Synthetic (*S*)-5-(Benzoyloxy)-6-oxohexanoic Acid Ethyl Ester and [*S*,*S*-(*E*)]-3-(Hydroxymethyl)oxiranebutanoic Acid Methyl Ester, Important Synthons for Leukotrienes B_4 and A_4, from D-Arabinose

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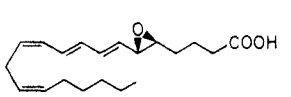
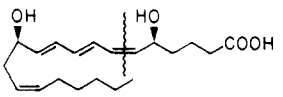
D-Arabinose was converted to [*S*-(*R**,*S**)]-5-(benzoyloxy)-6,7-dihydroxyheptanoic acid ethyl ester by β-elimination of its derivative 2,3:4,5-di-*O*-isopropylidene-D-arabinose dipropyl mercaptal, hydride reduction of the resulting ketene thioacetal, benzoylation, mercaptal hydrolysis, Wittig–Horner olefination, and catalytic reduction. Subsequent glycol cleavage gave the leukotriene B_4 synthon (*S*)-5-(benzoyloxy)-6-oxohexanoic acid ethyl ester (**14**), whereas monobenzoylation led to [*S*-(*R**,*S**)]-5,7-bis(benzoyloxy)-6-hydroxyheptanoic acid ethyl ester, convertible in two steps to the leukotriene A_4 precursor [*S*,*S*-(*E*)]-3-(hydroxymethyl)oxiranebutanoic acid methyl ester (**18**).

Leukotrienes, arachidonic acid derived metabolites of great biological significance, are present in tissue at extremely low concentrations, so that experimental quantities are only accessible by chemical synthesis. The so-called slow reacting substance of anaphylaxis (SRS-A), identified as a mixture of leukotrienes C_4, D_4, and E_4, is biochemically and synthetically derived from leukotriene A_4 (**1**), which assumes a key position in the lipoxygenase branch of the arachidonic acid cascade. Leukotriene B_4 (**2**), an important chemotactic substance, is similarly generated from leukotriene A_4 in polymorphonuclear leukocytes by enzymic hydrolysis, but its chemical synthesis requires a de novo process.[1]

The basic strategy of the first synthesis of leukotriene B_4 by Corey et al.[2] has been maintained in all subsequent ones[3-8] with only one exception[9] and consists of a final assembly of a chiral, allylic C_{14} phosphorane with a chiral C_6 aldehyde as indicated in **2**, followed by chromatographic



1, Leukotriene A_4



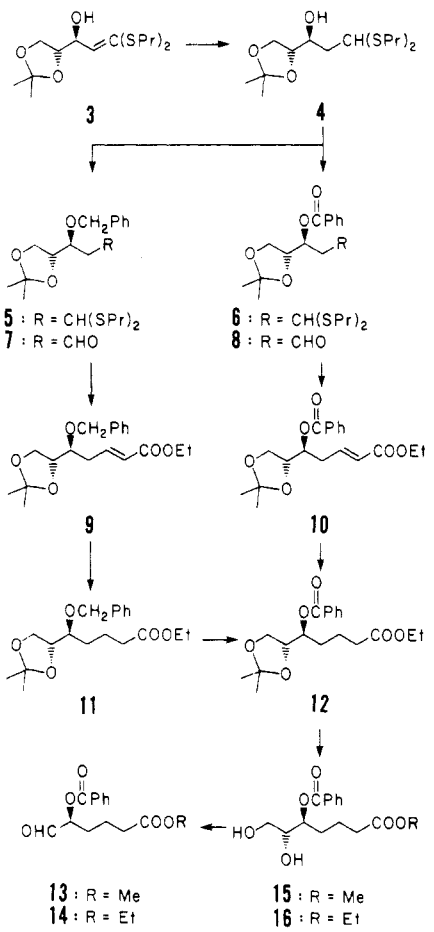
2, Leukotriene B_4

separations of the resulting *E*, *Z* mixture and hydrolytic removal of the protecting groups. Moreover, aldehyde **13**,[2,3] originally employed as the C_6 chiron, together with its ethyl analogue **14**,[4] has enjoyed general acceptance in all later synthetic modifications of the $C_{14} + C_6$ approach.

Three routes[2-4] leading to **13** or **14** use 2-deoxy-D-ribose as starting material and rely either on some degree of regioselectivity in hydroxyl-group differentiation with the concomitant need for chromatographic removal of undesired regioisomers, or on the precarious stability of a terminal epoxide in the presence of a vicinal hydroxyl group in an alkaline environment. Alternatively, **13** and a closely related derivative thereof were prepared by enantioselective reduction of the corresponding oxo precursors with either bakers' yeast[7] or Midland's (−)-9-pinanyl-BBN,[9] respectively. Most recently, **14** was prepared from D-mannitol.[8]

In an attempt to find a reaction sequence capable of furnishing **13** or **14** in multigram quantities without the need for critical chromatographic separations, we selected D-arabinose, which is much more economical than 2-deoxy-D-ribose, as our starting material and converted it to the 2-deoxy-4,5-*O*-isopropylidene-D-*erythro*-pentose dipropyl mercaptal (**4**) (Scheme I) via 2,3:4,5-di-*O*-isopropylidene-D-arabinose dipropyl mercaptal and **3** by es-

Scheme I



(1) For recent reviews, see: (a) Green, R. H.; Lambeth, P. F. *Tetrahedron* **1983**, *39*, 1687–1721. (b) Scheinmann, F.; Ackroyd, J. In *Leukotriene synthesis: A new class of biologically active compounds including SRS-A*; Raven: New York, 1984. (c) *The Leukotrienes. Chemistry and biology*; Chakrin, L. W., Bailey, D. M., Eds.; Academic: New York, 1984. (d) Rokach, J.; Adams, J. *Acc. Chem. Res.* **1985**, *18*, 87–93.

(2) Corey, E. J.; Marfat, A.; Goto, G.; Brion, F. *J. Am. Chem. Soc.* **1980**, *102*, 7984–7985.

(3) Corey, E. J.; Marfat, A.; Munroe, J.; Kim, K. S.; Hopkins, P. B.; Brion, F. *Tetrahedron Lett.* **1981**, *22*, 1077–1080.

(4) Guindon, Y.; Zamboni, R.; Lau, C.-K.; Rokach, J. *Tetrahedron Lett.* **1982**, *23*, 739–742.

(5) Zamboni, R.; Rokach, J. *Tetrahedron Lett.* **1982**, *23*, 2631–2634.

