produces either optical antipode of homoserine or β-amino-γ-hydroxybutanoic acid. Using the method described previously,[3] anhydride **2** was reduced with $NaBH_4$ in THF at 0 °C to give lactone **5** in 92% yield. Both of these compounds have proven to be useful chiral synthons[10-12] and are both important biological compounds in their own right.[1,13-15] Furthermore, all of these procedures are readily modified for isotopic enrichments (e.g., see Scheme IV).

## Experimental Section

**Sodium 2(*S*),4-Dihydroxybutyrate (1).** L-Malic acid (1.34 g, 0.01 mol) was dissolved in trifluoroacetic anhydride (6 mL), and the the excess anhydride and acid were removed in vacuo. The remaining solid, *O*-TFA-L-malic anhydride, was opened by methanolysis to the monoacid, dried, and lyophilized from $H_2O$. The resulting powder was dissolved in THF (10 mL) and cooled to 0 °C, and a $BH_3$–THF solution (20 mL, 1 M) was added dropwise. After 2 h the reaction was quenched with methanol (10 mL), the THF and methanol were removed in vacuo, and the product was evaporated from MeOH several times to remove the methyl borate. The remaining oil, a mixture of 2,4-dihydroxybutyric acid lactone and the corresponding methyl ester, was treated with aqueous sodium carbonate (0.011 mol). Evaporation of the water gave the spectroscopically clean sodium salt of 2,4-dihydroxybutyrate: $^1H$ NMR ($D_2O$, 500 MHz) δ 1.62 (m, 1 H, β-H), 1.81 (m, 1 H, β′-H), 3.50 (br t, $J$ = 7.5 Hz, 2 H, γ,γ′-H), 3.96 (q, $J$ = 4.5 Hz, 1 H, α-H); $^{13}C$ NMR ($D_2O$, 100.6 MHz) δ 37.3 (t, $J$ = 127.4 Hz, C-3), 59.4 (t, $J$ = 143.5 Hz, C-4), 70.6 (d, $J$ = 145.6 Hz, C-2), 182.1 (br s, C-1).

**1-Methyl *N*-(Trifluoroacetyl)-L-aspartate (3).** L-Aspartic acid (3.99 g, 0.03 mol) and trifluoroacetic anhydride (20 mL) were reacted as above. Following the MeOH addition, the dried residue was carefully triturated several times with ether/petroleum ether (1:2), and the resulting fine suspension was filtered to remove **4**: 6.0 g, 82%; mp 115-116 °C; $[\alpha]^{20}_D$ −40° (2.0 g/100 mL $CH_3OH$) (D isomer, $[\alpha]^{20}_D$ +40.5° (2.0 g/100 mL $CH_3OH$); IR ($CHCl_3$) 3410 (w), 3035 (w), 2957 (w), 1750 (shoulder), 1729 (s), 1234 (m), 1172 (m) $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 500 MHz) δ 2.97 (dd, $J$ = 18, 4.5 Hz, 1 H, β-H), 3.17 (dd, $J$ = 18, 4 Hz, 1 H, β′-H), 3.80 (s, 3 H, methoxy), 4.84 (m, 1 H, α-H), 7.39 (br s, 1 H, NH); $^{13}C$ NMR ($D_2O$, 100.6 MHz) δ 35.7 (td, $J$ = 132.2, 4.8 Hz, β-C), 50.3 (d, $J$ = 142.6 Hz, α-C), 54.3 (q, $J$ = 149.1 Hz, $OCH_3$), 116.5 (q, $J$ = 285.8 Hz, $CF_3$), 159.5 (qd, $J$ = 37.6, 3.6 Hz, $CF_3CO$), 172.1 (m, C-1), 174.5 (m, γ-C); $Cl^+$ MS $m/z$ 244 $(M + H)^+$, 256 $(M - OH)^+$, 212 $(M - OCH_3)^+$, 198 $(M - COOH)^+$, 184 $(M - CH_2COOH)^+$, 114 $(M - C_4H_7O_4)^+$. Anal. Calcd for $C_7H_8NO_4F_3$: C, 34.54; H, 3.32; N, 5.76. Found: C, 34.27, H, 3.09; N, 5.85.

