^{1}H NMR δ 0.50–2.30 (a broad envelope with a sharp singlet at 2.05, 14 H), 3.05–3.25 (m, 1 H), 6.60 (br, 1 H), 6.60–7.49 (m, 4 H); electron-impact mass spectrum, *m/e* 260 (M^+).

Preparation of 3-Cyclohexylbenzofuran (14). Prepared in quantitative crude yield from **13c** by the method used for the synthesis of **8**; thick-layer chromatography on silica gel (hexane) gave pure **14** (65%): IR ($CHCl_3$) 3.41, 3.50, 6.87, 8.40 (br) μm; ^{1}H NMR δ 0.70–2.30 (m, 10 H), 2.50–3.00 (br, 1 H), 7.00–7.90 (m, 5 H); electron-impact mass spectrum, *m/e* 200 (M^+).

Preparation of Cyclohexyl 2-(Formyloxy)phenyl Ketone (15a). To a solution of **14** (15.0 mg, 0.08 mmol) in dry dichloromethane (1 mL) cooled to −78 °C was added a saturated solution of ozone in dichloromethane over 5 min. The pale-blue reaction mixture was allowed to stir at −78 °C for 10 min and was then warmed to room temperature over 1 h. Dimethyl sulfide (0.5 mL, large excess) was added and the solution stirred at room temperature for 1 h. The solvent was evaporated, and the residue was dissolved in ether, washed with water, dried and evaporated to give **15a** (15.1 mg, 86%): IR ($CHCl_3$) 5.75, 5.94 μm; ^{1}H NMR δ 0.90–3.50 (m, 1 H), 7.00–8.00 (m, 4 H), 8.30 (s, 1 H).

Preparation of Cyclohexyl 2-Hydroxyphenyl Ketone (15b). To a solution of crude formate ester **15c** (10.6 mg, 0.05 mmol) in methanol (1 mL) was added 1 N NaOH (0.5 mL). The resulting purple reaction mixture was stirred at room temperature for 12 h, acidified with 1 N HCl, and extracted into ether. The organic layer was washed with water, dried, and evaporated to give **15b** (9.0 mg, 100%): IR ($CHCl_3$) 6.13, 6.75, 6.94, 8.26 μm; ^{1}H NMR δ 1.00–2.12 (m, 10 H), 3.30 (br, 1 H), 6.70–7.90 (m, 4 H), 8.80 (s, 1 H); electron-impact mass spectrum, *m/e* 204 (M^+).

Acknowledgment. This work was supported by the National Institutes of Health (Grant No. CA 25787) and the National Science Foundation (Grant No. CHE79-23640). The experimental contributions of Dr. John Wetzel and Tim Miller (undergraduate research participant, Summer 1980) are gratefully acknowledged.

Registry No. **3a**, 2065-23-8; **3b**, 86728-16-7; **3c**, 86728-17-8; **4**, 69515-13-5; **5a**, 80548-39-6; **5b**, 86728-18-9; **5c**, 86728-19-0; **6a**, 86728-20-3; **6b**, 86728-21-4; **7**, 86728-22-5; **8**, 5010-79-7; **9**, 86728-23-6; **9b**, 86728-24-7; **10a**, 86728-25-8; **10b**, 86728-26-9; **10c**, 86728-27-0; **11**, 13130-19-3; (*E*)-**12**, 86728-28-1; (*Z*)-**12**, 86728-29-2; *cis*-**13a**, 86728-30-5; *trans*-**13a**, 86728-31-6; *cis*-**13b**, 86728-32-7; *trans*-**13b**, 86728-33-8; *cis*-**13c**, 86728-34-9; *trans*-**13c**, 86728-35-0; **14**, 53707-88-3; **15a**, 86728-36-1; **15b**, 18066-52-9; ethyl (diethylphosphono)phenoxyacetate, 86728-37-2; ethyl (cyclopentylidene)phenoxyacetate, 86728-38-3; benzene, 71-43-2.

