37.2, and 20.2. Anal. Calcd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.4. Found: C, 64.62; H, 6.18.

Acknowledgment. Financial support was provided by the National Institutes of Health (GM 28384).

Registry No. **2**(R_1 = R_2 = CH_3), 38410-83-2; (±)-**2**(R_1 = R_2 = CH_3), 96613-68-2; **2**(R_1 = n-C_5H_{11}, R_2 = CH_3), 132486-46-5; (±)-**2**(R_1 = n-C_5H_{11}, R_2 = CH_3), 132377-81-2; **2**(R_1 = C_6H_{11}, R_2 = C_2H_5), 132486-47-6; (±)-**2**(R_1 = C_6H_{11}, R_2 = C_2H_5), 132377-82-3; **2**(R_1 = Ph, R_2 = CH_3), 124649-67-8; (±)-**2**(R_1 = Ph, R_2 = CH_3), 81691-59-0; **2**(R_1 = p-MeOPh, R_2 = CH_3), 122517-80-0; **3a**, 132377-61-8; **3b**, 132377-62-9; (±)-**3b**, 132486-48-7; **3c**, 132377-63-0; **3d**, 132377-64-1; **3e**, 132377-65-2; (±)-**3e**, 132486-49-8; **3f**, 132377-66-3; **3g**, 124605-43-2; **3h**, 132377-67-4; **3i**, 132377-68-5; **3j**, 132377-69-6; **4a**, 132377-78-7; **5a**, 132377-79-8; **5b**, 132377-80-1; **6a**, 132377-70-9; **6b**, 132377-71-0; **6c**, 132377-72-1; (±)-**6c**, 132486-50-1; **6d**, 132486-44-3; **7**, 132486-45-4; **8a**, 132377-73-2; **8b**, 132377-74-3; **8c**, 132377-75-4; **8d**, 132377-76-5; **9**, 132377-77-6; **10**, 85549-54-8; **11**, 100939-32-0; **12**, 55528-54-6; nosyl chloride, 98-74-8; tosyl chloride, 98-59-9.

Supplementary Material Available: ^1H and ^{13}C NMR of compounds **3c**, **3g**, **6a**, and **8c** (8 pages). Ordering information is given on any current masthead page.

Highly Diastereoselective Michael Addition of Lithiated Camphor Imines of Glycine Esters to α,β-Unsaturated Esters. Synthesis of Optically Pure 5-Oxo-2,4-pyrrolidinedicarboxylates of Unnatural Stereochemistry

Shuji Kanemasa,* Akira Tatsukawa, and Eiji Wada

Institute of Advanced Material Study and Department of Molecular Science and Technology, Interdisciplinary Graduate School of Engineering Sciences, Kyushu University, Kasugakoen, Kasuga 816, Japan

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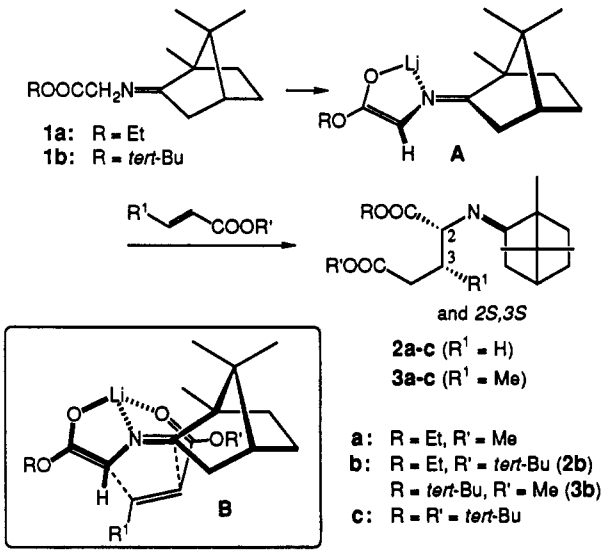
The lithium enolates of camphor imines of glycine esters underwent highly diastereoselective Michael additions to α,β-unsaturated esters. The tightly chelated structure of the *Z,E* enolates and the selective approach of the α,β-unsaturated esters to the *re* face of the enolates were responsible for the high diastereoselectivity observed. The use of alkylidenemalonate acceptors led to the diastereospecific formation of Michael adducts. Removal of the camphor auxiliary of the adducts and concomitant cyclization led to optically pure enantiomeric 5-oxo-2,4-pyrrolidinedicarboxylates of unnatural stereochemistry.

Introduction

Enhanced reactivity and high stereoselectivity were recently observed in the cycloaddition of ester-stabilized N-metalated azomethine ylides to α,β-unsaturated carbonyl compounds.[1,2] The high stereoselectivity arose from a combination of two kinds of attractive interactions operating in the transition state: a frontier orbital interaction between the dipole and the dipolarophile and chelation of the metal ion by the carbonyl oxygen atoms of the ylide and the dipolarophile.[3,4] This type of frontier orbital controlled and chelation-controlled transition state was also apparently involved in the highly stereoselective Michael addition of metalated imines of α-amino esters.[5]

Although several chiral nucleophilic glycine equivalents have been developed and have been widely utilized for the asymmetric synthesis of α-amino acids and their derivatives,[6,7] reports of Michael additions that employ such reagents are few.[8] Most of these reported that a satisfactory level of diastereoselectivity was obtained with respect to the diastereotopic face of the nucleophile. Few, however, discussed the stereoselectivity displayed in the formation of the new carbon–carbon bond.[9]

Scheme I



(1) Tsuge, O.; Kanemasa, S.; Yoshioka, M. *J. Org. Chem.* **1988**, *53*, 1384–1391.

(2) Barr, D. A.; Grigg, R.; Gunaratne, H. Q. N.; Kemp, J.; McMeekin, P.; Sridharan, V. *Tetrahedron* **1988**, *44*, 557–570.

(3) Another structure for of the N-metalated azomethine ylide is that of a chelated metal enolate. Because there is little significant difference between the two structures, and the reaction in which the species takes part is a Michael addition, the enolate structure and designation are employed here. See: ref 4.

(4) Kanemasa, S.; Yoshioka, M.; Tsuge, O. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 869–874.

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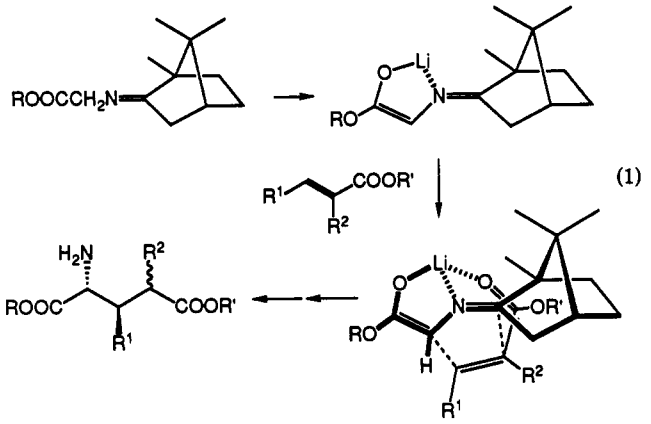
(6) (a) Oguri, T.; Kawai, N.; Shioiri, T.; Yamada, S.-I. *Chem. Pharm. Bull.* **1978**, *26*, 803–808. (b) Nakatsuka, T.; Miwa, T.; Mukaiyama, T. *Chem. Lett.* **1981**, 279–282. (c) Schöllkopf, U.; Groth, U.; Deng, C. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 798–799. (d) Seebach, D.; Naef, R. *Helv. Chim. Acta* **1981**, *64*, 2704–2708. (e) Belokon, Y. N.; Bulychev, A. G.; Vitt, S. V.; Struchkov, Y. T.; Batsanov, A. S.; Timofeeva, T. V.; Tsryapkin, V.; Ryzhov, M. G.; Lysova, L. A.; Bakhmutov, V. I.; Belikov, V. M. *J. Am. Chem. Soc.* **1985**, *107*, 4252–4259. (f) Ikegami, S.; Hayama, T.; Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett.* **1986**, *27*, 3403–3406. (g) Evans, D. A.; Weber, A. E. *J. Am. Chem. Soc.* **1986**, *108*, 6757–6761. (h) Schöllkopf, U.; Tiller, T.; Bardenhagen, J. *Tetrahedron* **1988**, *44*, 5333–5342.

(7) Oppolzer, W.; Moretti, R.; Thomi, S. *Tetrahedron Lett.* **1989**, *30*, 6009–6010.

(8) (a) Schöllkopf, U.; Pettig, D.; Busse, U.; Egert, E.; Dyrubusch, M. *Synthesis* **1986**, 737–740. (b) Minowa, N.; Hirayama, M.; Fukatsu, S. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 1761–1766. (c) Pettig, D.; Schöllkopf, U. *Synthesis* **1988**, 173–175. (d) Schöllkopf, U.; Pettig, D.; Schulze, D.; Klinge, M.; Egert, E.; Benecke, B.; Noltemeyer, M. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1194–1195. (e) Fitzi, R.; Seebach, D. *Tetrahedron* **1988**, *44*, 5277–5292. (f) Achqar, A. E.; Baumzebra, M.; Roumestant, M.-L. *Tetrahedron* **1988**, *44*, 5319–5332.

0022-3263/91/1956-2875$02.50/0

Described here is an attempt to develop a new methodology for using the asymmetric version of the stereoselective Michael addition of metalated imine esters. Thus, camphor imines of α-amino esters were lithiated and were employed as nucleophiles in reactions with α,β-unsaturated esters (eq 1).[10,11] Not only the stereoselectivity observed in the formation of the new carbon–carbon bond but also the diastereoselectivity observed with respect to the enolate face will be discussed in detail.

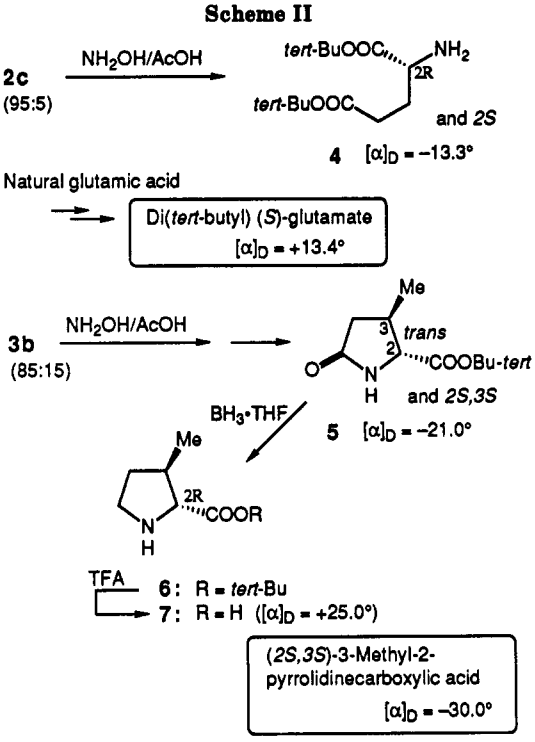


Results and Discussion

Reversible Lithiation of the Camphor Imines. The imine derived from natural (1*R*,4*R*)-camphor and ethyl aminoacetate (ethyl [(1*R*,4*R*)-bornylideneamino]acetate (**1a**)) was readily lithiated by lithium bromide (1.5 equiv) and triethylamine (1.2 equiv) in tetrahydrofuran (THF) at room temperature. The enolate A (R = Et) then reacted with methyl acrylate to give a 75:25 mixture (50% de) of the two diastereomeric Michael adducts **2a** (Scheme I). However, the reversible lithiation took place so sluggishly, or the position of the equilibrium was so strongly in favor of the free imine, that the yield of Michael adducts **2a** was only 49% after 24 h (entry 1, Table I).[12,13]

The major isomer of **2a** was assigned the 2*R* configuration, hence the minor was the 2*S* isomer. This assignment was based on the fact that the related derivative **2c** could be converted to glutamate **4**, as outlined in Scheme II. The formation of (2*R*)-**2a** as the maior diastereomer was consistent with a reaction that proceeded through transition state B (R¹ = H, R = Et, R′ = Me),[1,5] where the attack on the acrylate occurred from the bottom (*re* face) of *Z,E* enolate A.[14] Such bottomside attack was consistent with the selectivity observed in the alkylation of enolate A.[10] The deep involvement of the frontier orbital controlled and chelation-controlled transition state B or related transition state will be discussed later in connection with a recently proposed reaction mechanism.[9f-h]

Scheme II



The use of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), instead of triethylamine, permitted the smooth lithiation of **1a**. Consequently, the acrylate adducts **2a** were obtained in 73% yield and 54% de after 30 min at room temperature (entry 2). Catalytic amounts (10 mol %) of lithium bromide and DBU were sufficient to force the reaction to completion after a few minutes at 0 °C. Thus, larger diastereomeric excesses were produced (entries 3 and 4). The use of a bulkier α,β-unsaturated ester, *tert*-butyl acrylate, led to a larger (68%) diastereomeric excess (entry 5) than that obtained (54% de) with methyl acrylate (entry 2).

