Reactions of α-Hydroxy Carbonyl Compounds with Azodicarboxylates and Triphenylphosphine: Synthesis of α-*N*-Hydroxy Amino Acid Derivatives

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Reaction of aliphatic α-hydroxy esters with azodicarboxylates and triphenylphosphine in the presence of either $CbzNHOCH_2Ph$ or $trOCNHOCH_2Ph$ provides a direct route to protected α-*N*-hydroxy amino acids. Similar reactions with aromatic α-hydroxy carbonyl compounds and derivatives result in predominate oxidation to the corresponding α-oxo carbonyl derivatives.

The Mitsunobu reaction[1] (eq 1) has recently been used quite extensively in organic synthesis. Our previous

$$\underset{1}{RO_2CN{=}NCO_2R} + \underset{2}{Ph_3P} + R'OH + nuc \longrightarrow \underset{3}{nuc\text{-}R'} + \underset{4}{Ph_3P{=}O} + \underset{5}{RO_2CHNNHCO_2R} \quad (1)$$

success in utilizing this versatile reaction for the synthesis of β-lactams[2] and *N*-alkylhydroxamate constituents of various microbial iron chelators[3] prompted us to further explore its utility. We were especially interested in developing an efficient synthesis of chiral α-*N*-hydroxy amino acids **10**, compounds of increasing interest.[4] An attractive route would be the direct alkylation of substituted hydroxamates **9** with chiral α-hydroxy esters **8** (Scheme I). This route was especially appealing since the required α-hydroxy carboxylic acids **8** are readily available in optically pure form by deaminative hydroxylation of amino acids (**6** → **7** → **8**, Scheme I)[5] and the Mitsunobu reaction (eq 1) usually proceeds with clean inversion at the carbinol center. Herein we report on the scope of the direct synthesis of a variety of substituted α-*N*-hydroxy amino acids by the procedure outlined in Scheme I. The formation of other unusual products from the Mitsunobu reaction with a variety of α-hydroxy carbonyl containing substrates is also described.

Formation of Protected α-*N*-Hydroxy Amino Acids. Several reactions of α-hydroxy esters **8** with nucleophiles under the Mitsunobu conditions (**1** + **2**) have already been reported.[1] However, our choice of hydroxamate nucleophile **9** required further consideration, since alkylation of simple *N*-acyl O-protected hydroxylamines gives mixtures of the N-alkylated products (hydroxamates) and O-alkylated products (hydroximates).[6] Alternatively, alkylations of *N*-alkoxycarbonyl O-substituted hydroxylamines proceed cleanly on nitrogen.[6] For this reason and because it contains the readily removable trOC and benzyl protecting groups, *N*-[(trichloroethoxy)carbonyl]-*O*-benzylhydroxylamine ($trOCNHOCH_2Ph$, **11**) was initially used as the nucleophile. Indeed, reaction of **11** with a number of α-hydroxy methyl esters **8** and the Mitsunobu reagents (**1** + **2**) in THF provided the desired trOC-α-*N*-benzyloxy amino acid esters **12** in 20–82% yields (Table I). In no case, however, was the *N*-hydroxy amino acid derivative **12** the sole product. The predominant side products were the enol adducts **13** and **14** derived from the substrate **8** and the azodicarboxylate **1**. The yields of **12** appear to depend on the steric effects of the alkyl substituent (R) of the α-hydroxy ester **8** and probably reflect a correspondingly decreased ability of the hydroxamate nucleophile to approach the site bearing the eventual leaving group. Thus, the competing side reactions become more

Scheme I

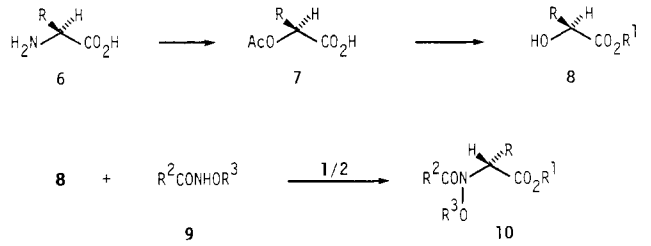
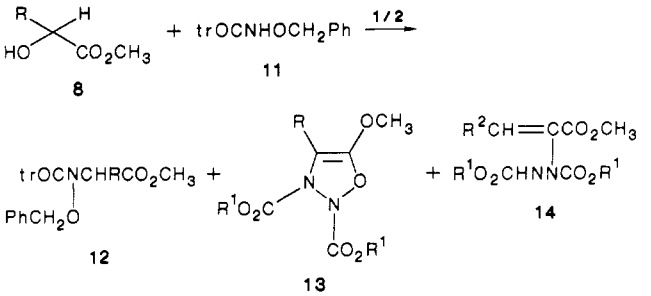


Table I. Alkylation of 11 with α-Hydroxy Esters under the Mitsunobu Conditions



entry	8, R	12, %	13, %	14, %
1	**8a**, H[a]	30		
2	**8b**, CH_3[b]	82	9	
3	**8c**, CH_3CH_2	59	9	
4	**8d**, $(CH_3)_2CH$	20	48	
5	**8e**, $(CH_3)_2CHCH_2$	50	14	10
6	**8f**, $PhCH_2$	43	20	11

[a] Two other compounds were also isolated [$trOCN(CH_3)OCH_2Ph$ (**15**), 23%; $HOCH_2CO_2CH_2CO_2CH_3$ (**16**), 22%]. Substitution of $CbzNHOCH_2Ph$ for **11** resulted in formation of $CbzN(CH_3)OCH_2Ph$ in 23% yield along with another unidentified product. The exact mechanism of the methyl transfer from the methyl glycoxylate to the hydroxamate has not yet been determined but may involve formation of an α-lactone derivative as in the diazotization of α-amino acids. [b] The N-methylated hydroxamate **15** was also isolated in 10% yield. Substitution of $CbzNHOCH_2Ph$ (**17**) for **11** provided the expected product $CbzN(OCH_2Ph)CH(CH_3)CO_2CH_3$ (**18**) in 47% yield along with 10% of the enol corresponding to **13**.

† Fellow of the Alfred P. Sloan Foundation (1981–1985) and recipient of a Career Development Award with the NIH (1983–1988).

(1) Mitsunobu, O. *Synthesis* **1981**, 1–28.
(2) Miller, M. J.; Mattingly, P. G.; Morrison, M. A.; Kerwin, J. F., Jr. *J. Am. Chem. Soc.* **1980**, *102*, 7026–7032.
(3) Maurer, P. J.; Miller, M. J. *J. Am. Chem. Soc.* **1983**, *105*, 240–245.
(4) (a) Ottenheijm, H. C.; Herscheid, J. D. M. *Chem. Rev.* **1986**, *86*, 697. (b) Kolasa, T.; Chimiak, A. *Tetrahedron* **1974**, *30*, 3591–3595. (c) Feenstra, R. W.; Stokkingreef, E. H. M.; Nivard, R. J. F.; Ottenheijm, H. C. J. *Tetrahedron Lett.* **1987**, *28*, 1215.
(5) For similar reactions, see: Testa, E.; Nicolaus, B. J. R.; Mariani, L.; Pagani, G. *Helv. Chim. Acta* **1963**, *46*, 766.

0022-3263/87/1952-4978$01.50/0

Scheme II

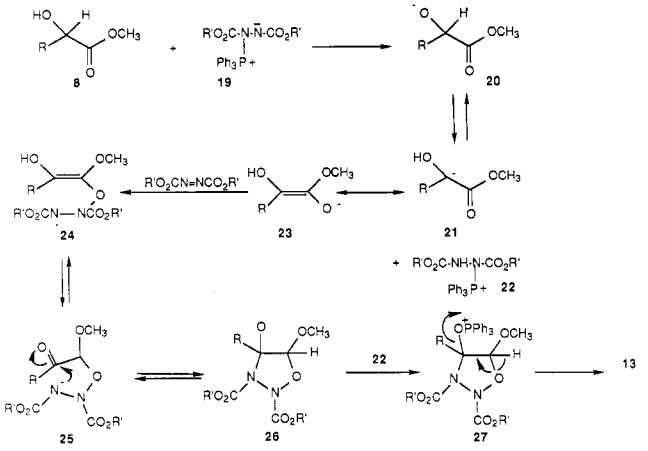
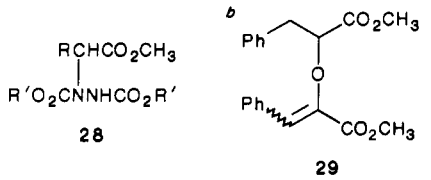


Table II. Reaction of α-Hydroxy Esters with 1/2 (2:1)

R of 8	13, %	14, %	other products, %
H	11		14[a]
CH_3	23	26	
CH_3CH_2	36	18	
$(CH_3)_2CH$	80		9[a]
$(CH_3)_2CHCH_2$	30	30	
$PhCH_2$	33	49	9[b]

[a] The reduced azodicarboxylate alkylation product



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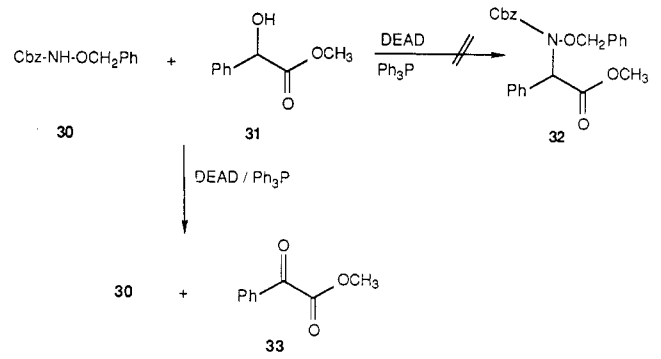
dominant. Although not yet fully studied, a potential mechanism for the formation of the adducts **13** and **14** is provided in Scheme II.

