then removed under reduced pressure. The residue was chromatographed on silica gel eluted with 50% ethyl acetate in hexane to give 1.45 g (96%) of phenol **34a**: R_f 0.22 (in 25% acetone in methylene chloride); NMR 0.73-3.07 (m, 26 H), 3.23-3.97 (m, 2 H), 6.00-6.53 (m, 1 H), 6.63-6.90 (m, 2 H) 6.93-7.17 (m, 1 H); IR (film) 3285, 1590, 1465, 1375, 1340, 1285, 1265, 1240, 1215, 1085, 1065, 1045, 1025, 975, 890, 775, 745, 735, 720 cm^{-1}; mass spectrum, calcd for $C_{31}H_{56}O_3Si_3$ [M + of tris(trimethylsilyl) derivative] *m/e* 560.3537, found *m/e* 560.3524. Anal. Calcd for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 74.27; H, 9.29.

2-Cyano-15-cyclohexyl-2-decarboxy-9-deoxy-13,14-dihydro-2',9α-methano-4,5,6,16,17,18,19,20-octanor-3-oxa-3,7-(1',3'-*inter*-phenylene)-PGF$_1$ (34b). A solution of 1.31 g (3.80 mmol) of phenol **34a**, 11.3 g (81.5 mmol) of anhydrous potassium carbonate, and 8.79 mL (139 mmol) of chloroacetonitrile in 40 mL of acetone was refluxed for 48 h, cooled, and partitioned between 1:1 brine-water and ethyl acetate. The organic extract was washed with brine and dried (Na_2SO_4). The solvents were removed under reduced pressure, and the residue was chromatographed on silica gel eluted with 50% ethyl acetate in hexane to give 1.33 g (91%) of nitrile **34b**: R_f 0.40 (in 20% acetone in methylene chloride); NMR δ 0.73-3.00 (m, 26 H), 3.17-3.93 (m, 2 H), 4.77 (s, 2 H), 6.73-7.03 (m, 2 H), 7.17 (dd, $J_1 = J_2 = 7.5$ Hz, 1 H); IR (mull) 3330, 2240, 1725, 1685, 1605, 1585, 1445, 1275, 1235, 1175, 1110, 1080, 1025, 975, 890, 775 cm^{-1}; mass spectrum, calcd for $C_{24}H_3NO_3$ *m/e* 383.2475, found *m/e* 383.2460. Anal. Calcd for $C_{24}H_{33}NO_3$: C, 75.16; H, 8.67; N, 3.74. Found: C, 75.13; H, 8.59; N, 3.51.

15-Cyclohexyl-9-deoxy-13,14-dihydro-2',9α-methano-4,5,6,16,17,18,19,20-octanor-3-oxa-3,7-(1',3'-*inter*-phenylene)-PGF$_1$ (3). A solution of 0.97 g (2.53 mmol) of nitrile **34b** and 17 mL of 25% aqueous sodium hydroxide in 58 mL of methanol was stirred at reflux for 6 h, cooled to 0 °C, acidified to pH 5 with 1 M aqueous hydrochloric acid, and partitioned between ethyl acetate and brine. The organic extract was dried (Na_2SO_4), and the solvents were removed in vacuo to give **3** as a light-yellow solid. Recrystallization from ethyl acetate and hexane afforded 0.95 g (93%) of **3** (U-68,215) as a white solid (identical in all respects with authentic material prepared previously by an unambiguous route[2]): mp 119-120 °C; R_f 0.54 (in the organic phase of an equilibrated mixture of 9:2:5:10 ethyl acetate-acetic acid-cyclohexane-water); NMR (CD_3COCD_3) δ 0.70-4.00 (m, 29 H), 4.68 (s, 2 H), 6.60-6.90 (m, 2 H), 7.10 (dd, $J_1 = J_2 = 7.5$ Hz, 1 H); IR (mull) 3380, 1735, 1710, 1605, 1590, 1455, 1420, 1375, 1260, 1255, 1105, 1085, 1025, 1015, 910, 895, 775, 740 cm^{-1}; mass spectrum, calcd for $C_{33}H_{58}O_5Si_3$ [M + of tris(trimethylsilyl) derivative] *m/e* 618.3592, found *m/e* 618.3576; $[\alpha]_D$ +41° (*c* 0.864, 95% EtOH). Anal. Calcd for $C_{24}H_{34}O_5$: C, 71.61; H, 8.51. Found: C, 71.71; H, 8.63.

Acknowledgment. Helpful discussions and observations by Dr. J. M. Timko of The Upjohn Co. concerning the equilibration-reduction step (**30** → **32a**) are gratefully acknowledged. We thank R. L. Johnson, R. A. Morge, and J. H. Kinner of The Upjohn Co. for the preparation of intermediates.

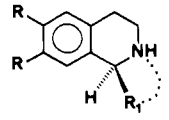
Asymmetric Synthesis of 2-Alkylpyrrolidines and Piperidines. Synthesis of (+)-Metazocine

A. I. Meyers,* Daniel A. Dickman, and Thomas R. Bailey

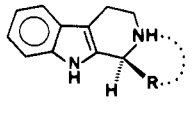
Contribution from the Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523. *Received July 1, 1985*

Abstract: Asymmetric alkylation of piperidines and pyrrolidines in the 2-position was efficiently accomplished by using a chiral formamidine derived from L-valinol. Since the saturated ring systems could not be metalated due to high pK_a's, the unsaturated systems were employed which possessed allylic protons. After asymmetric alkylation was complete (a mixture of 8-30% SN_2' alkylation was also observed), the formamidines were removed to give 2-alkylpyrrolines and 2-alkyltetrahydropyridines. Reduction of the unsaturation using Rh/C furnished the piperidine and pyrrolidine in 95-98% ee. Application of this method to the benzomorphan (+)-metazocine was also accomplished in 98% ee.

Our previous successes with asymmetric alkylation of tetrahydroisoquinolines **1**[1] and β-carbolines **2**[2] via chiral formamidines have led us to explore similar processes with simple saturated heterocycles such as pyrrolidine and piperidine. If this extension



1, R = H, R_1 = alkyl, cycloalkyl



2, R = alkyl, cycloalkyl

of the process was successful, a route to a variety of piperidine and pyrrolidine alkaloids and other important substances would be accessible.[3] However, the extension to simple saturated heterocycles was not routine and required major modification via an alternative approach. The successful implementation of this process forms the subject of this report.

