δ 51.69, 50.87; IR 3440, 3010, 2980, 1740, 1500, 1290, 1210, 1025, 720 cm^{-1}. Anal.

***N*-[Ethoxy[1-[[(phenylmethoxy)carbonyl]amino]-2-methylpropyl]phosphinyl]-L-alanine methyl ester (7Vc)**: method A, 3:1 EtOAc–hexanes, 75% yield as a mixture of 4 diastereomers in the ratio of 4:4:1:1; ^{1}H NMR δ 7.34 (m, 5), 5.10 (m, 1), 5.00 (d, 0.4, J = 10.6), 4.94 (d, 0.4, J = 10.9), 4.09–3.80 (m, 4), 3.70, 3.70, 3.67, 3.65 (4 s, 3), 3.23 (dd, 0.4, J = 9.4, 9.4), 3.10 (dd, 0.4, J = 9.7, 10.2), 2.23 (m, 1), 1.37–1.19 (m, 6), 1.00–0.93 (m, 6); ^{31}P NMR δ 28.69, 28.13, 27.99, 26.99; IR 3440, 3020, 2990, 1730 (br), 1510, 1390, 1150, 1030 cm^{-1}. Anal.

***N*-[Ethoxy[1-[[(phenylmethoxy)carbonyl]amino]-2-methylpropyl]phosphinyl]-L-phenylalanine methyl ester (7Vd)**: method A, 3:1 EtOAc–hexanes, 74% yield as a mixture of four diastereomers in the ratio of 6:17:26:1; ^{1}H NMR δ 7.36–7.06 (m, 10), 5.11 (m, 2), 5.26, 5.20, 4.96, 4.87 (4 d, 1, J = 10.6), 4.28 (m, 1), 4.03–3.53 (m, 3), 3.68, 3.63, 3.59 (3 s, 3), 3.12–2.75 (m, 3), 2.12 (m, 1), 1.21–1.10 (m, 3), 0.96–0.87 (m, 6); ^{31}P NMR δ 28.49, 28.01, 27.97, 26.85; IR 3440, 3400, 3000, 1725 (b), 1500, 1290, 1240, 1120, 1090, 1030, 700 cm^{-1}. Anal.

***N*-[Ethoxy[1-[[(phenylmethoxy)carbonyl]amino]-2-phenylethyl]phosphinyl]-L-valine methyl ester (7Fe)**: method A, 1:1 EtOAc–hexanes, 67% yield as two separate diastereomers in the ratio of 2:3. Diastereomer A: ^{1}H NMR δ 7.25 (m, 10), 5.19 (d, 1, J = 10.2), 5.01 (d, 1, J = 12.2), 4.96 (d, 1, J = 12.2), 4.28 (m, 1), 4.10–3.98 (m, 2), 3.87 (m, 1), 3.67 (s, 3), 3.21 (ddd, 1, J = 3.0, 3.0, 13.0), 2.91 (m, 1), 2.82 (m, 1), 2.07 (m, 1), 1.24 (t, 3, J = 6.8), 0.94 (d, 3, J = 6.8), 0.78 (d, 3, J = 6.9); ^{31}P NMR δ 28.28. Diastereomer B: ^{1}H NMR δ 7.25 (m, 10), 5.16 (d, 1, J = 9.5), 4.96 (m, 2), 4.27 (m, 1), 4.12–4.06 (m, 2), 3.86 (m, 1), 3.69 (s, 3), 3.23 (m, 1), 3.04 (dd, 1, J = 10.8, 10.8), 2.93 (m, 1), 2.09 (m, 1), 1.29 (m, 3), 0.89 (d, 3, J = 6.8), 0.81 (d, 3, J = 6.9); ^{31}P NMR δ 29.11; IR 3440, 3020, 1730, 1510, 1300, 1215, 1040 cm^{-1}. Anal.

Benzyl ethyl [1-[[(phenylmethoxy)carbonyl]amino]-2-methylpropyl]phosphonate (7Vf): method B, 1:1 EtOAc–hexanes, 52% yield as a mixture of two diastereomers: ^{1}H NMR δ 7.31 (m, 5), 5.07 (m, 5), 4.02 (m, 3), 2.19 (m, 1), 1.19 (q, 3, J = 7.1), 0.99 (d, 3, J = 6.7), 0.98 (d, 3, J = 6.7); ^{31}P NMR δ 25.31; IR 3430, 3000, 1740, 1510, 1290, 1220, 1045, 700, 670 cm^{-1}. Anal.

Ethyl isopropyl [1-[[(phenylmethoxy)carbonyl]amino]-2-methylpropyl]phosphonate (7Vg): method B, 3:2 EtOAc–hexanes, 33% yield as a mixture of two diastereomers; ^{1}H NMR δ 7.23 (m, 5), 5.13 (d, 1, J = 12.2), 5.07 (d, 1, J = 12.2), 5.00 (d, 1, J = 9.5), 4.68 (dq, 1, J = 6.3, 6.3), 4.02 (q, 2, J = 7.1), 3.95 (ddd, 1, J = 4.0, 10.8, 14.3), 2.18 (m, 1), 1.29 (d, 3, J = 6.2), 1.27 (d, 3, J = 6.2), 1.22 (t, 3, J = 7.1), 0.99 (d, 3, J = 6.8), 0.97 (d, 3, J = 6.8); ^{31}P NMR δ 23.73, 23.61; IR 3020, 2990, 1740, 1510, 1290, 1220, 1045, 1010, 725, 670 cm^{-1}. Anal.

Ethyl (2*S*)-2-[[ethoxy[1-[[(phenylmethoxy)carbonyl]amino]-2-methylpropyl]phosphinyl]oxy]propanoate (7Vi): method B, 1:1 EtOAc–hexanes, 60% yield as a mixture of two pairs of diastereomers in the ratio of 17:22:32:28. Diastereomers A and B: ^{1}H NMR δ 7.31 (m, 5), 5.43 (d, 0.5, J = 9.0), 5.11 (m, 2), 5.11–4.60 (m, 1.5), 4.21–3.98 (m, 5), 2.22 (m, 1), 1.53–1.32 (m, 3), 1.27 (t, 3, J = 7.0), 1.25 (t, 3, J = 7.2), 1.02–0.95 (m, 6); ^{31}P NMR δ 25.73, 24.72. Diastereomers C and D: ^{1}H NMR δ 7.34 (m, 5), 5.45 (d, 0.5, J = 9.0), 5.11 (m, 2.5), 5.07–4.80 (m, 1), 4.35 (q, 0.5, J = 7.1), 4.21–3.65 (m, 4.5), 2.24 (m, 1), 1.52 (d, 1.5, J = 6.9), 1.46 (d, 1.5, J = 7.0), 1.39–1.21 (m, 6), 1.01–0.95 (m, 6); ^{31}P NMR δ 26.30, 26.07. Mixture of diastereomers A–D: IR 3020, 2980, 1745, 1510, 1215, 1030, 720 cm^{-1}. Anal.

