Simultaneous Amino and Carboxyl Group Protection for α-Branched Amino Acids

David B. Berkowitz* and Michelle L. Pedersen

Department of Chemistry, University of Nebraska–Lincoln, Lincoln, Nebraska 68588-0304

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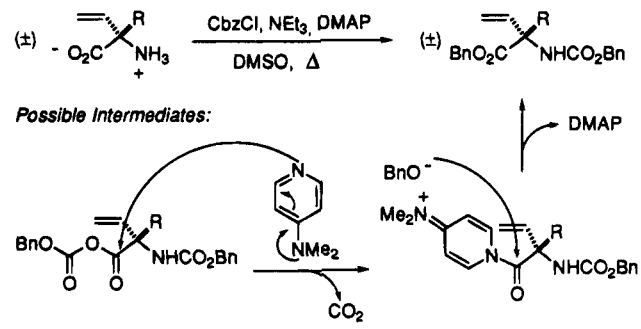
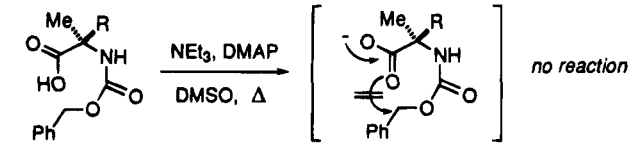
In the areas of peptide engineering and pharmaceutical chemistry, α-branched amino acids have found widespread and significant application. α-Alkyl amino acids exhibit helix-inducing propensities and are useful building blocks for *de novo* design of peptides and proteins.[1] α-Branched amino acids are useful as enzyme inhibitors and drugs. For example, α-methyl-DOPA (Aldomet), a commercial antihypertensive, reached over $140 million in sales in 1990.[2] We have been particularly interested in α-vinyl amino acids. Several of these, such as α-vinylhistidine,[3] α-vinylornithine,[4] α-vinyl-DOPA,[5] α-vinyl-*m*-tyrosine,[3] and α-vinylserine,[5] and α-vinylglutamate,[6] are known enzyme inhibitors.

We recently reported a convenient procedure for the synthesis of α-vinyl amino acids from the parent amino acids.[7] Given the chemical versatility of the vinyl functionality, these derivatives may be viewed as simple building blocks for more complex, chain-extended, α-branched amino acids. Such schemes require the presence of suitable protecting groups for the amino and carboxyl groups. However, initial attempts to introduce the benzyloxycarbonyl (Cbz) group onto the α-amino group of free α-vinyl amino acids using the usual Schotten–Baumann conditions [CbzCl, NaOH (aq)][8] met with little success. Under these conditions, benzyl chloroformate is apparently hydrolyzed faster than it reacts with the α-amino group of α-vinyl amino acids. Other established N-benzyloxycarbonylation reagents, including *O*-(benzyloxycarbonyl)-*N*-hydroxysuccinimide (Z-OSu)[9] and [*p*-((benzyloxycarbonyl)oxy)phenyl]dimethylsulfonium methyl sulfate (Z-ODSP),[10] also failed, presumably due to the sterically congested environment about the amino group. Indeed, the problems associated with amino group carbonylation for α-branched amino acids are well known and have been described by others.[11]

Scheme 1



Scheme 2



7 R = H
8 R = vinyl

Presuming that use of an organic solvent would prolong the lifetime of CbzCl in the reaction mixture, and thereby facilitate the desired N-benzyloxycarbonylation, we heated α-vinyl amino acids with CbzCl in a variety of polar organic solvents (CH_3CN, DMF, DMPU, HMPA, DMSO). The best results were obtained with CbzCl, NEt_3, and catalytic DMAP, in DMSO at 50 °C. *Under these conditions, provided that excess CbzCl was present, both the α-amino (Cbz) and α-carboxyl (Bn) groups could be protected in a single step, in good yield (Table 1).* Furthermore, amino (α-vinylornithine and α-vinyllysine) and hydroxylic (α-vinyl-DOPA) side chains could also be protected as the corresponding carbamates or carbonates in the same pot, given sufficient CbzCl.

To our knowledge, this is the first report of the simultaneous N-benzyloxycarbonylation and benzyl esterification of an α-amino acid. The esterification step is mechanistically intriguing and has precedent from the work of Kim.[12] Because of the requirement for DMAP in the reaction, we, as Kim,[12] favor a mechanism in which a mixed carbonic carboxylic anhydride forms to initially activate the α-carboxyl group, followed by DMAP-induced fragmentation to a pyridinium benzyloxide salt with release of CO_2. This is illustrated in Scheme 1.