An additional chiral center was created at the 3-position of the adducts when methyl crotonate was used in the Michael reaction with the enolate A (R = Et). However, the enolate, when generated under equilibrating conditions, showed a disappointingly poor reactivity toward methyl crotonate, which suggested that a low concentration of enolate A was detrimental to Michael additions to acrylates with β-alkyl substituents.[15,16] Neither lithium bromide (1.5 equiv) and triethylamine (1.2 equiv) nor catalytic amounts of lithium bromide and DBU (both 10 mol %) were totally effective in promoting the Michael addition

(9) (a) Yamaguchi, M.; Tsukamoto, M.; Tanaka, S.; Hirao, I. *Tetrahedron Lett.* **1984**, *25*, 5661–5664. (b) Heathcock, C. H.; Oare, D. A. *J. Org. Chem.* **1985**, *50*, 3022–3024. (c) Yamaguchi, M. *J. Synth. Org. Chem., Jpn.* **1986**, *44*, 405–420 (a review), and references cited therein. (d) Yamaguchi, M.; Hasebe, K.; Tanaka, S.; Minami, T. *Tetrahedron Lett.* **1986**, *27*, 959–962. (e) Oare, D. A.; Heathcock, C. H. *Tetrahedron Lett.* **1986**, *51*, 6169–6172. (f) Oare, D. A.; Heathcock, C. H. In *Topics in Stereochemistry*; Eliel, E. L., Wilen, S. H., Eds.; Wiley: New York, 1989; pp 227–407, and references cited therein. (g) Oare, D. A.; Henderson, M. A.; Sanner, M. A.; Heathcock C. H. *J. Org. Chem.* **1990**, *55*, 132–157. (h) Oare, D. A.; Heathcock, C. H. *Ibid.* **1990**, *55*, 157–172. (i) Yamaguchi, M.; Torisu, K.; Minami, T. *Chem. Lett.* **1990**, 377–380.

(10) The alkylation of camphor imines of glycinates has been reported: (a) McIntosh, J. M.; Mishra, P. *Can. J. Chem.* **1986**, *64*, 726–731. (b) McIntosh, J. M.; Leavitt, R. K. *Tetrahedron Lett.* **1986**, *27*, 3839–3842. (c) McIntosh, J. M.; Leavitt, R. K.; Mishra, P.; Cassidy, K. C.; Drake, J. E.; Chadha, R. *J. Org. Chem.* **1988**, *53*, 1947–1952.

(11) Part of this work was reported in communication form. See: Kanemasa, S.; Tatsukawa, A.; Wada, E.; Tsuge, O. *Chem. Lett.* **1989**, 1301–1304.

(12) Lithium enolate A (R = *t*-Bu), generated irreversibly from **1b** and butyllithium, did react readily with methyl acrylate even at −78 °C, as described below. This observation suggested that the low yield of **2a** and **2a′** was due to the difficulty in effecting lithiation with lithium bromide and triethylamine.

(13) Although it was sluggish, the lithiation of imine **1a** with lithium bromide and triethylamine was surprising because methyl 2-[(2,2-dimethylpropylidene)amino]acetate, which is sterically less hindered than imine **1a**, was not lithiated under the similar reaction conditions. See: ref 5.

(14) The Evans nomenclature with regard to metal enolate isomerism is adopted here. See: Evans, D. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. III, p 11.

(15) Apparently the addition step is rate-determining in the reaction of lithiated imine **1a** with methyl crotonate, even when the enolate was generated with lithium bromide and triethylamine. The decreased reactivity of lithium enolate A (R = Et) toward methyl crotonate could be due to a serious steric repulsion by the camphor moiety.

(16) The relative rates of lithiation and cycloaddition of 2-(benzylideneamino)alkanoates have been discussed. See: ref 1.

Table I. Michael Addition of Lithiated Camphor Imines 1 to α,β-Unsaturated Esters[a]

entry	imine	α,β-unsaturated ester	reaction conditions: lithiation reagent[d]	temp (°C)	time (h)	product	yield (%)[b]	diastereomeric ratio[c]
1	**1a**	methyl acrylate	LiBr (1.5)/NEt_3 (1.2)	rt	24	**2a**	49	75:25
2	**1a**	methyl acrylate	LiBr (1.5)/DBU (1.2)	rt	30 min	**2a**	73	77:23
3	**1a**	methyl acrylate	LiBr (0.1)/DBU (0.1)	rt	2 min	**2a**	65	80:20
4	**1a**	methyl acrylate	LiBr (0.1)/DBU (0.1)	0	1 min	**2a**	76	82:18
5	**1a**	*tert*-butyl acrylate	LiBr (1.5)/DBU (1.2)	rt	5 min	**2b**	63	84:16
6	**1a**	methyl crotonate	LiBr (1.5)/NEt_3 (1.2)	rt	48	recovered		
7	**1a**	methyl crotonate	LiBr (0.2)/DBU (0.1)	rt	2	recovered		
8	**1b**	methyl crotonate	LiBr (1.5)/DBU (1.2)	rt	2	**3b**	81	74:26
9	**1b**	*tert*-butyl crotonate	LiBr (1.5)/DBU (1.2)	rt	4	**3c**	83	74:26
10	**1b**	methyl crotonate	LDA (1.1)	−78	5	**3b**	88	60:40
11	**1b**	methyl crotonate	LDA (0.5)/NEt_3 (0.6)	−78	13	**3b**	67	78:22
12	**1b**	methyl crotonate	LDA (1.1)/H_2O (1)	−78	13	**3b**	88	80:20
13	**1b**	methyl crotonate	LDA (1.1)/BF_3·Et_2O (1)	−78	13	**3b**	95	84:16
14	**1b**	methyl crotonate	LDA (1.1)/*t*-BuOH (1)	−78	13	**3b**	100	85:15
15	**1b**	*tert*-butyl acrylate	*n*-BuLi (1.1)/*t*-BuOH (1)	−78	18	**2c**	89	95:5
16	**1b**	methyl crotonate	*n*-BuLi (1.1)/*t*-BuOH (1)	−78	18	**3b**	98	86:14
17	**1b**	*tert*-butyl crotonate	*n*-BuLi (1.1)/*t*-BuOH (0.5)	−78	15	**3c**	69	94:6
18	**1b**	*tert*-butyl crotonate	*n*-BuLi (1.1)/*t*-BuOH (1)	−78	18	**3c**	88	95:5
19	**1b**	*tert*-butyl crotonate	*n*-BuLi (1.1)/*t*-BuOH (2)	−78	15	**3c**	78	93:7
20	**1b**	*tert*-butyl crotonate	*n*-BuLi (1.1)/*t*-BuOH (3)	−78	15	**3c**	80	92:8
21	**1b**	methyl methacrylate	*n*-BuLi (1.1)/*t*-BuOH (1)	−78	18	**8a**	90	60:40[e]
22	**1b**	*tert*-butyl methacrylate	*n*-BuLi (1.1)/*t*-BuOH (1)	−78	18	**8b**	83	50:50[e]
23	**1b**	dimethyl ethylidenemalonate	*n*-BuLi (1.1)/*t*-BuOH (1)	−78	3	**10a**	67	86:14[f]
24	**1b**	dimethyl propylidenemalonate	*n*-BuLi (1.1)/*t*-BuOH (1)	−78	2	**10b**	92	single
25	**1b**	dimethyl (2,2-dimethylpropylidene)-malonate	*n*-BuLi (1.1)/*t*-BuOH (1)	−78	2	**10c**	86	single
26	**1b**	dimethyl benzylidenemalonate	*n*-BuLi (1.1)/*t*-BuOH (1)	−78	2	**10d**	94	single
27	**1b**	dimethyl (*E*)-2-butenylidenemalonate	*n*-BuLi (1.1)/*t*-BuOH (1)	−78	2	**10e**	96	single
28	**1b**	dimethyl (*E*)-cinnamylidenemalonate	*n*-BuLi (1.1)/*t*-BuOH (1)	−78	2	**10f**	68	single
29	**1b**	dimethyl (*E*)-(3-methoxypropenylidene)-malonate	*n*-BuLi (1.1)/*t*-BuOH (1)	−78	2	**10g**	60	single
30	**1b**	methyl cinnamate	*n*-BuLi (1.1)/*t*-BuOH (1)	−78	18	**13**	100	81:19

[a] All reactions were performed in THF according to the procedure described in the Experimental Section. [b] Isolated yield of the diastereomeric mixture. [c] From the ^1H NMR spectrum of the crude reaction mixture. [d] The number of equivalents used is in parentheses. [e] Mixture of two 4-isomers. [f] Minor product was assumed to be the 2*S*,3*R* isomer.[24]

of the imine to methyl crotonate (entries 6 and 7).

However, imine **1b**, after lithiation with lithium bromide (1.5 equiv) and DBU (1.2 equiv), did react with methyl or *tert*-butyl crotonate go give a 74:26 mixture of two diastereomers of adduct **3b** or **3c**, respectively (Scheme I; entries 8 and 9). The formation of only two of four possible diastereomers was due to the high anti selectivity (2*R**,3*R**) displayed in the Michael addition, which presumably proceeded through the frontier orbital controlled and chelation-controlled transition state B (R = *t*-Bu, R^1 = Me, R′ = Me or *t*-Bu) and its enantiomeric counterpart (Scheme I).[5]

The assignment of the 2*R**,3*R** configuration to **3b**, and hence to **3c**, was confirmed by the fact that *tert*-butyl *trans*-3-methyl-5-oxopyrrolidine-2-carboxylate (**5**) was the sole stereisomer produced upon removal of the camphor chiral controller of **3b** (Scheme II; entry 2, Table II). The enantiomeric purity of **3** was almost certainly maintained during the removal of the chiral controller because no epimerization at the 3-position was observed. Thus, the enantiomeric excess of **5** that was obtained from an 85:15 mixture of **3b** [75% de, $[\alpha]_D$ −21.0° (*c* 1.01, $CHCl_3$)] was calculated to be 70% on the basis of the optical rotation of optically pure (2*R*,3*R*)-**5** [$[\alpha]_D$ −30.0° (*c* 1.02, $CHCl_3$)]. The preparation of (2*R*,3*R*)-**5** is outlined in Scheme V.