(6) Mills, L. S.; North, P. C. *Tetrahedron Lett.* **1983**, *24*, 409–410.

(7) Han, C.-Q.; DiTullio, D.; Wang, Y.-F.; Sih, C. J. *J. Org. Chem.* **1986**, *51*, 1253–1258.

(8) Lemerrer, Y.; Gravier, C.; Languinmicas, D.; Depezay, J. C. *Tetrahedron Lett.* **1986**, *27*, 4161–4164.

(9) Nicolaou, K. C.; Zipkin, R. E.; Dolle, R. E.; Harris, B. D. *J. Am. Chem. Soc.* **1984**, *106*, 3548–3551.

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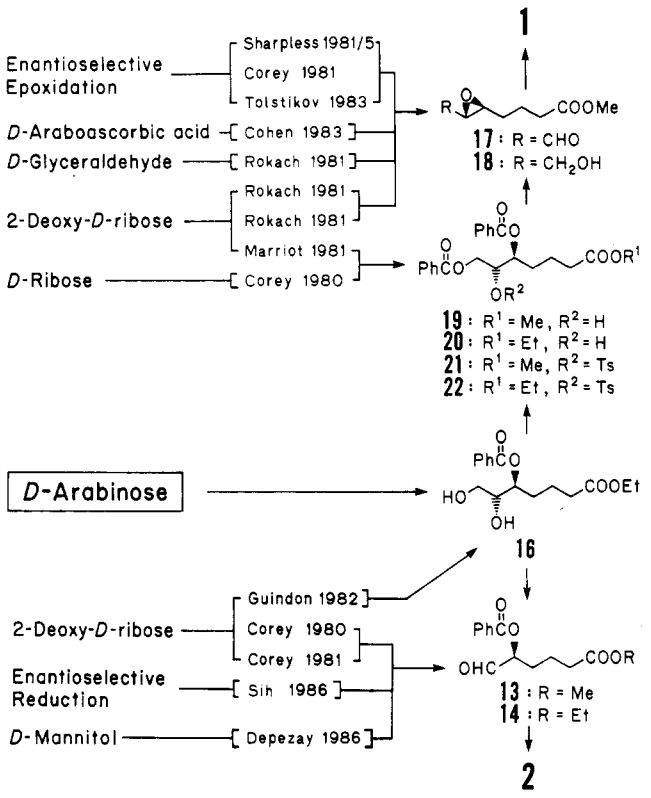
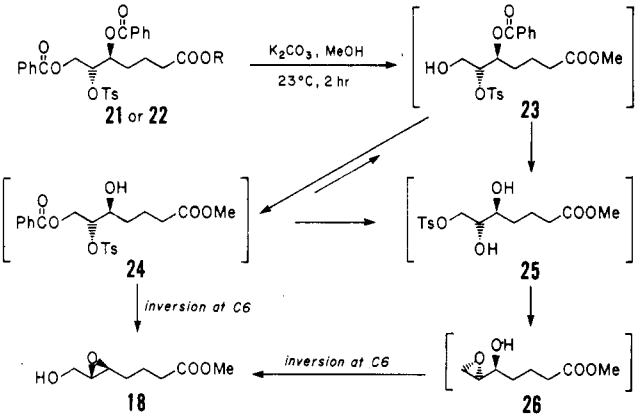
Scheme II



tablished procedures.[10,11a,b] Further elaboration of **4** toward the target compound **14** (Scheme I) was originally influenced by the observed instability of 2-deoxy-3-*O*-(*tert*-butyldiphenylsilyl)-L-*erythro*-pentose, derived from the antipode of the ethyl analogue of **4** by *tert*-butyldiphenylsilylation and mercaptal hydrolysis, and used as an intermediate in one of the C_{14} phosphorane syntheses.[5] In our hands, this silyl ether proved prone to β-elimination under reaction conditions with hexylidenephosphorane at −78 °C, particularly when the reaction was carried out on a scale in excess of 25 g.[12] Fearful of enhanced instability of an acyl or aroyl analogue such as **8**, we prepared instead benzyl ether **7** by hydrolysis of mercaptal **5**. A subsequent olefination of **7** with triethyl phosphonoacetate indeed furnished the unsaturated ester **9** in good yield. Simultaneous reduction of the olefinic double bond and hydrogenolysis of the benzyl ether function by catalytic hydrogenation over Pd/C was unsuccessful as it furnished a mixture of **11** and its debenzylated derivative. Even more surprisingly, catalytic transfer hydrogenation with palladium hydroxide and cyclohexene, known as a debenzylating agent,[13] reduced the olefinic double bond selectively without affecting the benzyl ether function at all. The benzyl group of the resulting **11** was then oxidized with ruthenium tetraoxide[14] to the benzoyl stage, thus providing the diester **12** whose conversion to the desired C_6 synthon **14** via diol **16** has already been reported.[4]

Scheme III



Encouraged by the stability of benzyl ether **7**, we then prepared benzoate **8** via **6** and were able to effect a Wittig–Horner olefination yielding the unsaturated diester **10** in high yield and without evidence of β-elimination. Catalytic hydrogenation of **10** gave **12** so that an alternative and more direct route from D-arabinose to **14** was established.

The nonbiomimetic, enantiospecific leukotriene A_4 syntheses that have appeared in the literature have much in common with the first synthesis by Corey et al.[15] as they involve the intermediacy of [*S*,*S*-(*E*)]-3-(hydroxymethyl)oxiranebutanoic acid methyl ester, **18** (Scheme II). This important chiron was originally prepared from D-ribose[15] and subsequently by enantioselective epoxidation,[16] from D-araboascorbic acid,[17] 2-deoxy-D-ribose,[18] and D-glyceraldehyde.[19] The syntheses of **17** from D-ribose[15] and 2-deoxy-D-ribose[18c] pass through the common triester **19**, which is readily converted to the tosylate **21**; a subsequent treatment with potassium carbonate in methanol generates the epoxy alcohol **18**, which is then oxidized to the aldehyde **17** under Collins conditions.

With the diester **16** available from D-arabinose, triester **20** is now also accessible by regioselective benzoylation of the hydroxymethyl group of **16** and leads to **18** via **22**, so that D-arabinose can function as a source of chirality for both **1** and **2** as illustrated in Scheme II.

Although the tetraester **21** has been previously converted to the epoxy alcohol **18** by treatment with potassium

(10) Wong, M. Y. H.; Gray, G. R. *J. Am. Chem. Soc.* **1978**, *100*, 3548–3553.

