for 12 h and poured into ice-water (300 mL), and the crude product was collected by filtration. The solid was dissolved in sodium bicarbonate solution (20 g in 150 mL water) and filtered to remove any insoluble solid. The filtrate was treated with activated charcoal, heated to boiling, and filtered to give a clear yellow solution that was treated with a cold sodium hydroxide solution (20.0 g in 100 mL water). An immediate precipitation of sodium HAT-hexacarboxylate as a yellow solid occurred, and complete precipitation of the salt was effected by the addition of ethanol (30 mL). The product was filtered, washed with 50% aqueous alcohol (3 × 50 mL), and dried under vacuum [100 °C (0.1 torr)] to afford 4.53 g of the polysodium salt of **5**: IR (KBr pellet) μ 1618 cm^{-1} (>C=O); ^{13}C NMR (D_2O/H_2O) δ 140.00 (s, internal carbons), 151.08 (s, peripheral carbons), 171.70 (s, carboxylate carbons).

The **free acid** was obtained as follows: Polysodium HAT-hexacarboxylate (2.52 g, 40 mmol) was suspended in water (100 mL), heated to 50 °C, and acidified by adding concentrated HCl (100 mL). The mixture that formed was heated at 90 °C for 1 h, then was filtered, washed with 10% HCl (3 × 25 mL), and finally washed with deionized water 2 × 25 mL). The product was dried at 120 °C (0.1 torr) to give **5** (1.88 g, 89.5%) as its sesquihydrate: mp >350 °C; ^{13}C NMR (D_2O/dilute NH_4OH) δ 140.1 (s, internal Ar carbons), 151.2 (s, peripheral Ar carbons), 171.7 (s, carboxyl carbons); IR (KBr pellet) μ 1730 cm^{-1} (>C=O); UV (Me_2SO) 278 nm, 316.

Anal. Calcd for $C_{18}H_6N_6O_{12}\cdot1.5H_2O$: C, 41.16; H, 1.73; N, 15.99. Found: C, 41.07; H, 1.91; N, 15.82.

The **hexamethyl ester** was prepared as follows: A solution of hexaacid acid **5** (525 mg of the sesquihydrate, 1 mmol) in absolute methanol (200 mL) and concentrated sulfuric acid (1 mL) was heated to reflux with stirring for 10 h. The solid was collected by filtration, washed with aqueous methanol (50 mL), and dried at 100 °C and 0.01 torr for 6 h to provide a cream colored solid (490 mg, 84%) that could be recrystallized from acetonitrile: mp >350 °C; ^{13}C NMR (Me_2SO-d_6) δ 164.02 (s, ester carbonyl carbons), 145.08 (s, internal or peripheral Ar carbons), 142.23 (s, internal or peripheral Ar carbons), 53.63 (s, methyl carbons); ^{1}H NMR ($CDCl_3/CF_3COOH$) δ 4.17 (s, CH_3); IR (KBr pellet) μ 1750 cm^{-1} (strong, C=O); UV (Me_2SO) 274 nm, 312; FAB mass spectrum, m/e 583 ($M^+ + 1$).

Anal. Calcd for $C_{24}H_{18}N_6O_{12}$: C, 49.48; H, 3.09; N, 14.43. Found: C, 49.12; H, 3.14; N, 14.50.

Hexaazatriphenylenehexacarboxylic Acid Trianhydride (6). HAT-hexacarboxylic acid (1.25 g, 23.8 mmol; **5**) was added to freshly distilled acetic anhydride (60 mL) and heated to 115 ± 2 °C under a nitrogen atmosphere. The vigorously stirred mixture turned to a clear brown solution within 10 min, then heating was discontinued, and the solution was allowed to cool over a period of 20 min. The solvent was removed by rotary evaporation under reduced pressure, and the residue was recrystallized from acetonitrile and benzene (by using a few drops of trifluoroacetic anhydride as desiccant) to give **6** (963 mg, 95%) as moisture-sensitive needles: mp >350 °C; ^{13}C NMR (CD_3CN) δ 159.58 (s, carbonyl carbons), 148.62 (s, internal or peripheral Ar carbons), 148.15 (s, internal or peripheral Ar carbons); IR (KBr) μ 1820 (strong), 1880 cm^{-1} (>C=O).

Anal.[12] Calcd for $C_{18}N_6O_9\cdot0.6\,H_2O$: C, 47.51; H, 0.27; N; 18.47. Found: C, 47.88; H, 0.30; N, 18.11.

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Allylic Selenides in Organic Synthesis: New Methods for the Synthesis of Allylic Amines

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Oxidative rearrangement of allylic selenides in the presence of various amine nucleophiles provides synthetic access to a variety of allylic amine derivatives. The stereochemical outcome of these reactions has been investigated, and is consistent with a [2,3]-sigmatropic rearrangement mechanism. Several D-α-amino acids and racemic β,γ-unsaturated α-amino acids were prepared in this manner. A variant of this process employing an achiral allylic selenide and chiral amide afforded protected allylic amines in low diastereoisomeric excess.

The amine function is nearly ubiquitous in the molecules of nature. For this reason, methods which provide synthetic access to amines are of some significance. Allylic amines, for example, are both useful synthetic intermediates[1] and are a common structural element in naturally occurring substances.[2] Unfortunately, unlike the closely related allylic alcohol function, for which many synthetic methods exist, allylic amines are available by a relatively limited number of procedures.[3] We describe in this paper a complete account of our own synthetic studies of allylic amine synthesis using organoselenium intermediates.[4]

We became concerned with the preparation of optically active allylic amines, due to an interest in peptide isosteres

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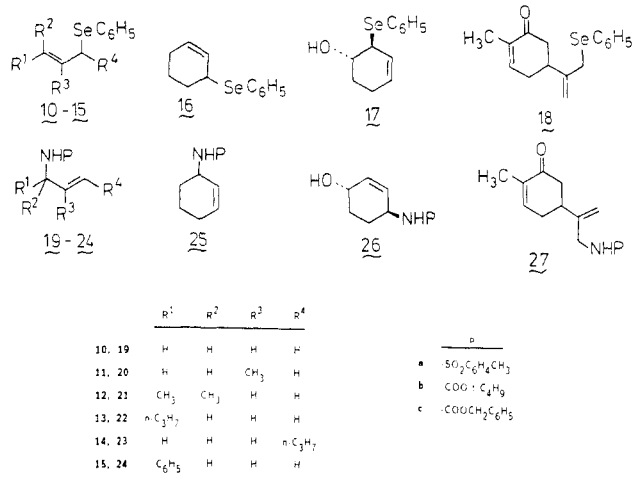
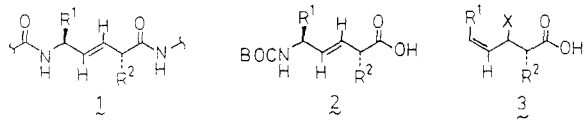
0022-3263/86/1951-5243$01.50/0

Table I. Preparation of N-Protected, Primary Allylic Amines from Allylic Selenides



selenide	protected amine	yield of protected amine, %: TsNClNa (P = Ts)	t-$C_4H_9OCONClNa$ (P = COO-t-C_4H_9)	$C_6H_5CH_2O$-CONClNa (P = COOC-$H_2C_6H_5$)	t-C_4H_9 $OCONH_2$· Ip_2NEt, NCS (P = COO-t-C_4H_9)	$C_6H_5CH_2O$-$cONH_2$· Ip_2NEt, NCS (P = COOC-$H_2C_6H_5$)
10	**19a–c**		78	70	67	82
11	**20a–c**				92	95
12	**21a–c**	88	70	87	71	72
13	**22a–c**	88	78	60	81	86
14	**23a–c**	74			63	63
15	**24a–c**	84	65	70	95	71
16	**25a–c**	74	85	78	50	77
17	**26a–c**	91			82	80
18	**27a–c**				77	58

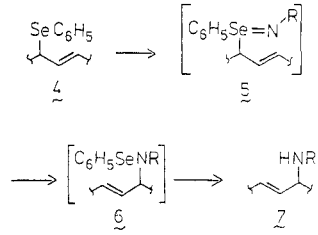
of general structure **1**.[5] Our interest was enhanced by the unavailability of these substances in stereochemically homogeneous form,[6] despite their demonstrated biochemical potential.[7] We considered general strategies for the preparation of building blocks **2**, in which R^1 and R^2 represent a variety of naturally occurring amino acid side chains. One hypothetical approach, which attempts to



remedy the standard problems associated with the generation of remote chiral centers, involves an allylic migration of some unspecified group X in **3** to provide, in a stereocontrolled manner, the required carbon to nitrogen bond of **2**. Available methods, however, seemed inappropriate due to functionality in the side chains R^1 and R^2, as well as the β,γ-relationship of the alkene linkage to the carbonyl group in **2**. The extreme mildness of the conditions required for the widely used allylic selenoxide to allylic alcohol transformation[8] suggested that the corresponding rearrangement of allylic selenimides might be useful for allylic amine synthesis. Furthermore, the stereocontrolled nature of [2,3]-sigmatropic rearrangements,[9] suggested that the organoselenium rearrangement might be well suited to this problem. Our program to study allylic amine synthesis via allylic selenides was thus initiated and is described herein.