Irreversible Lithiation and Diastereoselective Michael Addition. Given the unsatifactory levels of diastereoselectivity and the low reactivity that were observed with the lithium enolate A that was prepared under equilibrating conditions, a method for the irreversible lithiation of imine **1** was needed in order to obtain a high concentration of enolate and to effect Michael addition at a lower temperature.[17]

Table II. Hydrolytic Cyclization of the Michael Adducts 2, 3, 8, 10 and 13[a]

entry	adduct	reaction time (h)	product[b]	yield (%)[c]
1	**2c**	2	**4**	68
2	**3b**	2	**5**	72
3	**8a**	2	**9**[d]	88
4	**8b**	2	**9**[e]	77
5	**10a**	4	**11a**	93
6	**10b**	4	**11b**[f]	84
7	**10c**	7 d[g]	**11c**[f]	34
8	**10d**	4	**11d**[f]	64
9	**10e**	4	**11e**[f]	90
10	**10f**	4	**11f**[f]	75
11	**10g**	4	**11g**[f]	77
12	**13**	2	(2*R**,3*R**)-**12**	82

[a] All reactions were performed under reflux in ethanol in the presence of hydroxylamine acetate (2 equiv). [b] Unless otherwise noted, the cyclized products were obtained as single diastereoisomers. [c] Isolated yield. [d] A 60:40 mixture of 2*R*,4*R* and 2*R*,4*S* stereoisomers. [e] A 50:50 mixture of 2*R*,4*R* and 2*R*,4*S* stereoisomers. [f] Obtained in optically pure form. [g] One equivalent of acetic acid was present.

Therefore, the lithiation of a bulky imine ester, *tert*-butyl [(1*R*,4*R*)-bornylideneamino]acetate (**1b**) by lithium diisopropylamide (LDA) or butyllithium at −78 °C in THF was attempted.[18] Although the subsequent Michael addition of the enolate A (R = *t*-Bu) to methyl crotonate took

(17) For the irreversible metalation of the imines of α-amino esters, see: (a) ref 5. (b) Kanemasa, S.; Yoshioka, M.; Tsuge, O. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 2196–2200. (c) Kanemasa, S.; Uchida, O.; Wada, E.; Yamamoto, H. *Chem. Lett.* **1990**, 105–108.

(18) The attempted lithiation of the ethyl ester **1a** with butyllithium, or even with LDA, gave a comple mixture of products.

place smoothly at −78 °C to give 88% of the Michael adducts **3b**, the diastereomeric excess of the products was only 20% (entry 10, Table I).

It was found, after some efforts aimed at optimizating the lithiation, that the presence of an additive, like triethylamine, water, boron trifluoride diethetate, or *tert*-butyl alcohol, in solutions of the enolate led to an improvement in the diastereomeric excess to, at best, 70% (entries 11–14).[19] However, a procedure that involved treating **1b** first with butyllithium and then with an equimolar amount of *tert*-butyl alcohol at −78 °C gave the best results (72% de) (entry 16).

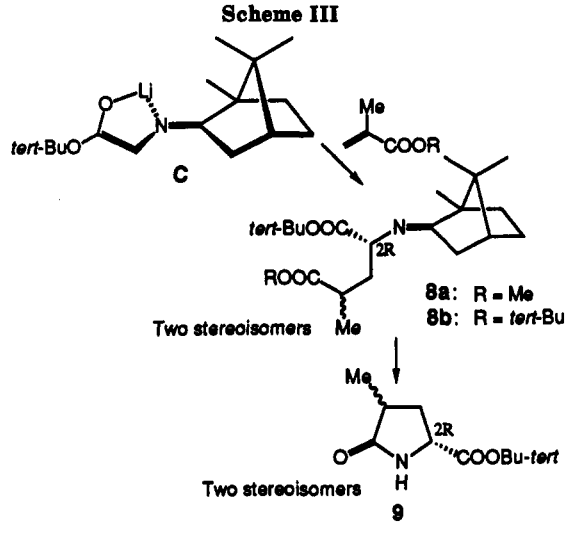
The use of a more bulky acceptor such as *tert*-butyl acrylate or coronate in place of a methyl ester afforded levels of diastereoselectivity as high as 90% de (entries 15 and 18). Although as many as 3 equiv of *tert*-butyl alcohol were used, the use of only 1 equiv gave both the highest chemical yield and the largest diastereomeric excess (entries 17–20).

The camphor chiral auxiliary was readily removed by refluxing the acrylate adducts **2c** (a 95:5 mixture of diastereomers) with hydroxylamine acetate in ethanol. A good yield of di-*tert*-butylglutamate (**4**) was obtained (entry 1, Table II).[10] A comparison of the optical rotation of the latter [$[\alpha]_D$ −13.3° (*c* 1.47, $CHCl_3$)] with that of di-*tert*-butyl glutamate [$[\alpha]_D$ +13.4° (*c* 1.27, $CHCl_3$)] prepared by esterification[20] of natural glutamic acid showed that glutamate **4c**, and hence imines **2a–c**, possessed unnatural 2*R* configuration (Scheme II).

The major diastereomer of the crotonate adducts **3b** was assigned the 2*R*,3*R* configuration because it could be transformed to the antipode of *trans*-3-methyl-L-proline,[21] (2*R*,3*R*)-3-methyl-2-pyrrolidinecarboxylic acid (**7**). Thus, the 85:15 mixture of diastereomers (70% de) of **3b** was treated with hydroxylamine acetate to give *tert*-butyl *trans*-3-methyl-5-oxopyrrolidine-2-carboxylate (**5**) as the sole stereoisomer. Reduction of the amide moiety of **5** with borane–THF gave *tert*-butyl *trans*-3-methyl-2-pyrrolidinecarboxylate (**6**). Ester **6** was hydrolyzed without further purification with trifluoroacetic acid (TFA) to give **7** in 57% of overall yield (Scheme II). Comparison of the optical rotation ([α]$_D$ +25.0° (*c* 0.16, H_2O)] of **7** with that[21] [$[\alpha]_D$ −30.0° (*c* 1.00, H_2O)] of *trans*-3-methyl-L-proline confirmed the assignment of the 2*R*,3*R* configuration to **7**. Thus, no epimerization at the 2-position of **5** occurred during removal of the camphor auxiliary from **3b**.

Epimerization of the Michael Adducts. Michael adducts derived from (alkylideneamino)acetates bear an additional acidic α-hydrogen atom, which can be deprotonated under the alkaline conditions of the Michael addition. Epimerization at this position is a serious complication in Michael additions,[5] because it causes partial collapse of the kinetically controlled high stereoselectivity. It was thus fortunate that no epimerization was observed in the Michael addition of the lithiated camphor imines **1** to crotonates. Adducts **3a–c** were always obtained as mixtures of only two, not four, 2*R**,3*R** diastereomers[22] under the reaction conditions employed (overnight at room temperature with lithium bromide and DBU in THF, overnight at −78 °C with butyllithium in THF).

Scheme III



The extremely ready deprotonation of the carbon atom at the 2-position has been discussed in connection with the acrylate adduct derived from metalated ethyl [(2,2-dimethylpropylidene)amino]acetate.[5] Because such epimerization would tend to lower the optical purity of the acrylate Michael adducts of **1**, the possibility that epimerization of **2a–c** occurred was briefly investigated. Thus, treatment of the *tert*-butyl esters **2b** (diastereomeric ratio = 76:24) with LDA (1 equiv) in THF at −78 °C for 2 h gave a 72% yield of recovered **2b** (76:24) after chromatography. Similarly, an 86:14 mixture of compounds **2b** was treated with lithium bromide and triethylamine (1 equiv each) at room temperature for 1 h to give a 68% yield of unchanged **2b** (86:14).[23] Thus, it was apparent that no significant epimerization of even the most readily enolizable acrylate adducts **2** occurred.

This difficulty in effecting 2-epimerization was fully consistent with the efficient steric inhibition by both the *tert*-butyl and bornylidene moieties that was observed in the LDA-induced deuteration of *tert*-butyl 2-(bornylideneamino)propanoate derivatives.[10a]

Highly Diastereoselective Reaction of Methacrylates and Alkylidenemalonates. The reaction of enolate C with methyl or *tert*-butyl methacrylate at −78 °C provided mixtures of comparable amounts of the two diastereomeric adducts **8a** and **8b** (Scheme III; entries 21 and 22, Table I). These were converted to mixtures of stereoisomeric *tert*-butyl 4-methyl-5-oxo-2-pyrrolidinecarboxylate (**9**), the isomeric ratios of which were identical with those of the parent compounds, **8a** and **8b** (entries 3 and 4, Table II). This result indicated that **8a** and **8b** were diastereomeric with respect to the 4-position, which must have been nonstereoselectively protonated during water quenching. Thus, the diastereoselectivity of the Michael addition was considered to be 100%. The absolute configuration at the 2-position was tentatively designated 2*R*, because the reaction was postulated to proceed through transition state B.

The steric repulsion of the α-methyl substituent of the approaching methacrylate by the camphor moiety appeared to be an important factor in the generation of such a high degree of diastereoselectivity. A second attempt at diastereoselective trapping, by alkylation of the anion

(19) There is no satisfactory explanation for the effect of these additives. For a discussion of the complex structure of lithium enolates see: Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1624–1654.

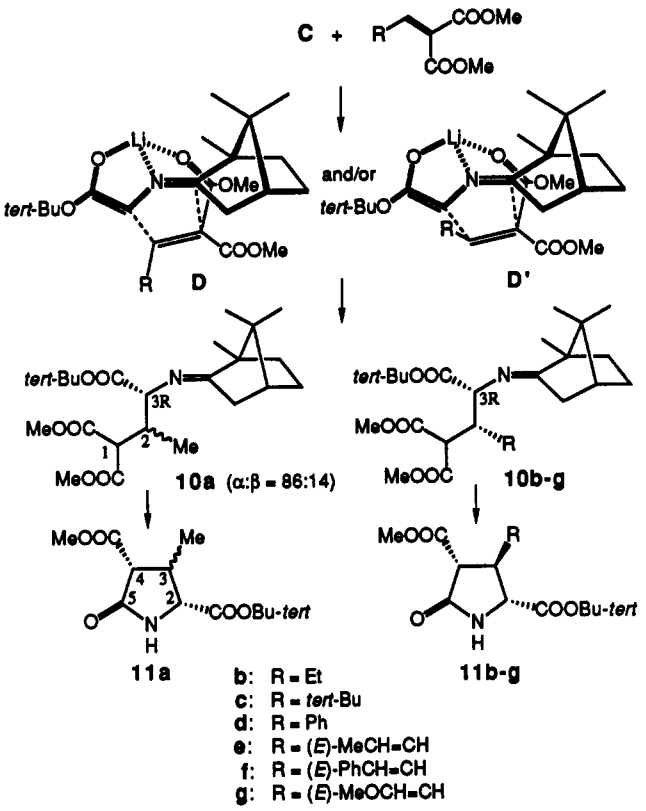
(20) Anderson, G. W.; Callahan, F. M. *J. Am. Chem. Soc.* **1960**, *82*, 3359–3363.

(21) Kollonitsch, J.; Scott, A. N.; Doldouras, G. A. *J. Am. Chem. Soc.* **1966**, *88*, 3624–3626.

(22) Epimerization at the 2-position of **3a–c** would lead to 2*R**, 3*S** diastereomers, which, on hydrolytic removal of the camphor moiety, would give *cis*-3-methyl-2-oxo-5-pyrrolidinecarboxylates. However, these mixtures of two diastereomeric Michael adducts each gave only one isomeric *trans*-pyrrolidine.

(23) No equilibration was observed when several samples of **2b** with different diastereomeric ratios were treated with lithium bromide and triethylamine under similar conditions.

Scheme IV



of the Michael adduct with methyl iodide or benzyl bromide, failed.

The Michael addition of enolate C to dimethyl alkylidenemalonates (α,β-unsaturated esters with an α-methoxycarbonyl substituent) led, in most cases, to the exclusive formation of adducts **10b–g** as single diastereomers (Scheme IV; entries 24–29, Table I). An exception was dimethyl ethylidenemalonate (entry 23), which gave an 86:14 mixture of the 2-epimers **10a**.[24] The 3*R* configuration was assigned to **10a–g** because the reaction was assumed to proceed through transition state D, in which the α-methoxycarbonyl moiety cis to the β substituent R of the α,β-unsaturated ester would effectively discriminate between the diasterotopic faces of enolate C. When it was bulky, the β substituent R occupied the sterically favored exo position as shown in the representation of transition state D (Scheme IV). When R was small, for example, when R = Me, the formation of the 2*S*,3*R* diastereomer of **10a** by way of approach D′ occurred.