Oxidation of α-Hydroxy Carbonyl Compounds and Derivatives. Since such a mechanism (Scheme II) does not require the presence of a hydroxamate nucleophile like **11**, the reactions were repeated with deletion of **11**. Indeed, with the exception of entry 1, the yields of **13** and **14** generally increased. As shown in Table II, the yields were most significantly increased when a 2:1 ratio of Mitsunobu reagents (**1** to **2**) was used (as required in the mechanism shown in Scheme II). In some cases (entries 1, 4, and 6), small amounts of products were obtained from reactions of other nucleophiles (present or generated) with the activated α-hydroxy esters.

Interestingly, reactions of aromatic α-hydroxy carbonyl systems with hydroxamates under the Mitsunobu conditions did not provide any of the alkylated hydroxamates. For example, reaction of 100 mol % each of diethyl azodicarboxylate (DEAD, **1**, R′ = Et) and Ph_3P (**2**) with *N*-(carbobenzoyl)-*O*-benzylhydroxylamine (**30**) and racemic methyl mandelate (**31**)[8] in dry THF did not produce the expected protected α-*N*-hydroxy-α-phenylglycine (**32**), but phenylglyoxylic acid methyl ester (**33**) (Scheme III). TLC

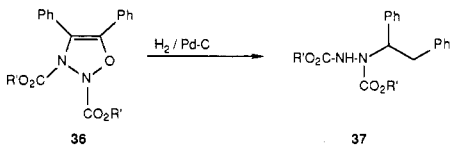
Scheme III



analysis during the reaction and subsequent chromatographic purification also indicted that while all of the DEAD had been consumed during the reaction, some of the Ph_3P and methyl mandelate (**31**) remained. The hydroxamate **30** was recovered almost quantitatively. Repetition of the reaction under the same conditions but with 200 mol % of DEAD resulted in complete consumption of DEAD, Ph_3P, and methyl mandelate, but still no reaction of the hydroxamate **30**. Chromatographic separation provided the phenylglycoxylate **33** in 85% yield.

Repetition of these reactions without the hydroxamate **30** gave similar results. Treatment of methyl mandelate (**31**) with 100 mol % each of DEAD and Ph_3P resulted in complete consumption of DEAD, a 40% yield of methyl phenylglyoxylate (**33**), and recovery of some Ph_3P and **31**. Use of a 2:1 ratio of DEAD to Ph_3P resulted in essentially quantitative oxidation of **31** to **33** as well as complete reduction of DEAD and oxidation of Ph_3P to $Ph_3P{=}O$.[7] Since oxidation of alcohols by DEAD alone has been previously reported, we considered that perhaps just competitive separate reactions of DEAD with the alcohol **31** and with Ph_3P were occurring. Subsequent generation of H_2DEAD and $Ph_3P{=}O$ from the latter reaction could then occur by aqueous quenching of the DEAD–Ph_3P adduct during workup or chromatography. However, all attempts to oxidize methyl mandelate (**31**) with DEAD alone under similar reaction conditions failed. Thus, again, a 2:1 mixture of DEAD to Ph_3P appeared to be required for complete oxidation.

To test the scope of this oxidation reaction, a number of phenylcarbinols were subjected to the reaction with DEAD–Ph_3P (2:1). The results are summarized in Table III. Indeed, the reaction with benzoin (entry 2) also provided the oxidation product **35**, but in only 20% yield. In this case the enol adduct **36** was the major product (43%). Thus, the reaction with benzoin appeared to be more like that of the α-alkyl α-hydroxy esters described earlier (Table II). The structure of the enol adduct **36** was confirmed by hydrogenation to **37** (eq 2).



36 37 (2)

Since all the reactions of DEAD–Ph_3P (2:1) with alcohols studied thus far required eventual removal of the α-proton, we decided to test the reaction on substrates with less acidic α-protons. Not unexpectedly, reaction of α-phenethyl alcohol (**38**; entry 3, Table III) simply provided the alkylated azodicarboxylate **39** from a normal Mitsunobu type reaction. The implication was that indeed a relatively acidic α-proton was required to initiate the oxidation. Subsequent studies with other aromatic α-hydroxy car-

(6) Maurer, P. J.; Miller, M. J. *J. Am. Chem. Soc.* **1982**, *104*, 3096–3101.

(7) (a) Yoneda, F.; Suzuki, K.; Nitta, Y. *J. Org. Chem.* **1967**, *32*, 727–729. (b) For report of an oxidation of an allylic alcohol under the Mitsunobu conditions, see: Brown, R. F. C.; Caldwell, K. B.; Gatehouse, B. M.; Teo, P. Y. T. *Aust. J. Chem.* **1985**, *38*, 1339.

(8) *Dictionary of Organic Compounds*; Oxford University: New York, 1965, Vol. 4, p 2052.

(9) *Dictionary of Organic Compounds*; Oxford University: New York, 1965, Vol. 1, p 344.

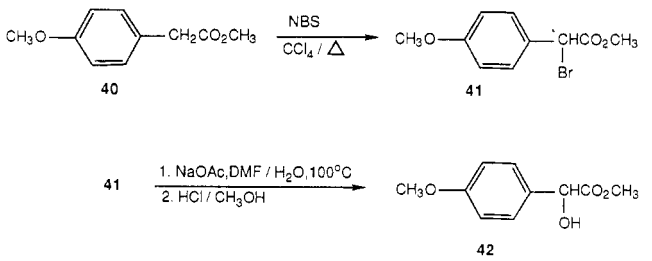
(10) Reference 8, p 2051.

(11) Mattingly, P. G.; Miller, M. J. *J. Org. Chem.* **1981**, *46*, 1557.

Table III. Reactions of Aromatic α-Hydroxy Carbonyl Compounds with 1/2 (2:1)

Entry	Substrate	Products (%)
1	31	$PhCOCO_2CH_3$ 33 (97%)
2	$PhCOCH(OH)Ph$ 34	$PhCOCOPh$ 35 (20%); 36 (43%)
3	$PhCH(OH)CH_3$ 38	$R'O_2CNHNCO_2R'$ / CH_3CHPh 39 (35%)
4	MeO-C6H4-CH(OH)CO2Me 42	MeO-C6H4-COCO2Me 43 (50%)
5	$PhCH(OH)CONHCH_2Ph$ 44	$PhCOCONHCH_2Ph$ 45 (35%); 46 (6%)
6	$PhCH(OH)CONMe_2$ 47	$PhCOCONMe_2$ 48 (45%)
7	PhC(=NOH)CH(OH)Ph 49	PhC(=NOH)COPh 50 (11%) + PhCHO 51 (71%) + PhCN 52 (50%)
8	PhC(=NOCH2Ph)CH(OH)Ph 53	PhC(=NOCH2Ph)COPh 54 (20%); 55 (50%)
9	56	57 (24%); 58 (13%)
10	$PhCH(OH)CN$ 59	$PhCO_2CH(CN)Ph$ 61 (67%)
11	62	63 (8%); 64 (4%)

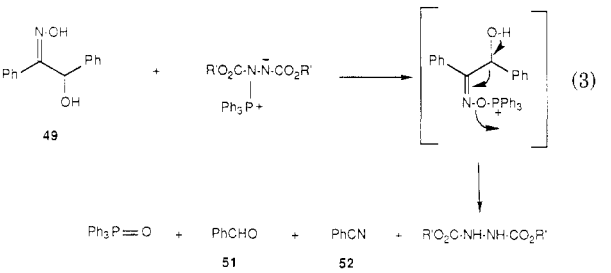
Scheme IV



bonyl compounds (Table III) appear to verify that increased α-proton acidity leads to a cleaner oxidation process. Reaction of methyl *p*-methoxymandelate (**42**; Table III, entry 4, synthesized by the procedure outlined in Scheme IV) with diisopropyl azodicarboxylate (DIAD, 1 R = *i*-Pr)-Ph_3P (2:1) provided only a 50% yield of the ketone **43**. Similarly, reaction of the *N*-benzylamide **44** (Table III, entry 5) with DIAD–Ph_3P provided only a 35% yield of the ketone **45** and a small amount of adduct **46** along with recovered starting material. Surprisingly, attempting the same reaction with even more DIAD–Ph_3P (4:2) decreased the yield of the oxidation product **45** to 4% and increased the yield of the adduct **46** to 21%. Subjection of the keto amide **45** to the same reaction conditions did not produce any of the adduct **46**, thus indicating that **45** is not an intermediate for formation of **46**.

As expected, no adduct similar to **46** was formed from the reaction of DIAD–Ph_3P with *N*,*N*-dimethylmandelamide (**47**). Instead, the usual oxidation product **48** was isolated in 45% yield.

