was removed under high vacuum. The residue obtained was subjected to chromatography. From both VQMs were obtained three compounds: the major isomer derived from 1,8-addition and a pair of diastereoisomers derived from 1,6-addition.

2-Methoxy-4-(1-ethenyl-2-nitropropyl)phenol (7a, R^1 = Me, R^2 = NO_2) Acetate. Selected data. Erythro or threo isomer: yield 9%; mp 88–90 °C; ^1H NMR ($CDCl_3$) δ 3.70 (dd, 1 H, *J* = 8.1, 10.2 Hz, C*H*CH=CH_2), 4.81 (dq, 1 H, *J* = 6.3, 10.2 Hz, $CHNO_2$), 5.15 (m, 2 H, CH_2=CH), 5.92 (ddd, 1 H, *J* = 8.1, 10.3, 18.0 Hz, C*H*=CH_2). Other diastereoisomer: yield 12%; mp 105–110 °C; ^1H NMR ($CDCl_3$) δ 3.83 (dd, 1 H, *J* = 9.0, 9.0 Hz, C*H*CH=CH_2), 4.85 (dq, 1 H, *J* = 6.3, 9.0 Hz, $CHNO_2$), 5.20 (m, 2 H, CH_2=CH), 5.90 (ddd, 9.0, 10.3, 18.0 Hz, C*H*=CH_2).

(*E*)-2-Methoxy-4-(4-nitro-1-pentenyl)phenol (8a, R^1 = Me, R^2 = NO_2) Acetate: yield 56%; oil; IR (neat) 1545, 1263, 1195 cm^{-1}; UV (EtOH) λ_{max} 254 nm (ε 15 940), 293 (5180); ^1H NMR ($CDCl_3$) δ 1.52 (d, 3 H, *J* = 6.7 Hz, CH_3CH), 2.25 (s, 3 H, CH_3CO), 2.72 (m, 2 H, CH_2), 3.80 (s, 3 H, CH_3O), 4.62 (ddq, 1 H, *J* = 6.7, 6.7, 6.7 Hz, C*H*CH_3), 5.95 (dt, 1 H, *J* = 7.2, 16.5 Hz, CH_2C*H*=CH), 6.43 (d, 1 H, *J* = 16.5 Hz, C*H*=$CHCH_2$), 6.90 (br s, 3 H, aromatic H); MS, *m/z* (relative intensity) 279 (M^+, 22), 237 (96), 190 (100).

2,6-Dimethoxy-4-(1-ethenyl-2-nitropropyl)phenol (7b, R^1 = Me, R^2 = NO_2) Acetate. Selected data. Erythro or threo isomer: yield 10%; mp 132 °C; ^1H NMR δ 3.62 (dd, 1 H, *J* = 8.2, 10.2 Hz, C*H*CH=CH_2), 4.80 (dq, 1 H, 6.2, 10.2 Hz, $CHNO_2$), 5.15 (m, 2 H, CH_2=CH), 5.93 (ddd, 1 H, *J* = 8.2, 10.3, 18.0 Hz, C*H*=CH_2). Other diastereoisomer: yield 8%; mp 150–152 °C; ^1H NMR ($CDCl_3$) δ 3.83 (dd, 1 H, *J* = 8.5, 8.5 Hz, C*H*CH=CH_2), 4.82 (dq, 1 H, *J* = 6.2, 8.5 Hz, $CHNO_2$), 5.21 (m, 2 H, CH_2=CH), 5.88 (ddd, 1 H, *J* = 8.5, 10.3, 18.0 Hz, C*H*=CH_2).

(*E*)-2,6-Dimethoxy-4-(4-nitro-1-pentenyl)phenol (8b, R^1 = Me, R^2 = NO_2) Acetate: yield 60%; oil; IR (neat) 1725, 1190, 1130 cm^{-1}; UV (EtOH) λ_{max} 263 nm (ε 10 170); ^1H NMR ($CDCl_3$) δ 1.52 (d, 3 H, *J* = 6.6 Hz, CH_3CH), 2.31 (s, 3 H, CH_3CO), 2.72 (m, 2 H, CH_2), 3.79 (s, 6 H, CH_3O), 4.62 (m, 1 H, $CHNO_2$), 6.03 (dt, 1 H, *J* = 6.9, 16.5 Hz, C*H*CH_2), 6.40 (d, 1 H, 16.5 Hz, C*H*=$CHCH_2$), 6.60 (s, 2 H, aromatic H); MS, *m/z* (relative intensity) 309 (M^+, 10), 267 (100), 220 (58).

Reactions of 4a and 4b with Acetylacetone. General Procedure. A solution of 3.0 mmol of VQM (**4a** in 80 mL of CCl_4, **4b** in 40 mL of benzene) was added to a mixture of 1 mL of acetylacetone (10 mmol) and 0.02 mL of Et_3N. The end of the reaction (80 min for **4a**, 120 min for **4b**) was monitorized by the disappearance of VQM (TLC). The solution was evaporated and the residual oil was subjected to reverse-phase column chromatography (silica gel, Merck LiChroprep RP-18, 40 g, MeCN–water 1:1 as the eluant).

3-Acetyl-4-ethenyl-4-(4-hydroxy-3-methoxyphenyl)butan-2-one (7a, R^1 = R^2 = CH_3CO): yield 22%; mp 61–62 °C (cyclohexane); IR (Nujol) 1725, 1695, 1515 cm^{-1}; UV (EtOH) λ_{max} 283 nm (ε 3670); ^1H NMR ($CDCl_3$) δ 1.91 and 2.24 (s, 3 H each, CH_3CO), 3.87 (s, 3 H, CH_3O), 4.10 (dd, 1 H, *J* = 7.6, 11.6, C*H*CH=CH_2), 4.21 (d, 1 H, *J* = 11.6 Hz, C*H*$COCH_3$), 5.05 (m, 2 H, CH_2=CH), 5.58 (s, 1 H, OH), 5.85 (ddd, 1 H, *J* = 7.6, 10.0, 17.2 Hz, C*H*=CH_2), 6.67–6.84 (m, 3 H, aromatic H); MS, *m/z* (relative intensity) 262 (M^+, 14), 219 (64), 131 (100).

(*E*)-3-Acetyl-6-(4-hydroxy-3-methoxyphenyl)-5-hexen-2-one (8a, R^1 = R^2 = CH_3CO): yield 41%; mp 73–75 °C (cyclohexane); IR (Nujol) 1715, 1700, 1235 cm^{-1}; UV (EtOH) λ_{max} 267 nm (ε 15 680), 290 (sh, 9000); ^1H NMR ($CDCl_3$) δ 2.18 (s, 6 H, CH_3CO), 2.70 (m, 2 H, CH_2), 3.75 (t, 1 H, *J* = 7.2, C*H*$COCH_3$), 3.86 (s, 3 H, CH_3O), 5.60 (s, 1 H, OH), 5.86 (dt, 1 H, *J* = 5.2, 16.0 Hz, CH=C*H*CH_2), 6.35 (br d, *J* = 16.0 Hz, C*H*=$CHCH_2$), 6.80 (s, 3 H, aromatic H); MS, *m/z* (relative intensity) 262 (M^+, 22), 219 (57), 137 (100).

