zone 125 mg (49%) of the α-anomer was obtained as colorless needles upon crystallization from MeOH. From the slower migrating zone 65 mg (25%) of the β-anomer was crystallized (MeOH). Both compounds were identical with those obtained by solid–liquid phase-transfer glycosylation in all respects.

Glycosylation of 3 with 7b Employing Purine Nucleoside Phosphorylase. Compound **3** (5 mg, 0.033 mmol) was suspended in Sörensen phosphate buffer (0.07 M, pH 7.5), and 2-deoxy-α-D-ribofuranose 1-phosphate (**7b**) (10 mg, 0.049 mmol) was added after addition of purine nucleoside phosphorylase from bovine spleen (3.25 units); the reaction mixture was stirred at 25 °C for 2 h. From the supernatant solution a sample of 10 μL was taken and applied on a TLC plate. As reference compounds authentic samples of the β-nucleoside **1** and the α-nucleoside **2** were used. Tenfold development of the plate in solvent D identified the enzymatically prepared nucleoside as the faster migrating β-anomer.

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Registry No. 1, 110457-87-9; 2, 110457-88-0; 3, 67410-64-4; 4b, 110472-07-6; 5, 110457-84-6; 7a, 4330-21-6; 7b, 17039-17-7; 8a, 110457-85-7; 8b, 110457-90-4; 9a, 110457-86-8; 9b, 110457-89-1; *N,N*-dimethylformamide diethyl acetal, 1188-33-6.

Practical Enantioselective Synthesis of a Homotyrosine Derivative and (*R,R*)-4-Propyl-9-hydroxynaphthoxazine, a Potent Dopamine Agonist

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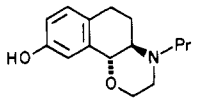
Two enantioselective routes were developed to prepare chiral amino acid derivative **4**. The key step in the first route was catalytic hydrogenation of acrylate derivative **3** using chiral rhodium catalysts. In the second route the key step was acylation of 2-chloroanisole with (*R*)-aspartic anhydride (**8**), wherein chlorine acts as a removable directing group. Cyclization of (*R*)-homotyrosine **4b** to tetralone **13** and reduction to tetralol **14** occurred with preservation of enantiomeric purity. The process for converting amide **19** to (*R,R*)-4-propyl-9-hydroxynaphthoxazine [(+)-PHNO, **1**] has been simplified and optimized.

Introduction

A new class of dopamine agonists recently has attracted attention[1] due to tremendous potency and a selective mode of action at the D_2 receptors. In particular, (*R,R*)-4-propyl-9-hydroxynaphthoxazine [(+)-PHNO, **1**] has therapeutic potential for treatment of Parkinson's disease.[2] The previously reported[1] syntheses of **1** began with 7-methoxy-1-tetralone and required a resolution to obtain the pharmacologically active *R,R* enantiomer. Herein we describe the first enantioselective synthesis of **1**.



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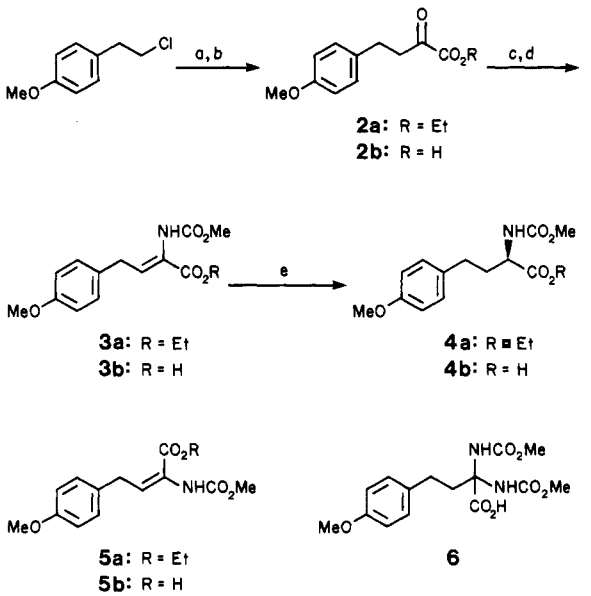
In designing a practical, asymmetric synthesis we chose (*R*)-homotyrosine **4** as our intermediate target.[3] Incentive for this approach was provided by the intramolecular Friedel–Crafts cyclization of aryl amino acids developed by McClure and co-workers[4] and more recently by Nordlander[5] and Rapoport.[6] Based on these reports, we believed that enantiomeric purity could be preserved in going from (*R*)-homotyrosine **4b** to the enantiomerically secure bicyclic intermediate **14**. Furthermore, we concluded that a practical, enantioselective synthesis of the requisite am-

Scheme I[a]



[a] (a) Mg/THF; (b) $(EtO_2C)_2$; H_3O^+; (c) H_2NCO_2Me/*p*-TSA/tol/reflux/$-H_2O$; (d) HCl/tol/80 °C; (e) H_2 (3 atm)/[Rh(NBD)-((*S,S*)-chiraphos)]ClO_4/MeOH.

(1) (a) Jones, J. H.; Anderson, P. S.; Baldwin, J. J.; Clineschmidt, B. V.; McClure, D. E.; Lundell, G. F.; Randall, W. C.; Martin, G. E.; Williams, M.; Hirschfield, J. M.; Smith, G.; Lumma, P. K. *J. Med. Chem.* **1984**, *27*, 1607–1613. (b) Dykstra, D.; Hazelhoff, B.; Mulder, T. B. A.; De-Vries, J. B.; Wynberg, H.; Horn, A. S. *Eur. J. Med. Chem.-Chim. Ther.* **1985**, *20*, 247–250. (c) Perrone, R.; Berardi, F.; Bettoni, G.; Tortorella, V. *Farmaco. Ed. Sci.* **1985**, *40*, 422–428.

(2) Grandas Perez, F. J.; Jenner, P. G.; Nomoto, M.; Stahl, S.; Quinn, N. P.; Parkes, J. D.; Critchley, P.; Marsden, C. D. *Lancet* **1986**, 906.

(3) The carbamate derivative was chosen over the propanamide to prevent racemization via an aza lactone during the cyclization process (**4b** → **13**).

(4) McClure, D. E.; Arison, B. H.; Jones, J. H.; Baldwin, J. J. *J. Org. Chem.* **1981**, *46*, 2431–2433.

(5) Nordlander, J. E.; Njorge, F. G.; Payne, M. J.; Warman, D. *J. Org. Chem.* **1985**, *50*, 3481–3484.

(6) Buckley, T. E., III; Rapoport, H. *J. Org. Chem.* **1983**, *48*, 4222–4232 and references cited therein.

0022-3263/87/1952-5143$01.50/0

Table I. Enantioselective Hydrogenation

entry	substrt	catalyst[a]	solvent	pressure, psi	R/S ratio[b]
1	**3a**	$[Rh(NBD)_2]ClO_4$ + (*S,S*)-chiraphos	THF/HOAc (10:1)	40	78:22
2	**3a**	$[Rh(NBD)_2]ClO_4$ + (*S,S*)-chiraphos	EtOH/HOAc (10:1)	40	72:28
3	**3a**	$[Rh(NBD)_2]ClO_4$ + (*S,S*)-chiraphos	MeOH	40	75:25
4	**3b**	$[Rh(NBD)Cl]_2$ + (−)-DIOP	$PhCH_3$/MeOH (1:2)	40	78:22
5	**3b**	$[Rh(NBD)Cl]_2$ + (*S,S*)-chiraphos	$PhCH_3$/MeOH (1:2)	40	NR
6	**3b**	$[Rh(NBD)Cl]_2$ + (−)-DIOP	$PhCH_3$/MeOH (1:2)	40	76:24
7	**3b**	$[Rh(NBD)Cl]_2$ + (−)-DIOP	MeOH	15	NR
8	**3b**	$[Rh(NBD)Cl]_2$ + (−)-DIOP	MeOH/H_2O + $NaHCO_3$	15	NR
9	**3b**	$[Rh(NBD)_2]ClO_4$ + (−)-DIOP	MeOH	40	74:26
10	**3b**	$[Rh(NBD)_2]ClO_4$ + (−)-DIOP	MeOH/H_2O (2.3:1)	40	74:26
11	**3b**	$[Rh(NBD)_2]ClO_4$ + (−)-DIOP	EtOH	40	75:25
12	**3b**	$[Rh(NBD)_2]ClO_4$ + (−)-DIOP	MeOH + Et_3N	40	35:65
13	**3b**	$[Rh(NBD)_2]ClO_4$ + (*R*)-BINAP	MeOH	40	25:75
14	**3b**	$[Rh(NBD)_2]ClO_4$ + (*S*)-BINAP	MeOH	40	72:28
15	**3b**	$[Rb(NBD)_2]ClO_4$ + (*R*)-prophos	MeOH	40	10:90
16	**3b**	$[Rh(NBD)_2]ClO_4$ + (*S,S*)-BPPM	MeOH	40	90:10
17	**3b**	$[Rh(NBD)_2]ClO_4$ + (*R,R*)-DIPAMP	MeOH	40	5:95
18	**3b**	$[Rh(NBD)_2]ClO_4$ + (*S,S*)-chiraphos	EtOH	40	91:9
19	**3b**	$[Rh(NBD)_2]ClO_4$ + (*S,S*)-chiraphos	MeOH/H_2O (2.3:1)	40	89:11
20	**3b**	$[Rh(NBD)_2]ClO_4$ + (*S,S*)-chiraphos	MeOH/H_2O + $NaHCO_3$	40	NR
21	**3b**	$[Rh(NBD)_2]ClO_4$ + (*S,S*)-chiraphos	MeOH + Et_3N	40	NR
22	**3b**	$[Rh(NBD)_2]ClO_4$ + (*S,S*)-chiraphos	MeOH	5	88:12
23	**3b**	$[Rh(NBD)_2]ClO_4$ + (*S,S*)-chiraphos	MeOH	100	70:30
24	**3b**	$[Rh(NBD)_2]ClO_4$ + (*S,S*)-chiraphos	MeOH	40	91:9

[a] Catalysts were preformed by mixing the rhodium complex and the chiral ligand in the appropriate solvent. The chiral ligands are illustrated in Figure 1. The active catalyst was not isolated except for the preparative run described in the experimental section. [b] Enantiomer ratios determined by chiral HPLC (entries 1–3) or by chiral capillary GC as the methyl ester derivatives (entries 4–24). NR = no reaction.

ino acid derivative **4b** should be possible. In fact, we have developed two approaches to (*R*)-homotyrosine **4b**: The first, more general route, relies on the asymmetric hydrogenation of amino acrylate **3**, and the second, more specific route, begins with the chiral starting material (*R*)-aspartic acid. It should be noted that although for our needs the *R* enantiomer was the target, both methods are equally capable of producing the *S* enantiomer.

