F NMR (CD_3CN) δ −78.65 (s, $CF_3SO_3^-$); ^{13}C NMR (CD_3CN) δ 136.39 (d, J_{C-P} = 2.8 Hz), 134.01 (d, J_{C-P} = 12.8 Hz), 131.13 (d, J_{C-P} = 13.9 Hz) (all Ph), 125.68 (d, J_{C-P} = 31.0 Hz, C≡CP$^+$), 121.8 (q, J = 320 Hz, $CF_3SO_3^-$), 119.49 (d, J_{C-P} = 100.6 Hz, ipso), 61.77 (d, J_{C-P} = 190.5 Hz, C≡CP$^+$), 28.77 (CH_2), 26.91 (CH_2), 20.99 (d, J_{C-P} = 3.5 Hz, CH_2); ^{31}P NMR (CD_3CN) δ 6.69 (s, Ph_3P^+); FAB HRMS m/z 791.212 45 (M − $CF_3SO_3^-$)$^+$, calcd for $C_{46}H_{40}F_3O_3P_2S$ 791.212 54.

Acknowledgment. This work was supported by the NCI of NIH (2ROCA16903).

Registry No. **4a**, 122482-73-9; **4b**, 138877-31-3; **5a**, 138877-32-4; **5b**, 138877-33-5; **5c**, 138877-34-6; **6**, 138877-35-7; **7**, 138877-36-8; **8a**, 138877-37-9; **8b**, 138877-39-1; **9a**, 138877-41-5; **9b**, 138877-43-7; **9c**, 138877-45-9; **10**, 138877-47-1; **11a**, 138877-49-3; **11b**, 138877-51-7; **12a**, 138877-53-9; **12b**, 138877-55-1; **12c**, 138877-57-3; Ph_3P, 603-35-0.

Supplementary Material Available: ^{1}H and ^{13}C NMR spectra of all compounds for which elemental analyses were not obtained (14 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Stereoselective Synthesis of β-Lactams by Oxidative Coupling of Dianions of Acyclic Tertiary Amides†

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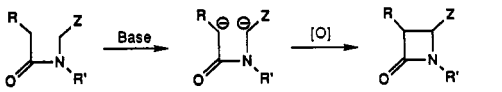
Tertiary amides $RCH_2CON(R')CH_2Z$, where Z is an electron-withdrawing group, were converted into dianions by treatment with 2 equiv of *n*-butyllithium or *tert*-butyllithium, and the dianions were oxidized with *N*-iodosuccinimide (NIS) or a Cu(II) carboxylate to form β-lactams stereoselectively. The stereochemistry of β-lactam formation depends on the oxidant; NIS is cis-selective, whereas Cu(II) is nonselective or slightly trans-selective. A high degree of asymmetric induction in the formation of β-lactams was achieved by using (*R*)-1-phenylethylamine as a chiral auxiliary. This asymmetric ring closure was applied to the preparation of *cis*-β-lactam **31**, an intermediate for the synthesis of the monobactam antibiotic carumonam.

Introduction

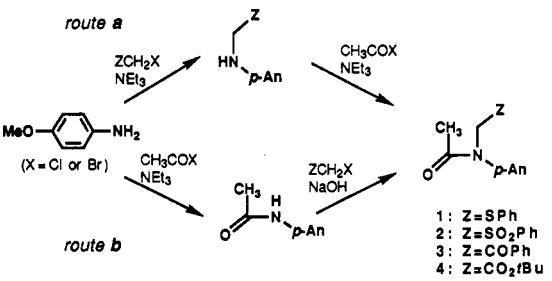
During the last few decades, numerous publications have appeared on the synthesis of β-lactams.[1] The reactions employed for forming the azetidinone ring can be roughly classified as follows:[2] (i) ketene–imine [2 + 2] cycloaddition, (ii) olefin–isocyanate [2 + 2] cycloaddition, (iii) aldol-type reactions of an ester enolate with an imine, (iv) intramolecular condensation of a β-amino acid, (v) intramolecular substitution of a β-hetero-substituted amide, and (vi) cyclization of an α,β-epoxy amide. All these methods involve *substrate control*; i.e., the stereochemistry of β-lactam formation is controlled by the structure of a precursor. Accordingly, β-lactams of undesired stereochemistry can be produced from some precursors.[3] We have been exploring a new method which allows us to control the stereochemistry of ring formation by proper choice of a reagent (*reagent control*). This paper details the synthesis of β-lactams through an intramolecular oxidative coupling of dianions generated from acyclic tertiary amides,[4] wherein the choice of oxidant is crucial for the control of stereochemistry.

The basic concept of the present reaction is summarized in Scheme I. An amide $RCH_2CON(R')CH_2Z$, wherein R and R′ are substituents or protecting groups and Z is an electron-withdrawing group, is converted into the corresponding dianion with 2 molar equiv of base. Intramolecular oxidative coupling of the dianion gives the desired

Scheme I



Scheme II



† Dedicated to Professor Hitosi Nozaki on the occasion of his 70th birthday.

‡ Present address: Institute of Chemical Research, Kyoto University, Uji, Kyoto 611, Japan.

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Table I. Synthesis of β-Lactams 8–11 by Oxidative Coupling of Dianions Derived from 4–7

entry	substrate	base[a]	additive[b]	oxidant[c] (molar equiv)	temp[d] (°C)	product	yield[e] (%)	cis:trans
1	4	*n*-BuLi	DABCO	$Cu(OAc)_2$ (3.0)	−78	8	40	
2	4	*t*-BuLi	PPh_4Br	NIS (1.3)	−95 to −70	8	39	
3	5	*t*-BuLi	none	$Cu(OCOPh)_2$ (2.5)	−78	9	40	3:2
4	5	*t*-BuLi	none	NIS (1.3)	−78	9	38	10:0
5	5	*t*-BuLi	PPh_4Cl	NIS (1.3)	−78	9	46	10:0
6	5	*t*-BuLi	PPh_4Br	NIS (1.3)	−95 to −70	9	51	10:0
7	6	*t*-BuLi	PPh_4Br	$Cu(OAc)_2$ (2.5)	−78	10	43	1:2
8	6	*t*-BuLi	PPh_4Br	NIS (1.3)	−95 to −70	10	78	12:1
9	7	*t*-BuLi	PPh_4Br	$Cu(OAc)_2$ (2.5)	−78	11	77	1:2
10	7	*t*-BuLi	PPh_4Br	NIS (1.3)	−95 to −70	11	48	7:1

[a] Dianions were generated in THF with 2.2 molar equiv of a base at −78 °C for 0.5–1 h. [b] DABCO (2.2 molar equiv) was added prior to the addition of butyllithium. PPh_4X (2.2 molar equiv) was added after the generation of the dianion. [c] DMF was used as a solvent for Cu(II) salts and THF for NIS. [d] Temperature for oxidation of the enolate. [e] Combined yield of *cis*- and *trans*-β-lactams.

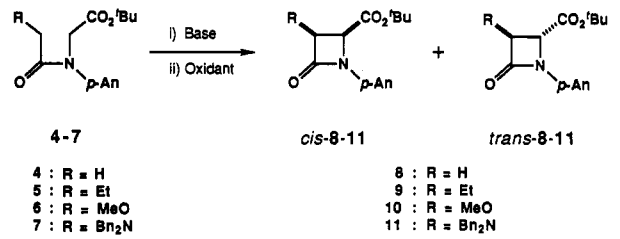
β-lactam.[5] We expected that the stereochemistry of the ring closure would be affected by the nature of the oxidant. Related oxidative coupling reactions have been used to form four-membered carbocyclic rings, albeit in low yields.[6] In this paper, we describe characteristic features of the reaction sequence in Scheme I with emphasis on the stereochemistry.

Results and Discussion

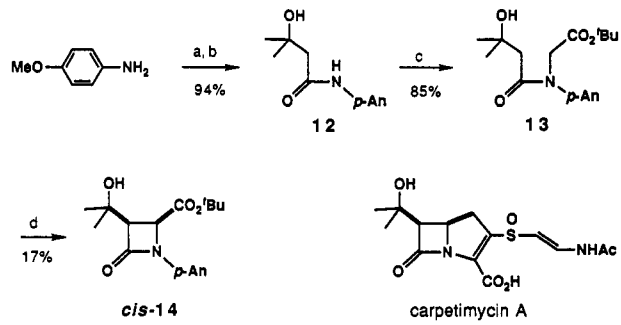
Preparation of Acyclic Amides and Dianion Formation. The starting materials 1–4 are readily prepared by alkylation of *p*-anisidine (*p*-AnNH$_2$) followed by acylation or vice versa as summarized in Scheme II. In order to determine which electron-withdrawing groups are suitable for dianion formation, amides 1–4 were treated in tetrahydrofuran (THF) with 2.2 molar equiv of a base combined with a coordinative additive. The reagents employed were lithium diisopropylamide (LDA)/hexamethylphosphoric triamide (HMPA) and *n*-butyllithium (*n*-BuLi)/1,4-diazabicyclo[2,2,2]octane (DABCO) at −78, −40, −20, or 0 °C. Quenching with a mixture of CD_3CO_2D and CD_3OD at each temperature followed by MS and ^1H NMR spectrometry of the recovered deuterated material allowed us to estimate the percentage of dianion formation for each substrate. Substrate and % dideuterium incorporation (% recovery of the amide after treatment with *n*-BuLi/DABCO at −78 °C) follow; **1**, 13% (57%); **2**, decomposition; **3**, 83% (49%); **4**, 91% (quantitative). Reactions at higher temperatures lost much of the amide. Use of LDA/HMPA at various temperatures resulted in less incorporation of deuterium and/or less recovery of the amide. On the basis of the results, the *tert*-butoxycarbonyl group was selected as Z in Scheme I.

β-Lactam Synthesis by Intramolecular Oxidative Coupling of Dianions. Amide **5** was prepared from *p*-anisidine in 93% overall yield according to route b in Scheme II. Dianion formation from **5** was quantitatively achieved by treatment with 2.2 molar equiv of *t*-BuLi. After a survey of one- or two-electron oxidants, *N*-iodosuccinimide (NIS) and Cu(II) carboxylates[7] were found to be effective for C–C bond formation (Table I). Furthermore, the presence of tetraphenylphosphonium halide slightly improved the yields of oxidative coupling (entries 5 and 6 vs entry 4).[8] Noteworthy is the stereochemistry of the β-lactams. With amide **5** as substrate, the use of NIS as the oxidant afforded the *cis*-β-lactam exclusively either in the presence or in the absence of an additive (entries 4–6). In a similar manner, amides **4**, **6**, and **7** were treated with 2.2 molar equiv of *n*- or *t*-BuLi and subsequently with an oxidant. The results summarized in Table I show that NIS gives the *cis*-β-lactam selectively irrespective of the substituent R, whereas Cu(II) is effective for nonselective or slightly trans-directive ring closure.[9] For example, treatment of the dianion derived from **6** with

Scheme III



Scheme IV[a]



[a] Key: (a) AcCl, Et_3N; (b) *n*-BuLi then acetone; (c) $BrCH_2CO_2$-*t*-Bu, NaOH, $BnNEt_3$ Cl; (d) *n*-BuLi, TMEDA, PPh_4Br then $CuCl_2$.

(3) To invert the undesired configuration, additional steps for epimerization are required. Examples are seen in (a) Chiba, T.; Nakai, T. *Chem. Lett.* **1985**, 651. (b) Aratani, M.; Hirai, H.; Sawada, K.; Yamada, A.; Hashimoto, M. *Tetrahedron Lett.* **1985**, *26*, 223. (c) Klich, M.; Teutsch, G. *Tetrahedron* **1986**, *42*, 2677.

(4) Parts of this work have been published in preliminary form: Kawabata, T.; Sumi, K.; Hiyama, T. *J. Am. Chem. Soc.* **1989**, *111*, 6843.

(5) Although a similar ring formation has been reported, the stereochemical aspects of β-lactam formation have never been discussed. Simig, G.; Doleschall, G.; Hornyák, G.; Fetter, J.; Lempert, K.; Nyitrai, J.; Huszthy, P.; Gizur, T.; Kajtár-Peredy, M. *Tetrahedron* **1985**, *41*, 479.

(6) Yields of 15–37% were reported. (a) Whitesides, G. M.; SanFilippo, J., Jr.; Casey, C. P.; Panek, E. J. *J. Am. Chem. Soc.* **1967**, *89*, 5302. (b) Kobayashi, Y.; Taguchi, T.; Morikawa, T.; Tokuno, E.; Sekiguchi, S. *Chem. Pharm. Bull.* **1980**, *28*, 262. (c) Minami, T.; Okada, Y.; Nomura, R.; Hirota, S.; Nagahara, Y.; Fukuyama, K. *Chem. Lett.* **1986**, 613. (d) Babler, J. H.; Sarussi, S. J. *J. Org. Chem.* **1987**, *52*, 3462.

(7) The oxidative coupling of enolates has been carried out with Cu(OTf)$_2$ or $CuCl_2$, but $Cu(OAc)_2$ or $Cu(OBz)_2$ turned out to be suitable for the present reaction. (a) Maryanoff, C. A.; Maryanoff, B. E.; Tang, R.; Mislow, K. *J. Am. Chem. Soc.* **1973**, *95*, 5839. (b) Knowles, W. S.; Sabacky, M. J.; Vineyard, B. D.; Weinkauff, D. J. *Ibid.* **1975**, *97*, 2567. (c) Ito, Y.; Konoike, T.; Harada, T.; Saegusa, T. *Ibid.* **1977**, *99*, 1487. (d) Kobayashi, Y.; Taguchi, T.; Tokuno, E. *Tetrahedron Lett.* **1977**, 3741.

