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The Synthesis of Cyclopropyl Tyrosine

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The synthesis of *Z*-cyclopropyl tyrosine (∇^ZTyr) using a thiazoline intermediate has been completed. Several routes were examined.

During our work on the dehydro (*1*) and cyclopropyl enkephalins (*2*) we have been interested in the synthesis of a conformationally restricted form of the very important N-terminal amino acid tyrosine. It has become quite clear from structure activity studies (*3*) that virtually any modification of the Tyr^1 moiety destroys the analgesic activity of the enkephalin molecule. We felt that the introduction of a rigid form of tyrosine having all its functionality intact leading to an increased hyrolytic stability at the Tyr^1–Gly^2 bond might lead to an analgesic compound with improved medicinal characteristics. The structural similarity between the tyramine moiety of morphine and the amino terminal tyrosine residue of enkephalin has lead to speculation that the brain binding sites of the enkephalins and of morphine might be the same (*4*). The introduction of a morphinelike rigidity into the enkephalin molecule vis-à-vis cyclopropyl tyrosine is therefore envisioned.

One of our approaches to the synthesis of ∇^ZTyr was modeled on the method used earlier (*5*) in the synthesis of ∇^ZPhe (Scheme 1). With the 4-hydroxyl group of **2** protected by acetylation (*6*), the cyclopropanation step using diazomethane was well behaved, but the last step in the sequence using Meerwein's reagent to remove the *N*-benzoyl group proceeded in only 25% yield, making this procedure impractical.

In an attempt to improve on this process, we investigated a second synthetic sequence (Scheme 2) also used previously (*7*) in the synthesis of ∇Phe. The *o*-(*t*-butoxycarbonyl)oxazolone (**6**) was used as starting material so that a phthaloyl instead of a benzoyl group could be removed in the last step of the synthesis. The acid (**7**) was obtained in good yield, but only small amounts of the cyclopropane (**8**) could be isolated from the mixture formed when **7** was treated with diazomethane. The NMR spectrum of the mixture indicated the possible presence of a pyrazoline, as found (*7*) in the previous work, but pyrolysis of the mixture did not afford cyclopropane. The failure of this cyclopropanation reaction, we believe, is

