Synthesis of FPL 64176 by 1,3-Dipolar Cycloaddition

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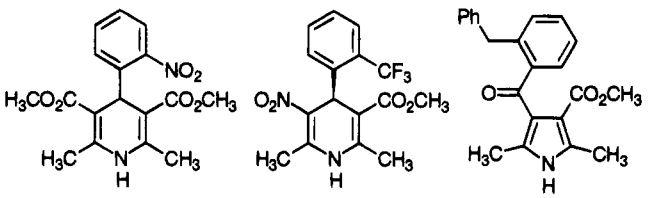
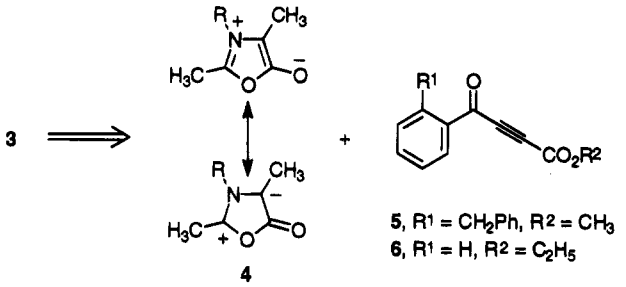
The regulation of calcium movement is critically important for cellular survival and function. It is therefore not surprising that cells have developed a variety of ways to both transport and store calcium. One of the major pathways in which calcium enters the cell is by passage through voltage-dependent calcium channels. Several types of voltage-dependent calcium channels are known, the best characterized being the L-type channel. This is largely due to the availability of a variety of synthetic ligands which act at this channel. Several classes of compounds are known to block the L-channel,[1,2] the best known being 1,4-dihydropyridines, exemplified by agents such as nifedipine (**1**). Comparatively, only a small number of compounds are known to promote calcium entry through the L-channel.[3,4] Most of these compounds are 1,4-dihydropyridines such as (*S*)-Bay K 8644 (**2**).[5] Recently a novel benzoylpyrrole, FPL 64176 (**3**), was described as a potent activator of L-type calcium channels.[6-8] Having exhausted the supply of **3** which had been graciously provided by Fisons, and desiring to study this compound in more detail by patch clamp electrophysiology, we decided to undertake its synthesis. In this note we describe a new synthesis of **3** which involves the 1,3-dipolar cycloaddition of an *in situ*-generated azomethine ylide and an electron deficient acetylene.



1 **2** **3**

In a retrosynthetic sense, we believed that **3** could be derived from the 1,3-dipolar cycloaddition of mesoionic 1,3-oxazole **4**[9] and electron deficient acetylene **5**. Mesoionic oxazoles such as **4** may be generated *in situ* by the acetic anhydride-induced tandem acetylation–cyclodehydration of appropriately substituted amino acids. Interception of the azomethine ylide contained within **4** by the dipolarophile and subsequent loss of CO_2 from the primary cycloadduct would be expected to afford a 1-substituted pyrrole.[10] Removal of the substituent from the pyrrole nitrogen should complete the synthesis.

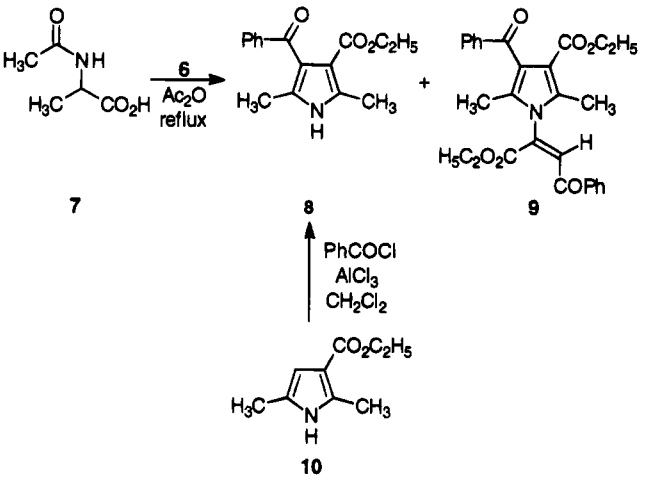
The dipolarophiles used in this study were prepared according to known procedures. Thus, generation of the lithium acetylides of either methyl or ethyl propiolate with *n*-BuLi in THF/ether at −100 °C and subsequent reaction with either 2-benzylbenzaldehyde or benzaldehyde afforded the corresponding carbinols. Jones oxidation of these carbinols cleanly gave the desired activated alkynes **5** and **6**.[11]