Further studies were performed to determine the effect on the oxidation process of protecting the carbonyl group. Subjection of the oxime **49** (Table III, entry 7) to the Mitsunobu conditions (2:1, DIAD–Ph_3P) provided the keto oxime **50** in only 11% yield. The major products were benzaldehyde (**51**) and benzonitrile (**52**), which were presumably formed by the alternate reaction with the DIAD–Ph_3P adduct shown in eq 3. As expected, reaction

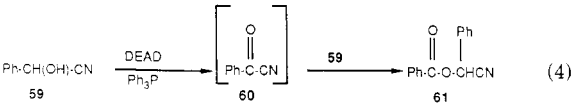


(3)

of the protected oxime **53** (Table III, entry 8) under the same conditions avoided the formation of benzaldehyde and benzonitrile. Instead, the oxidation product **54** was isolated in 40% yield along with 20% of the adduct **55**. Interestingly, substitution of DEAD for DIAD in this reaction decreased the yield of oxidation product **54** to 20% and increased the amount of isolated adduct **55** to 50% (presumably because of a steric problem with DIAD).

Reaction of the hydroxy ketal **56** with DIAD–Ph_3P (2:1) provided only a 24% yield of oxidation product **57** along with 13% of the bis(alkylated) azodicarboxylate **58** and a 50% recovery of **56**. Thus, as expected, masking the carbonyl group (entries 7–9) avoided formation of enolization products (like **36**, entry 2) but did not completely inhibit the oxidation process.

Reaction of mandelonitrile (**59**) with DIAD–Ph_3P (2:1) provided a 67% yield of the ester **61** plus small amounts of DIAD adducts. Presumably **61** was formed by oxidation of some of the mandelonitrile to **60**, which then acylated remaining **59** (eq 4).



(4)

Finally, as anticipated, reaction of methyl atrolactate (**62**, Table III) with DIAD–Ph_3P (2:1) could not provide an oxidation product. About 80% of the starting material **62** was recovered, and small amounts of the hydrazide alkylation products **63** (8%) and **64** (4%) were obtained.

In summary, while reaction of simple alkyl α-hydroxy carbonyl systems with nucleophiles under the Mitsunobu conditions can provide the corresponding substitution products (Table I and ref 1), similar reactions with aromatic α-hydroxy carbonyl containing substrates gives predominantly the corresponding oxidation products or azodicarboxylate adducts (Table III).

Other aspects of the utility of the α-*N*-hydroxy amino acid syntheses (Table I) and the mild oxidations (Table III) are being developed in our laboratories.

Experimental Section

General Methods. Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra (IR) were recorded on a Perkin-Elmer 727B

spectrophotometer. Proton NMR spectra were obtained on Varian EM-390 or Nicolet NB-300 spectrometers. Chemical shifts are reported relative to tetramethylsilane (δ units). Mass spectra were recorded on an AEI Scientific Apparatus MS 902 or on a Finnigan MAT system. Field desorption spectra were taken by Dr. John Occolowitz (Eli Lilly and Co.). Elemental analyses were performed by Midwest Microlabs, Indianapolis, IN, and MHW, Phoenix, AZ. Optical rotations were measured with a Rudolf Autopol III polorimeter.

General Procedure for the Synthesis of the α-Hydroxy Acid Esters 8 from Amino Acids: α-Acetoxy Acids 7.[5] To a solution of 0.1 mol of amino acid in 300 mL of glacial acetic acid was added portionwise 0.2 mol of $NaNO_2$ (with intermittent cooling with a cold water bath to maintain the reaction near room temperature). After the addition, the reaction was continued 1 h, and then acetic acid was removed in vacuo. Water was added, and product was extracted with ethyl ether. The ether layer was washed with water, dried over $MgSO_4$, and evaporated to give the *O*-acetyl derivatives of the α-hydroxy acids. The yields and properties of the products are given below.

Compound D-**7b** was prepared from D-alanine: oil; 85% yield; $[\alpha]_D$ +28.7° (*c* 5, CH_2Cl_2); NMR ($CDCl_3$) δ 1.48 (d, 3 H, *J* = 7 Hz), 2.1 (s, 3 H), 5.08 (q, 1 H, *J* = 7 Hz), 8.23 (br s, CO_2H); IR (thin film) 1725, 1740 (sh) cm^{-1}.

Compound DL-**7c** was obtained from D,L-α-aminobutyric acid: oil, 94% yield; NMR ($CDCl_3$) δ 1.0 (t, 3 H, *J* = 7 Hz), 1.9 (m, 2 H), 2.16 (s, 3 H), 5.0 (t, 1 H, *J* = 6 Hz), 10.07 (br s, CO_2H); IR (thin film) 1720, 1745 (sh) cm^{-1}; MS (CI, isobutane) *m/e* 147 (M + 1).

Compound L-**7d** was prepared from L-valine: 98% yield; $[\alpha]_D$ −28.2° (*c* 1.5, CH_2Cl_2); NMR ($CDCl_3$) δ 1.0 (d, *J* = 7 Hz, 6 H), 2.13 (s, 3 H), 2.2 (m, 1 H), 4.90 (d, 1 H, *J* = 4 Hz), 8.4 (br s, CO_2H); IR (thin film) 1720, 1740 (sh) cm^{-1}.

Compound L-**7e** was synthesized from L-leucine: 92% yield; oil; $[\alpha]^D$ −25.6° (*c* 6, CH_2Cl_2); NMR ($CDCl_3$) δ 0.9 (m, 6 H), 1.73 (m, 3 H), 2.1 (s, 3 H), 5.05 (t, 1 H, *J* = 6 Hz), 8.95 (br s, CO_2H); IR (thin film) 1725, 1745 cm^{-1}.

Compound DL-**7f** was obtained from DL-phenylalanine: 93% yield; NMR ($CDCl_3$) δ 2.04 (s, 3 H), 3.18 (m, 2 H), 5.23 (m, 1 H), 7.30 (s, 5 H), 9.6 (br s, CO_2H); IR (thin film) 1725, 1740 cm^{-1}; MS, *m/e* 208 (M^+), 148.

α-Hydroxy Acid Methyl Esters 8a–f. To a solution of 0.1 mol of α-acetoxy acid **7** or α-hydroxy acid in 200 mL of absolute methanol at −40 °C was added dropwise 8.1 mL (0.11 mol) of thionyl chloride, and the reaction mixture was left for 48 h at room temperature. Then, the methanol was evaporated in vacuo to give the desired α-hydroxy acid methyl esters (all were obtained as oils). The yields and properties are given below.

Glycolic acid and DL-lactic acid methyl esters (**8a** and DL-**8b**) were synthesized as above from commerically available α-hydroxy acids in 60% and 63% yields, respectively. Compound D-**8b**: 50% yield; $[\alpha]_D$ +15.25° (*c* 2, CH_2Cl_2); NMR ($CDCl_3$) δ 1.4 (d, 3 H, *J* = 7 Hz), 3.76 (s, 3 H), 4.36 (q + br s, 2 H); IR (thin film) 3400 (ν(O—H)), 1740 (ν(C=O)) cm^{-1}; MS, *m/e* 105 (M + 1).

Compound DL-**8c**: 67% yield; NMR ($CDCl_3$) δ 0.93 (t, 3 H, *J* = 7 Hz), 1.7 (m, 2 H), 2.84 (br s, 1 H), 3.75 (s, 3 H), 4.17 (t, 1 H, *J* = 6 Hz); IR (thin film) 3420 (ν(O—H)), 1740 (ν(C=O)) cm^{-1}; MS, *m/e* 118 (M^+), 117, 88.

Compound L-**8d**: 82% yield; $[\alpha]_D$ +3.0 (*c* 4, MeOH); ^1H NMR ($CDCl_3$) δ 0.95 (dd, 6 H, *J* = 7 Hz), 2.05 (m, 1 H), 3.0 (br s, 1 H), 3.76 (s, 3 H), 4.05 (d, 1 H, *J* = 3 Hz); IR (thin film) 3470 (ν(O—H)), 1740 (ν(C=O)) cm^{-1}; MS (CI, isobutane) *m/e* 133 (M + 1).

Compound L-**8e**: 90% yield; $[\alpha]_D$ −4.96 (*c* 5, CH_2Cl_2); NMR ($CDCl_3$) δ 0.92 (d, 6 H, *J* = 7 Hz), 1.55 (t, 2 H, *J* = 6 Hz), 1.8 (m, 1 H), 2.95 (br s, 1 H), 3.73 (s, 3 H, 4.2 (t, 1 H, *J* = 6 Hz); IR (thin film) 3460 (ν(O—H)), (ν(C=O)) 1745 cm^{-1}.

Compound DL-**8f**: 78% yield; NMR ($CDCl_3$) δ 3.0 (m, 3 H), 3.72 (s, 3 H), 4.4 (m, 1 H), 7.27 (s, 5 H); IR (thin film) 3460 (ν(O—H)), 1750 (ν(C=O)) cm^{-1}; MS (CI, isobutane) *m/e* 181 (M + 1), 180 (M^+).

General Procedure for Reaction of α-Hydroxy Acid Esters 8 with Ph_3P–DIAD (Table II). To a solution of 2 mmol of α-hydroxy acid methyl ester **8** and **2** mmol of Ph_3P in 10 mL of THF was added dropwise 4 mmol of DIAD, and the reaction mixture was stirred overnight. The THF was then removed in vacuo, and the oily residue was separated on a silica gel column with Skelly B–EtOAc (9:1) as eluent. The yields and properties of products are given below (all compounds were oils unless noted otherwise).