(11) (a) The reason for the use of the dipropyl instead of the known diethyl mercaptal was twofold. D-Arabinose dipropyl mercaptal is considerably less soluble than the diethyl analogue and can thus be purified by recrystallization with minimum losses. In addition, we repeated the Zamboni–Rokach leukotriene B_4 synthesis which commences with L-arabinose diethyl mercaptal and utilizes the antipodal ethyl analogues of **3** and **4**. To avoid the presence of three antipodal pairs in the same laboratory, the internal propyl label for the D series was desirable. (b) All compounds described herein are carbohydrate-derived and are more consistently represented by carbohydrate nomenclature so that our use of the Chemical Abstracts nomenclature is limited to the title and abstract.

(12) (*E*)-4,5-*O*-Isopropylidene-D-*glycero*-pent-2-enose: 200-MHz NMR ($CDCl_3$) δ 1.43, 1.47 (2 s, Me_2C), 3.75 (dd, 1, H5a, $J_{4,5a}$ = 7 Hz and J_{gem} = 8 Hz), 4.26 (dd, 1, H5b, $J_{4,5b}$ = 7 Hz and J_{gem} = 8 Hz), 4.80 (ddd, 1, H4, $J_{3,4}$ = 5.5 Hz, $J_{4,5a}$ = $J_{4,5b}$ = 7 Hz), 6.37 (ddd, 1, H2, $J_{1,2}$ = 8 Hz, $J_{2,3}$ = 16 Hz, $J_{2,4}$ = 1.5 Hz), 6.77 (dd, 1, H3, $J_{2,3}$ = 16 Hz, $J_{3,4}$ = 5.5 Hz), 9.61 (d, 1, H1, $J_{1,2}$ = 8 Hz).

(13) Hanessian, S.; Liak, T. J.; Vanasse, B. *Synthesis* **1981**, 396–397.

(14) (a) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936. (b) Schuda, P. F.; Cichowicz, M. B.; Heimann, M. R. *Tetrahedron Lett.* **1983**, *24*, 3829–3830.

(15) Corey, E. J.; Clark, D. A.; Goto, G.; Marfat, A.; Mioskowski, C.; Samuelsson, B.; Hammarström, S. *J. Am. Chem. Soc.* **1980**, *102*, 1436–1438, 3663.

(16) (a) Rossiter, B. E.; Katsuki, T.; Sharpless, B. *J. Am. Chem. Soc.* **1981**, *103*, 464–465. (b) Corey, E. J.; Hashimoto, S.; Barton, A. E. *J. Am. Chem. Soc.* **1981**, *103*, 721–722. (c) Tolstikov, G. A.; Miftakhov, M. S.; Tolstikov, A. G.; Lesnikova, E. T. *Zh. Org. Khim.* **1985**, *19*, 463; *Chem. Abstr.* **1983**, *98*, 215363e. (d) Rossiter, B. E. In *Asymmetric Synthesis*; Academic: New York, 1985; Vol. 5, p 223.

(17) Cohen, N.; Banner, B. L.; Lopresti, R. J.; Wong, F.; Rosenberger, M.; Liu, Y.-Y.; Thom, E.; Liebman, A. A. *J. Am. Chem. Soc.* **1983**, *105*, 3661–3672.

(18) (a) Rokach, J.; Zamboni, R.; Lau, C.-K.; Guindon, Y. *Tetrahedron Lett.* **1981**, *22*, 2759–2762. (b) Rokach, J.; Lau, C.-K.; Zamboni, R.; Guindon, Y. *Tetrahedron Lett.* **1981**, *22*, 2763–2766. (c) Marriott, D. P.; Bantick, J. R. *Tetrahedron Lett.* **1981**, *22*, 3657–3658.

(19) Rokach, J.; Young, R. N.; Kakushima, M.; Lau, C.-K.; Seguin, R.; Frenett, R.; Guindon, Y. *Tetrahedron Lett.* **1981**, *22*, 979–982.

carbonate in methanol,[15] the underlying mechanism is not obvious as evident from Scheme III. The first step in this sequence is suspected to be the solvolysis of the terminal benzoate leading to triester **23**. A following displacement of the tosyloxy group by the incipient hydroxymethyl terminus, benzoate solvolysis, and epoxide migration would lead to a cis-3-(hydroxymethyl)oxiranebutanoate, which is not observed. The product **18** is therefore most likely formed from alcohol **23** after benzoyl migration leading to **24**, tosyloxy displacement by the incipient hydroxy group at C5, and benzoate solvolysis at C6. Benzoate solvolysis of **23** or **24** in preference to epoxide formation of **24**, subsequent tosyl migration to yield **25**, and loss of the tosyloxy group without inversion to give **26**, followed by a single inversion at C6 in the course of an epoxide migration leading to **18**, is another conceivable, albeit less likely, sequence.

Experimental Section

IR (Digilab FTS-M) and NMR spectra (Varian XL-100, XL-200, and XL-400) and optical rotations (Perkin-Elmer spectropolarimeter 241) were recorded with the indicated solvents. EI+ mass spectra (Varian MAT CH5 and VG 7070E-HF) were obtained at an ionizing voltage of 70 eV and 250 °C ion-source temperature. TLC was performed with E. Merck silica gel G60 F-254 plates, and Woelm 32–63-μm silica gel served for column chromatograms. Solutions were dried with magnesium sulfate unless stated otherwise and were evaporated under reduced pressure. Melting points were determined on a hot stage (Thermopan, Reichert) and are reported without correction.

D-Arabinose Di-1-propyl Mercaptal. D-Arabinose (112.6 g, 0.75 mol) was dissolved in concentrated hydrochloric acid (115 mL) in a 2-L three-necked flask with mechanical stirring and ice cooling. To the cold, stirred solution was added a slow stream of propyl mercaptan (136 mL, 1.5 mol). The solution quickly thickened and solidified, and a white solid mass was obtained within minutes. After 1 min, chilled water was layered on top of the precipitate, which prevents discoloration. The mass was allowed to remain in the ice bath for 5 min and was then broken up into pieces, mixed with additional water, and homogenized to a white slurry, which was filtered. The white cake was washed with chilled water, and the resulting moist solid was recrystallized by dissolving in hot 2-propanol (total volume 400 mL) and adding water (total volume 1 liter). Filtration, washing with cold water (500 mL), and drying over potassium hydroxide gave cream-colored prisms of D-arabinose dipropyl mercaptal, 192.5 g (90%), mp 128–130 °C. Dissolving this material in boiling 2-propanol (400 mL) followed by addition of water (200 mL) to the hot solution afforded the mercaptal as long, white needles (186.5 g) after refrigeration, filtration, and washing with a small quantity of petroleum ether: mp 131–131.5 °C (lit.[20] mp 130 °C); $[\alpha]^{25}_D$ −12.57° (*c* 2.93, methanol) (lit.[20] $[\alpha]^{24}_D$ −10.6°).