4

5, $R^1 = CH_2Ph$, $R^2 = CH_3$
6, $R^1 = H$, $R^2 = C_2H_5$

In model studies, we examined the cycloadditions of **6** to *in situ*-generated mesoionic 1,3-oxazoles. For example, refluxing a mixture of *N*-acetylalanine (**7**), **6**, and acetic anhydride afforded a complex mixture from which pyrroles **8** and **9** were isolated in low yield. The structure of **8** was confirmed by alternate synthesis. Friedel–Crafts acylation of ethyl 2,5-dimethylpyrrole-3-carboxylate (**10**) with benzoyl chloride/$AlCl_3$ gave **8** which was identical in all respects to the product isolated from the cycloaddition. The structure of **9** was assigned on the



7 **8** **9** **10**

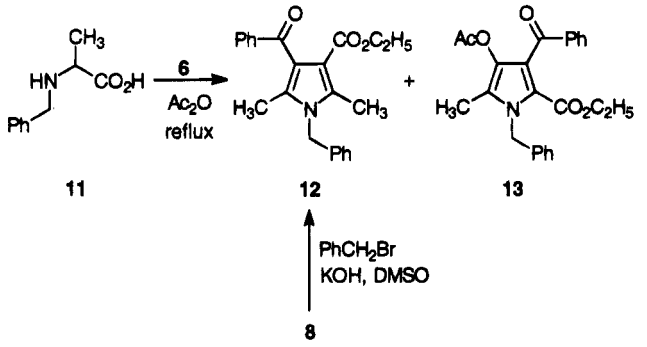
basis of NMR techniques which were able to differentiate between the four possible olefin isomers. In the ^1H-coupled ^{13}C NMR spectrum, no resolved coupling was observed between the olefinic proton and the carbon of the benzoyl carbonyl group, indicating a geminal relationship between these nuclei. Consistent with this, a 10 Hz ($^3J_{CO,H}$) coupling was observed between the olefinic proton and the carbon of the carboxylic ester carbonyl, indicating a vicinal relationship between these nuclei.

(1) Janis, R. A.; Silver, P. J.; Triggle, D. J. *Adv. Drug Res.* **1987**, *16*, 311–591.
(2) Rampe, D.; Triggle, D. J. *Trends Pharmacol. Sci.* **1990**, *11*, 112–115.
(3) Triggle, D. J.; Rampe, D. *Trends Pharmacol. Sci.* **1989**, *10*, 507–511.
(4) Rampe, D.; Kane, J. M. *Drug Dev. Res.* **1994**, *33*, 344–363.
(5) Schramm, M. G.; Towart, T. R.; Franckowiak, G. *Nature (Lond.)* **1983**, *303*, 535–537.
(6) McKechine, K.; Killingback, P. G.; Naya, I.; O'Conner, S. E.; Smith, G. W.; Wattam, D. G.; Wells, E.; Whitehead, Y. M.; Williams, G. E. *Br. J. Pharmacol.* **1989**, *98*, 673P.
(7) Zheng, W.; Rampe, D.; Triggle, D. J. *Mol. Pharmacol.* **1991**, *40*, 734–741.
(8) Rampe, D.; Lacerda, A. E. *J. Pharmacol. Exp. Ther.* **1991**, *259*, 982–987.
(9) Gingrich, H. L.; Baum, J. S. *The Chemistry of Heterocyclic Compounds*; Weissberger, A.; Taylor, E. C., Ed.; Wiley: New York, 1986; Vol. 45, pp 731-961.
(10) Huisgen, R.; Gotthardt, H.; Bayer, H. O.; Schaefer, F. C. *Chem. Ber.* **1970**, *103*, 2611–2624.
(11) Midland, M. M.; Tramontano, A.; Cable, J. R. *J. Org. Chem.* **1980**, *45*, 28–29.

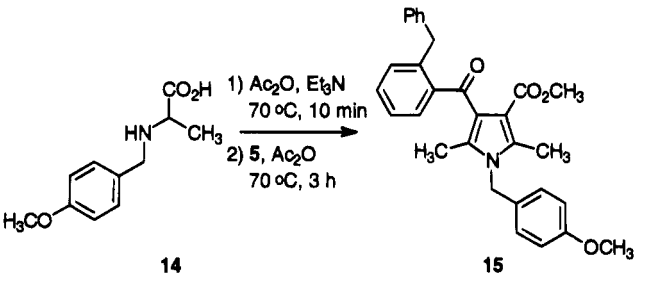
0022-3263/95/1960-4947$09.00/0

This value, however, was intermediate in magnitude for distinguishing (*E*)- versus (*Z*)-olefin geometry[12] so it could not be used for that assignment. The olefin geometry was assigned as depicted in **9** based on strong NOEs observed between both of the pyrrole methyl groups and the olefinic proton. These NOEs would not be observed for the (*Z*)-isomer.