***N*-[(2*S*)-2-[[Ethoxy[1-[[(phenylmethoxy)carbonyl]amino]-2-phenylethyl]phosphinyl]oxy]-4-methylpentanoyl]-L-alanine methyl ester (7Fj)**: method B, 3:1 EtOAc–hexanes, 47% yield as a 3:2 mixture of diastereomers; ^{1}H NMR δ 7.65 (d, 1, J = 7.4), 7.26 (m, 10), 5.34, 5.04 (br, 1), 5.00 (m, 2), 5.04–4.81 (m, 1), 4.79 (m, 2), 4.11 (m, 2), 3.70, 3.69 (s, 3), 3.26 (m, 1), 2.90 (m, 1), 1.84–1.65 (m, 3), 1.42 (d, 3, J = 7.2), 1.27, 1.25 (t, 3, J = 7.0), 0.93 (m, 6); ^{31}P NMR δ 24.62, 23.93; IR 3440, 3020, 2960, 1720 (br), 1670, 1510, 1450, 1220, 1160, 1035, 700 cm^{-1}. Anal.

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Synthesis of the Dipeptide Hyroxyethylene Isostere of Leu-Val, a Transition State Mimic for the Control of Enzyme Function

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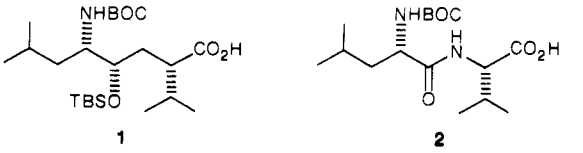
Received March 8, 1988

Dipeptide isosteres have recently begun to attract attention because of their ability to mimic the transition states of proteolytic enzymes or to alter or enhance the function of regulatory peptides. We have developed a general approach that may be used to prepare a diverse array of dipeptide hydroxyethylene isosteres. As an example we have prepared a mimic of Leu-Val, the cleavage site of the enzyme renin. The sequence begins with leucinal **8**, which is converted to the aldehyde **15ct** by addition of vinylmagnesium bromide to form an allylic alcohol. This is converted to the acetonide, ozonized, and equilibrated to give the trans aldehyde **15t** as the primary product. A Wadsworth–Emmons olefination followed by hydrogenation affords the ester **30** as a mixture of isomers. Hydrolysis of the acetonide and purification gives the desired lactone **26β** in 23% overall yield from BOC-leucinol.

The synthesis and biological evaluation of dipeptide isosteres for the development of novel backbone modified peptides that maintain the original side chains is an area of considerable interest.[1] In general, modifications of this type result in increased stability toward enzymatic degradation and may result in greater selectivity, prolonged activity, and improved inhibitory activity.

Scheme I



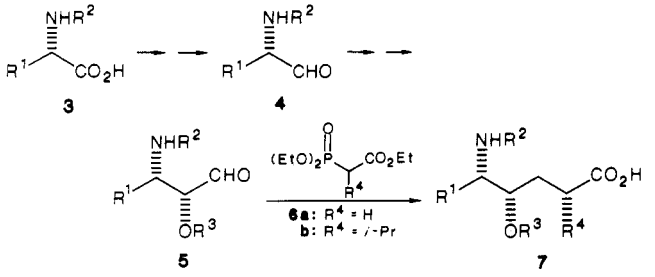
1 **2**

We now describe a stereoselective approach to the synthesis of **1**, a hydroxyethylene isostere of the dipeptide

(1) (a) Tourwe, D. *Janssen Chim. Acta* **1985**, *3*, 3. (b) Holladay, M. W.; Salituro, F. G.; Rich, D. H. *J. Med. Chem.* **1987**, *30*, 375. (c) Holladay, M. W.; Rich, D. H. *Tetrahedron Lett.* **1983**, *24*, 4401. (d) Evans, B. E.; Rittle, K. E.; Homnick, C. F.; Springer, J. P.; Hirshfield, J.; Veber, D. F. *J. Org. Chem.* **1985**, *50*, 4615. (e) Spaltenstein, A.; Carpino, P. A.; Miyake, F.; Hopkins, P. B. *Tetrahedron Lett.* **1986**, *27*, 2095. (f) Hanson, G. J.; Lindberg, T. *J. Org. Chem.* **1985**, *50*, 5399. (g) Kempf, D. J. *J. Org. Chem.* **1986**, *51*, 3921. (h) Fray, A. H.; Kaye, R. L.; Kleinman, E. F. *J. Org. Chem.* **1986**, *51*, 4828.

0022-3263/88/1953-4503$01.50/0

Scheme II



LeuVal **2**, which when incorporated into a renin inhibitory peptide gives it improved stability and activity.

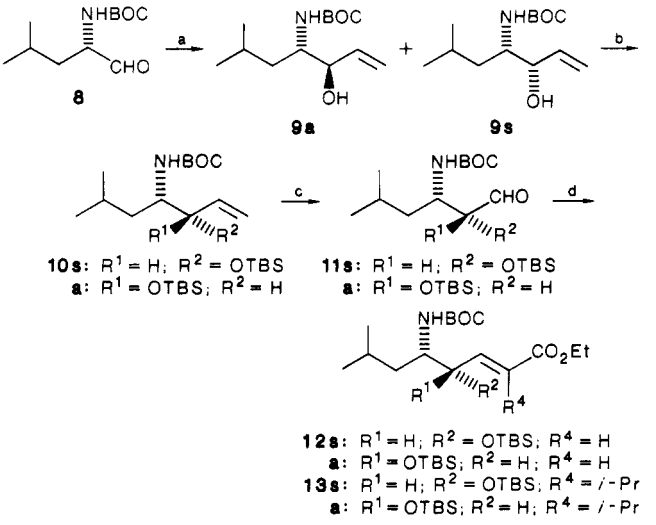
In the development of our design we felt that a strategy that would readily allow modifications of the side chains would be advantageous for the preparation of a variety of derivatives. Scheme II illustrates our design, which has its genesis in the readily available amino aldehydes **4** and the phosphonates **6**. It was felt that these would be ideal starting materials for a variety of hydroxyethylene dipeptide isosteres. The only limitation would be the ability to alkylate the Emmons reagent with suitable precursors of R^4.

Results and Discussion

In keeping with this design and our immediate goal for the preparation of **1**, *t*-BOC-L-leucinal was prepared from *t*-BOC-L-leucine (R^1 = isobutyl, R^2 = *t*-BOC). Thus, diborane reduction of the acid gave the alcohol, which was oxidized with pyr–SO_3 complex in DMSO.[2] It should be noted that other methods for effecting this oxidation generally result in considerable racemization of the aldehyde. Treatment of the aldehyde **8** with vinylmagnesium bromide gives 1:2 mixture of the anti and syn alcohols **9a** and **9s**.[3] The Grignard addition is best performed in toluene at −30 °C in the presence of $LiClO_4$ and gives a 77% yield of the alcohols. Numerous other modifications of the conditions failed to improve the yield or the syn/anti ratio. The primary side reaction in the addition is enolization of the aldehyde since starting material was always isolated from the reaction even when a large excess of Grignard reagent was used. Attempts to suppress enolization through the use of $CeCl_3$ were entirely unsuccessful (perhaps explaining why there are no aldehyde examples in the original publications on the use of this method[4]). In fact, this modification gave only recovered racemic aldehyde, leucinol and a number of unidentified products.