As previously reported, the *tert*-butylformamidines of pyrrolidine and piperidine **3** are readily metalated with *tert*-butyllithium and, after conversion to the mixed cuprates, give high yields of alkylated products, **5**.[4] When these saturated heterocycles were transformed into formamidines **4** derived from L-valinol,[1,2] in an attempt to generate the α-lithioanions in a chiral environment, no metalation occurred at −78 °C, and as the temperature was allowed to warm to ~−45 °C, only addition of *t*-BuLi to the C=N link of the formamidine **6** took place. It was soon apparent that the oxygen ligand in the formamidine **4** was responsible for a complex with the lithium base **7**, which kept the latter at a distance such that the α-proton could not be satisfactorily removed. As the temperature was allowed to rise, the *t*-BuLi merely added to the formamidine π-system. Of further significance is the high pK_a for the α-protons in **3** and **4** relative to those in **1** and **2** which have been successfully deprotonated by using the chiral formamidines. The higher pK_a of **3** and **4** (no deprotonation at −78 °C) must, therefore, open up the alternative reaction path leading to **6**.

The failure to metalate **4** prompted us to incorporate an "activating element" such that the pK_a of the α-proton would be within the range of a common base. Toward this end, the 3-

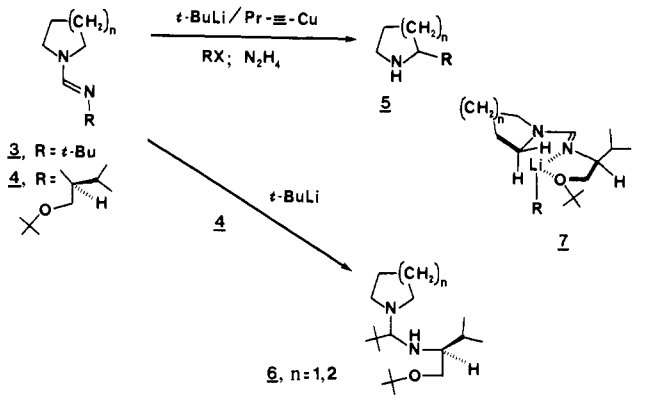
(1) (a) Meyers, A. I.; Boes, M.; Dickman, D. A. *Angew. Chem., Int. Ed. Eng.* **1984**, *23*, 448. (b) Meyers, A. I.; Fuentes, L. M. *J. Am. Chem. Soc.* **1983**, *105*, 117. (c) Meyers, A. I.; Fuentes, L. M.; Kubota, Y. *Tetrahedron* **1984**, *40*, 1361.

(2) Loewe, M. F.; Meyers, A. I. *Tetrahedron Lett.* **1985**, *26*, 3291.

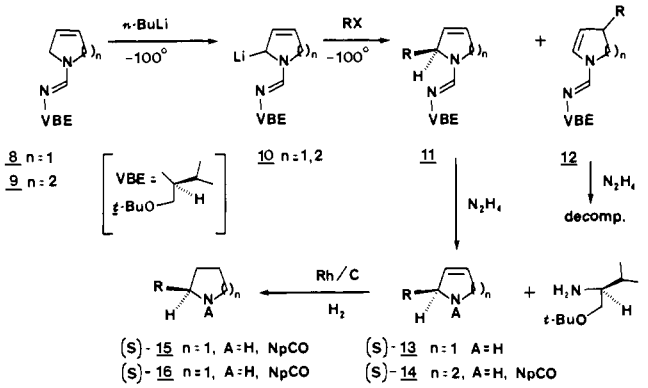
(3) Guerrier, L.; Royer, J.; Grierson, D. S.; Husson, H.-P. *J. Am. Chem. Soc.* **1983**, *105*, 7754.

(4) Meyers, A. I.; Edwards, P. D.; Rieker, W. F.; Bailey, T. R. *J. Am. Chem. Soc.* **1984**, *106*, 3270.

0002-7863/85/1507-7974$01.50/0



pyrroline **8** and the 1,2,5,6-tetrahydropyridine **9** formamidines were prepared by direct exchange in toluene at reflux with the amines and (*S*)-*N*,*N*-dimethyl-*N'*-(*tert*-butoxy-2-amino-3-methylbutyl)formamidine,[1] in 80–85% yield. Treatment of **8** with



n-butyllithium (−100 °C, THF) gave *complete deprotonation to the orange anion* **10** *in 5–7 min*, and this was followed by addition of a 20% solution of alkyl halide in THF (−100 °C, dropwise). After complete alkylation, the solution was quenched with excess methanol to give a 92:8 mixture (NMR of vinyl signals) of **11** and **12**. The latter arises from allylic transposition. It was not necessary to separate this mixture since hydrazinolysis gave only the 2-substituted 3-pyrroline, **13** (A = H), in 76% overall yield from **8**. The minor product **12** had decomposed during the hydrazinolysis and could not be isolated nor identified. Presumably the 2-pyrroline, under these conditions, polymerized or gave water soluble products. Also recovered along with **13** was an 80–85% yield of the *l*-valinol *t*-butyl ether, which was separated by bulb-to-bulb distillation and may be reused. Reduction of **13** with 5% Rh/C afforded the 2-substituted pyrrolidines **15** (A = H) in 95–96% ee. The enantiomeric purity was assessed on the naphthamide **15** (A = NpCO) by HPLC analysis using the chiral Pirkle column[5] (Table I). Use of Rh/C for the reduction to **15** proceeds without racemization, whereas Pd/C or $LiAlH_4$–$CoCl_2$ led to 5–10% racemization.