An alternative intramolecular benzyl transfer mechanism is also conceivable due to the increased nucleophilicity of a carboxylate anion in DMSO as compared to H_2O. However, such a transformation would be constrained to a less than optimal *7-endo-tet* transition state. This is illustrated in Scheme 2. In tests of this mechanism, subjecting authentic *N*-Cbz-alanine (**7**) or *N*-Cbz-α-vinylalanine (**8**) to the reaction conditions, sans CbzCl, failed to give any benzyl transfer, with 80–85% of the starting carbamate being recovered unchanged.

The protection method described herein appears to be preparatively useful only for relatively hydrophobic

(1) Altmann, E.; Nebel, K.; Mutter, M. *Helv. Chim. Acta* **1991**, *74*, 800–806, and references cited therein.
(2) α-Methyl-DOPA: Stinson, S. C. Chiral Drugs. *Chem. Eng. News*, **1992**, *252* (Sept. 28), 46–79.
(3) α-Vinyl-DOPA and α-vinyl-*m*-tyrosine: (a) Maycock, A. L.; Aster, S. D.; Patchett, A. A. *Enzyme-Activated Irreversible Inhibitors*; Seiler, N., et al., Eds.; Elsevier, North Holland, 1978; pp 211–220. (b) Maycock, A. L.; Aster, S. D.; Patchett, A. A. *Develop. Biochem.* **1979**, *6*, 115–129. (c) Jung, M. J.; Palfreyman, M. G.; Ribereau-Gayon, G.; Bey, P.; Metcalf, B. W.; Koch-Weser, J.; Sjoerdsma, A. *Ibid.* **1979**, *6*, 131–144. (d) Ribereau-Gayon, G.; Danzin, C.; Palfreyman, M. G.; Aubry, M.; Wagner, J.; Metcalf, B. W.; Jung, M. J. *Biochem. Pharm.* **1979**, *28*, 1331–1335.
(4) α-Vinylornithine: Danzin, C.; Casara, P.; Claverie, N.; Metcalf, B. W. *J. Med. Chem.* **1981**, *24*, 16–20.
(5) α-Vinylserine: Tendler, S. J. B.; Threadgill, M. D.; Tisdale, M. J. *J. Chem. Soc., Perkin Trans. I* **1987**, 2617–2623.
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(7) (a) Pedersen, M. L.; Berkowitz, D. B. *Tetrahedron Lett.* **1992**, *33*, 7315–7318. (b) Pedersen, M. L.; Berkowitz, D. B. *J. Org. Chem.* **1993**, *58*, 6966–6975.
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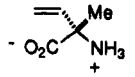
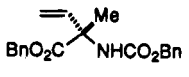
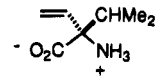
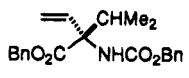
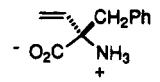
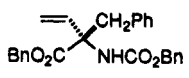
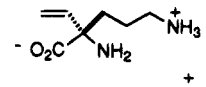
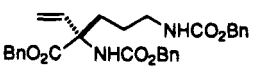
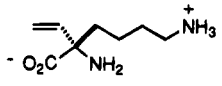
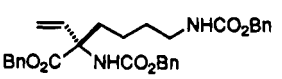
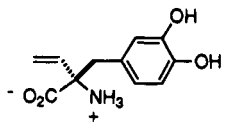
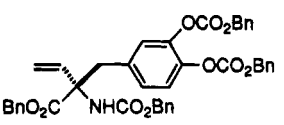
(11) Turk, J.; Panse, G. T.; Marshall, G. R. *J. Org. Chem.* **1975**, *40*, 953–955.
(12) (a) Kim, S.; Lee, J. I.; Kim, Y. C. *J. Org. Chem.* **1985**, *50*, 560–565. (b) Kim, S.; Kim, Y. C.; Lee, J. I. *Tetrahedron Lett.* **1983**, *24*, 3365–3368.