Results

(A) Enantioselective Synthesis of (*R*)-Homotyrosine 4 via Asymmetric Hydrogenation. The success of this approach hinged on whether the catalytic asymmetric hydrogenation method using chiral rhodium catalysts developed by Knowles[7] and countless others[8] could be extended to the reduction of acrylate derivative **3**. By the nature of the substituents on the olefin we expected to obtain a reasonable degree of facial selectivity.

The requisite pyruvates **2a** and **2b** were prepared by reacting the Grignard reagent derived from 2-(4-methoxyphenyl)ethyl chloride with diethyl oxalate.[9] The resultant crude keto ester **2a** was then hydrolyzed to give crystalline keto acid **2b** in 80% overall yield. Condensation of **2b** with methyl carbamate and catalytic *p*-toluenesulfonic acid in toluene at 80 °C gave an imposing mixture of (*Z*)-olefin **3b**, (*E*)-olefin **5b**, and dicarbamate adduct **6** in a ratio of 3:3:4, respectively (Scheme I). Treatment of this complex mixture with gaseous HCl not only eliminated one carbamate moiety from **6** to produce acrylates **3b** and **5b** but also catalyzed the isomerization of **5b** to **3b**. Thus, the toluene suspension of **3b**, **5b**, and **6** could be converted to a suspension of **3b**. Filtration afforded pure, crystalline (*Z*)-acrylate **3b** in 90% yield from keto acid **2b**. In a similar fashion, keto ester **2a** was condensed with methyl carbamate to give (*Z*)-acrylate ester **3a**.

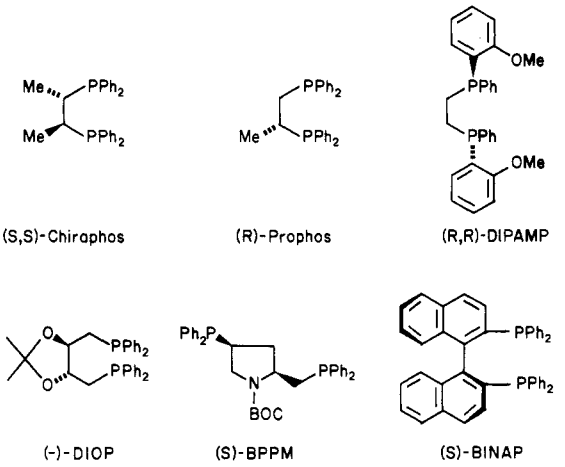


Figure 1. Chiral ligands.

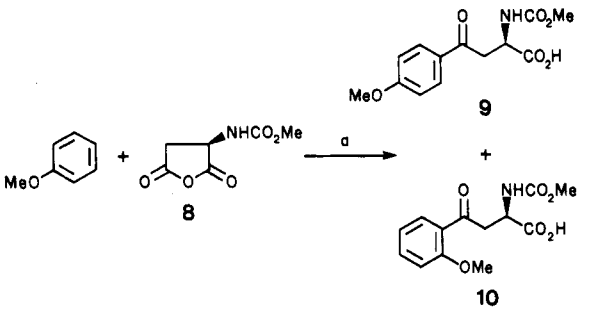
The asymmetric hydrogenation of both ester **3a** and acid **3b** was investigated under a variety of conditions (see Table I). From inspection of the entries numerous features of the reduction became apparent, some of the more important are as follows: (1) acid **3b** provided better facial selectivity than ester **3a**; (2) reduction of the triethylamine salt of acid **3b** reversed the facial selectivity; (3) the highest enrichment for the *R* enantiomer (80% ee) was obtained by using the (*S,S*)-chiraphos ligand (Figure 1) in MeOH; and (4) the highest enrichment for the *S* enantiomer (90% ee) was obtained by using the DIPAMP ligand in MeOH.

For our preparative needs we employed the conditions of entry 24. In this manner, acrylate **3b** was converted in nearly quantitative yield to a 9:1 mixture of the *R* to *S* enantiomers of **4b**. A single recrystallization of this mixture from hexanes/ethyl acetate then gave ≥98% enantiomerically pure *R*-acid **4b** in 80% yield from **3b**.

(B) Enantioselective Synthesis of Homotyrosine 4b from (*R*)-Aspartic Acid. The strategy of this approach was to incorporate (*R*)-aspartic acid, via a Friedel–Crafts

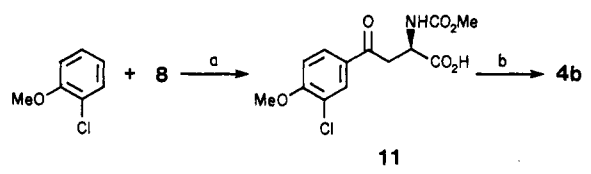
(7) Vineyard, B. D.; Knowles, W. S.; Sabacky, M.; Bachman, G. L.; Weinkauff, D. J. *J. Am. Chem. Soc.* **1977**, *99*, 5946–5952 and references cited therein.
(8) Marko, L.; Bakos, J. In *Aspects of Homogeneous Catalysis*; Ugo, R., Ed.; D. Reidel: Boston, 1981; Vol. 4, pp 145–202.
(9) Weinstock, L. M.; Currie, R. B.; Lovell, A. V. *Synth. Commun.* **1981**, *11*, 943–946.

Scheme II[a]



[a] (a) $AlCl_3/CH_2Cl_2/MeNO_2$; H_3O^+.

Scheme III[a]



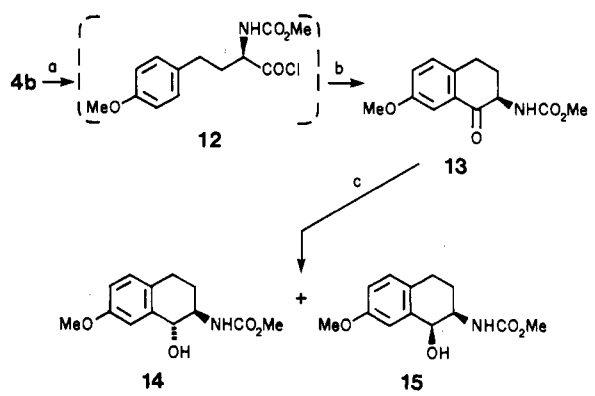
[a] (a) $AlCl_3/CH_2Cl_2/MeNO_2$; H_3O^+; (b) H_2 (3 atm)/*i*-PrOH/H_2/Pd–C.

acylation of anisole, as the chiral synthon for the side chain of (*R*)-homotyrosine **4b**. The success of this approach required control of regioselectivity at two sites; that is, acylation must occur at the β-carbonyl of the anhydride and at the para position of anisole. No problem was anticipated with selectivity at the β-carbonyl position. This preference has been demonstrated by Reifenrath et al.[10] with *N*-phthaloylaspartic anhydride and more recently by Nordlander and co-workers[11] with *N*-(trifluoroacetyl)aspartic anhydride. There was, however, cause for concern with regards to exclusive attack at the para position of anisole. The literature reports dealing with acylation of anisole range from exclusive para attack[12] to nearly equal ortho and para attack[13] depending on the acylation reagent.

Anhydride **8** was best prepared by first acylating (*R*)-aspartic acid with methyl chloroformate under Schotten–Baumen conditions and then dehydrating the resultant diacid **7** with trifluoroacetic anhydride.[14] Crystalline anhydride **8** was isolated in 90% overall yield. Acylation of anisole with anhydride **8** in the presence of $AlCl_3$ proceeded smoothly under either heterogeneous (CH_2Cl_2) or homogeneous ($MeNO_2/CH_2Cl_2$) conditions. Unfortunately, the product isolated was a 7:3 mixture of desired para-substituted **9** to ortho-substituted **10** (Scheme II). The ratio was only slightly responsive to changes in reaction conditions. *N*-(Trifluoroacetyl)aspartic anhydride[11] gave similar selectivity.

At this point we decided to investigate the use of a removable blocking group on the aromatic ring. For this purpose, chlorine seemed to be the best choice based on both economics and the possibility of removal concurrent with the ketone-to-methylene reduction. In practice, acylation of 2-chloroanisole with anhydride **8** gave an excellent yield of a single isomer, the desired para ketone. Crystallization afforded a 94% isolated yield of **11** based on anhydride **8**. Therefore, *the o-chloro substituent directs acylation exclusively para to the methoxy group.* As hoped, catalytic reduction of **11** with a palladium catalyst simultaneously reduced the ketone and removed the chlorine directing group to provide a 94% yield of >99% enantiomerically pure (*R*)-**4b**[15] (Scheme III).

Scheme IV[a]



[a] (a) Oxalyl chloride/CH_2Cl_2/DMF; (b) $TiCl_4/CH_2Cl_2$; H_3O^+; silica gel; (c) $NaAlH_2(OCH_2CH_2OCH_3)_2$/*t*-BuOMe/tol; sodium potassium tartrate.

