Synthesis and Resolution of 2-Arylalkyl-2-(tetrazol-5-yl)-*N*-arylalkylcarboxamides. A New Class of Chiral Sterically Hindered Tetrazole Derivatives [1]

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Chiral, racemic 2-arylalkyl-2-(tetrazol-5-yl)-*N*-arylalkylcarboxamides **3** were conveniently prepared from ethyl cyanoacetate in four steps. The synthetic methodology developed is a facile way of introducing bulky substituents into a peptide-like framework, affording intermediate α-arylalkyl-α-amidonitriles. These nitriles were sufficiently activated to give, upon treatment with ammonium azide in dimethylformamide at 145° for twenty-four to thirty hours, the corresponding tetrazoles in good yields. It has been determined that an optically pure α-arylalkyl-α-amidonitrile epimerized to give diastereomeric products under the above conditions. A procedure for the fractional crystallization of the (*S*)-(-)-α-methylbenzylamine salts **4** of the tetrazoles to give the optically enriched tetrazoles **5** was also developed.

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Introduction.

Tetrazoles are an important class of heterocycles, particularly valuable for their broad spectrum of medicinal properties [2-5]. The tetrazole moiety has an acidity which is comparable to that of an amino acid carboxylate [2,3]. Several peptide and amino acid derivatives in which a tetrazolyl group is used as a carboxylate isostere have been reported [4]. In addition to peptides and amino acids, chiral prostaglandin analogs have been prepared in which an incorporated tetrazole moiety acts as a carboxylate mimic [5].

We report in this paper a novel route to a series of chiral, sterically hindered tetrazole derivatives, and their resolution from diastereomeric salts of (*S*)-(-)-α-methylbenzylamine by fractional crystallization. The compounds prepared are formally chiral geminal dicarboxylic acid analogs, one acid moiety being the tetrazole substituent and the other a carboxamide. These chiral, nonracemic tetrazoles were prepared for use as chiral catalysts in the stereoselective syntheses of chiral phosphate and phosphonate esters *via* the Phosphoramidite method [6].

Results and Discussion.

The general route for the synthesis and resolution of racemic tetrazoles **3** is depicted in Scheme 1. Potassium carbonate-mediated alkylation of ethyl cyanoacetate in refluxing acetone, followed by alkaline hydrolysis of the α-alkyl ester gave either the α-diphenylmethyl **1a** (54%) or the α-9-fluorenyl **1b** (93%) cyanoacetic acids, both crystalline solids. The fluorenylation occured within four hours, whereas the diphenylmethylation required twenty-four hours to reach completion. The conformational rigidity of 9-bromofluorene relative to bromodiphenylmethane made the former a much more reactive alkylation substrate. Conversion of acids **1** to the corresponding acid chlorides under mild conditions, followed by treatment with a sterically hindered amine, gave the racemic α-arylalkyl-α-cyanoamides in yields of 50-93% (Table 1). Previous work in our laboratory [7] had determined that ethyl cyanoacetate and its amide derivatives were excellent substrates for 1,3-dipolar cycloaddition of azide ion to form the tetrazole acids using the classical conditions for tetrazole synthesis, ammonium chloride and sodium azide in a heated solution of dimethylformamide [8]. Nitriles **2** required a temperature of 145° and a reaction time of twenty-four to thirty hours to form tetrazoles **3**. Yields of the racemic tetrazoles, with the exception of **3d**, were uniformly good, 68-85% (Table 1).

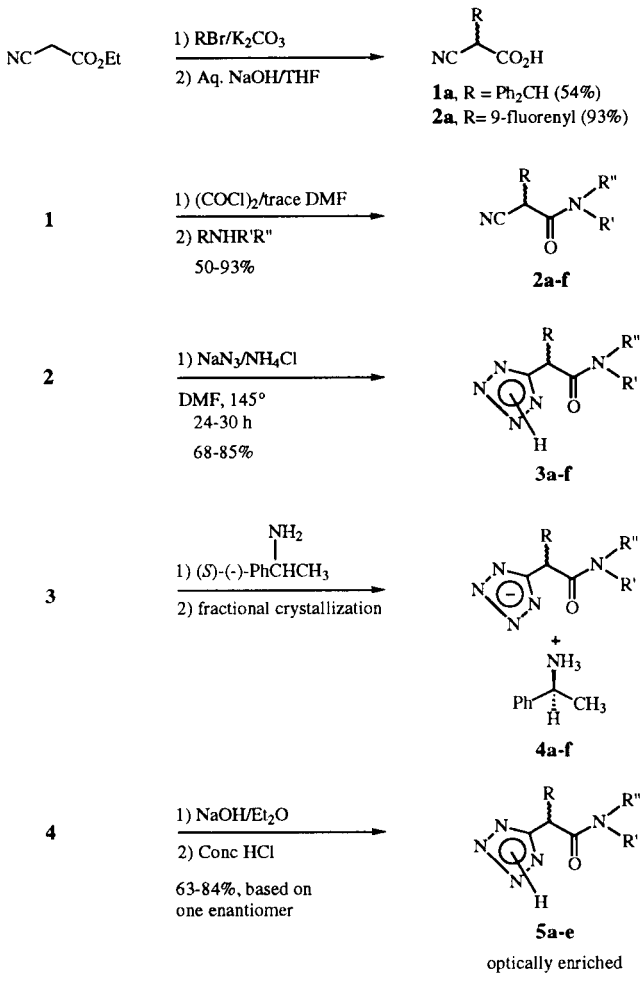
Table 1

Structures and Yields of Nitriles **2** and Tetrazoles **3** Prepared Using the Route Depicted in Scheme 1