Stereoselective Reductions of Substituted Cyclohexyl and Cyclopentyl Carbon–Nitrogen π Systems with Hydride Reagents[1]

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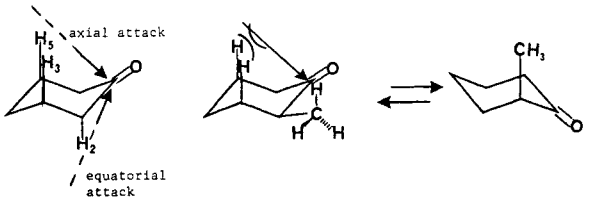
Reductions of 3- and 4-substituted cyclohexyl imines, iminium salts, and enamines (via iminium ions) with various hydride reagents reveal that while small reagents ($NaBH_4$, $NaBH_3CN$) favor axial approach as observed with the corresponding ketones, even moderately bulky reagents (i.e., acetoxyboranes) attack preferentially from the equatorial side. This is in direct contrast to the results observed for the same reagents with the corresponding ketones and is interpreted as implying that additional steric interactions induced by the nitrogen substituents encumber axial attack by substituted hydride reagents and force approach from the equatorial direction. The very bulky tri-*sec*-butylborohydride anion affords highly stereodiscriminating equatorial attack. Reductions of 2-alkylcyclohexyl and 2-alkylcyclopentyl imines and enamines also proceed with high stereoselectivity to give *cis*-2-alkyl cyclic amines with both hindered and unhindered reagents. This is interpreted to be the result of (1) augmented steric interactions between nitrogen substituents and equatorial 2-alkyl groups (1,3-allylic strain) which induces conformational changes to favor the axial 2-alkyl conformer and (2) hindrance toward equatorial approach by reagents induced by axial alkyl substituents. The result is that equatorial approach is favored with equatorial 2-alkyl conformers and preferential axial approach with axial 2-alkyl conformers, leading to stereoselective production of *cis*-2-alkylamines. *trans*-2-*n*-Propyl-4-*tert*-butylcyclohexanone is reduced by $LiBH(sec\text{-}Bu)_3$ preferentially from the axial direction in contrast to the usual highly selective equatorial attack observed with other cyclohexanones.

Unraveling the mechanism and stereochemistry of cyclic ketone reductions has occupied the interests of chemists for almost 3 decades and has been the subject of numerous and diverse investigations.[2] Although several explanations have been suggested to account for the observed trends in stereoisomer profiles obtained, none are completely satisfactory for all situations. Nevertheless, several general conclusions emerge which allow at least qualitative predictions of the expected stereochemistry outcome in the reductions of cyclohexanones. Thus, the preferred direction of ring attack (axial or equatorial) depends on both the bulkiness of the hydride reagent and the steric environment surrounding the carbonyl. With simple, unhindered cyclohexanones, small reagents such as $NaBH_4$ and $LiAlH_4$ favor approach from the axial direction, leading to a predominance of the equatorial alcohols. For instance, 4-*tert*-butylcyclohexanone affords 83–92% *trans*-4-*trans*-

Chart I



(1) Presented at the 14th Central Regional Meeting of the American Chemical Society, Midland, MI, June 1982.

(2) For recent, excellent reviews concerning the mechanism and factors controlling the stereochemistry of ketone reductions see: (a) Wigfield, D. C. *Tetrahedron* **1979**, *35*, 449. (b) Boone, J. R.; Ashby, E. C. *Top. Stereochem.* **1979**, *11*, 53. (c) Hajos, A. "Complex Hydrides"; Elsevier: New York, 1979; Chapter 12. (d) See also: Giddings, M. R.; Hydec, J. *Can. J. Chem.* **1981**, *59*, 459. (e) Cieplak, A. *J. Am. Chem. Soc.* **1981**, *103*, 4540.

0022-3263/83/1948-3412$01.50/0

butylcyclohexanol with $NaBH_4$,[3a,b] $LiAlH_4$,[4a-c] or $NaAlH_4$.[3d] The reason for such discrimination is not completely settled,[2] but one explanation suggests that tortional strain experienced by the encroaching reagent and the C_2 and C_6 axial hydrogens surpasses the steric interactions encountered by the reagent with the C_3 and C_5 syn-axial hydrogens[4] (Chart I) although other explanations are available.[2]

The attachment of other substituents to equatorial sites about the ring does not alter substantially the preference for axial attack. Thus, 2-methylcyclohexanone gives 60–82% of *trans*-2-methylcyclohexanol with the same reagents. The slightly diminished preference for axial approachment has been atributed to the introduction of an additional proximate hydrogen from the methyl group (effectively a third syn-axial hydrogen) which gives some additional shielding[3c,5] from the axial side coupled with an augmented population of the axial methyl conformer which, upon axial attack, affords the cis isomer[2,3c] (Chart I).