Table II. Friedel–Crafts Cyclization

entry	Lewis acid	yield **4b** → **13**, %	racemization,[a] %
1	$FeCl_3 \cdot MeNO_2$	85–90	<2.5
2	$AlCl_3$	50	>10
3	$AlCl_3 \cdot MeNO_2$	65	>10
4	$SnCl_4$	60	not determined
5	$TiCl_4$	86–90	<2.0

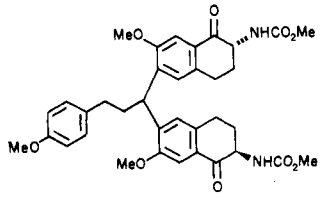
[a] enantiomeric purity of **13** determined by chiral HPLC (Pirkle-1A).

(C) Conversion of (*R*)-Homotyrosine 4b to Nonracemizable Alcohol 14. With chiral homotyrosine **4b** readily available from either of the routes described above, we were able to test the key requirement of our strategy—that cyclization to tetralone **13** and stereospecific trans reduction to alcohol **14** could be effected without racemization.

Treatment of a CH_2Cl_2 solution of homotyrosine **4b** with 1.1 equiv of oxalyl chloride in the presence of 0.05 equiv of DMF afforded a high yield of acid chloride **12** (Scheme IV). Attempts to purify the acid chloride or allowing the solution to stand at room temperature caused slow but noticeable decomposition to the *N*-carboxy anhydride derivative and a variety of polymers. Therefore, we immediately treated the acid chloride solution with Lewis acid to promote cyclization to tetralone **13**. A variety of Lewis acids was investigated. The results are summarized in Table II. Besides racemization, the major side reaction was polymerization.[16] Although the polymers were easily

(10) Reifenrath, W. D.; Bertelli, D. J.; Micklus, M. J.; Fries, D. S. *Tetrahedron Lett.* **1976**, 1959.
(11) Nordlander, J. E.; Payne, M. J.; Njorge, F. G.; Vishwanath, V. M.; Han, G. R.; Laikos, G. D.; Balk, M. A. *J. Org. Chem.* **1985**, *50*, 3619–3622.
(12) Berliner, E. *Org. React. (N.Y.)* **1949**, *5*, 229–289.
(13) Nordlander, J. E.; Payne, M. J.; Njorge, F. G.; Balk, M. A.; Laikos, G. D.; Vishwanath, V. M. *J. Org. Chem.* **1984**, *49*, 4107–4111.
(14) Diacid **7** could also be dehydrated with oxalyl chloride, methyl chloroformate, or ketene to give anhydride **8**.

(15) The enantiomeric purity of (*R*)-**4b** was >99% before crystallization. In a similar manner homochiral (*S*)-**4b** was prepared from (*S*)-aspartic acid.
(16) A byproduct (ca. 2–4%) was found to possess structure i.



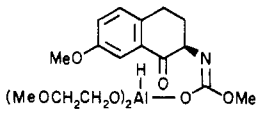
i

removed by filtration through silica gel, their formation resulted in a sizable yield loss with most of the Lewis acid catalysts. Polymerization was best controlled with $FeCl_3$·$MeNO_2$ or $TiCl_4$. Fortunately, these catalysts also resulted in negligible racemization. The two catalyst systems displayed one difference that was of considerable practical importance—$FeCl_3$·$MeNO_2$-catalyzed cyclizations gave optimum results at relatively low concentration (0.05 M), whereas $TiCl_4$-catalyzed cyclizations worked best at higher concentration (0.5 M).

After a typical quench (aqueous HCl), the CH_2Cl_2 layer containing tetralone **13** was filtered through silica gel. The purpose of the silica gel treatment was to remove residual polymeric materials. If allowed to remain, these polymers interfered with recrystallization of the tetralone and subsequent intermediates. Evaporation of the filtrate then provided tetralone **13** in 90% yield as a white solid in >97% purity.

Initial reductions of tetralone **13** were done by using $NaBH_4$.[1] These conditions, however, produced a significant amount of the unwanted cis-isomer **15** (**14**/**15** = 86:14) and resulted in ca. 20% racemization. Therefore, we looked at a variety of other reducing agents. Borane, $Zn(BH_4)_2$, and L- and K-Selectride gave even more of the undesired cis-isomer **15**. Sodium bis(2-methoxyethoxy)-aluminum hydride (SMEAH) on the other hand provided increased stereoselection, higher yield, and negligible racemization.[17] Thus, addition of tetralone **13** to a solution of SMEAH in THF, toluene, or *t*-BuOMe resulted in a ca. 95:5 ratio of **14** and **15**. Crystallization of the crude product afforded pure **14** in 88–92% yield. Analysis of the Mosher ester of **14** by HPLC indicated >99% enantiomeric purity.

Interestingly, reversing the order of addition (SMEAH added to a solution of **13**) resulted in incomplete reduction and racemization. To explain these observations, a discussion of the mechanism is in order. The first-formed intermediate is postulated to be complex **16**. This is evidenced by vigorous hydrogen evolution, as well as the required stoichiometry, i.e., at least 1.1 mol equiv of SMEAH is required for high conversion. Intramolecular reduction via **16** would be expected to give the observed trans stereochemistry.[18] Reduction of **16** is apparently much faster than abstraction of the proton at C-2 since no racemization is observed. When SMEAH is added to the tetralone, however, intermediate **16** has another option. It can react with excess tetralone present to give the bis adduct **17**. Now lacking a hydride responsible for fast



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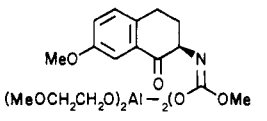
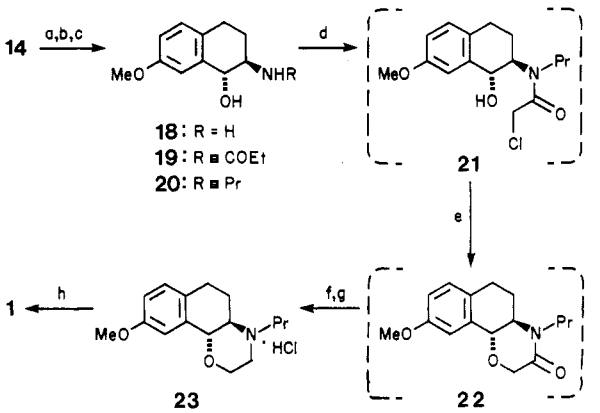


17

intramolecular reduction, the C-2 proton is more susceptible to abstraction, resulting in greater racemization. Intermediate **17** is eventually reduced intermolecularly but at a much slower rate. Evidence to support this proposed mechanism was also obtained by adding SMEAH to the tetralone and closely following the conversion of tetralone **13** to alcohols **14** and **15**. At the point where the rate of reduction noticeably dropped, the reaction was quenched. Although the *trans*-**14** had good enantiomeric purity, the recovered tetralone was racemic.

Scheme V[a]



[a] (a) KOH/MeOH/H_2O; (b) $(EtCO)_2O$; (c) BH_3·Me_2S/THF; NaOH/H_2O; (d) $ClCH_2COCl/Na_2CO_3/H_2O$/tol; (e) NaOH/H_2O/tol/*n*-Bu_4NCl; (f) $NaAlH_2(OCH_2CH_2OCH_3)_2$/tol; NaOH/$H_2O$; (g) HCl; (h) $MeSO_3H$/methionine.

(D) Preparation of (*R*,*R*)-4-Propyl-9-hydroxynaphthoxazine 1 from Homochiral Alcohol 14. Carbamate **14** was transformed to amide **19** by a simple one-pot procedure. Saponification of **14** with KOH in aqueous MeOH afforded a solution of primary amino alcohol (Scheme V). Addition of propanoic anhydride then gave the product which crystallized directly from the reaction mixture. Amide **19** was isolated by filtration in 93% yield. Reduction of the amide could be accomplished with BH_3·Me_2S, $LiAlH_4$, $NaBH_3OAc$, or SMEAH to give crystalline *N*-propylamino alcohol **20** in high yield (>90%).

Conversion of amino alcohol **20** to the naphthoxazine structure is based on chemistry reported by Jones et al.[1a] with several process improvements incorporated. A two-phase mixture of **20** in toluene and aqueous Na_2CO_3 was treated with excess chloroacetyl chloride to give chloro amide **21**. Addition of aqueous NaOH and *n*-Bu_4NCl, a phase-transfer catalyst, followed by vigorous stirring at room temperature affected cyclization to oxazinone **22**. The toluene layer was separated, washed with water, and dried. Treatment with SMEAH then gave oxazine which was isolated by crystallization of its HCl salt **23**. The overall yield of **23** from **20** was 94%.

Demethylation of **23** could be accomplished with the usual reagents (e.g., pyr·HCl or BBr_3). We found, however, that the procedure described by Yajima and co-workers[19] was operationally simpler and afforded a higher yield of product. With this procedure, ether **23** was aged in methanesulfonic acid and methionine at room temperature until the transfer–alkylation was complete. The reaction mixture was diluted with water and the pH adjusted to cause crystallization of pure free base **1** in 93% yield. Treatment with HCl then afforded the HCl salt in 97% yield.

Summary

Two efficient methods for preparing enantiomerically pure homotyrosine **4b** have been described. The asymmetric catalytic reduction approach starting from 2-(4-methoxyphenyl)ethyl chloride gave acid **4b** in 58% overall yield, whereas the approach starting from (*R*)-aspartic acid afforded **4b** in 80% yield. (*R*)-Homotyrosine **4b** was shown

(17) Reduction of the *N*-TFA protected tetralone with SMEAH afforded a 1:1 mixture of cis and trans alcohols.

(18) The sodium borohydride reduction undoubtedly involves a similar intramolecular hydride transfer. In this case, however, the intermediate must involve a looser, dative bonding of the tetralone and the reducing agent.

(19) Fujii, N.; Irie, H.; Yajima, H. *J. Chem. Soc., Perkin Trans. 1* **1977**, 2288–2289.

to be a productive (i.e., 61–62.5% overall yield) precursor to homochiral 1.