(8) Reactions of **4**, **6**, and **7** were not performed in the absence of tetraphenylphosphonium bromide. In the case of substrate **24**, the presence of the salt did not affect the yield of the oxidative coupling reaction (Table III, entry 1 vs entry 2).

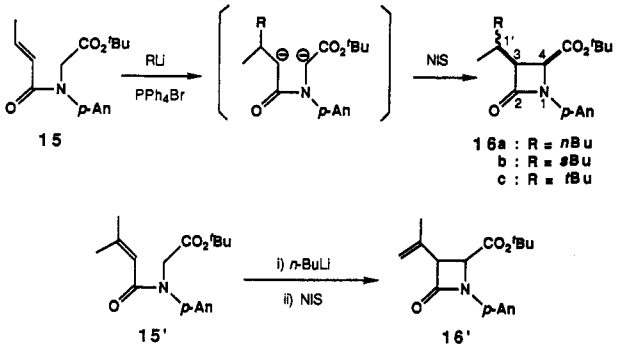
(9) The relative configuration of C_3 and C_4 was determined by $J_{3,4}$ = 5–7 Hz for the cis isomer and 1–3 Hz for the trans isomer.

Table II. Synthesis of β-Lactams 18–21 by Oxidative Coupling of Dianions Derived from 17

entry	base[a] (molar equiv)	additive[b]	oxidant[c] (molar equiv)	temp[d] (°C)	yield[e] (%)	ratio of 18:19:20:21
1	*t*-BuLI (2.2)	PPh_4Br	NIS (1.3)	−95 to −70	30	7[f]:2:1[h]
2	*t*-BuLi (2.2)	TMEDA	NIS (1.3)	−95 to −70	17	>8[f]:1:1[h]
3	*s*-BuLi (2.2)	TMEDA	NIS (1.3)	−95 to −70	31	>8[f]:1:1[h]
4	*n*-BuLi (2.2)	TMEDA	NIS (1.3)	−95 to −70	22	>8[f]:1:1[h]
5	*s*-BuLi (4.0)	TMEDA	NIS (3.2)	−95 to −70	41	84[g]:8:5:3
6	*n*-BuLi (4.0)	TMEDA	NIS (3.2)	−95 to −70	58	90[g]:5:3:2
7	*n*-BuLi (4.0)	TMEDA	NIS (3.2)	−78	60	84[g]:8:5:3
8	*n*-BuLi (4.0)	TMEDA/LDA	NIS (3.2)	−95 to −70	53	90[g]:5:3:2
9	*n*-BuLi (4.0)	TMEDA	$Cu(OAc)_2$ (4.5)	−78	63	35[g]:17:32:16

[a] Dianions were generated at −78 °C for 0.5–1 h. [b] TMEDA (2.2 molar equiv) was added prior to the addition of base. PPh_4Br (2.2 molar equiv) and LDA (1.0 molar equiv) were added after the generation of the dianion. [c] DMF was used as a solvent for Cu(II) salts and THF for NIS. [d] Temperature at which oxidation of the dianion was carried out. [e] Combined yield of β-lactams 18–21. [f] Determined by 90-MHz ^1H NMR. [g] Determined by 400-MHz ^1H NMR. [h] Combined ratio of **20** and **21**.

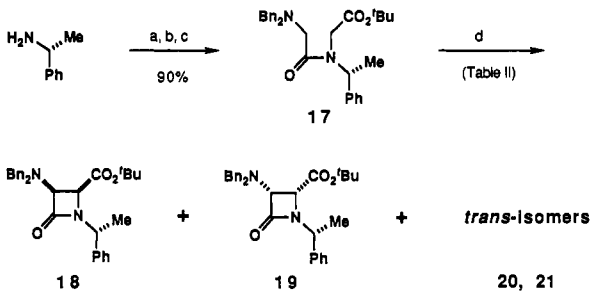
Scheme V



NIS gave a 12:1 mixture of *cis*- and *trans*-**10**, whereas copper(II) acetate afforded a 1:2 mixture (entries 7 and 8). It is evident that the stereochemical course of the reaction is affected by the nature of the oxidant rather than the structure of the starting material.[10]

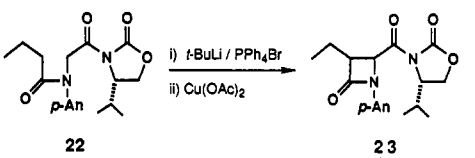
We applied the reaction to the synthesis of *cis*-**14**, a possible intermediate to the antibiotic carpetimycin A.[11] Since the introduction of the *cis*-1-hydroxy-1-methylethyl substituent at C(3) by aldol reaction of a 2-azetidinone is troublesome,[12] stereoselective construction of *cis*-**14** has synthetic value. Amide **13** was prepared from *p*-anisidine in 80% overall yield (Scheme IV). Attempted cis-directive cyclization of the trianion of **13** with NIS failed, but oxidation with Cu(II) chloride afforded *cis*- and *trans*-**14** in a ratio of 5:1 in 17% combined yield. Although the chemical yield is not high, this synthesis of *cis*-**14** is straightforward.

Scheme VI[a]



[a] Key: (a) $BrCH_2CO_2$-*t*-Bu, NEt_3; (b) $BrCH_2COBr$, NEt_3; (c) Bn_2NH, NET_3; (d) base, additive then oxidant.

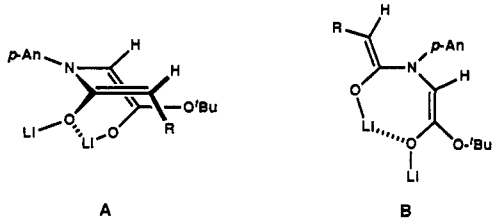
Scheme VII



The dianion intermediates are alternatively available through conjugate addition to α,β-unsaturated amides as shown in Scheme V. When crotonamide **15** was treated with 2.2 equiv of *n*-BuLi, abstraction of the α proton of the ester carbonyl was followed by conjugate addition of *n*-Bu^- to produce a dianion. Subsequent oxidation with NIS afforded 3,4-*cis*-β-lactam **16a** in 48% yield. Although stereocontrol of the ring closure was achieved, a ~1:1 mixture of C(1′) isomers resulted. Using *s*-BuLi and *t*-BuLi, **16b** and **16c** were obtained similarly. Though PhLi and MeLi also gave the β-lactams, the yields were not satisfactory. When 3-methyl-2-butenamide **15′** was treated with *n*-BuLi, double proton abstraction took place to give, after NIS oxidation, a 1:1 mixture of *cis*- and *trans*-**16′** in 30% yield.

Asymmetric Synthesis. The finding that NIS behaved as an excellent oxidant for stereocontrolled oxidative coupling encouraged us to explore the possibility of

(10) The observed stereochemical outcome might be explained as follows. Although no evidence is available, the dilithium enolates of **4**–**7** are assumed to have an intramolecularly chelated conformation A. Iodonium ion would attack the enolate moiety from outside the periphery of A to give an iodide. Subsequently, spontaneous ring closure by intramolecular nucleophilic substitution would proceed before conformational change to give rise to the *cis*-β-lactam. Alternatively, the ring closure may be effected by concerted electron flow from the amide enolate through the ester enolate to iodonium ion while keeping conformation A. Although the hetero atoms of **6** and **7** might coordinate to Li, this coordination would not change conformation A as the stereochemical outcome was the same. On the other hand, oxidation with Cu(II) should involve a single electron transfer to produce a diradical intermediate responsible for the non- or trans-selective ring closure. The stability or lifetime of the diradical intermediate affects the cis/trans ratio of the products: stable diradicals give thermodynamically favored *trans*-β-lactams. Conformation A should be crucial not only for the high stereoselectivity but also for the smooth four-membered ring formation, since an extended conformation B is anticipated to give oligomerized products on reaction with the oxidant. Conformation of amide and ester enolates are discussed in: (a) Allinger, N. L.; Eliel, E. L.; Wilen, S. H. *Topics in Stereochemistry*; Wiley: New York, 1982; Vol. 13. (b) Morrison, J. D. *Asymmetric Synthesis*; Academic Press: Orlando, 1984; Vol. 3.



(11) (a) Nakayama, M.; Iwasaki, A.; Kimura, S.; Mizoguchi, T.; Tanabe, S.; Murakami, A.; Watanabe, I.; Okuchi, M.; Itoh, H.; Saino, Y.; Kobayashi, F.; Mori, T. *J. Antibiot.* **1980**, *33*, 1388. (b) Imada, A.; Nozaki, Y.; Kintaka, K.; Okonogi, K.; Kitano, K.; Harada, S. *Ibid.* **1980**, *33*, 1417.

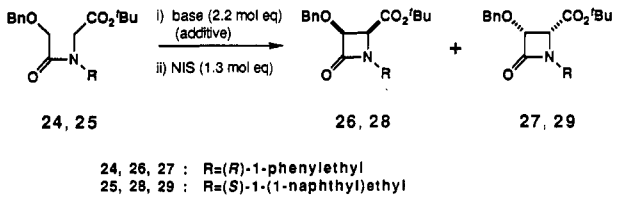
(12) (a) Natsugari, H.; Matsushita, Y.; Tamura, N.; Yoshioka, K.; Ochiai, M. *J. Chem. Soc., Perkin Trans. 1* **1983**, 403. (b) Shibasaki, M.; Ishida, Y.; Okabe, N. *Tetrahedron Lett.* **1985**, *26*, 2217. (c) Reference 3b.

Table III. Synthesis of β-Lactams 26–29 by Oxidative Coupling of Dianions Derived from 25 and 25[a]

entry	substrate	base[b]	additive[c]	products	yield[d] (%)	ratio 26:27 or 28:29
1	24	*t*-BuLi	none	26 + 27	68	2:1
2	24	*t*-BuLi	PPh_4Br	26 + 27	69	3:1
3	24	*t*-BuLi	TMEDA	26 + 27	65	3:2
4[e]	24	*t*-BuLi	TMEDA	26 + 27	40	3:1
5	24	KHMDS	none		~0	
6	25	*t*-BuLi	PPh_4Br	28 + 29	31	2:3

[a] Reactions were run in THF unless otherwise stated. Oxidation of the enolate was performed with 1.3 molar equiv of NIS at −95 to −78 °C. [b] Dianions were generated with 2.2 molar equiv of the base at −78 °C for 0.5–1 h. [c] TMEDA (2.2 molar equiv) was added prior to the addition of base. PPh_4Br (2.2 molar equiv) was added after the generation of the dianion. [d] Combined yield of 26 + 27 or 28 + 29. [e] Diethyl ether was used as a solvent.

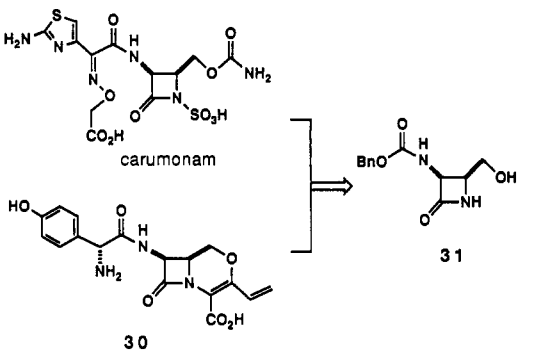
Scheme VIII



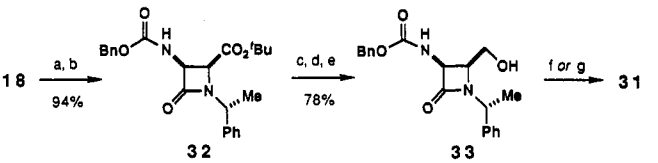
asymmetric synthesis. We employed optically active 1-phenylethylamine as a chiral auxiliary, since both enantiomers of the amine are commercially available. The requisite substrate **17**[13] was prepared from (*R*)-(+)-1-phenylethylamine in 90% overall yield through the sequence of alkylation, acylation, and substitution reactions (Scheme VI). Amide **17** was converted to the dianion, and oxidative coupling gave β-lactams **18–21**. To optimize the reaction conditions, base, additive, and oxidant were examined (Table II). The ratios of *cis*-β-lactams **18** and **19** to *trans*-β-lactams **20** and **21** were again high when NIS was employed as the oxidant (9–19:1, entries 1–8). The degree of asymmetric induction (ratio of **18**[14] to **19**) depended on the type of additive. Higher selectivity was attained with *N,N,N′,N′*-tetramethylethylenediamine (TMEDA) (>8–18:1, entries 2–7) than with tetraphenylphosphonium bromide (7:2, entry 1). The yields varied depending on the amount of base used. Four equivalents of base doubled the yield (entries 5–7 vs entries 2–4).[15] LDA as an extra ligand[16] did not affect the stereoselectivity at all (entry 6 vs entry 8). Thus the optimized reaction conditions were those of entry 6 (**18**:**19**:**20**:**21** = 90:5:3:2, 58% yield). The efficacy of the present synthesis is obvious when the degree of the asymmetric induction (90:5) is compared with those of previous β-lactam syntheses using 1-phenylethylamine as a chiral auxiliary (2.3–5.2:1 diastereoselectivity).[17] Use of copper(II) acetate as an oxidant gave a mixture of **18**, **19**, **20**, and **21** in a ratio of 35:17:32:16 (63% yield, entry 9).