Compounds **10–g** were each transformed, during removal of the camphor auxiliary, into a single enantiomer of the 3-substituted 5-oxo-2,4-pyrrolidinedicarboxylates **11b–g** in all cases (entries 6–11, Table II). The 3,4-trans stereochemistry was assigned because it was presumed that such stereochemistry was thermodynamically preferred. Similar treatment of **10a** (an 86:14 mixture of diastereomers) produced an inseparable 84:16 mixture of the stereoisomers of **11a**.

The removal of the 4-methoxycarbonyl substituent from **10** would give the optically pure derivatives of unnatural stereochemistry. Although **10a** and **10d** resisted demethoxycarbonylation under a variety of conditions, their derivatives, the 5-oxo-2,4-pyrrolidinedicarboxylates **11a** and

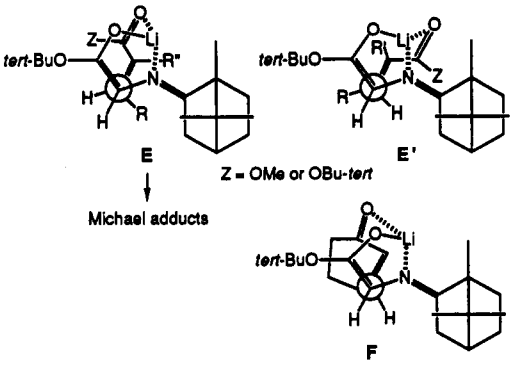
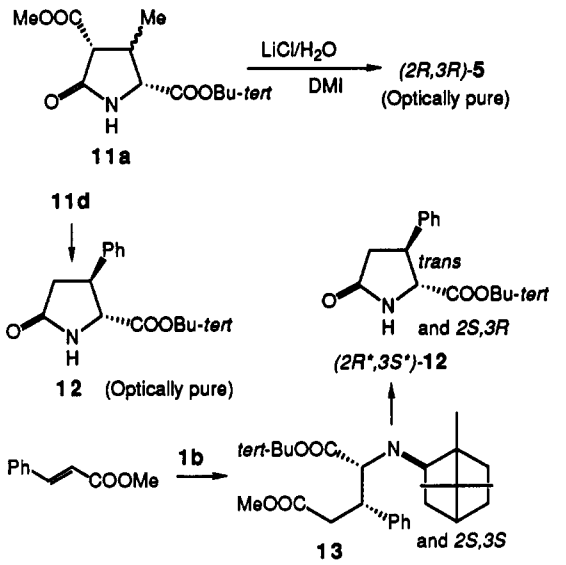


Figure 1. Presentation of Heathcock's synclinal, chelated, staggered transition state.

Scheme V



11d, underwent demethoxycarbonylation under mild conditions (130–140 °C, 4 h, wet lithium chloride, 1,3-dimethyl-2-imidazolidinone (DMI)) to give optically pure (4*R*,5*R*)-**5** (80%) and **12** (88%) (Scheme V).[25]

The high optical purity of (4*R*,5*R*)-**5** or **12** was confirmed by comparison of its optical rotation [corrected for the diastereomeric purity of Michael adduct **3c** or **13** (entry 30, Table I)] with that of its cyclic derivative **5** or (2*R**,3*S**)-**12**.

Thus, the Michael addition of enolate C to dimethyl alkylidenemalonates, followed by hydrolytic cyclization and demethoxycarbonylation, proved to be a reliable for the synthesis of optically pure 3-substituted derivatives of 5-oxo-2,4-pyrrolidinedicarboxylates and 5-oxo-2-pyrrolidinecarboxylates of unnatural stereochemistry.

Throughout this discussion, it was assumed that the diastereoselective Michael addition of lithiated **1** to α,β-unsaturated esters proceeded through a frontier orbital controlled and chelation-controlled transition state, i.e., B, D, or D′. The reaction mechanism currently accepted for the Michael addition of lithium enolates to α,β-unsaturated carbonyl compounds was proposed by Heathcock and co-workers,[9f-h] and it postulated a transition state that featured a chelation-bound eight-membered boat-chair conformation incorporating the s-cis conformer of the α,β-unsaturated carbonyl compound.

(24) Although the presence of the 2,3-cis isomer of **11a** (R = Me) was not confirmed spectroscopically, the minor diastereomer of **10a** was assigned the 2*S*,3*R* configuration on the basis of the mode of other Michael additions that displayed a similar high diastereoselectivity.

(25) The trans stereoisomer (2*R*,3*R*)-**5** was the only product isolated in pure form from the demethoxycarbonylation of **11a** (an 86:14 mixture of diastereomers). The attempted isolation of the minor product, the cis isomer (2*R*,3*S*)-**5**, was successful.

Although two energetically comparable boat-chair transition states, E and E′, can be drawn for the Heathcock model,[19f-h] which incorporates the s-trans conformer of an α,β-unsaturated ester (Figure 1), no evidence that the reaction proceeded through E′ was found. The dramatically improved diastereoselectivity produced by the introduction of an α substituent R′ (Me or COOMe), could be explained by a process that proceeded through E or the transition state D, proposed here. However, the observed null effect of the β substituent R (R = H, Me, and Ph) was inconsistent with that which would be expected if the reactions proceeded through transition state E (entries 15 and 17, 16 and 30, Table I). Also, a similar Michael addition to 2-cyclopentenone produced a 1:1 mixture of the stereoisomers of the Michael adduct,[26] a result that was inconsistent with a reaction involving the boat-chair transition state F.

Experimental Section

General. Melting points were determined with a Yanagimoto melting point apparatus and are uncorrected. IR spectra were recorded with JASCO IRA-1 and A-702 spectrometers. ^1H and ^{13}C NMR spectra were recorded with JEOL FX-100 (at 100 MHz for ^1H spectrum and at 25.05 MHz for ^{13}C spectrum) and GSX-270 (at 270 MHz for ^1H spectrum and at 67.94 MHz for ^{13}C spectrum) instruments. Chemical shifts are reported in parts per million downfield (δ) from internal trimethylsilane. Mass spectra and high resolution mass spectra (HRMS) were recorded with a JEOL-01SG-2 spectrometer operating at an ionization energy of 70 eV. Elemental analyses were performed with a Hitachi 026 CHN analyzer. For preparative column chromatography, Wako C-200, Wako C-300 (Wako), and Merck silica gel 60 were employed. Flash chromatography was performed with an EYELA EF-10 apparatus on a 20 × 180 mm column packed with 0.04–0.063-mm silica gel 60.

General Procedure for the Michael Additions of Lithiated Imines 1a and 1b Leading to 2, 3, 8, 10, and 13. Two typical procedures are described below.

(1) Reaction of Imine 1a with Methyl Acrylate in the Presence of LiBr/DBU. To a mixture of lithium bromide (0.13 g, 1.5 mmol), imine **1a** (0.236 g, 1.1 mmol), and methyl acrylate (0.095 g, 1.1 mmol) in dry THF (5 mL) was added, by means of a syringe under dry nitrogen, DBU (0.183 g, 1.2 mmol). The mixture was stirred at room temperature for 30 min, then was quenched with saturated aqueous ammonium chloride, and was extracted with dichloromethane (20 mL × 2). The combined extracts were dried ($MgSO_4$) and the solvent was evaporated undre reduced pressure. The residue was purified by column chromatography on silica gel to give **2a** (0.236 g, 73%).

(2) Reaction of Imine 1b with *tert*-Butyl Acrylate in the Presence of *n*-BuLi/*t*-BuOH. To a solution of butyllithium (1.6 M in hexane, 0.7 ml, 1.1 mmol) in THF (5 mL) were added, at −78 °C under nitrogen, imine **1b** (0.265 g, 1 mmol), *tert*-butyl alcohol (0.074 g, 1 mmol), and *tert*-butyl acrylate (0.192 g, 1.5 mmol) in that order. The mixture was stirred at −78 °C for 18 h, then was quenched with saturated aqueous ammonium chloride, and was extracted with diethyl ether (20 mL × 2). The combined extracts were dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel to give **2c** (0.35 g, 89%).

Michael additions to other α,β-unsaturated esters were performed under the reaction conditions listed in Table I.

General Procedure for the Hydrolytic Cyclization of Michael Adducts 3, 8, 10, and 13 to the γ-Lactams 5, 9, 11, and 12. As an example, the reaction of adduct **3b** is described as follows: To a solution of hydroxylamine acetate (2 mmol) prepared as described below was added adduct **3b** (0.365 g, 1 mmol). After 2 h of reflux, the mixture was poured into water (20 mL) and was extracted with dichloromethane (30 mL × 2). The combined extracts were dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel to give **5** (0.287 g, 72%).

The hydrolytic cyclization of the other Michael adducts was performed under the reaction conditions listed in Table II.

1-Ethyl Methyl *N*-[(1*R*,4*R*)-Bornylidene]glutamate (2a). (2*R*)-2a: colorless liquid from column chromatography on silica gel (hexane/diethyl ether, 1:1); IR (neat) 2970, 1735, 1680, 1440, 1160 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.80, 0.93, 0.98 (each s, each 3 H, Me), 1.22 (t, J = 7.3 Hz, 3 H, Et), 1.3–2.5 (m, 11 H, CH_2 and CH), 3.67 (s, 3 H, COOMe), 4.00 (dd, J_{2-3} = 8.8 and 4.7 Hz, 1 H, H-2), 4.13 (q, J = 7.3 Hz, 2 H, Et); ^{13}C NMR ($CDCl_3$) δ 11.43 (Me), 14.15 (Et), 19.02, 19.45 (each Me), 27.51, 27.80, 30.15, 32.35, 36.08, 43.90, 47.34 (camphor, C-3, and C-4), 51.53 (COOMe), 54.21 (C-1 of camphor), 60.78 (OEt), 62.82 (C-2), 171.72, 173.70 (each COO), 186.34 (C=N); MS m/z (rel intensity) 324 (M^+ + 1, 19), 323 (M^+, 22), 251 (17), 250 (base peak), 249 (12). Anal. Calcd for $C_{18}H_{29}NO_4$: C, 66.83; H, 9.04; N, 4.33. Found: C, 66.93; H, 8.79; N, 4.23.

(2*S*)-2a: ^1H NMR ($CDCl_3$) δ 0.75, 0.93, 0.98 (each s, each 3 H, Me), 3.65 (s, 3 H, COOMe), 3.97 (dd, J_{2-3} = 9.2 and 5.0 Hz, 1 H, H-2).

***tert*-Butyl 1-Ethyl *N*-[(1*R*,4*R*)-Bornylidene]glutamate (2b). (2*R*)-2b:** colorless liquid from column chromatography on silica gel (hexane/diethyl ether, 1:1); IR (neat) 2980, 1730, 1680, 1370, 1150 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.80, 0.93, 0.99 (each s, each 3 H, Me), 1.22 (t, J = 7.0 Hz, 3 H, Et), 1.44 (s, 9 H, *t*-Bu), 1.3–2.5 (m, 11 H, CH_2 and CH), 3.99 (dd, J_{2-3} = 8.8 and 4.0 Hz, 1 H, H-2), 4.13 (q, J = 7.0 Hz, 2 H, Et); ^{13}C NMR ($CDCl_3$) δ 11.45 (Me), 14.15 (Et), 19.04, 19.45 (each Me), 27.50, 27.99, 31.50, 32.44, 36.05, 43.89, 47.31 (camphor, C-3, and C-4), 28.13 (*t*-Bu), 54.15 (C-1 of camphor), 60.68 (OEt), 62.88 (C-2), 80.11 (COOBu-*t*), 171.83, 172.59 (each COO), 186.13 (C=N); MS m/z (rel intensity) 366 (M^+ + 1, 24), 365 (M^+, 40), 310 (10), 309 (50), 308 (25), 280 (20), 264 (11), 251 (17), 250 (base peak), 236 (74), 235 (19), and 57 (16). Anal. Calcd for $C_{21}H_{35}NO_4$: C, 69.00; H, 9.65; N, 3.83. Found: C, 69.05; H, 9.49; N, 3.80.