Experimental Section

General. Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 237B spectrometer. NMR spectra were recorded on a Bruker AM-300 spectrometer (^{1}H NMR at 300 MHz, ^{13}C NMR at 75 MHz). Specific rotations were determined at 20 °C on a Perkin-Elmer 241 polarimeter. Concentrations (*c*) for specific rotations are reported in units of g/100 mL. Analytical gas chromatography (GC) was carried out on a Hewlett-Packard 5890A gas chromatograph equipped with a split mode injector and flame ionization detector. Helium was used as the carrier gas. The following capillary columns were employed: 30 m × 0.32 mm DB-17 (J&W Associates); 25 m × 0.31 mm Chirasil-Val III (Alltech Inc.). Analytical high-performance liquid chromatography (HPLC) was carried out by using a Spectra Physics SP-8700 pump, LDC SpectroMonitor III variable wavelength detector, and the following columns: 4.6 mm × 25 cm Zorbax Phenyl (DuPont), 4.6 mm × 25 cm Zorbax C-8 (DuPont), 4.6 mm × 25 cm Zorbax Si (DuPont), 4.6 mm × 25 cm Pirkle 1-A (Regis), and 4.6 mm × 25 cm Pirkle covalent L-phenylglycine.

Reactions were carried out under an atmosphere of N_2. As necessary, CH_2Cl_2, DMF, $MeNO_2$, *t*-BuOMe, THF, and toluene, were dried over 3A or 4A molecular sieves. Residual water content was determined by Karl Fisher titration.

Ethyl 2-Oxo-4-(4-methoxyphenyl)butanoate (2a). Grignard Reagent. To a mechanically stirred suspension of 24.3 g (1.00 mol) of Mg in 25 mL of dry THF was added 20 mL of a solution of 85.5 g (0.500 mol) of 2-(4-methoxyphenyl)ethyl chloride in 300 mL of dry THF. The mixture was heated at reflux until the reaction initiated. The remaining THF solution was added at a rate to maintain the reaction at reflux (0.5 h). The mixture was heated at reflux an additional 0.5 h, cooled to 25 °C, and then filtered to remove the excess Mg. **Acylation.** To a mechanically stirred, cooled (−20 °C) solution of 146 g (1.00 mol) of diethyl oxalate in 120 mL of dry THF was added the Grignard reagent solution over a 1-h period. The mixture was stirred an additional 1 h at −20 °C and then rapidly quenched by the addition of 100 mL of 6 M aqueous HCl. The mixture was stirred 0.5 h at 0 °C, diluted with 500 mL of hexanes, and then partitioned. The upper organic phase was washed with brine (2 × 150 mL), dried over Na_2SO_4, and concentrated in vacuo to give 190 g of a yellow oil (keto ester **2a** and excess diethyl oxalate). The diethyl oxalate was removed by vacuum distillation [40–45 °C (0.1 mmHg)] to leave 110 g of crude keto ester **2a**. This material was used as is in the next step. An analytical sample was prepared by vacuum distillation [Kugelrohr, 115–117 °C (0.02 mm Hg)]: ^{1}H NMR ($CDCl_3$) δ 7.12 (d, 2, *J* = 8.8 Hz, H-2′, H-6′), 6.82 (d, 2, *J* = 8.8 Hz, H-3′, H-5′), 4.30 (q, 2, *J* = 7.3 Hz, $CO_2CH_2CH_3$), 3.78 (s, 3, OCH_3), 3.13 (t, 2, *J* = 7.6 Hz, 2 H-3), 2.90 (t, 2, *J* = 7.6 Hz, 2 H-4), 1.45 (t, 3, *J* = 7.3 Hz, $CO_2CH_2CH_3$). Anal. Calcd for $C_{13}H_{16}O_4$: C, 66.08; H, 6.84. Found: C, 65.96; H, 7.09.

Ethyl (2*Z*)-2-[(Methoxycarbonyl)amino]-4-(4-methoxyphenyl)but-2-enoate (3a). A mechanically stirred solution of 110 g (0.466 mol) of crude keto ester **2a**, 105 g (1.40 mol) of methyl carbamate, and 8.25 g (43.4 mmol) of *p*-toluenesulfonic acid in 2.75 L of dry toluene was heated at reflux for a 12-h period. The solution was cooled to 20 °C, washed with 1 M aqueous $NaHCO_3$ (2 × 1 L), and H_2O (2 × 1 L), dried over $MgSO_4$, and concentrated in vacuo to 136 g of a yellow solid (HPLC analysis: 85:15 mixture of **3a** to **5a**). The solid was suspended in 600 mL of 8:2 hexanes/EtOAc and the mixture stirred for 4 h at 20 °C. The mixture was filtered and the cake washed with 150 mL of cold 9:1 hexanes/EtOAc. The solid was dried in vacuo to afford 65 g of **3a** as a white solid (HPLC analysis: 95:5 **3a** to **5a**). This material was used as is in the next step. An analytical sample of **3a** was purified by flash chromatography (75:25 hexanes/EtOAc, **5a** eluted before **3a**) followed by recrystallization from 75:25 hexanes/EtOAc: mp 72.5–73.5 °C; ^{1}H NMR ($CDCl_3$) δ 7.12 (d, 2, *J* = 8.8 Hz, H-2′, H-6′), 6.86 (d, 2, *J* = 8.8 Hz, H-3′, H-5′), 6.74 (t, 1, *J* = 7.3 Hz, H-3), 6.28 (br s, 1, NH), 4.23 (q, 2, *J* = 7.3 Hz, OCH_2CH_3), 3.80 (s, 3, OCH_3), 3.75 (s, 3, CO_2CH_3), 3.50 (d, 1, *J* = 7.3 Hz, 2 H-4), 1.30 (t, 3, *J* = 7.3 Hz, OCH_2CH_3); ^{13}C NMR (DMSO-d_6) δ 164.5 (s, C-1), 158.2 (s, C-4′), 154.8 (s, CO_2CH_3), 135.8 (d, C-3), 130.7 (s, C-1′), 129.5 (d, C-2′, C-6′), 125.3 (s, C-2), 114.0 (d, C-3′, C5′), 63.4 (t, OCH_2CH_3), 55.2 (q, OCH_3), 52.6 (q, CO_2CH_3), 33.8 (t, C-4), 14.2 (q, OCH_2CH_3). Anal. Calcd for $C_{15}H_{19}NO_5$: C, 61.41; H, 6.54; N, 4.78. Found: C, 61.57; H, 6.50; N, 4.81.

E-Isomer **5a**: ^{1}H NMR ($CDCl_3$) δ 7.15 (d, 2, *J* = 8.7 Hz, H-2′, H-6′), 6.90 (m, 1, H-3), 6.83 (d, 2, *J* = 8.7 Hz, H-3′, H-5′), 6.80 (br s, 1 NH), 4.32 (q, 2, *J* = 7.2 Hz, OCH_2CH_3), 3.88 (d, 1, *J* = 7.4 Hz, 2 H-4), 3.78 (s, 3, OCH_3), 3.69 (s, 3, CO_2CH_3), 1.35 (t, 3, *J* = 7.2 Hz, OCH_2CH_3); ^{13}C NMR (DMSO-d_6) δ 164.0 (s, C-1), 158.0 (s, C-4′), 154.4 (s, CO_2CH_3), 132.1 (d, C-3), 130.3 (s, C-1′), 129.3 (d, C-2′, C-6′), 124.7 (s, C-2), 113.9 (d, C-3′, C-5′), 61.8 (t, OCH_2CH_3), 55.2 (q, OCH_3), 52.2 (q, CO_2CH_3), 33.3 (t, C-4), 14.0 (q, OCH_2CH_3).

Ethyl (2*R*)-2-[(Methoxycarbonyl)amino]-4-(4-methoxyphenyl)butanoate (4a). A suspension of 60 g (0.205 mol) of **3a**, 0.65 g (0.91 mmol) of [Rh((*S*,*S*)-chiraphos)(NBD)]ClO_4[20] in 33 mL of HOAc and 275 mL of oxygen-free THF was pressurized with H_2 (40 psi) and then agitated for 24 h at 20 °C. Upon completion, the vessel was vented and thoroughly flused with N_2. The solution was concentrated in vacuo to give 67.2 g of a brown oil. The crude oil was dissolved in 180 mL of 1:1 hexanes/EtOAc and the solution treated with 36 g of silica gel (E. Merck Si-60, 60–200 mesh). The mixture was filtered and the silica gel washed with 90 mL of 1:1 hexanes/EtOAc. The filtrates were combined and concentrated in vacuo to afford 60 g (99%) of **4a** as a yellow oil. Chiral capillary GC analysis (Chirasil-Val III, 200 °C) afforded an 80:20 ratio of (*R*)-**4a** (t_R 19.50 min) to (*S*)-**4a** (t_R 19.05 min). An analytical sample was purified by flash chromatography (8:2 hexanes/EtOAc): ^{1}H NMR (DMSO-d_6) δ 7.69 (d, 1, *J* = 8.3 Hz, NH), 7.11 (d, 2, *J* = 8.3 Hz, H-2′, H-6′), 6.85 (d, 2, *J* = 8.3 Hz, H-3′, H-5′), 4.09 (m, 2, OCH_2CH_3), 3.94 (m, 1, H-2), 3.72 (s, 3, OCH_3), 3.44 (s, 3, CO_2CH_3), 2.55 (m, 2, 2 H-4), 1.87 (m, 2, 2 H-3), 1.17 (t, 3, *J* = 7.3 Hz, OCH_2CH_3); ^{13}C NMR (DMSO-d_6) δ 172.4 (s, C-1), 157.4 (s, C-4′), 156.6 (s, CO_2CH_3), 132.6 (s, C-1′), 129.2 (d, C-2′, C-6′), 113.7 (d, C-3′, C-5′), 60.3 (t, OCH_2CH_3), 54.8 (q, OCH_3), 53.2 (d, C-2), 51.4 (q, CO_2CH_3), 32.8 (t, C-3), 30.4 (t, C-4), 14.0 (q, OCH_2CH_3). Anal. Calcd for $C_{15}H_{21}NO_5$: C, 61.00; H, 7.17; N, 4.74. Found: C, 60.97; H, 7.02; N, 4.88.