Compound **8a** gave 30 mg (11%) of **13a**: NMR ($CDCl_3$) δ 1.27 (m, 12 H), 3.83 (s, 3 H), 5.0 (m, 2 H), 6.1 (s, 1 H); IR (film) 1750, 1720 (ν(C=O)) cm^{-1}; MS, *m/e* 274 (M^+).

Compound **8b** gave 130 mg (23%) of **13b**: NMR ($CDCl_3$) δ 1.24 (m, 6 H), 1.34 (d, 6 H, *J* = 6 Hz), 1.87 (s, 3 H), 3.8 (s, 3 H), 4.96 (m, 2 H); IR (film) 1760, 1735 (ν(C=O)), 1670 (ν(C=C)) cm^{-1}; MS, *m/e* 288 (M^+).

Compound **8c** gave 220 mg (36%) of **13c** and 110 mg (18%) of **14c**. **13c**: NMR ($CDCl_3$) δ 1.0 (t, 3 H, *J* = 7 Hz), 1.33 (m, 12 H), 2.3 (q, 2 H, *J* = 7 Hz), 3.84 (s, 3 H), 5.0 (m, 2 H); IR (film) 1760 and 1740 (ν(C=O)), 1675 (ν(C=C)) cm^{-1}; high-resolution mass spectrum for $C_{13}H_{22}N_2O_6$ calcd 302.14781, found 302.148. **14c**: NMR ($CDCl_3$) δ 1.27 (m, 12 H), 2.13 (d, 3 H, *J* = 7 Hz), 3.8 (s, 3 H), 5.0 (m, 2 H), 6.77 (m, 2 H); IR (film) 3340 (ν(N—H)), 1730, 1760 (sh), 1740 (sh) (ν(C=O)), 1650 (sh) (ν(C=C)) cm^{-1}; high-resolution mass spectrum for $C_{13}H_{22}N_2O_6$ calcd 302.147 81, found 302.148.

Compound **8d** gave 40 mg (9%) of **28** and 380 mg (80%) of **13d**. **28**: NMR ($CDCl_3$) δ 1.27 (m, 18 H), 3.03 (m, 1 H), 3.87 (m + s, 4 H), 5.06 (m, 2 H); IR (film) 3340 (ν(N—H)), 1760, 1730, 1695 (ν(C=O)) cm^{-1}; MS, *m/e* 318 (M^+). **13d**: NMR ($CDCl_3$) δ 1.05 (t, 6 H, *J* = 7 Hz), 1.33 (m, 12 H), 2.9 (septet, 1 H, *J* = 7 Hz), 3.8 (s, 3 H), 5.0 (m, 2 H); IR (film) 1760 and 1730 (ν(C=O)) cm^{-1}; MS, *m/e* 316 (M^+).

Compound **8e** gave 200 mg (30%) of **13e** and 200 mg (30%) of **14e**. **13e**: NMR ($CDCl_3$) δ 0.95 (d, 6 H, *J* = 6 Hz), 1.2 (m, 6 H), 1.33 (d, 6 H, *J* = 6 Hz), 1.87 (m, 1 H), 2.18 (dd, 2 H, *J* = 6, 3 Hz), 3.76 (s, 3 H), 5.0 (m, 2 H); IR (film) 1760, 1730 (ν(C=O)), 1670 (ν(C=C)) cm^{-1}; MS, *m/e* 330 (M^+), 271 (M − 59). **14e**: mp 52–54 °C; NMR ($CDCl_3$) δ 1.03 (d, 6 H, *J* = 6 Hz), 1.23 (m, 12 H), 3.04 (m, 1 H), 3.76 (s, 3 H), 4.95 (m, 2 H), 6.4 (d, 1 H, *J* = 9 Hz), 6.84 (br s, 1 H); MS, *m/e* 330 (M^+), 331 (M + 1). Anal. Calcd for $C_{15}H_{26}N_2O_6$: C, 54.54; H, 7.93; N, 8.48. Found: C, 54.39; H, 8.26; N, 8.60.

Compound **8f** gave 60 mg (18%) of **29**, 24 mg (33%) of **13f**, and 300 mg (49%) of **14f**. **29**: NMR ($CDCl_3$) δ 3.27 (d, 2 H, *J* = 6 Hz), 3.17 (s, 3 H), 3.43 (s, 3 H), 5.1 (t, 1 H, *J* = 6 Hz), 6.95 (s, 1 H), 7.3 (s + m, 8 H), 7.7 (m, 2 H); IR (film) 1740 and 1718 (ν(C=O)), 1660 and 1630 (ν(C=C)) cm^{-1}; high-resolution mass spectrum for $C_{20}H_{20}O_5$ calcd 340.1311, found 340.132. **13f**: mp 77–79 °C; NMR ($CDCl_3$) δ 0.97 (d, 3 H, *J* = 6 Hz), 1.27 (m, 9 H), 3.2 (d, 2 H, *J* = 4.5 Hz), 3.83 (s, 3 H), 4.63 (septet, 1 H, *J* = 6 Hz), 5.06 (septet, 1 H, *J* = 6 Hz), 7.27 (s, 5 H); IR (film) 1760 and 1740 (ν(C=O)), 1680 (ν(C=C)) cm^{-1}; MS, *m/e* 364 (M^+), 365 (M + 1). Anal. Calcd for $C_{18}H_{24}N_2O_6$: C, 59.34; H, 6.59; N, 7.69. Found: C, 59.12; H, 6.76; N, 7.49. **14f**: NMR ($CDCl_3$) δ 1.23 (m, 12 H), 3.63 (s, 3 H), 5.0 (m, 2 H), 7.2 (s, 1 H), 7.33 (2 s, 5 H); MS *m/e* 365 (M + 1), 364 (M^+); IR (film) 3330 (ν(N—H)), 1750 and 1710 (ν(C=O)) cm^{-1}.

General Procedure for Reaction of α-Hydroxy Acid Methyl Esters 8a–f with CbzNHOBzl or trOCNHOBzl in the Presence of Ph_3P–DIAD (Table I). To a solution of 1 mmol of α-hydroxy acid methyl ester, 1 mmol of trOCNHOBzl or CbzNHOBzl, and 1.5 mmol of Ph_3P in 10 mL of THF was added dropwise 1.5 mmol of DIAD, and the reaction mixture was left overnight. After the THF was evaporated in vacuo, the residue was separated on a silica gel column with Skelly B–EtOAc (9:1) as eluent. The yield and properties of products are given below (all products were oils unless indicated otherwise).

Reaction of 2.5 mmol of **8a** and 2.5 mmol of **11** gave 280 mg (30%) of **12a**, 180 mg (23%) of **15**, and 40 mg (22%) of **16**. **12a**: NMR ($CDCl_3$) δ 3.7 (s, 3 H), 4.17 (s, 2 H), 4.84 (s, 2 H), 5.0 (s, 2 H), 7.40 (s, 5 H); IR (film) 1760 and 1730 (ν(C=O)) cm^{-1}; MS, *m/e* 371 (M^+). **15**: NMR ($CDCl_3$) δ 3.1 (s, 3 H), 4.8 (s, 2 H), 4.9 (s, 2 H), 7.37 (s, 5 H); IR (film) 1720, 1740 (sh) (ν(C=O)) cm^{-1}. **16**: NMR ($CDCl_3$) δ 3.8 (s + m, 4 H), 4.03 (d, 2 H, *J* = 6 Hz), 4.73 (s, 2 H); IR (film) 3350 (ν(O—H)), 1760, 1740, 1720 (ν(C=O)) cm^{-1}; high-resolution mass spectrum for $C_5H_8O_5$ calcd 148.0372, found 148.05.

Reaction of 5 mmol of **8a** and 5 mmol of CbzNHOBzl (**17**) gave 960 mg of a single unidentified product [NMR ($CDCl_3$) δ 3.66 (s, 3 H), 4.1 (s, 2 H), 4.85 (s, 2 H), 4.9 (s, 2 H), 5.16 (s, 2 H), 5.23 (s, 2 H), 7.4 (s, 10 H), 7.5 (s, 1 H); IR (film) 3350 (ν(N—H)), 1750,

1720, and 1710 (ν(C=O)) cm^{-1}; MS, m/e 587, 586, 330. Anal. Found: C, 67.73; H, 5.76; N, 5.11] and 150 mg (22%) of CbzN(CH$_3$)OCH$_2$Ph [NMR (CDCl$_3$) δ 3.17 (s, 3 H), 4.94 (s, 2 H), 5.29 (s, 2 H), 7.5 (m, 10 H)].