	R	R'	R"	Yield, **2**, %	Yield, **3**, %
a	Ph_2CH	(S)-(-)-$PhCHCH_3$	H	56	68
b	Ph_2CH	Ph_2CH	H	50	80
c	Ph_2CH	Bn	Bn	93	71
d	Ph_2CH	9-fluorenyl	H	83	35
e	9-fluorenyl	Ph_2CH	H	64	85
f	9-fluorenyl	(S)-(-)-α-naphthylethyl	H	66	68

The chiral center bearing the nitrile in compounds **2** also has a carboxamido substituent, making the methine proton attached fairly acidic. It was therefore considered probable that optically active compounds **2** would racemize or epimerize under the rather harsh reaction conditions used to form tetrazoles **3**, since similar compounds have been prepared and found to epimerize under far milder

Scheme 1



conditions [9]. To confirm this probability, an optically enriched or optically pure nitrile of type **2** was required. Attempted separation of the diastereomers of **2a**, both chromatographically and *via* fractional crystallization, failed. However, it was discovered that in attempting to recrystallize crude **2f** from a hot solution of ethyl acetate and heptane, a fractional crystallization was effected, in which a single diastereomer, in greater than 90% optical purity, was obtained. It was evident that fractional crystallization had occurred when a 400 MHz proton nmr spectrum of recrystallized **2f** in deuteriochloroform was compared to the analogous spectrum of the crude compound known to contain both of the diastereomers of **2f**. The latter spectrum had twice the number of resolvable proton signals as the former spectrum, due to the magnetic anisochrony of the protons observed for this diastereomeric pair of compounds. Optically pure **2f** was then subjected to the condition for tetrazole synthesis, and after a twenty-four hour reaction, the proton nmr spectrum (DMSO-d_6)of the corresponding tetrazole **3f** was recorded. The spectrum showed signals indicating the presence of both diastereomeric products in approximately equal quantities, identical by comparison with the spectrum of the product **3f** prepared from the epimeric mixture of nitriles **2f**. This indicates complete epimerization of optically enriched **2f**.

Tetrazole **3a** proved to be a model compound for the experimental investigation leading to the successful resolution of enantiomeric tetrazoles **3b-e**. The use of (*S*)-(-)-α-methylbenzylamine to synthesize the amide **2a** gave two diastereomeric compounds, each of which had significantly different chemical shifts for certain sets of proton nmr signals. Though the preparation of the (*S*)-α-methylbenzylamine salt **4a** was not absolutely necessary to effect physical separation of a diastereomeric tetrazole, it was found that fractional crystallization of the diastereomeric mixture of salts **4a** prepared from **3a** (using hot acetonitrile containing a trace of methanol) provided a single diastereomeric salt. Within a few trials, it became possible to fractionally crystallize **4a** from hot acetonitrile containing a trace of methanol reproducibly, obtaining a single diastereomeric salt as the crystalline precipitate. This fractional crystallization provided a precedent, on which the resolutions of tetrazoles **3b-e** were predicated.

Optical purity was assessed, where possible, using 400 MHz nmr spectroscopy. Diastereomeric tetrazole **3a** exhibited magnetic anisochrony of its resolvable protons in both its neutral **3a** and salt **4a** forms. Therefore, a diminution of proton signals in the spectrum corresponding to one of the diastereomers of salt **4a** subsequent to fractional crystallization could be correlated with an enhancement in optical purity of **4a**, and the complete disappearance of the second set of signals indicated that (to the limits of nmr detection), a single diastereomer was present. A comparison of the spectra of optically pure **4a** and **5a** (obtained by treatment of **4a** with 10% sodium hydroxide/ether for 15 minutes and then concentrated hydrochloric acid) showed proton signals corresponding to a single diastereomer, indicating that negligible epimerization had occurred in the presence of aqueous base at room temperature for this period of time. The resistance of **5a** to epimerization in the presence of 10% sodium hydroxide was most likely due to the ionization of the tetrazole moiety before the methine proton attached to the chiral center could be abstracted by hydroxide. Hydroxide thus was not a strong enough base to perform the second proton abstraction to form the dianion. Epimerization of **5a** using stronger bases was not attempted, although prolonged stirring of **5a** with 10% sodium hydroxide at room temperature (3 hours) produced no noticeable change in its nmr spectrum after neutralization with hydrochloric acid. Enantiomeric **3c**, in deuteriochloroform containing two equivalents of (*S*)-(-)-2,2,2-triflouro(9-anthryl)-ethanol [10], showed a reproducible magnetic aniso-

chrony in its proton nmr signals, indicating the formation of two diastereomeric complexes, one for each enantiomer of **3c**. This phenomenon proved to be an excellent probe for the optical purity of **5c**, which was determined to be at least 90% optically pure. Unfortunately, compounds **4b,d,e** and **5b,d,e** showed no magnetic anisochrony in their proton spectra, either with the aforementioned chiral shift reagent or with excess added tris[3-(trifluoromethylhydroxymethylene)-(+)-camphorato]-europium(III). Therefore no useful assessment of the optical purities of **5b,d,e** could be made on the basis of high field nmr analysis. Each of the resolved compounds **5b-e** had a measurable optical rotation (see Experimental). Although measurable rotations were by no means satisfactory criteria of optical purity, the unequivocal high field nmr spectroscopic determination of high optical purity in the cases of the fractional crystallizations leading to the isolation of **5a** and **5c** provided model diastereomeric and enantiomeric systems, and a basis for expecting that analogous compounds resolved under similar conditions were optically enriched to a significant extent.