In a similar manner, the formamidine of tetrahydropyridine **9** was metalated with 1.1 equiv of *n*-BuLi (−78 °C, THF) in the presence of various electrophiles to give mixtures of 2- and 4-substituted derivatives (Table I). Unfortunately, the ratios **11**/**12** (n = 2) were not as high as in the pyrrolidine cases. Nevertheless, hydrazine treatment, as above, gave only a single product, **14** (A = H). Although the chemical yields of **14** were somewhat lower, the fact that **12** (n = 2) decomposes and is completely absent in the workup still makes this an attractive procedure. Transformation of **14** (A = H) to its 1-naphthoyl derivative **14** (A = NpCO) and HPLC analysis on the chiral Pirkle column indicated that the reaction had proceeded in 91–96% ee, when compared to racemic material of **14** (A = NpCO). Catalytic hydrogenation, as above, gave the 2-substituted piperidines **16** (A = H) in 70–80%

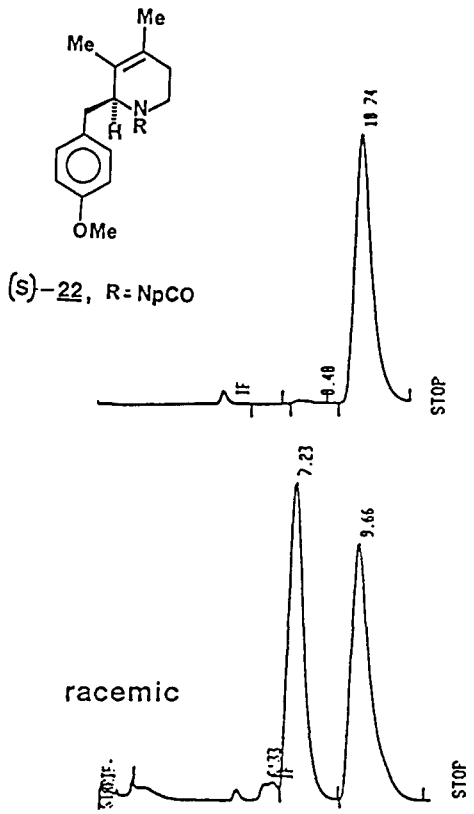


Figure 1. HPLC traces on chiral column for racemic and synthetic **22**.

yields, and these products were again transformed into their naphthamides **16** (A = NpCO) and analyzed for enantiomeric purity. The % ee was identical within limits of detection to the tetrahydropyridines **14**, confirming that no racemization occurs when a Rh/C catalyst is employed. The absolute configuration of **15** and **16** (A = H) is assigned as *S*, based on literature precedent.[6] All the known (*S*)-alkylpyrrolidines and (*S*)-alkylpiperidines possess a positive rotation, and this was also observed in the present study.

It is important to state that the facile metalation observed with **8** and **9**, in comparison to the inertness of the saturated derivatives **4** (n = 1, 2), indicates that allylic activation appears to be the major factor toward proton removal. This would imply that the "axially" situated proton in **7** is removed by the base and is consistent with our earlier observations[7] in the isoquinoline and β-carboline series.

As a demonstration of this asymmetric C–C bond-forming reaction, we have prepared (+)-metazocine, a potent analgesic[8] shown in Scheme I. Starting with 3,4-lutidine (**17**), transformation to 3,4-dimethyl-1,2,5,6-tetrahydropyridine (**18**) was carried out as shown. The latter was exchanged with the chiral valinol formamidine to give **19** ($[\alpha]^{25}_D$ −51.6°) which was metalated and alkylated with *p*-methoxybenzyl chloride (−100 °C, THF) to give a 2:1 mixture of 2- and 4-substitution (**21**) in 97% combined yield. Radial chromatography separation gave 50% pure 2-substituted material which was subjected to hydrazine treatment, furnishing **20** ($[\alpha]^{25}_D$ −88°) in 44% overall yield from **19**. HPLC analysis of the naphthamide **22** on the Pirkle column showed that **20** was greater than 98% enantiomerically pure (Figure 1). Methylation, via the formamide, gave the *N*-methyl derivative **23** ($[\alpha]^{25}_D$ −6.8°), and Grewe cyclization with HBr[9] afforded (+)-metazocine (**24**)

(5) Pirkle, W. H.; Welch, C. J.; Mahler, G. S.; Meyers, A. I.; Fuentes, L. M.; Boes, M. *J. Org. Chem.* **1984**, *49*, 2504.

(6) Archer, J. F.; Boyd, D. R.; Jackson, W. R.; Grundon, M. F.; Khan, W. A. *J. Chem. Soc. C* **1971**, 2560. It was noted using the chiral HPLC column that the *S*-enantiomer always eluted after the *R*-enantiomer in racemic mixtures (c.f. ref 8 above).

(7) Loewe, M. F.; Boes, M.; Meyers, A. I. *Tetrahedron Lett.* **1985**, *26*, 3295.

(8) May, E. L.; Eddy, N. B. *J. Org. Chem.* **1959**, *24*, 1435.