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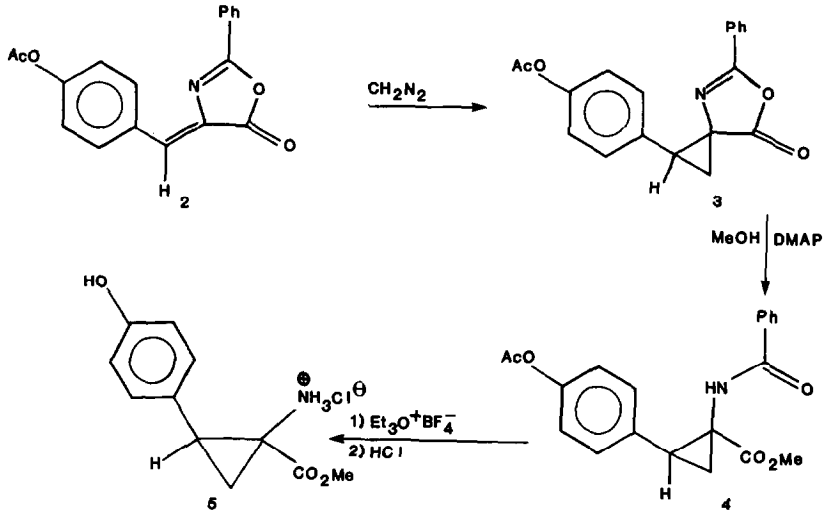
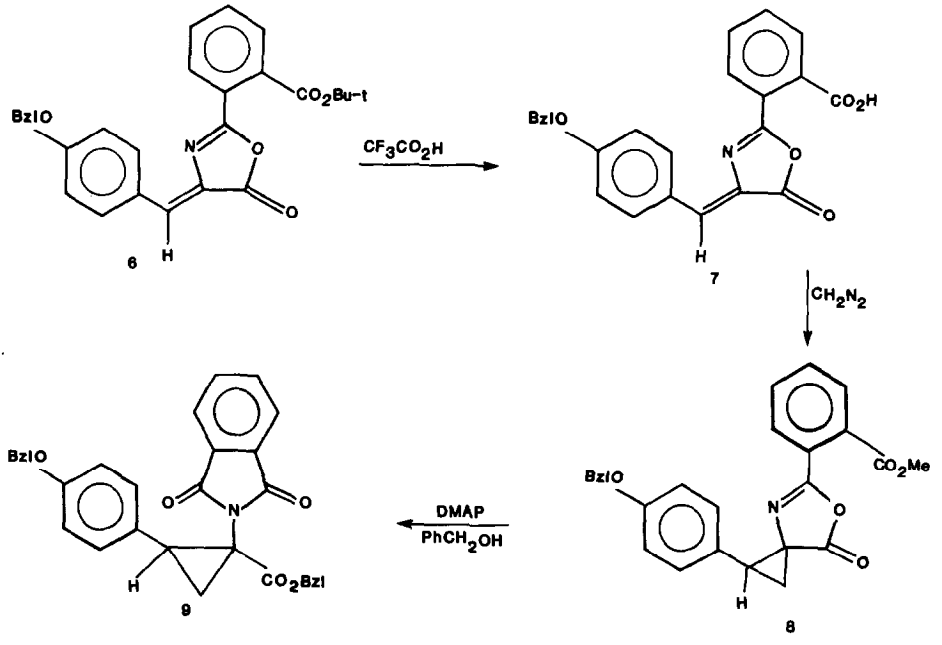
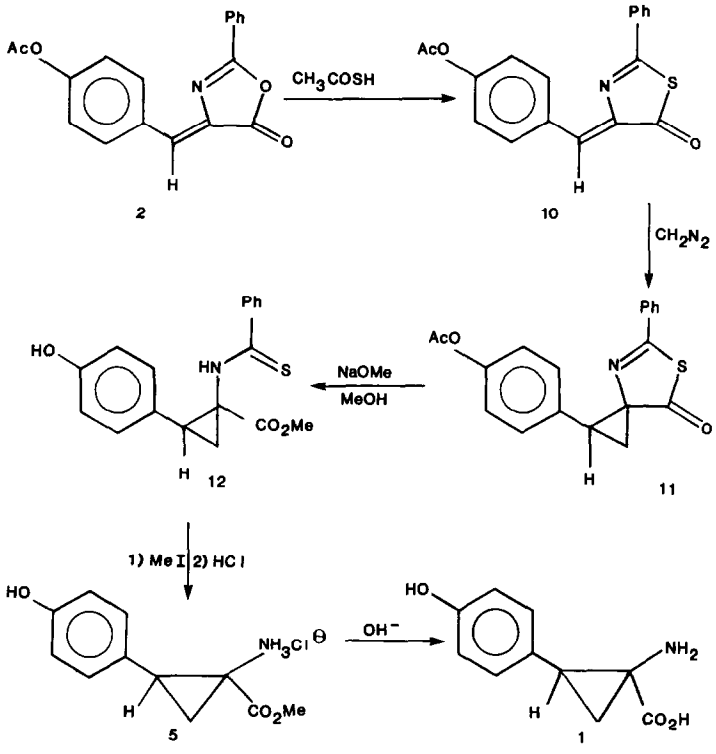


SCHEME 1

related to the greater electron-releasing effect of the *p*-benzyloxy group (compared to the *p*-acetoxy function of **2**) and to the presence of the *o*-carbomethoxy substituent on the benzene ring at the 2-position of the oxazolone ring. Our experience with various substrates in this reaction indicates that both of these groups are



SCHEME 2



SCHEME 3

deleterious to the yield of cyclopropane. Consistent with our work on halogen compounds (*8*), electron-attracting groups on the double bond favor cyclopropane formation, and conjugation of the double bond with the phenyl ring at the oxazolone 2-position is also favorable since 2-methyl oxazolones are known to give poor yields of cyclopropanes (*9*). The results reported here support the thesis that the deconjugation of the benzene ring at position 2, due to the steric effect of the *o*-carbomethoxy group, causes the cyclopropanation yield to suffer. This approach to the synthesis was obviously not acceptable and we looked into a third method using thiazolone intermediates.

When the oxazolone **2** was converted into thiazolone **10** (Scheme 3), the reaction with diazomethane proceeded in good yield and the product (**11**) was a readily characterizable solid. Surprisingly, the thiazolone ring did not undergo 4-dimethylaminopyridine (DMAP)-catalyzed methanolysis, as does the oxygen analog, but the older cleavage method using sodium methoxide as catalyst was carried out successfully. The resulting thioamide (**12**) was readily deblocked by methylation with methyl iodide followed by mild hydrolysis of the resulting thioimidate salt giving **5** in quite acceptable yield. Simple base-catalyzed hydrolysis then gave the desired ∇^{Z}Tyr (**1**) in good yield (Scheme 3).