3-Acetyl-4-ethenyl-4-(4-hydroxy-3,5-dimethoxyphenyl)-butan-2-one (7b, R^1 = R^2 = CH_3CO) Acetate: yield 22%; mp 106 °C (cyclohexane); IR (KBr) 1795, 1220, 1143 cm^{-1}; UV (EtOH) λ_{max} 267 nm (ε 2640); ^1H NMR ($CDCl_3$) δ 1.92, 2.23, and 2.30 (s, 3 H each, CH_3CO), 3.80 (s, 6 H, CH_3O), 4.15 (dd, 1 H, *J* = 6.0, 11.4 Hz, C*H*CH=CH_2), 4.23 (d, 1 H, *J* = 11.4 Hz, C*H*$COCH_3$), 5.10 (m, 2 H, CH_2=CH), 5.88 (dddd, 1 H, *J* = 1.8, 6.0, 9.6, 16.8 Hz, C*H*=CH_2), 6.43 (s, 2 H, aromatic H); MS, *m/z* (relative intensity) 335 (M + 1, 15), 249 (95), 231 (90), 161 (100).

(*E*)-3-Acetyl-6-(4-hydroxy-3-methoxyphenyl)-5-hexen-2-one (8b, R^1 = R^2 = CH_3CO): yield 45%; oil; IR ($CHCl_3$) 1725, 1480, 1120 cm^{-1}; UV (EtOH) λ_{max} 272 nm (ε 12 750); ^1H NMR δ 2.18 (s, 6 H, CH_3CO), 2.70 (m, 2 H, CH_2), 3.76 (t, 1 H, *J* = 7.2 Hz, C*H*$COCH_3$), 3.87 (s, 6 H, CH_3O), 5.50 (s, 1 H, OH), 5.90 (dt, 1 H, *J* = 5.2, 16.0 Hz, CH=C*H*CH_2), 6.33 (br d, 1 H, *J* = 16.0 Hz, C*H*=$CHCH_2$), 6.52 (s, 2 H, aromatic H); MS, *m/z* (relative intensity) 292 (M^+, 2), 182 (22), 85 (69), 83 (100).

Registry No. **1a**, 32811-40-8; **1b**, 20675-96-1; **2a**, 5932-68-3; **2b**, 20675-95-0; **3a**, 97-53-0; **3b**, 6627-88-9; **4a**, 10570-85-1; **4b**, 58623-87-3; **5a** (R = Me, acetate), 94930-69-5; **5a** (R = Et, acetate), 94930-70-8; **5a** (R = $PhCH_2$, acetate), 94930-71-9; **5a** (R = PhCH=$CHCH_2$, acetate), 94930-72-0; **5a** (R = 4-$OMeC_6H_4$, acetate), 94930-73-1; **5a** (R = CH_3CO, acetate), 53890-24-7; **5b** (R = Me), 66463-74-9; **5b** (R = Et), 84700-94-7; **5b** (R = $PhCH_2$), 84700-95-8; **5b** (R = PhCH=$CHCH_2$), 84700-96-9; **6a** (R = Me, acetate), 94930-74-2; **6a** (R = Et), 94930-75-3; **6a** (R = $PhCH_2$, acetate), 94930-76-4; **6a** (R = PhCH=$CHCH_2$, acetate), 94930-77-5; **6a** (R = Ph, acetate), 94930-78-6; **6a** (R = 2-$OMeC_6H_4$, acetate), 94930-79-7; **6a** (R = 4-$OMeC_6H_4$, acetate), 94930-80-0; **6a** (R = CH_3CO), 94930-81-1; **6b** (R = Me), 94930-82-2; **6b** (R = Et), 94930-83-3; **6b** (R = $PhCH_2$), 94930-84-4; **6b** (R = PhCH=$CHCH_2$, Me ether), 94930-85-5; **6b** (R = Ph), 94930-86-6; **6b** (R = 2-$OMeC_6H_4$, acetate), 94930-87-7; **6b** (R = 4-$OMeC_6H_4$), 94930-88-8; **6b** (R = 4-$NO_2C_6H_4$), 94930-89-9; **6b** (R = CH_3CO), 94930-90-2; (*R*,R**)-**7a** (R^1 = Me, R^2 = NO_2, acetate), 94930-91-3; (*R*,S**)-**7a** (R^1 = Me, R^2 = NO_2, acetate), 94930-98-0; **7a** (R^1 = R^2 = CH_3CO), 94930-95-7; (*R*,R**)-**7b** (R^1 = Me, R^2 = NO_2, acetate), 94930-93-5; (*R*,S**)-**7b** (R^1 = Me, R^2 = NO_2, acetate), 94930-99-1; **7b** (R^1 = R^2 = CH_3CO, acetate), 94930-97-9; **8a** (R^1 = Me, R^2 = NO_2, acetate), 94930-92-4; **8a** (R = R^2 = CH_3CO), 94930-96-8; **8b** (R^1 = Me, R^2 = NO_2, acetate), 94930-94-6; **8b** (R^1 = R^2 = CH_3CO, acetate), 94956-21-5; MeOH, 67-56-1; EtOH, 64-17-5; $PhCH_2OH$, 100-51-6; PhCH=$CHCH_2OH$, 104-54-1; PhOH, 108-95-2; 2-$OMeC_6H_4OH$, 90-05-1; 4-$OMeC_6H_4OH$, 150-76-5; 4-$NO_2C_6H_4OH$, 100-02-7; CH_3CO_2H, 64-19-7; $EtNO_2$, 79-24-3; $CH_2(COCH_3)_2$, 123-54-6.

Chemoselective N-Ethylation of Boc Amino Acids without Racemization

Donald W. Hansen, Jr.* and Daniel Pilipauskas

Department of Medicinal Chemistry, Searle Research and Development, Division of G. D. Searle and Co., Skokie, Illinois 60077

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The Boc derivatives of amino acids such as phenylalanine, methionine, and tyrosine benzyl ethers have been selectively ethylated to give, respectively, the enantiomerically pure Boc-*N*-ethyl amino acids **12**, **20**, and **23**. The benzyl, trimethylsilyl, and *tert*-butyldimethylsilyl groups were employed as transient protecting groups for the phenolic hydroxyl in the synthesis of Boc-Et-Tyr (**25**).