In order to prevent Michael addition of the desired pyrrole to the dipolarophile, a blocking group for the pyrrole nitrogen was clearly required. We therefore examined the reaction of *N*-benzylalanine (**11**) and **6**. Refluxing a mixture of **11**, benzoylacetylene **6**, and acetic anhydride resulted in the isolation of pyrroles **12** and **13** in 6% and 24% yields, respectively. The structure of **12** was easily verified by alternate synthesis. Thus, benzylation of **8** gave **12** which was also identical with the minor product from the cycloaddition. The major identifiable product of the cycloaddition, pyrrole **13**, was examined by spectral techniques and the various fragments were identified; however, the specific structure could not be discerned. Ultimately its structure was proven by single crystal x-ray analysis.[13] The formation of **13** presumably occurred by Michael addition of *N*-benzylalanine to the dipolarophile followed by ring closure and subsequent acetylation.[14,15] To the best of our knowledge, the formation of acetoxypyrroles such as **13** has not been described as a competing reaction with the 1,3-dipolar cycloaddition process.



The isolation of the desired cycloadduct **12** as a low yielding minor product was at first disappointing. On the other hand, since Michael addition of **11** to the dipolarophile was competing with cyclodehydration to the mesoionic **4** (R = CH_2Ph), it seemed plausible that the formation of **13** could be circumvented by simply forming the mesoionic species in the absence of the dipolarophile. This indeed proved to be the case since reaction of *N*-benzylalanine (**11**), Et_3N, and acetic anhydride at 70 °C for 5 min followed by addition of **6** gave the desired pyrrole **12** in 58% yield with no observable formation of **13** by TLC. Similarly, reaction of 4-methoxybenzylalanine (**14**)[16] and **5** gave pyrrole **15** in 56% yield. While these results were encouraging, we could not complete the synthesis of FPL 64176 using either of these materials since the benzyl protecting groups on both **12** and **15** could not be effectively removed under a variety of conditions (*e.g.*, H_2, $Pd(OH)_2/C$; $AlCl_3$, anisole; CAN, aqueous CH_3CN).



In our search for a suitable protecting group for the pyrrole nitrogen, we recently became aware of a publication describing the 4-nitrophenethyl group as a protecting group for pyrroles containing electron-withdrawing groups.[17] Removal of this protecting group may be accomplished by treatment with DBU in acetonitrile. These conditions seemed ideally suited to our needs. We therefore decided to examine *N*-(4-nitrophenethyl)alanine (**19**) as a precursor to 1,3-oxazole **4** (R = $4\text{-}NO_2C_6H_4CH_2CH_2$). Reaction of 4-nitrophenethylamine (**16**) and ethyl α-bromopropionate (**17**) gave the desired amino ester **18** in 81% yield. Hydrolysis of the carboxylic ester with LiOH and subsequent acidification gave the corresponding amino acid **19**. Heating **19** to 70 °C in acetic anhydride in the presence of Et_3N, followed by addition of alkyne **5**, afforded the desired cycloadduct **20** in 49% yield. Heating a solution of **20**, DBU, and DMF to 100 °C for 3 h gave FPL 64176 (**3**) in 85% yield. This material was identical in all respects to an authentic sample prepared by our previously published Friedel–Crafts based route.[18]

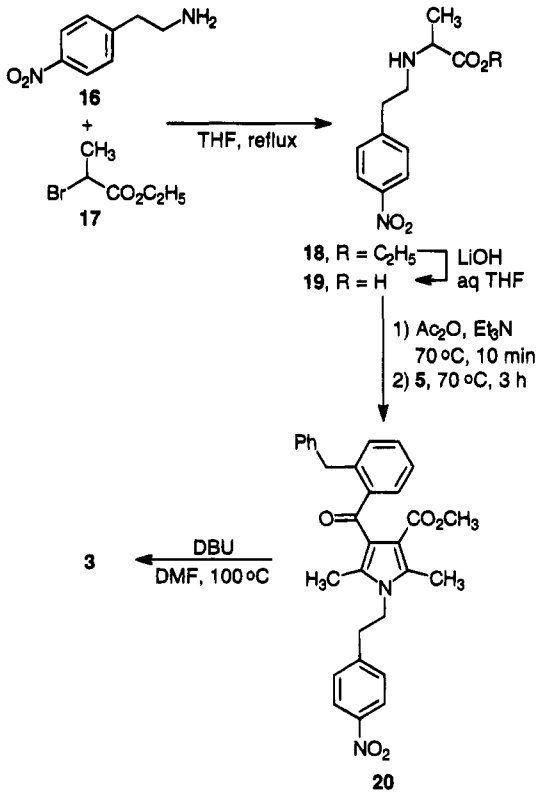
In conclusion, we have prepared FPL 64176 in four linear steps from commercially available starting materials using a 1,3-dipolar cycloaddition-based route. In addition, the viability of the 4-nitrophenethyl protecting group in this type of reaction sequence has been demonstrated.

