A Modified Bischler–Napieralski Procedure for the Synthesis of 3-Aryl-3,4-dihydroisoquinolines

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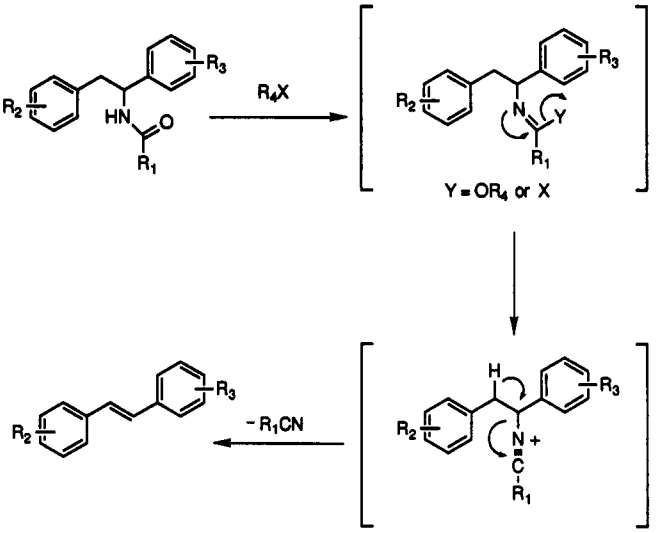
A modification of the Bischler–Napieralski reaction for the cyclization of (1,2-diphenylethyl)amides to the 3-aryl-3,4-dihydroisoquinolines is presented. Elimination of the amide group as the nitrile via the retro-Ritter reaction is avoided by its conversion to an *N*-acyliminium intermediate with oxalyl chloride–$FeCl_3$. Removal of the oxalyl group in refluxing MeOH–sulfuric acid provides the 3,4-dihydroisoquinolines in moderate to high yields. The method is also highly effective with (2-phenylethyl)amides.

Introduction

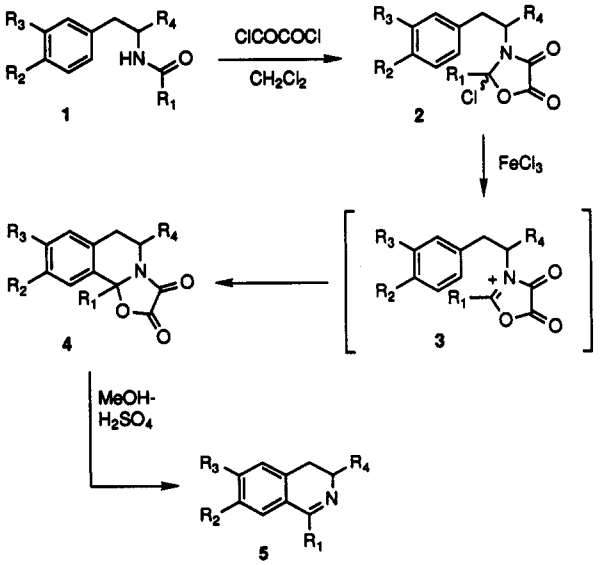
Of the variety of methods that have been developed for the synthesis of the isoquinoline ring system, probably the most commonly used procedure is the Bischler–Napieralski reaction.[1] This method, however, is often ineffective for the synthesis of 3-arylisoquinolines.[2] The 3-arylisoquinolines, a class of isoquinoline alkaloids,[1d] are important intermediates for the synthesis of the protoberberine, pavine, isopavine, and benzo[*c*]phenanthridine isoquinoline alkaloids, as well as being of interest as possible medicinal agents.[3] Surprisingly, the deficiencies in this 100-year-old reaction as applied to 3-arylisoquinolines have not been overcome. We now wish to report an effective modification of the Bischler–Napieralski procedure for the synthesis of 3-aryl-3,4-dihydroisoquinolines.

The Bischler–Napieralski reaction occurs by activation of the amide group with an O-acylating agent (Scheme I). Loss of the acyloxy group or chloride provides the nitrilium intermediate, which is subsequently trapped by the aryl group to form the 3,4-dihydroisoquinoline.[4] The nitrilium moiety of 1,2-diphenylethane derivatives, however, is lost as the nitrile to form the stilbene via a retro-Ritter reaction.[2a,b] Only when the aryl group is highly activated does ring closure occur.[2d] The intermediacy of the nitrilium ion can be completely avoided with oxalyl chloride[5] (Scheme II). Before the nitrogen can eliminate the acyloxy group, the second acyl chloride acylates the nitrogen to form a 2-chlorooxazolidine-4,5-dione **2**.[5b] The subsequent *N*-acyliminium ion **3** acts as a superior acylating agent that does not eliminate to the stilbene. To the best of our knowledge, this is the first application of oxalyl chloride to the Bischler–Napieralski reaction.