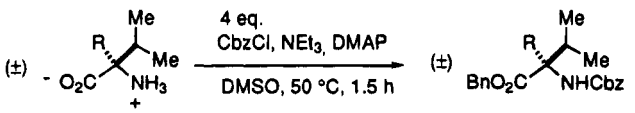
0022-3263/94/1959-5476$04.50/0

Table 1

α-Vinyl Amino Acid[a]	Equiv. CbzCl	Product[a]	Yield
(±) **1a** 	3.5	(±) **1b** 	62%
2a 	4	**2b** 	73%
3a 	4	**3b** 	82%
4a 	5	**4b** 	62%
5a 	5	**5b** 	60%
6a 	8	**6b** 	47%

[a]All compounds are racemic; wedges and dashes are drawn for clarity.

Scheme 3



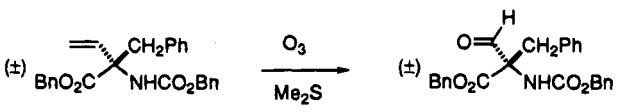
compound	9	10	11	2b
R	H	Me	Et	vinyl
yield	21%	41%	54%	73%

amino acids, such as α-branched amino acids, presumably due to their greater solubility in DMSO. But it is precisely for α-branched amino acids, in which the amino group is particularly hindered, that this chemistry is most valuable. In support of this solubility argument, a qualitative correlation between size of the alkyl chain and percent yield was observed. This is illustrated for several α-branched valine analogues in Scheme 3.

In summary, this is the first report of a one-pot procedure for the protection of amino acids with both carbamate (amino group) and benzyl ester protecting groups. The procedure is most efficient for relatively hydrophobic, α-branched amino acids. The nature of the carbamate and ester protecting groups could presumably be changed by simply varying the alkyl chloroformate employed. Moreover, when combined with our α-vinylation methodology,[7a] this procedure provides a direct route from α-amino acids to their *N*-Cbz, benzyl ester protected, α-vinyl derivatives. These, in turn, are expected to find broad application as building blocks for novel α-branched amino acids. For instance, it may be possible to directly chain-extend and functionalize these with Heck chemistry, as was recently demonstrated for *N*-Cbz-vinylglycine.[13]

On the other hand, the *N*-Cbz-protected α-vinyl amino esters reported herein may be transformed into the corresponding α-formyl amino acids. For example, ozonolysis of **3b** proceeds smoothly to yield the protected, α-formylphenylalanine **12** (Scheme 4). Olefination of such protected, α-formyl amino acids would provide a complementary strategy for branch extension. Indeed, modified Wittig olefinations of related carbamate-protected α-amino aldehydes, derived from unbranched amino acids,[14] as well as α-branched amino acids,[15] are well known. For such applications, hydrogenolytically cleavable protecting groups, such as those installed herein, are especially attractive, as they might be removed in the same operation in which the α-side chain is saturated.

Scheme 4



Experimental Section

General. All general experimental procedures were as described previously.[7b] The starting α-vinyl amino acids (±)-**1a**–**6a** were synthesized as reported.[7b] Elemental analyses were satisfactory for **1b**–**3b** but did not match expectations for **4b**–**6b**. In these cases, purity was judged by ^{1}H NMR and compound identity was verified by HRMS.

General Procedure for Amino and Carboxyl Group Protection. (±)-Benzyl *N*-(Benzyloxycarbonyl)-α-vinylphenylalanine (3b). To a suspension of (±)-**3a** (560 mg, 2.9 mmol), NEt_3 (1.6 mL, 12 mmol), and 4-(dimethylamino)pyridine (71 mg, 0.59 mmol) in dry DMSO (3 mL) at 10 °C was added benzyl chloroformate (1.9 mL, 13 mmol), dropwise and with stirring. After being stirred for 1.5 h at 50 °C, the reaction mixture was diluted with EtOAc (150 mL) and extracted with $NaHCO_3$ (aq,

(13) Crisp, T. G.; Glink, P. T. *Tetrahedron* **1992**, *48*, 3541–3556.

(14) (a) Matsuura, F.; Hamada, Y.; Shioiri, T. *Tetrahedron Lett.* **1994**, *35*, 733–736. (b) DiGiovanni, M. C.; Misiti, D.; Zappia, G.; Monache, G. D. *Tetrahedron* **1993**, *49*, 11321–11328. (c) Jegham, S.; Das, B. C. *Tetrahedron Lett.* **1988**, *29*, 4419–4422. (d) Kogen, H.; Nishi, T. *J. Chem. Soc., Chem. Commun.* **1987**, 311–312.