Experimental Section

Melting points are uncorrected. ^{1}H-NMR spectra were obtained at 300 MHz. Chemical shifts are reported in δ values with Me_4Si (δ = 0.00) as an internal standard for ^{1}H spectra. The ^{13}C-NMR spectra were referenced using the literature chemical shift values versus Me_4Si of the NMR solvents $CDCl_3$ (δ = 77.0), DMSO-d_6 (δ = 39.5). ^{1}H- and ^{13}C-NMR spectra determined in D_2O were referenced to external sodium 3-(trimethylsilyl)propionate (δ = 0.00). When necessary, additional 1D- and 2D-NMR spectra were obtained using standard Varian pulse sequences to aid in structure assignments. Criteria used to establish identity were superimposable IR and NMR spectra, mixture mp determination, and identical R_f values in two solvent systems.

Methyl 4-Hydroxy-4-(2-benzylphenyl)-2-butynoate. To a solution of methyl propiolate (0.76 g, 9.0 mmol) in 4:1 THF/ether (10 mL) at −100 °C was added dropwise *n*-BuLi (3.7 mL, 2.5 M, 9.2 mmol). After 10 min, a solution of 2-benzylbenzaldehyde[19] (1.68 g, 8.57 mmol) in THF (5 mL) was added dropwise and the reaction was allowed to warm slowly to rt (*ca.* 3 h). A saturated solution of NH_4Cl (4 mL) was added. The aqueous layer was acidified (pH ~ 4) with 1 N HCl (2 mL) before being extracted with ether (3 × 10 mL). The combined organic extracts

(12) Gregory, B.; Hinz, W.; Jones, R. A.; Arques, J. S. *J. Chem. Res. (S)* **1984**, 311.
(13) X-ray analysis performed by Dr. J. C. Huffman, Department of Chemistry, Indiana University, Bloomington, IN 47405-4001.
(14) Kolar, P.; Tisler, M. *Synth. Commun.* **1994**, *24*, 1887–1893.
(15) Gupta, S. K. *Synthesis* **1975**, 726–727.
(16) Quitt, P.; Hellerbach, J.; Vogler, K. *Helv. Chim. Acta* **1963**, *46*, 327–333.
(17) Edstrom, E. D.; Wei, Y. *J. Org. Chem.* **1994**, *59*, 6902–6903.
(18) Dalton, C. R.; Kane, J. M.; Rampe, D. *Tetrahedron Lett.* **1992**, *33*, 5713–5716.
(19) Durst, T.; Kozma, E. C.; Charlton, J. L. *J. Org. Chem.* **1985**, *50*, 4829–4833.



were dried over $MgSO_4$. The solvent was evaporated at reduced pressure. The residue was purified by flash chromatography[20] (25% EtOAc/hexane) affording the desired alcohol as a yellow oil: 2.26 g (94%); IR (thin film) 3414 (OH), 2237 (C≡C), 1716 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.66 (m, 1H), 7.31–7.11 (m, 8H), 5.66 (d, 1H, J = 5.8 Hz), 4.18 (d, 1H, J = 16.0 Hz), 4.11 (d, 1H, J = 16.0 Hz), 3.75 (s, 3H), 2.45 (d, 1H, J = 5.8 Hz); ^{13}C NMR ($CDCl_3$) δ 153.7, 139.9, 138.3, 136.5, 131.1, 129.2, 128.7, 128.6, 127.3, 127.1, 126.3, 86.4, 77.6, 61.7, 52.8, 38.3; EIMS, m/z (relative intensity) 280 (100, M^+). Anal. Calcd for $C_{18}H_{16}O_3$: C, 77.13; H, 5.75. Found: C, 77.31; H, 5.83.

Methyl 4-Oxo-4-(2-benzylphenyl)-2-butynoate (5). To a solution of methyl 4-hydroxy-4-(2-benzylphenyl)-2-butynoate (1.50 g, 5.34 mmol) in ether (20 mL) at 0 °C was added Jones reagent (10.7 mL of a solution of 5% CrO_3 in 10% H_2SO_4, 5.34 mmol).[19] After 20 min, the aqueous portion was extracted with ether (3 × 10 mL). The combined organic portions were dried over $MgSO_4$, and the solvent was evaporated at reduced pressure. The residue was purified by flash chromatography (25% EtOAc/hexane) affording **5** as a yellow oil: 1.04 g (70%); IR (thin film) 1722 (CO), 1653 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.21 (dd, 1H, J = 0.4, 6.8 Hz), 7.51 (dt, 1H, J = 1.5, 7.5 Hz), 7.39 (t, 1H, J = 7.5 Hz), 7.29–7.11 (m, 6H), 4.41 (s, 2H), 3.85 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 177.0, 152.7, 143.5, 139.8, 134.2, 134.0, 133.7, 132.1, 129.0, 128.3, 126.6, 126.1, 81.2, 79.3, 53.3, 39.3; EIMS, m/z (relative intensity) 278 (100, M^+). Anal. Calcd for $C_{18}H_{14}O_3$: C, 77.68; H, 5.07. Found: C, 77.78; H, 5.36.