Summary.

A four-step route to a novel series of sterically hindered racemic chiral tetrazoles from ethyl cyanoacetate has been demonstrated. It has been ascertained that optically enriched nitriles of type **2** epimerized or racemized completely during the course of the 1,3-dipolar cycloaddition used to form the tetrazole. Resolution of compounds **3** could be effected by conversion to the (*S*)-(-)-α-methylbenzyl amine salts **4** and fractional crystallization. The physical separation of diastereomeric tetrazoles **3a** and the resolution of enantiomeric tetrazoles **3c** in the above manner gave the corresponding highly optically enriched tetrazoles **5a** and **5c**, the optical purity of which (≥ 90%) were confirmed using high field nmr analyses. The isolation of **5a** and **5c** in highly optically pure form was indicative of the optical stability of compounds of this type to treatment with 10% aqueous sodium hydroxide. The synthesis developed is a versatile method for preparing a wide variety of chiral nonracemic tetrazolyl carboxamides, which may have potential in biochemical and medicinal applications.

EXPERIMENTAL

All chemicals and solvents were of reagent grade. Acetone was dried by distillation from anhydrous potassium carbonate and used immediately after it was distilled. Methylene chloride was distilled from phosphorus pentoxide and stored over 4A° molecular sieves under an atmosphere of argon. Melting points were determined using a Fisher-Johns melting point apparatus and are uncorrected. The ir spectra were obtained using a Unicam SP 1000 spectrometer. Proton nmr spectra were obtained using a Bruker WP 400 MHz spectrometer. Mass spectra were obtained using a Finnegan MAT 90 spectrometer. Microanalyses were performed by Midwest Microlab, Indianapolis, IN. Optical rotations were measured on a JASCO DIP 370 digital polarimeter at 25°, using a mercury source set at 546 nm.

(±)-2-Cyano-3,3-diphenylpropionic Acid (**1a**).

Ethyl cyanoacetate (12.0 g, 0.106 mole), bromodiphenylmethane (29.3 g, 0.118 mole) and potassium carbonate were combined in dry acetone (500 ml) and vigorously stirred. The suspension was refluxed 24 hours, then concentrated *in vacuo* and chromatographed (silica, 10% ethyl acetate/hexanes) to give a tan oil which consisted mostly (>85% by ^{1}H nmr) of the α-alkylated ester. This oil was dissolved in tetrahydrofuran (200 ml), and a solution of potassium hydroxide (25.0 g, 0.446 mole) in water (100 ml) was added with stirring, and the mixture stirred 18 hours. Most of the tetrahydrofuran was removed *in vacuo*, then the aqueous layer was washed with ether (2 x 200 ml), then diluted with water to a volume of 400 ml, immersed in an ice bath, and acidified to *p*H = 2 with concentrated hydrochloric acid. The resulting precipitate was collected by vacuum filtration, air-dried, and recrystallized from isopropyl ether (14.34 g, 54%), mp 158.5-159°; ir (potassium bromide): ν 3200 (br), 2140, 1755 cm^{-1}; ^{1}H nmr (acetone-d_6): δ 7.5-7.1 (m, 10 H, aromatic), 4.7 (d, 1 H, J = 8 Hz, $HCPh_2$), 4.2 (d, 1 H, J = 8 Hz, chiral methine) ppm; ms: m/z 251 (M+).

Anal. Calcd. for $C_{16}H_{13}NO_2$: C, 76.5; H, 5.2; N, 5.6. Found: C, 76.4; H, 5.1; N, 5.6.

(±)-2-Cyano-2-(9-fluorenyl)-acetic Acid (**1b**).

9-Bromofluorene (14.67 g, 0.0598 mole) was added to a vigorously stirred dry acetone (350 ml) suspension containing ethyl cyanoacetate (6.76 g, 0.0598 mole) and potassium carbonate (30 g, 0.303 mole). The resulting mixture was refluxed 4 hours and cooled to rt. A solution of sodium hydroxide 10 g, 0.250 mole) in water (60 ml) was then added to the mixture, and the resulting solution stirred 18 hours at rt. The solution was carefully concentrated *in vacuo* to remove most of the acetone, and water (500 ml) was added, and the diluted aqueous solution was washed with ether (2 x 300 ml). The aqueous layer was then transferred to a 1 l Erlenmeyer flask, diluted to 750 ml with water, cooled to 0°, and gradually acidified to *p*H = 2 with concentrated hydrochloric acid. The thus formed white crystalline precipitate was collected by vacuum filtration, washed with 500 ml of water, and then air dried overnight (13.85 g, 93%), mp 197-198°; ir (potassium bromide): ν 3460 (br), 2180, 1765, 1720, 1710 cm^{-1}; ^{1}H nmr (acetone-d_6): δ 7.7-7.0 (m, 10 H, aromatic), 4.5 (d, 1 H, J = 4 Hz, fluorenyl methine), 4.15 (d, 1 H, J = 4 Hz, chiral methine) ppm; ms: m/z 249 (M+).