Increasing the steric congestion about the reaction site either by placement of alkyl groups at the C_3 and C_5 axial positions or by enlarging the hydride reagent lowers, often drastically, the favoring the axial attack.[2] The most spectacular examples of this involve the enormously obese reagents tri-*sec*-butylborohydride,[6a,b] trisiamylborohydride,[6c] dimestylborohydride,[6d] and triisopropoxyborohydride.[6e] These reagents demonstrate nearly total reversal in directional preferences in that equatorial attack is almost exclusively favored for all cyclohexanones.[2,6] Apparently, the extreme size of such hydrides produces such severe interactions with the C_3 and C_5 axial hydrogens that the tortional interactions generated by equatorial approach are overwhelmed. Synthetically, the reagents provide excellent procedures for the preparation of nearly isomerically pure axial alcohols.[6]

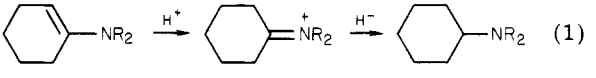
Further discussions, results, and other features of ketone reductions are provided by the comprehensive reviews available,[2] but, at least, much data and information are available to assist in achieving predictable synthetic aims. In constrast to this, a relative paucity of literature exists concerning the stereochemistry of corresponding carbon–nitrogen π bond reductions[7] although the control of such conversions to give amines is often of great importance in synthetic applications. The comparative lack of concern apparently stems from the meager available studies which suggest that carbon–nitrogen π reductions behave similarly to the corresponding cyclic ketones, namely, the small reagents (e.g., $LiAlH_4$, $NaBH_4$, $NaBH_3CN$) preferentially approach unhindered systems from the axial side[2] while bulky reagents (trialkylborohydrides,[6a-c] Hantzsch ester,[7b] dialkylcyanoborohydrides[7e]) are directed toward equatorial attack, leading to axial products.

This paper reports a systematic exploration of hydride reductions of various cyclic carbon–nitrogen π systems (imines, iminium ions) to amines and reveals that while such conversions share some features of ketone reductions, in many instances substantial stereochemical differences are exhibited which are induced by nitrogen substituents and require additional considerations in predicting preferred direction of approach to the C–N π bond. Since the factors which affect stereochemistry appear substantially different for 3- and 4-alkyl vs. 2-alkyl cyclic systems, the two classes will be presented and discussed separately.

Results and Discussion

The requisite imines,[7k] enamines,[8a] and iminium salts[8b] were readily prepared from the ketones and primary or secondary amines, or amine salts, respectively. In all cases, the ratio of isomer amines produced upon reduction were determined by GC. Confirmations of isomer assignments were accomplished by independent synthesis via reduction of the corresponding substituted cyclic oximes with Na/C_2H_5OH to amine mixture rich in the equatorial isomers[9] followed by conversion to the appropriate secondary or tertiary amines and/or assignment by assumption that lithium tri-*sec*-butylborohydride (L-Selectride, Aldrich) reductions provide the axial amines preferentially. We noted that in all the 3- and 4-substituted cases the axial amine isomers eluted first in analysis by GC, while the elution order of 2-alkyl systems varied (Experimental Section).

3- and 4-Substituted Cyclohexyl Carbon–Nitrogen Systems. Tables I and II display reduction results for 3- and 4-substituted cyclohexyl imines, iminium salts (Table I), and enamines (Table II) with several hydride reagents. Included for comparison are results for 4-*tert*-butylcyclohexanone. For iminium salts and imines the hydrides utilized ranged from the highly nucleophilic L-Selectride and $NaAlH_2(OCH_2CH_2OCH_3)_2$ to electrophilic borane derivatives and included very bulky $LiBH(sec\text{-}C_4H_9)_3$ and "small" ($NaBH_4$, $NaBH_3CN$) reagents. Reductions of enamines were conducted in acidic media to ensure generation of necessary iminium ion intermediates[10] (eq 1).