Scheme I



Scheme II



Results and Discussion

Treatment of the amide 1 with oxalyl chloride formed

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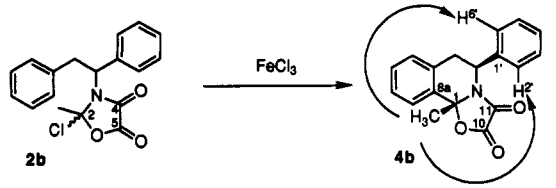
Table I. Cyclization of (Phenylethyl)amides 1 to the 3,4-Dihydroisoquinolines 5

entry	amide	R_1	R_2	R_3	R_4	product	yield, %
1	**1a**	H	H	H	Ph	**5a**	72
2	**1b**	CH_3	H	H	Ph	**5b**	88
3	**1c**	Ph	H	H	Ph	**5c**	0
4	**1d**	$PhCH_2$	H	H	Ph	**5d**	55
5	**1e**	H	OCH_3	OCH_3	3,4-$(CH_3O)_2$Ph	**5e**	63
6	**1f**	CH_3	OCH_3	OCH_3	3,4-$(CH_3O)_2$Ph	**5f**	55
7	**1g**	H	OCH_3	OCH_3	Ph	**5g**	60
8	**1h**	CH_3	OCH_3	OCH_3	Ph	**5h**	79
9	**1i**	H	H	H	3,4-$(CH_3O)_2$Ph	**5i**	25
10	**1j**	CH_3	H	H	H	**5j**	82
11	**1k**	CH_3	OCH_3	OCH_3	H	**5k**	80
12	**1l**	CH_3	H	Cl	H	**5l**	92
13	**1m**	CH_3	H	NO_2	H	**5m**	5
14	**1n**	CH_3	H	H	CO_2CH_3	**5n**	77

Scheme III



^{13}C NMR ($CDCl_3$): C-2, 108.0, 107.1 ppm
: C-4, 151.5, 151.4 ppm
: C-5, 155.2, 155.0 ppm
IR ($CDCl_3$): 1830, 1750 cm^{-1}

^{13}C NMR ($CDCl_3$): C-1, 91.0 ppm
: C-10, 158.0 ppm
: C-11, 153.2 ppm
IR ($CDCl_3$): 1805, 1730 cm^{-1}

the intermediate **2**, which was stable in solution for at least 24 h. The formation of the 2-chlorooxazolidine-4,5-dione **2b** from **1b** was characterized by the two carbonyl absorptions in the infrared and the ^{13}C NMR (Scheme III). The chlorine-bearing carbon gave ^{13}C NMR signals at 108.0 and 107.1 ppm. The doubling of the signals for C-2, C-4, and C-5 of the oxazolidine-4,5-dione, as well as most of the remaining signals, indicated the presence of diastereomers. The chlorine was subsequently removed by addition of a Lewis acid to form the *N*-acyliminium ion **3**.[6] Iron(III) chloride was found to be the most effective Lewis acid of those tested ($TiCl_4$, $SnCl_4$, $AlCl_3$, and BF_3·OEt_2). Cyclization occurred to provide **4**, the oxalyl adduct of the isoquinoline. The oxazolidine-4,5-dione **4b** was identified by the carbonyl absorptions in the infrared and detailed NMR studies. The COLOC 2-D[7] NMR experiment was used to establish long-range ^1H–^{13}C connectivities with the key correlation observed from the 1-methyl to a substituted aromatic, C-8a. A SELJRES[8] experiment (irradiation of H-3) provided assignment of all carbons two and three bonds from H-3, thereby distinguishing C-10 from C-11 and permitting assignment of the other two substituted aromatics. NOE difference studies were used to establish the relative stereochemistry of the major isomer. An 8% NOE enhancement was observed from the 1-CH_3 to $H_{2',6'}$, as noted by the arrows on **4b**, thus defining their syn relationship. The oxalyl adduct **4** was then converted to the 3,4-dihydroisoquinoline **5** in refluxing methanol–sulfuric acid (19:1).

A variety of substrates were studied to evaluate the scope of the reaction. The formamide, acetamide, benzamide, and phenylacetamide **1a–d** were prepared from commercially available 1,2-diphenylethylamine. The methoxylated derivatives **1e–i** were prepared by Friedel–Crafts acylation of veratrole with the corresponding phenylacetyl chloride[3e] or phenyl Grignard addition to the *N,O*-dimethylhydroxyamide,[9] followed by the Leuckardt reaction,[10] to convert the ketone to the formamide. Hydrolysis of the formyl group was followed by acylation with the appropriate acylating agent.