2-Deoxy-4,5-*O*-isopropylidene-D-*erythro*-pentose Dipropyl Mercaptal (4). D-Arabinose di-1-propyl mercaptal (112 g, 0.394 mol) was suspended in acetone (1 L) and cooled in an ice bath, and concentrated sulfuric acid (15 mL) was added to the mechanically stirred suspension. The ice bath was removed after 10 min and the solution neutralized after 18 h by the addition of powdered, anhydrous sodium carbonate (35 g) and vigorous stirring for several hours. The suspension was filtered, and the filtrate was evaporated, taken up in toluene (500 mL), stirred with magnesium sulfate for 1 h, filtered again, and evaporated to yield 2,3:4,5-di-*O*-isopropylidene-D-arabinose dipropyl mercaptal as a light straw-colored syrup (141.6 g, 98.6%). This material is suitable for the next step but does contain a small amount of starting material, which will crystallize from the syrup upon prolonged standing at ambient temperature. A small sample of the dipropyl mercaptal was distilled for analysis (bath temperature 250 °C, ca. 0.1 Torr) to give a colorless syrup: $[\alpha]^{25}_D$ +81.49° (*c* 1.0, methanol); 100-MHz NMR ($CDCl_3$) δ 0.99 and 1.00 (2 t, 2 Me, J = 7.5 Hz), 1.33, 1.37, 1.40, 1.44 (4 s, 4 Me), 1.50–1.83 (m, 2 CH_2), 2.60–2.80 (m, 2 CH_2S), 3.93–4.35 (m, 6, H1–5).

Anal. Calcd for $C_{17}H_{32}O_4S$: C, 56.01; H, 8.85. Found: C, 55.85; H, 8.93.

A solution of this dipropyl mercaptal (141.6 g, 0.388 mol) in tetrahydrofuran was treated with potassium *tert*-butoxide in a mixture of dimethyl sulfoxide and tetrahydrofuran as described.[10,21] yielding 2-deoxy-4,5-*O*-isopropylidene-D-*erythro*-pent-1-enose propyl mercaptal (**3**) as a straw-colored syrup: 108.9 g; 91.5%; IR 3440 (OH), 2960 cm^{-1} (alkyl); 100 MHz NMR ($CDCl_3$) δ 0.99, 1.00 (2 t, 2 Me, J = 7.5 Hz), 1.37, 1.44 (s, Me_2C), 1.4–1.75 (m, 2 CH_2), 2.28 (d, C3-OH, J = 3 Hz), 4.89 (m, H3), 5.90 (d, H2, $J_{2,3}$ = 8 Hz); MS, m/e (relative intensity) 307 (1, MH^+), 289 (8, M − OH), 231 (8, M − SPr), 205 (100, M − (2,2-dimethyl-1,3-dioxolan-4-yl)).

A solution of **3** in tetrahydrofuran was reduced with lithium aluminum hydride as described for the ethyl analogue[10] to afford **4** as a colorless syrup: 87%; TLC, (4:1, hexane–ethyl acetate) R_f 0.38; $[\alpha]^{25}_D$ −5.86° (*c* 1.4, $CHCl_3$); 100-MHz NMR ($CDCl_3$) δ 0.99 (t, 2 Me, J = 7.5 Hz), 1.42, 1.35 (2 s, Me_2C), 1.62 (m, 2 CH_2 of Pr), 1.87 (m, 2, H2), 2.61 (m, CH_2S), 3.66–4.20 (m, 6, H1, H3–5, C3-OH).

Anal. Calcd for $C_{14}H_{28}O_3S_2$: C, 54.51; H, 9.15. Found: C, 54.58; H, 9.35.

3-*O*-Benzyl-2-deoxy-4,5-*O*-isopropylidene-D-*erythro*-pentose Dipropyl Mercaptal (5). Sodium hydride (1.56 g, 50% mineral oil dispersion) was washed with petroleum ether under nitrogen and suspended in *N,N*-dimethylformamide (5 mL) at 0 °C. A solution of **4** (10 g, 32.4 mmol) in *N,N*-dimethylformamide (10 mL) was added dropwise to the stirred suspension at 0–5 °C, and after 1 h, a solution of benzyl bromide (4.24 mL, 35.6 mmol) in *N,N*-dimethylformamide (5 mL) was added. The mixture was stirred at 0–5 °C for 30 min and at room temperature for 3 h and then extracted with ether (2 × 100 mL) after addition of water. The combined extracts were washed with water four times and once with brine, dried, and evaporated. Chromatography of the residue was 1:9 ethyl acetate–hexane afforded pure **5** (10.54 g, 81.6%) and with 1:4 ethyl acetate–hexane unreacted **4** (1.08 g, 10.8%). Mercaptal **5** as obtained as a colorless syrup: TLC (4:1 hexane–ethyl acetate) R_f 0.49; $[\alpha]^{25}_D$ −2.46° (*c* 0.9, $CHCl_3$); 100-MHz NMR ($CDCl_3$) δ 0.96 (t, 2 Me of Pr, J = 7.5 Hz), 1.33, 1.41 (2 s, Me_2C), 1.53 (m, 2 CH_2 of Pr), 1.94 (m, 2, H2), 1.55 (m, 2 CH_2S), 4.00 (m, 5, H1, H3–5), 4.62, 4.76 (AB, CH_2Ph, J_{gem} = 11.5 Hz), 7.31 (s, C_6H_5).

Anal. Calcd for $C_{21}H_{34}O_3S$: C, 63.28; H, 8.60; S, 16.09. Found: C, 62.77; H, 8.48; S, 16.26.