Intramolecular oxidative coupling of the dianion of amide **22** occurred, but with low stereoselectivity. Treatment of **22** with 2.2 molar equiv of *t*-BuLi followed by copper(II) acetate[18] afforded **23** as a mixture of two cis isomers (3:2) and two trans isomers (3:2). Though nonselective, this

Scheme IX



Scheme X[a]



[a] Key: (a) 10% Pd–C, HCO_2NH_4; (b) BnOCOCl, propylene oxide; (c) CF_3CO_2H; (d) CH_2N_2, (e) $NaBH_4$, THF–H_2O; (f) $(NH_4)_2S_2O_8$, K_2HPO_4; (g) *n*-BuLi, then Na, NH_3, then BnOCOCl.

reaction is suitable for the preparation of all possible chiral stereoisomers for biological testing,[19] since the four isomers are readily separable by preparative TLC.

Asymmetric ring closure of benzyloxy-substituted amide **24** afforded *cis*-β-lactams **26** and **27**[20] exclusively, irrespective of the kind of additive or the solvent (Table III, entries 1–4). Selectivity, however, was low in every case. Use of (*S*)-(−)-1-(1-naphthyl)ethylamine as a chiral auxiliary turned out futile (entry 6). Each β-lactam **26** or **27** could be isolated in optically pure form and thus may be employed as a synthetic intermediate for alkoxy-substituted β-lactam antibiotics[21] and enzyme inhibitors.[22,23]

(13) Amide **17** exists as a 3:2 mixture of *Z* and *E* isomers in $CDCl_3$ solution as revealed by 400-MHz ^1H NMR. See Experimental Section.

(14) The absolute configuration of **18** was determined to be (3*S*,4*S*) by transformation into **31**. See text.

(15) The reason is not yet clear. Low yields of the products (Table II, entries 1–4) are not ascribed simply to the low efficiency of dianion formation, because the dianion was formed nearly quantitatively when 2.2 mol equiv of *sec*-butyllithium was used (entry 3). A possible role of the additional alkyllithium may be as a ligand for lithium in the enolate.

(16) Denmark, S. E.; Ares, J. J. *J. Am. Chem. Soc.* **1988**, *110*, 4432.

(17) The ratios of 2.3:1,[17a] 5.2:1,[17b] and 3:1[17c] were reported. (a) Ojima, I.; Suga, S.; Abe, R. *Chem. Lett.* **1980**, 853. (b) Shibasaki, M.; Ishida, Y.; Iwasaki, G.; Iimori, T. *J. Org. Chem.* **1987**, *52*, 3488. (c) Thomas, R. C. *Tetrahedron Lett.* **1989**, *30*, 5239.

(18) When oxidation of the dianion was performed with NIS, only *cis*-β-lactams were obtained in a 3:1 ratio (12% yield).

(19) Yoshida, A.; Hayashi, T.; Takeda, N.; Oida, S.; Ohki, E. *Chem. Pharm. Bull.* **1981**, *29*, 1854.

(20) The absolute configuration of **26–29** was tentatively assigned by analogy to **18** and **19**.

(21) Optically active β-lactams with an alkoxy substituent at C_3 are an important class of compounds because the substituent improves the biological activity of the parent β-lactam antibiotics. (a) Webber, J. A.; Ott, J. L. *Structure–Activity Relationship among the Semisynthetic Antibiotics*; Perlman, D., Ed.; Academic Press: New York, 1977; p 161. (b) Doherty, J. B.; Ashe, B. M.; Argenbright, L. W.; Barker, P. L.; Bonney, R. J.; Chandler, G. O.; Dahlgren, M. E.; Dorn, C. P., Jr.; Finke, P. E.; Firestone, R. A.; Fletcher, D.; Hagmann, W. K.; Mumford, R.; O'Grady, L.; Maycock, A. L.; Pisano, J. M.; Shah, S. K.; Thompson, K. R.; Zimmerman, M. *Nature* **1986**, *322*, 192. (c) Yoshioka, T.; Watanabe, A.; Isshiki, K.; Fukagawa, Y.; Ishikura, T. *Tetrahedron Lett.* **1986**, *27*, 4335.

(22) Ring-opening reactions[23] of **26–29** are expected to give β-amino acids like β-alkoxy-substituted aspartic acid enzyme inhibitors[22a–c] and new antibiotics.[22d–f] (a) Shive, W.; Macow, J. *J. Biol. Chem.* **1946**, *162*, 451. (b) Ifland, P. W.; Shive, W. *Ibid.* **1956**, *223*, 949. (c) Otani, T. T. *Arch. Biochem. Biophys.* **1963**, *101*, 131. (d) Ishiyama, T.; Furuta, T.; Takai, M.; Okimoto, Y.; Aizawa, S.; Shimazu, A.; Yonehara, H. *J. Antibiot.* **1975**, *23*, 821. (e) Teintze, M.; Hossain, M. B.; Barnes, C. L.; Leong, J.; van der Helm, D. *Biochemistry* **1981**, *20*, 446. (f) Sugawara, K.; Numata, K.; Konishi, M.; Kawaguchi, H. *J. Antibiot.* **1984**, *37*, 958.

Preparation of a Key Synthetic Intermediate to Carumonam. Optically active β-lactam **18** is structurally related to the monobactam antibiotic carumonam[24] and to *O*-2-isocephem **30**[25] (Scheme IX). Carumonam has excellent antibacterial activity against Gram-negative bacteria, including *Pseudomonas aeruginosa*, and is highly stable to β-lactamases.[24] Isocephem **30** is a candidate oral β-lactam antibiotics.[25] These antibiotics have both been prepared from chiral intermediate **31**, which has been synthesized through multistep operations,[26] some of which are not highly selective. Since **18** could be prepared stereoselectively in four steps from (*R*)-(+)-1-phenylethylamine, we studied its transformation to **31** (Scheme X). Hydrogenolysis[27] of **18** followed by benzyloxycarbonylation gave **32** in 94% yield. Conversion of the *tert*-butyl ester into alcohol **33** was effected by (1) removal of the *tert*-butyl group with trifluoroacetic acid, (2) esterification with excess diazomethane, and (3) reduction with sodium borohydride. Removal of the chiral auxiliary with $(NH_4)_2S_2O_8/K_2HPO_4$[28] provided **31**. Conversion of **33** into **31** was alternatively achieved by Birch reduction followed by benzyloxycarbonylation. The spectral data for **31** were identical with those reported.[24a,26e,f,28a] Thus a highly stereoselective route to the synthesis of **31** has been established starting from readily available (*R*)-(+)-1-phenylethylamine. This transformation has revealed the absolute configuration of **18** to be (3*S*,4*S*).

Experimental Section

General. Melting points were measured with a Yanagimoto Micro melting point apparatus and are uncorrected. ^1H NMR spectra (tetramethylsilane as an internal standard) were obtained with a Hitachi R-90H (90-MHz) or a Bruker AM-400 (400-MHz) spectrometer, chemical shifts being given in ppm units, and ^{13}C NMR spectra with a Bruker-400 instrument. IR spectra were recorded with a JACSO A-202 spectrometer. Specific rotations were measured with a Horiba SEPA-200 polarimeter. MS spectra were recorded with a Hitachi RMU-6MG spectrometer and exact MS spectra with a Hitachi M-80A spectrometer. TLC analyses were performed on commercial glass plates bearing a 0.25-mm layer of Merck Kieselgel 60 F_{254}. Preparative TLC plates were prepared using Merck Kieselgel PF_{254} or purchased from Merck Ltd (glass plates precoated with Kieselgel 60 F_{254}). Column chromatography was carried out with silica gel (Wakogel C-200). THF and diethyl ether were distilled over benzophenone ketyl before use. TMEDA and HMPA were distilled from calcium hydride. *N*,*N*-Dimethylformamide (DMF) was distilled from phosphorus pentoxide under reduced pressure. DABCO was used immediately after azeotropic removal of water with toluene. Tetraphenylphosphonium halides and copper(II) salts were dried at 60–70 °C and 100–110 °C, respectively, for 3 h under vacuum immediately before use.

***N*-(Benzoylmethyl)-*N*-(4-methoxyphenyl)acetamide (3) (Route a of Scheme II).** Phenacyl bromide (1.82 g, 9.2 mmol) was added to a solution of *p*-anisidine (0.75 g, 6.1 mmol) and triethylamine (2.54 mL, 18 mmol) in THF (10 mL) at 0 °C. After being stirred at room temperature for 1.5 h, the mixture was diluted with ethyl acetate and washed successively with 0.1 M HCl, saturated $NaHCO_3$, and saturated NaCl solution. The organic phase was dried over $MgSO_4$, filtered, and concentrated in vacuo to give brown solids, which were dissolved in dichloromethane (25 mL) and treated with triethylamine (2.70 mL, 19 mmol) followed by acetyl chloride (0.92 mL, 13 mmol) at 0 °C. After being stirred at the same temperature for 5 h, the mixture was diluted with ethyl acetate and washed successively with 1 M HCl, saturated $NaHCO_3$, and saturated NaCl solution. The organic phase was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (ethyl acetate:hexane = 1:1) to afford **3** (0.73 g, 43% yield from *p*-anisidine) as a pale yellow oil: R_f 0.32 (ethyl acetate:hexane = 2:1); ^1H NMR (90 MHz) ($CDCl_3$) δ 1.96 (s, 3 H), 3.81 (s, 3 H), 5.07 (s, 2 H), 6.89 (d, J = 9.0 Hz, 2 H), 7.31 (d, J = 9.0 Hz, 2 H), 7.4–7.7 (m, 3 H), 7.94 (dd, J = 7.9, 2.2 Hz, 2 H); IR ($CHCl_3$) 3010, 1700, 1650, 1510, 1380, 1245 cm^{-1}; MS m/z (rel intensity) 283 (M^+, 76), 241 (28), 178 (72), 136 (100), 105 (53), 77 (92), 43 (94); exact MS calcd for $C_{17}H_{17}NO_3$ M^+ 283.1207, found m/z 283.1235.

***N*-[(*tert*-Butoxycarbonyl)methyl]-*N*-(4-methoxyphenyl)acetamide (4).** Acetyl chloride (0.64 mL, 9.0 mmol) was added dropwise to a solution of *p*-anisidine (0.73 g, 6.0 mmol) and triethylamine (1.66 mL, 12 mmol) in dichloromethane (6 mL) cooled at 0 °C. After being stirred at the same temperature for 1.5 h, the mixture was diluted with ethyl acetate and washed successively with 0.1 M HCl, saturated $NaHCO_3$, and saturated NaCl solution. The organic phase was dried over $MgSO_4$, filtered, and concentrated in vacuo to afford nearly pure *N*-(4-methoxyphenyl)acetamide as a colorless solid: ^1H NMR (90 MHz) ($CDCl_3$) δ 2.14 (s, 3 H), 3.79 (s, 3 H), 6.85 (d, J = 9.0 Hz, 2 H), 7.39 (d, J = 9.0 Hz, 2 H). The solid dissolved in dichloromethane (20 mL) was treated with *tert*-butyl bromoacetate (3.08 mL, 18 mmol) and then with benzyltriethylammonium bromide (0.25 g, 0.92 mmol). To the resulting mixture was added 50% aq NaOH (1.0 mL) at 0 °C. After being stirred at room temperature for 17 h, the mixture was poured into saturated NH_4Cl solution and extracted with ethyl acetate. The organic phase was washed with water, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (ethyl acetate:hexane = 7:13) to afford **4** (1.41 g, 84% yield from *p*-anisidine) as colorless prisms: mp 58–60 °C (diisopropyl ether); R_f 0.33 (ethyl acetate:hexane = 1:1); ^1H NMR (90 MHz) ($CDCl_3$) δ 1.45 (s, 9 H), 1.88 (s, 3 H), 3.81 (s, 3 H), 4.21 (s, 2 H), 6.89 (d, J = 9.0 Hz, 2 H), 7.26 (d, J = 9.0 Hz, 2 H); IR (KBr) 2990, 1745, 1660, 1515, 1375, 1250, 1225, 1155 cm^{-1}; MS m/z (rel intensity) 279 (M^+, 16), 237 (4), 223 (7), 206 (10), 181 (50), 136 (100). Anal. Calcd for $C_{15}H_{21}NO_4$: C, 64.49; H, 7.58; N, 5.01. Found: C, 64.26; H, 7.70; N, 4.95.

***N*-(4-Methoxyphenyl)-*N*-[(phenylthio)methyl]acetamide (1).** This was prepared according to route b in Scheme II using chloromethyl phenyl sulfide as ZCH_2X (53% yield from *p*-anisidine): colorless oil; R_f 0.39 (ethyl acetate:hexane = 1:1); ^1H NMR (90 MHz) ($CDCl_3$) δ 1.80 (s, 3 H), 3.81 (s, 3 H), 5.17 (s, 2 H), 6.85 (d, J = 8.8 Hz, 2 H), 7.06 (d, J = 8.8 Hz, 2 H), 7.1–7.4 (m, 5 H); IR (neat) 3060, 3010, 2940, 1665, 1510, 1380, 1250, 1030 cm^{-1}; MS m/z (rel intensity) 287 (M^+, 2), 178 (28), 136 (100), 43 (30); exact MS calcd for $C_{16}H_{17}NO_2S$ M^+ 287.0978, found m/z 287.0975.