Results and Discussion

At the heart of a synthetic technique for the conversion of allylic selenides **4** to allylic amines **7** via sigmatropic rearrangement of the corresponding selenilimines **5** is the oxidative conversion of allylic selenides, which are readily available by a variety of routes,[10] to allylic selenilimines.[11,12]



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(12) (a) Oae, S.; Furukawa, N. *Sulfilimines and Related Derivatives*; American Chemical Society: Washington, DC, 1983. (b) For [2,3]-rearrangement of allylic sulfilimines, see: (a) Ash, A. S. F.; Challenger, F.; Greenwood, D. *J. Chem. Soc.* **1951**, 1877. (b) Ash, A. S. F.; Challenger, F. *J. Chem. Soc.* **1952**, 2792. (c) Briscoe, P. A.; Challenger, F.; Duckworth, P. S. *J. Chem. Soc.* **1956**, 1755. (d) Tamura, Y.; Matsushimi, H.; Minamikawa, J.; Iked, M.; Sumoto, K. *Tetrahedron* **1975**, *31*, 3035.

Sharpless reported in 1975 that chloramine T, a reagent commonly used in the oxidative conversion of sulfides to *N*-(*p*-tolylsulfonyl)sulfilimines, converts selenides to selenilimines and went on to report the first example of allylic amine synthesis using the allylic selenilimine strategy: Treatment of 10-(phenylseleno)-β-pinene (8) with 2.5 equiv of anhydrous chloramine T in methylene chloride afforded a 44% yield of sulfonamide **9**.[13] The latter experiment set the stage for our own studies. At the outset, our goals included (a) discovery of alternate methods for selenilimine preparation which avoid use of anhydrous chloramine T,[14] as well as afford amines in more flexibly protected forms, (b) improvement in the overall yield of the allylic amine, and (c) study of the stereochemistry of the rearrangement, specifically the newly formed carbon–nitrogen bond.

Primary Allylic Sulfonamides.[4a] Despite the disadvantages of the above described allylic sulfonamide preparation using anhydrous chloramine T (potential hazard associated with handling of chloramine T,[14] relative difficulty in removing the *p*-tolylsulfonyl protective group[15]), the availability of chloramine T prompted brief examination of this reaction. Table I provides a listing of the structures and yields of some of the allylic sulfonamides produced in this manner. Noteworthy is the fact that in *all* cases the sulfonamide product has experienced allylic rearrangement relative to the starting selenide, providing evidence in support of the [2,3]-sigmatropic rearrangement mechanism.

Carbamate-Protected Primary Amines. A variety of conditions for the removal of the *p*-tolylsulfonyl group from *p*-toluenesulfonamide-protected amines have been reported; however these methods tend to be relatively vigorous.[15] It was clear that the utility of the above described selenide to amine rearrangement would be severely limited if the sulfonamide moiety were a requirement. Since *N*-chlorocarbamates are known to convert sulfides to *N*-(alkoxycarbonyl)sulfilimines[16] (e.g. **28** → **29**), it seemed reasonable that these reagents might prove useful in the current reaction, affording a carbamate-protected amine as the final product. In fact, the *N*-chlorocarbamate salts **30a** and **30b**, which were prepared in a single step by *tert*-butyl hypochlorite oxidation of the parent carbamates,[17] are useful for this transformation.[4b]

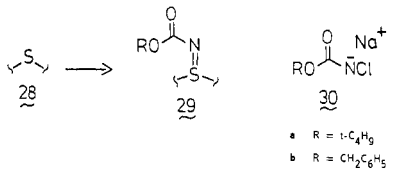


Table I illustrates the carbamate-protected allylic amines prepared by using reagents **30a** and **30b**. Like the previously discussed sulfonamide synthesis, this reaction is observed to proceed with allylic rearrangement. On the basis of kinetics studies,[18] it is reasonable to propose that the putative selenilimine intermediate arises by a circuitous pathway involving initial chlorination of selenium, followed by ligand reorganization, as illustrated in Scheme I. This speculative mechanism suggested that the above approach was unnecessarily complex: A pair of reagents, consisting of an oxidant to activate the selenium and a nitrogen nucleophile capable of effecting subsequent selenilimine formation, should be capable of promoting the current reaction. Such a modification would not only be more convenient, (avoiding preparation of an *N*-chlorocarbamate or *N*-chlorosulfonamide) but would also be safer and render more flexible the selection of the protective function for the primary amine product. In fact, this proved to be the case.[4c]

Scheme I

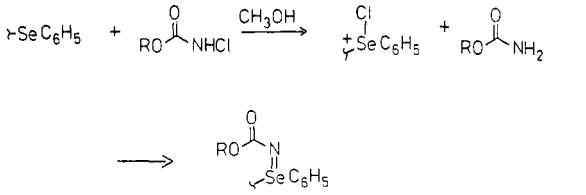
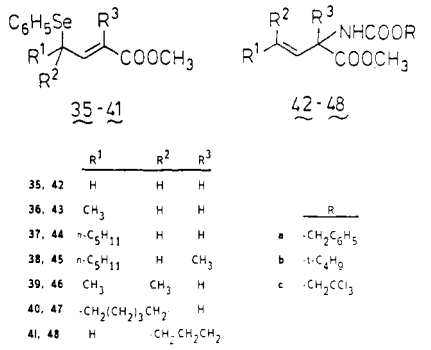


Table II. Preparation of Protected β,γ-Unsaturated α-Amino Acids from γ-(Phenylseleno) α,β-Unsaturated Esters



selenide	protected amino acid	yield of 42–48, %
35	**42a**	62
35	**42b**	66
36	**43b**	80
36	**43c**	72
37	**44a**	87
37	**44c**	77
38[a]	**45a**	73
38[a]	**45b**	74
39	**46b**	32
49	**47b**	12
41[b]	**48c**	30

[a] Selenide is an *E*/*Z* mixture. [b] Selenide contaminated with 20% of a substance believed to be the corresponding α-(phenylseleno) β,γ-unsaturated isomer.

Treatment of a cold, methanolic solution of each of the allylic selenides indicated in Table I, admixed with an excess (5 equiv) of diisopropylethylamine and 2.5 equiv of either benzyl or *tert*-butyl carbamate, with 2.5 equiv of *N*-chlorosuccinimide gave the benzyl and *tert*-butyl carbamate protected primary allylic amines indicated. In many cases, the substitution of the less expensive triethylamine for diisopropylethylamine afforded comparable yields of amine. In contrast, pyridine and 2,6-lutidine could not be used successfully.

In order to demonstrate the utility of this rearrangement in a more functionalized setting, the synthesis of a variety of protected β,γ-unsaturated α-amino acids (**34**) was undertaken.[4d] These substances were selected as targets due to both the limited number of currently known synthetic

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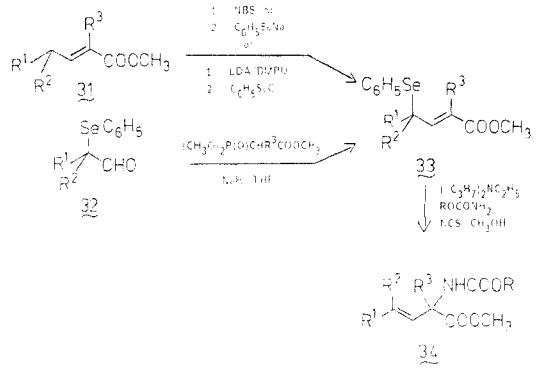
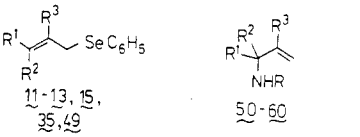
Scheme II



approaches to them and their demonstrated biochemical utility.[19] This method requires the availability of γ-(phenylseleno)-α,β-unsaturated esters (**33**) as starting materials for the rearrangement (Scheme II). In most cases (see Table II), an α,β-unsaturated methyl ester (**31**) was brominated,[20] and the resulting γ-bromo-α,β-unsaturated ester was converted to the γ-(phenylseleno)-α,β-unsaturated ester (**33**). Alternatively, this net γ-selenenylation could be achieved in a single operation,[21] by metalation of **31** with lithium diisopropylamide in the presence of several equivalents of *N,N'*-dimethylpropyleneurea[22] followed by treatment with benzeneselenenyl chloride. This method, however, afforded a lower yield of more difficultly purified material, relative to the two-step pathway. For esters **31** in which R^1 and R^2 were both alkyl, the bromination/displacement route failed. Instead, a Wadsworth–Horner–Emmons olefination of an α-phenylseleno aldehyde[23] (**32**) could be used.[24] The allylic selenides **33** were rearranged to the compounds shown in Table II. Noteworthy here is the use of (β,β,β-trichloroethyl)carbamate as the nitrogen nucleophile. The protected β,γ-unsaturated α-amino acids can be deprotected to afford the parent α-amino acids. Racemic vinyl glycine is available by this route in 18% overall yield from methyl crotonate.