2-Oxo-4-(4-methoxyphenyl)butanoic Acid (2b). Grignard Reagent. To a mechanically stirred suspension of 570 g (23.4 mol) of Mg in 600 mL of dry THF was added 500 mL of a solution of 2.00 kg (11.7 mol) of 2-(4-methoxyphenyl)ethyl chloride in 7.0 L of dry THF. The mixture was heated at reflux until the reaction initiated. The remaining THF solution was added at a rate to maintain the reaction at reflux (2.5 h). The mixture was heated at reflux an additional 0.5 h, cooled to 25 °C, and then filtered under a N_2 atmosphere to remove the excess Mg. **Acylation.** To a mechanically stirred, cooled (−20 °C) solution of 3.40 kg (23.4 mol) of diethyl oxalate in 2.8 L of dry THF was added the Grignard reagent solution over a 2.5-h period. The mixture was stirred an additional 1 h at −20 °C and then rapidly quenched by the addition of 2.5 L of 6 M aqueous HCl. The mixture was stirred 0.5 h at 0 °C, diluted with 11 L of hexanes, and then partitioned. The organic phase was washed with brine (2 × 3 L), dried over Na_2SO_4, and concentrated in vacuo to give 4.44 kg of a yellow oil (keto ester **2a** and excess diethyl oxalate). **Hydrolysis.** The crude keto ester **2a** was dissolved in 7.9 L of HOAc and 7.9 L of 10% aqueous H_2SO_4. The flask was fitted with a Dean–Stark trap and the mixture heated at reflux for 7 h (6.4 L of distillate removed). The mixture was cooled to 25 °C and diluted with 8.7 L of H_2O and the product extracted into 3 × 6 L of EtOAc. The EtOAc extracts were combined, washed with 6.3 L of 3 M aqueous NaCl, and extracted with 4 × 7.9 L of 1.2 M aqueous $NaHCO_3$. The $NaHCO_3$ extracts were combined, washed with 8 L of CH_2Cl_2, acidified to pH 1 with 4 L of 12 M aqueous HCl, and extracted with 4 × 4 L of CH_2Cl_2. The CH_2Cl_2 extracts were combined, washed with 8 L of brine, dried (Na_2SO_4), and concentrated in vacuo to afford 1.95 kg (80%) of keto acid **2b** as a white solid. An analytical sample was recrystallized from toluene: mp 77.5–79 °C; ^{1}H NMR (DMSO-d_6) δ 13.9 (br s, 1, CO_2H), 7.13 (d, 2, *J* = 8.5 Hz, H-2′, H-6′), 6.83 (d, 2, *J* = 8.5 Hz, H-3′, H-5′), 3.71 (s, 3,

(20) Fryzuk, M. D.; Bosnich, B. *J. Am. Chem. Soc.* **1977**, *99*, 6262–6267.

OCH_3), 3.09 (t, 2, J = 7.5 Hz, 2 H-3), 2.76 (t, 2, J = 7.5 Hz, 2 H-4); ^{13}C NMR (DMSO-d_6) δ 195.7 (s, C-2), 162.5 (s, C-1), 157.5 (s, C-4'), 132.4 (s, C-2', C-6'), 129.1 (d, C-1'), 113.7 (d, C-3', C-5'), 54.9 (q, OCH_3), 40.2 (t, C-3), 27.5 (t, C-4). Anal. Calcd for $C_{11}H_{12}O_4$: C, 63.44; H, 5.82. Found: C, 63.16; H, 6.04.

(2*Z*)-2-[(Methoxycarbonyl)amino]-4-(4-methoxyphenyl)-but-2-enoic Acid (3b). A flask fitted with a Dean–Stark trap was charged with 1.86 kg (8.94 mol) of keto acid **2b**, 1.08 kg (14.4 mol) of methyl carbamate, 9.0 g (47.2 mmol) of *p*-toluenesulfonic acid, and 8.0 L of toluene. The mixture was heated under vacuum (280 mmHg) at reflux (80 °C) for 7 h (120 mL of H_2O removed). HPLC analysis (Zorbax C-8; 40:60:0.1 MeCN/H_2O/H_3PO_4; 1.2 mL/min; 230 nm) afforded a 3:3:4 ratio of **3b** (t_R 5.89 min) to **5b** (t_R 7.71 min) to dicarbamate **6** (t_R 5.70 min). The system was returned to 1 atm and at 80 °C saturated with HCl gas over a 10-min period. The mixture was stirred for 2 h at 80 °C, cooled to 0 °C, and filtered. The cake was washed with cold toluene (2 × 2 L), air-dried, and then washed with H_2O (2 × 2 L). The product was dried in vacuo (35 °C) to afford 2.13 kg (90%) of **3b** as a white solid. HPLC analysis: >99:1 **3b** to **5b**; no dicarbamate **6**. An analytical sample was recrystallized from MeOH: mp 169–171 °C; ^1H NMR (DMSO-d_6) δ 12.6 (br s, 1, CO_2H), 8.70 (br, s, 1 NH), 7.13 (d, 2, J = 8.2 Hz, H-2', H-6'), 6.87 (d, 2, J = 8.2 Hz, H-3', H-5'), 6.46 (t, 1, J = 7.6 Hz, H-3), 3.72 (s, 3, OCH_3), 3.60 (s, 3, CO_2CH_3), 3.39 (d, 2, J = 7.6 Hz, 2 H-4); ^{13}C NMR (DMSO-d_6) δ 165.7 (s, C-1), 157.8 (s, C-4'), 155.1 (s, CO_2CH_2), 134.9 (d, C-3), 130.3 (s, C-1'), 129.5 (d, C-2', C-6'), 127.5 (s, C-2), 113.9 (d, C-3', C-5'), 54.9 (q, OCH_3), 51.7 (q, CO_2CH_3), 32.1 (t, C-4). Anal. Calcd for $C_{13}H_{15}NO_5$: C, 58.85; H, 5.71; N, 5.28. Found: C, 58.82; H, 5.83; N, 5.28.

In a separate experiment the *E*-isomer **5b** was isolated (chromatography on SP-207 resin, gradient elution with 10:90 MeCN/H_2O to 25:75 MeCN/H_2O, **3b** eluted first) and characterized by ^{13}C NMR: (DMSO-d_6) δ 165.7 (s, C-1), 157.6 (s, C-4'), 154.3 (s, CO_2CH_3), 132.1 (s, C-1'), 129.2 (d, C-2', C-6'), 128.7 (s, C-2), 124.7 (d, C-3), 113.7 (d, C-3', C-5'), 55.0 (q, OCH_3), 51.5 (q, CO_2CH_3), 32.1 (t, C-4).

(2*R*)-2-[(Methoxycarbonyl)amino]-4-(4-methoxyphenyl)-butanoic Acid (4b). Chiral Hydrogenation Route. A suspension of 182 g (0.684 mol) of **3b**, 0.80 g (9.7 mmol) of anhydrous NaOAc, and 1.02 g (1.41 mmol) of [Rh((*S,S*)-chiraphos)-(NBD)]ClO_4[20] in 1.0 L of oxygen-free MeOH was pressurized with H_2 (40 psi) and then agitated for 4 days at 20 °C. The vessel was vented and thoroughly flushed with N_2. The mixture was concentrated in vacuo to give 190 g of a yellow photochromic solid. Chiral capillary GC assay (Me ester derivative; Chirasil-Val III; 175 °C) afforded a 90:10 ratio of *R*-Me ester (t_R 30.4 min) to *S*-Me ester (t_R 30.8 min). The solid was dissolved in 900 mL of hot (60 °C) EtOAc and the solution treated with 180 g of silica gel (E. Merck Si-60, 40–63 μm). The mixture was filtered and the silica gel washed with 3 × 1 L of EtOAc. The EtOAc solution was concentrated to a volume of 1.0 L, seeded with **4b**, and slowly diluted with 1.6 L of hexanes. The mixture was cooled to 20 °C, aged for 4 h, and filtered and the cake washed with 2 × 100 mL of 7:3 hexanes/EtOAc. The product was dried in vacuo to afford 144 g (80%) of **4b** as white needles. Chiral capillary GC analysis (Me ester derivative) afforded a 99:1 ratio of *R*-Me ester to *S*-Me ester. An analytical sample was recrystallized from 3:1 hexanes/EtOAc: mp 113–114 °C; ^1H NMR ($CDCl_3$) δ 12.5 (br s, 1, CO_2H), 7.09 (d, 2, J = 8.5 Hz, H-2', H-6'), 6.82 (d, 2, J = 8.6 Hz, H-3', H-5'), 5.39 (br d, 1, J = 8.3 Hz, NH), 4.41 (m, 1, H-2), 3.77 (s, 3, OCH_3), 3.70 (s, 3, CO_2CH_3), 2.65 (t, 2, J = 7.8 Hz, 2 H-4), 2.17 (m, 1, H-3), 1.98 (m, 1, H-3); ^{13}C NMR (DMSO-d_6) δ 174.0 (s, C-1), 157.5 (s, C-4'), 156.7 (s, CO_2CH_3), 132.8 (s, C-1'), 129.3 (s, C-2', C-6'), 113.7 (s, C-3', C-5'), 54.9 (q, OCH_3), 53.1 (d, C-2), 51.4 (q, CO_2CH_3), 32.9 (t, C-3), 30.6 (t, C-4); $[\alpha]_{365}$ −55.0° (*c* 1.36, absolute EtOH). Anal. Calcd for $C_{13}H_{17}NO_5$: C, 58.42; H, 6.41; N, 5.24. Found: C, 58.44; H, 6.60; N, 5.28.