**(*S*)-α-Amino-γ-butyrolactone Hydrochloride.** **2** (2.43 g, 0.01 mol) and $BH_3$–THF (22 mL, 1.0 M) were reacted as above except that dilute $HCl/C_2H_5OH$ (2:1) at reflux for 12 h was required to hydrolyze the methyl ester and the *N*-TFA. The product was crystallized from $H_2O$/acetone: 1.26 g (92%); mp 219-220 °C; $[\alpha]^{20}_D$ −25.4° (2 g/100 mL $H_2O$) (D isomer, $[\alpha]^{20}_D$ +25.0°, (2 g/100 mL $H_2O$); $^1H$ NMR ($D_2O$, 500 MHz) δ 2.23 (m, 1 H, β-H), 2.59 (m, 1 H, β′-H), 4.24 (m, 2 H, α-H′, γ-H), 4.40 (td, 1 H, $J$ = 9, 1 Hz, γ-H); $^{13}C$ NMR ($D_2O$, 100.6 MHz) δ 27.56 (β-C), 49.41 (α-C), 68.26 (γ-C), 178.29 (C-1).

**(*S*)-*N*-(Trifluoroacetyl)-α-amino-γ-butyrolactone-γ,γ′-$d_2$ (7).** **2** (1.22 g, 5.0 mmol) was added to a suspension of $NaBD_4$ (0.42 g, 10 mmol, 98% D) in THF (10 mL). $BF_3$–$O(C_2H_5)_2$ (2 mL) was added at 0 °C, and after 2 h the reaction mixture was filtered and quenched with dilute HCl (5%, 10 mL). The solvent was removed in vacuo, and the residue was dried several times with $CH_3OH$ to remove the borate formed. The solid was treated with 5% HCl and lyophilized to a pure white powder, 0.95 g (96%, 98% $d_2$): $^1H$ NMR ($CDCl_3$, 500 MHz) δ 2.23 (t, $J$ = 12 Hz, 1 H, β-H), 2.92 (dd, $J$ = 8.5, 12.5 Hz, 1 H, β′-H), 4.57 (m, 1 H, α-H), 6.98 (br s, 1 H, NH); $^{13}C$ NMR (DMSO-$d_6$, 100.6 MHz) δ 27.2 (ddd, $J$ = 139.5, 133.6, 3.8 Hz, B-C), 48.7 (br d, $J$ = 141.8 Hz, α-C), 65.1 (br m, γ-C), 115.9 (q, $J$ = 287.9 Hz, $CF_3$), 156.6 (qt, $J$ = 36.9, 4.7 Hz, $CF_3CO$), 174.1 (br t, $J$ = 73o.6 Hz, C-1).

***B*,*B*-Diethylboroxazolidone (6).** To a suspension of very finely ground L-aspartic acid (1.33 g, 0.01 (mol) in THF was added triethylborane–THF (10 mL, 1.0 M). The mixture was refluxed under $N_2$ until the solution cleared. The solvent was removed under house vacuum, and the resulting oil was solidified and treated with petroleum ether. The product was collected by filtration as white powder: yield ~100%; $^1H$ NMR (acetone-$d_6$, 500 MHz) δ 0.336 (br q, $J$ = 8 Hz, 2 H, $CH_2$), 0.382 (br q, $J$ = 8 Hz, 2 H, $CH_2$), 0.746 (t, $J$ = 8 Hz, 3 H, $CH_3$), 0.757 (t, $J$ = 8 Hz, 3 H, $CH_3$), 2.89 (dd, $J$ = 18, 6.5 Hz, 1 H, β-H), 2.95 (dd, $J$ = 18, 4.5 Hz, β′-H), 3.98 (br m, 1 H, α-H), 5.41 (br s, 1 H, $NH_2$), 5.90 (br s, 1 H, $NH_2$); $^{13}C$ NMR (acetone-$d_6$, 100.6 MHz) δ 8.95 (qt, $J$ = 123.6, 4.7 Hz, $CH_3$), 9.20 (qt, $J$ = 123.6, 4.7 Hz, $CH_3$), 12.6 (br m, $W_{1/2}$ ~ 500 Hz, $CH_2$), 13.4 (br m, $W_{1/2}$ ~ 500 Hz, $CH_2$), 34.0 (tt, $J$ = 130.3, 4.0 Hz, β-C), 52.4 (dm, $J$ = 141.0, 3.6 Hz, α-C), 172.6 (q = $J$ = 7.1 Hz, C-4), 173.2 (br m, $J$ = 5.1 Hz, C-1), minor (6-membered) isomer resolved signals δ 8.48 ($CH_3$), 9.63 ($CH_3$), 38.4 (β-C), 60.5 (α-C).