Secondary Amines.[4e] In principle, the above described method is suitable for the synthesis of secondary amines, using a primary amine as the nitrogen nucleophile. Of concern was the ease of oxidation of primary and secondary amines, which might be incompatible with the oxidizing medium necessary for activation of the allylic selenide. Initial experiments using the standard protocol did provide a rearranged secondary amine product but in disappointingly low yield. A solution to the problem was quickly uncovered: Detty has demonstrated that NCS oxidation of methanolic solutions of selenides affords a species which, when treated with water, hydrolyzes to a selenoxide.[25] It was found that oxidative activation prior to the addition of the amine nucleophile enhances the yield of the rearrangement process. Table III illustrates the outcome of a variety of experiments in which 1.25 equiv of an allylic selenide admixed with 5 equiv of triethylamine was activated in methanol at −20 °C with 1.25 equiv of NCS and then treated with 1 equiv of a primary amine (or primary amine hydrochloride). The reaction accommodates aliphatic or aromatic amines. One trend is clear: As the resulting amine product becomes increasingly hindered, the yield of product declines. Attempts to produce a secondary amine in which both α-carbons were fully substituted met with failure. It is sometimes necessary to modify this standard protocol, for example, in the synthesis of **59**. In this case, the allylic selenide **35** appeared to yield an NCS-oxidation product in methanol which was unstable at −20 °C. In this case, the activation step was achieved at −78 °C, followed by warming to −60 °C, addition of the

Table III. Preparation of Secondary Amines from Allylic Phenyl Selenides



	R^1	R^2	R^3	R
11, 50	H	H	CH_3	$CH_2COOC_2H_5$
12, 51	CH_3	CH_3	H	C_6H_5
12, 52	CH_3	CH_3	H	$CH_2C_6H_5$
12, 53	CH_3	CH_3	H	C_6H_{11}
13, 54	n-C_3H_7	H	H	$CH_2C_6H_5$
15, 55	C_6H_5	H	H	CH_3
15, 56	C_6H_5	H	H	$CH_2C_6H_5$
15, 57	C_6H_5	H	H	$CH(CH_3)C_6H_5$
15, 58	C_6H_5	H	H	p-C_6H_4X
35, 59	$COOCH_3$	H	H	$CH(COOC_2H_5)CH_2C_6H_4OCH_2C_6H_5$
49, 60	n-C_3H_7	H	H	$CH_2CH_2C_6H_5$

selenide	amine	secondary amine	yield of 50–60, %
11	$C_2H_5OCOCH_2NH_2$·HCl	**50**	67
12	$C_6H_5NH_2$	**51**	72
12	$C_6H_5CH_2NH_2$	**52**	42
12	$C_6H_{11}NH_2$	**53**	19
13	$C_6H_5CH_2NH_2$	**54**	60
15	CH_3NH_2·HCl	**55**	83
15	$C_6H_5CH_2NH_2$	**56**	74
15	$C_6H_5CH(CH_3)NH_2$	**57**[a]	60
15	p-$O_2NC_6H_4NH_2$	**58a** (X = NO_2)	95
15	p-$BrC_6H_4NH_2$	**58b** (X = Br)	87
15	$C_6H_5NH_2$	**58c** (X = H)	60
15	p-$CH_3OC_6H_4NH_2$	**58d** (X = CH_3O)	48
35	*O*-benzyl-L-tyrosine ethyl ester hydrochloride	**59**[a]	61
49	$C_6H_5CH_2CH_2NH_2$	**60**	54

[a] A 1:1 mixture of diastereoisomers.

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(22) Mukhopadhyay, T.; Seebach, D. *Helv. Chim. Acta* **1982**, *65*, 385.

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(24) Wadsworth, W. S., Jr. *Org. React. (N.Y.)* **1977**, *25*, 76.

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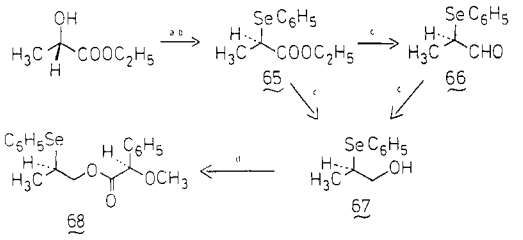
Scheme III[a]

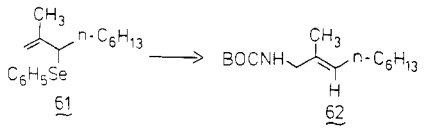


[a] (a) CH_3SO_2Cl, Et_3N; (b) C_6H_5SeNa; (c) DIBAL; (d) (*R*)-$C_6H_5CH(OCH_3)COCl$, C_5H_5N.

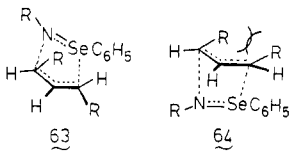
primary amine (*O*-benzyltyrosine ethyl ester hydrochloride), and slow warming to −40 °C.

Stereochemistry of the Rearrangement. The synthetic utility of sigmatropic rearrangements derives in part from their stereospecificity. The scope of the selenide to amine rearrangement would be enhanced if its degree of stereospecificity could be demonstrated to be high and of a predictable nature.

The stereochemistry of a number of [2,3]-sigmatropic rearrangements has been studied.[9] The closest relative is the rearrangement of allylic sulfoxides to allylic sulfenate esters.[9] Of the stereochemical observables, the two most important in the current context are olefin geometry and chirality of the heteroatom-bearing carbons in the starting material and product. The stereospecificity with respect to the double bond is established by inspection of the product olefin geometry in several previous examples: A vicinally disubstituted double bond in the amine product exhibits a strong preference (>95%) for the *E* geometry (Table I, selenide **14**; Table II, selenides **36–38**). One further example is the conversion of selenide **61** to amine **62**, formed as a 97:3 *E*/*Z* ratio. The olefin geometry in all



of these cases parallels that found for the sulfoxide to sulfenate ester rearrangement[26] and demonstrates that transition state **63** is favored over **64**. One may infer from

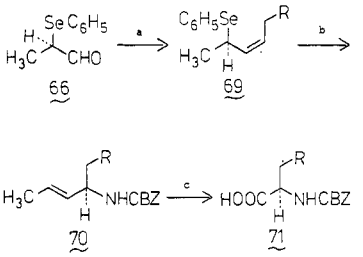


these experiments that the ability of this reaction to transfer chirality across an allylic unit is high: An allylic selenide in which the selenium-bearing carbon is chiral and of high enantiomeric excess should provide an amine product of roughly equivalent enantiomeric excess. Experimental verification of this point has been achieved but only with difficulty since optically active allylic selenides of general form **69** were not available prior to the present work.

A variety of optically active allylic selenides of general structure **69** were prepared by Wittig olefination of seleno aldehyde **66**. The selenoaldehyde **66** was prepared from ethyl (*S*)-lactate via the intermediacy of seleno ester **65** (Scheme III). Not surprisingly, the seleno aldehyde **66** was prone to racemization; this property plagued its synthesis and subsequent olefination. For example, DIBAL

(26) Evans, D. A.; Andrews, G. C.; Fujimoto, T. T.; Wells, D. *Tetrahedron Lett.* **1972**, 1389.

Scheme IV[a]



[a] (a) $RCH_2CH{=}P(C_6H_5)_3$, $C_6H_5CH_3$; (b) $C_6H_5CH_2OCONH_2$, Et_3N, NCS; (c) (i) O_2, (ii) CrO_3, H_2SO_4, CH_3COCH_3, H_2O.

Table IV. Preparation of Protected D-α-Amino Acids

	R	yield, % 69 (*Z*/*E*)	70	71	ee of 71, %
a	H	63 (88:12)	56	65	79
b	C_6H_5	69 (90:10)	64	72	78
c	*i*-C_3H_7	58 (95:5)	59	67	78
d	*n*-C_3H_7		45[a]	58	84

[a] Overall yield from **66**.

reduction of **65** in 3:1 methylene chloride/hexanes at −78 °C afforded a solution of aldehyde **66** (presumably as an aluminum complex) which was of high (~95%) optical purity, as demonstrated by the addition of a second equivalent of DIBAL to the cold reaction mixture, to form the primary alcohol **67**, which was then assayed for enantiomeric excess by conversion to the mandelate ester **68**.[27] However, attempts to isolate **66** from DIBAL reduction reactions with standard aqueous procedures afforded **66** of low optical purity, again as demonstrated by reduction ($NaBH_4$, C_2H_5OH) and esterification to **68**. Reasoning that the racemization was being enhanced by acidic aluminum salts, experiments with alternate aluminum complexation sites were conducted (e.g., Me_2SO, DMF, sodium fluoride added subsequent to reduction but prior to workup) and met with some success. A protocol in which the reduction mixture was treated with several equivalents of DMF and silica gel, followed by direct cannula transfer of the cold suspension onto a silica gel column, and elution with methylene chloride afforded **66** of 90–98% enantiomeric excess.

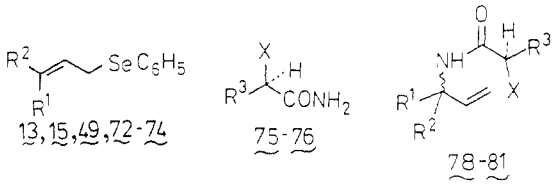
A variety of Wittig olefination conditions converted **66** to **69a** but of low specific rotation (Scheme IV). The selenide **69a** was processed sequentially to **70a** and **71a**; enantiomer excess analysis of **71a** (vide infra) provided an upper bound on the extent of racemization during the **66** to **69a** conversion and allowed us to calculate the specific rotation of optically pure **69a**. Since it was unknown whether the overall conversion of **69a** to **71a** was free of racemization, this approach was not without risk. Fortunately, it succeeded, and a useful protocol was developed. The conditions which uniquely afforded an acceptable yield, *Z*/*E* ratio (determined by GC and ^1H NMR), and specific rotation for selenides **69** involved coupling of **66** to salt-free ylides generated in toluene–hexane by treatment of alkyltriphenylphosphonium bromide salts with *n*-butyllithium (Table IV).[28] Unfortunately, this procedure afforded selenides **69** which contained 5–12% of the corresponding *E* isomer.

The selenide to amine rearrangement was effected by the standard protocol for carbamate-protected amine

(27) Haller, R.; Schneider, H. J. *Arch. Pharm. (Weinheim. Ger.)* **1974**, *307*, 31.