(*R*)-*N*-(Methoxycarbonyl)aspartic Acid (7). To a mechanically stirred, cooled (0 °C) solution of 133 g (1.00 mol) of (*R*)-aspartic acid and 160 g (4.00 mol) of NaOH in 500 mL of H_2O was added 125 mL (153 g, 1.62 mol) of MeOCOCl over a 0.5-h period. The solution was aged 1 h at 20 °C, cooled to 0 °C, and then cautiously acidified to pH 1 with 200 mL of 12 M aqueous HCl. The solution was concentrated in vacuo and the resultant white solid extracted with three 2.0-L portions of hot (60 °C) *i*-PrOAc. The extracts were combined and concentrated in vacuo to afford 182 g (95%) of **7** as a white solid. An analytical sample was recrystallized from *i*-PrOAc: mp 152–153 °C; ^1H NMR (DMSO-d_6) δ 11.5 (br s, 2, CO_2H), 7.45 (br d, 1, J = 8.4 Hz, NH), 4.33 (m, 1, H-2), 3.55 (s, 3, CO_2CH_3), 2.72 (dd, 1, J = 5.4, 16.6 Hz, H-3), 2.55 (dd, 1, J = 8.3, 16.6 Hz, H-3); ^{13}C NMR (DMSO-d_6) δ 172.9 (s, C-1), 171.8 (s, C-4), 156.5 (s, CO_2CH_3), 51.6 (q, CO_2CH_3), 50.6 (d, C-2), 30.1 (t, C-3); $[\alpha]_{589}$ −7.0° (*c* 1.07, absolute EtOH). Anal. Calcd for $C_6H_9NO_6$: C, 37.70; H, 4.75; N, 7.33. Found: C, 37.40; H, 4.66; N, 7.21.

(*R*)-*N*-(Methoxycarbonyl)aspartic Anhydride (8). To a mechanically stirred suspension of 181 g (0.947 mol) of **7** in 3.60 L of *i*-PrOAc at 20 °C was added 188 mL (280 g, 1.33 mol) of $(CF_3CO)_2O$ over a 0.5-h period. The solution was aged 1 h at 35 °C, concentrated in vacuo to a volume of 1.6 L, cooled to 20 °C, seeded, and, with vigorous stirring, slowly diluted with 7.7 L of dry hexanes. The suspension was stirred 1 h at 0 °C and filtered and the cake washed with two 420-mL portions of 5:1 hexanes/*i*-PrOAc. The product was dried in vacuo to afford 156 g (95%) of **8** as a free-flowing white crystalline solid. An analytical sample was recrystallized from *i*-PrOAc: mp 134–138 °C; ^1H NMR (DMSO-d_6) δ 8.04 (d, 1, J = 7 Hz, NH), 4.67 (m, 1, H-2), 3.58 (s, 3, CO_2CH_3), 3.25 (dd, 1, J = 10, 18 Hz, H-3), 2.92 (dd, 1, J = 6.7, 18 Hz, H-3); ^{13}C NMR (DMSO-d_6) δ 172.2 (s, C-1), 169.8 (s, C-4), 156.3 (s, CO_2CH_3), 52.1 (q, CO_2CH_3), 50.3 (d, C-2), 34.7 (t, C-3). Anal. Calcd for $C_6H_7NO_5$: C, 41.62; H, 4.07; N, 8.09. Found: C, 41.43; H, 4.27; N, 8.14.

(2*R*)-2-[(Methoxycarbonyl)amino]-4-oxo-4-(3-chloro-4-methoxyphenyl)butanoic Acid (11). To a mechanically stirred, cooled (0 °C) suspension of 298 g (2.24 mol) of anhydrous $AlCl_3$ in 1.79 L of dry CH_2Cl_2 were added 121 mL (136 g, 2.24 mol) of dry $MeNO_2$ and 170 mL (191 g, 1.34 mol) of 2-chloroanisole over a 0.5 h period. The solution was warmed to 20 °C, and 155 g (0.895 mol) of **8** was added portionwise over a 0.5-h period. The vessel was fitted with an efficient reflux condenser and the mixture heated to reflux for a 24-h period. During the reaction the vessel was swept with N_2 to remove HCl as it was generated. The mixture was cooled to 20 °C and then cautiously quenched into a rapidly stirred mixture of 2.2 kg of ice, 2.2 L of 2 M aqueous H_3PO_4, and 4.5 L of *i*-PrOAc. The mixture was partitioned and the organic layer washed with 2.2 L of 2 M aqueous H_3PO_4 and 2.2 L of brine. The solution was filtered through Celite, concentrated in vacuo to a volume of 2.2 L, cooled to 20 °C, seeded, and with vigorous stirring slowly diluted with 6.7 L of hexanes. The suspension was stirred for 1 h at 0 °C and filtered and the cake washed with two 450-mL portions of 3:1 hexanes/*i*-PrOAc. The product was dried in vacuo to afford 266 g (94%) of **11** as a white solid. An analytical sample was recrystallized from MeOH: mp 152–153 °C; ^1H NMR ($CDCl_3$) δ 9.5 (br s, 1, CO_2H), 7.97 (d, 1, J = 1.9 Hz, H-2'), 7.85 (dd, 1, J = 2.0, 8.6 Hz, H-6'), 6.97 (d, 1, J = 8.7 Hz, H-5'), 5.91 (d, 1, J = 8.4 Hz, NH), 4.77 (m, 1, H-2), 3.97 (s, 3, OCH_3), 3.70 (dd, 1, J = 4.3, 18.5 Hz, H-3), 3.67 (s, 3, CO_2CH_3), 3.51 (dd, 1, J = 3.8, 18.5 Hz, H-3); ^{13}C NMR (DMSO-d_6) δ 194.3 (s, C-4), 173.1 (s, C-1), 158.3 (s, C-4'), 156.3 (s, CO_2CH_3), 129.8 (s, C-3'), 129.6 (d, C-2'), 129.1 (d, C-6'), 121.3 (s, C-1'), 112.4 (d, C-5'), 56.6 (q, OCH_3) 51.4 (q, CO_2CH_3), 49.7 (d, C-2), 39.3 (t, C-3); $[\alpha]_{589}$ −50.6° (*c* 1.29, absolute EtOH). Anal. Calcd for $C_{13}H_{14}ClNO_6$: C, 49.46; H, 4.47; N, 4.44. Found: C, 49.22; H, 4.46; N, 4.43.

(2*R*)-2-[(Methoxycarbonyl)amino]-4-(4-methoxyphenyl)-butanoic Acid (4b). Aspartic Acid Route. A glass reactor containing a solution of 265 g (0.840 mol) of **11** in 1.32 L of 1:1 THF/H_2O was purged with N_2, charged with 13.2 g of 10% Pd/C, pressurized with H_2 (40 psi), and then agitated at 20 °C for a 24-h period. Upon completion, the vessel was vented and thoroughly flushed with N_2. The mixture was filtered through a pad of Solka-Floc and the catalyst cake washed with two 132-mL portions of THF. The filtrate and washings were combined and concentrated in vacuo to remove the THF. The remaining mixture was extracted with three 660-mL portions of hot (60 °C) *i*-PrOAc. Chiral capillary GC analysis, prior to crystallization (Me ester derivative; Chirasil-Val III; 175 °C) afforded a >99:1 ratio of *R*-Me ester (t_R 30.4 min) to *S*-Me ester (t_R = 30.8 min). The organic layers were combined, washed with 660 mL of brine, concentrated in vacuo to a volume of 660 mL, seeded, and with vigorous stirring slowly diluted with 2.0 L of hexanes. The suspension was stirred

for 1 h at 0 °C, filtered, and the cake washed with 660 mL of cold 5:1 hexanes/*i*-PrOAc. The product was dried in vacuo to afford 211 g (94%) of **4b** as white needles. The physical properties (mp, ^{1}H NMR, ^{13}C NMR, $[\alpha]_{589}$) were identical with those of material prepared above.

[(2*R*)-1,2,3,4-Tetrahydro-7-methoxy-1-oxo-2-naphthalenyl]carbamic Acid, Methyl Ester (13). Acid Chloride. To a mechanically stirred, cooled (0 °C) suspension of 210 g (0.786 mol) of **4b** and 3.1 mL (2.9 g, 0.04 mol) of dry DMF in 575 mL of dry CH_2Cl_2 was added 72 mL (105 g, 0.825 mol) of $(COCl)_2$. The mixture was aged 5 min at 0 °C and then 55 min at 20 °C. **Caution**: HCl, CO_2, and CO are generated by the reaction. The acid chloride solution should be used immediately. **Cyclization.** To a mechanically stirred, cooled (0 °C) solution of 215 mL (372 g, 1.96 mol) of $TiCl_4$ in 570 mL of dry CH_2Cl_2 was added the acid chloride solution over a 15-min period. The internal temperature was maintained below 5 °C during the addition. HCl is generated by the reaction. The mixture was aged for 0.5 h at 0 °C and was then cautiously quenched into a rapidly stirred mixture of 2.4 kg of ice, 800 mL of concentrated aqueous HCl, and 2.0 L of CH_2Cl_2. After 15 min the mixture was partitioned, and the aqueous layer extracted with 800 mL of CH_2Cl_2. The organic layers were combined, washed with 3.1 L of 3 M aqueous HCl, 3.1 L of 1 M aqueous $NaHCO_3$, and 3.1 L of brine. The organic solution was treated with 400 g of silica gel (E. Merck, Si-62, 60–200 mesh) and stirred for 0.5 h and the silica gel removed by filtration. The silica gel cake was washed with four 4.0-L portions of CH_2Cl_2. The filtrate and washings were combined and concentrated in vacuo to afford 176 g (90%) of **13** as a white solid. An analytical sample was recrystallized from EtOH: mp 136–137 °C; ^{1}H NMR ($CDCl_3$) δ 7.46 (d, 1, J = 2.7 Hz, H-8), 7.16 (d, 1, J = 8.5 Hz, H-5), 7.08 (dd, 1, J = 2.7, 8.5 Hz, H-6), 5.93 (br s, 1, NH), 4.42 (m, 1, H-2), 3.83 (s, 3, OCH_3), 3.72 (s, 3, CO_2CH_3), 3.16 (m, 1, H-4), 2.95 (m, 1, H-4), 2.73 (m, 1, H-3), 1.92 (m, 1, H-3); ^{13}C NMR (DMSO-d_6) δ 195.1 (s, C-1), 157.7 (s, C-7), 156.5 (s, CO_2CH_3), 136.3 (s, C-8a), 132.3 (s, C-4a), 130.2 (d, C-5), 121.1 (d, C-6), 109.2 (d, C-8), 56.7 (d, C-2), 55.2 (q, OCH_3), 51.3 (q, CO_2CH_3), 29.9 (t, C-4), 27.2 (t, C-3); $[\alpha]_{589}$ +66.6° (*c* 1.03, abs EtOH). Anal. Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.82; H, 6.33; N, 5.67.