**(*S*)-α-Amino-γ-butyrolactone Hydrochloride.** L-Aspartic acid (1.33 g, 0.01 mol) was treated with triethylborane–THF (10 mL, 0.01 mol) to prepare the amino acid–borane complex described above. This clear solution was cooled to 0 °C with an ice–water bath, $BH_3$–THF (12 mL, 1.2 mmol) was added dropwise, and the mixture was stirred for an additional 2 h at 0 °C. Hydrochloric acid (5%, 10 mL) was added, and the solvent was removed under house vacuum at 60 °C. The remaining residue was redissolved in a small amount of HCl (5%, 15 mL), refluxed for 30 min to allow for complete hydrolysis of the boron complex, dried in vacuo, redissolved, and dried with MeOH several times to remove the boric acid. The residue was crystallized from aqueous acetone to give white crystals: 1.18 g (86%); NMR spectra as above; $[\alpha]^{20}_D$ −26.8° (1 g/100 mL $H_2O$) [lit.[15] $[\alpha]^{26}_D$ −27.0° (*c* = 5)] (D isomer, $[\alpha]^{20}_D$ +27.1° (1 g/100 mL $H_3O$). Anal. Calcd for $C_4H_8NO_2Cl$: C, 34.92; H, 5.87; N, 10.18. Found: C, 34.99; H, 5.54; N, 10.20.

(10) Previous syntheses include: Armstrong, M. D. *J. Am. Chem. Soc.* **1948**, *70*, 1756-9. Weiss, S.; Stekol, J. A. *J. Am. Chem. Soc.* **1951**, *73*, 2497-9.

(11) Ramsamy, K.; Olsen, R. K.; Emery, T. *Synthesis* **1982**, 42-3. (b) Bajgrowicz, J. A.; Hallaoui, A. E.; Jacquier, R.; Pigiere, C.; Viallefont, P. *Tetrahedron Lett.* **1984**, *25*, 2231-4. (c) Ozinskas, A. J.; Rosenthal, G. A. *J. Org. Chem.* **1986**, *51*, 5047-50.

(12) Walsh, C. *Enzymatic Reaction Mechanisms*; W. H. Freeman and Co.: New York, 1979; pp 823-27. Athtar, M.; Emery, V. C.; Robinson, J. A. *The Chemistry of Enzyme Actions*; Page, M. I., Ed.; Elsevier Science Publishing Co., Inc.: New York, 1984; pp 303-72. Ramalingam, K.; Woodward, R. W. *J. Org. Chem.* **1988**, *53*, 1900-03.

(13) Lynn, D. G.; Jaffe, K.; Cornwell, M.; Tramontano, W. *J. Am. Chem. Soc.* **1987**, *109*, 5858-9.

(14) Barker, J. L.; Nicoll, R. A.; Padjen, A. *J. Physiol. (London)* **1975**, *245*, 521-36.

(15) Windholz, M., Budavari, S., Eds. *The Merck Index, 10th ed.*; Merck: Rahway, NJ, 1983; p 4631, 10th ed.

## An Example of Regioselective Esterification by Intramolecular Acyl Transfer from a Tertiary Amine

Thomas G. Waddell,* Thalia Rambalakos, and Karen R. Christie

*Department of Chemistry, University of Tennessee at Chattanooga, Chattanooga, Tennessee 37403*

*Received February 5, 1990*

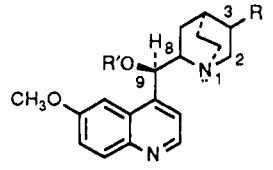
Despite the fact that the famous antimalarial quinine (1) has been known for 170 years, there is still considerable interest in its chemical and biological properties. Much of the most recent attention is due to the utility of quinine as a chiral resolving agent and catalyst.[1] In addition, however, malaria is still a worldwide problem, and quinine is the only antimalarial toward which resistance of the

(1) Dijkstra, G. D. H.; Kellogg, R. M.; Svendson, J. S.; Marko, I.; Sharpless, K. B. *J. Am. Chem. Soc.* **1989**, *111*, 8069 and references cited therein.