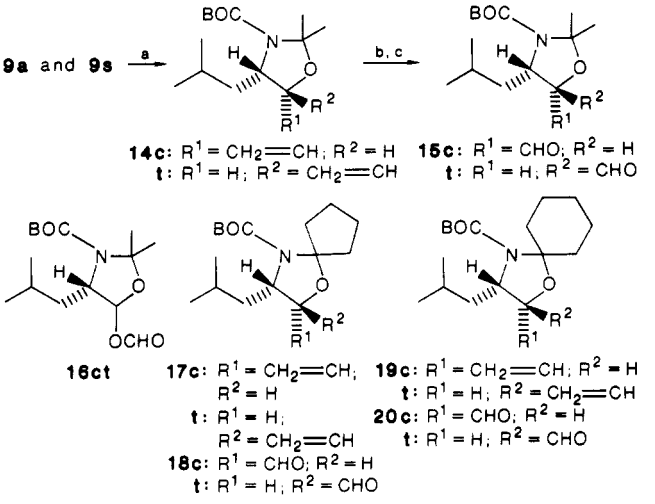
Protection of the alcohols **9a** and **9s** to give the silyl ethers **10s** and **10a** proceeded smoothly. Ozonolysis of the olefin gave a mixture of aldehydes **11s** and **11a**, but all attempts to carry out the Emmons coupling with phosphonate **6b** (R^1 = isopropyl) failed to give any product. Coupling with the unsubstituted phosphonate **6a** (R^4 = H) did proceed smoothly, indicating that steric factors were probably responsible for the failure in the substituted case. The poor syn/anti ratio and the failure of the desired coupling reaction led us to modify the protecting group from a *tert*-butyldimethylsilyl group to an *N,O*-acetonide. This has the advantage of reducing steric congestion around the aldehyde and opens the possibility for equilibration to the desired syn amino alcohol in analogy with Masamune's dioxolanes.[5] The oxazolines **14c** and **14t** were readily prepared from the hydroxy carbamate by treatment with dimethoxypropane, acetone, and TsOH. Ozonolysis of the mixture of olefins **14c** and **14t** in MeOH/CH_2Cl_2 afforded the aldehydes **15c** and **15t**. The ozonolysis initially proved problematic due to the formation of formate **16ct**.[6] The use of trimethyl phosphite or dimethyl sulfide as reductants of the hydroperoxide led to varying quantities of the formate. We found that formate formation could be completely suppressed by the addition of the ozonolysis mixture to a cold Zn/AcOH/H_2O/MeOH mixture. With the aldehyde in hand, the equilibration to the

Scheme III[a]



[a] (a) CH_2=CHMgBr, $PhCH_3$, $LiClO_4$, −30 °C; (b) TBSCl, Im, DMF; (c) MeOH, CH_2Cl_2, O_3, −78 °C; (d) NaH, $(EtO)_2P(O)$-CH_2CO_2Et.

Scheme IV[a]



[a] (a) Dimethoxypropane, TsOH; (b) MeOH, CH_2Cl_2, O_3; Zn, MeOH, AcOH, H_2O; (c) MeOH, K_2CO_3.

(2) For the preparation of protected amino acid aldehydes using the Parikh–Doering oxidation, see: Hamada, Y.; Shioiri, T. *Chem. Pharm. Bull.* **1982**, *30*, 1921. Hamada, Y.; Shioiri, T. *Tetrahedron Lett.* **1982**, *23*, 1193.

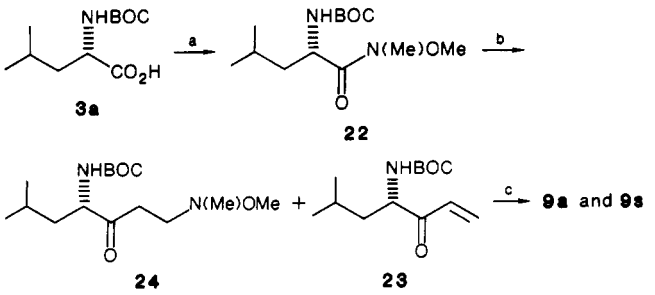
(3) Throughout this paper the descriptors **a** and **s** refer to the anti and syn stereochemical relationship respectively; **c** and **t** refer to cis and trans and **ct** refers to a cis/trans mixture.

(4) Inamoto, T.; Takiyama, N.; Nakamura, K. *Tetrahedron Lett.* **1985**, *26*, 4763. Imamoto, T.; Sugiura, Y.; Takiyama, N. *Tetrahedron Lett.* **1984**, *25*, 4233.

(5) Ko, S. Y.; Lee, A. W. M.; Masamune, S.; Reed, L. A. III; Sharpless, K. B.; Tuddenham, D.; Walker, F. J. *Science (Washington, D.C.)* **1983**, *220*, 949.

(6) For and example of a similar problem, see: Nicolaou, K. C.; Papatjis, D. P.; Claremon, D. A.; Magolda, R. L.; Dolle, R. E. *J. Org. Chem.* **1985**, *50*, 1440.

Scheme V[a]



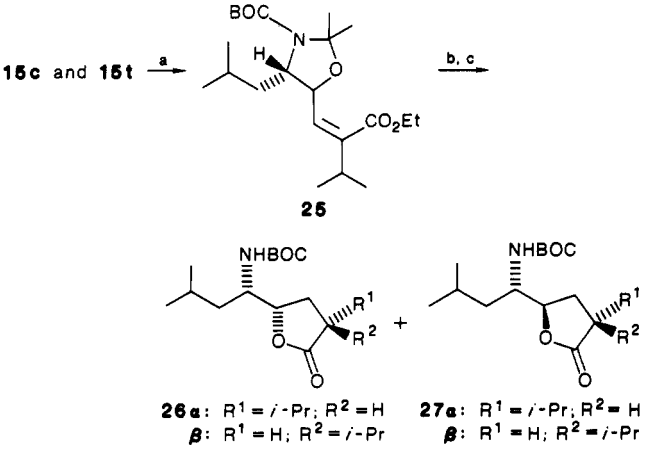
[a] (a) N(Me)OMe·HCl, DEPC; (b) CH_2=$CHMgBr$, THF; (c) $CeCl_3 \cdot 9H_3O$, $NaBH_4$, MeOH.

desired trans isomer was examined. Treatment of a 2:1 trans/cis mixture of aldehydes with K_2CO_3 in methanol gave a 6–7:1 trans/cis ratio of aldehydes **15t** and **15c**. This result is in contrast to the equilibration of the related dioxolanes, which gave trans/cis ratios of >20:1.[7] The less favorable equilibrium in our case is presumably due to the added gauche and 1,3-interactions imposed by the additional substituent on nitrogen as compared to oxygen. Although the 6–7:1 ratio was a major stereochemical improvement, we explored the possibility of enhancing this ratio even further by changing the ketal from a 2,2-dimethyl derivative to a spirocyclopentyl or a spirocyclohexyl derivative. By making the appropriate changes in the sequence, the corresponding cyclohexane and cyclopentane derivatives were prepared and equilibrated. The cyclopentane derivative gave 17:1 ratio of aldehydes **18t** and **18c**; the cyclohexane derivative proved even better, giving a 30:1 ratio of aldehydes **10t** and **20c** (Scheme IV). The ability to enhance the stereochemical preference by changing the nature of the ketal protecting group represents a major advance in the synthesis of stereochemically homogeneous amino alcohol derivatives with no known literature analogy.

We have also explored an alternative approach to **9a** and **9s** which did not proceed through the labile aldehyde **8**. BOC-leucine **3a** was converted to the *N,O*-dimethylhydroxylamine amide **22**[8] with DEPC (diethyl phosphorocyanidate). The amide was then treated with vinylmagnesium bromide to afford enone **23** along with amine **24**, the product of *N,O*-dimethylhydroxylamine addition. Attempts to minimize the amine addition product were not very successful; in fact, the percent of addition proved to be quite variable. After purification by chromatography, the enone **23** was reduced with $NaBH_4/CeCl_3$ in ethanol to afford the allylic alcohols **9a** and **9s** in a 1:1 ratio. Even though this route produced good quality material, it was abandoned in favor of the leucinal approach due to the chromatography so early in the sequence and the unavoidable amine addition byproduct.