The yields obtained in this sequence were maximized when each reaction was carried out in a nitrogen atmosphere. Oxidative loss of an electron from either the

oxygen or nitrogen atom with the formation of a cation radical could lead to an exothermic release of strain in the cyclopropane ring, leading to the numerous colored products observed experimentally. Work toward the incorporation of this product into Leu^5–enkephalin is underway.

EXPERIMENTAL

Methyl-Z-1-benzamido-2-p-acetoxyphenylcyclopropane Carboxylate (*4*)

A mixture of **3** (*10*) (1.8 g, 0.0056 mol), 4-dimethylaminopyridine (820 mg, 0.0067 mol), and MeOH (20 ml) was stirred for 3 h at room temperature (r.t.) and then the solvent was evaporated *in vacuo*. To the yellowish syrup was added $CHCl_3$ (20 ml) and the solution was washed with 10% citric acid and water, dried over Na_2SO_4, and then evaporated. The resulting residual oil was triturated with Et_2O–AcOEt and the obtainable crystals were filtered by suction to give **4** (1.5 g, 75.8%) as pale yellow solid, R_f (CH_3Cl–EtOH), 5 : 1) 0.57, 0.38. IR: $(KBr)_{max}$ cm^{-1} 3300, 1720, 1635, 1610.

(*Z*)-2-(*o-t-Butoxycarbonylphenyl*)-4-*p-benzyloxybenzylidene-5-oxazolone* (*6*)

A mixture of 4-benzyloxybenzaldehyde (19 g, 0.08 mol), *N*-(2-*t*-butoxycarbonylbenzoyl) glycine (*7*) (22.4 g, 0.08 mol), NaOAc (6.72 g, 0.08 mol), and Ac_2O (26.6 ml, 0.24 mol) was stirred 4 h at 100–110°C and the excess Ac_2O was evaporated *in vacuo*. The residue was extracted with AcOEt and the extract was washed with 10% Na_2CO_3, sat. NaCl soln., dried over anhydrous Na_2SO_4 and evaporated *in vacuo*. Et_2O (50 ml) was added to the residual oil and the mixture was allowed to stand overnight in a freezer. The resulting yellow solid was collected by filtration and washed with Et_2O to give **6** (13.1 g, 35.7%), mp 110–112°C; NMR ($CDCl_3$): 6.95–8.20 (m, 9H, arom. H, CH=), 5.15 (s, 2H, OCH_2), 1.5 (s, 9H, $CH_3 \times 3$); ir (KBr) cm^{-1} 1760, 1700, 1645.

Anal. Calcd for $C_{28}H_{25}NO_5$: C, 73.83; H, 5.53; N, 3.08. Found: C, 73.51; H, 5.48; N, 3.09.

(*Z*)2-(*2-Carboxyphenyl*)-4-*p-benzyloxybenzylidene-5-oxazolone* (*7*)

To a solution of **6** (13 g, 0.0285 ml) in CH_2Cl_2 (250 ml) was added CF_3COOH (75 ml) at r.t. and the mixture was stirred for 5 h. The mixture was concentrated under reduced pressure and the resulting solid was washed with AcOEt (50 ml) and filtered to give **7** (11.0 g, 96.5%) as yellow prisms, mp 193–194°C; ir (KBr) cm^{-1} 1795, 1770, 1710, 1690, 1650, 1600; NMR ($CDCl_3$ + DMSO-d_6); δ8.2 and 7.15 (q, 4H, ArH), 7.2–8.0 (m, 5H, ArH, HC=), 5.2 (s, 2H, OCH_2).

Anal. Calcd. for C, 72.17; H, 4.29; N, 3.51. Found: C, 72.11; H, 4.32; N, 3.42.

(*Z*)2-*p-Benzyloxyphenyl-5-*(*2-methoxycarbonylphenyl*)-6-*oxo-4-azaspiro*-[*2.4*] *hep-4-en-7-one* (*8*)

To a stirred ice-cold ethereal diazomethane solution, prepared from Diazald (32.2 g, 0.15 mol) in 350 ml of Et_2O, solid **7** (8.0 g, 0.02 mol) was added followed

by CH_2Cl_2 (50 ml). After stirring overnight, the solution was evaporated *in vacuo* and the resulting yellow syrup was chromatographed on silica gel (100 g, 60–200 mesh, Baker) by elution with $CHCl_3$. The syrup obtained was triturated with Et_2O and allowed to stand in freezer. The resulting crystals were collected by filtration to give **8** (0.5 g, 5.9%), mp 145–146°C ir (KBr) cm^{-1} 1800, 1740, 1630, 1605; NMR ($CDCl_3$): δ6.8–7.8 (m, 13H, ArH), 5.00 (s, 2H, OCH_2), 3.55 (s, 3H, OCH_3), 3.00–3.40 (m, 1H, ∇CH) 2.10–2.35 (m, 2H, ∇CH_2).