Reaction of 2 mmol of **8b** and 2 mmol of **11** gave 60 mg (10%) of **15**, 630 mg (82%) of **12b**, and 50 mg (9%) of **13**. **15**: NMR (CDCl$_3$) δ 3.1 (s, 3 H), 4.76 (s, 2 H), 4.9 (s, 2 H), 7.37 (s, 5 H); high-resolution mass spectrum for $C_{11}H_{12}NO_3Cl_3$ calcd 310.988 28, found 310.989. **12b**: NMR (CDCl$_3$) δ 1.76 (d, 3 H, J = 7 Hz), 3.7 (s, 3 H), 4.8 (m, 1 H), 4.9 (d, 2 H), 5.04 (d, 2 H), 7.4 (m, 5 H); IR (film) 1750, 1720 and 1670 (ν(C=O)) cm^{-1}; MS, m/e 385 (M$^+$), 278 (M - 107). Anal. Calcd for $C_{14}H_{16}NO_5Cl_3$: C, 43.69; H, 4.16; N, 3.64. Found: C, 43.54; H. 4.34; N, 3.83. **13b**: NMR (CDCl$_3$) δ 1.73 (m, 12 H), 1.94 (s, 3 H), 3.87 (s, 3 H), 5.04 (m, 2 H); IR (film) 1760 and 1740 (ν(C=O)), 1670 (ν(C=C)) cm^{-1}.

Reaction of 2 mmol of **8b** and 2 mmol of **17** gave 325 mg (47%) of **18b**, 90 mg (16%) of **13b**, and 270 mg (52%) of unreacted CbzNHOBzl. **18b**: NMR (CDCl$_3$) δ 1.76 (d, 3 H, J = 7 Hz), 3.6 (s, 3 H), 4.7 (q, 1 H, J = 7 Hz), 4.9 (d, 2 H), 5.23 (s, 2 H), 7.32 (s, 5 H), 7.4 (s, 5 H); IR (film) 1745 and 1715, 1680 (sh) (ν(C=O)) cm^{-1}; MS, m/e 343 (M$^+$), 208 (M - 135). **13b**: NMR (CDCl$_3$) δ 1.33 (m, 12 H), 1.9 (s, 3 H), 3.8 (s, 3 H), 5.0 (m, 2 H); IR (in Nujol) 1760, 1730, 1680 cm^{-1}; MS, m/e 288 (M$^+$).

Reaction of 1.5 mmol of **8c** and 1.5 mmol of **11** gave 350 mg (59%) of **12c** and 40 mg (9%) of **13c**. **12c**: NMR (CDCl$_3$) δ 1.0 (t, 3 H, J = 7 Hz), 2.03 (m, 2 H), 3.7 (s, 3 H), 4.56 (m, 1 H), 4.87 (s, 2 H), 5.03 (d, 2 H, J = 4.5 Hz), 7.36 (m, 5 H); IR (film) 1750 and 1720 (ν(C=O)) cm^{-1}; MS, m/e 399 (M$^+$). Anal. Calcd for $C_{15}H_{18}NO_5Cl_3$: C, 45.17; H, 4.52; N, 3.51. Found: C, 44.91; H, 4.67; N, 3.63. **13c**: NMR (CDCl$_3$) δ 1.0 (t, 3 H, J = 7 Hz), 1.33 (m, 12 H), 2.3 (q, 2 H, J = 7 Hz), 3.85 (s, 3 H), 5.0 (m, 2 H); IR (film) 1740, 1760 (sh) (ν(C=O)), 1675 (ν(C=C)) cm^{-1}.

Reaction of 2 mmol of **8d** and 2 mmol of **11** gave 170 mg (20%) of **12d** and 300 mg (48%) of **13d**. **12d**: $[\alpha]_D$ +17.0 (c 2.5, CH$_2$Cl$_2$); NMR (CDCl$_3$) δ 0.95 (dd, 6 H, J = 7, 1.5 Hz), 2.45 (m, 1 H), 3.72 (s, 3 H), 4.38 (d, 1 H, J = 7 Hz), 4.8 (s, 2 H), 5.0 (s, 2 H), 7.33 (m, 5 H); IR (film) 1745 and 1720 (ν(C=O)) cm^{-1}; MS, m/e 413 (M$^+$). **13d**: NMR (CDCl$_3$) δ 1.05 (t, 6 H, J = 7 Hz), 1.3 (m, 12 H), 2.9 (septet, 1 H, J = 7 Hz), 3.8 (s, 3 H), 5.0 (m, 2 H); IR (film) 1760 and 1730 (ν(C=O)), 1670 (ν(C=C)) cm^{-1}; MS, m/e 317 (M + 1), 316 (M$^+$), 274 (M - 42).

Reaction of 1.5 mmol of **8e** and 1.5 mmol of **11** gave 320 mg (50%) of **12e**, 50 mg (10%) of **14e**, 70 mg (14%) of **13e**, and 150 mg (30%) of recovered trOCNHOBzl. **12e**: $[\alpha]_D$ +15.2 (c 5, CH$_2$Cl$_2$); NMR (CDCl$_3$) δ 0.95 (d, 6 H, J = 7 Hz), 1.14 (m, 3 H), 3.70 (s, 3 H), 4.83 (m + s, 3 H), 5.0 (d, 2 H), 7.36 (m, 5 H); IR (film) 1750 and 1720 (ν(C=O)) cm^{-1}; high-resolution mass spectrum for $C_{17}H_{22}NO_5Cl_3$ calcd 425.056 37, found 425.056. **13e**: NMR (CDCl$_3$) δ 0.93 (d, 6 H, J = 6 Hz), 1.25 (m, 6 H), 1.33 (d, 6 H, J = 6 Hz), 1.87 (m, 1 H), 2.2 (dd, 2 H, J = 6, 3 Hz), 3.8 (s, 3 H), 5.0 (m, 2 H); IR (film) 1760 and 1730 (ν(C=O)), 1670 (ν(C=C)) cm^{-1}; MS, m/e 330 (M$^+$). **14e**: mp 52–53 °C; NMR (CDCl$_3$) δ 1.0 (d, 6 H, J = 6 Hz), 1.3 (m, 12 H), 3.33 (m, 1 H), 3.75 (s, 3 H), 5.0 (m, 2 H), 6.4 (br d, 1 H), 6.75 (br s, 1 H); IR (film) 3300 (ν(N—H)), 1750 and 1730 (ν(C=O)), 1650 (ν(C=C)) cm^{-1}; high-resolution mass spectrum for $C_{15}H_{26}N_2O_6$ calcd 330.179 11, found 330.180.

The reaction of 2 mmol of **8f** and 2 mmol of trOCNHOBzl (**11**) gave 400 mg (43%) of **12f**, 150 mg (20%) of **13f**, and 80 mg (11%) of **14f**. **12f**: NMR (CDCl$_3$) δ 3.27 (d, 1 H, J = 5 Hz), 3.36 (s, 1 H), 3.7 (s, 3 H), 4.7 (s, 2 H), 4.83 (s, 2 H), 4.97 (m, 1 H), 7.27 (s, 5 H), 7.33 (s, 5 H); IR (film) 1750 and 1720 (ν(C=O)) cm^{-1}; MS, m/e 461 (M$^+$). **13f**: mp 76–80 °C, NMR (CDCl$_3$) δ 0.97 (d, 3 H, J = 6 Hz), 1.24 (m, 9 H), 3.17 (d, 2 H, J = 4.5 Hz) 3.82 (s, 3 H), 4.63 (septet, 1 H, J = 6 Hz), 5.05 (septet, 1 H, J = 6 Hz), 7.27 (s, 5 H); IR (in Nujol) 1760, 1730 (ν(C=O)), 1670 (ν(C=C)) cm^{-1}. **14f**: NMR (CDCl$_3$) δ 1.26 (m, 12 H), 3.66 (s, 3 H), 5.0 (m, 2 H), 6.9 (br s, 1 H), 7.3 (s, 1 H), 7.33 (s, 5 H); high-resolution mass spectrum for $C_{18}H_{24}N_2O_6$ calcd 364.163 46, found 364.164.

***N*-Carbobenzoxy-*O*-benzylhydroxylamine (17).** To a solution of 6.15 g (50 mmol) of *O*-benzylhydroxylamine and 8.4 g (100 mmol) of NaHCO$_3$ in water–THF (1:1) was added dropwise 10.2 g (60 mmol) of carbobenzoxy chloride, and the reaction mixture was stirred at room temperature overnight. Then, THF was removed in vacuo, and the water layer was extracted with ethyl ether, washed with 10% citric acid and water, and dried over MgSO$_4$. Ethyl ether was evaporated in vacuo, and solid residue was crystallized from ethyl acetate–Skelly B to provide 12.0 g (97%) of **17**: mp 54–56 °C; NMR (CDCl$_3$) δ 4.8 (s, 2 H), 5.13 (s, 2 H), 7.36 (s, 10 H), 7.56 (s, 1 H); MS (CI, isobutane) m/e 258 (M + 1).

***N*-[(Trichloroethoxy)carbonyl]-*O*-benzylhydroxylamine (11).** The procedure was the same as that used for the preparation of **17**, but with (trichloroethoxy)carbonyl chloride as the acylating agent. Product was purified on a silica gel column with Skelly B–ethyl acetate (9:1) as the eluent. The product was obtained as an oil: 83% yield, 10 g; NMR (CDCl$_3$) δ 4.76 (s, 2 H), 4.87 (s, 2 H), 7.4 (s, 5 H), 7.9 (s, 1 H); MS, m/e 300, 298, 264, 262.