Ethyl 4-Benzoyl-2,5-dimethylpyrrole-3-carboxylate (8) and Ethyl (*E*)-3-Benzoyl-4-(ethoxycarbonyl)-2,5-dimethyl-α-(2-oxo-2-phenylethylidene)-1*H*-pyrrole-1-acetate (9). A mixture of D,L-*N*-acetylalanine (1.26 g, 9.61 mmol), ethyl 4-oxo-4-phenyl-2-butynoate (1.94 g, 9.61 mmol), and Ac_2O (10 mL) was heated with occasional swirling on a steam bath for 1 h. The excess Ac_2O was evaporated at reduced pressure leaving a brownish oil. Purification of the oil by flash chromatography using the step gradient 4% EtOAc/CH_2Cl_2 and 10% EtOAc/CH_2Cl_2 afforded two products, one with R_f = 0.17 (10% EtOAc/CH_2Cl_2) and the other with R_f = 0.60 (10% EtOAc/CH_2Cl_2). Further purification of the lower R_f material by radial chromatography (10% EtOAc/CH_2Cl_2, 4 mm plate) and subsequent crystallization from EtOAc/cyclohexane afforded **8** as colorless, matted needles: 0.22 g (8.4%); mp 133–135 °C; IR (KBr) 3296 (NH), 1673 (CO), 1639 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.01 (br s, 1H), 7.84–7.79 (m 2H), 7.53–7.36 (m, 3H), 3.74 (q, 2H, J = 7.1 Hz), 2.47 (s, 3H), 2.21 (s, 3H), 0.75 (t, 3H, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$) δ 194.3, 164.9, 140.1, 134.2, 132.2, 130.6, 129.1, 128.2, 120.5, 112.1, 59.5, 13.5, 12.5, 11.7; EIMS, m/z (relative intensity) 271 (47, M^+), 225 (100). Anal. Calcd for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32; N, 5.16. Found: C, 70.70; H, 6.40; N, 4.98. Trituration of the higher R_f material with Et_2O afforded a solid. Crystallization from EtOAc/hexane gave **9** as off-white needles: 0.50 g (22%); mp 141–143 °C; IR (KBr) 1722 (CO), 1700 (CO), 1673 (CO), 1653 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.02–7.97 (m, 2H), 7.88–7.83 (m, 2H), 7.70–7.38 (m, 6H), 7.08 (s, 1H), 4.13 (q, 2H, J = 7.1 Hz), 3.78 (q, 2H, J = 7.1 Hz), 2.55 (s, 3H), 2.29 (s, 3H), 1.05 (t, 3H, J = 7.1 Hz), 0.78 (t, 3H, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$) δ 193.5, 190.1, 164.4, 161.8, 140.5, 139.7, 136.0, 135.5, 134.3, 132.3, 132.2, 132.1, 129.1, 129.0, 128.7, 128.2, 121.3, 113.0, 62.8, 59.8, 13.5, 13.4, 11.8, 11.3; EIMS, m/z (relative intensity) 473 (30, M^+), 105 (100). Anal. Calcd for $C_{28}H_{27}NO_6$: C, 71.02; H, 5.75; N, 2.96. Found: C, 70.91; H, 5.86; N, 3.10.

Alternate Synthesis of 8. $AlCl_3$ (2.00 g, 15.0 mmol) was added portionwise to a stirred, room temperature solution of ethyl 2,5-dimethylpyrrole-3-carboxylate[21] (1.35 g, 8.07 mmol) and benzoyl chloride (1.17 g, 8.32 mmol) in CH_2Cl_2. After 30 min, the reaction was carefully poured into H_2O. The resulting mixture was stirred for 1 h before being extracted with CH_2Cl_2 (3 × 150 mL). The extracts were combined and dried over anhydrous $MgSO_4$. The solvent was evaporated at reduced pressure leaving a solid. Crystallization from acetone/hexane afforded **8** as colorless, matted needles: 1.95 g (91%); mp 134–135 °C, mixture mp 134–135 °C; spectral data identical to that presented above. Anal. Calcd for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32; N, 5.16. Found: C, 70.75; H, 6.29; N, 5.10.