In Table I the yields of the various substrates show a definite pattern. Acetamides for the most part were obtained in high yield. The formamides and the phenylacetamide also cyclized effectively, but in somewhat lower yields. The unactivated systems **1a**, **1b**, **1d** and **1i** were converted to the 3-aryl-3,4-dihydroisoquinolines **5a**, **5b**, **5d**, and **5i**, respectively. These compounds have not been reported in the literature; previous attempts at their synthesis have only provided stilbene or other byproducts.[2] These successful cyclizations show the broad potential of the method. The benzamide **1c** failed to cyclize. Although the IR and NMR showed the benzamide had been converted to the 2-chlorooxazolidine-4,5-dione **2c**, only intractable tars were obtained upon addition of $FeCl_3$. The increased steric bulk of the phenyl group may have prevented acylation. The systems that contain methoxyl groups (**1e–h**) also cyclized effectively. However, when the phenyl group attached to the amide-bearing carbon was more highly activated than the other phenyl group (entry 9, **1i** to **5i**) the yield was lower. The method can also be applied to simple, 3,4-dihydroisoquinolines. The (2-phenylethyl)acetamides **1j–l** were cyclized to the 3,4-dihydroisoquinolines **5j–l** in 82, 80, and 92% yields, respectively. The high yield of the cyclization, in particular with the unactivated systems, was a marked improvement over the traditional Bischler–Napieralski procedure.[1] The deactivated ring of *N*-[2-(4-nitrophenyl)ethyl]acetamide (**1m**) allowed only a 5% yield of the 3,4-dihydroisoquinoline **5m**. The recovery of starting material and the parent amine indicated the nitrated phenyl ring fails to be reactive enough for acylation with the *N*-acyliminium species.

The cyclization showed little sensitivity to changes in the reaction conditions. In the case of **1e** addition of $FeCl_3$ to the chlorooxazolidinedione **2e** and the inverse addition gave the same yield within a few percent. Similarly, the temperature of addition of the $FeCl_3$ (−78 °C to room temperature) showed no variance in the yield. The yield of the cyclization in some cases was lower if precautions were not taken to avoid oxidation of the 3,4-dihydroisoquinoline product. This required prompt workup and isolation of the product. Storage of the product under nitrogen or as a salt was beneficial.

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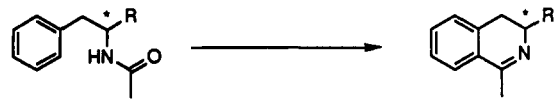
The ability to obtain chiral 3-aryl-3,4-dihydroisoquinolines from chiral 1,2-diarylethylamines with this reaction was demonstrated. (*R*)-(−)-1,2-Diphenylethylamine was prepared by resolution with (+)-tartaric acid;[11] the (−)-enantiomer was shown by Nakazaki[12] to have the *R* absolute stereochemistry. Cyclization of the (*R*)-acetamide **1b** and solvolysis of the resultant oxalyl adduct did not result in racemization of the chiral center. The chirality of the resolved amine and the 3,4-dihydroisoquinoline **5b** was determined on a chiral Pirkle L-phenylglycine column as the *N*-benzoyl compounds; the 3,4-dihydroisoquinoline was converted to the *N*-benzoyl enamide. This provides a highly effective synthetic route for the asymmetric synthesis of natural products and medicinal agents that contain the 3-arylisoquinoline ring system.

The importance of amino acids as chiral building blocks for asymmetric synthesis of natural products has been well-established.[13] The cyclization of chiral phenylalanine analogues without loss of chirality for the asymmetric synthesis of isoquinoline systems remains an important area of synthesis.[14] Application of the modified Bischler–Napieralski reaction for this purpose was studied with *N*-acetyl-(*S*)-phenylalanine methyl ester (**1n**). Due to the greater acidity of C-3 of **5n** versus **5b**, however, the 3-carbomethoxy-3,4-dihydroisoquinoline **5n** was obtained as the racemate.



1b: R = Ph (98.5:1.5 *R/S*) **5b**: R = Ph (98.5:1.5 *R/S*); 89%

1n: R = CO_2CH_3 (>99% *S*) **5n**: R = CO_2CH_3 (1:1 *S/R*); 77%

Summary

A modification of the Bischler–Napieralski reaction for the synthesis of 3-aryl-3,4-dihydroisoquinolines has been presented. This new method overcomes the problem of elimination of the amide group as the nitrile via the retro-Ritter reaction by formation of an *N*-acyliminium species with oxalyl chloride–$FeCl_3$. The potential of the method for the asymmetric synthesis of isoquinoline alkaloids containing the 3-arylisoquinoline ring system has been explored. The reaction also offers an alternative, mild method for the preparation of simple 3,4-dihydroisoquinolines.

Experimental Section

General. Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. NMR spectra were recorded in $CDCl_3$ on a Bruker AM-250 (250.1 MHz for ^1H and 62.9 MHz for ^{13}C); *J* valves are given in Hz. IR spectra were recorded in $CDCl_3$ on a Perkin-Elmer Model 1420 infrared spectrometer. Optical rotations were taken on a Perkin-Elmer Model 241 polarimeter using a 5-mL capacity (10-cm path length) quartz cell.

1,2-Bis(3,4-dimethoxyphenyl)ethanone was prepared according to the literature:[3e] mp 101–3 °C (lit.[15] mp 105 °C).

1-(3,4-Dimethoxyphenyl)-2-phenylethanone was prepared according to the literature:[3e] mp 101–103 °C (lit.[15] mp 105 °C).