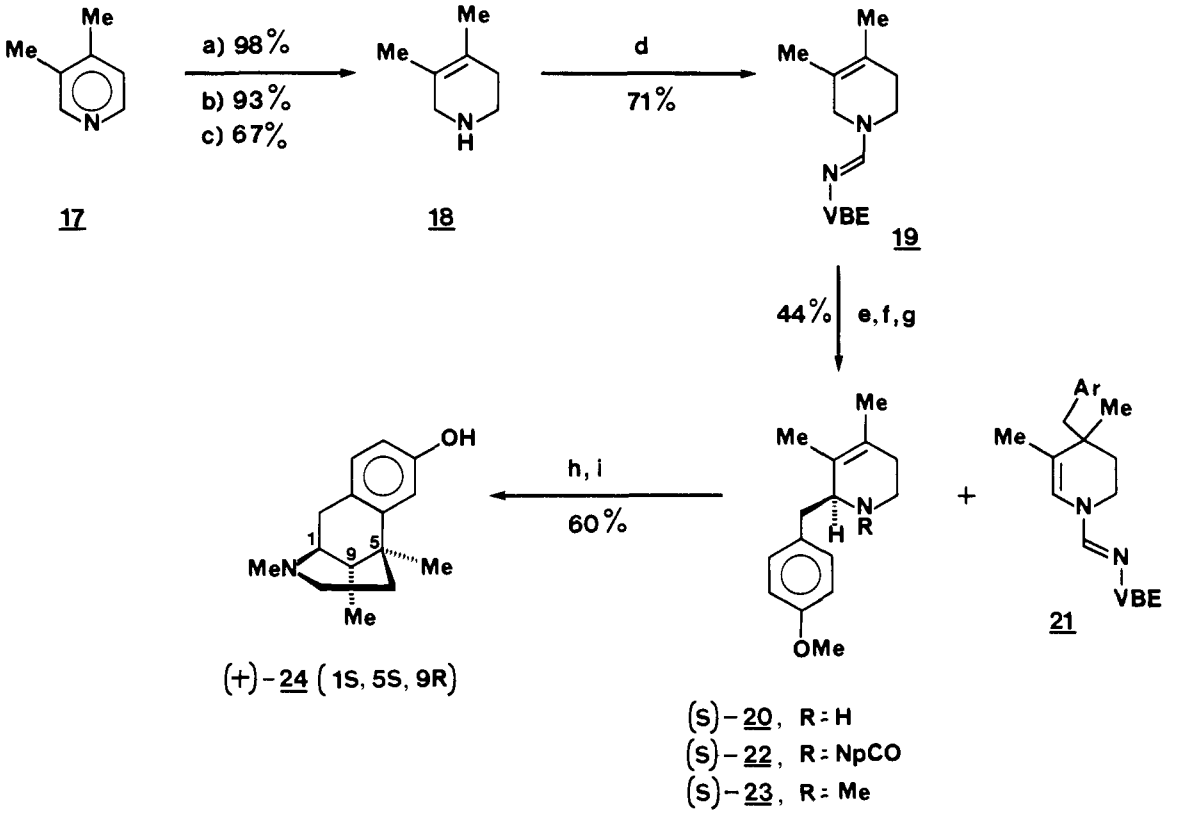
(9) Grewe, R. *Angew. Chem.* **1947**, *59*, 194.

Table I. Alkylation of 3-Pyrrolines **8** and 1,2,5,6-Tetrahydropyridines **9**

formamidine	Rx	ratio[a] **11/12**	overall yield (A = H)	% ee[b]	% yield (A = H)	% ee[b]	$[\alpha]^{25}_D$ (*c*, solv)
8	*n*-HeptBr	92:8	**13**, 64		**15**, 78	96	+5.69 (2.83, THF)
8	$Ph(CH_2)_3Br$	92:8	**13**, 76		**15**, 81	95	+7.61 (2,26, THF)
9	$PhCH_2Cl$	2:1	**14**, 48	96	**16**, 70	96	+0.2 (5.6, Et_2O)
9	*n*-HeptBr	2.3:1	**14**, 71	92	**16**, 77	92	+7.4 (1.7, Et_2O)
9	$Ph(CH_2)_3Br$	2:1	**14**, 69	91	**16**, 77	91	+7.0 (2.0, Et_2O)

[a] Determined by NMR integration of vinyl proton **11** (δ 5.75), **12** (δ 6.25). [b] Determined using J. T. Baker Dinitrophenyl Glycine Covalent HPLC column (RP-7113-0) and eluting with 5% *i*-PrOH–hexane. These ratios were compared to those of the racemic material prepared by alkylation of **3**.

Scheme I



(a) Benzyl bromide, acetone, reflux. (b) $NaBH_4$, EtOH, H_2O. (c) PhOCOCl, CH_2Cl_2, 25 °C; KOH, 18-crown-6, THF. (d) *N,N*-(*tert*-butoxy-2-amino-3-methylbutyl)formamidine, toluene, reflux. (e) *n*-BuLi, 3 equiv of *p*-$MeOC_6H_4CH_2Cl$, −78 °C, THF. (f) Radial chromatography, 5% Et_3N–hexane, silica gel. (g) N_2H_4–HOAc–EtOH (8:3:7), 50 °C. (h) EtO_2CH, $LiAlH_4$. (i) 48% HBr, 135 °C.

in 60% yield, $[\alpha]^{25}_D$ 81.3°, mp 178–180 °C [lit.[10] $[\alpha]^{25}_D$ 84.3°, mp 183–184 °C]. Since β-(+)-metacozine is known to have the 1*S*,5*S*,9*R* configuration, it further supports our assignment of the absolute configuration in the alkylation step as being *S*. Other benzomorphan derivatives have been prepared via this approach and will be reported in due course.

Experimental Section

(*S*)-*N*,*N*-Dimethyl-*N*′-(*tert*-butoxy-2-amino-3-methylbutyl)formamidine. (a) L-valinol. To a suspension of lithium aluminum hydride (14.6 g, 0.384 mol) in 330 mL of dry THF at room temperature was carefully added 30 g (0.256 mol) of L-valine. The reaction mixture was refluxed for 16 h and after cooling was poured into 250 mL of diethyl ether. To the ether layer was added slowly 15 mL of water, followed by 15 mL of 15% aqueous NaOH solution and 45 mL of water. The solution was filtered, and the precipitate was washed with ether. The organic layers were combined and dried over anhydrous K_2CO_3. Bulb-to-bulb distillation (50 °C; 0.1 torr) provided the product as a white solid (22.9 g, 87%) $[\alpha]^{25}_D$ +17.0° (c = 11.53)(in ethanol: ^1H NMR ($CDCl_3$) δ 0.95 (6 H, d, J = 6 Hz), 1.6 (1 H, m), 2.3 (3 H, br s), 2.6 (1 H, m), 3.5 (2 H, m).

(b) *N*-Formylvalinol. A solution of 13.0 g (0.126 mol) of L-valinol and 11.5 g (1.1 equiv) of ethyl formate was refluxed for 4 h under reflux. Concentration under vacuum afforded 16.6 g (100%) of the formamide as a viscous oil which crystallized upon standing: ^1H NMR ($CDCl_3$) δ 1.0 (6 H, d, J = 7 Hz), 1.8 (1 H, m), 3.4 (1 H, br s), 3.7 (3 H, m), 6.4 (1 H, v br m), 8.35 (1 H, m).