N-Substituted α-amino acids have not only been found to possess biological activity[1] but the substitution of N-alkyl α-amino acids into physiologically active peptides has led to materials with varied and enhanced biological ac-

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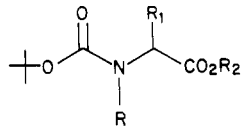
tivity.[2] Information concerning the backbone conformation of peptides has also been obtained by replacing amino acids with their *N*-methyl analogues.[3]

The use of N-alkylated α-amino acids in peptide synthesis generally requires that they be optically pure and N-protected with either an acid or base stable functionality. Recently, a useful high yield two-step synthesis of acid stable Fmoc-protected N-alkyl amino acids has been reported.[4] In our work we had need of enantiomerically pure *tert*-butoxycarbonyl (Boc) N-alkylated amino acids (1) and in particular we required the Boc-*N*-ethyl derivatives of phenylalanine (2), tyrosine (3), and methionine (4). The literature suggested that *N*-ethylphenylalanine,[5] its ethyl ester,[5c,6] and *N*-ethyltyrosine had been prepared but only in racemic form or of undetermined enantiomeric purity, while their Boc derivatives, until recently, were unknown.[1b,2b]



1, R = alkyl; R_1 = amino acid side chain functionality; R_2 = H
2, R = ethyl; R_1 = benzyl; R_2 = H
3, R = ethyl; R_1 = *p*-hydroxybenzyl; R_2 = H
4, R = ethyl; R_1 = $(CH_2)_2SMe$; R_2 = H
5, R = ethyl; R_1 = amino acid side chain functionality; R_2 = ethyl

To minimize our synthetic manipulations in obtaining enantiomerically pure 1, we needed a direct chemoselective N-ethylation of the Boc amino acids. Exhaustive alkylation to the *N*-ethyl ethyl ester (4) would not only necessitate an additional saponification step but this saponification, in the case of protected *N*-methyl amino acid methyl esters, is known to be accompanied by significant racemization.[7b,7d]

Scheme I

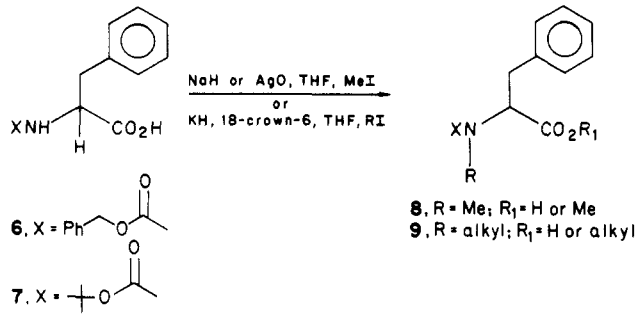


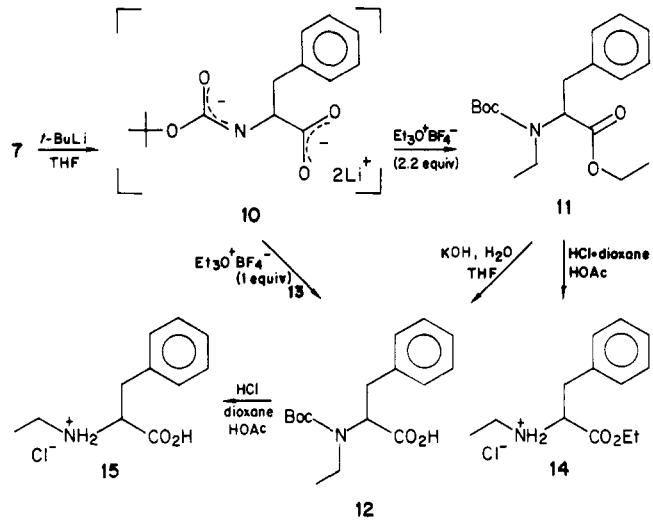
Table I

Boc-Phe $\xrightarrow{\text{base}}$ Boc-Et-Phe (12)

base	% yield (12)
t-BuLi	71
sec-BuLi	59
n-BuLi	63
PhLi	78
LDA	67

Our initial efforts were directed at the N-ethylation of Boc-Phe. Although the procedures of Benoiton[7] and Olsen[8] (Scheme I), where protected amino acids such as 6 and 7 are treated first with bases such as NaH or AgO followed by quenching of the intermediate anions with methyl iodide to produce 8, work well for the preparation of protected *N*-methyl amino acids, they are not applicable to N-ethylation.[5a] Very recently the use of KH/18-crown-6 with alkyl iodides including EtI has provided access to 1 in moderate to good yields and represents an alternative to the work described here.[2b]

Our efforts at using the Benoiton or Olsen procedures with ethyl iodide as an alkylating agent produced only a trace of products 11 and 12. This has been rationalized



by a β-elimination of HI from ethyl iodide[5a] and the steric resistance to ethyl iodide alkylation. We reasoned that for a successful reaction the dianion 10 had to be initially generated. This was accomplished by treatment of 7 with 2.2 equiv of the strong non-nucleophilic base *tert*-butyllithium at −78 to −20 °C. The first equivalent of base formed the lithium carboxylate whose proximity to the chiral α carbon proton was expected to prohibit racemization. The second equivalent produced a red solution of dianion 10 at −20 °C. Treatment of 10 with an excess (2.2 equiv) of the powerful alkylating agent triethyloxonium tetrafluoroborate 13[9] produced the dialkylated product Boc-Et-Phe-OEt (11). This ester (11) was saponified with KOH (2 equiv) in aqueous THF at room temperature to give the desired Boc-Et-Phe (12) in 75% overall yield from Boc-Phe after chromatography. Both 11 and 12 were also deblocked in quantitative yield and converted to 14 and

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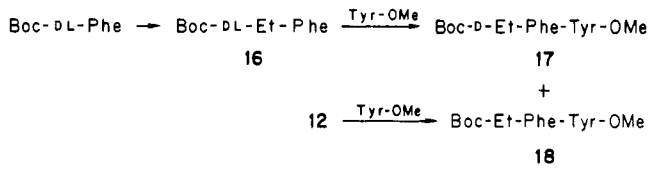
Scheme II



15, their respective HCl salts, with HCl/dioxane (6.2 N) in acetic acid.

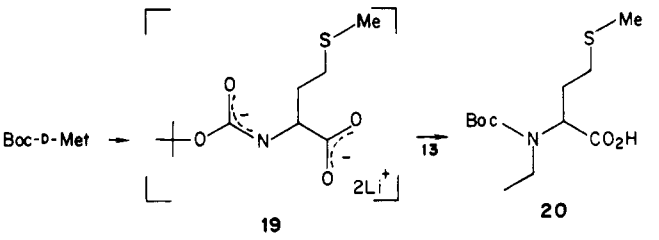
The selective alkylation of the nitrogen of **10**, the most kinetically reactive of the two anionic centers, was accomplished by treatment of **10** with a single equivalent of oxonium salt **13** at −78 °C. The reaction temperature was allowed to slowly rise to room temperature before quenching with 0.5 N $KHSO_4$ which afforded Boc-Et-Phe (**12**) directly in 71% yield after chromatography. Only a trace of ester (**11**) was observed by TLC and NMR of the crude reaction mixture.

In order to determine the significance of *tert*-butyllithium as base in the selective N-ethylation reaction, in simultaneous experiments, we compared the yields of **12** obtained by use of *tert*-butyllithium to those obtained from a variety of other strong bases (Table I). Somewhat surprisingly the yields of **12** as determined by analytical HPLC techniques indicated the reaction to be relatively insensitive to the character of the Li base.