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50 mL). The organic layer was further extracted with 1 N HCl (50 mL) and brine (50 mL). After drying ($MgSO_4$), the volatiles were evaporated in vacuo and the residue purified by flash SiO_2 chromatography (10% Et_2O–hexane) to give **3b** (1.0 g, 82%) as a white solid: mp 68–70 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 3.33 (d, J = 13 Hz, 1 H), 3.62 (d, J = 13 Hz, 1 H), 5.10–5.25 (m, 4 H), 5.27 (d, J = 10 Hz, 1 H), 5.28 (d, J = 17 Hz, 1 H), 5.68 (s, 1 H), 6.08 (dd, J = 10, 17 Hz, 1 H), 6.90–6.91 (m, 2 H), 7.10–7.20 (m, 3 H), 7.26–7.43 (m, 10 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 40.4, 65.1, 66.5, 67.8, 116.2, 126.9, 128.1, 128.20, 128.23, 128.4, 128.5, 128.6, 130.0, 130.3, 135.0, 135.4, 136.6, 136.8, 154.4, 171.2; IR (film) 3420–3330, 1723 cm^{-1}; HRMS (FAB, 3-NOBA) calcd for $C_{26}H_{25}NO_4Na$ $(M + Na)^+$ 438.1681, obsd 438.1685. Anal. Calcd for $C_{26}H_{25}NO_4$: C, 75.16; H, 6.07; N, 3.37. Found: C, 74.98; H, 6.22; N, 3.37.

Compounds **1b**, **2b**, **4b–6b**, and **9–11** were synthesized analogously (all reaction times were 1.5–2 h), with the molar ratios of CbzCl and yields indicated in Table 1 and Scheme 3, and displayed the following spectral characteristics.

(±)-Benzyl *N*-(benzyloxycarbonyl)-α-vinylalaninate (1b): mp 52–54 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 1.69 (s, 3 H), 5.07 (s, 2 H), 5.16 (s, 2 H), 5.22–5.25 (d, J = 11 Hz, 1 H), 5.28 (d, J = 17 Hz, 1 H), 5.61 (s, 1 H), 6.07 (dd, J = 11, 17 Hz, 1 H), 7.28–7.40 (m, 10 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.0, 60.6, 66.6, 67.5, 115.7, 127.9, 128.0, 128.1, 128.3, 128.4, 128.5, 135.4, 136.3, 137.6, 154.6, 172.3; IR (film) 3352, 1716 cm^{-1}; HRMS (FAB, 3-NOBA) calcd for $C_{20}H_{22}NO_4$ $(M + H)^+$ 340.1549, obsd 340.1546. Anal. Calcd for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24; N, 4.12. Found: C, 70.79; H, 6.34; N, 4.18.

(±)-Benzyl *N*-(benzyloxycarbonyl)-α-vinylvalinate (2b): mp 62–64 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 0.85 (d, J = 7 Hz, 3 H), 0.86 (d, J = 7 Hz, 3 H), 2.11–2.19 (m, 1 H), 4.96–5.30 (m, 7 H), 6.28 (dd, J = 11, 17 Hz, 1 H), 7.26–7.40 (m, 10 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.9, 17.5, 35.4, 65.4, 66.9, 67.3, 115.5, 128.1, 128.2, 128.23, 128.4, 128.46, 128.5, 133.9, 135.6, 136.4, 155.0, 171.7; IR (film) 3448–3258, 1727 cm^{-1}; HRMS (FAB, 3-NOBA) calcd for $C_{22}H_{25}NO_4Na$ $(M + Na)^+$ 390.1681, obsd 390.1685. Anal. Calcd for $C_{22}H_{25}NO_4$: C, 71.91; H, 6.86; N, 3.81. Found: C, 72.14; H, 6.66; N, 3.91.

(±)-Benzyl α,γ-bis-*N*-(benzyloxycarbonyl)-α-vinylornithinate (4b): ^1H NMR (300 MHz, $CDCl_3$) δ 1.15–1.28 (m, 1 H), 1.36–1.49 (m, 1 H), 1.98–2.10 (m, 1 H), 2.28–2.41 (m, 1 H), 3.03–3.15 (m, 2 H), 4.59–4.69 (m, 1 H), 5.01–5.31 (m, 8 H), 5.82 (s, 1 H), 5.99 (dd, J = 10, 17 Hz, 1 H), 7.27–7.50 (m, 15 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.2, 32.0, 40.5, 64.0, 66.6, 66.7, 67.8, 115.9, 128.1 (2 C), 128.2, 128.3 (2 C), 128.4, 128.5 (2 C), 128.6, 128.7, 135.1, 136.3, 136.6, 154.2, 156.3, 171.7; IR (film) 3439–3277, 1717 cm^{-1}; HRMS (FAB, 3-NOBA) calcd for $C_{30}H_{33}N_2O_6$ $(M + H)^+$ 517.2338, obsd 517.2341.