A solution containing 6.056 g (45.8 mmol) of *N*-formylvalinol in 100 mL of dioxane was placed in a pressure bottle equipped with a large stirring bar at 0 °C. The bottle was then charged with 60 mL (excess) of isobutene, and 18 mL of BF_3·Et_2O was added via syringe. The pressure bottle was sealed, and the cloudly reaction mixture was allowed to stir vigorously at room temperature. After 30 min, the solution became homogeneous and colorless, and the mixture was allowed to stir an additional 2.5 h. The excess isobutene was vented carefully, and the reaction mixture was taken up in CH_2Cl_2. Cautiously, 1 N KOH solution was added to the organic phase in a separatory funnel for neutralization, and the organic layer was washed several times with 1 N KOH solution. Upon drying over K_2CO_3, the solvent was removed under vacuum to afford 8.523 g (78%) of the *O*-*tert*-butylvalinol formamide as a viscous yellow oil. The crude product was then dissolved in 25 mL of ethanol and a 50% aqueous KOH solution (12.6 g of KOH; 12.6 mL of H_2O) and was refluxed under argon for 24 h. Upon cooling, the reaction mixture was extracted with ether, and the organic phase was washed with saturated $NaHCO_3$ solution. After drying over anhydrous K_2CO_3, the ether and ethanol were very carefully removed *cold* under vacuum (~20 mmHg) to provide the crude primary amine. To the amine was added 8.4 mL (63.2 mmol) of *N*,*N*-dimethylformamide dimethyl acetatl at room temperature, and the reaction mixture was allowed to stir under

(10) Casy, A. F.; Parulkar, A. P. *J. Med. Chem.* **1969**, *12*, 178.

argon at ambient temperature for 16 h. The solution was concentrated in vacuo and the crude product was subjected to bulb-to-bulb distillation (0.05 mmHg, 55–65 °C) which provided 7.84 g (81%) of the titled compound as a colorless liquid: IR (film) 1660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.23 (s, 1 H), 2.81 (s, 6 H), 1.16 (s, 9 H), 0.86 (d, J = 6.7 Hz, 3 H), 0.85 (d, J = 6.7 Hz, 3 H); $[\alpha]^{25}_D$ −15.9° (*c*, 0.98, THF).

Formamidine of 3-Pyrrolidine, 8. To a stirred solution of *N'*-(2*S*)-*tert*-butoxy-2-amino-3-methylbutyl-*N,N*-dimethylformamidine (7.621 g, 35.61 mmol) in 4 mL of toluene (2.7 g, 40.0 mmol) of 3-pyrroline (Aldrich contains 22% pyrrolidine) were added. The solution was heated at reflux under argon for 24 h. The crude reaction mixture was concentrated on a rotary evaporator and was purified on aluminum oxide (pH −8.1, Baker) column by elution with 10% EtOAc and 10% Et_3N in hexane. The resulting compound was distilled bulb-to-bulb at 130 °C (pot temperature), 0.45 torr, yielding 5.55 g of a clear liquid, 23.3 mmol, 83% yield; $[\alpha]^{25}_D$ −16.26° (*c* 1.79, THF); ^1H NMR (270 MHz, $CDCl_3$) δ 7.52 (s, 1 H), 5.82 (s, 2 H), 4.18 (s, 4 H), 3.57–3.52 (m, 1 H), 3.24–3.18 (m, 1 H), 2.73–2.67 (m, 1 H), 1.87–1.80 (m, 1 H), 1.16 (s, 9 H), 0.88 (d, 6 H, J = 6.75 Hz); IR (neat) 3070, 2975, 2920, 2863, 2835, 1657, 1621, 1475, 1410, 1375, 1360, 1348, 1300, 1197, 1077, 1015, 997, 880, 660 cm^{-1}. ^{13}C NMR (67.6 MHz, $CDCl_3$) δ 151.2, 126.1, 72.4, 71.7, 65.2, 53.8, 30.4, 27.8, 20.2, 18.3.

Metalation and Alkylation of 8—General Procedure. To a stirred solution of the formamidine **8** (0.05 M in THF) at −100 °C 1.03 equiv of *n*-butyllithium was added. The resulting solution was allowed to stir at −100 °C for 5–7 min, which by this time had become deep orange. A 20% solution, 1.03 equiv, of the alkyl halide in THF was added dropwise. The solution was allowed to stir an additional 20 min at this temperature before being quenched with MeOH. The reaction mixture was partitioned between 50 mL of dichloromethane and 50 mL of H_2O. This was followed by two additional extractions with dichloromethane. The combined organic layers were washed with brine, dried over K_2CO_3, and concentrated to a yellow oil, which was subjected to hydrazinolysis without further purification.

Hydrazinolysis of the 3-Pyrrolinylformamidines 11 and 12 (*n* = 1, 2—General Procedure. To a stirred solution of the crude alkylated formamidines **11** and **12** (n = 1,2) dissolved in an EtOH/H_2O solution (65:35) 4.0 equiv of H_2NNH_2 followed by 4.0 equiv of HOAc was added. The resulting solution was allowed to stir at 55 °C for 5.5 h under an argon atmosphere. The homogeneous solution was partitioned between saturated $NaHCO_3$ and dichloromethane and was extracted twice more with dichloromethane. The combined organic layers were washed with brine, dried over K_2CO_3, and concentrated to yield a yellow oil. The auxiliary and the 2-substituted 3-pyrroline or tetrahydropyridine was separated by distilling them apart at *reduced* pressure (bulb-to-bulb, 80 °C, 20 torr). The product arising from the cleavage of **12** (n = 1,2) was selectively destroyed and did not distill over. The second fraction, **13** or **14** (A = H), was found to be 85–90% pure by VPC. These crude products were subsequently reduced without further purification.

Reduction of 13 and 14 (A = H). To a stirred solution of the amine (0.02 M in methanol) a catalytic amount of 5% rhodium on carbon (1:20 catalyst/substrate) was added. The resulting solution was pressurized (50 psi) with H_2 and was allowed to stir an ambient temperature for a minimum of 5 h. The pressure bottle was opened, and the catalyst was removed by vacuum filtration. The solution was concentrated under reduced pressure and distilled bulb-to-bulb, which yielded the 2-substituted pyrrolidines that were 95+% pure by GC. These compounds were purified by preparative VPC (10% DC-710, 2% KOH, Chromosorb P) to yield 99+% pure compounds for final characterization.