***N*-(4-Methoxyphenyl)-*N*-[(phenylsulfonyl)methyl]acetamide (2).** Saturated $NaHCO_3$ (5 mL) and *m*-chloroperbenzoic acid (70%, 271 mg, 1.0 mmol) were added to a solution of **1** (105 mg, 0.37 mmol) in dichloromethane (2.5 mL). After the mixture was stirred at room temperature for 1 h, the dichloromethane layer was separated, and the aqueous layer was extracted with ethyl acetate. The combined organic phase was washed successively with saturated $Na_2S_2O_3$, saturated $NaHCO_3$, and saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by preparative TLC (ethyl acetate:hexane = 3:1) to give **2** (85 mg, 73%): R_f 0.45 (ethyl acetate:hexane = 3:1); ^1H NMR (90 MHz) ($CDCl_3$) δ 1.97 (s, 3 H), 3.83 (s, 3 H), 5.09 (s, 2 H), 6.90 (d, J = 9.0 Hz, 2 H), 7.32 (d, J = 9.0 Hz, 2 H), 7.4–7.7 (m, 3 H), 7.95 (d, J = 7.5 Hz, 2 H); IR ($CHCl_3$) 3015, 1655, 1515, 1385, 1250, 1220 cm^{-1}; MS m/z (rel intensity) 319 (M^+, 2), 178 (33), 136 (100), 43 (13); exact MS calcd for $C_{16}H_{17}NO_4S$ M^+ 319.0876, found m/z 319.0835.

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***N*-[(*tert*-Butoxycarbonyl)methyl]-*N*-(4-methoxyphenyl)butanamide (5).** Prepared according to route b in Scheme II using butanoyl chloride (93% yield from *p*-anisidine): colorless plates; mp 96–97.5 °C (diisopropyl ether); R_f 0.44 (ether:hexane = 2:1); ^{1}H NMR (90 MHz) ($CDCl_3$) δ 0.84 (t, J = 7.3 Hz, 3 H), 1.46 (s, 9 H), 1.5–1.8 (m, 2 H), 2.0–2.2 (m, 2 H), 3.82 (s, 3 H), 4.21 (s, 2 H), 6.89 (d, J = 9.0 Hz, 2 H), 7.25 (d, J = 9.0 Hz, 2 H); IR (KBr) 2990, 1745, 1660, 1515, 1370, 1225, 1155 cm^{-1}; MS m/z (rel intensity) 307 (M^+, 15), 237 (14), 181 (94), 136 (100). Anal. Calcd for $C_{17}H_{25}NO_4$: C, 66.42; H, 8.20; N, 4.56. Found: C, 66.40; H, 8.09; N, 4.50.

***N*-[(*tert*-Butoxycarbonyl)methyl]-*N*-(4-methoxyphenyl)methoxyacetamide (6).** To a solution of *p*-anisidine (0.57 g, 4.6 mmol) and triethylamine (2.6 mL, 18 mmol) in THF (20 mL) was added *tert*-butyl bromoacetate (2.3 mL, 14 mmol). After being stirred for 4 d at room temperature, the mixture was diluted with ethyl acetate and washed successively with 0.1 M HCl, saturated $NaHCO_3$, and saturated NaCl solution. The organic phase was dried over Na_2SO_4, filtered, and concentrated in vacuo to afford crude *N*-[(*tert*-butoxycarbonyl)methyl]-*p*-anisidine as a brown oil: ^{1}H NMR (90 MHz) ($CDCl_3$) δ 1.47 (s, 9 H), 3.74 (s, 3 H), 3.75 (s, 2 H), 3.9–4.1 (br s, 1 H), 6.68 (ABq, J_{AB} = 9.0 Hz, $\Delta\nu_{AB}$ = 18.3 Hz, 4 H). As this was labile, it was immediately used for the following reaction. A mixture of the above product, 1,3-dicyclohexylcarbodiimide (0.99 g, 4.8 mmol), 4-(dimethylamino)pyridine (55 mg, 0.46 mmol), methoxyacetic acid (0.37 mL, 4.8 mmol), and dichloromethane (15 mL) was stirred at room temperature for 45 h. Precipitates were removed by filtration and washed with ether. The combined filtrate was washed successively with 1 M HCl, saturated $NaHCO_3$, and saturated NaCl solution. The organic phase was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (ethyl acetate:hexane = 2:3) to afford **6** (1.09 g, 77% yield from *p*-anisidine) as colorless needles: mp 83.5–85 °C (recrystallized from toluene–hexane (1:3)); R_f 0.35 (ethyl acetate–hexane (2:1)); ^{1}H NMR (90 MHz) ($CDCl_3$) δ 1.46 (s, 9 H), 3.34 (s, 3 H), 3.82 (s, 5 H), 4.23 (s, 2 H), 6.90 (d, J = 9.0 Hz, 2 H), 7.26 (d, J = 9.0 Hz, 2 H); IR (KBr) 2990, 2940, 1740, 1670, 1510, 1365, 1320, 1245, 1155, 1140 cm^{-1}; MS m/z (rel intensity) 309 (M^+, 27), 253 (24), 236 (12), 180 (47), 57 (44), 45 (100). Anal. Calcd for $C_{16}H_{23}NO_5$: C, 62.12; H, 7.49; N, 4.53. Found: C, 62.24; H, 7.65; N, 4.57.

***N*-[(*tert*-Butoxycarbonyl)methyl]-*N*-(4-methoxyphenyl)(*N'*,*N'*-dibenzylamino)acetamide (7).** Triethylamine (0.37 mL, 2.7 mmol) and *tert*-butyl bromoacetate (0.29 mL, 1.8 mmol) were added to a THF (10 mL) solution of *p*-anisidine (0.11 g, 0.89 mmol) at 0 °C. The mixture was heated to reflux for 12 h, diluted with ethyl acetate, and washed successively with water, saturated $NaHCO_3$ and saturated NaCl solution. The organic phase was separated, dried over $MgSO_4$, filtered, and concentrated in vacuo to give a pale yellow oil which was dissolved in dichloromethane (4 mL) and treated with triethylamine (0.25 mL, 1.8 mmol) and bromoacetyl bromide (0.12 mL, 1.3 mmol) at −10 °C for 40 min. The reaction mixture was poured into saturated NH_4Cl solution and extracted with ethyl acetate. The organic phase was washed successively with 1 M HCl, saturated $NaHCO_3$, and saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated in vacuo to give a brown oil. The oily product was dissolved in THF (2 mL) and treated with triethylamine (0.25 mL, 1.8 mmol) followed by dibenzylamine (0.26 mL, 1.4 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 17 h. Workup as above followed by preparative TLC (ether:hexane = 3:2) afforded **7** (0.29 g, 68% yield from *p*-anisidine) as colorless prisms: mp 123–124 °C (diisopropyl ether); R_f 0.46 (ether:hexane = 3:2); ^{1}H NMR (90 MHz) ($CDCl_3$) δ 1.46 (s, 9 H), 3.09 (s, 2 H), 3.76 (s, 3 H), 3.84 (s, 4 H), 4.18 (s, 2 H), 6.71 (d, J = 9.0 Hz, 2 H), 6.98 (d, J = 9.0 Hz, 2 H), 7.2–7.4 (m, 10 H); IR (KBr) 2990, 1740, 1660, 1510, 1455, 1370, 1290, 1250, 1155 cm^{-1}; MS m/z (relative intensity) 475 (MH^+, 17), 401 (9), 383 (90), 327 (93), 210 (100). Anal. Calcd for $C_{29}H_{34}N_2O_4$: C, 73.39; H, 7.22; N, 5.90. Found: C, 73.37; H, 7.34; N, 5.79.

Typical Procedure for Oxidative Coupling. Synthesis of 4-(*tert*-Butoxycarbonyl)-3-methoxy-1-(4-methoxyphenyl)-2-azetidinones (10) (Table I, Entry 8). To a THF (4 mL) solution of **6** (67 mg, 0.22 mmol) was added *t*-BuLi (1.59 M in pentane, 0.30 mL, 0.48 mmol) at −78 °C. The mixture was stirred at −78 °C for 1 h and then poured into a THF (1 mL) suspension of tetraphenylphosphonium bromide (0.20 g, 0.48 mmol) which had been cooled to −78 °C. After stirring for 30 min, the mixture was cooled to −95 °C. NIS (63 mg, 0.29 mmol) dissolved in THF (1 mL) precooled to −95 °C was added all at once, and the reaction mixture was gradually warmed to −70 °C over a period of 1 h. The mixture was poured into saturated NH_4Cl solution and extracted with ethyl acetate. The organic layer was washed successively with saturated $Na_2S_2O_3$, saturated $NaHCO_3$, and saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by preparative TLC (ether:hexane = 9:1) to give *cis*-**10** (48 mg, 72%) and *trans*-**10** (4 mg, 6%). *cis*-**10**: colorless prisms, mp 101–102 °C (diisopropyl ether); R_f 0.63 (ether:hexane = 9:1); ^{1}H NMR (90 MHz) ($CDCl_3$) δ 1.46 (s, 9 H), 3.58 (s, 3 H), 3.78 (s, 3 H), 4.69 (d, J = 5.3 Hz, 1 H), 4.80 (d, J = 5.3 Hz, 1 H), 6.86 (d, J = 9.2 Hz, 2 H), 7.29 (d, J = 9.2 Hz, 2 H); IR (KBr) 2970, 1740, 1515, 1370, 1245, 1225, 1155, 1135 cm^{-1}; MS m/z (rel intensity) 307 (M^+, 14), 251 (44), 178 (29), 163 (19), 149 (100), 134 (39), 57 (35). Anal. Calcd for $C_{16}H_{21}NO_5$: C, 62.52; H, 6.88; N, 4.56. Found: C, 62.28; H, 6.91; N, 4.45. *trans*-**10**: colorless oil; R_f 0.71 (ether:hexane = 9:1); ^{1}H NMR (90 MHz) ($CDCl_3$) δ 1.45 (s, 9 H), 3.57 (s, 3 H), 3.78 (s, 3 H), 4.30 (d, J = 1.8 Hz, 1 H), 4.65 (d, J = 1.8 Hz, 1 H), 6.86 (d, J = 9.0 Hz, 2 H), 7.28 (d, J = 9.0 Hz, 2 H); IR ($CHCl_3$) 2990, 2940, 1760, 1510, 1455, 1390, 1300, 1240, 1150 cm^{-1}; MS m/z (rel intensity) 307 (M^+, 11), 251 (14), 178 (20), 164 (10), 149 (100), 134 (32), 57 (32); exact MS calcd for $C_{16}H_{21}NO_5$, M^+ 307.1382, found m/z 307.1418.

4-(*tert*-Butoxycarbonyl)-1-(4-methoxyphenyl)-2-azetidinone (8): colorless prisms; mp 93.5–95 °C (diisopropyl ether); R_f 0.39 (ethyl acetate:hexane = 1:2); ^{1}H NMR (90 MHz) ($CDCl_3$) δ 1.44 (s, 9 H), 3.05 (dd, J = 14.4, 3.0 Hz, 1 H), 3.33 (dd, J = 14.4, 5.5 Hz, 1 H), 3.78 (s, 3 H), 4.33 (dd, J = 5.5, 3.0 Hz, 1 H), 6.85 (d, J = 9.2 Hz, 2 H), 7.28 (d, J = 9.2 Hz, 2 H); IR ($CHCl_3$) 2990, 1750, 1515, 1390, 1370, 1245, 1155 cm^{-1}; MS m/z (rel intensity) 277 (M^+, 20), 221 (100), 179 (31), 176 (23), 149 (85), 134 (89). Anal. Calcd for $C_{15}H_{19}NO_4$: C, 64.96; H, 6.91; N, 5.05. Found: C, 65.03; H, 7.08; N, 5.03.

4-(*tert*-Butoxycarbonyl)-3-ethyl-1-(4-methoxyphenyl)-2-azetidinones (9). Prepared according to the procedure for synthesis of **10**. *cis*-**9**: colorless prisms; mp 92–93 °C (diisopropyl ether), R_f 0.48 (acetone:dichloromethane = 2:98); ^{1}H NMR (400 MHz) ($CDCl_3$) δ 1.12 (t, J = 7.5 Hz, 3 H), 1.46 (s, 9 H), 1.6–2.0 (m, 2 H), 3.45 (dt, J = 6.2, 8.0 Hz, 1 H), 3.78 (s, 3 H), 4.46 (d, J = 6.2 Hz, 1 H), 6.84 (d, J = 9.0 Hz, 2 H), 7.24 (d, J = 9.0 Hz, 2 H); IR (KBr) 2990, 2960, 1750, 1735, 1520, 1400, 1245, 1170 cm^{-1}; MS m/z (rel intensity) 305 (M^+, 16), 250 (20), 249 (100), 221 (10), 204 (19), 181 (31), 179 (28), 177 (47), 162 (27), 149 (51), 136 (38), 134 (80), 92 (18), 77 (24), 57 (92). Anal. Calcd for $C_{17}H_{23}NO_4$: C, 66.86; H, 7.59; N, 4.59. Found: C, 66.70; H, 7.43; N, 4.57. *trans*-**9**: ^{1}H NMR (90 MHz) ($CDCl_3$) 1.11 (t, J = 7.3 Hz, 3 H), 1.60 (s, 9 H), 1.6–2.0 (m, 2 H), 3.23 (dt, J = 2.5, 6.0 Hz, 1 H), 3.78 (s, 3 H), 4.07 (d, J = 2.5 Hz, 1 H), 6.88 (d, J = 9.0 Hz, 2 H), 7.56 (d, J = 9.0 Hz, 2 H); IR ($CHCl_3$) 2990, 1745, 1510, 1240, 1150 cm^{-1}; MS m/z (rel intensity) 305 (M^+, 16), 249 (96), 149 (80), 134 (100), 57 (88).