(28) Vedejs, E.; Meier, G. P.; Snoble, K. A. J. *J. Am. Chem. Soc.* **1981**, *103*, 2823.

Table V. Asymmetric Synthesis of Protected Primary Allylic Amines from Allylic Selenides and Chiral Amides



	R^1	R^2	R^3	X
15, 75, 78	H	C_6H_5	C_6H_5	OCH_3
72, 75, 78	C_6H_5	H	C_6H_5	OCH_3
49, 75, 79	H	i-C_3H_7	C_6H_5	OCH_3
73, 75, 79	i-C_3H_7	H	C_6H_5	OCH_3
13, 75, 80	H	n-C_3H_7	C_6H_5	OCH_3
74, 75, 80	n-C_3H_7	H	C_6H_5	OCH_3
49, 76, 81	H	i-C_3H_7	C_6H_{11}	OCH_3
73, 76, 81	i-C_3H_7	H	C_6H_{11}	OCH_3

selenide	amide	product	yield of 78–81, %	diastereomer ratio	de(%)
15	75	78	62	1.0:2.2	37
72	75	78	44	1.6:1.0	23
49	75	79	62	1.0:1.9	31
73	75	79	44	1.0:2.2	37
13	75	80	70	1.0:1.4	17
74	75	80		1.0:1.7	26
49	76	81	70	1.0:2.1	35
73	76	81	43	1.0:1.9	31

synthesis (Table IV). To establish the enantiomeric excess of the allylic amines, ozonolytic cleavage followed by Jones oxidation was employed to afford the protected amino acids **71**. The enantiomeric excess of these substances was assayed by HPLC analysis of the corresponding dansyl amino acids[29] (Table IV).

Despite the fact that compounds **69** are a mixture of stereoisomers, it is possible to semiquantitatively assess the stereofidelity of the selenide to amine rearrangement given the available data and the reasonable assumption that the undesired antipode of **70** arises both from *ent*-**69** (ca. 1–5% of the mixture of isomers containing **69**) and from the *E* isomer of **69** (ca. 5–12% of the mixture of isomers containing **69**). Taken together, these account for the presence of 6–17% of *ent*-**70** and thus a final enantiomeric excess of 66–88% for **70**, if the reaction occurred with complete transfer of chirality across the allylic system as depicted in transition state **63**. The observed values of 78–84% are within the range expected based on a stereocontrolled process. A more elegant demonstration of the stereofidelity of the selenide to amine rearrangement must await methods for the preparation of stereohomogeneous allylic selenides.

The obvious synthetic advantages of a version of the allylic selenide to allylic amine rearrangement capable of producing optically active allylic amines from *achiral* selenides prompted study of the reactions shown in Table V. A series of achiral allylic selenides bearing a phenyl, isopropyl, or *n*-propyl substituent with either cis or trans geometry was allowed to undergo oxidative rearrangement in conjunction with the indicated chiral amides. In principle, the transition states leading to the epimeric pairs represented by **78–81** are diastereomeric and might be expected to differ in their relative stabilities. Whether or not this difference is sufficient to provide a synthetically useful mixture of diastereomeric protected allylic amines could not be predicted a priori, since the structural details of the rearrangement are not precisely known. For this reason, a variety of selenides and chiral amides were surveyed (Table V). These data clearly illustrate that this reaction can, in principle, provide optically active amines; however, the diastereomeric excesses observed are low, ranging from 17% to 37% and are probably not currently of synthetic interest.

(29) Lam, S.; Chow, F.; Karmen, A. *J. Chromatogr.* **1980**, *199*, 295.

Conclusion

The oxidative rearrangement of allylic selenides to allylically transposed allylic amines is a mild and stereocontrolled method for the synthesis of functionalized amines. The various modifications described herein permit the formation of primary allylic amines protected as a sulfonamide, carbamate, or amide as well as secondary allylic aliphatic and aromatic amines in unprotected form. The reaction is highly regio- and stereocontrolled and, when an allylic selenide of defined chirality is available, may be used for the preparation of optically active allylic amines. Examples of the use of this reaction in synthesis include preparation of racemic β,γ-unsaturated α-amino acids and D-α-amino acids. The experimental procedures developed in the course of this study and described in detail in the following Experimental Section place the allylic selenide to allylic amine rearrangement alongside the allylic selenide to allylic alcohol rearrangement as a dependable and predictable reaction of utility in organic synthesis.

Experimental Section

General. Unless otherwise specified, commercial chemicals were used as received. Chloramine T hydrate was dried by the method of Sharpless.[30] Tetrahydrofuran was distilled under argon from sodium benzophenone ketyl. Methylene chloride was distilled under argon from calcium hydride. Methanol was distilled from magnesium methoxide. Air- or water-sensitive reactions were conducted under a positive argon atmosphere. Thin-layer chromatography (TLC) was performed on Merck precoated silica gel 60 plates (0.25 mm); flash column chromatography was performed with Merck silica gel 60 (230–400 mesh). High-pressure liquid chromatography (HPLC) was performed on a Du Pont instrument equipped with a UV spectrophotometer detector. Melting points were determined on a Fisher Johns melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Beckman AccuLab 4 or Perkin-Elmer Model 257 grating infrared spectrophotometer; only major or diagnostic peaks are noted. Proton nuclear magnetic resonance (NMR) spectra were determined on a Varian EM-360 (60 MHz), Varian CFT-20 (80 MHz), or Bruker WM 500 (500 MHz) spectrometer and, unless otherwise specified, are reported in parts per million (δ) downfield from internal tetramethylsilane (δ = 0.00). Coupling constants (J) are reported in hertz. Low-resolution mass spectra (LRMS) were measured on a Hewlett-Packard Model 5985 mass spectrometer; only major or diagnostic peaks are noted. High-resolution mass spectra (HRMS) were determined on a VG 7070H double-focusing mass spectrometer. Gas–liquid chromatography (GLC) was performed on a Hewlett-Packard 5790A capillary gas chromatograph. Optical rotations were measured on a Perkin-Elmer Model 141 Polarimeter and are recorded at ambient temperature at the D line of sodium. Combustion analyses were performed by Micanal of Tucson, AZ.

Preparation of Allylic Selenides. Method A: from Allylic Halides.[10a] **(2-Propenylseleno)benzene (10).** To a rapidly stirred suspension of 1.484 g (4.75 mmol) of diphenyl diselenide in 8 mL of ethanol under argon at 25 °C was slowly added 0.396 g (10.46 mmol) of sodium borohydride. The yellow solution was decolorized within seconds. To this suspension was added 2-propenyl bromide dropwise under argon at 25 °C. This was stirred 18 h, was diluted with ethyl acetate, and was washed sequentially with 10% aqueous sodium hydroxide, saturated aqueous sodium

(30) Sharpless, K. B.; Hori, T.; Truesdale, L. K.; Dietrich, C. O. *J. Am. Chem. Soc.* **1976**, *98*, 269. See also ref 14.

bicarbonate, and saturated aqueous sodium chloride. The organic layer was dried ($MgSO_4$), concentrated in vacuo, and chromatographed on silica gel (15% ethyl acetate–hexanes) to afford 1.25 g (77%) of **10** as a light yellow oil: ^1H NMR (80 MHz, $CDCl_3$) δ 3.46 (2 H, d, J = 8), 4.87 (1 H, d, J = 10), 4.92 (1 H, d, J = 16), 5.91 (1 H, ddt, J = 10, 16, 8), 7.40 (5 H, m).

Method B: from Allylic Alcohols. [(3-Methyl-2-butenyl)seleno]benzene (12). A 0.731-g (6.38 mmol) portion of methanesulfonyl chloride was added slowly via syringe to a stirred solution of 0.500 g (5.80 mmol) of 3-methyl-2-buten-1-ol and 1.47 g (14.5 mmol) of triethylamine in 10 mL of methylene chloride under argon at 0 °C. The mixture was stirred at 0 °C for 30 min and was used directly as described below. In another flask, 0.265 g (7.01 mmol) of sodium borohydride was slowly added to a suspension of 1.04 g (3.33 mmol) of diphenyl diselenide in 6 mL of ethanol under argon at 25 °C. The previously prepared mesylation reaction mixture was added to this white suspension via cannula over a period of about 2 min. This mixture was stirred for 30 min at 25 °C, then diluted with ethyl acetate, and washed sequentially with 10% aqueous hydrochloric acid, 10% aqueous sodium hydroxide, saturated aqueous sodium bicarbonate, and finally saturated aqueous sodium chloride. The organic layer was dried ($MgSO_4$) and chromatographed on silica gel (15% ethyl acetate–hexanes) then concentrated in vacuo to afford 0.914 g (70%) of **12** as a yellow oil: ^1H NMR (80 MHz, $CDCl_3$) δ 1.50 (3 H, s), 1.68 (3 H, s), 3.50 (2 H, d, J = 9), 5.30 (1 H, m), 7.2 (3 H, m), 7.4 (2 H, m).