Ethyl 4-Benzoyl-1-benzyl-2,5-dimethylpyrrole-3-carboxylate (12) and Ethyl 4-Acetoxy-3-benzoyl-1-benzyl-5-methylpyrrole-2-carboxylate (13).[22] A mixture of D,L-*N*-benzylalanine (2.93 g, 16.3 mmol), ethyl 4-oxo-4-phenyl-2-butynoate (3.28 g, 16.2 mmol), and Ac_2O (25 mL) was heated with occasional swirling on the steam bath for 30 min and then at reflux for 10 min. The excess Ac_2O was evaporated at reduced pressure leaving a greenish oil. Purification of the oil by flash chromatography (1.5% EtOAc/CH_2Cl_2) afforded two products, an oil with R_f = 0.22 (1.5% EtOAc/CH_2Cl_2) and a solid with R_f = 0.30 (1.5% EtOAc/CH_2Cl_2). Trituration of the lower R_f material with Et_2O/hexane afforded a beige solid. Crystallization from cyclohexane afforded **12** as an off-white solid: 0.38 g (6.4%); mp 108–110 °C; IR (KBr) 1695 (CO), 1647 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.87–7.82 (m, 2H), 7.53–7.26 (m, 6H), 7.00–6.95 (m, 2H), 5.12 (s, 2H), 3.72 (q, 2H, J = 7.1 Hz), 2.47 (s, 3H), 2.22 (s, 3H), 0.75 (t, 3H, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$) δ 193.8, 164.9, 140.2, 136.0, 135.3, 132.1, 132.0, 129.1, 129.0, 128.1, 127.7, 125.6, 120.7, 112.3, 59.5, 47.0, 13.4, 11.0, 10.7; EIMS, m/z (relative intensity) 361 (27, M^+), 91 (100). Anal. Calcd for $C_{23}H_{23}NO_3$: C, 76.43; H, 6.41; N, 3.88. Found: C, 76.41; H, 6.55; N, 4.12. Crystallization of the higher R_f material from toluene gave **13** as an off-white solid: 1.58 g (24%); mp 148–150 °C; IR (KBr) 1762 (CO), 1703 (CO), 1655 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.90–7.85 (m, 2H), 7.56–7.15 (m, 6H), 7.05–6.99 (m, 2H), 5.63 (s, 2H), 3.72 (q, 2H, J = 7.1 Hz), 2.14 (s, 3H), 2.08 (s, 3H), 0.66 (t, 3H, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$) δ 191.6, 169.1, 160.1, 138.8, 137.0, 132.7, 132.6, 129.2, 129.0, 128.8, 128.2, 127.4, 126.8, 125.8, 121.8, 118.2, 60.4, 48.5, 20.3, 13.1, 9.0; EIMS, m/z (relative intensity) 405 (10, M^+), 91 (100). Anal. Calcd for $C_{24}H_{23}NO_5$: C, 71.10; H, 5.72; N, 3.45. Found: C, 71.36; H, 5.92; N, 3.22.

Improved Cycloaddition Procedure for the Preparation of 12. A stirred mixture of D,L-*N*-benzylalanine (1.72 g, 9.60 mmol), Ac_2O (18 mL), and Et_3N (1.4 mL, 10 mmol) was warmed to 70 °C. After 5 min, a solution of ethyl 4-oxo-4-phenyl-2-butynoate (2.33 g, 1.15 mmol) and Ac_2O (2 mL) was added and the reaction was stirred at 70 °C for an additional 1.5 h. The excess Ac_2O was evaporated at reduced pressure leaving an oil which was purified by flash chromatography (3% EtOAc/CH_2-

(20) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925.

(21) Purchased from the Aldrich Chemical Co., Milwaukee, WI.

(22) The author has deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union road, Cambridge, CB2 1EZ, UK.

Cl_2). Trituration of the resulting oil with Et_2O induced the oil to solidify. Crystallization from cyclohexane afforded **12** as an off-white solid: 1.91 g (58%), mp 108–110 °C, mixture mp 108–110 °C; spectral data identical to that presented above. Anal. Calcd for $C_{23}H_{23}NO_3$: C, 76.43; H, 6.41; N, 3.88. Found: C, 76.34; H, 6.47; N, 3.80.

Alternate Synthesis of 12. Pyrrole **8** (1.50 g, 5.53 mmol) was added to a stirred, rt suspension of powered KOH (1.23 g, 21.9 mmol) and DMSO (11 mL). The resulting solution was stirred for 45 min before being cooled to 0 °C at which time benzyl bromide (1.4 mL, 12 mmol) was added in one portion. The cooling bath was removed, and the reaction was stirred for 2 h before being quenched into H_2O. The aqueous mixture was extracted with CH_2Cl_2 (3 × 150 mL). The extracts were combined and washed with H_2O (3 × 150 mL) before being dried over anhydrous $MgSO_4$. The solvent was evaporated at reduced pressure leaving a solid. Crystallization from CH_2Cl_2/hexane afforded **12** as colorless prisms: 1.67 g (84%), mp 108–109 °C, mixture mp 108–110 °C; spectral data identical to that presented above. Anal. Calcd for $C_{23}H_{23}NO_3$: C, 76.43; H, 6.41; N, 3.88. Found: C, 76.40; H, 6.44; N, 3.78.