0022-3263/90/1955-4765$02.50/0 

parasite *Plasmodium falciparum* has not yet been reported.[2] Important and new chemistry of quinine may yet be discovered. To this point, we became interested in constructing quinine derivatives which have been built into their structures electrophilic centers which might make covalent bonds with cellular protein or nucleic acid nucleophilic sites. Indeed, quinine itself effectively binds to plasma protein,[3] DNA,[4] and porphyrins[5] by noncovalent forces. It would be interesting then to combine these noncovalent binding properties with an ability to form strong covalent bonds to biomacromolecules. Such covalent bonding to bionucleophiles is a crucial mode of action for many antitumor substances.[6]

In order to preserve the noncovalent binding properties of quinine, functionalization and derivatization of the remote vinyl group were desired. Thus, treatment of **1** with $OsO_4/NaIO_4$ produced the aldehyde **2**[7] as a 1:1 mixture of C-3 epimers (see the Experimental Section). Reduction of **2** with $NaBH_4$ smoothly yielded the diol **3** as the corresponding epimeric mixture. The structure of **3** follows from its method of preparation and spectral data. The IR spectrum of **3** showed a strong OH (3200 $cm^{-1}$) but no C=O absorption. The EI-MS displayed $M^+$ at $m/e$ 328 with the base peak at $m/e$ 140 corresponding to [quinuclidine - $CH_2OH$]$^{\bullet+}$, as compared to quinine ($m/e$ 136, quinuclidine - $CH{=}CH_2$) and quininal **2** ($m/e$ 138, quinuclidine - CHO).

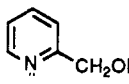


**1**: R = —CH=CH$_2$; R′ = H
**2**: R = ~CHO; R′ = H
**3**: R = ~CH$_2$OH; R′ = H
**4**: R = ~CH$_2$OH; R′ = OCCH=CHPh

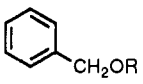
It is clear from molecular models that the $CH_2OH$ in **3** is much less hindered than the bulky secondary C-9 OH. We therefore expected esterification to take place predominantly or exclusively at the C-10 OH.[8] Since cinnamoyl esters have been shown to impart antitumor activity to certain natural products,[9] cinnamoylation of **3** with 1.1 equiv of cinnamoyl chloride in benzene/$Et_3N$ was attempted. To our surprise, the more hindered C-9 ester **4** was obtained in good yield! The structure of **4** was established with certainty by spectral data and comparisons. Briefly, the mass spectrum of **4** showed, in addition to $M^+$ at $m/e$ 458, a major fragment ion at 140 (46% of base peak) characteristic of [quinuclidine - $CH_2OH$]$^{\bullet+}$ (vida supra). The IR spectrum of **4** as expected showed both OH (3400 $cm^{-1}$) and C=O (1710 $cm^{-1}$) absorptions. In the NMR (listed in the Experimental Section), H-9 appeared as a doublet at 6.73 ppm, identical with the corresponding H-9 signal (6.73 ppm) in quinine *O*-cinnamoate (**1**: R′ = COCH=CHPh). The $CH_2O$ signal in **4** appeared as a broad peak at 3.50 ppm. Finally, for comparison, we prepared **1** (R = $CH_2OCOCH{=}CHPh$, R′ = $COCH_3$) in the analogous fashion from quinine *O*-acetate. In this diester, the esterified $CH_2O$ appeared at 4.16 ppm, a signal not present in **4**.

To explain this remarkable regioselectivity in the esterification of diol **3**, we propose that the more nucleophilic N-1 is acylated first, followed by intramolecular transfer of the cinnamoyl group to the neighboring C-9 OH. Models indicate that this transfer is feasible and that the C-10 OH, although less hindered, is too far away to participate. It has been determined that quinine acylated on nitrogen should prefer the "open" conformation[1] where the *N*-acyl group and the OH lie on opposite sides of the quinoline ring. If this conformation were rigidly fixed, intramolecular acyl transfer would not be possible. However, the single bonds C-4′–C-9 and C-9–C-8 allow free rotation, and the required orientation of the groups can readily be achieved during the course of the reaction.