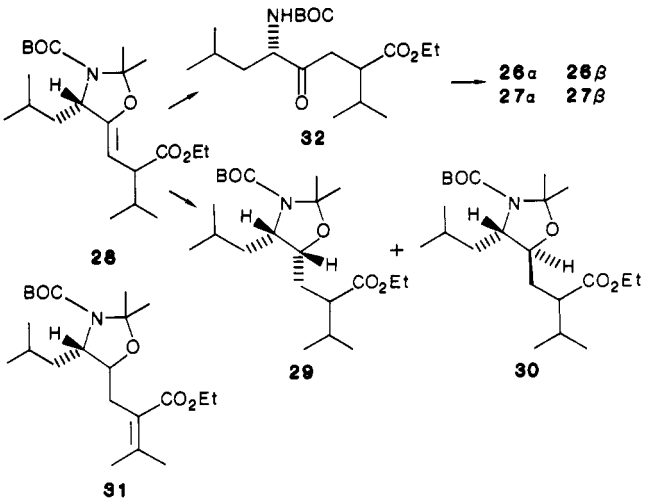
The remaining carbons for the hydroxyethylene isostere were appended via a Wadsorth–Emmons reaction. Thus the 6–7:1 mixture of aldehydes **15t** and **15c** was homologated with the phosphonate **6b** to afford a mixture of esters **25** in 76% yield. The mixture was hydrogenated over rhodium on carbon at 50 psi, and the crude saturated esters were hydrolyzed to form a mixture of lactones **26**α, **26**β, **27**α, and **27**β (Scheme VI). The ratio of **26/27** is 6.4:1, while the ratio of **26**β/**26**α = 1.15:1 and the ratio of **27**β/**27**α = 1.6:1. The isomers are readily purified by a combination of chromatography and crystallization. The

Scheme VI[a]



[a] (a) *t*-BuOK, THF, *6b*; (b) Rh/C, H_2, 50 psi, (c) HCl, AcOH, H_2O.

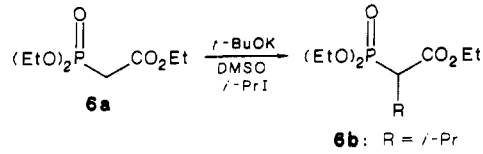
Scheme VII



desired isomer **26**β is the best crystallizer and is thus easily purified. At this point the overall yield of lactone **26**β is 27% based on BOC-leucinal **8**. To our surprise, when the related spirocyclohexyloxazoline **20t** was carried through the sequence, we obtained similar ratios of lactones **26–27**. This was at first attributed to isomerization of either the aldehyde or the unsaturated ester during the Emmons condensation, but later during a large-scale run with the acetonide aldehyde, a considerable quantity of the ketone **32** was isolated. A likely precursor to **32** is vinyl ether **28**, which could result from isomerization of ester **25**. As we could find no evidence for the base-induced isomerization during the Emmons condensation, this suggests the possibility of rhodium-catalyzed isomerization during the hydrogenation. Initial attempts to reduce the olefin **25** with Pd/C led to extensive isomerization to olefin **31**, which was characterized by the two methyl singlets in the NMR at δ 1.87 and 2.03.[9] This unsaturated ester could be reduced but only after extended periods at 50 psi. The use of Rh/C proved far more effective; however, except in one run a considerable amount of ketone **32** was isolated after the hydrolysis. This was established by reduction of **32** to the lactones **26** and **27** with $NaBH_4$. We believe that this ketone has its genesis in a Rh-catalyzed isom-

(7) Masamune, S.; Choy, W. Aldrichimica *Acta* **1982**, *15*, 47.
(8) Dufour, M.-N.; Jouin, P.; Poncet, J.; Pantaloni, A.; Castro, B. *J. Chem. Soc., Perkin Trans. 1*, **1986**, 1895.
(9) For a related example, see: Bernardi, L.; Buchi, G. *Experientia* **1975**, *13*, 466.

Scheme VIII



6a

6b: R = i-Pr

erization of the olefin **25** to the vinyl ether **28**, which upon hydrolysis gives ketone **32**[10] (Scheme VII). Moreover, this isomerization accounts for the fact that regardless of the ratio of the aldehydes going into the Emmons reaction we always obtain similar ratios of final product. The reason for this is probably that once the olefin has isomerized to the vinyl ether **28**, reduction from the less hindered face is preferred, which then leads to the undesired (4*R*) configuration in the final lactone. It should be possible to eliminate this problem by going to higher pressure,[11] but these experiments were not performed.

In order to improve the efficiency of the sequence we examined the isomerization of lactone **26**α. This isomerization gave an equilibrium ratio of β/α isomers of 1:1.7 in accord with the conformational principles governing the relative stabilities of 1,3-disubstituted cyclopentane derivatives[12] and provides a means for converting the wrong isomer into the desired lactone **26**β.

A point that has not been addressed but is rather critical to the overall success of the sequence is the preparation of the phosphonate **6b**. In our early work this phosphonate was prepared by the Arbuzov reaction of methyl 2-bromoisovalerate and triethyl phosphite at 120 °C. It rapidly became clear both from the literature and from practical experience that this was not going to be viable on a large scale since the yield was only 20% and the isolation required a high-vacuum distillation. The fact that malonates could be alkylated with secondary alkyl halides led[13] us to examine the related process with triethyl phosphonoacetate. Thus when a solution of triethyl phosphonoacetate, *t*-BuOK, and isopropyl iodide in DMSO was heated to 40 °C, the phosphonate **6b** was obtained in 93% yield after workup (Scheme VIII).

In conclusion we have developed an efficient synthesis of the hydroxyethylene isostere of the dipeptide Leu-Val, which proceeds in 23% overall yield from BOC-leucinol. Also, since amino aldehyde derivatives are generally available, the chemistry developed here should be applicable to the preparation of a wide variety of dipeptide isosteres.

Experimental Section

(3*R*,4*S*)- and (3*S*,4*S*)-4-[(*tert*-Butyloxycarbonyl)-amino]-6-methyl-1-hepten-3-ol (9). The THF in 11 mL of vinylmagnesium bromide (Aldrich, 1 M) was displaced with 11 mL of toluene under reduced pressure on the rotary evaporator. The vinylmagnesium bromide/toluene solution was transferred via syringe to a 100-mL three-necked flask equipped with a thermometer, addition funnel, and mechanical stirrer. The flask was charged with 10 mL of toluene and 171 mg (1.61 mmol) of lithium perchlorate[14] and cooled to −43 °C. A solution of 1.082 g (5.03 mmol) of BOC-leucinal in 10 mL of toluene was added dropwise over 10 min. The temperature rose to −32 °C. After the solution stirred for 6 min at −32 °C, 4 mL of saturated ammonium chloride were added followed by 20 mL of water and 1 mL of 5% HCl. The product was isolated with ethyl acetate (2 × 25 mL), dried over magnesium sulfate, filtered, and concentrated under reduced pressure to afford a clear oil. Flash chromatography[15] (150 g of silica gel, 20–40% EtOAc/Chex) gave 0.945 g (77.3% yield) of a colorless oil, which crystallized upon standing. The alcohol can be recrystallized from pentane at −50 °C with a 66% recovery, mp 42–47 °C. TLC: EM silica gel 60 20% EtOAc/Chex, R_f 0.19, Ninhydrin char; ^{1}H NMR ($CDCl_3$): 5.80 (m, 1 H), 5.3 (m, 2 H), 4.85 (br d, NH), 4.10 (m, 1 H), 3.7 (m, 1 H), 1.46 (s, *t*-Bu), 0.93 (d, iPr) ppm; ^{13}C NMR ($CDCl_3$): 156.70, 156.33, 138.28, 136.87, 116.30, 115.89, 79.53, 79.12, 75.68, 74.90, 53.41, 53.32, 52.85, 40.64, 38.86, 28.28, 24.72, 23.48, 23.36, 23.22, 21.92, 21.66 ppm. IR (film): 3440, 3021, 2980, 2960, 1705, 1503, 1393, 1369, 1249, 1216, 1166 cm^{-1}. Anal. Calcd for $C_{13}H_{25}NO_3$: C, 64.16; H, 10.36; N, 5.76. Found: C, 64.48; H, 10.29; N, 5.69.