Anal. Calcd. for $C_{16}H_{11}NO_2$: C, 77.1; H, 4.4; N, 5.6. Found: C, 77.0; H, 4.6; N, 5.7.

(±)-2-Arylalkyl-2-cyano-*N*-arylalkyl-carboxamides **2a-f**.

General Procedure.

In a typical experiment [a] the acid (1.5 g, 6.0 mmoles) was suspended in dry methylene chloride (30 ml), containing a drop of dimethylformamide and cooled to 0°, then neat oxalyl chloride (1.5 ml, 17 mmoles) was added and the mixture warmed to rt and stirred 2.5 hours. Solvent and excess oxalyl chloride were removed *in vacuo*, and dry benzene (50 ml) was added and

removed *in vacuo* to evaporate residual traces of oxalyl chloride. The acid chloride was then dissolved in dry methylene chloride (75 ml), transferred to an addition funnel and added dropwise to a stirring, dry methylene chloride (100 ml) solution at 0° containing the amine (one equivalent), triethylamine (three equivalents), and dimethylamino pyridine (0.10 equivalent). The mixture was warmed to rt, stirred 45 minutes, washed with water (150 ml), 10% hydrochloric acid (150 ml), and water (150 ml). The organic phase was dried (magnesium sulfate) and concentrated *in vacuo* to give the crude amides **2a-f**, which were recrystallized from chloroform/isopropyl ether. [a] In the case of the *N*-(9-fluorenyl)amide **2d**, the hydrochloride salt of 9-aminofluorene was used, and the amount of triethylamine used was doubled from three to six equivalents.

(±)-2-Cyano-3,3-diphenyl-*N*-(*S*)-(-)-α-methylbenzylaminopropionamide (**2a**).

This compound was obtained in a yield of 56%, mp 183-184°; ir (potassium bromide): ν 3320, 2265, 1685, cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.4-6.9 (m, 15 H, aromatic), 6.05 (br, 1 H, amide NH), 5.0 (two d, 1 H, J = 7 Hz, α-methylbenzyl methine), 4.85 (two d, 1 H, J = 6 Hz, $HCPh_2$), 4.1 (two d, J = 6 Hz, chiral methine), 1.3 (two d, J = 7 Hz, α-methylbenzyl methyl) ppm; ms: (CI-pos) m/z 355.1 (M + 1).

Anal. Calcd. for $C_{24}H_{22}N_2O$: C, 81.4; H, 6.2; N, 7.9. Found: C, 81.4; H, 6.4; N, 7.8.

(±)-2-Cyano-3,3-diphenyl-*N*-diphenylmethylpropionamide (**2b**).

This compound was obtained in a yield of 50%, mp 214-215°; ir (potassium bromide): ν 3350, 3100, 2260, 1675 cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.4-6.8 (m, 20 H, aromatic), 6.5 (d, br, 1 H, J = 8 Hz, amide NH), 6.1 (d, 1 H, J = 8 Hz, $HCPh_2$-NH), 4.9 (d, 1 H, J = 6 Hz, $HCPh_2$-CH), 4.2 (d, 1 H, J = 6 Hz, chiral methine) ppm; ms: m/z 416 (M+).

Anal. Calcd. for $C_{29}H_{24}N_2O$: C, 83.7; H, 5.8; N, 6.7. Found: C, 83.6; H, 5.9; N, 6.8.

(±)-2-Cyano-3,3-diphenyl-*N*,*N*-dibenzylpropionamide (**2c**).

This compound was obtained in a yield of 93%, mp 166-167°; ir (potassium bromide): ν 3120, 3080, 2160, 1680 cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.5-6.9 (m, 20 H, aromatic), 5.0 (d, 1 H, J = 11 Hz, $HCPh_2$), 4.5 (four d, 4H, benzyl methylenes), 4.45 (d, 1 H, J = 11 Hz, chiral methine) ppm; ms: m/z 430 (M+).

Anal. Calcd. for $C_{30}H_{26}N_2O$: C, 83.7; H, 6.0; N, 6.5. Found: C, 83.7; H, 6.0; N, 6.6.

(±)-2-Cyano-3,3-diphenyl-*N*-(9-fluorenyl)propionamide (**2d**).

This compound was obtained in a yield of 83%, mp 245-246°; ir (potassium bromide): ν 3271, 2088, 1651 cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.5-6.9 (m, 18 H, aromatic), 6.2 (d, br, 1 H, J = 9 Hz, amide NH), 6.05 (d, 1 H, J = 9 Hz, 9-fluorenyl methine), 5.0 (d, 1 H, J = 7 Hz, $HCPh_2$), 4.25 (d, 1 H, J = 7 Hz, chiral methine) ppm; ms: m/z 414 (M+).

Anal. Calcd. for $C_{29}H_{22}N_2O$: C, 84.0; H, 5.4; N, 6.8. Found: C, 84.3; H, 5.5; N, 6.9.

(±)-2-Cyano-2-(9-fluorenyl)-*N*-diphenylmethylacetamide (**2e**).

This compound was obtained in a yield of 64%, mp 200-201°; ir (potassium bromide): ν 3440, 3200, 2245, 2140, 1710, 1495 cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.7-7.1 (m, 18 H, aromatic), 6.65 (d, br, 1 H, J = 8 Hz, amide NH), 6.3 (d, 1 H, J = 8 Hz, $HCPh_2$-NH), 4.75 (d, 1 H, J = 4 Hz, fluorenyl methine), 4.25 (d, 1 H, J = 4 Hz, chiral methine) ppm; ms: m/z 414 (M+).