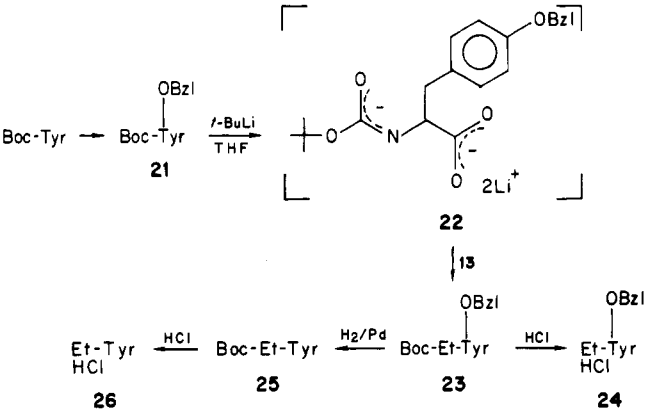
It is interesting to note that the optical rotations of **12** obtained either by direct ethylation of **10** or from saponification of **11** were essentially identical in $CHCl_3$ at 589 nm [−126.2 ± 5.0° (from **7**); −120.2 ± 5.1° (from **11**)]. This suggests, in contrast to the situation encountered in the synthesis of Boc-*N*-methyl amino acids,[5a] that little racemization occurred during the saponification, possibly because of steric protection of the α carbon proton by the somewhat bulkier *N*-ethyl group. To determine whether monoethylation was not only chemoselective but also occurred to give enantiomerically pure **12**, Boc-DL-Et-Phe (**16**) was prepared from Boc-DL-Phe (Scheme II). This material was then coupled with Tyr-OMe by using standard mixed anhydride techniques to give a chromatographically separable mixture of diastereomers **17** and **18**. Boc-Et-Phe (**12**) prepared both directly from **7** and from saponification of ethyl ester **11** was also coupled with Tyr-OMe and the products were analyzed by analytical HPLC. It was found that there was less than 1% racemization during direct monoalkylation and 2.4% overall from diethylation and saponification.

The chemoselective N-ethylation of Boc-methionine is complicated by its possession of the additional nucleophilic dialkyl sulfide functionality. It is well-known that the sulfide sulfur is readily alkylated[9b,10] to produce sulfonium salts which may undergo further transformations.[11] When our N-ethylation procedure was applied to Boc-D-Met, the dianion (**19**) was presumably generated. Treatment of **19** with a single equivalent of oxonium salt (**13**) produced the desired *N*-ethyl acid **20** (88% before chromatography).

The chemoselective N-ethylation of Boc-Tyr is also complex due to the additional acidic functionality, the phenolic hydroxyl, it possesses. When this group was protected as its benzyl ether (**21**), the dianion (**22**) was generated and selectively alkylated under conditions identical with those of Boc-Phe (**7**) to give Boc-Et-Tyr(Bzl) (**23**) in 56% yield after chromatography. This material was both deprotected by treatment with HCl to give **24** or



hydrogenated to give **25** which was further deprotected to produce HCl salt **26**.



The problem with the preparation of **25** via Boc-Tyr(Bzl) (**21**) is that it requires two separate synthetic steps over direct ethylation. The direct chemoselective N-ethylation is theoretically possible from the trianion of Boc-Tyr (**27**) if preparable, since the order of decreasing acidity of protons on **27** is as numbered below (Scheme III). In reality, the trianion of **27** could not be generated under our conditions and on treatment of **27** with 2 equiv of base, salt **28** precipitated. The addition of HMPA was required to solubilize this salt.

We felt we could circumvent this problem by in situ protection of the phenol as its silyl ether followed by the generation of dianion (**31**), the N-alkylation of **31** with a single equivalent of **13**, and an aqueous acid workup to produce Boc-Et-Tyr (**25**) all in one vessel. Our initial attempts utilized the *tert*-butyldimethylsilyl group as the protecting group since silyl intermediate **29** could be isolated and fully characterized. This material (**29**) was subsequently treated with 2 equiv of *t*-BuLi and ethylated with 1 equiv of **13**. The silyl protecting group was removed by acidic workup generating Boc-Et-Tyr (**25**) in low yield (10%) as determined by analytical HPLC.

The treatment of dianion **28** with an equivalent of Me_3SiCl was assumed to generate intermediate salt (**30**) since the phenoxy oxygen is the more nucleophilic. The second dianion **31** was presumably produced by the addition of another equivalent of *t*-BuLi to **30**. N-Ethylation of **31** was accomplished by the selective quenching of the carbamate anion of **31** with 1 equiv of oxonium salt **13** generating **25** (22%) after an acidic workup. No effort was made to optimize yields in either case. This latter procedure with Me_3Si as a temporary protecting group represents a direct one pot preparation of **25** from Boc-Tyr.

Experimental Section

Melting points were determined on a Thomas-Hoover Unimelt capillary apparatus and are not corrected. Unless otherwise stated, IR spectra were taken in $CHCl_3$. NMR spectra were recorded at 80 MHz and chemical shifts are expressed in parts per million downfield from the internal standard Me_4Si (δ 0). Microanalyses were determined by the Searle Laboratories Microanalytical Department under the direction of E. Zielinski. A Perkin-Elmer

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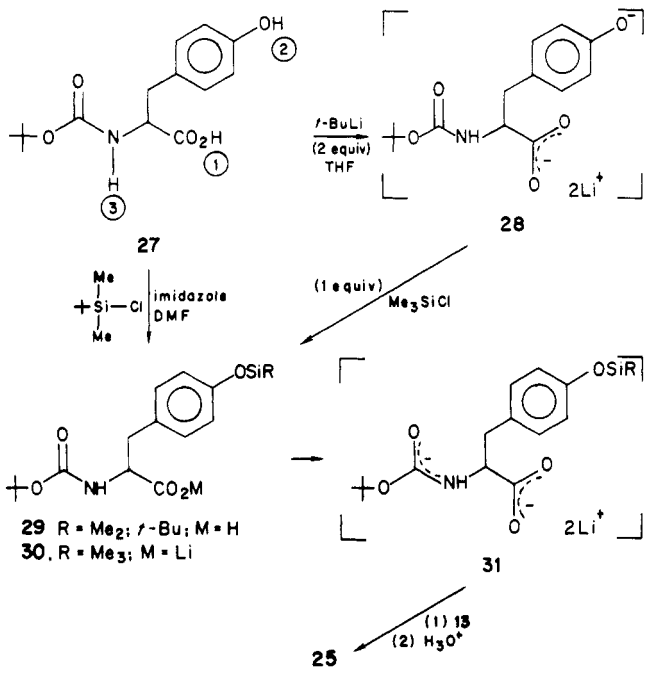
Scheme III



Model 241 polarimeter with a 0.1% solution of test material in a microcell with a 10-cm path length was employed at 25 °C to record optical rotations.