4-(*tert*-Butoxycarbonyl)-3-(*N*,*N*-dibenzylamino)-1-(4-methoxyphenyl)-2-azetidinones (11). *cis*-**11**: colorless oil; R_f 0.48 (ether:hexane = 3:2); ^{1}H NMR (400 MHz) ($CDCl_3$) δ 1.51 (s, 9 H), 3.77 (s, 3 H), 3.99 (ABq, J_{AB} = 13.9 Hz, $\Delta\nu_{AB}$ = 37.1 Hz, 4 H), 4.46 (d, J = 5.5 Hz, 1 H), 4.65 (d, J = 5.5 Hz, 1 H), 6.84 (d, J = 9.0 Hz, 2 H), 7.1–7.5 (m, 12 H). IR ($CHCl_3$) 2980, 2940, 1745, 1515, 1400, 1370, 1245, 1150 cm^{-1}; MS m/z (rel intensity) 472 (M^+, 3), 444 (4), 371 (2), 343 (9), 238 (13), 237 (67), 208 (42), 175 (13), 118 (47), 91 (100); exact MS calcd for $C_{29}H_{32}N_2O_4$ M^+ 472.2359, found m/z 472.2360. *trans*-**11**: colorless prisms; mp 136–137.5 °C (diisopropyl ether); R_f 0.41 (ether:hexane = 3:2); ^{1}H NMR (400 MHz) ($CDCl_3$) δ 1.35 (s, 9 H), 3.62 (d, J = 13.2 Hz, 2 H), 3.76 (s, 3 H), 3.97 (d, J = 13.2 Hz, 2 H), 4.41 (d, J = 2.1 Hz, 1 H), 4.44 (d, J = 2.1 Hz, 1 H), 6.84 (d, J = 9.2 Hz, 2 H), 7.2–7.5 (m, 12 H). IR (KBr) 2990, 1745, 1735, 1515, 1250, 1145 cm^{-1}; MS m/z (rel intensity) 472 (M^+, 4), 444 (5), 371 (3), 343 (21), 237 (68), 208 (34), 118 (39), 91 (100); exact MS calcd for $C_{29}H_{32}N_2O_4$ M^+ 472.2359, found m/z 472.2347.

***N*-[(*tert*-Butoxycarbonyl)methyl]-*N*-(4-methoxyphenyl)-3-hydroxy-3-methylbutanamide (13).** To a solution of *N*-(4-methoxyphenyl)acetamide (prepared from 172 mg of

p-anisidine according to route b of Scheme II) in THF (15 mL) cooled at 0 °C was added *n*-BuLi (1.56 M in hexane, 1.88 mL, 2.9 mmol). The mixture was stirred for 30 min at 0 °C, treated with acetone (0.51 mL, 7.0 mmol), stirred for additional 20 min, poured into saturated NH_4Cl solution, and extracted with ethyl acetate. The organic layer was washed with saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by preparative TLC (ether, double development) to give **12** (291 mg, 94% yield from *p*-anisidine) as a colorless solid: R_f 0.33 (ether, double development); ^1H NMR (90 MHz) ($CDCl_3$) δ 1.31 (s, 6 H), 2.47 (s, 2 H), 3.76 (s, 3 H), 4.1 (brs, 1 H), 6.82 (d, J = 9.2 Hz, 2 H), 7.39 (d, J = 9.2 Hz, 2 H), 8.3 (brs, 1 H); IR (KBr) 3340, 2990, 1645, 1610, 1510, 1240 cm^{-1}. To a solution of **12** (178 mg, 0.80 mmol), *tert*-butyl bromoacetate (0.39 mL, 2.4 mmol), and benzyltriethylammonium bromide (30 mg, 0.11 mmol) in dichloromethane (2.5 mL) was added 50% NaOH solution (0.15 mL) at 0 °C. After being stirred at the same temperature for 4 h, the mixture was poured into saturated NH_4Cl solution and extracted with ethyl acetate. The organic layer was washed with saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by preparative TLC (ethyl acetate:hexane = 3:2) to afford **13** (0.23 g, 85%) as colorless prisms: mp 79–80 °C (diisopropyl ether); R_f 0.33 (ether:hexane = 5:1); ^1H NMR (90 MHz) ($CDCl_3$) δ 1.17 (s, 6 H), 1.46 (s, 9 H), 2.25 (s, 2 H), 3.85 (s, 3 H), 4.24 (s, 2 H), 5.15 (s, 1 H), 6.93 (d, J = 9.0 Hz, 2 H), 7.25 (d, J = 9.0 Hz, 2 H); IR (KBr) 3420, 2985, 1750, 1620, 1510, 1250, 1220, 1150 cm^{-1}; MS m/z (rel intensity) 337 (M^+, 14), 264 (9), 237 (22), 181 (100), 136 (84), 59 (22), 57 (17). Anal. Calcd for $C_{18}H_{27}NO_5$: C, 64.07; H, 8.06; N, 4.15. Found: C, 63.97; H, 8.14; N, 4.06.

4-(*tert*-Butoxycarbonyl)-3-(1-hydroxy-1-methylethyl)-1-(4-methoxyphenyl)-2-azetidinones (14). *n*-BuLi (1.52 M hexane solution, 0.40 mL, 0.59 mmol) was added to a solution of **13** (62 mg, 0.18 mmol) and TMEDA (91 mL, 0.59 mmol) in THF (4 mL) at −78 °C. The mixture was stirred at −78 °C for 30 min and then poured into a THF (1 mL) suspension of tetraphenylphosphonium bromide (0.25 g, 0.59 mmol) which had been cooled to −78 °C. After stirring for 30 min, the mixture was added all at once to a solution of copper(II) chloride (87 mg, 0.63 mmol) in DMF (2 mL) precooled to −78 °C. The resulting mixture was stirred for 2 h at the same temperature and then poured into saturated NH_4Cl solution and extracted with ethyl acetate. The organic layer was washed successively with saturated $Na_2S_2O_3$, saturated $NaHCO_3$, and saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by preparative TLC (ether:hexane = 5:1) to give a mixture of *cis*- and *trans*-**14** (10 mg, 17%). The ratio of *cis*-**14** to *trans*-**14** was estimated to be 5:1 based on the ^1H NMR spectrum of the mixture. Further separation by preparative TLC (acetone:dichloromethane = 3:97, double development) afforded pure *cis*-**14** and *trans*-**14**, respectively. *cis*-**14**: colorless needles, mp 142–143.5 °C (diisopropyl ether); R_f 0.26; ^1H NMR (90 MHz) ($CDCl_3$) δ 1.39 (s, 3 H), 1.48 (s, 12 H), 2.9 (br s, 1 H), 3.67 (d, J = 6.2 Hz, 1 H), 3.78 (s, 3 H), 4.51 (d, J = 6.2 Hz, 1 H), 6.87 (d, J = 9.0 Hz, 2 H), 7.26 (d, J = 9.0 Hz, 2 H); IR ($CHCl_3$) 3530, 2990, 1730, 1705, 1515, 1320, 1240, 1145 cm^{-1}; MS m/z (rel intensity) 335 (M^+, 6), 279 (66), 261 (28), 221 (30), 176 (46), 149 (44), 134 (85), 123 (70), 83 (63), 57 (100); exact MS calcd for $C_{18}H_{25}NO_5$ M^+ 335.1731, found m/z 335.1738. *trans*-**14**: R_f 0.23; ^1H NMR (90 MHz) ($CDCl_3$) δ 1.37 (s, 3 H), 1.47 (s, 9 H), 1.51 (s, 3 H), 3.29 (d, J = 2.9 Hz, 1 H), 3.78 (s, 3 H), 4.38 (d, J = 2.9 Hz, 1 H), 6.87 (d, J = 9.0 Hz, 2 H), 7.26 (d, J = 9.0 Hz, 2 H); IR ($CHCl_3$) 2990, 1740, 1510, 1150 cm^{-1}; MS m/z (rel intensity) 335 (M^+, 27), 279 (100), 221 (26), 190 (86), 176 (88), 149 (74), 134 (79), 123 (71), 57 (89); exact MS calcd for $C_{18}H_{25}NO_5$ M^+ 335.1731, found m/z 335.1738.

***N*-[(*tert*-Butoxycarbonyl)methyl]-*N*-(4-methoxyphenyl)-2-butenamide (15).** Prepared according to route b in Scheme II starting from *p*-anisidine (2.15 g, 17 mmol) and crotonyl chloride (1.87 mL, 19 mmol) (46% yield from *p*-anisidine): colorless plates; mp 114–116 °C (diisopropyl ether); R_f 0.53 (acetone:dichloromethane = 5:95); ^1H NMR (90 MHz) ($CDCl_3$) δ 1.45 (s, 9 H), 1.73 (dd, J = 6.8, 1.5 Hz, 3 H), 3.83 (s, 3 H), 4.28 (s, 2 H), 5.76 (dd, J = 15.4, 1.5 Hz, 1 H), 6.93 (d, J = 9.0 Hz, 2 H), 6.96 (dq, J = 15.4, 6.8 Hz, 1 H), 7.26 (d, J = 9.0 Hz, 2 H); IR (KBr) 2980, 1745, 1670, 1630, 1515, 1370, 1250, 1225, 1150 cm^{-1}; MS m/z (rel intensity) 305 (M^+, 21), 249 (10), 204 (10), 181 (66), 136 (61), 69 (100). Anal. Calcd for $C_{17}H_{23}NO_4$: C, 66.86; H, 7.59; N, 4.59. Found: C, 66.82; H, 7.71; N, 4.44.

3,4-*cis*-4-(*tert*-Butoxycarbonyl)-1-(4-methoxyphenyl)-3-(1-methylpentyl)-2-azetidinone (16a). Amide **15** (158 mg, 0.43 mmol) was subjected to the *typical procedure for oxidative coupling* using NIS as the oxidant. The crude reaction product was purified by preparative TLC (acetone:dichloromethane = 1.5:98.5) to give **16a** (75 mg, 48%) as a mixture of two epimers. Each was separated by preparative TLC (ether:hexane = 2:3, double development) to give isomer A and isomer B in a 1.2:1 ratio. Isomer A: colorless prisms; mp 77–78.5 °C (methanol); R_f 0.65; ^1H NMR (90 MHz) ($CDCl_3$) δ 0.92 (t, J = 6.0 Hz, 3 H), 0.95 (d, J = 6.4 Hz, 3 H), 1.2–2.2 (m, 7 H), 1.45 (s, 9 H), 3.31 (dd, J = 10.5, 5.5 Hz, 1 H), 3.78 (s, 3 H), 4.43 (d, J = 5.5 Hz, 1 H), 6.84 (d, J = 8.8 Hz, 2 H), 7.23 (d, J = 8.8 Hz, 2 H); IR ($CHCl_3$) 2940, 1740, 1510, 1460, 1395, 1370, 1240, 1145 cm^{-1}; MS m/z (rel intensity) 361 (M^+, 7), 305 (100), 277 (16), 233 (16), 179 (38), 176 (85), 134 (91), 57 (72); exact MS calcd for $C_{21}H_{31}NO_4$ M^+ 361.2251, found m/z 361.2227. Isomer B: colorless prisms; mp 93–95 °C (methanol); R_f 0.60; ^1H NMR (90 MHz) ($CDCl_3$) δ 0.89 (t, J = 6.0 Hz, 3 H), 1.19 (d, J = 6.6 Hz, 3 H), 1.0–2.2 (m, 7 H), 1.45 (s, 9 H), 3.31 (dd, J = 10.0, 5.9 Hz, 1 H), 3.78 (s, 3 H), 4.42 (d, J = 5.9 Hz, 1 H), 6.85 (d, J = 9.0 Hz, 2 H), 7.24 (d, J = 9.0 Hz, 2 H); IR ($CHCl_3$) 2940, 1740, 1510, 1460, 1395, 1370, 1240, 1145 cm^{-1}; MS m/z (rel intensity) 361 (M^+, 9), 305 (100), 176 (69), 149 (26), 134 (79), 57 (62); exact MS calcd for $C_{21}H_{31}NO_4$ M^+ 361.2251, found m/z 361.2231.

3,4-*cis*-4-(*tert*-Butoxycarbonyl)-1-(4-methoxyphenyl)-3-(2,3-dimethylbutyl)-2-azetidinone (16b). This was obtained in 15% yield as a mixture of stereoisomers and as a colorless oil: ^1H NMR ($CDCl_3$) δ 0.79 and 0.83 (2d, J = 6.0 Hz, 3 H, ratio 1:2), 0.86–0.96 (m, 5 H), 1.05 and 1.09 (2d, J = 6.0 Hz, 3 H, ratio 1:2), 1.24–1.31 (m, 2 H), 1.44 (s, 9 H), 3.46–3.64 (m, 1 H), 3.78 (s, 3 H), 4.40, 4.41, 4.43, and 4.44 (4d, J = 6.0 Hz, 1 H, ratio 55:15:5:25), 6.84 (d, J = 9.0 Hz, 2 H), 7.23 (d, J = 9.0 Hz, 2 H); IR ($CHCl_3$) 2950, 1740, 1515, 1250, 1150 cm^{-1}; MS m/z (rel intensity) 361 (M^+, 5), 305 (M^+ − *t*-Bu, 20), 232 (5), 57 (100).

3,4-*cis*-4-(*tert*-Butoxycarbonyl)-1-(4-methoxyphenyl)-3-(2,3,3-trimethylpropyl)-2-azetidinone (16c): 25% yield, colorless oil: ^1H NMR ($CDCl_3$) δ 0.94 (s, 9 H), 1.18 (d, J = 7.0 Hz, 3 H), 1.48 (s, 9 H), 1.75–1.82 (m, 1 H), 3.70 (2d, J = 6.0 Hz, 1 H), 3.78 (s, 3 H), 4.40 (d, J = 6.0 Hz, 1 H), 6.85 (d, J = 9.0 Hz, 2 H), 7.26 (d, J = 9.0 Hz, 2 H); IR ($CDCl_3$) 2940, 1740, 1520, 1040 cm^{-1}; MS m/z (rel intensity) 361 (M^+, 5), 305 (M^+ − *t*-Bu, 20), 232 (5), 57 (100).