2-(3,4-Dimethoxyphenyl)-1-phenylethanone was prepared by the addition of phenylmagnesium bromide to the *N,O*-dimethylhydroxyamide[9] of 3,4-dimethoxyphenylacetic acid: mp 80–81 °C (lit.[16] mp 87–88 °C).

***N*-(1,2-Diphenylethyl)formamide (1a)** was prepared by formylation[17] of 1,2-diphenylethylamine with methyl formate: mp 111.5–112.5 °C (lit.[18] mp 123–124 °C).

General Procedure for the Synthesis of Formamides. The formamides **1e**, **1g**, and **1i** were obtained from the respective ketones using the Leuckardt reaction.[3e,10]

***N*-[1,2-Bis(3,4-dimethoxyphenyl)ethyl]formamide (1e)**: mp 137.5–138.5 °C (lit.[18] mp 130–131 °C).

***N*-[2-(3,4-Dimethoxyphenyl)-1-phenylethyl]formamide (1g)**: mp 124–127 °C (lit.[19] mp 120–121 °C; lit.[20] mp 130–131.5 °C).

***N*-[1-(3,4-Dimethoxyphenyl)-2-phenylethyl]formamide (1i)**: mp 118–120 °C (lit.[18] mp 121–122 °C).

General Procedure for the Synthesis of Acetamides. The amines for **1f** and **1h** were obtained by hydrolysis of the formamides **1e** and **1g**, respectively, in refluxing MeOH–2 N HCl (5:2). Acetic anhydride (2 equiv) was added to a mixture of the amine, 5 N NaOH (4 equiv), and CH_2Cl_2 at 5 °C.

***N*-(1,2-Diphenylethyl)acetamide (1b)**: mp 147–149 °C (lit.[2a] mp 154–157 °C).

***N*-[1,2-Bis(3,4-dimethoxyphenyl)ethyl]acetamide (1f)**: mp 159.5–161.5 °C (lit.[18] mp 162–163 °C).

***N*-[2-(3,4-Dimethoxyphenyl)-1-phenylethyl]acetamide (1h)**: mp 139.5–141.5 °C; IR 3440, 1665, 1510, 1260 cm^{-1}; ^1H NMR δ 7.29 (m, 3 H), 7.19 (m, 2 H), 6.73 (d, *J* = 8.3, 1 H), 6.60 (dd, *J* = 8.3, 1.9, 1 H), 6.41 (d, *J* = 1.9, 1 H), 5.82 (br d, *J* = 7.0, 1 H), 5.25 (q, *J* = 7.4, 1 H), 3.84 (s, 3 H), 3.70 (s, 3 H), 3.06 (m, 2 H), 1.97 (s, 3 H). Anal. Calcd for $C_{18}H_{21}NO_3$: C, 72.20; H, 7.08; N, 4.68. Found: C, 72.51; H, 7.20; N, 4.70.

***N*-[2-Phenylethyl]acetamide (1j)**: mp 48–49 °C (lit.[1b] mp 45 °C).

***N*-[2-(3,4-Dimethoxyphenyl)ethyl]acetamide (1k)**: mp 94–95.5 °C (lit.[21] mp 94–95 °C).

***N*-[2-(4-Chlorophenyl)ethyl]acetamide (1l)**: mp 90–91 °C. Anal. Calcd for $C_{10}H_{12}NOCl$: C, 60.75; H, 6.13; N, 7.09. Found: C, 60.86; H, 6.06; N, 6.92.

***N*-[2-(4-Nitrophenyl)ethyl]acetamide (1m)**: mp 135.5–138 °C. Anal. Calcd for $C_{10}H_{12}N_2O_3$: C, 57.67; H, 5.82; N, 13.46. Found: C, 57.45; H, 5.85; N, 13.28.

***N*-[1,2-Diphenylethyl]benzamide (1c)** was prepared by addition of benzoyl chloride to 1,2-diphenylethylamine: mp 175.5–177 °C (lit.[2a] mp 183–185 °C).

***N*-[(1,2-Diphenylethyl)phenyl]acetamide (1d)** was prepared by addition of phenylacetyl chloride to 1,2-diphenylethylamine: mp 179.5–181 °C (lit.[2a] mp 189–191 °C).

***N*-Acetyl-(*S*)-phenylalanine methyl ester (1n)** was prepared by addition of acetic anhydride (5.8 mL, 16.7 mmol) and triethylamine (4.05 mL, 29.21 mmol), sequentually, at room temperature to a slurry of (*S*)-phenylalanine methyl ester hydrochloride (3.0 g, 13.91 mmol) in CH_2Cl_2 (87% yield): mp 87–88.5 °C (lit.[22] mp 86–87 °C); $[\alpha]^{25}D$ 105.3° (*c* 1.0, $CHCl_3$) [(lit.[22] $[\alpha]^{25}D$ 101.5° (*c* 1.0, $CHCl_3$)].