(2*S*)-2b: ^1H NMR ($CDCl_3$) δ 0.77, 0.93, 0.99 (each s, each 3 H, Me), 1.43 (s, 9 H, *t*-Bu).

Di-*tert*-butyl *N*-[(1*R*,4*R*)-Bornylidene]glutamate (2c). (2*R*)-2c: colorless liquid from column chromatography on silica gel (hexane/diethyl ether, 1:1); IR (neat) 2980, 1730, 1680, 1370, 1155 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.81, 0.93, 0.99 (each s, each 3 H, Me), 1.1–2.5 (m, 11 H, CH_2 and CH), 1.42, 1.44 (each s, each 9 H, *t*-Bu), 3.88 (dd, J_{2-3} = 9.2 and 4.4 Hz, 1H, H-2); ^{13}C NMR ($CDCl_3$) δ 11.49, 19.02, 19.60 (each Me), 27.49, 31.58, 32.40, 36.07, 43.86, 47.30 (camphor, C-3, and C-4), 28.03, 28.12 (each *t*-Bu), 54.07 (C-1 of camphor), 63.71 (C-2), 80.11, 80.32 (each COOBu-*t*), 171.07, 172.77 (each COO), and 185.70 (C=N); MS m/z (rel intensity) 393 (M^+, 12), 337 (18), 320 (17), 281 (48), 280 (69), 236 (base peak), 222 (22), and 57 (22). Anal. Calcd for $C_{23}H_{39}NO_4$: C, 70.18; H, 9.99; N, 3.56. Found: C, 70.39; H, 10.03; N, 3.32.

(2*S*)-2c: ^1H NMR ($CDCl_3$) δ 0.76, 0.92, 0.96 (each s, each 3 H, Me), 1.43, 1.44 (each s, each 9 H, *t*-Bu).

1-Ethyl Methyl (2*R,3*R**)-2-Methyl-*N*-[(1*R*,4*R*)-bornylidene]glutamate (3a). (2*R*,3*R*)-3a:** colorless liquid from column chromatography on silica gel (hexane/ethyl acetate, 1:1); IR (neat) 2980, 1740, 1680, 1440, and 1170 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.76, 0.92, 0.97 (each s, each 3 H, Me), 1.00 (d, J_{Me-3} = 7.0 Hz, 3 H, 3-Me), 1.23 (t, J = 7.0 Hz, 3 H, Et), 1.3–2.8 (m, 10 H, CH_2 and CH), 3.66 (s, 3 H, COOMe), 3.81 (d, J_{2-3} = 7.3 Hz, 1 H, H-2), 4.14 (q, J = 7.0 Hz, OEt); ^{13}C NMR ($CDCl_3$) δ 11.45, 14.21, 16.86, 19.02, 19.44 (each Me), 27.53, 32.34, 33.36, 36.15, 36.96, 43.89, 47.37 (camphor and C-3, and C-4), 51.39 (COOMe), 54.30 (C-1 of camphor), 60.64 (OEt), 68.90 (C-2), 171.46, 173.46 (each COO), 186.26 (C=N); MS m/z (rel intensity) 338 (M^+ + 1, 11), 337 (M^+, 20), 265 (18), 264 (base peak), 236 (19). Anal. Calcd for $C_{19}H_{31}NO_4$: C, 67.62; H, 9.26; N, 4.15. Found: C, 67.44; H, 9.05; N, 4.01.

1-*tert*-Butyl Methyl (2*R,3*R**)-3-Methyl-*N*-[(1*R*,4*R*)-bornylidene]glutamate (3b). (2*R*,3*R*)-3b:** colorless liquid from column chromatography on silica gel (hexane/diethyl ether, 1:1); IR (neat) 3000, 1740, 1685, 1380, 1170, 740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.77, 0.92, 0.97 (each s, each 3 H, Me), 0.98 (d, J_{Me-3} = 7.0 Hz, 3 H, 3-Me), 1.42 (s, 9 H, *t*-Bu), 1.2–2.7 (m, 10 H, CH_2 and CH), 3.65 (s, 3 H, COOMe), 3.68 (d, J_{2-3} = 7.7 Hz, 1 H, H-2); ^{13}C NMR ($CDCl_3$) δ 11.45, 16.75, 19.01, 19.52 (each Me), 27.53 (camphor), 28.02 (*t*-Bu), 32.31, 33.38, 36.13, 36.98, 43.92, 47.33 (camphor, C-3, and C-4), 51.27 (COOMe), 54.17 (C-1 of camphor), 69.75 (C-2),

(26) Kanemasa, S.; Yoshioka, M.; Wada, E. Unpublished result.

80.75 (COOBu-*t*), 170.54, 173.46 (each COO), 185.57 (C=N); MS *m/z* (rel intensity) 365 (M^+, 6), 309 (18), 308 (25), 265 (18), 264 (85), 250 (32), 95 (25), 85 (66), 83 (base peak). Anal. Calcd for $C_{21}H_{35}NO_4$: C, 69.00; H, 9.65; N, 3.83. Found: C, 68.87; H, 9.59; N, 3.59.

(2*S*,3*S*)-3b: ^1H NMR ($CDCl_3$) δ 0.73, 0.93, 0.97 (each s, each 3 H, Me), 1.44 (s, 9 H, *t*-Bu), 3.64 (s, 3H, COOMe).

Di-*tert*-butyl (2*R,3*R*)-3-Methyl-*N*-[(1*R*,4*R*)-bornylidene]glutamate (3c). (2*R*,3*R*)-3c**: pale yellow liquid from column chromatography on silica gel (hexane/ethyl acetate, 1:1); IR (neat) 2970, 1725, 1675, 1370, 1150, 735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.77, 0.92, 0.98 (each s, each 3 H, Me), 0.99 (d, J_{Me-3} = 7.0 Hz, 3 H, 3-Me), 1.1–2.6 (m, 10 H, CH_2 and CH), 1.43, 1.45 (each s, each 9 H, *t*-Bu), 3.66 (d, J_{2-3} = 7.7 Hz, 1 H, H-2); ^{13}C NMR ($CDCl_3$) δ 11.48, 16.41, 19.04, 19.52 (each Me), 27.52 (camphor), 28.05, 28.16 (each *t*-Bu), 32.40, 33.56, 36.17, 38.50, 43.92, 47.34 (camphor, C-3, and C-4), 54.17 (C-1 of camphor), 69.92 (C-2), 79.95, 80.75 (each COOBu-*t*), 170.71, 172.49 (each COO), 185.47 (C=N); MS *m/z* (rel intensity) 407 (M^+, 8), 295 (31), 294 (77), 250 (base peak), 236 (28), and 57 (94). Anal. Calcd for $C_{24}H_{41}NO_4$: C, 70.72; H, 10.14; N, 3.44. Found: C, 70.56; H, 9.92; N, 3.45.

(2*S*,3*S*)-3c: ^1H NMR ($CDCl_3$) δ 0.73, 0.88, 0.98 (each s, each 3 H, Me), 1.44, 1.48 (each s, each 9 H, *t*-Bu), 3.64 (d, J_{2-3} = 7.7 Hz, 1 H, H-2).

Removal of the Camphor Moiety of 2c To Give 4. To a solution of hydroxylamine hydrochloride (0.14 g, 2 mmol) in ethanol (5 mL) were added sodium acetate (2 mmol) and **2c** (0.786 g, 2 mmol). The mixture was refluxed for 2 h and then was poured into water (30 mL). Extraction with dichloromethane (30 mL × 2) and chromatography of the extract on silica gel (hexane/ethyl acetate, 1:1) gave di-*tert*-butyl glutamate (**4**) (0.352 g, 68%): colorless liquid; IR (neat) 3400, 2980, 1730, 1255, 1160, 760 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.44, 1.47 (each s, each 9 H, *t*-Bu), 1.8–2.1 (2 H, m, 3-H), 2.36 (t, J_{4-3} = 7.7 Hz, 2 H, H-4), 3.45 (dd, J_{2-3} = 7.7 and 5.5 Hz, 1 H, H-2), 4.55 (br s, 2 H, NH_2); ^{13}C NMR ($CDCl_3$) δ 28.02, 28.08 (each *t*-Bu), 29.45 (C-3), 31.71 (C-4), 53.88 (C-2), 80.43, 81.57 (each COO-*t*), 172.36, 173.90 (each s, COO); MS *m/z* (rel intensity) 260 (M^+ + 1, 9), 158 (17), 130 (17), 102 (base peak), 84 (42), 57 (59). Anal. Calcd for $C_{13}H_{25}NO_4$: C, 60.19; H, 9.65; N, 5.40. Found: C, 60.27; H, 9.46; N, 5.13.

***tert*-Butyl *trans*-3-methyl-5-oxopyrrolidine-2-carboxylate (5)**: colorless needles (acetone/hexane); mp 86–88 °C; IR (KBr) 3240, 2980, 1730, 1640, 1220, 1150, 740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.28 (d, J_{Me-3} = 6.6 Hz, 3 H, 3-Me), 1.48 (s, 9 H, *t*-Bu), 2.03 (m, 1 H, H-3), 2.54 (m, 2 H, H-4), 3.71 (d, J_{2-3} = 5.5 Hz, 1 H, H-2), 6.51 (br, 1 H, NH); ^{13}C NMR ($CDCl_3$) δ 20.04 (3-Me), 27.99 (*t*-Bu), 34.17 (C-4), 38.31 (C-3), 63.34 (C-2), 82.34 (COOBu-*t*), 170.94, 177.47 (each COO); MS *m/z* (rel intensity) 199 (M^+, 2), 98 (base peak), 57 (44), 55 (41). Anal. Calcd for $C_{10}H_{17}NO_3$: C, 60.28; H, 8.60; N, 7.03. Found: C, 60.01; H, 8.88; N, 6.92.

Reduction of 5 with Borane–THF Followed by Hydrolysis to 7. To a solution of **5** (0.292 g, 1.5 mmol) in THF (5 mL) was added drop-by-drop at 0 °C BH_3·THF (0.96 M in THF, 3.1 mL, 3 mmol). The mixture was refluxed for 2 h and then was quenched with methanol (2 mL). The mixture was evaporated to dryness under reduced pressure. The residue (0.273 g) was purified by column chromatography on silica gel (hexane/dichloromethane, 1:1) to give **6** (0.185 g, 66%): ^1H NMR ($CDCl_3$) δ 1.23 (d, *J* = 7.0 Hz, 3 H, 3-Me), 1.48 (s, 9 H, *t*-Bu), 1.8–2.3 (m, 4 H, H-3, H-4, and NH), 3.1–3.4 (m, 2 H, H-5), 3.82 (br, 1 H, H-2). Crude **6** (0.185 g) was dissolved in trifluoroacetic acid (1.5 mL), and the solution was stirred at room temperature for 2 h. The mixture was then evaporated to dryness under reduced pressure. The oily residue was treated with concentrated aqueous ammonia, and then the mixture was extracted with dichloromethane (20 mL × 5). The combined extracts were dried ($MgSO_4$) and evaporated to dryness under reduced pressure to give **7** (0.111 g, 86%) as a colorless solid: mp 243–248 °C (lit.[21] mp 240–248 °C); $[\alpha]_D$ +25.0° [*c* 0.16, H_2O].