If the regioselectivity observed in the acylation of the diol **3** is due to intramolecular acyl transfer from nitrogen, this event should be demonstrable in more simple molecules. Thus, when 2-pyridylcarbinol (**5**) (1 equiv) and benzyl alcohol (**6**) (1 equiv) were esterified in refluxing benzene with cinnamoyl chloride (1 equiv), cinnamoate esters **7** and **8** were produced in a ratio of 2.2:1. Without some special role of the N atom, a statistical 1:1 ester ratio would be expected in this competition experiment. More dramatic is the competition between *N*,*N*-dimethylethanolamine (**9**) and isoamyl alcohol (**10**). From these *aliphatic* alcohols, the cinnamoate ester **11** (from **9**) formed *exclusively* (as determined by NMR of the ester product). The enhanced degree of intramolecular acyl transfer from the aliphatic tertiary amine is expected (and is also seen in **3**) since an aliphatic nitrogen atom is more nucleophilic than a pyridine-type nitrogen. The compounds **5**–**9** in the above competition experiments were chosen not so much to model diol **3** as to demonstrate the event of intramolecular acyl transfer in related systems.



**5**: R = H
**7**: R = OCCH=CHPh



**6**: R = H
**8**: R = OCCH=CHPh

$(CH_3)_2\ddot{N}CH_2CH_2OR$

**9**: R = H
**11**: R = OCCH=CHPh

$(CH_3)_2CHCH_2CH_2OR$

**10**: R = H

A reasonable alternate explanation for these results might exist. Assuming a strong intramolecular OH···$N_1$ hydrogen bond, the oxygen atom of the above amino alcohols might be more negative, nucleophilic, and reactive than the oxygen of the simple alcohols. However, we feel that this explanation for the observed regioselectivity is not tenable for several reasons. To begin, when quinine *O*-acetate (**1**: R′ = $COCH_3$) in $CDCl_3$ was mixed with 1 equiv of cinnamoyl chloride, changes in the NMR spectrum were seen that are indicative of N-1 acylation (our required intermediate). Notably, the signal for the $\alpha$-H of the cinnamoyl group (half of an AB quartet) split into two signals, representing cinnamoyl chloride and another cinnamoyl species (N-1 acylated). Furthermore, the signal for H-9, in quinine O-acetate was shifted downfield by at least 1 ppm upon addition of the cinnamoyl chloride. We have observed a similar downfield shift for H-9 when quinine *O*-acetate is converted to its N-1 oxide. Significantly, a quantitative yield of starting quinine *O*-acetate was recovered from the above-described NMR solution.

(2) Verpoorte, R.; Schripsema, J.; van der Leer, T. In *The Alkaloids*; Academic Press: New York, 1988; Vol. 34, Chapter 6, p 332.
(3) Goodman, L. S.; Gilman, A. *Pharmacological Basis of Therapeutics*, 4th ed.; MacMillan: London, 1970; p 1115.
(4) Salerni, O. L. *Natural and Synthetic Organic Medicinal Compounds*; Mosby: St. Louis, 1976; pp 204–6.
(5) Behere, D. V.; Goff, H. M. *J. Am. Chem. Soc.* **1984**, *106*, 4945.
(6) Lee, K. H.; Ibuka, T.; Kim, S. H.; Vestal, B. R.; Hall, I. H. *J. Med. Chem.* **1975**, *18*, 812.
(7) Gueremy, P. C.; Uzan, A.; Tamen, J. C. *Arzneim-Forsch (Drug-Res.)* **1972**, *22*, 1336.
(8) Such regioselectivity has been observed in diterpene alkaloids. Jiang, Q.; Pelletier, S. *Tetrahedron Lett.* **1988**, *29*, 1875.
(9) Lee, K. H.; Meck, R.; Piantadosi, C. *J. Med. Chem.* **1973**, *16*, 299.

Thus, we have evidence that the N-acylated intermediate in the acyl transfer mechanism does form in the quinine system. In addition (in the quinine system), there is apparently no evidence of an OH to N-1 hydrogen bond.[1] Finally, intramolecular acyl migrations from amide N to OH are well known in aliphatic systems[10] including peptides.[11]

In summary, with our present results, we provide what we believe to be the first example of regioselective esterification induced by intramolecular acyl transfer from a tertiary amine. Our opinion on this point is supported by a careful survey of *Chemical Abstracts*. Having established this mechanistic event, experiments are in progress with the design to prepare other quinine derivatives with electrophilic functionality at the desired C-10 position.