Boc-*N*-ethyl-L-phenylalanine Ethyl Ester (11). *t*-Boc-L-Phe (2.65 g, 10.0 mmol) and 50 mL of THF (distilled from Na) were added to a dry flask (100 mL) maintained under an Ar atmosphere. After cooling this mixture to −78 °C, a solution of *t*-BuLi in pentane (12 mL, 22 mmol) was syringed into the stirred mixture. The reaction was maintained at −78 °C for 30 min and then −20 °C for 1 h before adding solid triethyloxonium tetrafluoroborate (Alfa) rinsed with anhydrous ether (4.2 g, 22 mmol) in one portion to the dark red solution. The mixture was stirred at −20 °C for 30 min before being warmed to 0 °C and poured into cold (0 °C) water (200 mL). After diluting this mixture with CH_2Cl_2 (200 mL), the organic layer was separated, extracted with 5% $NaHCO_3$ (3 × 50 mL) and water (1 × 50 mL), and dried (Na_2SO_4). Removal of the solvent under reduced pressure gave 3.03 g (94%) of a pale yellow solid which by NMR was greater than 95% **11**. This material was chromatographed on a Waters Prep 500 with a 50 × 300 mm Porasil cartridge and eluting with toluene to give **9** as a white solid: mp 58–61 °C; $[\alpha]^{25}_D$ −131.5° (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 2800–3100, 1740, 1700, 1480, 1450, 1370, 1290, 1160 cm^{-1}; ^1H NMR (CD_2Cl_2) δ 0.88 (t, *J* = 7 Hz, 3), 1.25 (t, *J* = 8 Hz, 3), 1.42 (s, 9), 2.8–3.4 (m, 4), 3.8–4.3 (m, 3), 7.20 (s, 5).

Anal. Calcd for $C_{18}H_{27}NO_4$ (321.43): C, 67.26; H, 8.47; N, 4.36. Found: C, 67.50; H, 8.51; N, 4.40.

(A) Boc-*N*-ethyl-L-phenylalanine (12). To a magnetically stirred solution of *t*-Boc-L-Phe (13.25 g, 50 mmol) in 200 mL of dry THF, cooled to −78 °C under Ar, a solution of *t*-BuLi in pentane (58 mL, 110 mmol) was added dropwise over a 20-min period. The solution was stirred at this temperature for 20 min before warming to −20 °C and stirring for an additional 30 min. Triethyloxonium tetrafluoroborate (9.5 g, 50 mmol) was added in one portion to the dark red solution and the mixture allowed to warm to room temperature (45 min) before it was poured into 200 mL of ice water. This mixture was diluted with CH_2Cl_2 (250 mL) and the aqueous layer (pH 13) was separated. The organic layer was washed with water (2 × 200 mL), dried (Na_2SO_4), and filtered, and all solvent was removed under reduced pressure to give a small amount of residue which showed only trace amounts of ethyl ester **11**. The combined aqueous washes were brought to pH 5 with 0.5 N $NaHSO_4$ (150 mL) before they were extracted with CH_2Cl_2 (3 × 200 mL). These CH_2Cl_2 extracts were dried (Na_2SO_4) and filtered, and all solvent was removed under reduced pressure to give a light yellow viscous oil. This material was chromatographed on a Waters Prep 500 by using a 50 × 300 mm reverse-phase PrepPak 500 C_{18} column and eluting with a 75:25:1 mixture of $MeOH/H_2O/HOAc$ to give 10.3 g (71%) of **12** as a white solid: mp 64–66 °C (lit.[12] oil); $[\alpha]^{25}_D$ −126.2 (*c* 1.0, $CHCl_3$) [lit.[12] $[\alpha]^{25}_D$ −108.2 (*c* 1.0, $CHCl_3$)]; IR ($CHCl_3$) 3520, 2800–3400, 1730, 1710, 1490, 1460, 1370, 1300 cm^{-1}; ^1H NMR (CD_2Cl_2) δ 0.85 (t, *J* = 8 Hz, 3), 1.44 (s, 9), 2.5–2.8 (m, 1), 2.8–3.3 (m, 3), 3.8–4.2 (m, 1), 7.20 (s, 5).

Anal. Calcd for $C_{16}H_{23}NO_4$ (293.37): C, 65.51; H, 7.90; N, 4.77. Found: C, 65.51; H, 8.11; N, 4.82.

(B) 12 via Saponification of 11. A solution of KOH (1.85 g, 28 mmol) in 100 mL of water (0.28 N) was added to a mixture of **12** (4.46 g, 14 mmol) in THF (50 mL). After this mixture was stirred for 3.5 h at room temperature, it was diluted with 200 mL of CH_2Cl_2 and the aqueous layer was brought to pH 4 with 0.5 N $NaHSO_4$ (50 mL). The phases were separated and the aqueous layer washed with CH_2Cl_2 (2 × 30 mL). The combined organic layer was washed with 75 mL of brine before it was dried (Na_2SO_4) and filtered, and all solvent was removed under reduced pressure. The residue was chromatographed on silica (CC-4) and eluted with 5% EtOAc/toluene to give 3.03 g (75%) of **12**: $[\alpha]^{25}_D$ −120.2 (*c* 1.0, $CHCl_3$), −158.4 (*c* 1.0, MeOH).

***N*-Ethyl-L-phenylalanine Ethyl Ester Hydrochloride (14).** To a magnetically stirred solution of **11** (1.4 g, 4.4 mmol) dissolved in 23 mL of HOAc (glacial) was added 7.3 mL (44 mmol) of a HCl/dioxane (6.07 N) solution. After this mixture has stirred for 20 min at room temperature all solvent was removed under reduced pressure. The clear viscous oil residue was triturated with anhydrous Et_2O to give **14** as a white solid. This salt was suction filtered, washed with Et_2O, and dried in vacuo producing 980 mg (88%) of **14**: $[\alpha]^{25}_D$ 42.7 (*c* 1.0, MeOH); IR (KBr) 2600–3000, 1730, 1540, 1450, 1270, 1060, 1010 cm^{-1}; ^1H NMR (CD_3CO_2D) δ 1.10 (t, *J* = 6 Hz, 3), 1.37 (t, *J* = 6 Hz, 3), 3.0–3.7 (m, 4), 4.14 (q, *J* = 6 Hz, 2), 4.3–4.5 (m, 1), 7.25 (s, 5).

Anal. Calcd for $C_{13}H_{20}NO_2Cl$ (257.76): C, 60.58; H, 7.82; Cl, 13.75; N, 5.43. Found: C, 61.07; H, 8.00; Cl, 13.55; N, 5.48.

***N*-Ethyl-L-phenylalanine Hydrochloride (15).** When a procedure identical to the preparation of **14** was used, **12** (1.4 g, 4.8 mmol) was converted with HCl/dioxane (10 equiv) into 1.04 g (95%) of white solid **13**: $[\alpha]^{25}_D$ +25.3 (*c* 1.0, MeOH); IR (KBr) 3300–3700, 2600–3200, 1740, 1460, 1370 cm^{-1}; ^1H NMR (CD_3CO_2D) δ 1.34 (t, *J* = 6 Hz, 3), 3.0–3.5 (m, 4), 4.2–4.5 (m, 1), 7.27 (s, 5).