1-*tert*-Butyl methyl (2*R*,4*R)-2-[(1*R*,4*R*)-bornylideneamino]-4-methylglutarate (8a)**: pale yellow liquid (an inseparable 60:40 mixture of two diastereomers by ^1H NMR analysis) from column chromatography on silica gel (hexane/ethyl acetate, 1:1 v/v); IR (neat) 2970, 1730, 1680, 1450, 1150 cm^{-1}; ^1H NMR ($CDCl_3$) of the major diastereomer δ 0.81, 0.92, 0.98 (each s, each 3 H, Me), 1.18 (d, J_{Me-4} = 7.0 Hz, 3 H, 4-Me), 1.41 (s, 9 H, *t*-Bu), 3.66 (s, 3 H, COOMe); ^1H NMR ($CDCl_3$) of the minor diastereomer δ 0.81, 0.92, 0.98 (each s, each 3 H, s, Me), 1.42 (s, 9 H, *t*-Bu), 1.14 (d, J_{Me-4} = 7.0 Hz, 3 H, 4-Me), 3.67 (s, 3 H, COOMe); overlapping signals at 1.1–2.5 (m, 10 H, CH_2 and CH), 3.8–3.9 (m, 1 H, 2-H); ^{13}C NMR ($CDCl_3$) δ 11.43, 11.54, 17.05, 18.26, 19.01, 19.60, 19.63 (each Me), 27.52, 28.02, 32.24, 35.82, 36.04, 36.11, 36.39, 36.51, 43.87, 47.30 (camphor, C-3, and C-4), 51.56, 51.59 (each COOMe), 54.10, 54.14 (each C-1 of camphor), 62.82, 63.05 (each C-2), 80.90, 80.99 (each COOBu-*t*), 170.87, 171.10, 176.94 (COO), 185.51, 186.03 (each C=N); MS *m/z* (rel intensity) 365 (M^+, 8), 307 (16), 265 (22), 264 (base peak), 222 (21), 57 (16). Anal. Calcd for $C_{21}H_{35}NO_4$: C, 69.00; H, 9.65; N, 3.83. Found: C, 68.80; H, 9.26; N, 3.97.

Di-*tert*-butyl (2*R*,4*R)-2-[(1*R*,4*R*)-bornylideneamino]-4-methylglutarate (8b)**: pale yellow liquid (an inseparable 60:40 mixture of two diastereomers by ^1H NMR analysis) from column chromatography on silica gel (hexane/ethyl acetate, 3:2); IR (neat) 2980, 1725, 1675, 1370, and 1160 cm^{-1}; ^1H NMR ($CDCl_3$) of the major diastereomer δ 0.81, 0.93, 1.00 (each s, each 3 H, Me), 1.15 (d, J_{Me-4} = 7.0 Hz, 4-Me), 1.43, 1.45 (each s, each 9 H, *t*-Bu); ^1H NMR ($CDCl_3$) of the minor diastereomer δ 0.80, 0.93, 0.98 (each s, each 3 H, Me), 1.08 (d, J_{Me-4} = 7.0 Hz, 4-Me), 1.42, 1.44 (each s, each 9 H, *t*-Bu); overlapping signals at 1.2–2.5 (m, 10 H, CH_2 and CH), 3.8–3.9; ^{13}C NMR ($CDCl_3$) δ 11.45, 11.53, 16.90, 18.56, 19.04, 19.58, 19.61 (each Me), 27.46, 27.51, 28.03, 28.11, 28.13, 32.20, 32.37, 36.00, 36.11, 36.53, 36.99, 37.13, 43.89, 47.33 (camphor, C-3, and C-4), 54.05, 54.10 (each C-1 of camphor), 63.01, 63.11 (each 2-C), 79.85, 79.98, 80.76, 80.88 (each COOBu-*t*), 171.07, 171.21, 175.89, 175.99 (each COO), 185.24, 185.83 (each C=N); MS *m/z* (rel intensity) 407 (M^+, 16), 334 (20), 295 (28), 294 (91), 278 (21), 251 (20), 250 (base peak), 222 (77), 95 (30), and 57 (30). Anal. Calcd for $C_{24}H_{41}NO_4$: C, 70.71; H, 10.14; N, 3.44. Found: C, 70.67; H, 10.02; N, 3.51.

***tert*-Butyl (2*R*,4*R**)-4-methyl-5-oxopyrrolidine-2-carboxylate (9)**: colorless needles (a mixture of two stereoisomers) from column chromatography on silica gel (hexane/ethyl acetate, 1:1); mp 110–111 °C; IR (KBr) 3230, 1730, 1700, 1650, 1220, 1160 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.20, 1.21 (each d, J_{Me-4} = 7.0 Hz, 3 H, 4-Me), 1.47, 1.48 (each s, 9 H, *t*-Bu), 1.7–2.7 (m, 3 H, H-3 and H-4), 4.0–4.1 (m, 1 H, H-2), 6.48, 6.56 (each br, 1 H, NH); ^{13}C NMR ($CDCl_3$) δ 15.84, 15.95 (each 4-Me), 27.95 (*t*-Bu), 33.59, 33.64 (each C-3), 34.67, 36.10 (each C-4), 54.40, 54.46 (each C-2), 82.03, 82.13 (each COOBu-*t*), 171.10, 171.54 (each C-5), 180.12, 181.30 (each COOBu-*t*); MS *m/z* (rel intensity) 199 (M^+, 1), 99 (30), 98 (base peak), 57 (22). Anal. Calcd for $C_{10}H_{17}NO_3$: C, 60.28; H, 8.60; N, 7.03. Found: C, 60.51; H, 8.51; N, 7.04.

***tert*-Butyl 1,1-dimethyl (3*R*)-3-[(1*R*,4*R*)-bornylideneamino]-2-methyl-1,1,3-propanetricarboxylate (10a)**: pale yellow liquid (an inseparable 86:14 mixture of 2*R*,3*R* and 2*S*,3*R* isomers) from column chromatography on silica gel (hexane/chloroform, 4:1); IR (neat) 2960, 1730, 1670, 1260, 1150 cm^{-1}; ^1H NMR ($CDCl_3$) of the major diastereomer δ 0.76, 0.92, 0.95 (each s, each 3 H, Me), 1.11 (d, J_{Me-2} = 6.7 Hz, 3 H, 2-Me), 1.2–2.5 (m, 7 H, CH_2 and CH), 1.43 (s, 9 H, *t*-Bu), 2.91 (m, 1 H, H-2), 3.70, 3.73 (each 3 H, s, COOMe), 3.77 (overlapping, 1 H, H-1), 3.83 (d, J_{3-2} = 9.9 Hz, 1 H, H-3); ^1H NMR ($CDCl_3$) of the minor diastereomer δ 0.68, 0.74, 1.01 (each s, each 3 H, Me), 1.45 (s, 9 H, *t*-Bu), 3.81, 3.85 (each s, each 3 H, COOMe); ^{13}C NMR ($CDCl_3$) the major diastereomer δ 11.49, 13.35, 19.01, 19.50 (each Me), 27.50 (camphor), 27.98 (*t*-Bu), 31.96, 36.14, 36.40, 43.84, 47.52 (camphor and C-2), 51.47, 52.01, 52.25 (COOMe and C-1), 54.31 (C-1 of camphor), 68.62 (C-3), 81.14 (COOBu-*t*), 169.07, 169.87, 170.15 (each COO), 187.06 (C=N); MS *m/z* (rel intensity) 423 (M^+, 8), 367 (27), 366 (61), 323 (20), 322 (base peak), 236 (30). Anal. Calcd for $C_{23}H_{37}NO_6$: C, 65.22; H, 8.81; N, 3.31. Found: C, 65.04; H, 8.69; N, 3.17.

***tert*-Butyl 1,1-dimethyl (2*R*,3*R*)-3-[(1*R*,4*R*)-bornylideneamino]-2-ethyl-1,1,3-propanetricarboxylate (10b)**: colorless liquid from column chromatography on silica gel (hexane/ethyl acetate, 4:1); IR (neat) 2960, 1730, 1670, 1365, 1145 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.77, 0.91, 0.93 (each s, each 3 H, Me), 0.94 (t, *J* = 7.0 Hz, 3 H, Et), 1.1–2.5 (m, 9 H, CH_2, CH, and Et), 1.42 (s, 9 H, *t*-Bu), 2.92 (m, 1 H, H-2), 3.70, 3.72 (each s, each 3 H, COOMe), 3.79 (d, J_{1-2} = 4.0 Hz, 1 H, H-1), 3.94 (d, J_{3-2} = 8.4 Hz, 1 H, H-3); ^{13}C NMR ($CDCl_3$) δ 11.46, 12.56, 19.01, 19.59 (Me and Et), 22.65 (Et), 27.49 (camphor), 27.98 (*t*-Bu), 31.65, 36.03, 42.85, 43.82, 47.50 (camphor and C-2), 51.10, 51.99, 52.18 (COOMe and C-1), 54.27 (C-1 of camphor), 67.49 (C-3), 81.05 (COOBu-*t*), 169.44,

170.12, 170.56 (each COO), 186.52 (C=N); MS *m/z* (rel intensity) 438 (M^+ + 1, 28), 437 (M^+, 67), 381 (47), 380 (99), 337 (22), 336 (base peak), 306 (22), 265 (70), 250 (29), 209 (87). Anal. Calcd for $C_{24}H_{39}NO_6$: C, 65.87; H, 8.98; N, 3.20. Found: C, 65.54; H, 8.78; N, 3.18.

***tert*-Butyl 1,1-dimethyl (2*R*,3*R*)-3-[(1*R*,4*R*)-bornylideneamino]-2-*tert*-butyl-1,1,3-propanetricarboxylate (10c)**: pale yellow liquid from column chromatography on silica gel (hexane/ethyl acetate, 4:1); IR (neat) 2980, 1740, 1220, 1150, 735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.82, 0.87, 0.91 (each s, each 3 H, Me), 0.89 (s, 9 H, *t*-Bu), 1.45 (s, 9 H, *t*-Bu), 1.2–2.5 (m, 7 H, CH_2 and CH), 3.36 (dd, J_{2-1} = 6.6 and J_{2-3} = 5.5 Hz, 1 H, H-2), 3.61 (d, J_{1-2} = 6.6 Hz, 1 H, H-1), 3.61, 3.73 (each s, each 3 H, COOMe), 4.09 (d, J_{3-2} = 5.5 Hz, 1 H, H-3); ^{13}C NMR ($CDCl_3$) δ11.29, 18.99, 19.87 (each Me), 27.36 (camphor), 27.98, 28.22 (each *t*-Bu), 30.93 (camphor), 34.08 (*t*-Bu), 36.47, 43.96, 47.67, 49.72 (camphor and C-2), 51.65, 51.75, 52.19 (COOMe and C-1), 54.41 (C-1 of camphor), 64.23 (C-3), 80.44 (COOBu-*t*), 169.25, 170.71, 170.94 (each COO), 185.33 (C=N); MS *m/z* (rel intensity) 466 (M^+ + 1, 23), 409 (32), 408 (base peak), 364 (95), 352 (83), 308 (68), 57 (55). Anal. Calcd for $C_{26}H_{43}NO_6$: C, 67.06; H, 9.31; N, 3.01. Found: C, 67.55; H, 9.35; N, 2.70.

***tert*-Butyl 1,1-dimethyl (2*R*,3*R*)-3-[(1*R*,4*R*)-bornylideneamino]-2-phenyl-1,1,3-propanetricarboxylate (10d)**: pale yellow liquid from column chromatography on silica gel (hexane/ethyl acetate, 4:1); IR (neat) 2970, 1720, 1430, 1260, 1150 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.75, 0.93, 0.98 (each s, each 3 H, Me), 1.18 (s, 9 H, *t*-Bu), 1.3–2.6 (m, 7 H, CH_2 and CH), 3.53, 3.65 (each s, each 3 H, COOMe), 3.94 (d, J_{1-2} = 6.6 Hz, 1 H, H-1), 4.23 (dd, J_{2-3} = 9.9 and J_{2-1} = 6.6 Hz, 1 H, H-2), 4.47 (d, J_{3-2} = 9.9 Hz, 1 H, H-3), 7.2–7.3 (m, 5 H, Ph); ^{13}C NMR ($CDCl_3$) δ 11.49, 19.02, 19.45 (each Me), 27.42 (camphor), 27.63 (*t*-Bu), 31.65, 36.43, 43.84, 47.72, 47.89 (camphor and C-2), 52.08, 52.24 (each COOMe), 53.97 (C-1), 54.44 (C-1 of camphor), 68.29 (C-3), 80.92 (COOBu-*t*), 127.20, 127.99, 129.43, 138.75 (each Ph), 168.73, 168.89, 169.30 (each COO), 187.90 (C=N); MS *m/z* (rel intensity) 485 (M^+, 7), 384 (30), 208 (base peak), 164 (20), 121 (26). Anal. Calcd for $C_{28}H_{39}NO_6$: C, 69.25; H, 8.10; N, 2.88. Found: C, 69.43; H, 8.02; N, 2.71.