3-*O*-Benzoyl-2-deoxy-4,5-*O*-isopropylidene-D-*erythro*-pentose Dipropyl Mercaptal (6). Benzoyl chloride (0.5 mL, 4.3 mmol) was added to a solution of **4** (1.172 g, 3.80 mmol) in dichloromethane (5 mL) and pyridine (5 mL). The mixture was kept at room temperature overnight, diluted with dichloromethane, and extracted repeatedly with sodium hydrogen carbonate solution, followed by dilute phosphoric acid to remove pyridine, and once again with sodium hydrogen carbonate solution. Drying and evaporation gave **6** as a colorless syrup, 1.54 g (98%). Analytically pure material was obtained upon chromatography with hexane–dichloromethane: TLC (4:1 hexane–ethyl acetate) R_f 0.60; $[\alpha]^{25}_D$ −37.95° (*c* 0.8, ethanol); 400-MHz NMR ($CDCl_3$) δ 0.96 (t, 2 Me of Pr, J = 7 Hz), 1.35, 1.41 (2 s, Me_2C), 1.57 (sextet, 2 CH_2 of Pr, J = 7 Hz), 2.15 (ddd, 1, H2a, J_{gem} = 15 Hz, $J_{1,2a}$ = 4 Hz, $J_{2a,3}$ = 9 Hz), 2.28 (ddd, 1, H2b, J_{gem} = 15 Hz, $J_{1,2b}$ = 9 Hz, $J_{2b,3}$ = 4 Hz), 2.53, 2.64 (2 m, 2 each, H2 of Pr), 3.86 (dd, 1, H1, $J_{1,2a}$ = 4 Hz and $J_{1,2b}$ = 9 Hz), 3.91 (dd, 1, H5a, $J_{4,5a}$ = 6 Hz, J_{gem} = 8.5 Hz), 4.09 (dd, 1, H5b, $J_{4,5b}$ = 6 Hz, J_{gem} = 8.5 Hz), 4.31 (dt, 1, H4, $J_{3,4}$ = $J_{4,5a}$ = $J_{4,5b}$ = 6 Hz), 5.54 (ddd, 1, H3, $J_{2a,3}$ = 9 Hz, $J_{2b,3}$ = 4 Hz, $J_{3,4}$ = 6 Hz), 7.44 (t, 2, H3, H5, of Ph J_{ortho} = 8 Hz), 7.56 (tt, 1, H4 of Ph, J_{ortho} = 8 Hz, J_{meta} = 1.5 Hz), 8.04 (dd, 2, H2, H6 of Ph); MS, m/e (relative intensity) 412 (7, M^+), 397 (3, M − Me), 337 (3, M − SC_3H_7), 279 (24, M − SC_3H_7 − C_3H_6O), 215 (25, M − SC_3H_7 − PhCOOH), 157 (100, M − SC_3H_7 − C_3H_6O − PhCOOH).

Anal. Calcd for $C_{21}H_{32}O_4S_2$: C, 61.13; H, 7.82. Found: C, 61.14; H, 7.74.

(20) Zinner, H.; Brandner, H.; Rembarz, G. *Chem. Ber.* **1956**, *89*, 800–813.

(21) Dichloromethane was used as extraction solvent, and the chromatographic step was omitted.

2-Deoxy-3-*O*-benzyl-4,5-*O*-isopropylidene-D-*erythro*-pentose (7) and 5-*O*-Benzyl-2,3,4-trideoxy-6,7-*O*-isopropylidene-D-*erythro*-hept-2-enoic Acid Ethyl Ester (9). A solution of **5** (10 g) in 4:1 acetonitrile–water (100 mL) was added to a stirred suspension of $HgCl_2$ (15 g) and yellow HgO (6.0 g) in the same solvent (200 mL) at 0–5 °C. The mixture was stirred efficiently for 30 min in an ice bath and then filtered. The solid was washed with 1:1 dichloromethane–hexane. The organic phase was washed with 5 M NaOAc, water, and saturated sodium chloride solution, dried, filtered, and evaporated to yield **7** as a colorless syrup (6.44 g, 97%): TLC (2:1 hexane–ether) R_f 0.18; IR 1725 cm^{-1} (aldehyde C=O); 100-MHz NMR ($CDCl_3$) δ 1.33, 1.39 (2 s, Me_2C), 2.72 (dd, 2, H2, $J_{1,2}$ = 2.5 Hz and $J_{2,3}$ = 5.5 Hz), 3.70–4.23 (m, 4, H3–5), 4.60 (s, 2, CH_2Ph), 7.31 (s, 5, Ph), 9.81 (t, H1, $J_{1,2}$ = 2.5 Hz); MS, *m/e* (relative intensity) 264 (3, M^+), 249 (2, M – Me), 173 (6, M – Bz), 163 (M – (2,2-dimethyl-1,3-dioxolan-4-yl)).

Triethyl phosphonoacetate (10.6 mL, 0.0534 mol) was added to a suspension of sodium hydride (50% mineral oil dispersion, 2.34 g, 0.0488 mol) in tetrahydrofuran (40 mL) at 0–5 °C. The resulting solution was stirred for 1 h at 25 °C, and a solution of aldehyde **7** (6.45 g, 0.0244 mol) in tetrahydrofuran (30 mL) was added during 10 min without exceeding the internal temperature of 28 °C. Stirring at room temperature was continued for an additional hour. The solution was then evaporated and the residue distributed between ethyl acetate and water. The ethyl acetate extract was washed with brine, dried, and evaporated. The residue was purified by chromatography on silica gel (1:4 ethyl acetate–hexane) to yield **9** as a colorless syrup (6.61 g, 81%):[22] TLC (2:1 hexane–ether) R_f 0.31; $[\alpha]^{25}_D$ +17.21° (*c* 0.5, $CHCl_3$); 200-MHz NMR ($CDCl_3$) δ 1.30 (t, Me of Et, J = 7 Hz), 1.35, 1.42 (2 s, Me_2C), 2.55 (m, 2, H4), 3.50 (m, 1, H5), 3.37 (m, 1, H6), 4.07 (m, 2, H7), 4.21 (q, CH_2 of Et), 4.57, 4.64 (AB, 2, CH_2 of benzyl, J_{gem} = 12 Hz), 6.93 (d, 1, H2, $J_{2,3}$ = 16 Hz), 7.05 (m, 1, H3), 7.33 (s, 5, Ph).

Anal. Calcd for $C_{19}H_{26}O_5$: C, 68.24; H, 7.84. Found: C, 67.91; H, 7.99.