Method C:[10b] Alkylation of Selenium-Stabilized Carbanions. [(1-Propyl-2-propenyl)seleno]benzene (14). To 7 mL of tetrahydrofuran in a flame-dried flask under argon was added 0.768 g (7.61 mmol) of diisopropylamine. This was cooled to 0 °C and 3.30 mL (6.98 mmol) of 2.1 M n-butyllithium in hexanes was added via syringe over a period of 2 min. This was stirred for 30 min and then cooled to −78 °C. To this mixture was added 1.25 g (6.35 mmol) of 3-(phenylseleno)propene dropwise via syringe, and the mixture was stirred for 20 min. 1-Iodopropane (2 g, 7.6 mmol) was added via syringe, and this was stirred for 20 min. A 10-mL portion of hexanes was added, and the mixture was warmed to 25 °C and filtered through a plug of Celite 503. The filtrate was concentrated in vacuo and chromatographed on silica gel (15% ethyl acetate–hexanes) to afford **14** as a colorless oil: ^1H NMR (500 MHz, $CDCl_3$) δ 0.85 (3 H, t, J = 6), 1.44 (2 H, m), 1.68 (2 H, dt, J = 7, 7), 3.68 (1 H, dt, J = 4, 7), 4.54 (1 H, d, J = 16), 4.63 (1 H, d, J = 10), 7.40 (5 H, m).

Preparation of 4-Methylbenzenesulfonamide-Protected Allylic Amines. The sulfonamides **21a–26a** were prepared by the method described below in detail for **21a**.

4-Methyl-*N*-(1,1-dimethyl-2-propenyl)benzenesulfonamide (21a). To a rapidly stirred suspension of 0.202 g (0.89 mmol) of anhydrous chloramine T[30] in 1 mL of methanol under argon at 25 °C was added 0.100 g (0.44 mmol) of [(3-methyl-2-butenyl)seleno]benzene. The mixture was stirred for 24 h at 25 °C, filtered through a plug of Celite 503, and then chromatographed on silica gel (30% ethyl acetate–hexanes). The product-containing fractions were concentrated in vacuo to afford 0.932 g (88%) of **21a** as a colorless oil: ^1H NMR (80 MHz, $CDCl_3$) δ 1.28 (6 H, s), 2.40 (3 H, s), 4.77 (1 H, br s), 4.90 (1 H, d, J = 11), 5.04 (1 H, d, J = 17), 5.79 (1 H, dd, J = 11, 17), 7.21 (2 H, d, J = 8), 7.72 (2 H, d, J = 8); IR ($CHCl_3$) 3380 (N–H), 3270 (N–H), 1610 (Ar), 1510 (Ar), 1330 (S=O), 1150 (S=O), 1100, 1000, 930, 810, 660 cm^{-1}; LRMS (EI), m/e 240 (M^+ + 1), 224 ($M^+ - CH_3$), 212 ($M^+ - C_2H_3$), 155 (p-$CH_3C_6H_4SO_2$); HRMS (EI) calcd for $C_{12}H_{17}NO_2S$ 239.0981; found 239.0964. Anal. C, H, N, O, S.

Methyl 4-(Phenylseleno)-2(*E*)-butenoate (35). Methyl crotonate (6.0 g, 60 mmol) was brominated as described by Löffler et al.[20] using N-bromosuccinimide (11.7 g, 66 mmol) in carbon tetrachloride (63 mL) to afford methyl 4-bromo-2(*E*)-butenoate as a light yellow oil, 7.9 g (74%): ^1H NMR (80 MHz, $CDCl_3$) δ 3.75 (3 H, s), 4.0 (2 H, dd, J = 8, 1), 6.0 (1 H, dt, J = 16, 1), 7.0 (1 H, dt, J = 16, 8).

An ethanolic solution of phenyl selenide anion was prepared from 0.47 g (1.5 mmol) of diphenyl diselenide and 0.12 g (3.3 mmol) of sodium borohydride in 4.7 mL of ethanol at 0 °C. To this solution was added 0.50 g (2.8 mmol) of methyl 4-bromo-2(*E*)-butenoate. The resulting solution was stirred 10 min at 0 °C diluted with ethyl acetate, and washed sequentially with saturated aqueous sodium bicarbonate and saturated aqueous sodium chloride. The resulting organic extracts were dried ($MgSO_4$) and concentrated in vacuo. The crude product was chromatographed on silica gel (25% ether–hexanes) to afford 4.90 g (86%) of methyl 4-(phenylseleno)-2(*E*)-butenoate (**35**) as a colorless oil: ^1H NMR (80 MHz, $CDCl_3$) δ 3.5 (2 H, dd, J = 8, 1), 3.7 (3 H, s), 5.6 (1 H, dt, J = 15, 1), 7.0 (1 H, dt, J = 15, 8), 7.2–7.6 (5 H, m); IR (neat) 1740 (C=O), 1665 (C=C) cm^{-1}; LRMS (EI), m/e 256 (M^+), 99 ($M^+ - SeC_6H_5$). Anal. C, H.

Methyl 4-(Phenylseleno)-2(*E*)-nonenoate (37). The title compound was prepared by three methods.

Method A: Bromination–Displacement. Methyl 2(*E*)-nonenoate (2.0 g, 11.7 mmol) and 2.3 g (12.9 mmol) of N-bromosuccinimide were heated at reflux for 5 h in 12.5 mL of carbon tetrachloride. The resulting mixture was cooled to 25 °C and filtered, and the filtrate was distilled in vacuo to afford 2.46 g (84%) of methyl 4-bromo-2(*E*)-nonenoate (bp 93–113 °C, 0.7 mm) as a colorless liquid: ^1H NMR (80 MHz, $CDCl_3$) δ 0.9 (3 H, m), 1.3 (8 H, m), 2.4 (2 H, m), 3.7 (3 H, s), 4.5 (1 H, m), 5.9 (1 H, d, J = 15), 6.9 (1 H, dd, J = 15, 8). This bromide (2.0 g, 8.03 mmol) was treated with ethanolic phenyl selenide anion [from 1.30 g (4.2 mmol) of diphenyl diselenide and 0.35 g (9.2 mmol) of sodium borohydride in 16 mL of ethanol] to afford, after extractive isolation and column chromatography on silica gel (10% ether–pentane), 2.25 g (86%) of methyl 4-(phenylseleno)-2(*E*)-nonenoate (**37**) as a pale yellow oil.

Method B:[21] Lithiation–Selenenylation. Lithium diisopropylamide [prepared from 0.624 g (6.2 mmol) of diisopropylamine and 2.26 mL (5.9 mmol) of 2.6 M n-butyllithium in hexanes in 3.6 mL tetrahydrofuran] at −78 °C was treated with 2.12 mL of N,N-dimethylpropyleneurea (DMPU)[22] and stirred 30 min. Methyl 2(*E*)-nonenoate (1.0 g, 5.9 mmol) in 1.5 mL of THF was added, and the mixture was stirred 10 min at −78 °C. The resulting dark yellow enolate solution was treated with 1.46 g (7.64 mmol) of benzeneselenenyl chloride in 3.4 mL of THF, stirred 10 min at −78 °C, warmed to 25 °C, and stirred 1 h. The mixture was quenched with water and extracted with ether. The ether extracts were washed with several portions of aqueous 1 M lithium chloride, dried ($MgSO_4$), and concentrated in vacuo. Column chromatography on silica gel afforded **37**, 0.77 g (40%) as a pale yellow oil.

Method C:[24] Wadsworth–Horner–Emmons Homologation. Methyl (dimethoxyphosphinyl)acetate (122 mg, 0.67 mmol) was added to a stirred slurry of 18 mg (0.74 mmol) of sodium hydride in THF (3.2 mL) at 25 °C. The mixture was stirred 1 h and treated with 200 mg (0.74 mmol) of 2-(phenylseleno)heptanal (prepared by the method of Sharpless[23a]). The resulting mixture was stirred 15 min at 25 °C, diluted with water, and extracted with ether. The organic extracts were dried ($MgSO_4$), concentrated in vacuo, and column chromatographed on silica gel (5% ethyl acetate–hexanes) to afford 135 mg (62%) of **37** as a colorless oil. Samples of **37** prepared by these three routes were spectroscopically identical: ^1H NMR (80 MHz, $CDCl_3$) δ 0.9 (3 H, m), 1.3 (8 H, m), 3.7 (3 H, s), 3.8 (1 H, m), 5.3 (1 H, d, J = 16), 6.8 (1 H, dd, J = 16, 10), 7.2–7.6 (5 H, m); IR (neat) 1730 (C=O), 1650 (C=C), 1450, 1280, 735 cm^{-1}; LRMS (EI), m/e 326 (M^+), 169 ($M^+ - C_6H_5Se$), 109, 95, 81, 67. Anal. C, H.

Preparation of Carbamate-Protected β,γ-Unsaturated α-Amino Acids. The compounds **42–48** were prepared by the method described below for **43c**.

Methyl 2-[[(2,2,2-Trichloroethoxy)carbonyl]amino]-3-(*E*)-pentenoate (43c). A solution of 200 mg (0.743 mmol) of methyl 4-(phenylseleno)-2(*E*)-pentenoate (**36**), 429 mg (2.23 mmol) of 2,2,2-trichloroethyl carbamate, 466 mg (4.39 mmol) of trimethyl orthoformate, and ca. 2 mg of p-toluenesulfonic acid hydrate in 2.0 mL of methanol at 25 °C was stirred 30 min, treated with 576 mg (4.46 mmol) of N,N-diisopropylethylamine, and cooled to 0 °C. N-Chlorosuccinimide (298 mg, 2.23 mmol) was added, and the cold mixture was stirred 10 min. The reaction mixture was acidified to pH 1 with 5% aqueous hydrochloric acid, and was extracted with several portions of ether. The combined ether extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo. Chromatography on silica gel (40% ether–pentane) provided after concentration in vacuo 164 mg (72%) of methyl 2-[[(2,2,2-trichloroethoxy)carbonyl]amino]-3(*E*)-pentenoate (**43c**) as a colorless oil: ^1H NMR (500 MHz, $CDCl_3$) δ 5.84 (1 H, dq, J = 15, 7,

CH_3CH=), 5.64 (1 H, d, J = 6, NH), 5.50 (1 H, dd, J = 15, 5, =CHCH), 4.84 (1 H, dd, J = 6, 5, =CHCH), 4.76 (1 H, d, J = 13, $OCH_aH_bCCl_3$), 4.71 (1 H, d, J = 13, $OCH_aH_bCCl_3$), 3.78 (3 H, s, OCH_3), 1.73 (3 H, d, J = 7, CH_3CH=); IR (neat) 3440, 3360 (NH), 1750, 1530 (NHC=O), 980 (C=C, trans) cm^{-1}; LRMS (EI), m/e 303, 305, 307 (M^+), 244, 246, 248 ($M^+ - CO_2CH_3$) 131, 133, 135 ($CCl_3CH_2^+$).