General Cyclization Procedure. The amide **1** was suspended in CH_2Cl_2 (0.1 M; dried over 3A molecular sieves). Oxalyl chloride (110 mol %) was added via syringe over a few minutes. The mixture was stirred at room temperature for 30 min. The progress of the reaction could be followed by IR (for **1b** the amide carbonyl absorbance (1680 cm^{-1}) disappeared as the chlorooxazolidinone **2b** carbonyl absorbances (1830, 1750 cm^{-1}) intensified) or HPLC (the amide **1b** and chlorooxazolidinone **2b** eluted at 3.1 and 4.5

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min, respectively (C-8 MICROSORB; 50:50:0.1 CH_3CN–H_2O–trifluoroacetic acid; 1.5 mL/min, 230 nm)). The solution was cooled to <–10 °C, and $FeCl_3$ (120 mol %) was added as a solid all at once or portionwise. The mixture was allowed to warm slowly to room temperature until all the intermediate had cyclized (6–18 h) as detected by HPLC: **4b** eluted at 5.8 min. Aqueous 2 N HCl (equal volume) was added to quench the reaction. The mixture was well stirred at room temperature for 1 h, and the layers were separated. The organic layer was washed with brine. After evaporation of the solvent the oxalyl adduct **4** was converted to the 3,4-dihydroisoquinoline **5** directly.

***cis*-6,10b-Dihydro-10b-methyl-5-phenyl-5*H*-oxazolo[2,3-*a*]isoquinoline-2,3-dione (4b).** The solution of **4b** in CH_2Cl_2 was dried (Na_2SO_4), filtered, and concentrated. The residue was triturated with ethyl ether, whereupon the product solidified. The mixture was well-stirred at room temperature until the solid was dispersed and then was cooled in an ice bath for 1 h. The solid was filtered, washed with cold ethyl ether, and suction dried. An analytical sample was obtained by recrystallization from cyclohexane–ethyl acetate: mp 156–156.5 °C (gas evolution); IR 3100–3000, 1805, 1730, 1390, 1220 cm^{-1}; ^1H NMR δ 7.6–7.3 (m, 9 H), 5.45 (dd, J = 7.9, 6.9, 1 H), 3.50 (dd, J = 16.7, 6.9, 1 H), 3.30 (dd, J = 16.7, 7.9, 1 H), 1.78 (s, 1 H); ^{13}C NMR δ 158.0, 153.2, 138.1, 136.0, 131.4, 129.8, 129.1, 128.3, 127.8, 126.5, 123.7, 91.0, 54.1, 33.5, 29.9. Anal. Calcd for $C_{18}H_{15}NO_3$: C, 73.70; H, 5.16; N, 4.78. Found: C, 73.87; H, 5.25; N, 4.76.

General Procedure for the Conversion of the Oxalyl Adduct to the 3,4-Dihydroisoquinoline. Crude **4** from the cyclization reaction was slurried in MeOH-concentrated H_2SO_4 (19:1, ~0.1 M), and the mixture was heated at reflux until the oxalyl group had been removed (12–18 h). The progress of the reaction could be followed by HPLC: for **4b** the oxalyl adduct and the 3,4-dihydroisoquinoline eluted at 3.6 and 2.8 min, respectively (MICROSORB C-8; 60:40:0.1 CH_3CN–H_2O–trifluoroacetic acid; 1.5 mL/min; 230 nm). The mixture was cooled, and the volatiles were evaporated under vacuum. The residue was partitioned between water and isopropyl acetate. The organic layer was washed twice with 2 N HCl. The combined aqueous layers were basified with concentrated ammonium hydroxide. The product was extracted into CH_2Cl_2. The organic layer was washed with brine and dried (Na_2SO_4). The product was isolated by evaporation of the solvent.

3,4-Dihydro-3-phenylisoquinoline (5a) was purified by silica gel chromatography (ethyl acetate–hexane) and obtained in 72% overall yield from **1a**: mp 80.5–81.5 °C; IR 3100–2850, 1625, 1570, 1450, 1205 cm^{-1}; ^1H NMR δ 8.52 (d, J = 2.8, 1 H), 7.5–7.25 (overlapping m, 8 H), 7.19 (br d, J = 6.9, 1 H), 4.72 (ddd, J = 13.9, 6.0, 2.8, 1 H), 2.97 (m, 2 H); ^{13}C NMR δ 160.3, 144.0, 136.0, 131.3, 128.4, 127.4, 127.32, 127.27, 126.94, 126.92, 61.3, 33.7. Anal. Calcd for $C_{15}H_{13}N$: C, 86.91; H, 6.33, N, 6.76. Found: C, 86.91; H, 6:56; N, 6.67.

3,4-Dihydro-1-methyl-3-phenylisoquinoline (5b) was purified by silica gel chromatography (ethyl ether–hexane) and obtained in 88% overall yield from **1b**: mp 65–67 °C; IR 3100–2820, 1625, 1450, 1370, 1300, 1295 cm^{-1}; ^1H NMR δ 7.58 (m, 1 H), 7.5–7.25 (overlapping m, 7 H), 7.23 (m, 1 H), 4.58 (ddq, J = 13.4, 6.0, 1.9, 1 H), 2.93 (m, 2 H), 2.55 (d, J = 1.9, 3 H); ^{13}C NMR δ 164.5, 144.2, 136.8, 130.9, 129.3, 128.4, 127.4, 127.1, 127.0, 126.9, 125.4, 60.7, 34.6, 23.3. Anal. Calcd for $C_{16}H_{15}N$: C, 86.82; H, 6.84; N, 6.33. Found: C, 86.84; H, 7.02; N, 6.25.