Anal. Calcd. for $C_{29}H_{22}N_2O$: C, 84.0; H, 5.4; N, 6.8. Found: C, 84.2; H, 5.4; N, 6.7.

(±)-2-Cyano-2-(9-fluorenyl)-*N*-(S)-α-naphthylethylacetamide (**2f**).

This compound was obtained in a yield of 66%; ^1H nmr (acetone-d_6): δ 8.4-7.0 (m, 15 H, aromatic), 6.05 (two d, 1 H, α-naphthylethyl methine), 4.7, 4.55 (two d, 1 H, J = 5.5 Hz, fluorenyl methine), 4.35 (two d, 1 H, J = 5.5 Hz, chiral methine), 1.65 (two d, 3 H, J = 7 Hz, α-naphthylethyl methyl) ppm; ir (potassium bromide): ν 3327, 2100, 1655 $cm.^{-1}$.

Compound **2f**, Optically Enriched.

Crude **2f** (2.00 g, 5.00 mmoles) was dissolved in hot ethyl acetate (75 ml) and then diluted with heptane (50 ml) and allowed to stand, sealed, overnight. A gelatinous precipitate formed, which was isolated by vacuum filtration (900 mg, 45%), mp 197-198°. The major absorption bands of the ir of optically pure **2f** were similar to those of the ir of crude **2f**. The precipitate turned out to be microcrystalline, and the proton nmr of fractionally crystallized **2f** showed some marked differences; a single doublet at δ 4.7 ppm (instead of two such doublets at 4.7 and 4.5 ppm), 1 H, J = 5.5 Hz, a single doublet at δ 4.4 ppm (instead of two such doublets at 4.4 ppm) and a single doublet at δ 1.65 ppm (instead of two such doublets at 1.65 ppm). The loss of doubling of proton nmr signals, as a result of fractional crystallization, was evidence of the isolation of optically pure **2f**: [α] = +68.4° c = 0.005, acetone.

Anal. Calcd. for $C_{28}H_{22}N_2O$: C, 83.6; H, 5.5; N, 7.0. Found: C, 83.5; H, 5.6; N, 7.0.

(±)-2-Arylalkyl-2-(tetrazol-5-yl)-*N*-arylalkylcarboxamides **3a-f**.

General Procedure.

In a typical experiment, the nitrile **3** (4 mmoles), ammonium chloride (532 mg, 9.85 mmole), and sodium azide (640 mg, 9.85 mmoles) were combined in dimethylformamide (25 ml), and the resulting suspension was placed in an oil bath preheated to 145°, and stirred 24-30 hours. The mixture was then cooled in an ice bath, and made alkaline with 10% aqueous sodium hydroxide (10 ml), and diluted to a volume of 100 ml with water. The alkaline aqueous solution was extracted with ether (2 x 50 ml), then transferred to a 600 ml beaker, again diluted to a volume of 300 ml with water, cooled in an ice bath, and gradually acidified to *p*H = 2 with concentrated hydrochloric acid. The resulting white solids were collected by vacuum filtration, air-dried overnight, and recrystallized from tetrahydrofuran/isopropyl ether. All tetrazoles decomposed upon reaching their respective melting points. **CAUTION: sodium azide is an extremely toxic and explosive compound, and appropriate care and precautions should be taken when using it, and in isolating labeling and disposing of the aqueous and organic waste resulting from its use.** All azide waste was made alkaline with 50% sodium hydroxide prior to its storage and disposal.

(±)-2-(Tetrazol-5-yl)-3,3-diphenyl-*N*-(*S*)-α-methylbenzylpropionamide (**3a**).

This compound was obtained in 68% yield when the reaction time was 24 hours, mp 249-250°; ir (potassium bromide): ν 3270, 1630, 1520, 1440, 1330, 1010 cm^{-1}; ^1H nmr (acetone-d_6): δ 7.8 (d, 1 H, J = 7 Hz, amide NH), 7.6-7.0 (m, 15 H, aromatic),

5.4, 5.3 (two d, 1 H, J = 13 Hz, $HCPh_2$), 4.9 (two d, 1 H, J = 13 Hz, chiral methine) 1.3 (two d, 3 H, J = 7 Hz, α-methylbenzyl methine) ppm; ms: (CI-pos) m/z 397 (M + 1).

Anal. Calcd. for $C_{24}H_{23}N_5O$: C, 72.5; H, 5.8; N, 17.6. Found: C, 72.3; H, 5.8; N, 17.4.

(±)-2-(Tetrazol-5-yl)-3,3-diphenyl-*N*-diphenylmethylpropionamide (**3b**).

Compound **3b** was obtained in 80% yield after a reaction time of 30 hours, mp 284-285°; ir (potassium bromide): ν 3233, 1653, 1554, 1495, 1454, 1072, 1051 cm^{-1}; ^1H nmr (acetone-d_6): δ 8.35 (d, 1 H, J = 8 Hz, amide NH), 7.6-6.9 (m, 20 H, aromatic), 5.9 (d, 1 H, J= 12 Hz, HC-$CHPh_2$), 5.5 (d, 1 H, J = 12 Hz, chiral methine) ppm; ms: m/z 459 (M+).