Anal. Calcd for $C_{11}H_{16}NO_2Cl$ (229.71): C, 57.52; H, 7.02; Cl, 15.43; N, 6.10. Found: C, 57.39; H, 6.96; Cl, 15.26; N, 5.79.

Evaluation of Base Efficiency in Direct Preparation of 12. The standard procedure described above for the chemoselective N-ethylation of Boc-Phe was used to evaluate the series of bases listed below. The dianion was generated from **7** (2.6 g, 10 mmol) with 10 mmol of each of the following bases: *sec*-BuLi (45 mL) in cyclohexane; *n*-BuLi (50 mL) in hexane; LDA (90 mL) in THF; *t*-BuLi (50 mL) in pentane; PhLi (50 mL) in cyclohexane/Et_2O. The dianion was quenched with triethyloxonium tetrafluoroborate (1.9 g, 10 mmol) and the reaction was worked up in the usual manner. The yields of **12** were quantitatively determined for each reaction by using a Waters Associates HPLC with a Supelco LC18 column eluting with 40% acetonitrile/water. A 200-nm monitor was employed to compare the absorbance of **12** from each reaction with a pure standard.

Boc-*N*-ethyl-D,L-phenylalanine (16). Our standard procedure was utilized to convert Boc-DL-Phe (13.3 g, 50 mmol) through treatment with *t*-BuLi (53 mL, 100 mmol) followed by triethyloxonium tetrafluoroborate (9.5 g, 50 mmol) to **16** (8.5 g, 58%) after the usual workup. The NMR and IR spectra of **16** were identical with those of **12** but the melting point was significantly different,[12] mp 137–138 °C.

Anal. Calcd for $C_{16}H_{23}NO_4$ (293.37): C, 65.51; H, 7.90; N, 4.77. Found: C, 65.33; H, 8.02; N, 4.78.

Boc-*N*-ethyl-D-phenylalanyl-L-tyrosine Methyl Ester (17) and Boc-*N*-ethyl-L-phenylalanyl-L-tyrosine Methyl Ester (18). To a magnetically stirred CH_2Cl_2 (60 mL) solution of **16** (5.7 g, 17.7 mmol) maintained under an argon blanket and cooled to 0 °C was added *N*-methylmorpholine (3.58 g, 35.4 mmol). After this mixture was cooled to −78 °C, isobutylchloroformate (2.42

(12) Personal communication with one of the authors of ref 2b. (P. Gesellchen) has revealed that the physical data which they reported for Boc-Et-Phe (**12**) was in error. Their correct optical rotation for Boc-Et-Phe (isolated as an oil) is $[\alpha]_D^{25}$ −108.2 (*c* 1.0, $CHCl_3$).

g, 17.7 mmol) was added and this mixture was allowed to slowly warm to just 20 °C before again cooling to −78 °C. Tyr-OMe·HCl (4.10 g, 17.7 mmol) was added in one portion and the mixture warmed to room temperature. After the reaction was stirred overnight, the majority of the solid *N*-methylmorpholine hydrochloride was filtered off through a Celite pad. The filter cake was washed extensively with CH_2Cl_2 and the filtrate with 0.5 N $KHSO_4$ (3 × 100 mL). The combined aqueous wash was extracted with 75 mL of CH_2Cl_2. After the combined organic extracts were washed with brine (100 mL), they were dried (Na_2SO_4) and filtered, and all solvent was removed under reduced pressure to yield 8.7 g of a colorless oil. A 400-mg sample of this mixture of diastereomers was separated on a Beckman HPLC apparatus by using a 9.4 × 500 mm Partisil column and eluting with heptane/EtOAc/THF (75:20:5) to give **17** (0.17 g, 42%) and **18** (0.17 g, 42%). **17**: $[\alpha]^{25}_D$ 95.6 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 3600, 3200–3500, 2800–3100, 1750, 1680, 1520, 1370, 1290, 1260 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (t, *J* = 7 Hz, 3), 1.40 (s, 9), 2.8–3.4 (m, 6), 3.63 (s, 3), 4.3–4.6 (m, 1), 4.6–4.8 (m, 1), 6.54 (bd, *J* = 8 Hz, 2), 6.67 (bd, *J* = 8 Hz, 2), 6.9–7.2 (m, 5).

Anal. Calcd for $C_{26}H_{34}N_2O_6$ (470.58): C, 66,36; H, 7.28; N, 5.95. Found: C, 66.24; H, 7.15; N, 5.89.

18: $[\alpha]^{25}_D$ −50.0 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 3600, 3200–3500, 2800–3100, 1750, 1680, 1520, 1370, 1290, 1260 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.82 (t, *J* = 7 Hz, 3), 1.42 (s, 9), 2.8–3.3 (m, 6), 3.62 (s, 3), 4.2–4.4 (m, 1), 4.6–4.8 (m, 1), 6.58 (d, *J* = 8 Hz, 2), 6.80 (d, *J* = 8 Hz, 2), 6.9–7.2 (m, 5).

Anal. Calcd for $C_{26}H_{34}N_2O_6$ (470.58): C, 66.36; H, 7.28; N, 5.95. Found: C, 66.09; H, 7.33; N, 5.92.

Boc-*N*-ethyl-L-phenylalanyl-L-tyrosine Methyl Ester (18). (A) The procedure described above was used to couple **12** (2.2 g, 7.4 mmol), prepared by direct monoethylation of Boc-L-Phe, with L-Tyr-OMe·HCl (1.71 g, 7.4 mmol). For this mixed anhydride procedure, 1.5 g (14.7 mmol) of *N*-methylmorphine and 1.0 g (7.4 mmol) of isobutyl chloroformate were utilized to produce 3.4 g of a product oil. A quantative HPLC analysis of the product was carried out with a Waters Associates HPLC with a Supelco LC18 column and eluted with 40% acetonitrile/water. A 200-nm moniter was employed in a comparison of the absorbance of pure standards of **17** and **18** with their absorbance in the product. Quantitation was based on a single weighing of each sample and standard. Serial dilutions of the standards were used as points on a standard curve to determine that **18** was present in >99% with **17** making up less than 0.5%.

(B) In a duplicate experiment, **18** was prepared by the mixed anhydride coupling of **12** (1.5 g, 5.1 mmol) obtained by saponification of **11** with Tyr-OMe·HCl (1.2 g, 5.1 mmol). For this coupling, 1.0 g (10.2 mmol) of *N*-methylmorpholine and 0.7 g (5.1 mmol) of isobutyl chloroformate were used to obtain 2.1 g of the crude **18** product solid. Analysis of this material as described in part A above showed that **18** was produced in 96% and **17** in 1.2% yield.