1-Benzyl-3,4-dihydro-3-phenylisoquinoline (5d) was purified by silica gel chromatography (15% ethyl acetate–hexanes) and obtained in 55% overall yield from **1d** as a tan oil: as hydrochloride mp 210–211 °C; IR 3100–2820, 1620, 1600, 1570, 1490, 1450, 1300, 1280 cm^{-1}; ^1H NMR δ 7.61 (m, 3 H), 7.53–7.20 (overlapping m, 11 H), 4.75 (br dd, J = 13.9, 5.6, 1 H), 4.36 (dd, J = 14.8, 1.9, 1 H), 4.21 (d, J = 14.8, 1 H), 2.97 (m, 2 H); ^{13}C NMR δ 165.9, 144.3, 137.8, 137.4, 130.5, 128.5, 128.44, 128.42, 127.4, 127.0, 126.8, 126.3, 125.8, 60.9, 42.9, 34.9. Anal. Calcd for $C_{21}H_{19}N$·HCl: C, 78.36; H, 6.28; N, 4.35. Found: C, 78.50: H, 6.15; N, 4.15.

3,4-Dihydro-3-(3,4-dimethoxyphenyl)-6,7-dimethoxyisoquinoline (5e) was purified by silica gel chromatography (ethyl acetate–hexanes) and obtained in 63% overall yield from **1e**: mp 115.5–117 °C (lit.[2c] mp 117 °C); IR 3010–2940, 1600, 1570, 1510, 1460, 1350, 1285, 1260, 1230, 1120 cm^{-1}; ^1H NMR δ 8.38 (d, J = 2.8, 1 H), 7.08 (d, J = 2.0, 1 H), 6.96 (dd, J = 8.3, 2.0, 1 H), 6.90 (s, 1 H), 6.87 (d, J = 8.3, 1 H), 6.68 (s, 1 H), 4.60 (ddd, J = 13.4, 6.9, 2.8, 1 H), 3.93 (s, 6 H), 3.91 (s, 3 H), 3.89 (s, 3 H), 2.87 (m, 2 H); ^{13}C NMR δ 159.5, 151.4, 148.9, 148.0, 147.9, 136.9, 129.6, 121.4, 118.9, 111.0, 110.3, 61.0, 56.1, 56.0, 55.9, 55.8, 33.4. Anal. Calcd for $C_{19}H_{21}NO_4$: C, 69.70; H, 6.48; N, 4.28. Found: C, 69.79; H, 6.63; N, 4.14.

3,4-Dihydro-6,7-dimethoxy-3-(3,4-dimethoxyphenyl)-1-methylisoquinoline (5f) was purified by silica gel chromatography (ethyl acetate) and obtained in 55% overall yield from **1f** as a tan oil: mp 112–115 °C as hydrochloride–methanol solvate (methanol–ethyl ether); IR 3000–2830, 1605, 1270, 1510, 1460, 1340, 1300, 1260 cm^{-1}; ^1H NMR δ 7.06 (s, 1 H), 7.05 (d, J = 1.9, 1 H), 6.91 (dd, J = 8.3, 1.9, 1 H), 6.83 (d, J = 8.3, 1 H), 6.72 (s, 1 H), 4.59 (m, 1 H), 3.931 (s, 3 H), 3.927 (s, 3 H), 3.90 (s, 3 H), 3.85 (s, 3 H), 2.92 (m, 2 H), 2.54 (d, J = 1.9, 3 H); ^{13}C NMR δ 165.1, 151.9, 148.9, 148.1, 147.8, 135.8, 130.9, 121.6, 118.9, 111.1, 110.6, 110.3, 109.3, 59.5, 56.2, 56.0, 55.87, 55.84, 33.7, 22.8. Anal. Calcd for $C_{20}H_{23}NO_4$·HCl·CH_3OH: C, 61.33; H, 6.92; N, 3.40. Found: C, 61.52; H, 6.90; N, 3.42.

3,4-Dihydro-6,7-dimethoxy-3-phenylisoquinoline (5g) was purified by silica gel chromatography (ethyl acetate–hexanes) and obtained in 60% overall yield from **1g**. An analytical sample was prepared by recrystallization from ethyl acetate–cyclohexane: mp 103–104.5 °C (lit.[2c] mp 108 °C); IR 3100–2840, 1625, 1605, 1570, 1510, 1460, 1350, 1280, 1260, 1240, 1120 cm^{-1}; ^1H NMR δ 8.40 (d, J = 2.8, 1 H), 7.5–7.25 (overlapping m, 5 H), 6.90 (s, 1 H), 6.69 (s, 1 H), 4.67 (ddd, J = 13.4, 6.5, 2.8, 1 H), 3.93 (s, 3 H), 3.92 (s, 3 H), 2.89 (m, 2 H); ^{13}C NMR δ 159.7, 151.4, 148.0, 144.1, 129.5, 128.4, 127.0, 126.9, 121.3, 110.3, 61.3, 56.1, 56.0, 33.4. Anal. Calcd for $C_{17}H_{17}NO_2$: C, 76.37; H, 6.42; N, 5.24. Found: C, 76.31; H, 6.47; N, 5.06.