Optical Purity Determinations (HPLC, via Pirkle Column)—Preparation of α-Naphthamides 14, 15, and 16 (A = NpCO)—General Procedure. To a stirred solution (0.1 M) of the amines **13**, **14**, and **15** (A = H) in dry dichloromethane at ambient temperature, 5 equiv of triethylamine followed by 1.5 equiv of α-naphthoyl chloride was added. The solution was allowed to stir at ambient temperature overnight. The reaction was worked up by partitioning the crude reaction mixture between dichloromethane and 10% aqueous KOH. The aqueous layer was extracted with 2 × 50 mL portions of dichloromethane. The combined organic layers were washed with brine, dried over K_2CO_3, and concentrated, yielding a yellow solid, which was purified on a silica gel plate with 25% EtOAc and 75% hexanes as the elution solvent.

The optical purity of the 2-substituted pyridines or pyrrolidines was determined by injecting the naphthamide onto a Baker dinitrophenylglycine Covalent HPLC column No. RP-7113-0, with 5% 2-propanol in hexane as the elution solvent. The HPLC instrument used was the Waters 440; and the flow rate was 3.0 mL/min. In order to achieve base-line separation, the compounds, on occasion, had to be recycled 2–3 times through the HPLC column.

(*S*)-2-(3-phenylpropyl)pyrrolidine 15: bp 120 °C (0.03 torr, pot temperature); $[\alpha]^{25}D$ +7.61° (*c* 2.26, THF); % ee = 95%; ^1H NMR (270 MHz, $CDCl_3$) δ 7.32–7.12 (m, 5 H), 3.05–2.78 (m, 3 H), 2.63 (t, 2 H, J = 7.45 Hz), 2.20–2.00 (br s, 1 H), 2.00–1.16 (m, 8 H); IR (neat) 3580–3150, 3082, 3062, 2930, 2860, 1740, 1670, 1650, 1603, 1498, 1452, 1400, 740, 692 cm^{-1}; ^{13}C NMR (67.6 MHz, $CDCl_3$) δ 142.4, 128.3, 128.1, 125.5, 59.1, 46.4, 36.1, 36.0, 31.8, 29.1, 25.3.

(*S*)-2-Heptylpyrrolidine 15: bp 105 °C (20 torr, pot temperature); $[\alpha]^{25}_D$ +5.69° (*c* 2.83, THF); % ee = 96; ^1H NMR (270 MHz, $CDCl_3$) δ 3.07–2.82 (m, 3 H), 2.52–2.28 (br s, 1 H), 1.94–1.67 (m, 4 H), 1.57–1.24 (m, 12 H), 0.88 (t, 3 H, J = 6.59 Hz); IR (neat) 3490–3100, 2950, 2920, 2874, 1610, 1530, 1455, 1392, 1183, 1110, 1075, 795, 709 cm^{-1}; ^{13}C NMR (67.6 MHz, $CDCl_3$) δ 59.5, 46.6, 36.6, 32.0, 31.9, 29.8, 29.3, 27.5, 25.5, 22.6, 13.9.

Formation of 1,2,5,6-Tetrahydropyridineformamidine 9. A solution of 0.490 g (5.9 mmol) of 1,2,5,6-tetrahydropyridine and 1.27 g (5.9 mmol) of (*S*)-*N,N*-dimethyl-*N'*-(*tert*-butoxy-2-amino-3-methylbutyl)formamidine in 1 mL of toluene was heated at 85 °C for 48 h. Concentration and flash chromatography on silica gel, eluting with 5% Et_3N in hexanes, afforded 0.968 g (65%) of the product as a colorless oil: IR (film) 3030, 2965, 2920, 2860, 1645, 1455, 1385, 1360, 1250, 1230, 1195, 1075, 880 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86 (6H, d, J = 6.8 Hz), 1.15 (9 H, s), 1.81 (1 H, m), 2.14 (2 H, m), 2.71 (1 H, m), 3.18 (1 H, dd, pa J = 7.1, 8.8 Hz), 3.33 (2 H, t, J = 5.6 Hz), 3.50 (1 H, dd, J = 5.5, 8.8 Hz), 3.79 (2 H, m), 5.69 (1H, m), 5.80 (1 H, m), 7.30 (1 H, s).

Metalation and Alkylation of 9. General Procedure for 14. To a 0.05 M solution of degassed chiral formamidine **9** and 3 equiv of the alkyl halide, in dry THF under argon, 1.1 equiv of the *n*-BaLi was slowly added. After the yellow color discharged (10 min 2 h), the reaction mixture was warmed to −20 °C and diluted with hexane. The organic phase was extracted with 1 N HCl, and excess electrophile could be removed by concentration of the hexane/THF layer. The acid wash was basified with 20% KOH solution, and the milky aqueous phase was extracted with diethyl ether. The organic phase was dried over anhydrous K_2CO_3, concentrated in vacuo, and filtered through a silica gel plug eluting with 5% Et_3N in hexanes. The mixture of regioisomers (**11** and **12**) was dissolved in 95% EtOH, and 8 equiv of anhydrous hydrazine and 3 equiv of glacial acetic acid were added. The reaction mixture was heated at 50 °C for 12–16 h. The ethanol was removed cold under vacuum, and the residue was taken up in methylene chloride. The organic phase was washed with saturated aqueous $NaHCO_3$, and dried over anhydrous K_2CO_3. Bulb-to-bulb distillation at 80 °C, 25–30 torr provided the recovered *O-tert*-butyl-L-valinol. Further bulb-to-bulb distillation of the pot residue at 0.05 torr afforded the 2-substituted 1,2,5,6-tetrahydropyridine **14** as a colorless oil. Hydrogenation to the piperidine **16** was accomplished by the reduction procedure (Rh/C) given above. The enantiomeric purity of **16** was determined as in the case of the pyrrolidines **15**.