Anal. Calcd. for $C_{26}H_{21}NO_5$: C, 73.05; H, 4.95; N, 3.28. Found: C, 72.81; H, 5.01; N, 3.21.

Benzyl(Z)-1-phthalimido-2-p-benzyloxyphenylcyclopropanecarboxylate (***9***)

A mixture of **8** (500 mg, 1.17 mmol), dimethylaminopyridine (142 mg, 1.16 mmol), benzyl alcohol (1.7 ml), and THF (2 ml) was stirred for 2 days at r.t. The solvent was removed *in vacuo,* the resulting residue was extracted with AcOEt, and the extract was washed with 10% citric acid, sat. NaCl soln., dried over anhydrous Na_2SO_4, and evaporated *in vacuo*. The residual solid was washed with Et_2O and filtered to give **9** (450 mg, 76.4%), mp 147–150°C; ir (KBr) cm^{-1} 1710, 1600; NMR ($CDCl_3$): δ6.6–7.8 (m, 18H, ArH), 5.15 (s, 2H, CH_2), 4.90 (s, 2H, CH_2), 3.2–3.5 (m, 1H, ∇CH), 2.15–2.5 (m, 2H, ∇CH_2).

(Z)-2-Phenyl-4-p-acetoxybenzylidene-5-thiazolone (***10***)

A mixture of **2** (*10*) (24.6 g, 0.08 mol), Et_3N (0.5 ml), and thioacetic acid (30 ml, 0.42 mol) was stirred at 85–90°C for 18 h and the excess of thioacetic acid was evaporated *in vacuo*. The resulting orange solid was triturated with EtOH (150 ml), filtered, and recrystallized from benzene–EtOH to give 17.5 g of **2** (67.8%), mp 163–165°C; ir (KBr) cm^{-1} 1735, 1675; NMR ($CDCl_3$); δ8.0–8.4 (m, 4H, ArH), 7.2–7.65 (m, 6H, ArH, CH═), 2.31 (s, 3H, CH_3).

Anal. Calcd. for $C_{18}H_{13}NO_3S$: C, 66.86; H, 4.05; N, 4.33; S, 9.92. Found: C, 66.80; H, 4.08; N, 4.30; S, 9.99.

(Z)-1-p-Acetoxyphenyl-5-phenyl-6-thio-4-azaspiro-[2.4]hep-4-en-7-one (***11***)

To a solution of **10** (7.4 g, 0.022 mol) in CH_2Cl_2 (100 ml), ethereal CH_2N_2 prepared from Diazald (21.5 g, 0.1 mol) in Et_2O (200 ml) was added dropwise over a period of 1 h with ice cooling, and the mixture was stirred overnight at r.t. The solution was evaporated and the resulting solid was triturated with Et_2O and filtered to give 4.0 g of **11** (53.9%). Recrystallization from AcOEt/*n*-hexane gave pure **11** as colorless needles, mp 148–150°C; NMR ($CDCl_3$): δ7.05–7.9 (m, 9H, ArH), 3.2–3.5 (m, 1H, ∇CH), 2.32–2.68 (m, 2H, ∇CH_2), 2.32 (s, 3H, CH_3); ir (KBr) cm^{-1} 1735, 1675.

Anal. Calcd. for $C_{19}H_{15}NO_3S$: C, 67.64; H, 4.48; N, 4.15; S, 9.50. Found: C, 67.64; H, 4.51; N, 4.16; S, 9.52.

Methyl (Z)-Thiobenzamido-2-p-hydroxyphenylcyclopropane Carboxylate (***12***)

To a suspension of **11** (3.37 g, 0.01 mol) in MeOH (80 ml) was added NaOMe (1.08 g, 0.02 mol) at 0°C and the reaction mixture was stirred 30 min with ice

cooling. HCl (1 N) was added to pH 3 and the MeOH was evaporated *in vacuo*. The remaining aqueous solution was extracted with CH_2Cl_2 and the extract was washed with water, dried over Na_2SO_4, and evaporated *in vacuo*. The resulting yellow syrup was chromatographed by elution with $CHCl_3$ (silica gel 60–200 mesh, Baker, 70 g) and the product was recrystallized from AcOEt–*n*-hexane to give **12** (1.86 g, 56.9%) as pale yellow prisms, mp 147–148°C. NMR ($CDCl_3$): δ8.9 (s, 1H, OH), 8.11 (br s, 1H, NH), 6.8–7.6 (m, 9H, ArH), 3.8 (s, 3H, CH_3), 3.00–3.30 (m, 1H, ∇CH), 2.2–2.40, 1.75–2.00 (m, 2H, ∇CH_2).