5-*O*-Benzyl-2,3,4-trideoxy-6,7-*O*-isopropylidene-D-*erythro*-heptanoic Acid Ethyl Ester (11). A mixture of **9** (4.20 g, 12.6 mmol), ethanol (150 mL), cyclohexene (75 mL), and 20% $Pd(OH)_2/C$ (0.5 g) was vigorously stirred and heated under reflux in a 100 °C bath for 18 h. The catalyst was removed by filtration and washed with ethanol. Evaporation of the filtrate gave **11** as a colorless syrup (3.85 g, 91%): TLC (4:1 hexane–ethyl acetate) R_f 0.48; $[\alpha]^{25}_D$ +10.43° (*c* 0.9, $CHCl_3$); IR 1738 cm^{-1} (ester C=O); 100-MHz NMR ($CDCl_3$) δ 1.27 (t, Me of Et), 1.37, 1.42 (2 s, Me_2C), 1.48–1.90 (m, 4, H3, H4), 2.31 (t, 2, H2, $J_{2,3}$ = 7 Hz), 3.51 (m, 1, H5), 4.00 (m, 3, H6, H7), 4.12 (q, CH_2 of Et), 4.64 (s, CH_2 of benzyl), 7.34 (s, 5, Ph); MS, *m/e* (relative intensity) 336 (<1, M^+), 321 (2, M – Me), 291 (1, M – OEt), 235 (13, M – (2,2-dimethyl-1,3-dioxolan-4-yl)).

Anal. Calcd for $C_{19}H_{28}O_5$: C, 67.83; H, 8.39. Found: C, 67.73; H, 8.58.

2-Deoxy-3-*O*-benzoyl-4,5-*O*-isopropylidene-D-*erythro*-pentose (8) and 5-*O*-Benzoyl-6,7-*O*-isopropylidene-2,3,4-trideoxy-D-*erythro*-hept-2-enoic Acid Ethyl Ester (10). A solution of **6** (1.0 g, 2.42 mmol) in acetonitrile (7 mL) was added dropwise to a stirred mixture of $HgCl_2$ (1.45 g, 5.34 mmol) and yellow HgO (0.58 g, 2.68 mmol) in 4:1 acetonitrile–water (20 mL) at 0–5 °C. The mixture was stirred for 2 h in an ice bath and filtered through a Celite pad. The extract obtained by the addition of 1:1 dichloromethane–hexane was washed with 5 M sodium acetate solution and with brine, dried, and evaporated to yield **8** as a colorless syrup: 200-MHz NMR ($CDCl_3$) δ 1.37, 1.45 (2 s, Me_2C), 2.90 (dt, 2, H2, $J_{1,2}$ = 2 Hz and $J_{2,3}$ = 6.5 Hz), 3.91, 4.16 (AB of ABX, 2, H5, J_{gem} = 9 Hz, $J_{4,5a}$ = 7 Hz and $J_{4,5b}$ = 5.5 Hz), 4.39 (ddd, 1, $J_{3,4}$ = 6.5 Hz, $J_{4,5a}$ = 7 Hz, and $J_{4,5b}$ = 5.5 Hz), 5.53 (q, 1, H3, $J_{2,3}$ = $J_{3,4}$ = 6.5 Hz), 7.45 (t, 2, H3, H5 of Ph, J_{ortho} = 7.5 Hz), 5.58 (d, 1, H4 of Ph, J_{ortho} = 7.5 Hz), 8.03 (d, 2, H2, H6 of Ph, J_{ortho} = 7.5 Hz), 9.87 (t, 1 H1, $J_{1,2}$ = 2 Hz).

A solution of this aldehyde in tetrahydrofuran (5 mL) was added dropwise to a mixture previously prepared by stirring sodium hydride (60 mg, 2.5 mmol) and triethyl phosphonoacetate (583 mg, 2.6 mmol) in tetrahydrofuran (8 mL) at 22 °C for 1 h and cooling to –60 °C. The mixture was kept in a dry ice/ethanol bath for 12 h, and the product was isolated by the addition of ethyl acetate and saturated aqueous ammonium chloride solution, washing the ethyl acetate phase with saturated sodium chloride solution, drying, and evaporation. A flash chromatogram with 1:4 ethyl acetate–hexane separated a small quantity of the cis isomer and gave pure **10** as a colorless syrup: 0.75 g (89%); 100-MHz NMR ($CDCL_3$) δ 1.25 (t, 3, J = 7 Hz, Me of Et), 1.36, 1.40 (2 s, 6, $(CH_3)_2C$), 2.70 (m, 2, H4), 3.80–4.38 (m, 3, $OCHCH_2O$), 5.25 (q, 1, J = 5.5 Hz, H5), 5.81 (dt, 1, $J_{2,3}$ = 15.5 Hz and $J_{1,3}$ = 1 Hz, H2), 6.96 (dt, $J_{2,3}$ = 15.5 Hz and $J_{3,4a}$ = $J_{3,4b}$ = 8 Hz, H3), 7.30 (m, 3, H3,4,5 of Ph), 8.02 (m, 2, H2, H6 of Ph).

Anal. Calcd for $C_{19}H_{24}O_6$: C, 65.50; H, 6.94. Found: C, 65.42; H, 6.95.

Ethyl 5-*O*-Benzoyl-6,7-*O*-isopropylidene-2,3,4-trideoxy-D-*erythro*-heptonate (12). A mixture of diester **10** (5.6 g, 16 mmol), 10% palladium on carbon (0.5 g), and ethanol (40 mL) was stirred at a hydrogen pressure of 2 atm overnight to yield **12** (5.5 g, 97.7%) as a colorless oil after filtration and solvent removal: TLC (4:1 hexane–ethyl acetate) R_f 0.45; $[\alpha]^{25}_D$ +1.07° (*c* 1.0, ethanol), 200-MHz NMR ($CDCl_3$) δ 1.23 (t, 3, J = 7.5 Hz, Me of EtO), 1.36, 1.37 (2 s, 6, Me_2C), 1.79 (m, 4, H3, H4), 2.36 (t, 2, H2, J = 7 Hz), 3.94 (dd, 1, H7a, J_{gem} = 8.5 Hz, $J_{6,7a}$ = 6 Hz), 4.11 (dd, 1, H7b, J_{gem} = 8.5 Hz, $J_{6,7b}$ = 6 Hz), 4.13 (q, CH_2 of Et), 4.29 (dt, $J_{5,6}$ = $J_{6,7a}$ = $J_{6,7b}$ = 6 Hz), 5.25 (m, 1, H5), 7.46 (t, 2, J_{ortho} = 8 Hz, H3, H5 of Ph), 7.75 (tt, 1, J_{meta} = 2 Hz and J_{ortho} = 8 Hz, H4 of Ph), 8.06 (dd, 2, H2, H6 of Ph, J_{ortho} = 8 Hz, J_{meta} = 2 Hz); MS, *m/e* (relative intensity) 335 (19, M – Me), 249 (3, M – (2,2-dimethyl-1,3-dioxolan-4-yl)), 247 (15, M – Me – MeCO – EtO), 170 (14, M – Me – MeCO – PhCOOH), 105 (100, PhCO). Anal. Calcd for $C_{19}H_{26}O_6$: C, 65.13; H, 7.48. Found: C, 65.26; H, 7.56.