(4*S*,5*R*)- and (4*S*,5*S*)-3-(*tert*-Butyloxycarbonyl)-2,2-dimethyl-5-ethenyl-4-(2-methylpropyl)oxazolidine (14). A solution of 4.33 g (17.78 mmol) of allyl alcohols **9a** and **9s**, 16 mL of 2,2-dimethoxypropane, and 130 mg (0.69 mmol) of *p*-toluenesulfonic acid was stirred under N_2 for 68 h at room temperature. The solution was poured into 300 mL of 3% NaOH and extracted with ethyl ether (2 × 300 mL). The combined ether layers were dried over $MgSO_4$ and concentrated to afford a yellow oil. Purification by flash chromatography on 150 g of silica gel (5–10% EtOAc/Chex) gave 4.04 g (80.1% yield) of a colorless oil as a mixture of syn and anti diastereomers. Anal. Calcd for $C_{16}H_{29}O_3N$: C, 67.81; H, 10.31; N, 4.97. Found: C, 68.91; H, 10.32; N, 4.87. *Note*: The DMF could be replaced with acetone to give a 94.6% crude yield of the acetonide, but this was not optimized. Also the *p*-TsOH could be replaced with Dowex 50W-4X ion exchange resin. TLC conditions: EM silica gel 60, 10% EtOAc/Chex, R_f 0.38, vanillin/sulfuric acid. ^{1}H NMR ($CDCl_3$): 5.9 (m, vinyl CH, 1 H), 5.3 (m, vinyl CH_2, 2 H), 4.5 (t, C*H*O), 4.28 (d of d, J = 3.4 Hz, J = 7.4 Hz), 1.61 (s, 3 H), 1.51 (s, 3 H), 1.48 (s, 9 H), 0.91 (m, iPr) ppm. ^{13}C NMR ($CDCl_3$): 151.71, 138.19, 132.75, 118.88, 117.32, 94.13, 81.70, 79.67, 78.10, 60.37, 58.18, 40.04, 39.65, 28.45, 27.41, 25.38, 25.01, 23.94, 23.47, 22.14, 21.38 ppm. IR (film): 2950, 1795, 1460, 1390, 1360, 1250, 1175, 1085, 925, 770 cm^{-1}.

Cyclohexanespiro-2-[(4*S*,5*R*)- and (4*S*,5*S*)-3-(*tert*-butyloxycarbonyl)-5-ethenyl-4-(2-methylpropyl)oxazolidine] (19ct). To a solution of 1.83 g (7.51 mmol) of allyl alcohols **9a** and **9s** and 5 mL of triethyl orthoformate in 20 mL of freshly distilled cyclohexanone was added 191 mg of Dowex 50W-4X ion exchange resin. The mixture was stirred at room temperature under N_2 for 52 h. The resin was filtered off, and the filtrate was concentrated to an oil under vacuum. The crude oil was purified by flash chromatography (150 g silica gel, 5–30% EtOAc/Chex) to afford 1.64 g (67.6 % yield) of a pale yellow oil. TLC conditions: EM silica gel 60, 10% EtOAc/Chex, R_f 0.29, 0.30, vanillin/sulfuric acid. ^{1}H NMR ($CDCl_3$): 5.97 (m, vinyl CH, 1 H), 5.22 (m, vinyl CH_2, 2 H), 4.28 (br d, C*H*O, 1 H), 3.79 (br s, C*H*N, 1 H), 2.46 (br s, 1 H), 2.13 (br s, 1 H), 1.55 (m, 19 H), 1.19 (br s, 1 H), 0.91 (s, 6 H) ppm. ^{13}C NMR ($CDCl_3$): 151.81, 138.86, 133.16, 118.38, 116.60, 95.50, 81.43, 79.62, 60.31, 58.03, 35.93, 35.06, 28.51, 25.61, 25.09, 24.83, 23.94, 23.41, 23.32, 22.14, 21.43 ppm. HRMS, *m/e* calcd for $C_{19}H_{13}NO_3$ (M^+) 323.2460, found 323.2443. Anal. Calcd for $C_{19}H_{33}NO_3$: C, 70.55; H, 10.28; N, 4.33. Found: C, 70.08; H, 10.24; N, 3.94.

(4*S*,5*R*)- and (4*S*,5*S*)-3-(*tert*-Butyloxycarbonyl)-5-ethenyl-4-(2-methylpropyl)oxazolidine-2-spirocyclopentane (17ct). To a solution of 0.49 g (2.00 mmol) of allyl alcohols **9a** and **9s**, 1 mL of triethyl orthoformate, and 3 mL of cyclopentanone was added 0.110 g of Dowex 50W-4X ion exchange resin. After 3.3 h the suspension was filtered, and the filtrate was concentrated to a yellow oil, which was purified by flash chromatography (60 g of silica gel, 10% EtOAc/Chex) to afford 0.552 g (89.1% yield) of a pale yellow oil. TLC conditions: EM silica gel, 10% EtOAc/Chex, R_f 0.38, Ninhydrin. ^{1}H NMR ($CDCl_3$) (major isomer): 5.95 (m, vinyl CH, 1 H), 5.2 (m, vinyl CH_2, 2 H), 4.1. (d of d, J

(10) For examples, of Rh-catalyzed isomerizations, see: Botteghi, C.; Giacomelli, G. *Gazz. Chim. Ital.* **1976**, *106*, 1131. Smadja, W.; Ville, G.; Georgoulis, C. *J. Chem. Soc., Chem. Commun.* **1980**, 594.

(11) Evans, D. A.; Morrissey, M. M. *J. Am. Chem. Soc.* **1984**, *106*, 3866.

(12) *Conformational Analysis*; Eliel, E., Allinger, N. L. Angyal, S.J., and Morrison, G. A., Eds.; Wiley: New York, 1965; p 189f.

(13) Marvel, C. S. *Organic Synthesis*; Wiley: New York, 1955; Collect. Vol. III, p 495. Vlient, E. B.; Marvel, C. S.; Hsueh, C. M. *Ibid.* 1942; Collect. Vol. II, p 94.

(14) Lithium perchlorate was dried for 72 h at 140 °C (1 Torr).