Boc-*N*-ethyl-D-methionine (20). When the chemoselective N-ethylation procedure described for preparation of **12** was applied to the synthesis of **20**, Boc-D-Met (12.5 g, 50 mmol) was treated with a pentane solution of *t*-BuLi (48 mL, 105 mmol). Triethyloxonium tetrafluoroborate (9.5 g, 50 mmol) was then added to the presumed dianion of Boc-D-Met giving, after workup, 12.3 g (88%) of a light yellow viscous oil whose NMR was essentially identical with that of chromatographed material. A sample of this product was chromatographed on a low-pressure 25 × 1000 mm silica (Merck) column and eluted with 2–10% EtOAc/CH_2Cl_2 to produce the light yellow solid **20**: mp 46–55 °C; $[\alpha]^{25}_D$ 57.8 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 3600, 3500, 2400–3400, 1720, 1690, 1480, 1460, 1420, 1370, 1290, 1160 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.17 (t, *J* = 7 Hz, 3), 1.44 (s, 9), 2.09 (s, 3), 2.1–2.4 (m, 2), 2.4–2.7 (m, 2), 2.8–3.7 (m, 2), 4.0–4.5 (m, 1).

Anal. Calcd for $C_{12}H_{23}NO_4S$ (277.39): C, 51.96; H, 8.36; N, 5.05. Found: C, 51.94; H, 8.40; N, 4.94.

Boc-*N*-ethyl-*O*-benzyl-L-tyrosine (23). When our general chemoselective N-ethylation procedure was employed in the preparation of **23**, Boc-*O*-benzyl-L-tyrosine (37.1 g, 0.1 mol) was presumably converted to the dark red dianion by treatment with 105 mL (0.22 mol) of *t*-BuLi in pentane. The alkylation was carried out by addition of triethyloxonium tetrafluoroborate (19.0 g, 0.1 mol) which had been washed extensively with anhydrous Et_2O and dried. The usual workup procedure produced a light yellow viscous oil which was chromatographed on a Waters Prep 500 by using a reverse-phase PrepPak 500, C_{18} column and eluting with MeOH/H_2O/HOAc in a ratio of 69.5/20/0.5 to yield 22.2 g (56%) of the white solid **23**: mp 113–118 °C; $[\alpha]^{25}_D$ −101.2 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 3680, 3500, 2800–3400, 1720, 1690, 1610, 1510, 1450, 1420, 1370 cm^{-1}; ^1H NMR (CD_2Cl_2) δ 0.87 (t, *J* = 7 Hz, 3), 1.45 (s, 9), 2.5–3.0 (m, 1), 3.0–3.3 (m, 3), 3.8–4.2 (m, 1), 5.03 (s, 2), 6.86 (d, *J* = 9 Hz, 2), 7.08 (d, *J* = 9 Hz, 2), 7.35 (br s, 5).

Anal. Calcd for $C_{23}H_{29}NO_5$ (399.49): C, 69.15; H, 7.32; N, 3.51. Found: C, 69.13; H, 7.53; N, 3.49.

Boc-*N*-ethyl-L-tyrosine (25). A THF solution (100 mL) of **23** (10 g, 25 mmol) was hydrogenated in a Parr apparatus by using as catalyst 5% Pd/C (3.0 g). The reaction was run at room temperature for 39 h under an H_2 pressure of 50 psi. After the catalyst was filtered off and the solvent was removed under reduced pressure, the residue was chromatographed on a 25 × 1000 mm Bio-Sil-A column eluting with 4% MeOH/$CHCl_3$ to give 6.25 g (81%) of the white solid **25**: mp 75–80 °C dec; $[\alpha]^{25}_D$ −124.4 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 3680, 3600, 2800–3200, 1750, 1720, 1690, 1610, 1510, 1480, 1450, 1370, 1290, 1250, 1160, 1100 cm^{-1}; ^1H NMR (CD_2Cl_2) δ 0.86 (t, *J* = 7 Hz, 3), 1.45 (s, 9), 2.5–3.0 (m, 1), 3.0–3.3 (m, 3), 7.72 (d, *J* = 9 Hz, 2), 7.02 (d, *J* = 9 Hz, 2).

Anal. Calcd for $C_{16}H_{23}NO_5$ (309.37): C, 62.12; H, 7.49; N, 4.53. Found: C, 61.83; H, 7.49; N, 4.69.

***N*-Ethyl-*O*-benzyl-L-tyrosine Hydrochloride (24).** When the procedure for the preparation of **14** was applied to the synthesis of **24**, 1.0 g (2.5 mmol) of **23** in HOAc (40 mL) was treated with HCl/dioxane (8.3 mL, 50 mmol) to produce after workup 824 mg (98%) of the white solid salt **24**: $[\alpha]^{25}_D$ 25.4 (*c* 1.0, MeOH); IR (KBr) 3300–3680, 2200–3300, 1730, 1620, 1570, 1520, 1460, 1250, 1180, 1110, 1040 cm^{-1}; ^1H NMR (CD_3OD) δ 1.30 (t, *J* = 7 Hz, 3), 3.08, (q, *J* = 7 Hz, 2), 3.1–3.4 (m, 2), 4.18 (t, 1), 5.06 (s, 2), 6.95 (ab d, *J* = 9 Hz, 2), 7.22 (ab d, *J* = 9 Hz, 2), 7.34 (bs, 5).

Anal. Calcd for $C_{18}H_{22}NO_3Cl$ (335.84): C, 64.38; H, 6.60; N, 4.17. Found: C, 64.51; H, 6.51; N, 4.09.

***N*-Ethyl-L-tyrosine Hydrochloride (26).** By our standard procedure, **25** (1.0 g, 3.2 mmol) in HOAc (40 mL) was treated with HCl/dioxane (10 mL, 60 mmol) producing 770 mg (97%) of the white solid product **26**: $[\alpha]^{25}_D$ 52.2 (*c*, 1.0 HOAc); IR (KBr) 1740, 1620, 1600, 1520, 1460, 1270 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.22 (t, *J* = 6 Hz, 3) 2.93 (q, *J* = 6 Hz, 4) 2.7–3.3 (m, 2), 4.04 (bs, 1) 6.70 (ab d, *J* = 8 Hz, 2), 7.05 (ab d, *J* = 8 Hz, 2).

Anal. Calcd for $C_{11}H_{16}NO_3Cl$ (245.71): C, 53.77; H, 6.56; N, 5.70. Found: C, 54.03; H, 6.51; N, 5.66.

Boc-*O*-(*tert*-butyldimethylsilyl)-L-tyrosine (29). A DMF solution (75 mL) of Boc-Tyr (14.0 g, 50 mmol), *tert*-butyldimethylsilyl chloride (17.0 g, 110 mmol), and imidazole (15.0 g, 220 mmol) was stirred at room temperature under an Ar atmosphere for 48 h. After the reaction mixture was diluted with ether (500 mL), it was washed with water (5 × 100 mL), dried over Na_2SO_4, and filtered, and all solvent was removed under reduced pressure to yield 25.4 g of a pale yellow oil. A 16.3-g sample of this material was chromatographed on a Waters Prep 500 by using a 50 × 300 mm Porasil column and eluting with a 10/90/1 mixture of EtOAc/CH_2Cl_2/HOAc to give 11.4 (90%) of the white glass title product: $[\alpha]^{25}_D$ 45.3 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 3420, 2850–3050, 1740, 1710, 1610, 1510, 1370 cm^{-1}; ^1H NMR (CD_2Cl_2) δ 0.17 (s, 6), 0.95 (s, 9), 1.36 (s, 9), 2.9–3.0 (br d, 2), 4.2–4.6 (m, 1), 6.70 (d, *J* = 8 Hz, 2), 6.95 (d, *J* = 8 Hz, 2).