D,L-*N*-(4-Methoxybenzyl)alanine (14). To a solution of D,L-alanine (9.42 g, 106 mmol) in 2 M NaOH (50 mL) was added *p*-anisaldehyde (14.5 g, 104 mmol) in one portion. After 30 min, the mixture was cooled to 0 °C and $NaBH_4$ (1.6 g, 42 mmol) was added in small portions (gas evolution!). After an additional 30 min, *p*-anisaldehyde (7.80 g, 56.3 mmol) was added and the mixture stirred for 1 h. A second portion of $NaBH_4$ (1.6 g, 42 mmol) was added and after 4 h the mixture was neutralized to pH 6 with 1 N HCl. The solid which formed was collected by filtration, washed with cold water, and air-dried for 2 h at which time it was dissolved in 1 M NaOH (100 mL). Following extraction with ether (2 × 50 mL), the aqueous layer was neutralized to pH 6 with 1 N HCl. The resulting solid was collected by filtration and dried under vacuum affording **14** as a colorless solid: 9.33 g (46%); mp 245–247 °C; IR (KBr) 3429 (OH), 1614 (CO) cm^{-1}; ^1H NMR (DMSO-d_6/TFA) δ 7.45 (d, 2H, J = 8.7 Hz), 7.01 (d, 2H, J = 8.7 Hz), 4.13 (br s, 2H), 3.99 (m, 1H), 3.79 (s, 3H), 1.52 (d, 3H, J = 7.3 Hz); ^{13}C NMR (DMSO-d_6/TFA) δ 171.0, 160.2, 131.9, 123.6, 114.3, 55.3, 54.2, 48.3, 14.6; HRMS (FAB) calcd for $C_{11}H_{16}NO_3$ (M^+ + 1) 210.113019, found 210.114253.

Methyl 4-(2-benzylbenzoyl)-2,5-dimethyl-1-(4-methoxybenzyl)pyrrole-3-carboxylate (15). A solution of D,L-*N*-(4-methoxybenzyl)alanine (0.408 g, 2.11 mmol), Ac_2O (4 mL), and Et_3N (0.31 mL, 2.2 mmol) was heated to 70 °C for 10 min. A solution of **5** (0.703 g, 2.53 mmol) in Ac_2O (2 mL) was added dropwise (gas evolution), and the resulting mixture was stirred at 70 °C for 3 h. After cooling to rt, the reaction was evaporated at reduced pressure and the residue was purified by flash chromatography (25% EtOAc/hexane) affording **15** as a yellowish oil: 0.56 g (56%); IR (thin film) 1705 (CO), 1639 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.38–7.16 (m, 9H), 6.87 (s, 4H), 5.01 (s, 2H), 4.31 (s, 2H), 3.78 (s, 3H), 3.16 (s, 3H), 2.39 (s, 3H), 2.17 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 194.4, 165.5, 159.0, 141.1, 140.6, 134.9, 134.4, 130.7, 130.4, 129.5, 129.3, 128.2, 127.7, 126.8, 125.8, 125.5, 121.9, 114.4, 112.7, 55.3, 50.5, 46.4, 38.6, 10.9; EIMS m/z (relative intensity) 468 (100, M^+). Anal. Calcd for $C_{30}H_{29}NO_4$: C,77.06; H, 6.25; N, 3.00. Found: C, 76.92; H, 6.18; N, 3.02.

D,L-*N*-(4-Nitrophenethyl)alanine Ethyl Ester (18). A suspension of 4-nitrophenethylamine hydrochloride (5.15 g, 25.4 mmol) in $CHCl_3$ was treated with NH_3 gas for 20 min. Filtration of the NH_4Cl and evaporation of the filtrate afforded the free base which was dissolved in THF (40 mL). This solution was treated with ethyl 2-bromopropionate (2.30 g, 12.7 mmol), and the resulting mixture was heated to reflux for 24 h. After cooling, the solid 4-nitrophenethylamine hydrobromide was removed by filtration. The filtrate was evaporated, and the residue was purified by flash chromatography (EtOAc) affording **18** as a yellow oil: 2.73 g (81%); IR (thin film) 3327 (NH), 1732 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.16 (d, 2H, J = 8.8 Hz), 7.38 (d, 2H, J = 8.8 Hz), 4.17 (dq, 2H, J = 1.2, 7.4 Hz), 3.34 (q, 1H, J = 6.8 Hz), 2.98–2.76 (m, 4H), 1.66 (br s, 1H), 1.30–1.24 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 175.5, 147.7, 146.6, 129.5, 123.6, 60.7, 56.6, 48.4, 36.5, 19.0, 14.2; CIMS m/z (relative intensity) 267 (100, M^+ + 1). Anal. Calcd for $C_{13}H_{18}N_2O_4$: C, 58.63; H, 6.81; N, 10.52. Found: C, 58.47; H, 6.71; N, 10.74.