(15) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

= 2.94 Hz, J = 7.7. Hz, C*H*O, 1 H), 3.73 (br d, C*H*N, 1 H); 2.44 (br s, 1 H), 2.09 (br s, 1 H), 1.65 (br m, 9 H), 1.45 (s, *t*-Bu, 9 H), 0.9 (m, 6 H) ppm. ^{13}C NMR ($CDCl_3$) (both isomers): 151.57, 137.66, 132.83, 118.85, 117.35, 103.23, 81.81, 79.72, 78.49, 60.10, 57.71, 38.05, 28.53, 25.27, 24.94, 24.58, 24.38, 23.93, 21.50 ppm. IR ($CHCl_3$): 2960, 1700, 1460, 1385, 1363, 1250, 1175, 1113, 970, 925, 770 cm^{-1}. HRMS, m/e calcd for $C_{18}H_{31}NO_3$ (M^+) 309.2304, found 309.2298.

(4*S*,5*R*)- and (4*S*,5*S*)-3-(*tert*-Butyloxycarbonyl)-5-formyl-2,2-dimethyl-4-(2-methylpropyl)oxazolidine (15ct). A solution of 1.31 g of olefin **14ct** and two drops of Sudan III indicator solution in 25 mL of a 4:1 mixture of CH_2Cl_2/methanol was cooled to −78 °C and treated with ozone until the red color was bleached. The mixture was then purged with N_2 and cannulated into a −50 °C mixture of methanol/water (50 mL) containing 1.0 g of zinc powder and 1.0 mL of acetic acid. The solution was allowed to warm to room temperature, and the aldehyde was isolated with CH_2Cl_2. Chromatography gave 1.25 g (95% yield) of the aldehyde as mixture of diastereomers. ^{1}H NMR ($CDCl_3$): 9.85 (s, 1 H), 4.14 (br s), 1.62 (s, 3 H), 1.57 (s, 3 H), 1.47 (s, 9 H), (d, J = 6 Hz, 3 H), 0.96 (d, J = 6 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$): 151.14, 84.47, 80.22, 57.41, 56.78, 43.05, 40.34, 29.64, 28.39, 25.72, 23.71, 22.30, 21.18 ppm. IR (film): 3440, 3360, 2705, 1730, 1680, 1462, 1450, 1245, 1170, 1095, 1068, 850, 765 cm^{-1}. Anal. Calcd for $C_{15}H_{27}NO_4$: C, 63.13; H, 9.54; N, 4.91. Found: C, 62.89; H, 9.85; N, 4.64.

Aldehyde Equilibration. A suspension of the aldehyde **15ct** from above and 3.46 g (25.05 mmol) of anhydrous potassium carbonate in 200 mL of methanol was stirred at room temperature under nitrogen for 17.25 h. The solution was reduced in volume to 20 mL, poured into water, and extracted with ethyl acetate (2 × 50 mL). The combined extracts were dried over $MgSO_4$ and concentrated to an amber oil. NMR analysis of the oil shows it to be a 6:1 ratio of aldehydes. In general the ratio varied between 6–7:1, regardless of the base used or the quantity of base.

Cyclohexanespiro-2-[(4*S*,5*R*)- and (4*S*,5*S*)-3-(*tert*-butyloxycarbonyl)-5-formyl-4-(2-methylpropyl)oxazolidine] (20ct). A solution of 1.60 g of olefin **19ct** in a 4:1 mixture of CH_2Cl_2/methanol was cooled to −78 °C and treated with ozone until the characteristic blue color appeared. The solution was quenched with 1 mL of trimethyl phosphite and purged with N_2. The solution was allowed to warm to room temperature, and the aldehyde was isolated with CH_2Cl_2 as a pale yellow oil. ^{1}H NMR ($CDCl_3$): 9.83 (s, 1 H), 4.18 (br s, 1 H), 4.12 (s, 1 H), 2.38 (br s, 2 H), 1.6 (m, 12 H), 1.46 (s, 9 H), 1.24 (br s, 1 H), 0.96 (d, J = 7.2 Hz, 3 H), 0.94 (d, J = 6.4 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$): 202.65, 151.25, 96.67, 84.53, 80.18, 57.47, 56.60, 36.14, 28.44, 25.84, 24.60, 23.71, 23.44, 23.29, 21.22 ppm. HRMS, m/e calcd for $C_{18}H_{31}NO_4$ (M^+) 325.2253, found 325.2238.

Equilibration of the Aldehyde 20ct. A suspension of the aldehyde and 0.70 g (5.08 mmol) of anhydrous potassium carbonate in 50 mL of methanol was stirred at room temperature under nitrogen for 23 h. The solution was reduced in volume to 5–10 mL, poured into water, and extracted with ethyl acetate (2 × 30 mL). The combined extracts were dried over $MgSO_4$ and concentrated to a pale yellow oil. NMR analysis of the oil shows it to be a 30:1 ratio of aldehydes.

(4*S*,5*R*)- and (4*S*,5*S*)-3-(*tert*-Butyloxycarbonyl)-5-formyl-4-(2-methylpropyl)oxazolidine-2-spirocyclopentane (18ct). A solution of 1.49 g of olefin **17ct** in 25 mL of a 4:1 mixture of CH_2Cl_2/methanol was cooled to −78 °C and treated with ozone until the characteristic blue color appeared. The solution was quenched with 1 mL of trimethyl phosphite and purged with N_2. The solution was allowed to warm to room temperature, and the aldehyde was isolated with CH_2Cl_2 as a pale yellow oil. HRMS, m/e calcd for $C_{17}H_{29}NO_4$ (M^+) 311.2096, found 311.2093. ^{1}H NMR ($CDCl_3$): 9.82 (s, 1 H), 4.22 (m, 1 H), 3.48 (m, 1 H), 2.35 (m, 2 H), 1.61 (m, 9 H), 1.48 (d, 9 H), 0.95 (m, 6 H) ppm.

Equilibration of the Aldehyde 18ct. A suspension of the aldehyde and 0.67 g (4.85 mmol) of anhydrous potassium carbonate in 50 mL of methanol was stirred at room temperature under nitrogen for 23 h. The solution was reduced in volume to 5–10 mL, poured into water, and extracted with ethyl acetate (2 × 30 mL). The combined extracts were dried over $MgSO_4$ and concentrated to a pale yellow oil. NMR analysis of the oil showed it to be a 17:1 ratio of aldehydes.

Ethyl 2-(Diethoxyphosphoryl)-3-methylbutanoate (6b). To a solution of 188.26 g (0.84 mol) of triethyl phosphonoacetate in 350 mL of Burdick and Jackson DMSO at room temperature was added 103.68 g (0.92 mol) of *t*-BuOK. This resulted in a temperature rise to 57 °C. After 50 min the *t*-BuOK had all dissolved, and the temperature dropped to 39 °C. 2-Iodopropane was then added dropwise. When half of the iodide was added, the temperature had increased to 81 °C, and the mixture was cooled with an ice bath to 48 °C. The remaining iodide was then added over 5 min, and the ice bath was removed. The mixture was stirred at 50 °C for 40 min at which point GC analysis indicated the reaction to be complete. The mixture was poured into pH 7 buffer and extracted with MTBE (methyl *tert*-butyl ether) (3 × 350 mL). The combined extracts were washed with 500 mL of half-saturated NaCl solution, dried over $MgSO_4$, and concentrated to a pale yellow oil. Vacuum distillation (bp 98–105 °C, 0.32–0.45 Torr) afforded 207.37 g (92.7%) of product shown to be 96.7% pure by capillary GC. ^{1}H NMR ($CDCl_3$): 4.15 (m, 6 H); 2.60 (m, 2 H); 1.30 (m, 9 H) ppm.