(±)-Vinylglycine. Methyl 2-[[(*tert*-butylcarbonyl)oxy]-amino]-3-butenoate (1.54 g, 7.15 mmol) was added to 60 mL of 6 N aqueous hydrochloric acid. The solution was heated to reflux for 1.5 h and cooled to 25 °C. The mixture was washed with three 20-mL portions of chloroform, and the remaining aqueous layer was decolorized with activated charcoal followed by concentration in vacuo to dryness. The residue was chromatographed on Bio-Rad (analytical grade) anion-exchange resin AG1-X8, 50–100 mesh, chloride form, by eluting with 1.0 M aqueous acetic acid. The ninhydrin-positive fractions were combined and concentrated in vacuo. The resulting colorless solid was recrystallized from aqueous ethanol to afford 0.35 g (48%) of (±)-vinylglycine: mp 218–220 °C dec (lit. mp 218–220 °C dec[19i]); ^1H NMR (500 MHz, D_2O; referenced to internal acetone, δ 2.1) δ 4.1 (1 H, d, J = 5), 5.3 (2 H, m), 5.8 (1 H, ddd); LRMS (EI), m/e 74 ($M^+ - CH$=CH_2), 56 ($M^+ - CO_2H$). Anal. C, H, N.

Preparation of Secondary Amines: General Procedure. The amines **50–60** were prepared by the method described below, in detail, for the preparation of **58b**.

1-Phenyl-1-[(4-bromophenyl)amino]-2-propene (58b). A solution of 250 mg (0.915 mmol) of cinnamyl phenyl selenide (**15**) and 463 mg (4.58 mmol) of triethylamine in 4.6 mL of dry methanol was cooled to −25 °C. *N*-Chlorosuccinimide (122 mg, 0.915 mmol) was added, and the cold mixture was stirred for 5 min at −20 °C. The colorless solution was treated with 126 mg (0.732 mmol) of *p*-bromoaniline and allowed to warm to 25 °C over ca. 0.5 h. The volatiles were removed in vacuo, and the residue was chromatographed on silica gel (5% ethyl acetate–hexanes) to provide 183 mg (87%) of **58b** as a pale yellow oil: ^1H NMR (500 MHz, $CDCl_3$) δ 1.5 (1 H, br s), 4.88 (1 H, d, J = 6), 5.23 (1 H, d, J = 9), 5.25 (1 H, d, J = 17), 6.02 (1 H, ddd, J = 17, 9, 6), 6.47 (2 H, d, J = 9), 7.20 (2 H, d, J = 9), 7.2–7.4 (5 H, m); IR (neat) 3420 (NH), 3080, 3060, 3030, 1595, 1495 cm^{-1}; LRMS (EI), m/e 289, 287, (M^+), 157, 155, 130, 117 (100), 115, 104, 103, 102, 91, 90, 89, 78, 77, 76, 75; Anal. C, H, N.

***O*-Benzyl-*N*-(1-methoxy-1-oxo-3-buten-2-yl)-L-tyrosine Ethyl Ester (59a,b).** A solution of 125 mg (0.49 mmol) of methyl 4-(phenylseleno)butenoate and 303 mg (3.0 mmol) of triethylamine in 2.5 mL of dry methanol was cooled to −78 °C. *N*-chlorosuccinimide (66.0 mg, 0.49 mmol) was added, and the resulting slurry was warmed to −60 °C over 10 min. The turbid solution was treated with 131 mg (0.392 mmol) of *O*-benzyl-L-tyrosine ethyl ester hydrochloride and stirred for 2 h at −60 °C. Warming of the reaction mixture to 20 °C over 1 h, followed by evaporation of the volatiles in vacuo, provided crude **59**, which was carefully chromatographed on silica gel (25% ethyl acetate–hexanes) to yield 46 mg and 49 mg (combined yield 61%) of the two diastereomers **59a** and **59b**, respectively, both as colorless oils. **59a**: ^1H NMR (500 MHz, $CDCl_3$) δ 1.18 (3 H, t, J = 7), 2.97 (2 H, m), 3.49 (1 H, t, J = 7), 3.72 (3 H, s), 3.83 (1 H, d, J = 7), 4.12 (2 H, m), 5.04 (2 H, s), 5.24 (1 H, d, J = 8), 5.28 (1 H, d, J = 12), 5.77 (1 H, ddd, J = 12, 8, 7), 6.89 (2 H, d, J = 9), 7.12 (2 H, d, J = 9), 7.2–7.5 (5 H, m); IR (neat) 3320 (NH), 3085, 3070, 3060, 1745, 1738, 1610, 1515, 1030, 935 cm^{-1}; LRMS (EI); m/e 398 (M^+), 325, 201, 200 (100), 172, 157, 146, 140, 134, 119, 117, 112, 107, 99, 91, 86, 84, 77, 65. **59b**: ^1H NMR (500 MHz, $CDCl_3$) δ 1.16 (3 H, t, J = 7), 2.92 (2 H, m), 3.50 (1 H, t, J = 7), 3.68 (3 H, s), 3.86 (1 H, d, J = 7), 4.12 (2 H, m), 5.04 (2 H, s), 5.22 (1 H, d, J = 7), 5.26 (1 H, d, J = 11), 5.77 (1 H, ddd, J = 11, 7, 7), 6.89 (2 H, d, J = 8), 7.11 (2 H, d, J = 8), 7.2–7.5 (5 H, m); IR (neat) 3320 (NH), 3085, 3070, 3060, 1745, 1738, 1610, 1515, 1030, 935 cm^{-1}; LRMS (EI), m/e 398 (M^+), 339, 325, 201, 200 (50), 172, 157, 140, 134, 119, 117, 112, 99, 91 (100), 77, 65.

Ethyl (*R*)-2-(Phenylseleno)propanoate (65). A solution of ethyl (*S*)-lactate (11.8 g, 100 mmol) in 100 mL of methylene chloride was cooled to 0 °C. Excess triethylamine (18.4 mL, 132 mmol) was added, and then a solution of 8.5 mL (110 mmol) of methanesulfonyl chloride in 10 mL of methylene chloride was dripped into the vigorously stirred ester solution over 10 min. Another 1.0 mL (13 mmol) of methanesulfonyl chloride was added to complete the reaction. The mixture was shaken with 50 mL of 5% aqueous hydrochloric acid. The organic phase was washed with water and then saturated aqueous sodium chloride and dried ($MgSO_4$). Concentration in vacuo afforded 18.0 g (92%) of the mesylate **65** as a colorless oil: ^1H NMR (80 MHz, $CDCl_3$) δ 1.30 (3 H, t, J = 7), 1.58 (3 H, d, J = 7), 3.12 (3 H, s), 4.22 (2 H, q, J = 7), 5.07 (1 H, q, J = 7). Sodium formaldehydesulfoxylate dihydrate[31] (9.24 g, 60 mmol) was dissolved in 100 mL of 1 M aqueous sodium hydroxide and 50 mL of ethanol. While a stream of argon was continuously bubbled through the solution at 25 °C, diphenyl diselenide (15.60 g, 50 mmol) was added. After the mixture was stirred ca. 5 min, another 5 mL of 1 M aqueous sodium hydroxide was added. The mixture was stirred 0.5 h, and then 25 mL of Fisher pH 7 buffer concentrate was added. The solution was treated with 17.64 g (90 mmol) of the mesylate, followed by 100 mL of ethanol. The reaction was stirred ca. 5 min and was then extracted with 200 mL of ether. The extract was washed with water and then with saturated aqueous sodium chloride. Drying ($MgSO_4$) and concentration in vacuo yielded **65** as a pale yellow oil: ^1H NMR (80 MHz, $CDCl_3$) δ 1.16 (3 H, t, J = 7), 1.53 (3 H, d, J = 7), 3.73 (1 H, q, J = 7), 4.06 (2 H, q, J = 7), 7.26 (3 H, m), 7.57 (2 H, m).