Anal. Calcd. for $C_{29}H_{25}N_5O$: C, 75.8; H, 5.5; N, 15.3. Found: C, 76.1; H, 5.8; N, 15.2.

(±)-2-(Tetrazol-5-yl)-3,3-diphenyl-N,N-dibenzylpropionamide (**3c**).

Compound **3c** was obtained in 71% yield after a reaction time of 30 hours, mp 173-174°; ir (potassium bromide): ν 3200, 3100, 1660, 1640, 1515, 1470, 1380, 1170, 1110, 1090, 1055, 1045 cm^{-1}; ^1H nmr (acetone-d_6): δ 7.6-7.0 (m, 20 H, aromatic), 5.95 (d, 1 H, J = 12 Hz, $HCPh_2$), 5.0, 4.7, 4.45, 3.95 (four d, J = 17 Hz (one pair), 15 Hz (second pair), benzylic methylenes) ppm; ms: (CI-pos) m/z 474.1 (M + 1).

Anal. Calcd. for $C_{30}H_{27}N_5O$: C, 76.1; H, 5.7; N, 14.8. Found: C, 76.0; H, 5.9; N, 14.8.

(±)-2-(Tetrazol-5-yl)-3,3-diphenyl-*N*-(9-fluorenyl)propionamide (**3d**).

Compound **3d** was obtained in 35% yield after a reaction time of 24 hours, mp 283-284°; ir (potassium bromide): ν 3416, 1684, 1653, 1558, 1539, 1522 cm^{-1}; ^1H nmr (DMSO-d_6): δ 9.0 (d, 1 H, br, tetrazole NH), 8.9-6.9 (m, 18 H, aromatic), 6.6 (br, 1 H, amide NH), 6.25 (d, 1 H, J = 7 Hz, fluorenyl methine), 5.35 (d, 1 H, J = 14 Hz, $HCPh_2$), 5.0 (d, 1 H, J = 14 Hz, chiral methine) ppm; ms: (CI-pos) m/z 458 (M + 1).

Anal. Calcd. for $C_{29}H_{23}N_5O$: C, 76.2; H, 5.0; N, 15.3. Found: C, 76.2; H, 5.2; N, 15.4.

(±)-2-(Tetrazol-5-yl)-2-(9-fluorenyl)-*N*-diphenylmethylacetamide (**3e**).

Compound **3e** was obtained in 85% yield after a reaction time of 30 hours, mp 281-282°; ir (potassium bromide): ν 3335, 3100, 2600, 2500, 1675, 1570, 1465, 1380, 1090, 1060, 1040, 1010 cm^{-1}; ^1H nmr (acetone-d_6): δ 9.35 (d, 1 H, J = 6 Hz, tetrazole NH), 8.85 (d, 2 H, J = 7 Hz, aromatic), 7.45-6.9 (m, 16 H, aromatic), 6.25 (d, 1 H, J = 7 Hz, $HCPh_2$), 6.1 (br, 1 H, amide NH), 4.9 (d, 1 H, J = 10 Hz, fluorenyl methine), 4.3 (d, 1 H, J = 10 Hz, chiral methine) ppm; ms: m/z 457 (M +).

Anal. Calcd. for $C_{29}H_{23}N_5O$: C, 76.1; H, 5.0; N, 15.3. Found: C, 76.2; H, 5.1; N, 15.2.

(±)-2-(Tetrazol-5-yl)-*N*-(*S*)-(-)-α-naphtylethylacetamide, Stereochemical Course of the Formation of **3f** Using Optically Pure **2f**.

Compound **3f** was obtained in 68% yield after a reaction time of 24 hours, mp 291-292°; ir (potassium bromide): ν 3298, 1643, 1541, 1450, 1035 cm^{-1}; ^1H nmr (DMSO-d_6): δ 9.1 (two d, br, 1 H, J = 7 Hz, amide NH), 8.4-6.7 (m, 15 H, aromatic), 5.8 (m, 1 H, J = 7 Hz, α-naphthylethylmethine), 4.8 (two d, 1 H, J = 10 Hz, fluorenyl methine), 4.1 (two d, 1 H, J = 10 Hz, chiral methine), 1.5 (two d, 3 H, J = 7 Hz, α-naphthylethylmethyl) ppm. The reappearance of doubling of the signals assigned to the 9-fluorenylmethine, chiral center methine, and α-naphthylethylmethine and methyl protons, respectively indicated epimerization of the optically pure chiral center bearing the tetrazolyl substituent as a result of subjecting optically pure **2f** to the standard conditions for tetrazole synthesis; ms: m/z 445 (M +).

Anal. Calcd. for $C_{28}H_{23}N_5O$: C, 75.5; H, 5.2; N, 15.7. Found: C, 74.9; H, 5.2; N, 15.7.

(*S*)-(-)-α-Methylbenzylammonium Salts **4a-e**.

General Procedure.

In a typical experiment, the tetrazole (3.5 mmoles) was suspended in a small amount of solvent system [a] in a 50 ml Erlenmeyer flask, and (*S*)-(-)-α-methylbenzylamine (600 mg, 5.0 mmoles) was added. The mixture was heated gently on a steam bath, and additional solvent (10-20 ml) was added to fully dissolve any remaining solids. If any insoluble material was present after this time, the solution was hot gravity filtered. An optically active seed crystal, obtained from previous fractional crystallizations of the salt, was then added to the cooling solution, and the flask was covered and allowed to stand two days, after which the crystals were collected by vacuum filtration and washed with 10 ml of cold solvent. The optically enriched crystals thus obtained were recrystallized twice more from solvent, which, in the cases in which optical purity could be assessed, compounds **4a** and **5c**, see discussion, was sufficient to render the salts optically pure. [a] Different solvent systems were used: **4a**, 5% methanol/acetonitrile, **4b**, **4c**, pure acetonitrile, **4d**, **4e**, tetrahydrofuran, isopropyl ether.