(4*S*,5*R*)- and (4*S*,5*S*)-3-(*tert*-Butyloxycarbonyl)-2,2-dimethyl-4-(2-methylpropyl)-5-[3-(ethoxycarbonyl)-4-methyl-1-butenyl]oxazolidine (25). To a solution of 3.87 g (34.5 mmol) of potassium *tert*-butoxide in 40 mL of tetrahydrofuran at room temperature under N_2 was added dropwise over 5 min a solution of phosphonate **6b** (10.46 g, 41.44 mmol) in 20 mL of THF. The temperature rose from 23 °C to 30 °C during the addition. The hazy white solution became clear and orange. After the solution was stirred 34 min at room temperature, a solution of 4.88 g (17.09 mmol) of aldehyde **15ct** in 20 mL of THF was added over 2 min. The temperature rose from 24 °C to 32 °C during the addition. The orange solution was stirred for 1.75 h at room temperature and then at reflux for 3.5 h. The mixture was cooled and poured into 150 mL of water and 10 mL of saturated ammonium chloride, and the product was isolated with 3 × 100 mL of MTBE. The combined organic layers were washed with 100 mL of brine, dried over $MgSO_4$, and concentrated to a yellow oil. The oil was chromatographed on 560 g of silica gel, eluting with one column volume each of 10% and 20% ethyl acetate/cyclohexane to give 5.00 g (76% yield) of a pale yellow oil, which consisted of an inseparable mixture of diastereomers. ^{1}H NMR ($CDCl_3$) for two major diastereomers: 5.76 (d of d, J = 1.0 Hz, J = 9.3 Hz), 4.88 (d of d, J = 3.5 Hz, J = 9.1 Hz), 4.26 (m), 2.73 (m), 1.62 (s, 3 H), 1.49 (s, 3 H), 1.46 (s, 9 H), 1.32 (t, J = 5.7 Hz), 1.09 (d, J = 2.5 Hz), 1.05 (d, J = 4.2 Hz), 0.91 (m) ppm. ^{13}C NMR ($CDCl_3$) as a mixture of diastereomers: 168.0, 151.84, 142.83, 132.07, 79.75, 75.16, 61.46, 60.55, 60.49, 60.33, 40.46, 31.57, 31.35, 31.06, 28.44, 27.81, 27.29, 25.68, 25.15, 25.02, 24.64, 23.87, 22.04, 21.50, 21.38, 21.15, 20.93, 20.72, 20.62, 19.40, 14.18 ppm. IR (film): 1795, 1380, 1335, 1175, 1080, 770 cm^{-1}. Anal. Calcd for $C_{22}H_{39}NO_5$: C, 66.47; H, 9.89; N, 3.52. Found: C, 66.33; H, 9.89; N, 3.40.

(3*S*′,4*S*,5*R*)-, (3*R*′,4*S*,5*R*)-, (3*S*′,4*S*,5*S*)-, and (3*R*′,4*S*,5*S*)-3-(*tert*-Butyloxycarbonyl)-2,2-dimethyl-4-(2-methylpropyl)-5-[3′-(ethoxycarbonyl)-4′-methylbut-1′-yl]-oxazolidine (29, 30). To a solution of 9.2 g (24.0 mmol) of the ester **25** in 200 mL of methanol was addded 1.03 g of 5% Rh/C. This suspension was subjected to 50 psi of hydrogen in a Parr bottle. After 40 min the suspension was filtered through Solka Floc, and the filtrate was concentrated to a colorless oil. Yield 8.68 g, 94%. Anal. Calcd for $C_{22}H_{41}NO_5$: C, 66.13; H, 10.34; N, 3.51. Found: C, 65.83; H, 10.20; N, 3.40. The spectral data were uniformly uninformative due to the overlapping signals for all the isomers.

(2*S*,4*S*,5*S*)-, (2*R*,4*S*,5*S*)-, (2*S*,4*R*,5*S*)-, and (2*R*,4*R*,5*S*)-2-(2-Propyl)-4-hydroxy-5-[(*tert*-butyloxycarbonyl)amino]-7-methyloctanoic Acid γ-Lactone (26α, 26β, 27α, 27β). A solution of 8.68 g (22.5 mmol) of a mixture of esters **29** and **30** in 100 mL of 80% acetic acid/water and 1.5 mL of concentrated hydrochloric acid was stirred at room temperature for 7 h. The solution was poured into 500 mL of 3% NaOH and extracted (2 × 500 mL) with ethyl acetate. The combined ethyl acetate layers were dried over $MgSO_4$ and concentrated to a yellow oil. The crude oil was chromatographed on 560 g of silica gel, eluting with a 20–40% gradient of methyl *tert*-butyl ether/heptane. The fractions containing the lactone **26β** (2.00 g) were combined and crystallized from 30% EtOAc/heptane to afford

1.52 g (21.6% from BOC-leucinal) of white crystals of the (2S,4S,5S) isomer **26β**, which was 99.2% pure by HPLC. Mp: 146-148 °C. $[\alpha]^{25}_D$: -39.4° (c 1, ethanol). ^{1}H NMR ($CDCl_3$): 4.55 (d, J = 9.5 Hz, NH), 4.45 (t, J = 6.1 Hz), 3.86 (br m), 2.58 (br m), 2.0-2.35 (m), 1.48 (s, 9 H), 0.96 (d, J = 5.6 Hz, 3 H), 0.94 (m, 9 H) ppm. ^{13}C NMR ($CDCl_3$): 179.0, 156.08, 80.74, 79.54, 51.68, 45.66, 41.77, 29.07, 28.21, 26.25, 24.67, 22.99, 21.77, 20.27, 18.32 ppm. IR (film): 3427, 3320, 1754, 1667, 1677, 1524, 1275, 1200, 1164, 1060, 1035, 675 cm^{-1}. Anal. Calcd for $C_{17}H_{31}O_4N$: C, 65.14; H, 9.97; N, 4.47. Found: C, 65.35; H, 9.92; N, 4.38.

(2R,4S,5S) Isomer 26α. Mp: 94-96 °C. $[\alpha]_D$: -32.4° (c 1, ethanol). ^{1}H NMR ($CDCl_3$): 4.51 (d, J = 10.0 Hz, NH), 4.32 (d of d, J = 6.1 Hz, Jj = 10.0 Hz), 3.85 (d of t, J = 5.3 Hz, J = 9.9 Hz), 2.6 (m), 2.17 (m), 1.89 (m), 1.65 (m), 1.43 (s, 9 H), 1.01 (d, J = 7.1 Hz, 3 H), 0.92 (d, J = 6.5 Hz, 6 H), 0.88 (d, J = 9.6 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$): 177.92, 155.96, 79.82, 79.44, 50.10, 46.36, 42.37, 28.34, 27.42, 25.83, 24.76, 22.97, 21.84, 20.50, 17.85 ppm. IR (film): 3348, 3336, 1763, 1681, 1523, 1368, 1272, 1161 cm^{-1}. Anal. Calcd for $C_{17}H_{31}O_4N$: C, 65.14; H, 9.97; N, 4.47. Found: C, 65.13, H, 9.87; N, 4.49.