2(*R*)-(Phenylseleno)propanal (66). A stirred solution of ethyl (*R*)-2-(phenylseleno)propanoate (**65**) (540 mg, 2.10 mmol) in 7.0 mL of methylene chloride at −78 °C was treated with 2.3 mL (2.3 mmol, 1 M in hexanes) of DIBAL (added via syringe; run down the side of the flask to cool the DIBAL solution before exposure to the mixture). After the mixture was stirred 45 min, 0.32 mL (4.2 mmol) of dimethylformamide was added, and the solution was warmed to 0 °C. After the mixture was stirred 10 min, 3 g of silica gel was poured into the solution. The slurry was poured onto a bed of silica gel slurried with methylene chloride in a filter funnel. Elution with methylene chloride (aspirator suction) followed by concentration in vacuo afforded 388 mg (87%) of **66** as a yellow oil containing trace amounts of diphenyl diselenide and seleno alcohol (from over reduction). The material was used immediately with no further purification: ^1H NMR (500 MHz, $CDCl_3$) δ 1.46 (3 H, d, J = 7), 3.70 (1 H, dq, J = 3, 7), 7.20–7.40 (3 H, m), 7.44–7.66 (2 H, m), 9.44 (1 H, d, J = 3); IR ($CHCl_3$) 2820, 2720 (CHO), 1720 (C=O) cm^{-1}; LRMS (EI), m/e 212, 214 (M^+), 155, 157 ($C_6H_5Se^+$), 77 ($C_6H_5^+$); $[\alpha]^{25}_D$ +265–290° (c 18 mg/mL, CH_2Cl_2).

(±)-2-(Phenylseleno)propanal [(±)-66]. Benzeneselenenyl chloride (4.7 g, 24.5 mmol) was added to 15.2 g (262 mmol) of propanal stirred at 0 °C. The mixture was warmed to 25 °C, stirred 15 min, and diluted with ether. The solution was rinsed sequentially with saturated aqueous sodium bicarbonate, water, and saturated aqueous sodium chloride, dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (silica gel, 10% ethyl acetate–hexanes) followed by concentration in vacuo afforded 2.45 g (47%) of racemic (±)-**66** as a pale yellow oil. The ^1H NMR, IR, and LRMS were identical with those obtained for the optically active material (*R*)-**66**.

2(*R*)-(Phenylseleno)propanol (67). A stirred solution of 96 mg (0.45 mmol) of **66** in 3 mL of absolute ethanol at 0 °C was treated with excess sodium borohydride. After 15 min, three drops of acetone were added, and the solution was warmed to 25 °C. The mixture was diluted with water and extracted with four portions of ether. The organic extracts were combined, dried ($MgSO_4$), and concentrated in vacuo to yield 84 mg (87%) of **67** as a pale yellow oil: ^1H NMR (80 MHz, $CDCl_3$) δ 1.37 (3 H, d, J = 7), 2.16 (1 H, br s), 3.32 (1 H, tq, J = 7, 6), 3.48 (2 H, m), 7.22 (3 H, m), 7.50 (2 H, m). As a test of possible sources of racemization of aldehyde **66**, this alcohol was also made directly from **65** by using excess DIBAL: A solution of **65** (279.5 mg, 1.09 mmol) in 7.2 mL of methylene chloride at −78 °C was treated with 1.2 mL (1.2 mmol, 1 M in hexanes) of DIBAL (added via syringe, run down the inner surface of the flask) over 7 min. After the mixture was stirred 15 min another 1.2 mL of DIBAL was added. The mixture was warmed to 0 °C for 15 min and was quenched with water. The mixture was partitioned between pentane and water with mild agitation (to avoid an emulsion). The organic

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phase was dried ($MgSO_4$) and concentrated in vacuo, affording **67** (43%) as a pale yellow oil identical (^1H NMR, TLC) with material made by sodium borohydride reduction of **66**. The alcohol thus synthesized was >98% enantiomerically pure (see compound **68** experimental procedure for ee analysis).

Mandelate Ester 68. A stirred mixture of **67** (139 mg, 0.65 mmol), pyridine (160 μL, 2.0 mmol), and 2.5 mL of methylene chloride was treated with a solution of 185 mg (1.0 mmol) of (*R*)-2-methoxy-2-phenylacetyl chloride[27] in 2.0 mL of methylene chloride. After 20 min the material was concentrated in vacuo onto a small amount of silica gel and flash chromatographed (20% ethyl acetate–hexanes) to yield **68** as a slightly yellow oil: ^1H NMR (partial, 500 MHz, $CDCl_3$) δ 1.23 (*R,R* isomer, CH_3, d, J = 7), 1.26 (*R,S* isomer, CH_3, d, J = 7). An examination of the products of several reactions indicated that a specific rotation ($[\alpha]^{25}_D$) of 295° for **66** corresponded to 100% ee. An experiment using both the alcohol and the acid chloride as racemates provided a 1:1 mixture of the diastereoisomers.

(1*R*,2*Z*)-[(1-Methyl-2-butenyl)seleno]benzene (69a). Ethyltriphenylphosphonium bromide (2.60 g, 7.0 mmol) was suspended in dry toluene (32 mL) in a flame-dried centrifuge tube under an argon atmosphere (serum stopper). *N*-Butyllithium (3.0 mL, 2.1 M in hexanes) was added via syringe to the stirred mixture at 25 °C. After 1 h the ylide solution was cooled to −78 °C and centrifuged 10 min. A 16-mL aliquot of the supernatant was transferred via syringe into a dry flask under argon atmosphere at −78 °C and diluted with toluene (16 mL). The ylide was treated (via cannula) with a solution of 312 mg (1.46 mmol) of (*R*)-2-(phenylseleno)propanal in 2.0 mL of toluene and stirred for 0.5 h at −78 °C. The solution was then rapidly warmed to 0 °C, quenched with saturated aqueous sodium chloride, and extracted once with ethyl acetate. The extract was dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (silica gel, 10% ethyl acetate–hexanes) followed by concentration in vacuo afforded **69a**, 264 mg (80%) as a pale yellow oil, 88:12 *Z/E*: ^1H NMR (*Z* isomer, 500 MHz, $CDCl_3$) δ 1.38 (3 H, d, J = 7), 1.44 (3 H, d, J = 7), 4.26 (1 H, dq, J = 10, 7), 5.36 (1 H, dq, J = 11, 7), 5.42 (1 H, dd, J = 10, 11), 7.28 (3 H, m), 7.60 (2 H, m); IR ($CHCl_3$) 1580, 1480, 1440 (C=C) cm^{-1}); LRMS (EI), *m/e* 224, 226 (M^+), 155, 157 ($C_6H_5Se^+$), 77 ($C_6H_5^+$), 69 ($M^+ - C_6H_5Se$); $[\alpha]^{25}_D$ −168° (*c* 15.0 mg/mL, CH_2Cl_2).

(2*R*,3*E*)-2-[(Carbobenzyloxy)amino]-3-pentene (70a). A stirred solution of 302 mg (1.34 mmol) of **69a**, 615 mg (4.08 mmol) of benzyl carbamate, and 1.1 mL (7.9 mmol) of triethylamine in 5 mL of methanol was cooled to 0 °C in an ice bath and treated with 547 mg (4.05 mmol) of *N*-chlorosuccinimide. The ice bath was removed and the reaction mixture was allowed to warm to 25 °C. The reaction mixture was concentrated in vacuo and, after addition of THF and silica gel and concentration in vacuo, chromatographed on silica gel (15% ethyl acetate–hexanes) to provide, after concentration in vacuo, 164 mg (56%, *E/Z* > 99:1) of **70a** as a pale yellow oil: ^1H NMR (*E* isomer, 500 MHz, $CDCl_3$) δ 1.21 (3 H, d, J = 7), 1.67 (3 H, d, J = 7), 4.23 (1 H, m), 4.61 (1 H, br s), 5.10 (2 H, m), 5.42 (1 H, dd, J = 7, 16), 5.60 (1 H, dq, J = 16, 7), 7.28–7.40 (5 H, m); IR ($CHCl_3$) 3430 (NH), 1710, 1500 (NHC=O), 970 (CH=CH) cm^{-1}; LRMS (EI), *m/e* 219 (M^+), 204 ($M^+ - CH_3$), 91 ($C_7H_7^+$), 77 ($C_6H_5^+$): $[\alpha]^{25}_D$ +7.4° (*c* 7.9 mg/mL, CH_2Cl_2).

***N*-[(Phenylmethoxy)carbonyl]-D-alanine (71a).** Ozone was bubbled through an unstirred −78 °C solution of **70a** (155 mg, 0.71 mmol) in 9.0 mL of 5:1 methylene chloride–methanol until persistence of a faint blue color. Excess dimethyl sulfide (6 mL) was added, and the colorless solution was stirred at −78 °C for 5 min and then warmed to 25 °C. The mixture was concentrated in vacuo and then dissolved in 4 mL of acetone and cooled to 0 °C. About 6 mL of Jones reagent (7 g of CrO_3, 6.1 mL of concentrated sulfuric acid, and 30 mL of water) was added to the stirred solution. After being stirred for 5 min, the solution was diluted with water and was extracted four times with methylene chloride. The organic extracts were combined and extracted once with aqueous sodium hydroxide solution (pH 10). The basic aqueous phase was acidified with a small portion of concentrated aqueous hydrochloric acid and then extracted three times with fresh methylene chloride. The combination of the latter organic extracts, drying ($MgSO_4$), and concentration in vacuo afforded **71a**, 103 mg (65%), in 79% ee (see below).