(±)-Benzyl α,δ-bis-*N*-(benzyloxycarbonyl)-α-vinyllysinate (5b): ^1H NMR (300 MHz, $CDCl_3$) δ 0.93–1.02 (m, 1 H), 1.19–1.45 (m, 3 H), 1.92–2.02 (m, 1 H), 2.24–2.34 (m, 1 H), 3.01–3.10 (m, 2 H), 4.69–4.73 (m, 1 H), 5.00–5.27 (m, 8 H), 5.87 (s, 1 H), 6.01 (dd, J = 10, 17 Hz, 1 H), 7.26–7.39 (m, 15 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.6, 29.3, 34.5, 40.3, 64.2, 66.6, 66.7, 67.6, 115.5, 128.0, 128.1, 128.3 (2 C), 128.4 (2 C), 128.5, 128.6 (2 C), 135.1, 136.3, 136.5, 136.7, 154.3, 156.4, 171.8; IR (film) 3413–3298, 1716 cm^{-1}; HRMS (FAB, 3-NOBA) calcd for $C_{31}H_{35}N_2O_6$ $(M + H)^+$ 531.2495, obsd 531.2478.

(±)-Tris-*N,O,O'*-(benzyloxycarbonyl)-α-vinyl-DOPA, benzyl ester (6b): ^1H NMR (300 MHz, $CDCl_3$) δ 3.34 (d, J = 13 Hz, 1 H), 3.64 (d, J = 13 Hz, 1 H), 5.03–5.34 (m, 10 H), 5.71 (s, 1 H), 5.99 (dd, J = 10, 17 Hz, 1 H), 6.71–6.75 (m, 1 H), 6.92–6.98 (m, 3 H), 7.26–7.40 (m, 20 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 39.4, 65.0, 66.7, 68.0, 70.5, 70.6, 116.6, 122.5, 124.6, 126.9, 128.07, 128.1, 128.2, 128.3, 128.4, 128.45, 128.5, 128.57 (2 C), 128.61 (2 C), 128.64 (2 C), 128.7 (2 C), 134.7, 134.9, 136.4, 141.3, 141.9, 152.5, 152.6, 154.5, 170.7; IR (film) 3411 (br), 1767, 1722 cm^{-1}; MS (FAB, 3-NOBA/K_2CO_3) 754 (100) $(M + K)^+$; HRMS (FAB, 3-NOBA) calcd for $C_{42}H_{38}NO_{10}$ $(M + H)^+$ 716.2496, obsd 716.2497.

(±)-*N*-(Benzyloxycarbonyl)-α-vinylalanine (8). To a solution of **1b** (50.0 mg, 147 μmol) in THF (2 mL)/H_2O (0.5 mL) at 0 °C was added LiOH–H_2O (12.0 mg, 294 μmol). After being heated for 4 h at 50 °C, the reaction mixture was partitioned between 1 N HCl (20 mL) and EtOAc (25 mL). Drying ($MgSO_4$), filtration, evaporation, and flash chromatography (60:29:1; hexane–EtOAc–AcOH) gave **8** (27.0 mg, 75%): ^1H NMR (500 MHz, $CDCl_3$) δ 1.68 (s, 3 H), 5.11 (s, 2 H), 5.28 (d, J = 10 Hz, 1 H), 5.31 (d, J = 17 Hz, 1 H), 5.50 (br s, 1 H), 6.07 (dd, J = 10, 17 Hz, 1 H), 7.29–7.37 (m, 5 H); ^1H NMR (300 MHz, DMSO-d_6) δ 1.40 (s, 3 H), 4.95–5.05 (m, 2 H), 5.09 (d, J = 10 Hz, 1 H), 5.15 (d, J = 17 Hz, 1 H), 6.15 (dd, J = 10, 17 Hz, 1 H), 7.28–7.47 (m, 5 H), 7.72 (s, 1 H), 12.5 (s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.5, 60.6, 67.2, 116.2, 128.2, 128.3, 128.5, 136.0, 137.3, 155.4, 175.3; IR (film) 1715 cm^{-1}; HRMS (FAB, 3-NOBA) calcd for $C_{13}H_{15}NO_4Na$ $(M + Na)^+$ 272.0899, obsd 272.0893.