Compound **5a**.

α-Methylbenzylammonium salt **5a** was obtained from **4a** in 25% yield, mp 153-154°; ir (potassium bromide): ν 3250, 1734, 1653, 1558, 1541, 1496, 1450, 1414, 1086, 1030 cm^{-1}; ^1H nmr (DMSO-d_6): δ 8.0 (d, 1 H, J = 7 Hz, amide NH), 7.7-6.7 (m, 20 H, aromatic), 5.3 (d, 1 H, J = 9 Hz, $HCPh_2$), 5.0 (d, 1 H, J = 9 Hz, chiral methine), 4.7 (m, 2 H, J = 7 Hz, α-methylbenzyl methines), 1.3 (d, 3 H, J = 7 Hz, α-methylbenzylammonium methyl), 1.0 (d, 1 H, J = 7 Hz, α-methylbenzylamide methyl) ppm.

Compound **5b**.

α-Methylbenzylammonium salt **5b** was obtained from **4b** in 34% yield, mp 269-270°; ir (potassium bromide): ν 3395, 1655, 1549, 1495, 1452, 1412, 1369, 1188, 1091, 1030 cm^{-1}; ^1H nmr (acetone-d_6): δ 8.0 (br, 1 H, amide NH), 7.4-6.6 (m, 25 H, aromatic), 5.8 (d, 1 H, J = 4 Hz, $HCPh_2$-NH), 5.3 (d, 1 H, J = 12 Hz, $HCPh_2CH$), 5.O5 (d, 1 H, J = 12 Hz, chiral methine), 4.0 (m, 1 H, J = 7 Hz, α-methylbenzyl methine), 1.25 (d, 3 H, J = 7 Hz, α-methylbenzyl methyl) ppm.

Compound **5c**.

(*S*)-(-)-α-Methylbenzylammonium salt **5c** was obtained from **4c** in 29% yield, mp 183-184°; ir (potassium bromide): ν 1653, 1541, 1495, 1452, 1427, 1143, 1080, 1030 cm^{-1}; ^1H nmr (DMSO-d_6): δ 7.6-7.0 (m, 25 H, aromatic), 6.65 (d, 1 H, J = 6 Hz, amide NH, 6.0 (d, 1 H, J = 12 Hz, $HCPh_2$), 5.15 (d, 1 H, J = 12 Hz, chiral methine), 4.9, 4.7, 4.4, 4.0 (four d, 4

H, benzyl methylenes), 4.65 (m, 1 H, J = 6 Hz, α-methylbenzyl methine), 1.4 (d, 3 H, J = 6 Hz, α-methylbenzyl methyl) ppm.

Compound **5d**.

(*S*)-(-)-α-methylbenzylammonium salt **5d** was obtained from **4d** in 51% yield, mp 153-154°; 3290, 3220, 1690, 1560, 1550, 1510, 1465, 1425, 1100, 1075, 1040 cm^{-1}; ^1H nmr (acetone-d_6): δ 7.9-6.95 (m, 23 H, aromatic), 6.6 (d, 1 H, J = 7 Hz, amide NH), 6.3 (d, 1 H, J = 7 Hz, $HCPh_2$), 4.85 (d, 1 H, J = 9 Hz, fluorenyl methine), 4.6 (m, 1 H, J = 7 Hz, α-methylbenzyl methine), 4.5 (d, 1 H, J = 9 Hz, chiral methine), 1.3 (d, 1 H, J = 7 Hz, α-methylbenzyl methyl) ppm.

Compound **5e**.

α-Methylbenzylammonium salt **5e** was obtained from **4e** in 32% yield, mp 283-284°; ir (potassium bromide): ν 3240, 1695, 1662, 1653, 1576, 1558, 1539, 1506, 1496, 1473, 1450, 1419, 1057 cm^{-1}; ^1H nmr (DMSO-d_6): δ 8.7 (d, 1 H, J = 8 Hz, amide NH), 8.4-6.9 (m, 23 H, aromatic), 6.3 (d, 1 H, J = 8 Hz, $HCPh_2$), 5.2 (d, 1 H, J = 12 Hz, fluorenyl methine), 5.05 (d, 1 H, J = 12 Hz, chiral methine), 4.7 (d, 1 H, J = 7 Hz, α-methylbenzyl methine), 1.5 (d, 3 H, J = 7 Hz, α-methylbenzyl methyl) ppm.

Resolved, Optically Pure or Optically Enriched Tetrazoles **5a-e**.

General Procedure.

In a typical experiment, the fractionally crystallized salt **5** (0.212 mmole) was suspended in ether (10 ml), and an aqueous solution of sodium hydroxide (10% by mass, 10 ml) was then added with vigorous stirring, and then allowed to settle when all of the solid had dissolved. The ether layer was aspirated with a Pasteur pipet, and the aqueous layer washed with fresh ether (10 ml)with stirring. The aqueous layer was then transferred to a 150 ml beaker, diluted to a volume of 50 ml with water, put in an ice bath, and acidified with concentrated hydrochloric acid to *p*H = 2, and the resulting precipitate collected by vacuum filtration, air-dried overnight, and recrystallized from tetrahydrofuran/isopropyl ether.