(*S*)-2-Benzylpiperidine 16 (A = H): mp 37–39 °C; purified by bulb-to-bulb distillation (92 °C; 0.05 torr); ^1H NMR ($CDCl_3$) δ 1.50 (7 H, complex multiplets), 2.60 (4 H, m), 3.00 (1 H, m), 7.25 (5 H, m); $[\alpha]^{25}_D$ +0.2° (*c* 5.6, ether).

(*S*)-2-(3-Phenylpropyl)piperidine 16 (A = H): oil, purified by bulb-to-bulb distillation (100 °C, 0.05 torr); ^1H NMR ($CDCl_3$) δ 1.00–1.80 (11 H, m), 2.50 (2 H, m), 2.60 (2 H, t, J = 7.6 Hz), 3.04 (1 H, m), 7.20 (5 H, m); $[\alpha]^{25}_D$ 7.0° (*c* 2.0, ether). 3,5-Dinitrobenzoate mp 96–98 °C (ether–hexane). Anal. Calcd for $C_{21}H_{23}N_3O_5$: C, 63.46; H, 5.83; N, 10.57. Found: C, 63.08; H, 5.87; N, 10.62.

(*S*)-2-*n*-Heptylpiperidine 16 (A = H): oil, purified by bulb-to-bulb distillation (bp 95 °C; 0.05 torr); ^1H NMR ($CDCl_3$) δ 0.88 (3 H, t, J = 6.8 Hz), 1.27 (14 H, m), 1.60 (4 H, m), 1.80 (1 H, m), 2.40 (1 H, m), 2.62 (1 H, m), 3.06 (1 H, m); $[\alpha]^{25}_D$ 7.4° (*c* 1.7, ether).

3,4-Dimethyl-1,2,5,6-tetrahydropyridine, 18. A solution of 5.0 g (47 mmol) of 3,4-lutidine and 6.1 mL (52 mmol) of benzyl bromide in 48 mL of acetone was refluxed under argon for 1 h. Upon cooling, the *N*-benzyl-3,4-dimethylpyridinium bromide crystallized from the solution. Subsequent filtration provided 12.7 g (98%) of the pyridinium salt as a white powder, mp 199–201 °C. To a solution of the pyridinium salt (12.7 g, 45.6 mmol) in 100 mL of 80% aqueous methanol was *carefully* added 3.51 g (92.8 mmol) of $NaBH_4$ with cooling. After completion of the addition of $NaBH_4$, the solution was refluxed for 1 h. The methanol was removed under vacuum, and the crude residue was extracted with diethyl ether. The organic phase was washed with saturated $NaHCO_3$ solution, and dried over anhydrous K_2CO_3. Concentration followed by bulb-to-bulb distillation (0.05 torr; 75–80 °C) provided 8.6 g (93%) of *N*-benzyl-3,4-dimethyl-1,2,5,6-tetrahydropyridine as a viscous, colorless liquid: ^1H NMR ($CDCl_3$) δ 1.6 (6 H, br s), 2.1 (2 H, m), 2.5 (2 H, t, J = 5 Hz), 2.8 (2 H, m), 3.6 (2 H, s), 7.3 (5 H, s).

A solution of 15.5 g (77.5 mmol) of *N*-benzyl-3,4-dimethyl-1,2,5,6-tetrahydropyridine and 12.5 g (1.05 equiv) of phenyl chloroformate in 50 mL of CH_2C_{12} was stirred under argon for 14 h. Concentration of the reaction mixture followed by bulb-to-bulb distillation (0.05 torr;

70–75 °C) afforded 13.4 g of the phenyl carbamate as a viscous, colorless oil: IR (film) 2910 (br), 1725, 1590, 1500, 1455, 1425, 1340, 1290, 1245, 1205, 1165, 1130, 1075, 750, 690 cm^{-1}; ^1H NMR ($CDCl_3$) 1.6 (6 H, br s), 2.1 (2 H, m), 3.6 (2 H, t, J = 5 hz), 3.8 (2 H, m), 7.1 (5 H, m). To a solution of 3.0 g (13.0 mmol) of the phenyl carbamate in 40 mL of dry THF was added 2.0 g (36.0 mmol) of freshly powedered KOH and 0.18 g (5 mol %) of 18-crown-6. The reaction mixture was refluxed under argon for 16 h. Upon cooling, the solution was extracted with CH_2Cl_2, and the organic phase was washed several times with 20% aqueous KOH solution. The organic layer was dried over anhydrous K_2CO_3 and concentrated, and the crude product was distilled bulb-to-bulb (20 torr; 75 °C) to provide 0.89 g (67%) of 3,4-dimethyl-1,2,5,6-tetrahydropyridine as a colorless oil: ^1H NMR ($CDCl_3$) δ 1.58 (6 H, m), 2.00 (3 H, m), 2.90 (2 H, t, J = 5.9 Hz), 3.14 (2 H, br s). p-Nitrobenzamide derivative, mp 84–86 °C, recrystallized from ether/hexanes. Anal. Calcd for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76; Found: C, 64.70; H, 6.24; N, 10.61.

Formamidine 19. Using **18**, the formamidine **19** was prepared in the same manner as the unsubstituted tetrahydropyridine **9**: oil, purified by flash chromatography on silica gel eluting with 5% Et_3N in hexanes; IR (film) 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86 (6 H, d, J = 6.8 Hz), 1.15 (9 H, s), 1.63 (6 H, m), 1.80 (1 H, m), 2.04 (2 H, m), 2.67 (1 H, m), 3.17 (1 H, m), 3.29 (2 H, t, J = 5.8 Hz), 3.50 (1 H, m), 3.61 (2 H, m), 7.28 (1 H, s); $[\alpha]^{25}_D$ −51.6° (c 2.85 in $CHCl_3$).

(*S*)-2-(4-Methoxybenzyl)-3,4-dimethyl-1,2,5,6-tetrahydropyridine, 20: prepared by the general procedure described for metalation and alkylation of **9** (to give **14**); oil, purified by bulb-to-bulb distillation (0.05 torr; 105 °C); ^1H NMR ($CDCl_3$) δ 1.66 (3 H, br s), 1.71 (3 H, br s), 1.99 (2 H, m), 2.76 (6 H, m), 3.78 (3 H, s), 6.84 (2 H, d, J = 8.8 Hz), 7.13 (2 H, d, J = 8.5 Hz); $[\alpha]^{25}_D$ −88.0° (c 1.8, ether). The ee was determined as 99 ± 1% (Figure 1) from the α-naphthamide **22**.