***tert*-Butyl 1,1-dimethyl (2*R*,3*R*)-[(1*R*,4*R*)-bornylideneamino]-2-[(*E*)-1-propenyl]-1,1,3-propanetricarboxylate (10e)**: pale yellow liquid (column chromatography on silica gel (hexane/ethyl acetate, 3:1); IR (neat) 2970, 1730, 1430, 1240, 1150, 970 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.73, 0.91, 0.95 (each s, each 3 H, Me), 1.1–2.5 (m, 7 H, CH_2 and CH), 1.40 (s, 9 H, *t*-Bu), 1.64 (d, J_{Me-CH} = 4.8 Hz, 3 H, MeCH=), 3.63 (m, 1 H, H-2), 3.69 (s, 6 H, COOMe), 3.82 (d, J_{1-2} = 4.8 Hz, 1 H, H-1), 3.99 (d, J_{3-2} = 10.6 Hz, 1 H, H-3), 5.5–5.7 (m, 2 H, =CH); ^{13}C NMR ($CDCl_3$) δ 11.46, 18.04, 18.99, 19.41 (each Me), 27.52 (camphor), 27.96 (*t*-Bu), 31.82, 36.11, 43.80, 46.02, 47.59 (camphor and C-2), 51.86, 52.01, 52.19 (COOMe and C-1), 54.36 (C-1 of camphor), 67.23 (C-3), 80.89 (COOBu-*t*), 126.72, 130.38 (each =CH), 168.91, 169.64 (each COO), 187.35 (C=N); MS *m/z* (rel intensity) 449 (M^+, 1), 184 (76), 169 (base peak), 153 (51), 152 (57), 124 (48), 121 (69), 94 (37), 93 (41). Anal. Calcd for $C_{25}H_{39}NO_6$: C, 66.79: H, 8.75; N, 3.12. Found: C, 67.18; H, 8.49; N, 3.18.

***tert*-Butyl 1,1-dimethyl (2*R*,3*R*)-3-[(1*R*,4*R*)-bornylideneamino]-2-[(*E*)-2-phenylvinyl]-1,1,3-propanetricarboxylate (10f)**: pale yellow liquid from column chromatography on silica gel (hexane–ethyl acetate, 4:1); IR (neat) 2970, 1740, 1675, 1150, 730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.75, 0.92, 0.98 (each s, each 3 H, Me), 1.2–2.5 (m, 7 H, CH_2 and CH), 1.34 (s, 9 H, *t*-Bu), 3.67, 3.70 (each s, each 3 H, COOMe), 3.68 (m, 1 H, H-2), 3.95 (d, J_{1-2} = 4.8 Hz, 1 H, H-1), 4.11 (d, J_{3-2} = 10.3 Hz, 1 H, H-3), 6.41 (dd, J_{trans} = 15.8 and J_{CH-2} = 9.2 Hz, 1 H, H-2), 6.53 (d, J_{trans} = 15.8 Hz, 1 H, =CH), 7.2–7.4 (m, 5 H, Ph); ^{13}C NMR ($CDCl_3$) δ 11.48, 19.01, 19.42 (each Me), 27.53 (camphor), 27.95 (*t*-Bu), 31.88, 36.17, 43.83, 46.29, 47.53 (camphor and C-2), 51.92, 52.09, 52.31 (COOMe and C-1), 54.44 (C-1 of camphor), 67.02 (C-3), 81.14 (COOBu-*t*), 125.99, 126.45, 127.37, 128.39, 134.28, 137.22 (Ph and =CH), 168.84, 169.37, 169.53 (each COO), 187.60 (C=N); MS *m/z* (rel intensity) 511 (M^+, 10), 209 (16), 208 (base peak), 86 (31), 84 (44). Anal. Calcd for $C_{30}H_{41}NO_6$: C, 70.42; H, 8.08; N, 2.74. Found: C, 70.23; H, 8.06; N, 2.78.

***tert*-Butyl 1,1-dimethyl (2*R*,3*R*)-3-[(1*R*,4*R*)-bornylideneamino]-2-[(*E*)-2-methoxyvinyl]-1,1,3-propanetricarboxylate (10g)**: pale yellow liquid from column chromatography on silica gel (hexane/ethyl acetate, 4:1); IR (neat) 2960, 1730, 1670, 1430, 1150 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.73, 0.91, 0.95 (each s, each 3 H, Me), 1.1–2.5 (m, 7 H, CH_2 and CH), 1.39 (s, 9 H, *t*-Bu), 3.41 (dt, J_{2-3} = J_{2-CH} = 10.6, and J_{2-1} = 4.7 Hz, 1 H, H-2), 3.50 (s, 3 H, MeO), 3.70 (s 6 H, COOMe), 3.86 (d, J_{1-2} = 4.7 Hz, 1 H, H-1), 3.96 (d, J_{3-2} = 10.6 Hz, 1 H, H-3), 4.91 (dd, J_{trans} = 12.8 and J_{CH-2} = 10.6 Hz, 1 H, =CH), 6.45 (d, J_{trans} = 12.8 Hz, 1 H, =CHOMe); ^{13}C NMR ($CDCl_3$) δ 11.46, 18.99, 19.40 (each Me), 27.54 (camphor), 27.98 (*t*-Bu), 31.82, 36.13, 42.22, 43.80, 47.49 (camphor and C-2), 51.96, 52.12, 52.23 (COOMe and C-1), 54.35 (C-1 of camphor), 55.71 (MeO), 68.09 (C-3), 80.99 (COOBu-*t*), 97.82 (=CH), 150.75 (=CHOMe), 168.98, 169.58, 169.63 (each COO), 187.31 (C=N); MS *m/z* (rel intensity) 465 (M^+, 5), 208 (base peak), 164 (33), 69 (31). Anal. Calcd for $C_{25}H_{39}NO_7$: C, 64.48; H, 8.45; N, 3.01. Found: C, 64.98; H, 8.58; N, 2.80.

2-*tert*-Butyl methyl (2*R*,4*R*)-3-methyl-5-oxopyrrolidine-2,4-dicarboxylate (11a): colorless liquid (an inseparable 84:16 mixture of 2*R*, 3*R*, 4*R* and 2*R*, 3*S*, 4*R* diastereomers by ^{13}C NMR analysis) from column chromatography on silica gel (hexane/ethyl acetate, 1:1); IR (neat) 3210, 1720, 1700, 1230, 1150 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.33 (d, J_{Me-3} = 7.0 Hz, 3 H, 3-Me), 1.50 (s, 9 H, *t*-Bu), 2.89 (ddq, J_{3-4} = 8.8, J_{3-2} = 7.7, and J_{3-Me} = 7.0 Hz, 1 H, H-3), 3.13 (d, J_{4-3} = 8.8 Hz, 1 H, H-4), 3.74 (d, J_{2-3} = 7.7 Hz, 1 H, H-2); ^{13}C NMR ($CDCl_3$) of the major diastereomer δ 18.57 (3-Me), 27.98 (*t*-Bu), 38.13 (C-3), 52.70 (COOMe), 55.72 (C-4), 61.37 (C-2), 82.69 (COOBu-*t*), 169.09, 169.66 (each COO), 171.69 (C-5); ^{13}C NMR ($CDCl_3$) of the minor diastereomer δ 20.86 (3-Me), 38.14 (C-3), 52.21 (COOMe), 53.50 (C-4), 62.22 (C-2); MS *m/z* (rel intensity) 257 (M^+, 1), 157 (base peak), 156 (76), 124 (14), 57 (19). Anal. Calcd for $C_{12}H_{19}NO_5$: C, 56.02; H, 7.44; N, 5.44. Found: C, 56.15; H, 7.50; N, 5.53.

2-*tert*-Butyl methyl (2*R*,3*R*,4*R*)-3-ethyl-5-oxopyrrolidine-2,4-dicarboxylate (11b): pale yellow liquid from column chromatography on silica gel (hexane/ethyl acetate, 1:1); $[\alpha]_D$ −44.8° [*c* 0.33, $CHCl_3$]; IR (neat) 3200, 3120, 1720, 1280, 1160 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.97 (t, *J* = 7.3 Hz, 3 H, Et), 1.50 (s, 9 H, *t*-Bu), 1.5–1.9 (m, 2 H, Et), 2.86 (ddt, J_{3-4} = 7.3, J_{3-Et} = 7.0, and J_{3-2} = 6.2 Hz, 1 H, H-3), 3.16 (d, J_{4-3} = 7.3 Hz, 1 H, H-4), 3.76 (d, J_{2-3} = 6.2 Hz, 1 H, H-2), 3.78 (s, 3 H, COOMe), 6.75 (br, 1 H, NH); ^{13}C NMR ($CDCl_3$) δ 11.19 (Et), 27.16, 27.98 (Et and *t*-Bu), 44.06 (C-3), 52.81 (COOMe), 53.68 (C-4), 59.77 (C-2), 82.72 (COOBu-*t*), 169.61, 169.94 (each COO), 171.67 (C-5); MS *m/z* (rel intensity) 271 (M^+, 1), 215 (8), 171 (base peak), and 170 (74). Anal. Calcd for $C_{13}H_{21}NO_5$: C, 57.55; H, 7.80; N, 5.16. Found: C, 57.61; H, 7.86; N, 5.46.

2-*tert*-Butyl methyl (2*R*,3*R*,4*R*)-3-*tert*-butyl-5-oxopyrrolidine-2,4-dicarboxylate (11c): colorless liquid from column chromatography on silica gel (hexane/ethyl acetate, 1:1); $[\alpha]_D$ −15.8° [*c* 1.42, $CHCl_3$]; IR (neat) 3180, 1720, 1660, 1250, 1150 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.94 (s, 9 H, *t*-Bu), 1.49 (s, 9 H, *t*-Bu), 2.78 (dd, J_{3-4} = 4.4 and J_{3-2} = 3.0 Hz, 1 H, H-3), 3.24 (d, J_{4-3} = 4.4 Hz, 1 H, H-4), 3.75 (s, 3 H, COOMe), 3.90 (d, J_{2-3} = 3.0 Hz, 1 H, H-2), 7.17 (br, 1 H, NH); ^{13}C NMR ($CDCl_3$) δ 26.58, 27.88 (each *t*-Bu), 33.03 (*t*-Bu), 50.06 (C-3), 51.70 (C-4), 52.83 (COOMe), 57.00 (C-2), 82.37 (COOBu-*t*), 169.96, 170.94 (each COO), 172.52 (5-C); MS *m/z* (rel intensity) 300 (M^+ + 1, 1), 199 (78), 198 (base peak), 142 (17). Anal. Calcd for $C_{15}H_{25}NO_5$: C, 60.18; H, 8.42; N, 4.68. Found: C, 60.45; H, 8.27; N, 4.59.

2-*tert*-Butyl methyl (2*R*,3*R*,4*R*)-3-phenyl-5-oxopyrrolidine-2,4-dicarboxylate (11d): colorless needles from column chromatography on silica gel (hexane/ethyl acetate, 1:1); mp 86–89 °C; $[\alpha]_D$ +24.8° [*c* 0.56, $CHCl_3$]; IR (neat) 3180, 1720, 1230, 1150 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.40 (s, 9 H, *t*-Bu), 3.63 (d, J_{4-3} = 8.4 Hz, 1 H, H-4), 3.76 (s, 3 H, COOMe), 4.08 (dd, J_{3-4} = 8.4 and J_{3-2} = 7.3 Hz, 1 H, H-3), 4.19 (d, J_{2-3} = 7.3 Hz, 1 H, H-2), 6.83 (br s, 1 H, NH), 7.3–7.4 (m, 5 H, Ph); ^{13}C NMR ($CDCl_3$) δ 27.88 (*t*-Bu), 47.87 (C-4), 52.94 (COOMe), 55.95 (C-3), 61.38 (C-2), 82.98 (COOBu-*t*), 127.45, 127.84, 129.02, 139.61 (each Ph), 168.63, 169.17, 170.71 (COO and 5-C); MS *m/z* (rel intensity) 319 (M^+, 1), 218 (19), 187 (24), 186 (55), 160 (18), 158 (65), 130 (20), 57 (base peak). Anal. Calcd for $C_{17}H_{21}NO_5$: C, 63.93; H, 6.63; N, 4.39. Found: C, 63.68; H, 6.70; N, 4.47.