3,4-Dihydro-6,7-dimethoxy-1-methyl-3-phenylisoquinoline (5h) was purified by silica gel chromatography (ethyl acetate) and obtained in 79% overall yield from **1h** as a tan oil: mp 195–196 °C as hydrochloride (ethyl ether); IR 3100–2820, 1625, 1610, 1570, 1510, 1465, 1370, 1340, 1300, 1265, 1210, 1160, 1060 cm^{-1}; ^1H NMR δ 7.5–7.25 (overlapping m, 5 H), 7.06 (s, 1 H), 6.69 (s, 1 H), 4.55 (ddq, J = 13.4, 6.5, 2.0, 1 H), 3.94 (s, 3 H), 3.93 (s, 3 H), 2.85 (m, 2 H), 2.49 (d, J = 2.0, 3 H); ^{13}C NMR δ 164.0, 151.1, 147.6, 144.2, 130.5, 128.4, 127.0, 126.8, 122.2, 110.2, 109.0, 60.8, 56.2, 55.9, 34.2, 23.3. Anal. Calcd for $C_{18}H_{19}NO_2$·HCl: C, 68.23; H, 6.36; N, 4.41. Found: C, 67.98; H, 6.57; N, 4.40.

3,4-Dihydro-3-(3,4-dimethoxyphenyl)isoquinoline (5i) was purified by silica gel chromatography (ethyl acetate) and obtained in 25% overall yield from **1i** as an oil: IR 3160–2830, 1620, 1510, 1460, 1250 cm^{-1}; ^1H NMR δ 8.48 (d, J = 2.8, 1 H), 7.45–7.3 (m, 3 H), 7.18 (br d, J = 6.9, 1 H), 7.02 (d, J = 1.9, 1 H), 6.96 (dd, J = 7.9, 1.9, 1 H), 6.87 (d, J = 7.9, 1 H), 4.65 (ddd, J = 13.4, 6.5, 2.8, 1 H), 3.91 (s, 3 H), 3.89 (s, 3 H), 2.95 (m, 2 H); ^{13}C NMR δ 160.2, 148.9, 147.9, 136.6, 136.0, 131.3, 128.3, 127.4, 127.30, 127.26, 118.8, 111.0, 110.2, 60.8, 55.9, 55.8, 33.7. Anal. Calcd for $C_{17}H_{17}NO_2$: C, 76.37; H, 6.42; N, 5.24. Found: C, 76.00; H, 6.49; N, 5.15.

3,4-Dihydro-1-methylisoquinoline (5j) was purified by silica gel chromatography (ethyl acetate) and obtained in 82% overall yield from **1j**: mp 191–192 °C (lit.[23] mp 188–190 °C) as picrate salt (ethanol).

3,4-Dihydro-6,7-dimethoxy-1-methylisoquinoline (5k) was purified by silica gel chromatography (1% triethylamine–ethyl acetate) and obtained in 80% overall yield from **1k**. A sample was recrystallized from hexanes: mp 102–103 °C (lit.[24] mp 104–105 °C).

7-Chloro-3,4-dihydro-1-methylisoquinoline (5l) was purified by silica gel chromatography (ethyl acetate) and obtained in 92% overall yield from **1l**: mp 33–34.5 °C; mp 213–214.5 °C as hydrochloride (ethyl ether–ethanol; 9:1); mp 205–205.5 °C (lit.[25] 197–198 °C) as picrate (ethanol).

(*R*)-(–)-1,2-Diphenylethylamine. To a solution of (+)-tartaric acid (7.6 g, 50.7 mmol) in water (250 mL) was added (±)-1,2-diphenylethylamine (10.0 g, 50.7 mmol) over 5 mim. From the

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mixture crystals of the amine-tartrate began to form. The mixture was well-stirred for 28 h. The solid was filtered, washed with isopropyl alcohol (25 mL), and suction dried. The amine was isolated by addition of the salt to a mixture of CH_2Cl_2 (100 mL) and 2.5 N NaOH (200 mL). The layers were separated, and the aqueous layer was washed with CH_2Cl_2 (100 mL). The combined organic layers were washed with brine (50 mL) and dried (Na_2SO_4). The filtered solution was concentrated to dryness (2.45 g, 49% yield of theory): $[\alpha]^{25}D$ -44.64° (c 2, ethanol) [lit.[26] $[\alpha]^{25}D$ -45° (c 2, ethanol)]. The amine was found to be 98.4:1.6 *R/S* by assay as the benzamide on a chiral Pirkle L-phenylglycine covalent column: hexanes-CH_2Cl_2-isopropyl alcohol (80:15:5); 1.5 mL/min; 230 nm; *S* enantiomer, 7.99 min; *R* enantiomer, 8.9 min.