## Experimental Section

IR spectra were run using a Perkin-Elmer 1310 spectrophotometer. NMR spectra were obtained on a JEOL JNM-PMX 60 instrument in $CDCl_3$ solution (internal TMS). Analytical TLC made use of Merck precoated silica gel plates (0.25 mm), and preparative TLC purifications were done using commercial AnalTech Si gel G (2 mm) plates. The solvent system was 20% MeOH in $CHCl_3$–2% $NH_4OH$ in all cases, and visualization utilized UV or iodine vapor. Quinine, 2-pyridylcarbinol, benzyl alcohol, *N*,*N*-dimethylethanolamine, and isoamyl alcohol are all available from Aldrich Chemical Co. Organic solutions were dried over anhydrous $MgSO_4$.

**$OsO_4$/$NaIO_4$ Oxidation of Quinine (1).** In a 100-mL round-bottom flask 0.753 g of quinine (2.32 mmol) was added to 40 mL of 80% acetic acid with stirring. After cooling to 0 °C, 1.483 g of $NaIO_4$ (6.93 mmol) was added followed by a few crystals of $OsO_4$. The solution became opaque purple as it was stirred for 5 h on ice. The flask was refrigerated overnight, whereupon the now pale yellow solution was rotovaped. About 10 mL of water was added, and the mixture was rotovaped again. The resulting foam was dissolved in 50 mL of $CHCl_3$ and shaken with saturated $NaHCO_3$. The organic layer was separated, and the aqueous phase extracted with 25 mL of $CHCl_3$. The combined organic solution was dried, filtered, and evaporated to dryness to give 0.720 g (95%) of a yellow foam. **2**:[7] IR (neat) 3200 (OH), 1720 (C=O) $cm^{-1}$; NMR 9.73, 9.65 (CHO), 3.88, 3.83 (MeO) ppm. A 1:1 mixture of C-3 epimers was confirmed by examining the NMR of the acetate ester of **2**.

**$NaBH_4$ Reduction of Aldehyde 2.** The 0.720-g sample of **2** from the previous preparation was taken up in 30 mL of MeOH, and 0.536 g of $NaBH_4$ was added slowly at room temperature with stirring. After 1 h the reaction solution was diluted with 100 mL of water and extracted with 4 × 50 mL of $CHCl_3$. The combined organic solution was dried, filtered, and evaporated to dryness to give 0.573 g (79.6%) of a white foam. **3**: one spot on TLC ($R_f$ 0.2); IR ($CHCl_3$) 3200 (OH), 1622, 1595, 1510 $cm^{-1}$; EI-MS *m*/*e* (% base peak) 328 ($M^+$) (8.3), 313 (3.7), 297 (30), 269 (50), 189 (90), 140 (100). Compound **3** was not soluble enough to obtain an NMR spectrum.

**Cinnamoylation of Diol 3.** A 0.231-g sample of the diol **3** (0.704 mmol) in 30 mL of benzene (2 mL of $Et_3N$) was heated at reflux to dissolve the starting material. After cooling, 0.129 g of cinnamoyl chloride (0.775 mmol) was added, and the reaction solution was stirred and refluxed for 1.5 h ($CaCl_2$ drying tube). Stirring continued overnight at room temperature, whereupon the mixture was shaken with 5% NaOH. The organic layer was separated, washed once with water, dried, filtered, and evaporated. The crude product **4** (0.261 g), a pale yellow foam, showed one major spot on TLC ($R_f$ 0.6) with traces of starting **3** and a high $R_f$ impurity (diester). Product **4** was easily purified by prep TLC as described. **4**: IR (neat) 3400 (OH), 1710 (C=O), 1625, 1590, 1505 $cm^{-1}$; EI-MS *m*/*e* (% base peak) 458 ($M^+$) (63), 444 (19), 327 (27), 311 (100), 188 (94), 140 (44), 131 (79); NMR 8.73 (d, 1 H) (H-2′), 8.08 (d, 1 H) (H-8′), 7.83 (d, 1 H, *J* = 16 Hz) (cinnamoyl β-H), 6.73 (d, 1 H, *J* = 8 Hz) (H-9), 6.60 (d, 1 H, *J* = 16 Hz) (cinnamoyl α-H), 3.93 (s, 3 H) OMe), 3.50 ppm (2 H) ($CH_2O$).