Enantiomeric Excess Determination for 71a–e. Enantiomeric excess was evaluated by using HPLC analysis of the dansyl derivatives. The protected amino acids were deprotected as described in detail for the case of **71a**.[32] A mixture of *N*-[(phenylmethoxy)carbonyl]-D-phenylalanine (62.7 mg, 0.21 mmol), cyclohexene (0.15 mL, 1.5 mmol), and 20% $Pd(OH)_2$–C (18 mg) in 1.5 mL of ethanol was refluxed for 25 min. Water (3 mL) was added, and the mixture was filtered through a plug of Celite 503. The filtrate was concentrated in vacuo affording D-phenylalanine (32.6 mg, 94%) as a colorless solid. Dansylation was effected[33] by treating a solution of 5.3 mg (32 μmol) of D-phenylalanine in 150 μL of water, 100 μL of tetrahydrofuran, and 50 μL (360 μmol) of triethylamine with dansyl chloride (23.8 mg, 88 μmol) at 25 °C. The yellow solution was mixed by agitation for ca. 2 min. The mixture was extracted sequentially with four portions of ether. The resulting colorless aqueous phase contained the dansyl-D-phenylalanine, which was identical with authentic material (TLC, silica gel). The other protected amino acids were dansylated by the same procedure. The freshly prepared dansyl amino acids were diluted as necessary with acetonitrile and water to provide concentrations of ca. 2.5 mg/mL. HPLC analysis[29] was performed with a C-18 (reversed-phase) column (Dupont, 5 mm × 230 mm) at a flow rate of 1.0 mL/min, detection at 335 nm. The eluent used for ee analysis of the dansyl derivatives of **71b–71d** was a 1:15 mixture respectively of acetonitrile and a stock solution consisting of 2.30 g of L-proline, 2.50 g of copper(II) sulfate pentahydrate, 1.54 g of ammonium acetate, 800 mL of acetonitrile, and enough water to yield a final volume of 4 L (acetic acid or aqueous ammonium hydroxide was added to reach pH 7). The retention times (min) for dansyl phenylalanine, dansyl leucine, and dansyl norleucine respectively (D isomer, L isomer) were as follows: 40.5, 28.4; 23.7, 20.0; 32.8, 27.0. The eluent for ee analysis of the dansyl derivative of **71a** was a 1:17 mixture respectively of acetonitrile and a stock solution consisting of 2.30 g of L-proline, 2.50 g of copper(II) sulfate pentahydrate, 1.54 g of ammonium acetate, 400 mL of acetonitrile, and enough water to yield a final volume of 4 L (acetic acid or aqueous ammonium hydroxide was added to reach pH 7). Dansyl-D-alanine and dansyl-L-alanine had retention times of 40.2 and 33.3 min, respectively.

Diastereoselective Rearrangements Employing Amides. 75 and 76 as Nucleophilic Amines. The *N*-chlorosuccinimide-mediated rearrangements listed in Table V were conducted as described below for the preparation of **79**.

Amide 79. A solution of 50 mg (0.18 mmol) of [(4-methyl-2-(*Z*)-hexenyl)seleno]benzene (**73**) and (*R*)-2-methoxy-2-phenylacetamide (**75**) (61 mg, 0.26 mmol) in 0.8 mL of methanol at 25 °C was treated with 0.17 mL (1.54 mmol) of triethyl orthoformate and a small crystal of *p*-toluenesulfonic acid monohydrate. This mixture was stirred 0.5 h at 25 °C. *N,N*-Diisopropylethylamine (0.25 mL, 1.54 mmol) was added. The mixture was cooled to −78 °C (at which point it became heterogeneous) and was treated with 103 mg (0.77 mmol) of *N*-chlorosuccinimide. The mixture was warmed to 25 °C over 1 h, concentrated in vacuo, and chromatographed on silica gel (25% ethyl acetate–hexanes) to afford 28 mg (44%) of **79** as an oil. Care was taken to avoid any separation of the two diastereomers of **79** during the latter chromatography. The diastereomeric mixture **79** was not separated and was characterized by 500-MHz ^1H NMR. **79**, isomer i: ^1H NMR (500 MHz, $CDCl_3$) δ 0.85 (6 H, m), 1.8 (1 H, m), 3.4 (3 H, s), 4.3 (1 H, m), 3.63 (1 H, s), 4.95–5.25 (2 H, m), 5.8 (1 H, m), 6.75 (1 H, b), 7.3–7.5 (5 H, m). **79**, isomer ii: ^1H NMR (500 MHz, $CDCl_3$) δ 0.95 (6 H, m), 1.85 (1 H, m), 3.43 (3 H, s), 4.3 (1 H, m), 4.95–5.25 (2 H, m), 5.75 (1 H, m), 6.75 (1 H, b), 7.3–7.5 (5 H, m). The ratio of i/ii was 2.2:1.0 as determined by ^1H NMR integration. The same reaction conducted with the *E* selenide **49** afforded a 62% yield of **79** as a i/ii ratio of 1.9:1.0.

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Supplementary Material Available: Further details of the preparation of and/or spectroscopic data for compounds **11**, **13**, **15–18**, **19b,c**, **20b,c**, **21b,c**, **22a–c**, **23a–c**, **24a–c**, **25a–c**, **26a–c**, **27b,c**, **36**, **38–41**, **42a,b**, **43a**, **44a,b**, **45a,b**, **46–57**, **58a,c,d**, **60–62**, **69b–d**, **70b–d**, **71b–d**, **72–74**, **78**, **80**, **and 81** (16 pages) Ordering information is given on any current masthead page.

Syntheses of 5-, 7-, and 8-Methoxy-3-methyl-2-tetralone

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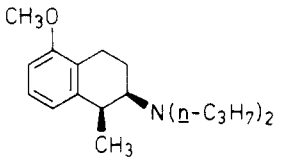
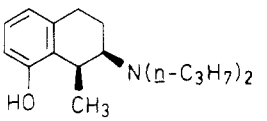
Two efficient syntheses of 5-methoxy- and 8-methoxy-3-methyl-2-tetralone and the synthesis of the 7-methoxy isomer via a different route are described. Also reported is the synthesis of 8-methoxy-3,3-dimethyl-2-tetralone. The regioselectivity of lithium carbanion formation in 1,6-, 1,7-, and 2,7-dihydroxynaphthalene is discussed. The latter compound undergoes dimetalation more easily than the other isomers.

Several 2-aminotetralin derivatives possess potent and selective dopamine- or 5-hydroxytryptamine-receptor-stimulating abilities.[1,2] Recently, it has been demonstrated that the introduction of methyl substituents, in the C1 or C2 positions of certain 2-aminotetralins changes the pharmacological profile.[3] Notably, (1*S*,2*R*)-5-methoxy-1-methyl-2-(di-*n*-propylamino)tetralin (**1**) appears to be



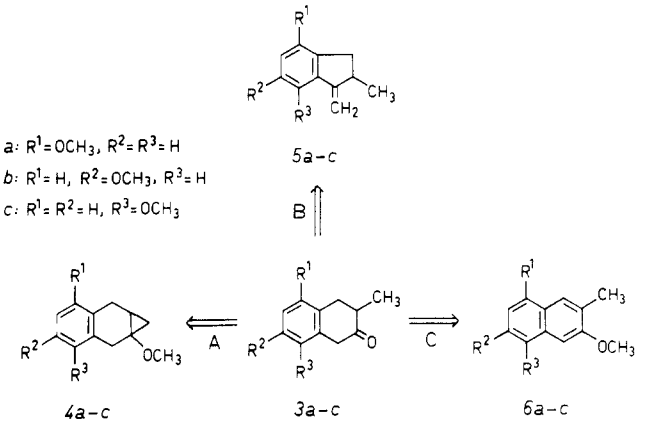
1



2

a dopamine-receptor antagonist with selectivity for dopamine autoreceptors[3a,4] and (1*S*,2*R*)-8-hydroxy-1-methyl-2-(di-*n*-propylamino)tetralin (**2**) is a highly potent 5-hydroxytryptamine-receptor agonist.[5] These interesting results provide impetus for the synthesis of C3-methyl-substituted 2-aminotetralin analogues. Access to the corresponding 3-methyl-2-tetralones would enable the preparation of the desired 2-amino-3-methyltetralins.[6]

Scheme I



At least four synthetic routes to C3-alkyl-substituted 2-tetralones have been reported previously: (a) 2-Tetralones can be carboxylated regiospecifically in the C3 position by use of magnesium methoxy carbonate.[7] Alkylation of the resulting β-keto esters followed by hydrolysis of the ester function and, finally, decarboxylation gives the target compounds. This strategy has been used by Cannon et al.[8] in their synthesis of some *trans*-6,7-dihydroxy-1,2,3,4,4a,5,10,10b-octahydrobenzo[*g*]quinolines. However, the carboxylation procedure and the removal of the carboxyl group are only moderately efficient reactions, thus making this approach less appealing. (b) Protection

(1) For recent review on dopamine-receptor agonists, see: Kaiser, C.; Tikam, J. *Med. Res. Rev.* **1985**, *5*, 145–229. Cannon, J. G. *Prog. Drug Res.* **1985**, *29*, 303–414.

(2) For recent reviews on 5-hydroxytryptamine-receptor agonists, see: Arvidsson, L.-E.; Hacksell, U.; Glennon, R. A. *Prog. Drug Res.*, in press. Glennon, R. A. In *CRC Handbook of Stereoisomers: Drugs in Psychopharmacology*; Smith, D. F., Ed.; CRC: Boca Raton, FL, 1984; pp 327–368.

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(6) 2-Aminotetralins are available from 2-tetralones by a variety of synthetic methods. See, for example: Hacksell, U.; Svensson, U.; Nilsson, J. L. G.; Hjorth, S.; Carlsson, A.; Wikström, H.; Lindberg, P.; Sanchez, D. *J. Med. Chem.* **1979**, *22*, 1469–1475.

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(8) Cannon, J. G.; Lee, T.; Beres, J. A.; Goldman, H. D. *J. Heterocyclic Chem.* **1980**, *17*, 1633–1636.

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