(1)

Stereochemical profiles obtained from imine and iminium salt reductions (Table I) disclosed that the unen-

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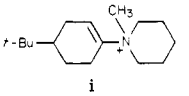
(10) Unprotonated enamines were not reduced by nucleophilic hydride reagents. To ensure that enamine reductions did not proceed via N-protonated intermediates by double bond addition, we prepared the analogous *N*-methyl salt i. Reduction attempts with $LiBH(sec\text{-}C_4H_9)_3$ returned on starting material.



i

Table I. Reductions of Imines and Iminium Salts with Hydride Reagents: [a]

R	R_1	R_2	compd	ratio of equatorial/axial attack (% yield isolated)							
				$NaBH_4$ $(CH_3)_2CHOH$ 25 °C	$NaBH_4$ CH_3OH 25 °C	$NaBH_3CN$ CH_3OH, H^+ 25 °C	$(CH_3)_3CNH_2BH_3$ CH_3COOH^b 25 °C	$(CH_3)_3CNH_2BH_3$ reverse[c] CH_3COOH 25 °C	$(CH_3)_2NHBH_3$ reverse[c] CH_3COOH 25 °C	$(CH_3OCH_2CH_2O)_2AlH_2Na$ THF	LiBH-(*sec*-Bu)$_3$ THF 66 °C
4-*t*-Bu	C_6H_5			46/54 (93)	32/68 (95)	53/47 (87)	70/30 (92)	84/16 (89)	72/28 (89)	60/40 (90)	99/1 (89)
4-*t*-Bu	C_6H_{11}		1a	35/65 (94)	31/69 (91)	52/48 (94)	22/78 (93)	77/23 (44)	66/34 (70)	58/42 (89)	95/1 (75)
4-*t*-Bu	$CH_2C_6H_5$			30/70 (82)		46/54 (87)	44/56 (88)		66/34 (74)	64/36 (94)	97/3[k] (77)
4-CH_3	C_6H_5			45/55 (95)	36/64 (91)	51/49 (89)	68/32 (85)	77/23 (85)	71/29 (70)	58/42 (90)	94/6 (79)
4-CH_3	C_6H_{11}		1b	35/65 (88)	35/65 (92)	52/48 (95)	24/76 (87)	73/27 (81)	48/52 (81)	56/44 (82)	92/8 (68)
3,3,5-*t*-$CH_3CH_2C_6H_5$				94/6 (90)		93/7 (90)	88/12 (98)			99/1 (85)	98/2 (80)
4-*t*-Bu	$(CH_2)_4$			14/86[d] (97)		36/64[d] (94)	53/47[e] (96)			70/30[f] (92)	94/6 (90)
4-*t*-Bu	CH_3	CH_3		16/84[d] (70)		42/58[d] (75)	51/49[e] (85)			72/28[g] (74)	94/6 (76)
4-CH_3	$(CH_2)_4$			22/78[d] (82)		36/64[d] (94)	44/56[e] (90)			70/30 (82)	85/15 (76)
4-*tert*-butylcyclohexanone				17/83[i]	14–15/86–85[i]	16/84[j]	8/92[k]	16/84[l]	8/92[m]	93/7[n]	

[a] The reductions were conducted under Ar or N_2 for 20–24 h with solutions 0.167 M in substrate and 0.50 M in hydride reagents unless otherwise noted. Ratios of isomers were determined by GLC. All new products gave spectral data and elemental analyses consistent with the assignments (Experimental Section). [b] Imine dissolved in CH_3COOH and hydride added immediately. [c] Hydride added to CH_3COOH and kept at 25 °C for 8 h to preform diacetoxyborane. [d] Conducted at reflux; concentration of hydride was 0.835 M. [e] Conducted in $(CH_3)_2CHOH$ at 25 °C. [f] Ratio 36/64 with $LiAlH_4$.[7a] [g] Ratio 37/63 with $LiAlH_4$.[7a] [h] Reference 7k reports 98/2. [i] Reference 3a; conducted at 0 °C. [j] Reference 11. [k] Reference 12; conducted in methanol. [l] Ammonia–borane also gave a 16/84 equatorial/axial ratio. [m] Conducted at 25 °C. [n] Reference 6a; conducted at 0 °C.