***N*-(*tert*-Butoxycarbonyl)-*N*-(4-methoxyphenyl)-3-methyl-2-butenamide (15′).** Prepared according to route b in Scheme II starting with *p*-anisidine (0.50 g, 4.0 mmol) and 3-methyl-2-butenoic acid (0.40 g, 4.0 mmol): colorless plates; mp 90 °C (hexane–ether); ^1H NMR (90 MHz) ($CDCl_3$) δ 1.45 (s, 9 H), 1.68 (d, J = 1.0 Hz, 3 H), 2.12 (d, J = 1.0 Hz, 3 H), 3.83 (s, 3 H), 4.27 (s, 2 H), 5.02 (br s, 1 H), 6.90 (d, J = 8.0 Hz, 2 H), 7.23 (d, J = 8.0 Hz, 2 H); IR ($CHCl_3$) 2980, 1740, 1675, 1515, 1250 cm^{-1}. Anal. Calcd for $C_{18}H_{25}O_4N$: C, 67.69; H, 7.89; N, 4.39. Found: C, 68.10; H, 7.74; N, 4.31.

4-(*tert*-Butoxycarbonyl)-1-(4-methoxyphenyl)-3-(1-methylethenyl)-2-azetidinones (16′). To a solution of 15′ (55 mg, 0.17 mmol) in THF (5.0 mL) was added *n*-BuLi (1.55 M, 0.44 mL, 0.68 mmol) at −78 °C. After being stirred for 1 h, the reaction mixture was poured quickly into the solution of NIS (78 mg, 0.34 mmol) in THF (2.0 mL) at −78 °C and stirred for 1 h at −78 °C. The reaction was quenched with saturated NH_4Cl solution and extracted with ether. The ethereal extract was washed successively with saturated $Na_2S_2O_3$ solution and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by preparative TLC (hexane:ethyl acetate = 2:1) gave 3,4-*trans*-4-(*tert*-butoxycarbonyl)-1-(4-methoxyphenyl)-3-(1-methylethenyl)-2-azetidinone **16′** (8 mg, 15%) and 3,4-*cis*-**16′** (8 mg, 15%) as a colorless oil. *trans*-**16′**: ^1H NMR ($CDCl_3$) δ 1.46 (s, 9 H), 1.86 (s, 3 H), 3.78 (s, 3 H), 3.86 (d, J = 2.5 Hz, 1 H), 4.23 (d, J = 2.5 Hz, 1 H), 5.02 (br s, 1 H), 5.11 (br s, 1 H), 6.87 (d, J = 9.0 Hz, 2 H), 7.29 (d, J = 9.0 Hz, 2 H); IR ($CHCl_3$) 2980, 1745, 1510, 1250, 1150, 1035 cm^{-1}; MS m/z (rel intensity) 317 (M^+, 15), 261 (M^+ − *t*-Bu, 5), 188 (18), 149 (100). *cis*-**16′**: ^1H NMR ($CDCl_3$) δ 1.41 (s, 9 H), 1.83 (s, 3 H), 3.78 (s, 3 H), 4.17 (d, J = 6.0 Hz, 1 H), 4.55 (d, J = 6.0 Hz, 1 H), 5.12 (br s, 1 H), 5.16 (br s, 1 H), 6.86 (d, J = 9.0 Hz, 2 H),

7.28 (d, J = 9.0 Hz, 2 H); IR($CHCl_3$) 2980, 1745, 1510, 1250, 1150, 1035 cm^{-1}; MS m/z (rel intensity) 317 (M^+, 15), 261 (M^+ – t-Bu, 40), 216 (12), 149 (100).

***N*-[(*tert*-Butoxycarbonyl)methyl]-*N*-[(*R*)-1-phenylethyl](*N'*,*N'*-dibenzylamino)acetamide (17).** Triethylamine (3.82 mL, 27 mmol) and *tert*-butyl bromoacetate (3.32 mL, 21 mmol) were added to a THF (40 mL) solution of (*R*)-1-phenylethylamine ($[\alpha]^{20}_D$ +40.7° (neat), 1.66 g, 14 mmol) at 0 °C. After being stirred at room temperature for 24 h, the mixture was diluted with ethyl acetate, washed successively with water, saturated $NaHCO_3$, and saturated NaCl solution. The organic phase was dried over $MgSO_4$, filtered, and concentrated in vacuo to give a pale yellow oil which was dissolved in dichloromethane (30 mL) and treated with triethylamine (2.84 mL, 21 mmol) and bromoacetyl bromide (1.42 mL, 17 mmol) at –20 °C for 1 h. The reaction mixture was poured into saturated NH_4Cl solution and extracted with ethyl acetate. The organic phase was washed successively with 1 M HCl, saturated $NaHCO_3$, and saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated in vacuo to give a brown oil. The oily product was dissolved in THF (30 mL) and treated successively with triethylamine (3.79 mL, 27 mmol) and dibenzylamine (3.92 mL, 21 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 15 h. Workup as above followed by column chromatography (silica gel, acetone:dichloromethane = 0.5:99.5 to 1:99) afforded **17** (5.81 g, 90% yield from (*R*)-1-phenylethylamine). Amide **17** exists as a 3:2 mixture of *Z* and *E* isomers in $CDCl_3$ solution as shown below: mp 69–70 °C (diisopropyl ether–hexane); R_f 0.37 (ether:hexane = 1:1); $[\alpha]^{20}_D$ +47.2° (*c* 0.83, $CHCl_3$); ^1H NMR (400 MHz) ($CDCl_3$) δ 1.18 and 1.37 (2s, intensity ratio = 3:2, 9 H), 1.40 (d, J = 7.0 Hz, 3 H), 3.25 and 3.37 (2ABq, J_{AB} = 13.4 Hz, $\Delta\nu_{AB}$ = 91.0 Hz; J_{AB} = 13.5 Hz, $\Delta\nu_{AB}$ = 10.8 Hz, intensity ratio = 3:2, 2 H), 3.33 and 3.35 (2d, J = 16.7, 18.4 Hz, intensity ratio = 2:3, 1 H), 3.93 and 4.17 (2d, J = 16.7, 18.4 Hz, intensity ratio = 2:3, 1 H), 3.45 (d, J = 13.3 Hz, 1.2 H), 3.74 (s, 1.6 H), 3.80 (d, J = 13.3 Hz, 1.2 H), 5.29 and 6.03 (2q, J = 7.0, 7.0 Hz, intensity ratio = 2:3, 1 H), 7.0–7.4 (m, 15 H); IR (KBr) 2980, 2950, 2850, 2810, 1740, 1655, 1445, 1370, 1230, 1150, 750, 695 cm^{-1}; MS m/z (rel intensity) 399 (M^+ – O-t-Bu, 2), 381 (27), 221 (20), 210 (100), 105 (20), 91 (99). Anal. Calcd for $C_{30}H_{36}N_2O_3$: C, 76.24; H, 7.68; N, 5.93%. Found: C, 76.22; H, 7.70; N, 5.89%.

4-(*tert*-Butoxycarbonyl)-3-(*N*,*N*-dibenzylamino)-1-[(*R*)-1-phenylethyl]-2-azetidinones 18–21 (Table II, entry 6). TMEDA (65 μL, 0.44 mmol) was added to a THF (5 mL) solution of **17** (93 mg, 0.20 mmol) at –78 °C under an argon atmosphere. To this mixture was added a hexane solution of *n*-BuLi (1.61 M, 0.49 mL, 0.80 mmol) at –78 °C. The mixture was stirred for 1 h at –78 °C and then cooled to –95 °C. NIS (141 mg, 0.64 mmol) dissolved in THF (3 mL) was cooled to –95 °C and poured into the reaction mixture all at once. The resulting mixture was warmed slowly to –70 °C over 1 h before quenching with methanol (1 mL). The mixture was poured into saturated NH_4Cl solution and extracted with ethyl acetate. The organic phase was washed successively with saturated $Na_2S_2O_3$, saturated $NaHCO_3$, and saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by preparative TLC (ethyl acetate:hexane = 1:3) to give a mixture of **18–21** (54 mg, 58% yield). The ratio (Table II) was estimated by ^1H NMR of the mixture. Each isomer was separated by preparative TLC (acetone:dichloromethane = 0.5:99.5). **18**: pale yellow oil; R_f 0.45; $[\alpha]^{20}_D$ +41.3° (*c* 1.53, $CHCl_3$); ^1H NMR (400 MHz) ($CDCl_3$) δ 1.54 (s, 9 H), 1.65 (d, J = 7.0 Hz, 3 H), 3.72 (d, J = 5.3 Hz, 1 H), 3.92 (ABq, J_{AB} = 13.9 Hz, $\Delta\nu_{AB}$ = 22.0 Hz, 4 H), 4.33 (d, J = 5.3 Hz, 1 H), 5.03 (q, J = 7.1 Hz, 1 H), 7.1–7.5 (m, 15 H); IR (neat) 2980, 1755, 1450, 1370, 1150 cm^{-1}; MS m/z (rel intensity) 470 (M^+, 0.5), 365 (0.8), 309 (1), 266 (6), 237 (21), 105 (22), 91 (100); exact MS calcd for $C_{30}H_{34}N_2O_3$, M^+, 470.2567, found m/z 470.2594. **19**: R_f 0.50; $[\alpha]^{20}_D$ –51.4° (*c* 0.68, $CHCl_3$); ^1H NMR (400 MHz) ($CDCl_3$) δ 1.50 (s, 9 H), 1.80 (d, J = 7.1 Hz, 3 H), 3.84 (d, J = 5.3 Hz, 1 H), 3.92 (ABq, J_{AB} = 13.8 Hz, $\Delta\nu_{AB}$ = 44.5 Hz, 4 H), 4.38 (d, J = 5.3 Hz, 1 H), 4.62 (q, J = 7.1 Hz, 1 H), 7.1–7.5 (m, 15 H); IR ($CHCl_3$) 2980, 1750, 1450, 1370, 1150 cm^{-1}; MS m/z (rel intensity) 470 (M^+, 1), 369 (2), 266 (12), 237 (61), 208 (47), 176 (39), 118 (69), 105 (62), 91 (100). Anal. Calcd for $C_{30}H_{34}N_2O_3$: C, 76.56; H, 7.28; N, 5.95. Found: C, 75.96; H, 7.43; N, 5.91. **20**: colorless needles; mp 120.5–121.5 °C (diisopropyl ether); R_f 0.33; $[\alpha]^{20}_D$ +7.1° (*c* 0.23, $CHCl_3$); ^1H NMR (400 MHz) ($CDCl_3$) δ 1.38 (s, 9 H), 1.57 (d, J = 7.2 Hz, 3 H), 3.35 (d, J = 13.4 Hz, 2 H), 3.77 (d, J = 13.4 Hz, 2 H), 3.83 (d, J = 2.0 Hz, 1 H), 4.20 (d, J = 2.0 Hz, 1 H), 5.06 (q, J = 7.2 Hz, 1 H), 7.1–7.5 (m, 15 H); IR (KBr) 2990, 1755, 1450, 1390, 1370, 1225, 1150 cm^{-1}; MS m/z (rel intensity) 470 (M^+, 2), 369 (2), 266 (14), 237 (35), 176 (32), 105 (22), 91 (100). Anal. Calcd for $C_{30}H_{34}N_2O_3$: C, 76.56; H, 7.28; N, 5.95. Found: C, 76.21; H, 7.40; N, 5.82. **21**: R_f 0.39; ^1H NMR (400 MHz) ($CDCl_3$) δ 1.31 (s, 9 H), 1.77 (d, J = 7.1 Hz, 3 H), 3.49 (d, J = 13.4 Hz, 2 H), 3.88 (d, J = 13.4 Hz, 2 H), 3.95 (d, J = 2.0 Hz, 1 H), 4.18 (d, J = 2.0 Hz, 1 H), 4.57 (q, J = 7.1 Hz, 1 H), 7.1–7.5 (m, 15 H).

***N*-[[(*S*)-2-Oxo-4-isopropyloxazoline-3-carbonyl]methyl]-*N*-(4-methoxyphenyl)butanamide (22).** *n*-BuLi (1.53 M in hexane, 1.47 mL, 2.2 mmol) was added to a solution of (*S*)-4-isopropyloxazolin-2-one (0.26 g, 2.0 mmol) in THF (25 mL) cooled to –78 °C. After the solution was stirred for 20 min at –78 °C, bromoacetyl chloride (0.22 mL, 2.7 mmol) was added. The resulting mixture was gradually warmed to 0 °C and then poured into saturated $NaHCO_3$ solution and extracted with ethyl acetate. The organic layer was washed successively with saturated $Na_2S_2O_3$, saturated $NaHCO_3$, and saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated in vacuo to give crude (*S*)-3-(bromoacetyl)-4-isopropyloxazolin-2-one as a brown oil: ^1H NMR (90 MHz) ($CDCl_3$) δ 0.90 (d, J = 6.5 Hz, 3 H), 0.92 (d, J = 6.5 Hz, 3 H), 2.2–2.6 (m, 1 H), 4.1–4.6 (m, 3 H), 4.53 (ABq, J_{AB} = 13.0 Hz, $\Delta\nu_{AB}$ = 13.9 Hz, 2 H). Starting with this crude bromide and *p*-anisidine (0.27 g, 2.2 mmol), **22** was prepared according to route a in Scheme II (0.45 g, 61% yield from (*S*)-4-isopropyloxazolin-2-one) as a pale yellow oil: R_f 0.43 (ether); $[\alpha]^{20}_D$ +47.5° (*c* 0.38, $CHCl_3$); ^1H NMR (90 MHz) ($CDCl_3$) δ 0.84 (t, J = 7.5 Hz, 3 H), 0.88 (d, J = 6.8 Hz, 3 H), 0.91 (d, J = 7.0 Hz, 3 H), 1.4–1.8 (m, 2 H), 2.12 (t, J = 6.6 Hz, 2 H), 2.2–2.6 (m, 1 H), 3.82 (s, 3 H), 4.1–4.5 (m, 3 H), 4.89 (ABq, J_{AB} = 17.0 Hz, $\Delta\nu_{AB}$ = 10.5 Hz, 2 H), 6.89 (d, J = 9.0 Hz, 2 H), 7.28 (d, J = 9.0 Hz, 2 H); IR ($CHCl_3$) 2970, 1780, 1715, 1660, 1510, 1390, 1250 cm^{-1}; MS m/z (rel intensity) 362 (M^+, 8), 292 (32), 163 (17), 136 (100), 43 (40). Anal. Calcd for $C_{19}H_{26}N_2O_5$: C, 62.96; H, 7.23; N, 7.73. Found: C, 62.87; H, 7.35; N, 7.53.