Diester **12** was also obtained, by oxidation of benzyl ether **11** as follows. Sodium metaperiodate (1.34 g) and a catalytic amount of ruthenium dioxide (8–10 mg) were added to a stirred solution of 11 (0.5 g) in 2:2:3 tetrachloromethane–acetonitrile–water (50 mL). The mixture was stirred overnight at room temperature, worked up as described,[14a] and purified by chromatography on silica gel with 1:4 ethyl acetate–hexane to give pure **12** (370 mg, 71%).

Ethyl 5-*O*-Benzoyl-2,3,4-trideoxy-D-*erythro*-heptonate (16). A mixture of **12** (5 g, 14.3 mmol), 1 M hydrochloric acid (21 mL), and ethanol (100 mL) was heated in an oil bath at 60 °C for 2 h, cooled, neutralized with sodium hydrogen carbonate, and evaporated. The residue was dissolved in ethyl acetate (100 mL) with a minimum quantity of water. The organic phase was combined with two additional ethyl acetate extracts and dried, and the residue was flash chromatographed on a 6.5 × 18 cm column with a gradient from hexane (2 L) to ethyl acetate (2 L) furnishing 1 g of starting material and 3.5 g of pure **16**:[4] TLC (1:1 hexane–ethyl acetate) R_f 0.20; 100-MHz NMR ($CDCl_3$) δ 1.24 (t, Me of Et, J = 8 Hz), 1.6–2.0 (m, 4, H3, H4), 2.37 (3, t, H2, $J_{2,3}$ = 6.5 Hz), 2.43 (OH), 2.73 (d, OH, J = 6 Hz), 3.67 (m, 3, H6, H7), 4.13 (q, CH_2 of Et), 5.20 (m, 1, H5), 7.50 (m, 3, H3–5 of Bz), 8.07 (dd, 2 H2, H6 of Bz, J_{ortho} = 8 Hz, J_{meta} = 2 Hz); MS, *m/e* (relative intensity) 279 (1, M – CH_2OH), 265 (3, M – EtO), 250 (2, M – H – COOEt), 249 (3, M – $C_2H_5O_2$).

Ethyl 2-*O*-Benzoyl-3,4,5-trideoxy-L-*glycero*-hexuronate (14). Glycol cleavage of **16** was essentially carried out as described for **15**.[2] Lead tetraacetate (4.5 g, 10.1 mmol) was added portionwise over a period of 5 min to a solution of **16** (3.1 g, 10 mmol) in dichloromethane (300 mL) at –40 °C and containing powdered sodium carbonate (9.3 g). The mixture was stirred at –40 °C for 35 min and flash chromatographed directly on a dry silica gel column (3.5 × 20 cm) with diethyl ether (1.5 L). The eluate was washed with aqueous sodium hydrogen carbonate solution and then with brine and dried, to yield **14** as a colorless syrup (2.8 g, 99%) after solvent removal at room temperature; TLC (1:2.5 hexane–ethyl acetate) R_f 0.35; $[\alpha]^{25}_D$ –32.85° (*c* 0.5, chloroform)[23] (lit.[4] $[\alpha]_D$ –46°); IR 1720 cm^{-1} (C=O); 400-MHz NMR ($CDCl_3$) δ 1.26 (t, Me of Et, J = 7.5 Hz), 1.87 (m, 2, H3), 1.98 (m, 2, H4), 2.40 (t, 2, H2, $J_{2,3}$ = 7 Hz), 4.14 (q, CH_2 of Et), 5.25 (dd, 1, H5,

(22) With equimolar reactants the yield of **9** was only 67%.

(23) Assuming the correctness of $[\alpha]_D$ –33.3° for **13**,[2] the calculated $[\alpha]_D$ for **14** is –31.6°, which is in agreement with our observed value but is lower than the reported one.[4]

$J_{4a,5}$ = 4 Hz, $J_{4b,5}$ = 8 Hz), 7.49 (t, 2, H3, H5 of Ph, J_{ortho} = 8 Hz), 7.62 (tt, 1, H4 of Ph, J_{ortho} = 8 Hz, J_{meta} = 1.5 Hz), 8.12 (dd, 1, H2, H6, J_{ortho} = 8 Hz, J_{meta} = 1.5 Hz), 9.65 (d, 1, H6, $J_{5,6} > 1$ Hz); MS, m/e (relative intensity) 278 (<1, M^+), 249 (2, M - CHO), 233 (1, M - EtO), 145 (10, M - Bz - C_2H_4), 128 (7, M - Bz - OEt), 105 (100, Bz).

Anal. Calcd for $C_{15}H_{18}O_5$: C, 64.74; H, 6.52. Found: C, 64.36; H, 6.54.

Ethyl 5,7-Di-*O*-benzoyl-2,3,4-trideoxy-D-*erythro*-heptonate (20). A stirred solution of **16** (115 mg, 0.37 mmol) in pyridine (1.5 mL) was cooled to 0–5 °C, and a solution of benzoyl chloride (54 mg, 0.38 mmol) was added dropwise. The mixture was kept at room temperature overnight and was then evaporated. Flash chromatography on a short column (1:1 ethyl acetate–hexane) eluted the triester. The pooled fractions were washed with dilute phosphoric acid to remove traces of pyridine and then with sodium hydrogen carbonate solution. Drying and evaporation gave **20** as a colorless syrup (125 mg, 81.5%): $[\alpha]^{25}_D$ +19.08° (*c* 0.14, chloroform) (lit.[18c] $[\alpha]^{25}_D$ +17.2%); 200-MHz NMR ($CDCl_3$) δ 1.24 (t, 3, Me of Et, J = 7 Hz), 1.7–2.0 (m, 4, H3, H4), 2.38 (t, 2, H2, $J_{2,3}$ = 7 Hz), 2.88 (d, 1, OH, $J_{6,OH}$ = 5 Hz), 4.13 (q, 2, CH_2 of Et, J = 7 Hz), 4.24 (m, 1, H6), 4.42 (dd, 1 H7a, $J_{6,7a}$ = 6 Hz and J_{gem} = 12 Hz), 4.58 (dd, 1, H7b, $J_{6,7b}$ = 3.5 Hz and J_{gem} = 12 Hz), 5.31 (m, 1, H5).