***N*-((*R*)-1,2-Diphenylethyl)acetamide (1b).** The (*R*)-(-)-1,2-diphenylethylamine (2.29 g, 11.6 mmol) was acylated with acetic anhydride as for the racemate **1b** (2.68 g, 96%). A sample was purified by recrystallization from ethyl acetate-cyclohexane: mp 163.5-164.5 °C (lit.[12] mp 166-167 °C); $[\alpha]^{25}D$ 14.7° (c 2.2, ethanol) [lit.[12] $[\alpha]^{18}D$ 35.7° (c 1.5, ethanol)].

(*R*)-3,4-Dihydro-1-methyl-3-phenylisoquinoline (5b). The chiral acetamide **1b** (0.505 g, 2.11 mmol) was cyclized and the resultant oxalyl adduct converted to the 3,4-dihydroisoquinoline **5b** (0.417 g, 89% yield). The material was purified by column chromatography (silica gel, ethyl acetate/hexanes): mp 91-93 °C; $[\alpha]^{24}D$ 126° (c 2.05, ethanol). The enantiomeric ratio of the material was obtained by conversion of the 3,4-dihydroisoquinoline to the enamide: The imine (56.1 mg, 0.25 mmol) was dissolved in CH_2Cl_2 (5 mL). Triethylamine (37 μL, 0.27 mmol) and benzoyl chloride (31 μL, 0.27 mmol) were added separately and sequentially at room temperature. The mixture was stirred at room temperature for 1 h. The volatiles were removed by evaporation, and the residue was taken up in toluene (5 mL). The salts were filtered, and the filtrate was concentrated under vacuum. The residue was assayed on a Pirkle L-phenylglycine covalent column: 80:20:1 hexanes-CH_2Cl_2-isopropyl alcohol; 1.5 mL/min; 230 nm; *S* enantiomer, 7.1 min; *R* enantiomer, 8.3 min. The material was a 98.5:1.5 *R/S* mixture, indicating no epimerization of the chiral center.

3-Carbomethoxy-3,4-dihydro-1-methylisoquinoline (5n) was isolated as a light orange oil in 77% yield by silica gel chromatography (hexanes-ethyl acetate (1:1)). The material was shown to be racemic by conversion of the imine to the *N*-benzoyleneamide as for (*R*)-**5b** and assay on a Pirkle L-phenylglycine covalent column (hexanes-CH_2Cl_2-ethanol (90:10:2)): mp 175-176 °C dec as hydrochloride (ethanol-ethyl ether); IR 3100-2850, 1730, 1625, 1435, 1285, 1255, 1205, 1170 cm^{-1}; ^1H NMR δ 7.51 (br d, *J* = 7.4, 1 H), 7.38 (m, 1 H), 7.31 (m, 1 H), 7.21 (br d, *J* = 7.4, 1 H), 4.19 (m, 1 H), 3.82 (s, 3 H), 2.96 (m, 2 H), 2.45 (d, *J* = 2.3, 3 H); ^{13}C NMR δ 173.3, 165.8, 135.4, 131.1, 129.1, 127.5, 127.3, 125.6, 59.8, 52.4, 28.3, 23.3. Anal. Calcd for $C_{12}H_{14}ClNO_2$: C, 60.12; H, 5.90; N, 5.84. Found: C, 59.88; H, 5.85; N, 5.82.

Supplementary Material Available: Experimental procedures and data for the synthesis of the ketones and amides 1 (9 pages). Ordering information is given on any current masthead page.

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Five-, Four-, and Three-Membered Carbocyclic Rings from 2-Deoxyribose by Intramolecular Nucleophilic Displacement Reaction

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1,3-Dithianes such as **4**, **9**, **11**, **13**, and **19** derived from 2-deoxy-D-ribose (**1**) undergo intramolecular displacement reactions to give three-, four-, and five-membered carbocyclic rings (**5**, **10**, **12**, **15**, and **20**). Cyclopropanes are favored over the cyclobutanes when starting from the epoxides **9** or **11**. Treatment of the tosylate **19** gives only a small yield of the corresponding cyclobutane **20**, the major product being the ketone **21**.

Introduction

Carbohydrates are useful starting materials for the synthesis of enantiomerically pure noncarbohydrate compounds.[1a-e] The construction of carbocyclic derivatives from sugars is particularly interesting because many important classes of compounds such as prostaglandins,[2] terpenes,[3] pheromones,[4] antibiotics,[5] antiviral compounds,[6] nucleic acid derivatives,[7] and pseudo sugars[8] that are potential enzyme inhibitors[9] can be prepared in enantiomerically pure form.

In many cases, the carbocyclic framework is constructed by cycloaddition reactions and the carbohydrate serves merely as a chiral template. Methods for the conversion of a carbohydrate to a carbocycle involving predominantly the carbon atoms of the starting sugar are rare,[10] and only

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