D,L-*N*-(4-Nitrophenethyl)alanine (19). To a solution of **18** (2.73 g, 10.2 mmol) in 1:1 THF/H_2O (15 mL) was added LiOH (0.270 g, 11.3 mmol). After stirring at rt for 12 h, the THF was evaporated at reduced pressure. The aqueous concentrate was extracted with ether (3 × 10 mL) before being acidified to pH 3 with concd HCl. The solid which formed was collected by filtration, washed with cold water (10 mL), and dried under vacuum affording **19** as an off-white solid: 1.93 g (79%); mp 242–243 °C; IR (KBr) 3431 (OH), 1601 (CO) cm^{-1}; ^1H NMR (D_2O) δ 7.73 (d, 2H, J = 8.0 Hz), 7.13 (d, 2H, J = 8.0 Hz), 3.04 (q, 1H, J = 7.0 Hz), 2.73–2.54 (m, 4H), 1.11 (d, 3H, J = 7.0 Hz); ^{13}C NMR (D_2O) δ 186.1, 151.4, 148.6, 132.5, 126.5, 61.7, 50.8, 38.2, 21.4; CIMS m/z (relative intensity) 239 (100, M^+ + 1). Anal. Calcd for $C_{11}H_{14}N_2O_4$: C, 55.46; H, 5.92; N, 11.76. Found: C, 55.10; H, 5.73; N, 11.79.

Methyl 4-(2-benzylbenzoyl)-2,5-dimethyl-1-(4-nitrophenethyl)pyrrole-3-carboxylate (20). A solution of D,L-*N*-(4-nitrophenethyl)alanine (0.200 g, 0.839 mmol), Ac_2O (1.6 mL), and Et_3N (0.13 mL, 0.88 mmol) was heated to 70 °C for 10 min. A solution of **5** (0.281 g, 1.01 mmol) in Ac_2O (1.0 mL) was added dropwise (gas evolution), and the resulting mixture was stirred at 70 °C for 3 h. After cooling to ambient temperature, the reaction was evaporated at reduced pressure, and the residue was purified by flash chromatography (25% EtOAc/hexane) affording **20** as a colorless solid: 0.204 g (49%); mp 136–138 °C; IR (KBr) 1707 (CO), 1635 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.16 (d, 2H, J = 8.5 Hz), 7.31–7.16 (m, 11H), 4.29 (s, 2H), 4.08 (t, 2H, J = 7.2 Hz), 3.16 (s, 3H), 3.05 (t, 2H, J = 7.2 Hz), 2.35 (s, 3H), 2.08 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 194.8, 165.3, 147.2, 144.7, 141.1, 140.5, 140.3, 134.0, 133.2, 130.9, 130.6, 129.7, 129.6, 129.3, 128.3, 125.9, 125.6, 124.0, 122.2, 112.9, 50.6, 44.4, 38.6, 36.4, 10.9; CIMS m/z (relative intensity) 497 (100, M^+ + 1). Anal. Calcd for $C_{30}H_{28}N_2O_5$: C, 72.56; H, 5.68; N, 5.64. Found: C, 72.37; H, 5.80; N, 5.56.

Methyl 4-(2-benzylbenzoyl)-2,5-dimethylpyrrole-3-carboxylate (3). A mixture of **20** (0.142 g, 0.286 mmol) and DBU (0.065 g, 0.43 mmol) in DMF (10 mL) was heated at 100 °C for 3 h. After cooling to rt, the mixture was poured into a separatory funnel and EtOAc (30 mL) was added. The organic phase was washed with 1 N HCl (3 × 10 mL), separated, and dried over Na_2SO_4. The solvent was evaporated at reduced pressure, and the residue was purified by flash chromatography (5% EtOAc/CH_2Cl_2) affording **3** as an off-white solid: 0.085 g (86%); mp 140–142 °C, mixture mp 140–142 °C. This material was identical in all respects with an authentic sample of **3**.

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Supporting Information Available: Copies of ^1H and ^{13}C NMR spectra for D,L-*N*-(4-methoxybenzyl)alanine (**14**) are provided. Also provided are copies of ^1H-coupled ^{13}C NMR and NOESY NMR spectra for pyrrole **9** (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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