(±)-Benzyl *N*-(benzyloxycarbonyl)valinate (9):[16] ^1H NMR (500 MHz, $CDCl_3$) δ 0.84 (d, J = 7 Hz, 3 H), 0.94 (d, J = 7 Hz, 3 H), 2.16–2.19 (m, 1 H), 4.34–4.36 (m, 1 H), 5.10–5.20 (m, 4 H), 5.25–5.27 (m, 1 H), 7.30–7.38 (m, 10 H).

(±)-Benzyl *N*-(benzyloxycarbonyl)-α-methylvalinate (10). From α-methylvaline:[11,17] ^1H NMR (500 MHz, $CDCl_3$) δ 0.86 (d, J = 7 Hz, 3 H), 0.92 (d, J = 7 Hz, 3 H), 1.58 (s, 3 H), 2.10–2.14 (m, 1 H), 5.02–5.18 (m, 4 H), 5.32 (s, 1 H), 7.27–7.38 (m, 10 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.1, 17.2, 18.7, 35.2, 66.6, 67.0, 69.7, 128.1, 128.2, 128.3, 128.4, 128.5, 128.54, 135.6, 136.3, 155.2, 173.5; IR (film) 3417–3319, 1719 cm^{-1}; HRMS (FAB, 3-NOBA) calcd for $C_{21}H_{26}NO_4$ $(M + H)^+$ 356.1862, obsd 356.1851.

(±)-Benzyl *N*-(benzyloxycarbonyl)-α-ethylvalinate (11). From α-ethylvaline:[18] ^1H NMR (500 MHz, $CDCl_3$) δ 0.71 (t, J = 7, 15 Hz, 3 H), 0.87 (d, 3 H, J = 7 Hz), 0.93 (d, J = 7 Hz, 3 H), 1.95–2.02 (m, 1 H), 2.43 (app quintet, J = 7 Hz, 1 H), 2.50–2.60 (m, 1 H), 5.03–5.09 (m, 2 H), 5.15–5.21 (m, 2 H), 5.89 (s, 1 H), 7.28–7.35 (m, 10 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 9.4, 18.4, 18.5, 25.8, 34.9, 66.8, 68.1, 68.9, 128.5, 128.7, 129.0, 129.1, 129.2, 129.3, 135.8, 137.4, 154.8, 173.8; IR (film) 3425–3352, 1717 cm^{-1}; HRMS (FAB, 3-NOBA) calcd for $C_{22}H_{28}NO_4$ $(M + H)^+$ 370.2018, obsd 370.2011.

(±)-Benzyl *N*-(Benzyloxycarbonyl)-2-aminomalonate Semialdehyde (12). Into a solution of **3b** (25 mg, 60 μmol) in CH_2Cl_2 (15 mL) at −78 °C was bubbled O_3 until a light blue color persisted. After 2 h of stirring at rt with Me_2S (1 mL), the volatiles were evaporated. The residue was partitioned between H_2O (20 mL) and EtOAc (2 × 20 mL). The organic extracts were then dried ($MgSO_4$), filtered, and concentrated to afford **12** (23 mg, 94%): ^1H NMR (300 MHz, $CDCl_3$) δ 3.49 (d, J = 14 Hz, 1 H), 3.57 (d, J = 14 Hz, 1 H), 5.07–5.24 (m, 4 H), 5.79 (s, 1 H), 6.79–6.82 (m, 2 H), 7.11–7.23 (m, 3 H), 7.26–7.44 (m, 10 H), 9.60 (s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 37.9, 67.9, 69.2, 72.4, 128.0, 128.9, 129.0, 129.2, 129.3, 129.4, 129.5, 130.4, 130.6, 134.4, 135.0, 136.6, 155.7, 167.3, 193.3; IR (film) 3444–3300, 1729 cm^{-1}; HRMS (FAB, 3-NOBA) calcd for $C_{25}H_{23}NO_5Na$ $(M + Na)^+$ 440.1474, obsd 440.1479.

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Supplementary Material Available: ^1H NMR spectra for compounds **4b**, **5b**, **6b**, **8**, and **10–12** as well as mass spectral data for **6b** (9 pages). This material is contained in 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.

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