3-Ethyl-4-[(*S*)-2-oxo-4-isopropyloxazoline-3-carbonyl]-1-(4-methoxyphenyl)-2-azetidinones (23). Amide **22** (57 mg, 0.16 mmol) was treated according to the *typical procedure for oxidative coupling* using $Cu(OAc)_2$ as the oxidant. The residue was purified by preparative TLC (acetone:dichloromethane = 5:95) to give **23** (30 mg, 52% yield) as a mixture of four stereoisomers. These were separated by preparative TLC (ether) to give four stereochemically pure β-lactams in a 3:3:2:2 ratio (cis:trans:cis:trans). **Isomer A**: R_f 0.61 (ether); $[\alpha]^{20}_D$ –169° (*c* 0.31, $CHCl_3$); ^1H NMR (90 MHz) ($CDCl_3$) δ 0.93 (d, J = 7.0 Hz, 3 H), 0.95 (d, J = 6.8 Hz, 3 H), 1.11 (t, J = 7.3 Hz, 3 H), 1.4–1.8 (m, 2 H), 2.2–2.6 (m, 1 H), 3.5–3.8 (m, 1 H), 3.77 (s, 3 H), 4.3–4.6 (m, 3 H), 5.62 (d, J = 5.9 Hz, 1 H), 6.84 (d, J = 9.2 Hz, 2 H), 7.20 (d, J = 9.2 Hz, 2 H); IR ($CHCl_3$) 2975, 1780, 1750, 1715, 1515, 1390, 1245 cm^{-1}; MS m/z (rel intensity) 360 (M^+, 37), 306 (10), 290 (9), 204 (10), 176 (49), 149 (74), 134 (100); exact MS calcd for $C_{19}H_{24}N_2O_5$ M^+ 360.1683, found m/z 360.1677. **Isomer B**: R_f 0.54 (ether); $[\alpha]^{20}_D$ +194° (*c* 0.19, $CHCl_3$); ^1H NMR (90 MHz) ($CDCl_3$) δ 0.90 (d, J = 7.0 Hz, 3 H), 0.92 (d, J = 7.0 Hz, 3 H), 1.10 (t, J = 7.3 Hz, 3 H), 1.8–2.2 (m, 2 H), 2.1–2.5 (m, 1 H), 3.21 (td, J = 7.0, 2.4 Hz, 1 H), 3.77 (s, 3 H), 4.2–4.6 (m, 3 H), 5.53 (d, J = 2.4 Hz, 1 H), 6.84 (d, J = 9.0 Hz, 2 H), 7.23 (d, J = 9.0 Hz, 2 H); IR ($CHCl_3$) 2970, 1780, 1750, 1710, 1515, 1390, 1245 cm^{-1}; MS m/z (rel intensity) 360 (M^+, 41), 290 (7), 204 (17), 176 (84), 149 (100), 134 (94); exact MS calcd for $C_{19}H_{24}N_2O_5$ M^+ 360.1683, found m/z 360.1679. **Isomer C**: R_f 0.46 (ether); $[\alpha]^{20}_D$ +211° (*c* 0.11, $CHCl_3$); ^1H NMR (90 MHz) ($CDCl_3$) δ 0.92 (d, J = 6.8 Hz, 6 H), 1.18 (t, J = 7.0 Hz, 3 H), 1.5–1.9 (m, 2 H), 2.2–2.6 (m, 1 H), 3.6–3.9 (m, 1 H), 3.77 (s, 3 H), 4.3–4.6 (m, 3 H), 5.45 (d, J = 5.9 Hz, 1 H), 6.84 (d, J = 9.2 Hz, 2 H), 7.22 (d, J = 9.2 Hz, 2 H); IR ($CHCl_3$) 2950, 1780, 1750, 1710, 1515, 1390, 1250 cm^{-1}; MS m/z (rel intensity) 360 (M^+, 49), 290 (13), 204 (12), 176 (54), 149 (71), 134 (100); exact MS calcd for $C_{19}H_{24}N_2O_5$ M^+ 360.1683, found m/z 360.1684. **Isomer D**: R_f 0.41 (ether); $[\alpha]^{20}_D$ –72.5° (*c* 0.32, $CHCl_3$); ^1H NMR (90 MHz) ($CDCl_3$) δ 0.91 (d, J = 7.0 Hz, 6 H), 1.09 (t, J = 7.3 Hz, 3 H), 1.8–2.1 (m, 2 H), 2.2–2.5 (m, 1 H), 3.26 (td, J = 6.5, 2.2 Hz, 1 H), 3.78 (s, 3 H), 4.2–4.6 (m, 3 H), 5.56 (d, J = 2.2 Hz, 1 H), 6.84 (d, J = 9.2 Hz, 2 H), 7.22 (d, J = 9.2 Hz, 2 H);

IR ($CHCl_3$) 2980, 1780, 1750, 1710, 1515, 1390, 1245 cm^{-1}; MS m/z (rel intensity) 360 (M^+, 44), 204 (16), 176 (89), 149 (97), 134 (100); exact MS calcd for $C_{19}H_{24}N_2O_5$ M^+ 360.1683, found m/z 360.1675.

N-[(*tert*-Butoxycarbonyl)methyl]-N-[(*R*)-1-phenylethyl]-2-(benzyloxy)acetamide (24). (*R*)-1-Phenylethylamine (1.66 g, 14 mmol) was treated with *tert*-butyl bromoacetate (3.32 mL, 21 mmol) as described in route a in Scheme II. The crude residue was dissolved in dichloromethane (30 mL) and cooled to −20 °C. To this solution was added triethylamine (2.87 mL, 21 mmol) and then (benzyloxy)acetyl chloride (2.60 mL, 17 mmol). After being stirred for 20 min at −20 °C, the mixture was poured into saturated NH_4Cl solution, and extracted with ethyl acetate. The organic layer was washed with 1 M HCl, saturated $NaHCO_3$, and saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (ethyl acetate:hexane = 1:4) to afford **24** [4.02 g, 77% yield from (*R*)-1-phenylethylamine] as colorless prisms. Amide **24** was a 1:1 mixture of *E* and *Z* isomers in $CDCl_3$ solution as shown below: mp 68–69 °C (diisopropyl ether); $[\alpha]^{20}_D$ +75.4° (*c* 1.01, $CHCl_3$); R_f 0.46 (ether:hexane = 2:1); ^1H NMR (400 MHz) ($CDCl_3$) δ 1.32 and 1.41 (a pair of s, 9 H), 1.47 and 1.58 (a pair of d, J = 7.1, 6.9 Hz, 3 H), 3.39 and 3.60 (pair of d, J = 16.9, 18.7 Hz, 1 H), 3.88 and 4.00 (pair of d, J = 18.7, 16.9 Hz, 1 H), 4.16 and 4.35 (pair of ABq, J_{AB} = 13.8 Hz, $\Delta\nu_{AB}$ = 26.4 Hz; J_{AB} = 13.4 Hz, $\Delta\nu_{AB}$ = 18.6 Hz, 2 H), 4.62 and 4.70 (pair of ABq, J_{AB} = 11.7 Hz, $\Delta\nu_{AB}$ = 11.2 Hz; J_{AB} = 11.6 Hz, $\Delta\nu_{AB}$ = 18.9 Hz, 2 H), 5.33 and 6.09 (pair of q, J = 6.9, 7.1 Hz, 1 H), 7.2–7.5 (m, 10 H); IR (KBr) 2985, 1730, 1650, 1445, 1235, 1165, 1095 cm^{-1}; MS m/z (rel intensity) 384 (M^+ + 1, 2), 327 (11), 326 (25), 221 (70), 178 (90), 105 (100), 91 (69), 57 (17). Anal. Calcd for $C_{23}H_{29}NO_4$: C, 72.03; H, 7.62; N, 3.65. Found: C, 71.87; H, 7.50; N, 3.43.

3-(Benzyloxy)-4-(*tert*-butoxycarbonyl)-1-[(*R*)-1-phenylethyl]-2-azetidinones (26 and 27) (Table III, entry 2). Amide **24** (86 mg, 0.22 mmol) was treated with *t*-BuLi followed by tetraphenylphosphonium bromide and NIS according to the *typical procedure for oxidative coupling*. The residue was purified by preparative TLC (ethyl acetate:hexane = 1:1) to give a mixture of *cis*-β-lactams **26** and **27** (59 mg, 69%) in a 3:1 ratio. Separation by preparative TLC (ether:hexane = 2:3, double development) afforded pure **26** and **27**. The absolute configuration of these was tentatively assigned by analogy to that of **18**. **26**: colorless oil; R_f 0.31 (ether:hexane = 2:3, double development); $[\alpha]^{20}_D$ −12.2° (*c* 1.98, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.43 (s, 9 H), 1.65 (d, J = 7.0 Hz, 3 H), 3.91 (d, J = 5.3 Hz, 1 H), 4.68 (d, J = 5.3 Hz, 1 H), 4.70 (s, 2 H), 5.01 (d, J = 7.0 Hz, 1 H), 7.2–7.4 (m, 10 H); IR (neat) 2980, 1760, 1730 (shr), 1455, 1370, 1350, 1215, 1160 cm^{-1}; MS m/z (rel intensity) 382 (M^+ + 1, 3), 297 (8), 178 (23), 105 (98), 91 (100), 57 (54); exact MS calcd for $C_{23}H_{28}NO_4$, M^+ + 1, 382.2016, found m/z 382.2016. **27**: colorless oil; R_f 0.36 (ether:hexane = 2:3, double development); $[\alpha]^{20}_D$ +24.0° (*c* 1.04, $CHCl_3$); ^1H NMR (90 MHz) ($CDCl_3$) δ 1.37 (s, 9 H), 1.79 (d, J = 7.0 Hz, 3 H), 3.97 (d, J = 5.1 Hz, 1 H), 4.62 (q, J = 7.0 Hz, 1 H), 4.71 (d, J = 5.1 Hz, 1 H), 4.72 (s, 2 H), 7.2–7.4 (m, 10 H); IR (neat) 2980, 1765, 1740 (shr), 1455, 1370, 1350, 1225, 1160 cm^{-1}; MS m/z (rel intensity) 382 (M^+ + 1, 1), 297 (4), 252 (4), 178 (16), 160 (10), 105 (41), 91 (100), 57 (19); exact MS calcd for $C_{23}H_{28}NO_4$, M^+ + 1, 382.2016, found m/z 382.2016.

N-[(*tert*-Butoxycarbonyl)methyl]-N-[(*S*)-1-(1-naphthyl)ethyl]-2-(benzyloxy)acetamide (25). Prepared by the procedure for synthesis of **24** using (*S*)-1-(1-naphthyl)-ethylamine (1.01 g, 5.9 mmol) instead of (*R*)-1-phenylethylamine [1.15 g, 88% yield from (*S*)-1-(1-naphthyl)ethylamine]: R_f 0.49 (ethyl acetate:hexane = 1:1); $[\alpha]^{20}_D$ −63.8° (*c* 1.10, $CHCl_3$); ^1H NMR (90 MHz) ($CDCl_3$) δ 1.11 (s, 9 H), 1.61 (d, J = 7.0 Hz, 3 H), 3.65 (ABq, J_{AB} = 18.0 Hz, $\Delta\nu_{AB}$ = 15.9 Hz, 2 H), 4.15 (s, 2 H), 4.60 (s, 2 H), 6.73 (q, J = 7.0 Hz, 1 H), 7.27 (s, 5 H), 7.3–8.2 (m, 7 H); IR (neat) 2970, 1735, 1650, 1440, 1365, 1150 cm^{-1}; MS m/z (rel intensity) 433 (M^+, 2), 271 (15), 228 (48), 155 (100), 91 (49); exact MS calcd for $C_{27}H_{31}NO_4$, M^+, 433.2250, found m/z 433.2231.

3-(Benzyloxy)-4-(*tert*-butoxycarbonyl)-1-[(*S*)-1-(1-naphthyl)ethyl]-2-azetidinones (28 and 29). Amide **25** (83 mg, 0.19 mmol) was treated as described above. The residue was purified by preparative TLC (acetone:dichloromethane = 3:97) to give a mixture of *cis*-β-lactams **28** and **29** (26 mg, 31%) in a 3:2 ratio: R_f 0.54 (acetone:dichloromethane = 3:97); ^1H NMR (90 MHz) ($CDCl_3$) δ 1.16 and 1.38 (2s, intensity ratio = 2:3, 9 H), 1.88 and 1.95 (2d, J = 7.5, 7.5 Hz, intensity ratio = 3:2, 3 H), 3.42 and 4.01 (2d, J = 4.6, 4.8 Hz, intensity ratio = 3:2, 1 H), 4.56 and 4.85 (2q, J = 7.5, 7.5 Hz, intensity ratio = 2:3, 1 H), 4.57 and 4.79 (2d, J = 4.6, 4.8 Hz, intensity ratio = 3:2, 1 H), 4.67 and 4.74 (2s, intensity ratio = 3:2, 2 H), 7.1–8.1 (m, 12 H); IR (neat) 2990, 1760, 1730 (shr), 1370, 1160 cm^{-1}; MS m/z (rel intensity) 432 (M^+ + 1, 0.1), 347 (4), 330 (1), 197 (100), 182 (36), 155 (98), 91 (87).