In another run using 1.2 equiv of cinnamoyl chloride, the high $R_f$ product was isolated and shown to be the corresponding diester of **3**: IR (neat) no OH, 1710 (C=O), 1634, 1620, 1590, 1575 $cm^{-1}$; NMR 8.75 (d, 1 H) H-2′), 8.08 (d, 1 H) (H-8′), 8.00–7.66 (2 doublets) (2 cinnamoyl β-H's), 6.70–6.30 (2 doublets) (2 cinnamoyl α-H's), 6.73 (d, 1 H, *J* = 8 Hz) (H-9), 4.16 (2 H) ($CH_2O$), 3.96 (s, 3 H) (OMe).

**2-Pyridylcarbinol/Benzyl Alcohol: Competition Experiment.** To a stirred solution of 0.311 g of **5** (2.85 mmol) and 0.314 g of **6** in 40 mL of benzene was added 0.470 g of cinnamoyl chloride (2.82 mmol). The reaction solution was stirred and refluxed ($CaCl_2$ drying tube) for 2 h then left in the refrigerator overnight. The resulting mixture was shaken thoroughly with 5% NaOH, and the organic layer was washed with water, dried, filtered, and evaporated to dryness (0.634 g, pale yellow, thick liquid). The NMR spectrum clearly indicated a 2.2:1 ratio of esters **7**:**8**, by integration of the signals at 5.37 and 5.17 ppm ($CH_2O$). These signals were shown to correspond to **7** and **8**, respectively, by comparison to authentic ester spectra.

***N*,*N*-Dimethylethanolamine/Isoamyl Alcohol: Competition Experiment.** An identical procedure was applied to alcohols **9** and **10** (3.4-mmol scale). The NMR of the ester product was nearly identical with that of authentic **11** and gave no indication of the presence of isoamyl cinnamoate.

**Acknowledgment.** We are grateful to the American Society of Pharmacognosy for financial support of this work through an Undergraduate Research Award. We also acknowledge the assistance provided by the UC Foundation Grote Chemistry Fund. Mass spectra were obtained through the generous help of the following colleagues: Alma Parker, Barry Henderson (Purdue University), Dr. Richard Pagni (University of Tennessee), Dr. W. Christie, R. Hettich (Oak Ridge National Lab.) Sunil Geevarghese provided technical assistance throughout the course of our work.

**Registry No.** **1**, 130-95-0; **2** (isomer 1), 127707-69-1; **2** (isomer 2), 127707-70-4; **3** (isomer 1), 127619-74-3; **3** (isomer 2), 127707-71-5; **4** (isomer 1), 127619-75-4; **4** (isomer 2), 127707-72-6; **4** (dicinnamate, isomer 1), 127619-76-5; **4** (dicinnamate, isomer 2), 127707-73-7; **5**, 586-98-1; **6**, 100-51-6; **7**, 127619-77-6; **8**, 78277-23-3; **9**, 108-01-0; **11**, 46742-18-1.

(10) Bernath, G.; Lang, K. L.; Tichy, M.; Pankova, M. *Acta Chim. Acad. Sci. Hung.* **1975**, *86*, 199.
(11) Iwai, K.; Ando, T. *Methods Enzymol.* **1967**, *11*, 263.

---

# Synthesis of β-Methoxy Enones via a New Two-Carbon Extension of Carboxylic Acids

Tomas Hudlicky,*[,1] Horacio F. Olivo,[2a] and Michael G. Natchus

*Department of Chemistry, Virginia Polytechnic Institute and State University, Blacksburg, Virginia 24060*

Eleuterio F. Umpierrez,[2b,c] Enrique Pandolfi,[2b] and Carla Volonterio[2b]

*Catedra de Quimica Organica, Facultad de Quimica, Montevideo, Uruguay*

*Received February 15, 1990*

We report a new procedure for the synthesis of aliphatic and aromatic β-methoxy enones by a two-carbon homol-

(1) Recipient of the Research Career Development Award (NIH-AI-00564), 1984–1989; to whom correspondance should be addressed.
(2) (a) We are indebted to CONACyT for financial assistance to H. F.O. during part of this work at Universidad Nacional Autonoma de Mexico and to Dr. Marta Albores-Velasco for her valuable guidance. (b) Partial effort from the Facultad de Quimica, Montevideo, resulted in the preparation of compounds **20**, **21**, **22**, and **23**. (c) Presented in part at the 3rd Brazilian Congress on Organic Synthesis, Sao Carlos, Brazil, January 1989.

0022-3263/90/1955-4767$02.50/0 