[(1*R*,2*R*)-1,2,3,4-Tetrahydro-1-hydroxy-7-methoxy-2-naphthalenyl]carbamic Acid, Methyl Ester (14). To a mechanically stirred, cooled (0 °C) solution of 310 mL (3.4 M in toluene, 1.05 mol) of sodium bis(2-methoxyethoxy)aluminum hydride in 2.8 L of dry *t*-BuOMe was added 175 g (0.702 mol) of **13** portionwise over a 0.5-h period. H_2 is generated by the reaction. The mixture was stirred an additional 0.5 h at 0 °C then cautiously quenched into a rapidly stirred, cooled (0 °C) solution of 3.5 L of 1 M aqueous sodium potassium tartrate. **Caution**: H_2 is generated as excess hydride is quenched. Following the quench, the mixture was diluted with 3.5 L of EtOAc, heated to 50 °C, and stirred rapidly for 0.5 h. The mixture was allowed to settle, and the two homogeneous layers were partitioned. The aqueous layer was extracted with 3.5 L of EtOAc. The organic layers were combined, washed with 3.5 L of 1 M aqueous sodium potassium tartrate, diluted with 7.0 L of toluene, and then washed with 3.5 L of brine. GC analysis (DB-17, 225 °C) afforded a 95:5 ratio of **14** (t_R 9.52 min) to **15** (t_R 8.70 min). HPLC analysis [(*R*)-Mosher ester derivative;[21] Zorbax-Si; 88:10:2 hexanes/CH_2Cl_2/*i*-PrOH; 1.5 mL/min; 254 nm] indicated a 99:1 ratio of the *R*,*R*,*R*-derivative (t_R 7.30 min) to the *S*,*S*,*R*-derivative (t_R 8.70 min). The solution was concentrated in vacuo to a volume of 3.5 L and seeded and the mixture stirred for 1 h at 0 °C. The mixture was filtered, and the cake washed with two 350-mL portions of cold (0 °C) toluene and two 350-mL portions of hexanes. The product was dried in vacuo to afford 159 g (90%) of **14** as white needles. GC ≥ 99:1 **14**/**15**. An analytical sample was recrystallized from *i*-PrOAc: mp 159–160 °C; ^{1}H NMR ($CDCl_3$) δ 7.06 (d, 1, J = 2.6 Hz, H-8), 6.99 (d, 1, J = 8.4 Hz, H-5), 6.76 (dd, 1, J = 2.6, 8.4 Hz, H-6), 5.07 (br d, 1, J = 7.3 Hz, NH), 4.52 (br t, 1, J = 6.8 Hz, H-1), 3.81 (m, 1, H-2), 3.77 (s, 3, OCH_3), 3.67 (s, 3, CO_2CH_3), 3.58 (br s, 1, OH), 2.86 (m, 1, H-4), 2.73 (m, 1, H-4), 2.15 (m, 1, H-3), 1.75 (m, 1, H-3); ^{13}C NMR (DMSO-d_6) δ 157.4 (s, C-7), 156.4 (s, CO_2CH_3), 140.2 (s, C-8a), 128.8 (d, C-5), 127.5 (s, C-4a), 133.1 (d, C-6), 112.5 (d, C-8), 70.2 (d, C-1), 54.8 (q, OCH_3), 53.8 (d, C-2), 51.0 (q, CO_2CH_3), 27.1 (t, C-4), 26.2 (t, C-3); $[\alpha]_{589}$ +64.2° (*c* 1.05, EtOH). Anal. Calcd for $C_{13}H_{17}NO_4$: C, 62.13; H, 6.82; N, 5.57. Found: C, 62.00; H, 6.92; N, 5.62.

***N*-[(1*R*,2*R*)-1,2,3,4-Tetrahydro-1-hydroxy-7-methoxy-2-naphthalenyl]propanamide (19). Hydrolysis.** To a mechanically stirred solution of 166 g (85% ≃ 141 g, 2.52 mol) of KOH in 1.1 L of H_2O and 470 mL of MeOH was added 158 g (0.629 mol) of **14**. The mixture was heated at reflux (internal temperature, 85 °C) for 6 h and then cooled to 50 °C. **Acylation.** To the solution was added 162 mL (165 g, 1.26 mol) of propanoic anhydride over a 1-h period. The mixture was cooled to 20 °C, diluted with 1.6 L of 2 M aqueous NaCl, cooled to 0 °C, and aged for 2 h. The mixture was filtered and the cake washed with 750 mL of cold 85:15 H_2O/MeOH and 750 mL of cold H_2O. The product was dried in vacuo to afford 146 g (93%) of **19** as a white solid. Chiral HPLC analysis (benzoate ester derivative; Pirkle-1A; 70:28:2 hexanes/CH_2Cl_2/*i*-PrOH; 1.5 mL/min; 230 nm) revealed a >99:1 ratio of the *R*,*R*-enantiomer (t_R = 7.9 min) to the *S*,*S*-enantiomer (t_R = 6.0 min). An analytical sample was recrystallized from EtOAc: mp 166–167 °C [lit.[1a] mp 162–163 °C]; ^{1}H NMR ($CDCl_3$) δ 7.10 (d, 1, J = 2.5 Hz, H-8), 7.00 (d, 1, J = 8.4 Hz, H-5), 6.77 (dd, 1, J = 2.5, 8.4 Hz, H-6), 5.80 (br d, J = 5.6 Hz, NH), 4.55 (dd, 1, J = 4.9, 7.6 Hz, H-1), 4.19 (d, 1, J = 4.9 Hz, OH), 4.05 (m, 1 H-2), 3.79 (s, 3, OCH_3), 2.90 (m, 1, H-4), 2.76 (m, 1, H-4), 2.27 (q, 2, J = 7.6 Hz, $COCH_2CH_3$), 2.10 (m, 1, H-3), 1.76 (m, 1, H-3), 1.03 (t, 3, J = 7.6 Hz, $COCH_2CH_3$); ^{13}C NMR (DMSO-d_6) δ 172.8 (s, C-1′), 157.4 (s, C-7), 140.0 (s, C-8a), 128.9 (d, C-5), 127.6 (s, C-4a), 113.1 (d, C-6), 112.8 (d, C-8), 70.2 (d, C-1), 54.9 (q, OCH_3), 51.6 (d, C-2), 28.4 (t, C-2′), 26.3 (t, C-4), 25.9 (t, C-3), 9.9 (q, C-3′); $[\alpha]_{589}$ +73.5° (*c* 1.01, absolute EtOH) [lit.[1a] $[\alpha]_{589}$ +71.0° (*c* 0.015, absolute EtOH)]. Anal. Calcd for $C_{14}H_{19}NO_3$: C, 67.44; H, 7.68; N, 5.62. Found: C, 67.60; H, 7.59; N, 5.67.

(1*R*,2*R*)-1,2,3,4-Tetrahydro-7-methoxy-2-(propylamino)-1-naphthalenol (20). To a mechanically stirred solution of 145 g (0.582 mol) of **19** in 2.9 L of dry THF was added 140 mL (10 M, 1.40 mol) of BH_3·Me_2S dropwise over a 0.5-h period. The mixture was heated at reflux for 1 h and cooled to 0 °C and the excess hydride cautiously quenched by the sequential addition of 425 mL of MeOH, 425 mL of H_2O, and 425 mL of 12 M aqueous HCl. The mixture was stirred for 1 h at 20 °C, concentrated in vacuo to remove the THF, diluted with 5.1 L of H_2O, and washed with 850 mL of EtOAc. The aqueous solution was made basic by the cautious addition of 1.3 L of 8.0 M aqueous NaOH with the internal temperature maintained at <20 °C. The precipitated product was extracted into CH_2Cl_2 (2 × 5.1 L). The combined organic layers were washed with H_2O (3.4 L) and brine (3.4 L), dried over Na_2SO_4, and concentrated in vacuo to afford 126 g (92%) of **20** as a white solid. Chiral HPLC assay (benzamide derivative; Pirkle covalent L-phenylglycine; 85:10:5 hexane/CH_2Cl_2/*i*-PrOH; 2.0 mL/min; 230 nm) afforded a >99:1 ratio of the *R*,*R*-enantiomer (t_R 11.3 min) to the *S*,*S*-enantiomer (t_R 10.2 min). An analytical sample was recrystallized from MeCN: mp 131–132.5 °C; ^{1}H NMR ($CDCl_3$) δ 7.10 (d, 1, J = 2.3 Hz, H-8), 6.98 (d, 1, J = 8.5 Hz, H-5), 6.74 (dd, 1, J = 2.3, 8.5 Hz, H-6), 4.38 (d, 1, J = 8.9 Hz, H-1), 3.78 (s, 3, OCH_3), 2.5–2.8 (m, 8), 2.1–2.25 (m, 1, H-4), 1.45–1.6 (m, 2, 2 H-2′), 0.95 (t, 3, J = 7.4 Hz, H_3-3′); ^{13}C NMR (DMSO-d_6) δ 157.3 (s, C-7), 140.7 (s, C-8a), 128.7 (d, C-5), 127.8 (s, C-4a), 112.7 (d, C-6), 112.2 (d, C-8), 71.1 (d, C-1), 60.0 (d, C-2), 54.8 (q, OCH_3), 48.6 (t, C-1′), 26.0 (t, C-4), 25.7 (t, C-3), 23.0 (t, C-2′), 11.7 (q, C-3′); $[\alpha]_{589}$ +45.0° (*c* 0.98, MeOH). Anal. Calcd for $C_{14}H_{21}NO_2$: C, 71.46; H, 8.99; N, 5.95. Found: C, 71.71; H, 8.91; N, 6.19.