Anal. Calcd for $C_{23}H_{26}O_7$: C, 66.65; H, 6.35. Found: C, 66.68; H, 6.55.

Registry No. 1, 71160-24-2; 2, 72059-45-1; 3, 111689-68-0; 4, 111689-69-1; 5, 111717-54-5; 6, 111689-70-4; 7, 103795-36-4; 8, 111689-73-7; 9, 111689-71-5; 10, 111689-74-8; 11, 111689-72-6; 12, 111768-78-6; 14, 82493-58-1; 16, 82493-57-0; 18, 73957-99-0; 20, 80311-46-2; D-arabinose, 10323-20-3; D-arabinose dipropyl mercaptal, 107618-44-0; 2,3:4,5-di-*O*-isopropylidene-D-arabinose dipropyl mercaptal, 107418-31-5; triethyl phosphonoacetate, 867-13-0; (*E*)-4,5-*O*-isopropylidene-D-*glycero*-pent-2-enose, 4757-80-6.

Synthesis of Semisynthetic Dipeptides Using *N*-Carboxyanhydrides and Chiral Induction on Raney Nickel. A Method Practical for Large Scale

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Methods useful for both laboratory and large-scale syntheses of the ACE inhibitors enalapril and lisinopril are described. The requisite dipeptides L-alanyl-L-proline and N^ϵ-(trifluoroacetyl)-L-lysyl-L-proline were prepared via *N*-carboxyanhydride (NCA) chemistry. These dipeptides undergo facile reductive alkylation with ethyl 2-oxo-4-phenylbutyrate over Raney nickel with high stereoinduction to afford the direct precursors of enalapril maleate and lisinopril. Kinetic and structural rationalizations are presented for understanding success or failure in forming NCAs and in their subsequent conversions to dipeptides.

Angiotensin-converting enzyme (ACE) inhibition is an effective therapy for the control of hypertension and congestive heart failure.[1a,b] We describe herein three- and five-step convergent syntheses of the ACE inhibitors N^2-[(*S*)-1-(ethoxycarbonyl)-3-phenylpropyl]-L-alanyl-L-proline (enalapril, **1a**)[2a,b] and N^2-[(*S*)-1-carboxy-3-phenylpropyl]-L-lysyl-L-proline (lisinopril, **2a**)[2a,c] from alanine and lysine, respectively, without need for classical protection group chemistry (Scheme I).

Previously reported syntheses of **1a** and **2a** suffered from poor yields due to length and/or poor diastereoselectivity in forming the desired asymmetry at the new optical center.[3a-d] Our approach centers about a reductive amination procedure whereby Schiff base formation followed by catalytic low-pressure hydrogenation in ethanol over Raney nickel affords **1a** and **7a** in 80–90% yield with high diastereoselectivity: **1a**(*SSS*):**1b**(*RSS*) = 87:13[4a] and **7a**(*SSS*):**7b**(*RSS*) = 95:5.[4a,b] The requisite dipeptides L-alanyl-L-proline (**5a**) and N^ϵ-(trifluoroacetyl)-L-lysyl-L-proline (**5b**) were readily prepared in kilogram quantities via *N*-carboxyanhydride (NCA) chemistry in water after first mastering the effects of the countercation and of the organic cosolvent during condensation, and by gaining an initimate understanding of the details of NCA formation.

Results and Discussion

A. Enalapril Maleate (17). *N*-Carboxyanhydride Formation. Except for a recent high-yielding but costly and multistep procedure for the preparation of Ala-NCA (**4a**) from Boc-alanine and oxalyl chloride,[5a] the literature suggests that only moderate yields (60–80%) can be expected for its direct preparation from alanine (**3a**) and phosgene.[5b,c] This is likely due to the near total insolubility of alanine (or alanine hydrochloride) in the reacting medium, which affords a sluggish reaction and thus allows time for side reactions to occur. We now report the preparation of Ala-NCA (**4a**) in 95% yield (unisolated) directly from alanine via an optimized Fuchs–Farthing procedure[5c] (Scheme II) similar to that recommended by Goodman.[5b]

(1) (a) Cleary, J. D.; Taylor, J. W. *Drug Intell. Clin. Pharm.* **1986**, *20*, 177–186. (b) Todd, P. A.; Heel, R. C. *Drugs* **1986**, *31*, 198–248.

(2) (a) Harris, E. E.; Patchett, A. A.; Tristram, E. W.; Wyvratt, M. J. U.S. Patent 4 374 829, 1982. (b) Enalapril is marketed under the trade name Vasotec (Merck & Co., Inc.). (c) Lisinopril will be marketed under the tradenames Prinivil (Merck & Co., Inc.) and Zestril (ICI).

(3) (a) Wyvratt, M. J.; Tristram, E. W.; Ikeler, T. J.; Lohr, N.; Joshua, H.; Springer, J. P.; Arison, B.; Patchett, A. A. *J. Org. Chem.* **1984**, *49*, 2816–2819. (b) Kaltenbronn, J. S.; DeJohn, D.; Krolls, U. *Org. Prep. Proced. Int.* **1983**, *15*, 35–40. (c) Urbach, H.; Henning, R. *Tetrahedron Lett.* **1984**, *25*, 1143–1146. (d) Wu, M. T.; Douglas, A. W.; Ondeyka, D. L.; Payne, L. G.; Ikeler, T. J.; Joshua, H.; Patchett, A. A. *J. Pharm. Sci.* **1985**, *74*, 352–354.

(4) (a) Blacklock, T. J.; Butcher, J. W.; Shuman, R. F. *Pept.: Struct. Funct., Proc. Am. Pept. Symp., 9th, 1985* **1985**, 787–790. (b) Blacklock, T. J.; Shuman, R. F., U.S. Patent pending.

(5) (a) Mobashery, S.; Johnston, M. *J. Org. Chem.* **1985**, *50*, 2200–2202. (b) Fuller, W. D.; Verlander, M. S.; Goodman, M. *Biopolymers* **1976**, *15*, 1869–1871. (c) Farthing, A. *J. Chem. Soc.* **1950**, 3222–3229.

0022-3263/88/1953-0836$01.50/0