***N*-Carbobenzoxy-*N*-methyl-*O*-benzylhydroxylamine.** To a solution of 1.95 g (7.6 mmol) of **17** and 0.7 g (5 mmol) of anhydrous K$_2$CO$_3$ was added 1.25 mL (20 mmol) of methyl iodide, and the reaction mixture was refluxed for 10 h. The product was chromatographed on a silica gel column with Skelly B–ethyl acetate (9:1) as eluent to provide 1.62 g (78%) of product as an oil: NMR (CDCl$_3$) δ 3.16 (s, 3 H), 4.94 (s, 2 H), 5.3 (s, 2 H), 7.5 (s, 10 H).

Mandelic Acid Methyl Ester (31). To a solution of 4.56 g (30 mmol) of mandelic acid and 3.36 g (40 mmol) of NaHCO$_3$ in 25 mL of DMF was added dropwise 3.73 mL (60 mmol) of methyl iodide, and the mixture was stirred for 24 h at room temperature. Subsequently, 100 mL of water was added, and the product was extracted with ethyl ether. The ether layer was washed with water, dried over anhydrous MgSO$_4$, and evaporated in vacuo to give 4.21 g (85%) of product: mp 47–48 °C (after crystallization from ethyl acetate–Skelly B), (lit.[8] mp 55 °C); NMR (CDCl$_3$) δ 3.6 (d, 1 H, J = 6 Hz), 3.72 (s, 3 H), 5.15 (d, 1 H, J = 6 Hz), 7.4 (m, 5 H).

Phenylglyoxylic Acid Methyl Ester (33). To a stirred solution of 0.83 g (5 mmol) of mandelic acid methyl ester (**31**) and 1.31 g (5 mmol) of Ph$_3$P in 10 mL of THF was added dropwise 1.66 mL (10 mmol) of diethyl azodicarboxylate (DEAD) or 2 mL (10 mmol) of diisopropyl azodicarboxylate (DIAD), and the reaction mixture was left overnight. The THF then was evaporated in vacuo, and the oily residue was separated on a silica gel column with Skelly B–ethyl acetate (9:1) as eluent to provide 0.8 g (97%) of **33**: IR (film) 1740 (ν(C=O)), 1695 (ν(C=O)) cm^{-1} (lit.[12] 1735, 1680 cm^{-1}); NMR (CDCl$_3$) δ 4.0 (s, 3 H), 7.57 (m, 3 H), 8.04 (m, 2 H) [lit.[12] δ 3.83 (s, 3 H), 7.25–7.70 (m, 5 H)]; MS, m/e 164 (M$^+$), 149 (M - 15), 105 (M - 59).

***O*-Acetyl-(*p*-methoxyphenyl)glycolic Acid Methyl Ester.** To a solution of (*p*-methoxyphenyl)bromoacetic acid methyl ester (**41**,[11] 5.18 g, 20 mmol) in 60 mL of DMF–H$_2$O (2:1) was added 1.64 g (20 mmol) of sodium acetate, and the mixture was refluxed 1 h at 100 °C. Subsequently, 100 mL of water was added, and the product was extracted with Et$_2$O and dried over anhydrous MgSO$_4$ to give 2.5 g (52%) of product as an oil: NMR (CDCl$_3$) δ 2.16 (s, 3 H), 3.7 (s, 3 H), 3.8 (s, 3 H), 5.9 (s, 1 H), 6.9 (d, 2 H, J = 7 Hz), 7.4 (d, 2 H, J = 7 Hz). Anal. Calcd for $C_{12}H_{14}O_5$: C, 60.50; H, 5.88. Found: C, 60.27; H, 5.95.

(*p*-Methoxyphenyl)glycolic Acid Methyl Ester (42). A solution of 1.9 g (8 mmol) of *O*-acetyl-(*p*-methoxyphenyl)glycolic acid methyl ester in 50 mL of MeOH was saturated with HCl and kept 24 h at room temperature. The methanol was then removed in vacuo to give 1.5 g (96%) of **42**: mp 32–34 °C; NMR (CDCl$_3$) δ 3.6 (br s, 1 H), 3.7 (s, 3 H), 3.74 (s, 3 H), 5.1 (s, 1 H), 6.87 (d, 2 H, J = 7 Hz), 7.33 (d, 2 H, J = 7 Hz); high-resolution mass spectrum for $C_{10}H_{12}O_4$ calcd 196.073 58, found 196.074.

***N*-Hydroxysuccinimide Ester of Mandelic Acid.** To a solution of 6.08 g (40 mmol) of mandelic acid and 4.6 g (40 mmol) of *N*-hydroxysuccinimide in 100 mL of ethyl acetate was added dropwise 8.24 g (40 mmol) of DCC in 50 mL of ethyl acetate. The reaction mixture was stirred 6 h at room temperature, dicyclohexylurea was filtered off, the residue was washed with ethyl acetate, and the filtrate was evaporated to dryness. After crystallization from ethyl acetate–Skelly B, 8.8 g (88%) (mp 84–6 °C) of product was obtained: NMR (CDCl$_3$) δ 2.78 (m, 4 H), 4.84 (m, 2 H), 7.46 (m, 5 H).

***N*-Benzylamide of Mandelic Acid (44).** To a solution of benzylamine (1.2 mL, 11 mmol) and 0.84 g (10 mmol) of NaHCO$_3$

(12) Gordon, E. M.; Pluscec, J. *J. Org. Chem.* **1979**, *44*, 1218–1221.

in THF–H_2O (1:1) was added 2.49 g (10 mmol) of the *N*-hydroxysuccinimide ester of mandelic acid in 20 mL of THF, and the reaction mixture was stirred overnight. After the THF was removed in vacuo, the product was filtered off and crystallized from ethyl acetate–Skelly B to provide 2.0 g (83%) of **44**: mp 85–86 °C; NMR ($CDCl_3$) δ 4.0 (br s, 1 H), 4.33 (d, 2 H, J = 6 Hz), 4.97 (s, 1 H), 6.8 (br s, 1 H), 7.27 (m, 5 H), 7.33 (s, 5 H). Anal. Calcd for $C_{15}H_{15}NO_2$: C, 74.69; H, 6.22; N, 5.81. Found: C, 74.75; H, 6.21; N, 5.87.

***N,N*-Dimethylamide of Mandelic Acid (47).** To a solution of 2 g (8 mmol) of the *N*-hydroxysuccinimide ester of mandelic acid in H_2O–THF (1:1) was added 4 mL (20 mmol) of a 25% solution of $(CH_3)_2NH$ in H_2O, and the reaction mixture was stirred 6 h at room temperature. After the THF was removed in vacuo, the precipitated product was filtered off and crystallized from ethyl acetate–Skelly B to give 0.9 g (64%) of **47**: mp 141–143 °C (lit.[10] mp 158 °C); NMR ($CDCl_3$) δ 2.76 (s, 3 H), 3.0 (s, 3 H), 4.76 (br s, 1 H), 5.2 (br s, 1 H), 7.37 (s, 5 H). Anal. Calcd for $C_{10}H_{13}NO_2$: C, 67.04; H, 7.26; N, 7.82. Found: C, 67.12; H, 7.32; N, 7.83.

Benzoin Oxime (49). To a solution of 2.12 g (10 mmol) of benzoin and 0.7 g (10 mmol) of hydroxylamine hydrochloride in THF–H_2O (2:1) was added 0.82 g (10 mmol) of sodium acetate, and the mixture was stirred overnight. The THF was removed in vacuo, and product was filtered from the aqueous solution. Then, the product was dissolved in ethyl ether and cooled to 0 °C to precipitate 1.2 g (66%) of *anti*-oxime, mp 147–148 °C (after crystallization from benzene) (lit.[9] mp 151–152 °C). The ethereal solution was concentrated and cooled again to precipitate 1 g (26%) of *syn*-oxime, mp 96–98 °C (after crystallization from ethyl acetate–Skelly B) (lit.[9] mp 99 °C).

***O*-Benzyloxime of Benzoin (53).** To a solution of 2.12 g (10 mmol) of benzoin and 1.6 g (10 mmol) of *O*-benzylhydroxylamine hydrochloride in THF–H_2O (2:1) was added 0.82 g (10 mmol) of sodium acetate, and the reaction mixture was stirred overnight. After the THF was evaporated, the product was extracted with ethyl acetate, dried over anhydrous $MgSO_4$, filtered, and evaporated to give 1.7 g (53%) of **53** as a mixture of *Z* and *E* isomers. Separation of the isomers on a silica gel column using methylene chloride–ethyl acetate (9:1) as eluent gave 0.77 g (45%) of the syn (*Z*) and 0.93 g (55%) of the anti (*E*) isomers. (*Z*)-oxime: NMR ($CDCl_3$) δ 3.94 (d, 1 H, J = 6 Hz), 5.2 (s, 2 H), 5.53 (d, 1 H, J = 6 Hz), 7.3 (m, 15 H). (*E*)-oxime: NMR ($CDCl_3$) δ 3.62 (d, 1 H, J = 9 Hz), 5.2 (s, 2 H), 6.17 (d, 1 H, J = 9 Hz), 7.4 (m, 13 H), 7.56 (m, 2 H).

Ethylene Ketal of Benzoin (56). A solution of 4.24 g (20 mmol) of benzoin, 95 mg (0.5 mmol) of *p*-toluenesulfonic acid monohydrate, and 1.4 mL (25 mmol) of ethylene glycol in benzene was refluxed under a Dean–Stark trap until reaction of benzoin was complete. After the benzene was evaporated, the solid product was washed with water, 3% aqueous $NaHCO_3$ and water and crystallized from benzene: 4.5 g, 97%; mp 129–130 °C; NMR ($CDCl_3$) δ 2.92 (d, 1 H, J = 3 Hz), 3.93 (m, 2 H), 4.1 (m, 2 H), 4.96 (d, 1 H, J = 3 Hz), 7.3 (m, 10 H).