(4a*R*,10b*R*)-3,4,4a,5,6,10b-Hexahydro-9-methoxy-4-propyl-2*H*-naphth[1,2-*b*]-1,4-oxazine Hydrochloride (23). Acylation. To a mechanically stirred suspension of 125 g (0.531 mol) of **20** in 1.25 L of toluene and 1.25 L of 1 M aqueous Na_2CO_3 at 20 °C was added 55 mL (78 g, 0.69 mol) of $ClCH_2COCl$ dropwise over a 1-h period. The mixture was stirred an additional 2 h at 20 °C to complete the reaction. **Cyclization.** To the suspension containing **21** were added 1.25 L of 2.8 M aqueous NaOH and 3.12 g (11.2 mmol) of *n*-Bu_4NCl. The mixture was stirred rapidly for 2 h at 20 °C. The mixture was partitioned and the aqueous phase extracted with 580 mL of toluene. The organic phases were combined, washed with H_2O (860 mL) and brine (860 mL), and

(21) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543–2549.

dried over Na_2SO_4 to afford a toluene solution of **22**. **Reduction.** To a mechanically stirred, heated (50 °C) solution of 234 mL (3.4 M in toluene, 0.796 mol) of sodium bis(2-methoxyethoxy)aluminum hydride in 375 mL of dry toluene was added the solution of **22** over a 1-h period. The solution was then heated for 1 h at 80 °C. The reaction mixture was cooled to 20 °C and the excess hydride quenched by the cautious addition of 1.3 L of 1.3 M aqueous NaOH. Following the addition of 3.1 g (11 mmol) of n-Bu_4NCl, the mixture was stirred rapidly for 4 h at 20 °C. The mixture was partitioned and the organic layer washed with 1.3 M aqueous NaOH (2 × 860 mL), H_2O (860 mL), and brine (860 mL), dried over Na_2SO_4, and concentrated in vacuo to afford **23** free base as an oil. The oil was dissolved in 2.1 L of 9:1 Et_2O/EtOH and then treated with 90 mL of 7 M HCl in EtOH. The mixture was cooled to 0 °C and stirred for 1 h. The mixture was filtered and the cake washed with 860 mL of 9:1 Et_2O/EtOH and 860 mL of Et_2O. The product was dried in vacuo to afford 149 g (94%) of **23**·HCl as a white solid. An analytical sample was recrystallized from MeCN: mp 230–232 °C [lit.[1a] mp 231–233 °C]; ^1H NMR (DMSO-d_6) [as free base] δ 6.98 (d, 1, J = 8.5 Hz, H-7), 6.92 (d, 1, J = 2.5 Hz, H-10), 6.73 (dd, 1, J = 2.5, 8.5 Hz, H-8), 4.15 (d, 1, J = 9.0 Hz, H-10b), 3.97 (dd, 1, J = 2.5, 11.5 Hz, H-2), 3.74 (dt, 1, J = 2.3, 11.5 Hz, H-2), 3.69 (s, 3, OCH_3), 2.68–2.85 (m, 4, H-1′, H-3, 2 H-6), 2.02–2.31 (m, 4, H-1′, H-3, H-4a, H-5), 1.33–1.52 (m, 3, 2 H-2′, H-5), 0.85 (t, 3, J = 7.8 Hz, 3 H-3′); ^{13}C NMR (DMSO-d_6) [as free base] δ 157.3 (s, C-9), 137.4 (s, C-10a), 128.8 (d, C-7), 126.7 (s, C-6a), 113.2 (d, C-8), 109.2 (d, C-10), 78.2 (d, C-10b), 66.6 (t, C-2), 62.1 (d, C-4a), 54.8 (q, OCH_3), 54.2 (t, C-3), 51.8 (t, C-1′), 26.5 (t, C-6), 23.8 (t, C-5), 18.6 (t, C-2′), 11.7 (q, C-3′); $[\alpha]_{589}$ +49.0° (c 1.09, EtOH) [lit.[1a] $[\alpha]_{589}$ +47.3° (c 0.103, EtOH)]. Anal. Calcd for $C_{16}H_{24}NO_2Cl$: C, 64.53; H, 8.11; N, 4.70. Found: C, 64.55; H, 8.11; N, 4.81.

(4a*R*,10b*R*)-3,4,4a,5,6,10b-Hexahydro-4-propyl-2*H*-naphth[1,2-*b*]-1,4-oxazin-9-ol Hydrochloride (1). Caution: 1 is a potent CNS agent. Do not allow solutions of 1 or solid 1 to come in contact with the skin, eyes, nose, or mouth! To a mechanically stirred suspension of 226 g (1.51 mol) of (±)-methionine in 1.5 L of $MeSO_3H$ at 20 °C was added 148 g (0.497 mol) of **23** portionwise over a 10-min period. The mixture was stirred for 40 h at 20 °C. The mixture was cooled to 5 °C and diluted with 1.5 L of H_2O and the pH adjusted to 13.5 with 3.6 L of 6.1 M aqueous NaOH while the temperature was maintained at <10 °C. Following the addition of 30 g of charcoal (Darco KB, prewashed with aqueous NaOH), the mixture was stirred for 1.5 h at 20 °C. The mixture was filtered through a pad of Super-Cel and the cake washed with 1.0 L of H_2O. The pH of the combined filtrates was adjusted to 9.0 with 300 mL of 12 M aqueous HCl and the mixture cooled to 0 °C and stirred for 1 h. The mixture was filtered and the cake washed with 3.1 L of cold H_2O. The free base was dried in vacuo and then dissolved in 1.6 L of EtOH at 40 °C. Following the addition of 12 g of charcoal (Darco G-60), the solution was filtered through a pad of Super-Cel. The solution was cooled to 20 °C, treated with 122 mL of 7 M HCl in EtOH over a 0.5-h period, and diluted with 1.6 L of Et_2O and the mixture stirred 1 h at 0 °C. The mixture was filtered and the cake washed with 1.5 L of cold 1:1 Et_2O/EtOH. The product was dried in vacuo at 30 °C to afford 127 g (90%) of **1**·HCl as a white crystalline solid: mp 303–305 °C [lit.[1b] mp >260 °C]; ^1H NMR (DMSO-d_6) [as the free base] δ 9.07 (s, 1, OH), 6.8–6.9 (m, 2, H-7, H-10), 6.57 (dd, 1, J = 1.9, 7.8 Hz, H-8), 4.11 (d, 1, J = 8.3 Hz, H-10b), 3.95 (br d, 1, J = 10.8 Hz, H-2), 3.74 (br t, 1, J = 11.2 Hz, H-2), 2.63–2.86 (m, 4, H-1′, H-3, 2 H-6), 2.00–2.35 (m, 4, H-1′, H-3, H-4a, H-5), 1.30–1.55 (m, 3, 2 H-2′, H-5), 0.90 (t, 3, J = 7.3 Hz, 3 H-3′); ^{13}C NMR (DMSO-d_6) [as the free base] δ 155.2 (s, C-9), 137.2 (s, C-10a), 128.6 (d, C-7), 124.8 (s, C-6a), 114.0 (d, C-8), 111.3 (d, C-10), 78.4 (d, C-10b), 66.6 (t, C-2), 62.2 (d, C-4a), 54.2 (t, C-3), 51.9 (t, C-1′), 26.5 (t, C-6), 24.0 (t, C-5), 18.6 (t, C-2′), 11.7 (q, C-3′); $[\alpha]_{589}$ +55.9° (c 1.0, 0.10 M HCl in MeOH).

A ^{31}P and ^1H NMR Study of the Conformations of a Series of Diastereomeric 3-Substituted *trans*-2,4-Dioxa-3-oxo- and *trans*-2,4-Dioxa-3-thioxo-3-phosphabicyclo[4.3.0]nonanes as Model Compounds for Cyclic Nucleotides

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A number of epimeric pairs of 3-X-*trans*-2,4-dioxa-3-Y-3-phosphabicyclo[4.3.0]nonanes (**1**, X = OCH_3, Y = O; **2**, X = OCH_3, Y = S; **3**, X = OPh, Y = O; **4**, X = OPh, Y = S; **5**, X = Cl, Y = O; **6**, X = Cl, Y = S; **7**, X = $N(CH_3)_2$, Y = O; **8**, X = $N(CH_3)_2$, Y = S; **9**, X = S, Y = O; **10**, X = O, Y = O) have been prepared and their configuration and conformation studied by ^{31}P and ^1H NMR. The cis isomers **1a–6a** and the trans isomers **7b** and **8b** are shown to populate exclusively chair conformation **18**. Their diastereomers **1b–6b**, **7a**, and **8a**, however, exist as an equilibrium between chair conformation **18** and twist conformation **19**. The mole fraction of twist is found to vary with the nature of the exocyclic substituents on the phosphorus atom, being maximal for the chloro compounds **5b** and **6b**. In addition, it is shown that the chair ⇄ twist equilibrium is solvent-sensitive. The charged compounds **9a**, **9b**, and **10** are in a chair conformation. The position of the negatively charged sulfur atom has no influence on the preferred conformation of the phosphorothioates **9a** and **9b**. The results for **9a** and **9b** are discussed in relation to the difference in biological activity of (S_P)- and (R_P)-cAMPS.

Introduction

3′,5′-Cyclic nucleotides, e.g., cAMP and cGMP, play a central role in hormone action and cell communication.[1] Recently, it was shown that the biological activity of cyclic nucleotide analogues, derivatized at phosphorus, is governed by the configuration on the phosphorus atom (S_P or R_P).[2] Furthermore, it was established that the conformation of the dioxaphosphorinane ring of comparable cyclic nucleotides is determined by the phosphorus configuration.[3] In this paper we present a detailed configu-

(1) See, e.g.: Miller, J. P. *Cyclic 3′,5′-Nucleotides: Mechanism of Action*; Cramer, H., Schultz, J., Eds.; Wiley: London, 1977; p 77.

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