(2S,4R,5S) Isomer 27α. Mp: 86-88.5 °C. $[\alpha]_D$: -56° (c 1, ethanol). ^{1}H NMR ($CDCl_3$): 4.65 (br d, J = 8.7 Hz, NH), 4.29 (br s), 3.78 (br s), 2.60 (m), 2.22 (m), 1.47 (s, 9 H), 1.07 (d, J = 6.7 Hz, 3 H), 0.95 (m, 9 H), ppm. ^{13}C NMR ($CDCl_3$): 177.52, 155.53, 80.46, 51.67, 46.51, 38.90, 28.23, 27.49, 26.78, 24.49, 23.52, 21.33, 20.45, 18.20 ppm. IR (film): 3339, 1785, 1696, 1675, 15.26, 1369, 1172, 1163, 930, 875 cm^{-1}. Found: C, 64.89; H, 9.99; N, 4.32.

The fourth isomer **27β** could not be obtained in pure form.

Keto ester **32** was obtained as a mixture of two diastereomers, from a different run of the sequence. ^{1}H NMR ($CDCl_3$): 5.08 (d, J = 7.6, NH), 5.00 (d, J = 7.2, NH), 4.10 (m, 1 H), 4.12 (m, CH_2O), 3.00 (m, 1 H), 2.79 (m, 1 H), 2.56 (d, J = 2.9 Hz), 2.49 (d, J = 2.9 Hz), 2.00 (m), 1.45 (s, t-Bu), 1.45 (s, t-Bu), 0.94 (m) ppm. ^{13}C NMR ($CDCl_3$): 209.18, 208.68, 174.37, 174.26, 155.45, 79.56, 60.25, 58.11, 57.44, 46.17, 45.73, 40.46, 40.33, 38.67, 37.37, 29.86, 28.20, 26.88, 24.82, 24.67, 23.24, 23.14, 21.68, 21.50, 20.05, 19.97, 19.51, 14.12 ppm. IR (film): 3350, 1720, 1705, 1510, 1365, 1250, 1170, 1010, 1020 cm^{-1}. Anal. Calcd for $C_{19}H_{35}O_5N$: C, 63.84; H, 9.87; N, 3.92. Found: C, 63.74; H, 10.07; N, 3.87.

4-[(*tert*-Butoxycarbonyl)amino]-6-methyl-1-hepten-3-one (23). A solution of 6.78 mmol of vinylmagnesium bromide in 20 mL of THF was cooled to -78 °C. A solution of 620 mg (2.26 mmol) of the amide in 5 mL of THF was then slowly added. After being stirred for 0.5 h, the mixture was warmed to room temperature and stirred overnight. The reaction mixture was poured into 40 mL of water and 2 mL of 2 N HCl and extracted with 4 × 20 mL of ethyl acetate. The combined ethyl acetate washes were dried over $MgSO_4$ and concentrated to afford an oil, which was chromatographed on silica gel with 15% EtOAc/hexane to afford 384 mg (70% yield) of the enone **23** along with 121 mg of the amine addition product. $[\alpha]_D$: -8.4°, (c 1.18, EtOH). ^{1}H NMR ($CDCl_3$): 6.40 (m, 2 H), 5.87 (d of d, J = 1.2 Hz, J = 9.85 Hz, 1 H), 5.16 (d, J = 8.0 Hz, 1 H), 4.63 (d of t, J = 3.9 Hz, J = 9.2 Hz, 1 H), 1.70 (m, 1 H), 1.50 (m, 2 H), 1.41 (s, 9 H), 0.97 (d, J = 6.5 Hz, 3 H), 0.90 (d, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$): 199.14, 155.46, 133.34, 129.57, 79.57, 55.66, 41.37, 28.23, 24.80, 23.19, 21.77 ppm. IR (film): 3340, 1700, 1610, 1510, 1500, 1362, 1250, 1155, 1040, 1020, 970, 775 cm^{-1}.

***N*-Methyl-*N*-methoxy-2-[(*tert*-Butoxycarbonyl)-amino]-4-methylpentanamide (22).** A solution of 30 mL of CH_2Cl_2, 2.49 g (10.0 mmol) of BOC-leucine, 2.8 mL (20.0 mmol) of triethylamine, and 1.2 g (12.0 mmol) of *N,O*-dimethylhydroxylamine hydrochoride at room temperature was treated with 3.03 mL (20.0 mmol) of DEPC (diethyl phosphorocyanidate). This resulted in an exothermic reaction (>40 °C). The solution was allowed to cool and stir overnight at room temperature and was poured into water, and the product was isolated with methylene chloride (3 × 25 mL). The methylene chloride extracts were washed with sodium bicarbonate, dried over $MgSO_4$, and concentrated to afford 2.57 g (94%) of the amide. MS, *m/e* calcd for $C_{13}H_{26}N_2O_4$: 275.1971. Found: 279.1958. $[\alpha]_D$: -27° (c 9.36, EtOH). ^{1}H NMR ($CDCl_3$): 5.00 (d, J = 9 Hz, NH), 4.74 (m, 1 H), 3.75 (s, 3 H), 3.1. (s, 3 H), 1.43 (s, 9 H), 1.00 (d, J = 3 Hz, 3 H), 0.92 (d, J = 3 Hz, 3 H) ppm. IR (film): 3323, 1710, 1660, 1500, 1390, 1365, 1250, 1170, 1045, 1020, 990 cm^{-1}.

Reduction of Enone 23. Sodium borohydride (114 mg, 3.0 mmol) was added to a solution of the enone (30 mg, 1.25 mmol) and $CeCl_3$ (47 mg, 0.125 mmol) in 5 mL of methanol at room temperature. The addition resulted in the vigorous evolution of gas. After 10 min TLC showed the reaction to be complete. The mixture was poured into water, and the allylic alcohols were isolated with ethyl acetate (3 × 20 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated to afford 290 mg (98% yield) of a viscous oil, which was identical with a sample of **9** prepared by the Grignard route except that the syn/anti ratio was 1:1 as determined by HPLC (1.5 mL/min, 15% EtOAc/hexane, silica gel, RI detector). The spectra data are identical with material prepared from the aldehyde.

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Total Synthesis of Sesquiterpenes via Intramolecular Ketene Cycloadditions: Isocomene and α-*cis*- and α-*trans*-Bergamotenes, an Approach to Seychellene

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Cyclobutanone **2**, a late intermediate in Wenkert's isocomene synthesis, was prepared by a six-step sequence in 10% overall yield. Carroll rearrangement of acetoacetate **9** gave ketone **10**. Peterson olefination with ethyl (trimethylsilyl)propionate followed by hydrolysis gave acid **12** as a mixture of double bond position isomers. Addition of the corresponding acid chlorides **13** to Et_3N in toluene at reflux gave cyclobutanone **4**. Isomerization of the double bond of **4** with hydriodic acid gave **2**. Isomerization of β-bergamotenes with hydriodic acid in benzene provided an effective route to the α-bergamotenes. Tricyclic ketone **28** was prepared by oxy-Cope rearrangement of allylic alcohol **27**. Oxy-Cope rearrangement of propargylic alcohol **32** gave cyclooctadienone **33**. Under some reaction conditions **33** was converted to cyclooctatrienolate **35**, which was protonated to give **36** and underwent electrocyclic ring opening to give **38**.

Stereospecific intramolecular cycloaddition of ketenes to alkenes has been extensively developed recently as a general method for the synthesis of polycyclic cyclobutanones.[2-4] Since this reaction proceeds in optimal yield

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