Anal. Calcd. for $C_{18}H_{17}NO_3S$: C, 66.03; H, 5.23; N, 4.28; S, 9.79. Found: C, 66.20; H, 5.23; N, 4.24.

(*Z*)-*Cyclopropyltryosine Methyl Ester Hydrochloride* (*5*)

(*a*) *From* ***12***. A mixture of **12** (1.0 g, 3.05 mmol), CH_3I (4.56 g, 32 mmol) and THF (5 ml) was stirred 24 h at r.t. and evaporated *in vacuo*. The resulting yellow syrup was dissolved in a mixture of MeOH (20 ml) and 2 N HCl (20 ml) and the solution was refluxed for 1 h. The MeOH was removed *in vacuo* and the remaining aqueous solution was washed with Et_2O and neutralized with solid $NaHCO_3$, and the precipitate was extracted into AcOEt. The extracts were washed with water and dried over anhydrous Na_2SO_4. Satd. HCl–Et_2O soln (5 ml) was added to the solution and it was evaporated *in vacuo*. The resulting solid was recrystallized from i-PrOH–Et_2O to give **5** (410 mg, 55%) as colorless prisms, mp 209–210°C (dec.); NMR (DMSO-d_6): δ8.9 (br s, 3H, NH_2, HO), 7.3 and 6.85 (2d, 4H, ArH), 3.82 (s, 3H, OCH_3), 3.50 (br s, 1H, OH), 2.92 (t, 1H, ∇CH), 1.85 (d, 2H, ∇CH_2).

Anal. Calcd. for $C_{11}H_{13}NO_3 \cdot HCl$: C, 54.22; H, 5.79; N, 5.75; Cl, 14.55. Found: C, 54.14; H, 5.81; N, 5.70; Cl, 14.59.

(*b*) *From* ***4***. To a solution of **4** (500 mg, 1.4 mmol) in CH_2Cl_2 (10 ml) was added Meerwein's reagent (1 M triethyloxonium tetrafluoroborate in CH_2Cl_2, 3.1 ml) under a N_2 atmosphere at r.t. The mixture was refluxed 2 h and stirred overnight at r.t. A K_2HPO_4 (540 mg, 3.1 mmol) solution (3 ml) was added to the reaction mixture at r.t. and the organic layer was separated, dried over anhydrous Na_2SO_4, and evaporated *in vacuo*. The resulting oil was dissolved in satd. HCl–Et_2O soln. (5 ml) with MeOH/dry ice cooling; 1 N HCl (5 ml) was added to the mixture which was stirred for 30 min at r.t. The aqueous layer was separated and evaporated, and the resulting syrup was triturated with Et_2O. The resulting solid was filtered and recrystallized from i-PrOH-Et_2O to give crude yellow **5** (85 mg, 24.9%), mp 191–196°C; ir: (KBr) cm^{-1} 1730, 1610.

(*Z*)-*Cyclopropyl Tyrosine Hydrochloride* (*1*)

A mixture of **5** (350 mg, 1.44 mmol) and 2 N NaOH (5 ml) was stirred for 3 h at r.t. and then acidified by addition of conc. HCl (pH 2) with ice cooling. The mixture was concentrated to dryness and the resulting residue was trituated with i-PrOH, the insoluble NaCl was filtered, and the filtrate was evaporated *in vacuo*. The yellow syrup was dissolved in i-PrOH (2 ml), Et_2O was added until cloudy and the mixture was allowed to stand at 5°C. The resulting colorless prisms of **1** (150 mg, 45%) were collected by filtration, mp 208–209°C (dec.) (lit (*9*), mp 190°C);

NMR (CD_3OD): δ7.2 and 6.8 (2d, 4H, ArH), 2.8 (t, 1H, ∇CH), 1.8 (d, 2H, ∇CH_2).

Anal. Calcd. for $C_{10}H_{11}NO_3 \cdot HCl\ \frac{1}{2}H_2O$: C, 50.32; H, 5.07; N, 5.87. Found: C, 50.52; H, 5.21; N, 5.77.

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