(*S*)-*N*-Methyl-2-(4-methoxybenzyl)-3,4-dimethyl-1,2,5,6-tetrahydropyridine, 23. A solution of 1.0 mmol of **20** in 2 mL of ethyl formate was heated at 40 °C for 12 h. The reaction mixture was concentrated in vacuo, and the crude formamide was dissolved in 5 mL of diethyl ether to which 2.0 mmol of $LiAlH_4$ was added. After stirring for 2 h at room temperature, the reaction was quenched successively with 10 drops of water, 6 drops of 20% aqueous KOH solution, and 10 drops of water. The solution was filtered and concentrated, and the crude product was subjected to bulb-to-bulb distillation under high vacuum to provide the *N*-methylamine as a colorless oil (0.05 torr; 105 °C): ^1H NMR ($CDCl_3$) δ 1.56 (3 H, s), 1.60 (3 H, s), 2.05 (2 H, m), 2.33 (3 H, s), 2.50 (1 H, m), 2.73 (2 H, d, J = 5.6 Hz), 2.93 (2 H, m), 3.73 (3 H, s), 6.78 (2 H, d, J = 6.6 Hz), 7.14 (2 H, d, J = 8.5 Hz); ^{13}C NMR ($CDCl_3$) δ 17.2, 18.8, 28.4, 36.2, 42.6, 46.6, 54.9, 67.0, 113.1, 124.9, 126.5, 129.7, 133.0, 157.3; $[\alpha]^{25}_D$ −6.8° (c 1.5, ether).

(+)-Metazocine, 24. A solution (0.5 M) of 0.160 g of **23** in 48% HBr was heated at 135 °C for 25 h. The cooled solution was diluted in 5 mL of water and made alkaline with saturated ammonium hydroxide. Extraction with CH_2Cl_2, drying, and concentration gave a solid which was purified by PTLC (silica, 60:15:25 hexane–Et_3N–ethyl acetate) to give 0.090 g (60%): mp 178–179 °C (acetone–water, 1:1); ^1H NMR ($CDCl_3$) δ 0.852 (3 H, d, J = 7.0 Hz), 1.31 (3 H, s), 1.90 (3 H, m), 2.17 (1 H, d of t, J = 3.0, 12.2 Hz), 2.41 (3 H, s), 2.50 (1 H, m), 2.68 (1 H, dd, J = 5.5, 18.2 Hz), 2.91 (1 H, m), 2.97 (1 H, d, J = 18.6 hz), 6.59 (1 H, dd, J = 2.5, 8.2 Hz), 6.69 (1 H, d, J = 2.5 Hz), 6.94 (1 H, d, J = 8.2 Hz); $[\alpha]^{25}_D$ +81.8° (c 0.83, ethanol).[11]

Acknowledgment. Financial support from the National Science Foundation is gratefully acknowledged. A.I.M. thanks the Alexander von Humboldt Foundation for a Senior Scientist Award (1984–1986) and the Faculty at the University of Wurzburg for their hospitality.

(11) May, E. L.; Ager, J. H. *J. Org. Chem.* **1959**, *24*, 1432.

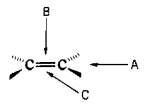
Factors Influencing Conformational Preferences in Cyclohexenes

Joseph B. Lambert*[1] and Dale E. Marko

Contribution from the Department of Chemistry, Northwestern University, Evanston, Illinois 60201. *Received June 20, 1985*

Abstract: Conformational preferences have been measured for the first time for 4-substituted cyclohexenes in a solvent of low polarity. Measurements were made for the substituents Cl, Br, I, OH, $OSiMe_3$, and CN and were compared with conformational preferences in cyclohexyl and *exo*-methylenecyclohex-3-yl. In the nearly nonpolar solvent CF_2Cl_2, in which intramolecular interactions are maximized, there is a much larger axial population for cyclohexen-4-yl than in cyclohexyl or *exo*-methylenecyclohex-3-yl. In particular, the dipolar interaction of the endocyclic double bond is reduced from that of the exocyclic double bond. This observation is confirmed by the almost negligible effect of symmetrizing the endocyclic double bond through 1,2-dimethyl substitution, in contrast with the large effect of symmetrizing the exocyclic double bond through 7,7-dimethyl substitution. Polar solvents increase the proportion of the axial conformer to a smaller extent for the endocyclic than for the exocyclic system, again in agreement with a lower dipolar effect in the endocyclic case. These results emphasize the anisotropic nature of the steric effects of double bonds.

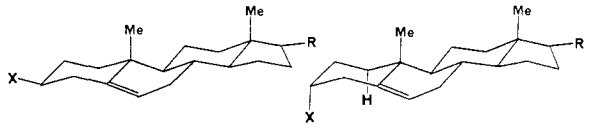
Steric interactions between distant groups within a molecule have been studied primarily in the context of saturated systems. The presence of a double bond in the interacting groups has a major influence on the nature of the steric effect. Whereas rapidly rotating alkyl groups like methyl and simple atoms like chloride or iodide interact with perturbing groups almost isotropically, i.e., independently of the direction of approach, a double bond should interact anisotropically. One can image three extreme modes of approach (**1**): from the end (A), face (B), or side (C). Sus-



1

ceptibility to induction of dipoles via van der Waals interactions is anisotropic in double and triple bonds. Moreover, if the bond is polar, particularly in carbonyl or imino groups, electrostatic interactions (dipole–dipole, dipole–quadrupole) should also be anisotropic. Thus the double bond presents a very complex surface to perturbing groups.

An example of the steric effect of double bonds may be found in 3-substituted cholest-5-enes, **2**. The α (axial) conformer has a gauche interaction with only one syn-axial hydrogen, since the



2-α **2-β**

other has been replaced by the double bond. How does the

0002-7863/85/1507-7978$01.50/0