Anal. Calcd for $C_{20}H_{33}NO_5Si$ (395.58): C, 60.73; H, 8.41, N, 3.54. Found: C, 60.81; H, 8.44; N, 3.38.

N-Ethylation of *t*-Boc-*O*-(*tert*-butyldimethylsilyl)-L-tyrosine (29). Following our general chemoselective N-ethylation procedure described above, Boc-*O*-(*tert*-butyldimethylsilyl)-L-tyrosine (2.26 g, 5.7 mmol) was treated with 6 mL (12.6 mmol) of *t*-BuLi in pentane. A deep yellow dianion solution was generated. Alkylation of the anion was achieved by subsequent addition of triethyloxonium tetrafluoroborate (1.1 g, 5.7 mmol). When dilution of the reaction with CH_2Cl_2 (300 mL) and 100 mL of 0.5 N $KHSO_4$ was complete, this mixture was shaken vigorously and the organic phase separated. The organic phase was further washed with 0.5 N $KHSO_4$ (125 mL). After extracting the combined aqueous extracts with CH_2Cl_2 (100 mL), the combined organic phases were dried (Na_2SO_4) and filtered, and all solvent

was removed under reduced pressure to provide 2.43 g of a light yellow oil. Analysis of this sample was carried out on a Waters Associate HPLC with a Partisil ODS-2 column monitoring a mobile phase of MeOH/H_2O/HOAc (200:200:4) at 280 nm. Standard solutions of **25** were used to generate a standard curve based on peak area from which the presence of Boc-Et-Tyr (**25**) was substantiated and a yield of 13% was determined.

Direct N-Ethylation of *t*-Boc-L-tyrosine through Use of a Trimethylsilyl Ether Intermediate. A magnetically stirred solution of Boc-L-Tyr (100 g, 35.5 mmol) in 150 mL of dry THF was cooled to −70 °C under Ar. A solution of *t*-BuLi in pentane (35.5 mL, 71 mmol) was then added dropwise over a 25-min period. After the resulting heterogeneous mixture was stirred for 0.5 h, trimethylsilyl chloride (35.5 mmol, 3.86 g) dissolved in 10 mL of THF was added dropwise (5 min) to the agitated mixture. The reaction temperature was allowed to warm at 0 °C before recooling to −70 °C and adding an additional 18 mL (35.5 mmol) of *t*-BuLi to the reaction. After the mixture was stirred at this temperature for 30 min, it was warmed to −20 °C and stirred at this temperature for an additional 30 min before adding triethyloxonium tetrafluoroborate (35.5 mmol, 6.7 g). The reaction was warmed to room temperature, stirred for 24 h, diluted with CH_2Cl_2 (600 mL), and extracted with 0.5 N $KHSO_4$ (3 × 200 mL). The aqueous washes were extracted with CH_2Cl_2 (150 mL). The combined CH_2Cl_2 extracts were dried (Na_2SO_4) and filtered, and all solvent was stripped off to provide 12.5 g of a pale yellow oil. As described in the previous experiment, HPLC analysis was used to determine that the desired product (**25**) was produced directly in 22% yield.

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Registry No. **7**, 13734-34-4; **11**, 94732-05-5; **12**, 70961-24-9; **13**, 368-39-8; **14**, 94799-50-5; **15**, 94732-06-6; **16**, 94732-07-7; **17**, 94732-08-8; **18**, 94732-09-9; **20**, 94732-10-2; **21**, 2130-96-3; **23**, 94732-11-3; **24**, 94732-12-4; **25**, 94732-13-5; **26**, 94732-14-6; **27**, 3978-80-1; **29**, 94732-15-7; **30**, 94732-16-8; Tyr-OMe·HCl, 3417-91-2; Boc-D-Met, 5241-66-7; Me_3SiCl, 75-77-4; Boc-DL-Phe, 4530-18-1; *tert*-butyldimethylsilyl chloride, 18162-48-6.

Basidiomycete Sesquiterpenes: The Silica Gel Induced Degradation of Velutinal Derivatives

Olov Sterner, Rolf Bergman, Jan Kihlberg, James Oluwadiya, and Börje Wickberg*

Division of Organic Chemistry 2, Lund Institute of Technology, S-221 00 Lund, Sweden

Giovanni Vidari, Maria De Bernardi, Federica De Marchi, Giovanni Fronza, and Paola Vita Finzi*

Dipartemento di Chimica Organica, Viale Taramelli 10, 27100 Pavia, Italy

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Derivatives of the pentacyclic sesquiterpene velutinal, occurring as fatty acid esters in *Lactarius* species and in other *Basidiomycetes*, form a number of previously isolated furanoid sesquiterpenes when degraded by silica gel. On the basis of the structure of isolated intermediates and products, a mechanism for the degradation is proposed.

Introduction

The velutinal esters **1a** and **1b** were recently isolated during a search for the chemical entities responsible for the so called sulphovanillin reaction, which is used as a diagnostic test in systematic mycology,[1] and independently during a search for the elusive precursors of previously isolated *Lactarius* sesquiterpenes.[2] In several *Lactarius* species the velutinal esters probably function as the "ammunition" in a chemical defense system, in which they are enzymatically converted to toxic sesquiterpenes within minutes whenever the mushroom is injured.[3] Unaffected specimens of these *Lactarius* species contain no sesquiterpenes in significant amounts besides the velutinal esters.[1,2] A number of previously reported sesquiterpenes from *Lactarius* species are in fact artifacts, formed during extraction and workup of the extracts. Free velutinal **1c**, its esters (**1a** and **1b**), and methyl acetal **1d** are labile compounds which on adsorption on silica gel form a number of furanoid sesquiterpenes[4] of lactarane and secolactarane type which have been isolated previously from different Basidiomycetes.[5] Rapid degradation also takes place on dissolving compounds **1a–d** in reagent grade methanol, as under other conditions where traces of acid are present.[6] The furanoid sesquiterpenes are formed via intermediate dihydrofurans. These profurans are very easily converted to furans by acidic catalysis, although many of them are stable enough to be isolated. In this paper we report a detailed investigation of the products formed when the three velutinal derivatives **1a**, **1c**, and **1d** are degraded by silica gel and in reagent grade methanol, and we suggest a mechanistic interpretation of the product patterns. The origin of a number of reported sesquiterpenes of *Lactarius* and *Russula*, whether they are true metabolites, secondary enzymatic products, or chemical artifacts, still remains to be established, and in that context the chemistry of velutinal is of central interest.

Materials and Methods

Hemiacetal esters **1a,b** were isolated, respectively, from an EtOAc extract of *L. vellereus* and from an EtOAc extract of *L. necator*, both species were collected in the south of Sweden during the autumns of 1982 and 1983. Apart

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