Ethylene Ketal of Benzil (57). A solution of 512 mg (2 mmol) of benzoin ethylene ketal **56** and 356 mg (2 mmol) of NBS was refluxed in CCl_4 for 15 h and then evaporated in vacuo. The residue was separated on a silica gel column to give 480 mg (94%) of **57**: mp 55–56 °C; IR (film) 1690, 1595 cm^{-1}; NMR ($CDCl_3$) δ 4.12 (br s, 4 H), 7.36 (m, 5 H), 7.45 (m, 3 H), 8.02 (m, 2 H); MS, m/e 254 (M^+), 238, 166.

Atrolactic acid methyl ester (62) was prepared in 81% yield by the method described for preparation of mandelic acid methyl ester (**31**). **62**: NMR ($CDCl_3$) δ 1.8 (s, 3 H), 3.76 (s, 3 H), 3.9 (s, 1 H), 7.37 (m, 3 H), 7.57 (m, 2 H); MS, (CI, isobutane) m/e 181 (M + 1), 180 (M^+).

Reactions of the α-Phenylcarbinols with Ph_3P–Azodicarboxylates (DEAD or DIAD). Generally, the alcohol (1–5 mmol) and Ph_3P (100 mol %) were dissolved in 10 mL of THF, and 200 mol % of either diethyl azodicarboxylate (DEAD) or diisopropyl azodicarboxylate (DIAD) was added at room temperature. The mixture was allowed to stir overnight and then evaporated to give an oily residue. Chromatography on silica gel with hexanes and ethyl acetate provided the products shown in the tables.

Reaction of benzoin (34, 5 mmol) with Ph_3P–DEAD provided 200 mg (20%) of dibenzoyl (benzil) (**35**), 250 mg (23%) of unreacted benzoin (**34**), and 800 mg (43%) of the benzoin adduct with DEAD (**36**). **35**: mp 91–93 °C (lit.[13] mp 95 °C); NMR ($CDCl_3$) δ 7.6 (m, 6 H), 8.06 (m, 4 H); IR (film) 1670, 1680 (ν(C=O)) cm^{-1}. **36**: mp 114–116 °C (after crystallization from ethyl acetate–Skelly B); IR (film) 1795, 1760 (ν(C=O)), 1680 (ν(C=C)) cm^{-1}; NMR ($CDCl_3$) δ 1.27 (t, 6 H, J = 6 Hz), 4.2 (q, 4 H, J = 6 Hz), 7.54 (m, 6 H), 7.94 (m, 4 H); MS, m/e 368 (M^+), 296 (M − 72), 293, 192. Anal. Calcd for $C_{20}H_{20}N_2O_5$: C, 65.22; H, 5.43; N, 7.61. Found: C, 65.22; H, 5.45; N, 7.56.

Reaction of benzoin (34, 5 mmol) with Ph_3P–DIAD provided 225 mg (21%) of dibenzoyl (**35**, mp 90–92 °C), 330 mg (31%) of benzoin (**34**), and 900 mg (45%) of the benzoin adduct with DIAD (**36**). **36**: mp 79–81 °C (after crystallization from ethyl acetate–Skelly B); IR (film) 1796, 1760 (ν(C=O)), 1680 (ν(C=C)) cm^{-1}; NMR ($CDCl_3$) δ 1.27 (d, 12 H, J = 7 Hz), 5.0 (m, 2 H, J = 7 Hz), 7.60 (m, 6 H), 7.94 (m, 4 H); MS, m/e 396 (M^+). Anal. Calcd for $C_{22}H_{24}N_2O_5$: C, 66.67; H, 6.06; N, 7.07. Found: C, 66.45; H, 6.07; N, 7.01.

Reaction of 1-phenylethanol (38, 2 mmol) with Ph_3P–DIAD gave 220 mg (35%) of *N*-(1-phenylethyl)hydrazine dicarboxylic acid diisopropyl ester **39** and 160 mg (65%) of unreacted substrate. **39**: IR (film) 3350 (ν(N—H)), 1760, 1730 (ν(C=O)) cm^{-1}; NMR ($CDCl_3$) δ 1.23 (d, 12 H, J = 6 Hz), 1.55 (d, 3 H, J = 7 Hz), 5.0 (septet, 2 H, J = 6 Hz), 5.5 (q, 1 H, J = 7 Hz), 6.16 (br s, 1 H), 7.36 (s, 5 H); MS, m/e 308 (M^+), 264, 222.

Reaction of (*p*-methoxyphenyl)glycolic acid methyl ester (42, 1 mmol) with Ph_3P–DIAD gave 100 mg (51%) of **43**: mp 38–40 °C; IR (in Nujol) 1740, 1680 (ν(C=O)) cm^{-1}; NMR ($CDCl_3$) δ 3.87 (s, 3 H), 3.97 (s, 3 H), 7.0 (d, 2 H, J = 9 Hz), 8.04 (d, 2 H, J = 9 Hz); high-resolution mass spectrum for $C_{10}H_{10}O_4$ calcd 194.057 93, found 194.058.

Reaction of the *N*-benzylamide of mandelic acid (44, 2 mmol) with Ph_3P–DIAD gave 170 mg (35%) of the *N*-benzylamide of phenylglyoxylic acid (**45**; mp 71–73 °C), 200 mg (42%) of unreacted amide **44**, and 30 mg (6%) of adduct **46**. **45**: IR (in Nujol) 3300 (ν(N—H)), 1680, 1670, 1600 (ν(C=O)) cm^{-1}; NMR ($CDCl_3$) δ 4.5 (d, 2 H, J = 6 Hz), 7.27 (s, 5 H), 7.35 (m, 4 H), 8.33 (m, 2 H); high-resolution mass spectrum for $C_{15}H_{13}NO_2$ calcd 239.094 63, found 239.095. **46**: IR (film) 1750, 1730 (ν(C=O)), 1650 (ν(C=N)) cm^{-1}; NMR ($CDCl_3$) δ 1.27 (m, 12 H), 4.9 (q, 2 H, J = 14 Hz) 5.0 (septet, 2 H, J = 6 Hz), 6.1 (s, 1 H), 7.23 (s, 5 H), 7.35 (s, 5 H); MS, m/e 409 (M^+), 367 (M − 42). Anal. Calcd for $C_{23}H_{27}N_3O_4$: N, 9.97; Found: N, 10.27.

Reaction of *N,N*-dimethylamide of mandelic acid (47, 1 mmol) with Ph_3P–DIAD gave 80 mg (45%) of **48**: IR (film) 1670, 1645 (ν(C=O)) cm^{-1}; NMR ($CDCl_3$) δ 3.0 (s, 3 H), 3.14 (s, 3 H), 7.65 (m, 3 H), 8.03 (dd, 2 H); MS, m/e 178, 177 (M^+), 149. Anal. Calcd for $C_{10}H_{11}NO_2$: M, 7.91. Found: N, 7.83.

Reaction of Benzoin Oxime (49; 2 mmol, Syn or Anti Isomers) with Ph_3–DEAD. In the case of the anti isomer, 150 mg (71%) of benzaldehyde (**51**) was isolated as well as 50 mg (11%) of the *anti*-monooxime of benzoin (**50**) as a complex with $^1/_2$ C_6H_6. **50**: crystallization from benzene–Skelly B, mp 70–72 °C (lit.[14] mp 70 °C); IR (film) 3300 (ν(OH)), 1670, 1690 (sh) (ν(C=O)) cm^{-1}; MS, m/e 225 (M^+). The syn isomer gave about 105 mg (50%) of benzaldehyde (**51**) and many unidentified products.

Reaction of the *O*-benzyloxime of benzoin (53, 2 mmol, mixture of syn and anti isomers) with Ph_3P–DEAD gave 120 mg (20%) of the mono-O-benzyloxime of benzil **54**, mp 62–5 °C, 30 mg (5%) of the anti-isomer, 110 mg (18%) of the syn-isomer, and 470 mg (50%) of an adduct with DEAD (**55**, R′ = Et). **54**: IR (film) 1670 (ν(C=O)), 1730 (ν(C=N—O)) cm^{-1}; NMR ($CDCl_3$) δ 5.13 and 5.23 (two s, 2:1, 2 H), 7.43 (m, 13 H), 8.03 (m, 2 H); MS, m/e 315 (M^+). **55**: mp 90–92 °C as a complex with $^1/_2$ C_6H_6 (after crystallization from benzene–Skelly B); IR (film) 3520 (ν(OH)) 3420 (ν(NH)), 1760 (ν(C=O)), 1710 (ν(C=N)) cm^{-1}; NMR ($CDCl_3$) δ 1.05 (m, 3 H), 1.27 (t, 3 H, J = 7 Hz), 3.87 (m, 2 H), 4.23 (q, 2 H, J = 7 Hz), 5.1 (s, 2 H), 6.1 (br d, 1 H, J = 9 Hz), 6.33 (br s, 1 H), 7.3 (m, 18 H); MS, m/e 530 (M^+), 514, 474. Anal.