(3*S*,4*S*)-3-[(Benzyloxycarbonyl)amino]-4-(*tert*-butoxycarbonyl)-1-[(*R*)-1-phenylethyl]-2-azetidinone (32). A suspension of **18** (354 mg, 0.75 mmol), ammonium formate (475 mg, 7.5 mmol), and 10% Pd–C (70 mg) in ethanol (10 mL) was heated under reflux for 4 h. Insoluble materials were removed by filtration and washed with hot ethanol. The combined filtrates were concentrated in vacuo. The residue was dissolved in dichloromethane (10 mL) and treated with propylene oxide (1.58 mL, 22 mmol) and benzyloxycarbonyl chloride (0.32 mL, 2.2 mmol). The mixture was stirred at room temperature for 3 h, diluted with ethyl acetate, and washed with saturated $NaHCO_3$ and saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (acetone:dichloromethane = 3:97) to afford **32** (300 mg, 94%) as a colorless oil: R_f 0.50 (acetone:dichloromethane = 5:95); $[\alpha]^{20}_D$ +3.9° (*c* 0.98, $CHCl_3$); ^1H NMR (90 MHz) ($CDCl_3$) δ 1.35 (s, 9 H), 1.58 (d, J = 7.3 Hz, 3 H), 3.99 (d, J = 5.1 Hz, 1 H), 4.97 (q, J = 7.3 Hz, 1 H), 5.07 (s, 2 H), 5.16 (dd, J = 10.0, 5.1 Hz, 1 H), 5.50 (br d, J = 10.0 Hz, 1 H), 7.31 (s, 10 H); IR (neat) 3300, 2980, 1765, 1730, 1535, 1240, 1155, 1050 cm^{-1}; MS m/z (rel intensity) 425 (M^+ + 1, 0.2), 277 (3), 221 (12), 160 (13), 105 (32), 91 (100). Anal. Calcd for $C_{24}H_{28}N_2O_5$: C, 67.90; H, 6.65; N, 6.60. Found: C, 68.00; H, 6.74; N, 6.34.

(3*S*,4*S*)-3-[(Benzyloxycarbonyl)amino]-4-(hydroxymethyl)-1-[(*R*)-1-phenylethyl]-2-azetidinone (33). Trifluoroacetic acid (3 mL) was added to a solution of **32** (165 mg, 0.39 mmol) dissolved in dichloromethane (3 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 30 min and at room temperature for 10 h and then diluted with toluene (10 mL) and concentrated under reduced pressure below 35 °C. The residue was dissolved in diethyl ether (2 mL) and treated with an ethereal solution of diazomethane. After removal of the solvent, the residue was purified by preparative TLC (acetone:dichloromethane = 5:95) to give a methyl ester: ^1H NMR (90 MHz) ($CDCl_3$) δ 1.57 (d, J = 7.0 Hz, 3 H), 3.60 (s, 3 H), 4.12 (d, J = 5.1 Hz, 1 H), 4.97 (q, J = 7.0 Hz, 1 H), 5.07 (s, 2 H), 5.25 (dd, J = 10.5, 5.1 Hz, 1 H), 7.31 (s, 10 H). To a solution of the methyl ester in THF (5 mL) was added a solution of sodium borohydride (150 mg, 3.9 mmol) in water (2 mL) at 0 °C. After being stirred at room temperature for 3 h, the mixture was diluted with ethyl acetate and washed with saturated NaCl solution. The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by preparative TLC (acetone:dichloromethane = 1:9) to afford **33** (108 mg, 78% from **32**) as colorless prisms: mp 86–87 °C (ethyl acetate–hexane); R_f 0.37 (acetone:dichloromethane = 1:9); $[\alpha]^{20}_D$ −41.7° (*c* 0.99, $CHCl_3$) [lit.[28] mp 84.5–85.9 °C and $[\alpha]^{20}_D$ −41° (*c* 0.82, $CHCl_3$)]; ^1H NMR (90 MHz) ($CDCl_3$) δ 1.74, (d, J = 7.3 Hz, 3 H), 3.5–3.8 (m, 3 H), 4.69 (q, J = 7.3 Hz, 1 H), 5.08 (dd, J = 10.0, 5.1 Hz, 1 H), 5.10 (s, 2 H), 5.82 (br d, J = 10.0 Hz, 1 H), 7.33 (s, 5 H), 7.37 (s, 5 H); IR ($CHCl_3$) 3440, 1745, 1720, 1510, 1450, 1395, 1375, 1315, 1230, 1060 cm^{-1}; MS m/z (rel intensity) 355 (M^+ + 1, 0.2), 247 (2), 207 (3), 132 (12), 116 (11), 105 (57), 100 (34), 99 (49), 91 (100), 79 (43), 77 (37), 55 (43). Anal. Calcd for $C_{20}H_{22}N_2O_4$: C, 67.78; H, 6.26; N, 7.91. Found: C, 67.56; H, 6.23; N, 7.91. Spectral and analytical data of **33** listed in ref 28a: IR ($CHCl_3$) 3420, 3300, 1745, 1720, 1512, 1450, 1390, 1370, 1310, 1230, 1060, 910, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.73, 2.2, 3.65, 4.74, 5.10, 5.93, 7.35; ^{13}C NMR ($CDCl_3$) δ 19.3, 52.9, 58.5, 59.2, 67.3, 126.8, 128.1, 128.5, 129.0, 130, 136, 140, 156, 167; MS m/z (CI-NH_3) 372 (M^+ + NH_4^+). Found: C, 67.55, H, 6.43, N, 7.83.

(3*S*,4*S*)-3-[(Benzyloxycarbonyl)amino]-4-(hydroxymethyl)-2-azetidinone (31). To a solution of ammonium persulfate (145 mg, 0.64 mmol) and potassium hydrogen phosphate (105 mg, 0.62 mmol) in water (0.5 mL) heated to 90 °C was added a solution of copper(II) sulfate (20 mg, 0.13 mmol) in water (0.5 mL) followed by a solution of **33** (70 mg, 0.20 mmol) in acetonitrile (3 mL). The reaction mixture was stirred for 2 h at 90 °C, cooled to room temperature, diluted with ethyl acetate, and washed with

saturated NaCl solution. The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by preparative TLC (acetonitrile:ethyl acetate = 1:2) to afford **31** (8.5 mg, 17%) as colorless prisms.

Alternative Synthesis of 31. To a solution of **33** (9.6 mg, 0.027 mmol) in THF–*tert*-butyl alcohol (10:1, 0.5 mL) was added butyllithium (1.55 M in hexane, 25 mL, 0.039 mmol) at −78 °C. The mixture was stirred at −78 °C for 30 min and was added to a solution of sodium (12 mg, 0.52 mmol) in liquid ammonium (1.5 mL) precooled to −78 °C, and the resulting mixture was stirred for 1 h. Powdered NH_4Cl was added to the mixture until the blue color disappeared. The solvents were removed under reduced pressure, and the residue was treated with water and 1 M HCl to adjust the pH to 3. The mixture was stirred for 30 min at room temperature and made alkaline (pH 8) with saturated $NaHCO_3$ solution. To the resulting mixture were added dichloromethane (2 mL) and benzyloxycarbonyl chloride (0.1 mL, 0.69 mmol). After the mixture was stirred at room temperature for 10 h, the dichloromethane layer was separated, and the aqueous layer was extracted with a 1:3 mixture of ethanol and chloroform. The combined organic phase was dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by preparative TLC (acetonitrile:ethyl acetate = 1:2) to afford **31** (3.9 mg, 58%) as colorless prisms: mp 129–130 °C (ethyl acetate–hexane); R_f 0.39 (acetonitrile:ethyl acetate = 1:2); $[\alpha]^{20}_D$ +8.7° (*c* 0.55, $CHCl_3$) [lit.[26e] mp 128.5–129.5 °C and $[\alpha]_D$ +8.6° (*c* 0.9, $CHCl_3$); lit.[28] mp 127–128 °C and $[\alpha]_D$ +9° (*c* 0.93, $CHCl_3$)]; ^1H NMR (DMSO-d_6) δ 3.3–3.8 (m, 3 H), 4.77 (t, J = 4.5 Hz, 1 H), 4.88 (dd, J = 9.8, 4.5 Hz, 1 H), 5.06 (s, 2 H), 7.34 (s, 5 H), 7.73 (d, J = 9.8 Hz, 1 H), 8.19 (br s, 1 H); ^1H NMR (acetone-d_6) δ 2.78 (br s, 1 H), 3.6–4.1 (m, 3 H), 4.15 (br s, 1 H), 5.08 (dd, J = 10.5, 6.0 Hz, 1 H), 5.10 (s, 2 H), 6.68 (br d, J = 10.5 Hz, 1 H), 7.36 (s, 5 H); IR (KBr) 3450, 3300, 1755, (sh), 1705, 1555, 1270, 1070 cm^{-1}; IR ($CHCl_3$) 3430, 1765, 1720, 1515, 1320, 1225, 1055 cm^{-1}; MS *m/z* (rel intensity) 250 (M^+, 0), 207 (19), 146 (8), 116 (42), 99 (13), 91 (100). The spectral data of **31** were identical with those reported [^1H NMR in DMSO-d_6[24a] or acetone-d_6[28a] and IR (KBr)[26f] or ($CHCl_3$)[28a]]. Physical data of **31** listed in ref 28a: mp 127.0–128.0 °C, $[\alpha]^{20}_D$ +9° (*c* 0.9305, $CHCl_3$); IR ($CHCl_3$) 3420, 1764, 1715, 1510, 1318, 1220, 1060 cm^{-1}; ^1H NMR (acetone-d_6) δ 3.7, 4.2, 5.1, 6.8, 7.35; MS *m/z* (CI-isob) 251 (MH^+).

Supplementary Material Available: ^1H NMR spectra of all compounds for which elemental analyses were not obtained (30 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Reaction of Pyrazole Addition to Quinones

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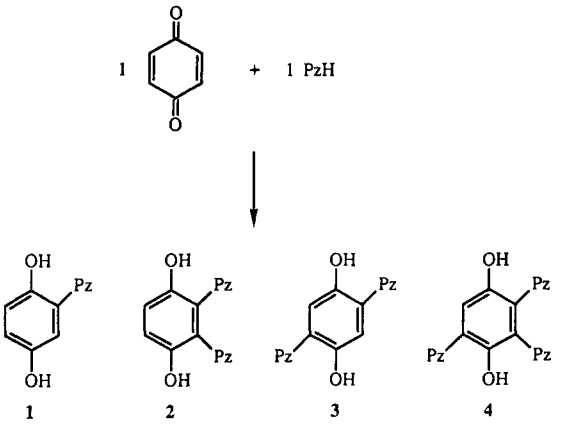
The reactions of pyrazole, 4-nitropyrazole, 3,5-dimethylpyrazole, and 4-chloro-3,5-dimethylpyrazole with 1,4-benzoquinone in dioxane have been analyzed. Mono- and 2,3-bis-adducts were obtained and only in the case of pyrazole was a 2,5-bis(pyrazol-1-yl)-1,4-dihydroxybenzene formed. Further oxidation of the mono- and bis-adducts with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) afforded the quinones, which in turn added 1 mol of azole (pyrazole and imidazole) to yield tetrapyrazolylquinols. Nitration of the 2,3-bis(pyrazol-1-yl)- and 2,3-bis(3,5-dimethylpyrazol-1-yl)-1,4-dihydroxybenzenes has been performed to prepare the corresponding 4-nitropyrazolyl derivatives.

We have recently reported that some mono- and bis(pyrazol-1-yl)-1,4-dihydroxybenzenes, structurally related to 2-(2-hydroxy-5-methylphenyl)benzotriazole (Tinuvin P), exhibit excellent stability to light.[1] These compounds were easily prepared by addition reaction of pyrazoles to 1,4-benzoquinone in dioxane. Depending on the nature of the pyrazole, mono- and bis-adducts are obtained. This reaction was performed for the first time with 3,5-dimethylpyrazole and the single product obtained was erroneously identified as 2,5-bis(3,5-dimethylpyrazol-1-yl)-1,4-dihydroxybenzene.[2] We proved by X-ray diffraction analysis that the structure of this product is 2,3-bis(3,5-dimethylpyrazol-1-yl)-1,4-dihydroxybenzene.[1] Furthermore, a minor product, identified as 2-(3,5-dimethylpyrazol-1-yl)-1,4-dihydroxybenzene, was also formed. Other authors[3] extended the reaction, in ethanol medium, to unsubstituted pyrazole and 4-chloropyrazole, obtaining different mixtures of addition compounds. Together with our previous work, these results suggest that this reaction is stongly dependent on the nature of the pyrazole involved and also on the solvent.

Scheme I[a]



[a] **a**, Pz = pyrazole; **b**, Pz = 3,5-dimethylpyrazole; **c**, Pz = 4-chloro-3,5-dimethylpyrazole; **d**, Pz = 4-nitropyrazole; **e**, Pz = 4-nitro-3,5-dimethylpyrazole.

In this study we have investigated the influence of the substituent on the pyrazole ring on the course of the re-

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