2-*tert*-Butyl methyl (2*R*,3*R*,4*R*)-3-[(*E*)-1-propenyl]-5-oxopyrrolidine-2,4-dicarboxylate (11e): pale yellow liquid from column chromatography on silica gel (hexane/ethyl acetate, 1:1);

$[\alpha]_D$ -10.8° [c 1.02, $CHCl_3$]; IR (neat) 3260, 1730, 1150, 965 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.48 (s, 9 H, t-Bu), 1.70 (d, J = 7.3 Hz, 3 H, Me), 3.33 (d, J_{4-3} = 9.5 Hz, 1 H, H-4), 3.48 (dt, J_{3-4} = 9.5 and J_{3-2} = J_{3-CH} = 7.7 Hz, 1 H, H-3), 3.79 (s, 3 H, COOMe), 3.84 (d, J_{2-3} = 7.7 Hz, 1 H, H-2), 5.48 (dd, J_{trans} = 15.4 and J_{CH-3} = 7.7 Hz, 1 H, =CH), 5.66 (dq, J_{trans} = 15.4 and J_{CH-Me} = 7.3 Hz, 1 H, =CH), 6.55 (br, 1 H, NH); ^{13}C NMR ($CDCl_3$) δ 17.81 (Me), 27.96 (t-Bu), 46.19 (C-3), 52.67 (COOMe), 54.13 (C-4), 59.98 (C-2), 82.50 (COOBu-t), 128.62, 129.17 (each =CH), 168.86, 169.44 (each COO), 171.63 (C-5); MS m/z (rel intensity) 283 (M^+, 2), 197 (14), 183 (62), 182 (base peak), 151 (21), 150 (76), 124 (23), 122 (55), 57 (81). Anal. Calcd for $C_{14}H_{21}NO_5$: C, 59.35; H, 7.47; N, 4.94. Found: C, 59.16; H, 7.51; N, 5.13.

2-*tert*-Butyl methyl (2*R*,3*R*,4*R*)-3-[(*E*)-2-phenylvinyl]-5-oxopyrrolidine-2,4-dicarboxylate (11f): colorless needles from column chromatography on silica gel (hexane/ethyl acetate, 4:1 to 1:1); mp 98-100 °C; $[\alpha]_D$ -27.5° [c 1.09, $CHCl_3$]; IR (KBr) 3280, 1720, 1370, 1160, 970 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.48 (s, 9 H, t-Bu), 3.46 (d, J_{4-3} = 9.5 Hz, 1 H, H-4), 3.70 (dt, J_{3-4} = 9.5 and J_{3-2} = J_{3-CH} = 8.1 Hz, 1 H, H-3), 3.80 (s, 3 H, COOMe), 3.98 (d, J_{2-3} = 8.1 Hz, 1 H, H-2), 6.20 (dd, J_{trans} = 16.0 and J_{CH-3} = 8.1 Hz, 1 H, =CH), 6.60 (d, J_{trans} = 16.0 Hz, 1 H, =CH), 7.3-7.4 (m, 6 H, Ph and NH); ^{13}C NMR ($CDCl_3$) δ 27.99 (t-Bu), 46.41 (C-3), 52.84 (COOMe), 54.02 (C-4), 59.70 (C-2), 82.89 (COOBu-t), 126.40, 126.73, 127.97, 128.64, 133.37, 136.19 (Ph and =CH), 168.63, 169.15 (each COO), 171.08 (C-5); MS m/z (rel intensity) 345 (M^+, 4), 289 (97), 244 (28), 230 (92), 212 (50), 185 (20), 184 (75), 129 (28), 128 (32), 57 (base peak). Anal. Calcd for $C_{19}H_{23}NO_5$: C; 66.07; H, 6.71; N, 4.06. Found: C, 65.80; H, 6.75; N, 4.05.

2-*tert*-Butyl methyl (2*R*,3*R*,4*R*)-3-[(*E*)-2-methoxyvinyl]-5-oxopyrrolidine-2,4-dicarboxylate (11g): colorless liquid from column chromatography on silica gel (hexane/ethyl acetate, 1:1); $[\alpha]_D$ - 12.4° [c 0.97, $CHCl_3$]; IR (neat) 3280, 1730, 1650, 1150, 935 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.48 (s, 9 H, t-Bu), 3.30 (d, J_{4-3} = 9.5 Hz, 1 H, H-4), 3.43 (ddd, J_{3-4} = 9.5, J_{3-CH} = 9.1, and J_{3-2} = 7.7 Hz, 1 H, H-3), 3.55 (s, 3 H, MeO), 3.79 (s, 3 H, COOMe), 3.82 (d, J_{2-3} = 7.7 Hz, 1 H, H-2), 4.73 (dd, J_{trans} = 12.9 and J_{CH-3} = 9.1 Hz, 1 H, =CH), 6.47 (d, 1 H, J_{trans} = 12.9 Hz, 1 H, =CHOMe), 7.05 (br, 1 H, NH); ^{13}C NMR ($CDCl_3$) δ 28.02 (t-Bu), 43.04 (C-3), 52.77 (COOMe), 55.15 (C-4), 56.20 (MeO), 60.65 (C-2), 82.79 (COOBu-t), 100.77 (=CH), 150.38 (=CHOMe), 168.71, 169.15 (each COO), 171.08 (C-5); MS m/z (rel intensity) 299 (M^+, 3), 243 (69), 198 (19), 184 (76), 167 (20), 166 (base peak), 138 (49), 111 (21), 69 (23). Anal. Calcd for $C_{14}H_{21}NO_6$: C, 56.16; H, 7.08; N, 4.68. Found: C, 56.42; H, 7.19; N, 4.65.

1-*tert*-Butyl methyl (2*R,3*R**)-2-[(1*R*,4*R*)-bornylidene-amino]-3-phenylglutarate (13)**: colorless prisms from column chromatography on silica gel (hexane/ethyl acetate, 1:1); mp 103-105 °C; IR (KBr) 3220, 1720, 1370, 1235, 1150 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.43 (s, 9 H, t-Bu), 2.54 (dd, J_{gem} = 17.2 and J_{4-3} = 7.3 Hz, 1 H, one of H-4), 2.85 (dd, J_{gem} = 17.2 and J_{4-3} = 9.3 Hz, 1 H, the other of H-4), 3.65 (ddd, J_{3-4} = 9.3, 7.3, and J_{3-2} = 5.9 Hz, 1 H, H-3), 4.14 (d, J_{2-3} = 5.9 Hz, 1 H, H-2), 6.72 (br, 1 H, NH), 7.2-7.5 (m, 5 H, Ph); ^{13}C NMR ($CDCl_3$) δ 27.86 (t-Bu), 38.46 (C-4), 44.19 (C-3), 63.77 (C-2), 82.16 (COOBu-t), 127.05, 127.24, 128.78, 142.01 (each Ph), 170.45 (C-5), 177.02 (COOBu-t); MS m/z (rel intensity) 261 (M^+, 2), 205 (48), 161 (28), 160 (base peak), 57 (7). Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33, N, 5.36. Found: C, 69.08; H, 7.35; N, 5.26.

General Procedure for the Demethoxycarbonylation of 11a and 11d Leading to (2*R*,3*R*)-5 and 12. The reaction of **11a** is typical. A mixture of **11a** (0.132 g, 0.5 mmol), lithium bromide (0.021 g, 0.5 mmol), water (0.009 g, 0.5 mmol), and dimethyl-2-imidazolidinone (DMI, 5 mL) was heated at 140 °C for 4 h. The mixture was then poured into ice/water and was extracted with diethyl ether (30 mL × 3). The combined extracts were dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel with hexane-ethyl acetate (1:1) to give (2*R*,3*R*)-**5** (0.08 g, 80%): $[\alpha]_D$ -30.0° [c 1.02, $CHCl_3$].

Similarly, **11d** was converted (130 °C, 4 h) to **12** in 88% yield. Compound **12** was purified by column chromatography on silica gel (hexane/ethyl acetate, 1:1).

***tert*-Butyl (2*R*)-3-phenyl-5-oxopyrrolidine-2-carboxylate (12)**: pale yellow liquid from column chromatography on silica gel (hexane/ethyl acetate, 4:1); $[\alpha]_D$ -38.9° [c 1.03, $CHCl_3$]; IR (neat) 2960, 1720, 1635, 1170 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.74, 0.90, 1.00 (each s, each 3 H, Me), 1.26 (s, 9 H, t-Bu), 1.3-2.9 (m, 9 H, CH_2 and CH), 3.52 (s, 3 H, COOMe), 3.88 (ddd, J_{3-4} = 9.9, 4.4, and J_{3-2} = 7.3 Hz, 1 H, H-3), 4.03 (d, J_{2-3} = 7.3 Hz, 1 H, H-2), 7.1-7.3 (m, 5 H, Ph); ^{13}C NMR ($CDCl_3$) δ 11.54, 18.98, 19.42 (each Me), 27.39 (camphor), 27.80 (t-Bu), 31.95, 36.11, 36.33, 43.72, 44.74 (camphor and C-4), 47.40 (C-3), 51.37 (COOMe), 54.27 (C-1 of camphor), 69.79 (C-2), 80.89 (COOBu-t), 126.75, 128.13, 128.46, 141.16 (each Ph), 169.87, 172.78 (each COO), 186.33 (C=N); MS m/z (rel intensity) 427 (M^+, 4), 208 (30), 162 (16), 131 (26), 121 (20), 103 (18), 91 (18), 77 (18), 57 (base peak). Anal. Calcd for $C_{26}H_{37}NO_4$: C, 73.03; H, 8.72; N, 3.28. Found: C, 73.11; H, 8.55; N, 3.28.

(2*S*,3*S*)-**12**: ^1H NMR spectrum ($CDCl_3$) δ 0.59, 1.00, 1.01 (each s, each 3 H, Me), 1.29 (s, 9 H, t-Bu), 3.50 (s, 3 H, COOMe), 4.01 (d, J_{2-3} = 7.3 Hz, 1 H, H-2).

Synthesis of β-Resorcylic Macrolides via Organopalladium Chemistry. Application to the Total Synthesis of (*S*)-Zearalenone

A. Kalivretenos, J. K. Stille,† and L. S. Hegedus*

Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523

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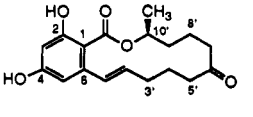
The β-resorcylic macrolides are a class of naturally occurring 12- and 14-membered macrolides. Zearalenone (1), a 14-membered macrolide of this type, displays useful biological activity, which has led to great synthetic interest. In this paper the intramolecular coupling reaction of an organostannane with an electrophile is used to construct β-resorcylic macrolides. The intramolecular coupling of an aryl iodide with a vinylstannane provided the highest yield of lactones. This methodology was then used to prepare (*S*)-zearalenone (1).

The β-resorcylic macrolides are a class of naturally occurring 12- and 14-membered macrolides.[1] Zearalenone (1),[2] a 14-membered macrolide of this type, exhibits anabolic, estrogenic, and antibacterial activity in vitro and in vivo.[1] Commerical applications of this compound have



Zearalenone (1)

led to great synthetic interest.[3] The macrocyclic ring of zearalenone has been prepared via intramolecular esteri-

† Deceased.

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