(13) Reference 9, p 333.
(14) Reference 9, p 235.

Calcd for $C_{27}H_{29}N_3O_6 \cdot {}^1/_2C_6H_6$: C, 67.92; H, 6.04; N, 7.92. Found: C, 67.69; H, 5.88; N, 7.79.

Reaction of the *O*-benzyloxime of benzoin (53, 2.5 mmol, syn and anti isomers) with Ph_3P–DIAD gave 300 mg (38%) of the mono-*O*-benzyloxime of benzil (**54**, mp 59–62 °C), 300 mg (37%) of *syn*-*O*-benzyloxime, and 250 mg (20%) of the adduct with DIAD (**55**, R′ = Pr). **55**: IR (film) 3550 (ν(O—H)), 3420 (ν(N—H)), 1760 (ν(C=O)), 1710 (ν(C=N)) cm^{-1}; NMR ($CDCl_3$) δ 1.0 (m, 6 H), 1.23 (d, 6 H, J = 6 Hz), 4.6 (m, 1 H), 5.0 (septet, 1 H, J = 6 Hz), 5.43 (s, 2 H), 6.4 (br s, 1 H), 6.66 (br d, 1 H, J = 9 Hz), 7.33 (m, 15 H); MS, m/e 558 (M^+), 503, 504, 376.

Reaction of the ethylene ketal of benzoin (56, 2 mmol) with Ph_3P–DIAD gave 170 mg (13%) of **58**, 120 mg (24%) of **57**, and 200 mg (38%) of unreacted substrate **21**. **58**: IR (film) 1750 (ν(C=O)) cm^{-1}; NMR ($CDCl_3$) δ 1.17 (d, 12 H, J = 6 Hz), 3.86 (m, 8 H), 4.78 (septet, 2 H, J = 6 Hz), 5.87 (s, 2 H), 7.23 (m, 10 H). **57**: IR (film) 1690 (ν(C=O)) cm^{-1}; NMR ($CDCl_3$) δ 4.22 (br s, 4 H), 7.37 (m, 5 H), 7.6 (m, 3 H), 8.08 (m, 2 H); MS, m/e 254 (M^+).

Reaction of mandelonitrile (59, 5 mmol) with Ph_3P–DEAD provided 400 mg (67%) of **61**: IR (film) 2240 (ν(C≡N)), 1730 (ν(C=O)) cm^{-1}; NMR ($CDCl_3$) δ 6.66 (s, 1 H), 7.45 (m, 8 H), 8.07 (m, 2 H); MS, m/e 238 (M + 1), 237 (M^+). Anal. Calcd for $C_{15}H_{11}NO_2$: C, 75.95; H, 4.64; N, 5.90. Found: C, 76.17; H, 4.68; N, 6.13. A small amount of another unidentified product was also obtained: IR (film) 2240 (ν(C≡N)), 1760, 1725 (ν(C=O)) cm^{-1}; NMR ($CDCl_3$) δ 1.33 (dt, 6 H, J = 7, 3 Hz), 4.2 (2 t, 4 H, J = 7 Hz), 7.5 (m, 3 H), 7.98 (m, 2 H); MS, m/e 345 (M + 1), 344 (M^+), 245.

Reaction of atrolactic acid methyl ester (62, 2 mmol) with Ph_3P–DIAD gave 40 mg (4%) of **64**, 60 mg (8%) of **63**, and 280 mg (78%) of unreacted substrate. **64**: IR (film) 1740 (ν(C=O)) 1760 (sh) cm^{-1}; NMR ($CDCl_3$) δ 1.27 (d, 12 H, J = 6 Hz), 1.95 (s, 3 H), 3.66 (s, 3 H), 4.9 (septet, 2 H, J = 6 Hz), 7.43 (m, 10 H). **63**: IR (film) 3530 (ν(N—H)), 1760, 1730 (ν(C=O)) cm^{-1}; NMR ($CDCl_3$) δ 1.27 (d, 12 H, J = 6 Hz), 1.76 (s, 3 H), 3.76 (s, 3 H), 5.1 (septet, 2 H, J = 6 Hz), 7.33 (m, 3 H), 7.56 (m, 2 H).

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Registry No. 1 (R = Et), 1972-28-7; 1 (R = *i*-Pr), 2446-83-5; 2, 603-35-0; D-**7b**, 18668-00-3; DL-**7c**, 37819-25-3; L-**7d**, 18667-97-5; L-**7e**, 3069-50-9; DL-**7f**, 69056-25-3; **8a**, 96-35-5; DL-**8b**, 2155-30-8; D-**8b**, 17392-83-5; DL-**8c**, 108740-81-4; L-**8d**, 24347-63-5; L-**8e**, 17392-84-6; DL-**8f**, 21632-25-7; **11**, 90195-00-9; **12a**, 110271-68-6; **12b**, 110271-69-7; **12c**, 110271-70-0; **12d**, 110271-71-1; **12e**, 110271-72-2; **12f**, 110271-73-3; **13a**, 110271-74-4; **13b**, 110271-75-5; **13c**, 110271-76-6; **13d**, 110271-77-7; **13e**, 110271-78-8; **13f**, 110271-79-9; **14b**, 110271-80-2; **14c**, 110271-81-3; **14e**, 110271-82-4; **14f**, 110271-83-5; **15**, 110271-84-6; **16**, 110271-85-7; **17**, 15255-86-4; **18b**, 110271-86-8; **28** (R = R′ = *i*-Pr), 110271-87-9; **28** (R = H, R′ = *i*-Pr), 110272-03-2; **29**, 110271-88-0; **31**, 771-90-4; **33**, 15206-55-0; **34**, 119-53-9; **35**, 134-81-6; **36** (R′ = Et), 110271-89-1; **36** (R′ = *i*-Pr), 110271-90-4; **37** (R′ = Et), 110271-91-5; **37** (R′ = *i*-Pr), 110271-92-6; **38**, 98-85-1; **39** (R′ = *i*-Pr), 110271-93-7; **41**, 50612-99-2; **42**, 13305-14-1; **43**, 32766-61-3; **44**, 4410-32-6; **45**, 28193-70-6; **46**, 110271-94-8; **47**, 2019-71-8; **48**, 51579-87-4; *anti*-**49**, 574-13-0; *syn*-**49**, 7110-50-1; *anti*-**50**, 574-15-2; **51**, 100-52-7; **52**, 100-47-0; *anti*-**53**, 110271-95-9; *syn*-**53**, 110271-96-0; **54**, 5344-75-2; **55** (R′ = Et), 110271-97-1; **55** (R′ = *i*-Pr), 110271-98-2; **56**, 5694-69-9; **57**, 6252-00-2; **58** (R = *i*-Pr), 110271-99-3; **59**, 532-28-5; **61**, 4242-46-0; **62**, 20731-95-7; **63** (R′ = *i*-Pr), 110272-00-9; **64** (R′ = *i*-Pr), 110272-01-0; H-D-Ala-OH, 338-69-2; H-L-Val-OH, 72-18-4; H-L-Leu-OH, 61-90-5; H-DL-Phe-OH, 150-30-1; H_2NOCH_2Ph, 622-33-3; CbzCl, 501-53-1; Cl_3CCH_2OCOCl, 17341-93-4; CbzN(Me)OCH_2Ph, 110272-02-1; $PhCH(OH)COOH$, 90-64-2; *p*-$MeOC_6H_4CH(OAc)COOMe$, 55538-79-9; $PhCH_2NH_2$, 100-46-9; Me_2NH, 124-40-3; $PhCH(OH)COPh$, 119-53-9; $PhCH_2ONH_2 \cdot HCl$, 2687-43-6; $HOCH_2CH_2OH$, 107-21-1; DL-α-aminobutyric acid, 2835-81-6; mandelic acid succinimido ester, 93799-43-0.

Selective Cleavage of the Allyl and Allyloxycarbonyl Groups through Palladium-Catalyzed Hydrostannolysis with Tributyltin Hydride. Application to the Selective Protection–Deprotection of Amino Acid Derivatives and in Peptide Synthesis

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N-Allyloxycarbonyl (Alloc) derivatives of amines and amino acids are quantitatively and very rapidly converted to free amino compounds by palladium-catalyzed hydrostannolytic cleavage with tributyltin hydride in the presence of a proton donor (acetic acid, *p*-nitrophenol, pyridinium acetate, water). A similar procedure can be used for the deprotection of allyl (All) carboxylates and allyl aryl ethers. Deprotection experiments were performed on various mixed *N*-Alloc and *O*-Bzl, *N*-Z and *O*-All, *N*-Alloc and *O*-*t*-Bu, and *N*-alloc- and *N*-Boc-protected amino acid derivatives. The palladium-catalyzed hydrostannolytic cleavage is fully compatible with the Bzl and Z protecting groups; furthermore the BOC and *t*-Bu groups and the Alloc and All groups appear to be orthogonal. The reliability of the Alloc methodology for temporary protection of the α-amino functions is illustrated by the solid-phase synthesis of the biologically active undecapeptide substance P.

There is always a constant need for new, easy to introduce and selectively removable protecting groups in peptide synthesis. This is especially true in solid-phase methodology where the design of protection schemes with three independent dimensions of orthogonality for N^{α} protection, permanent protection and anchoring linkage

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