Compound **5a** was obtained in 65% yield with an optical purity determined to be >95% by proton nmr (see Discussion), [α] = -1.31°, c = 0.006, acetone.

Compound **5b** was obtained in 84% yield, [α] = + 3.14°, c = 0.007, ethanol, the **5b** enantiomer was resolved with (*R*)-(+)-α-methylbenzylamine in 72% yield, [α] = -2.6°, c = 0.008, ethanol.

Compound **5c** was obtained in 63% yield, [α] = + 27.7°, c = 0.080, 2-propanol, optical purity determined to be >95% by proton nmr (see Discussion).

Compound **5d** was obtained in 77% yield, [α] = + 0.928°, c = 0.005, acetone.

Compound **5e** was obtained in 64% yield, [α] = + 1.64°, c = 0.005, ethanol.

REFERENCES AND NOTES

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[2a] R. N. Butler, *Adv. Heterocyclic Chem.*, **21**, 323 (1977); [b] *Comprehensive Heterocyclic Chemistry*, A. R. Katritzky, ed, 1984, pp 816-817, 828-829, 833-838; [c] H. Singh, A. S. Chawla, V. K. Kapoor, D. Paul, and P. K. Malhotra, *Prog. Med. Chem.*, **17**, 151 (1980); [d] C. Yoshida, K. Tanaka, R. Hattori, Y. Fukuoka, M. Komatsu, S. Kishimoto, and I. Saikawa, *J. Antibiot.*, **39**, 215 (1986); [e] P. R. Bernstein, E. P. Vacek, *Synthesis*, 1133 (1987); [f] D. M. Gapinski, C. R. Roman, L. E. Rinkema, and J. H. Fleisch, *J. Med. Chem.*, **31**, 172 (1988); [g] D. D. Schoepp, C. L. Smith, D. Lodge, S. D. Millar, J. D. Leander, A. Sacaan, and W. H. Lunn, *Eur. J. Pharmacol.*, **203**, 237 (1991).

[3a] R. M. Herbst, in *Essays in Biochemistry*, S. Graff, ed, John Wiley and Sons, New York, 1956, pp 141-155; [b] G. F. Holland and J. N. Pereira, *J. Med. Chem.*, **10**, 149 (1967); [c] C. W. Thornber, *Chem. Soc. Revs.*, **8**, 563 (1979).

[4a] J. M. McManus and R. M. Herbst, *J. Org. Chem.*, **24**, 1643 (1959); [b] Z. Grzonka, E. Rekowska, and B. Liberek, *Tetrahedron*, **27**, 2317 (1971); [c] P. Bey, C. Danzin, V. vanDorsselaer, P. Mamont, M. Jung, C. Tardiff, *J. Med. Chem.*, **21**, 50 (1978); [d] F. R. Atherton and R. W. Lambert, *Tetrahedron*, **39**, 2599 (1983); [e] D. W. Anderson, M. M. Campbell, and M. Malik, *Tetrahedron Letters*, **31**, 1755 (1990); [f] For some excellent work which includes a one-step transformation of a protected secondary amino acid carboxamide into the corresponding optically pure α-amino tetrazole, see J. V. Duncia, M. E. Pierce, and J. B. Santella III, *J. Org. Chem.*, **56**, 2395 (1991); [g] W. H. W. Lunn, D. D. Schoepp, D. O. Calligaro, R. T. Vasileff, L. J. Heinz, C. R. Salhoff, and P. J. O' Malley, *J. Med. Chem.*, **35**, 4608 (1992); [h] P. L. Ornstein, B. A. Arnold, D. Evrard, J. D. Leander, D. Lodge, and D. D. Schoepp, *Bioorg. Med. Chem. Letters*, **3**, 43 (1993); [i] J. A. Monn, M. J. Valli, R. A. True, D. D. Schoepp, J. D. Leander, and D. Lodge, *Bioorg. Med. Chem. Letters*, **3**, 95 (1993).

[5] T. K. Schaaf and H. J. Hess, *J. Med. Chem.*, **22**, 1340 (1979).

[6] M. A. Dorman, S. A. Noble, L. J. McBride, and M. H. Caruthers, *Tetrahedron*, **40**, 95 (1984).

[7] R. M. Moriarty and S. G. Levy, unpublished results (1990-1992).

[8a] W. G. Finnegan, R. A. Henry, and R. Lofquist, *J. Am. Chem. Soc.*, **80**, 3908 (1958); [b] P. K. Kadaba, *Synthesis*, 71 (1973).

[9] J. T. Repine, R. J. Himmelsbach, J. C. Hodges, J. S. Kaltenbronn, I. Sircar, R. W. Skeean, S. T. Brennan, T. R. Hurley, E. Lunney, C. C. Humblet, R. E. Weishaar, S. Rapundalo, M. J. Ryan, D. G. Taylor, S. C. Olson, B. M. Michniewicz, B. E. Kornberg, D. T. Belmont, and M. D. Taylor, *J. Med. Chem.*, **34**, 1935 (1991).

[10] W. H. Pirkle and D. L. Sikkenga, *J. Org. Chem.*, **42**, 1370 (1977).