cumbered reagent $NaBH_4$ in alcohol solvents at least qualitatively mimics the directional preference for attack on unhindered systems observed with ketones[2] in that the equatorial amines predominated, and this has also been demonstrated with $LiAlH_4$.[7a] As the bulk of the reagent increases, even moderately, the preference for axial attack concomitantly decreases as expected in analogy with ketones,[2] but the effect is far more pronounced as illustrated by comparisons with 4-*tert*-butylcyclohexanone. Even the monosubstituted $NaBH_3CN$[11] and $(CH_3)_3CNH_2BH_3$ (in methanol solvent)[12] showed substantial lessening of axial approach preference compared to this unhindered ketone, while disubstituted $NaAlH_2(OCH_2CH_2OCH_3)_2$ showed reversal of the axial attack preference displayed with 4-*tert*-butylcyclohexanone! Furthermore, reduction of imines (Table I) and enamines (Table II) in acetic acid afforded stereoselectivities that varied substantially depending on the manner in which the reductions were conducted. Thus, sequential addition of the substrate to acetic acid followed by the hydride reagent resulted variable but often far less stereodiscrimination than when the borane or borohydride was initially stirred with acetic acid for sufficient time to ensure formation of the corresponding acetoxyborane hydride reagent.[13,14] Under these latter conditions 3- and 4-alkyl-substituted cyclic systems afforded consistent and often remarkably high preferences for equatorial attack leading to axial amines. The dependency of the stereoselectivity on the hydride species present is strikingly illustrated with the imines **1a** and **1b** in which complete reversal of the cis/trans ratios was obtained. The results suggested that acetoxyboron hydrides behave, with carbon–nitrogen π systems, as highly bulky reagents which, in some cases, nearly mimic trialkylborohydrides[6] while unreacted amine–boranes and borhydride behave as much smaller reagents and favor axial approach.[15] Remarkedly, reductions of 4-*tert*-butylcyclohexanone with acetoxyboron hydrides gave completely opposite results in that attack occurred preferentially axial in analogy with unhindered reagents, including borohydride and amine–boranes (Table I).

The above results indicate that the reductions of carbon–nitrogen π bonds involve alternate or additional considerations of stereochemical control than those associated with ketones. We suggest that at least part of the differences for substituted boron hydrides arise from augmented steric interactions introduced by substituents on nitrogen which are absent in ketones. Such interactions may be manifested in that the encroaching reagent experiences encumberence from the nitrogen side of the π bond in addition to the steric and tortional effects of the ring bearing the carbon under siege. This is particularly true with iminium salts disubstituted at the nitrogen end. Thus, inspection of Drieding models of the pyrrolidine and piperidine iminium salts of 4-*tert*-butylcyclohexanone indicate substantial additional nonbonded interactions ex-

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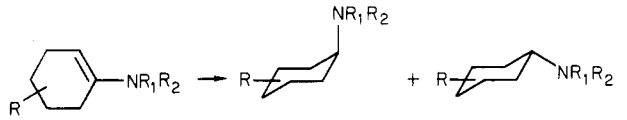
(15) The differing behavior between **1a** and **1b** compared to the *N*-cyclohexyl imines in Table I presumably reflects reduction rate differences. Thus, the aryl conjugated imines **1** are stabilized with respect to the aliphatic derivatives and remain unreduced until a significant portion of the hydride reagent has reacted with solvent to give acetoxyboron hydrides. The *N*-cyclohexyl imines, on the otherhand, are reduced relatively rapidly by largely unsubstituted reagent.

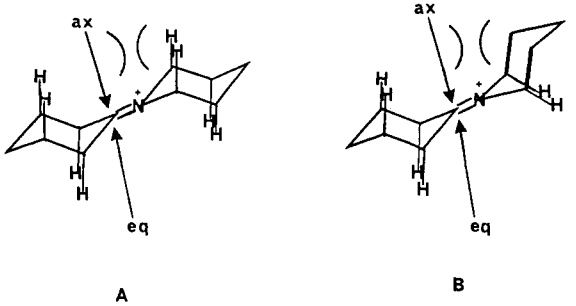
Table II. Reduction of 3- and 4-Alkylcyclohexyl Enamines with Acetoxyboron Hydrides[a]



R	R_1 and R_2	ratio of equatorial/axial attack (% yield isolated)						
		$NaBH_4$ CH_3COOH	$NaBH_3CN$ CH_3COOH	NH_3BH_3 CH_3COOH	$(CH_3)_2$-$NHBH_3$ CH_3COOH	$(CH_3)_3$-CNH_2BH_3 CH_3COOH	$(i\text{-}C_3H_7)_2$-$NHBH_3$ CH_3COOH	NH_3BH_3 CH_3OH, H^+
4-*t*-Bu	$(CH_2)_4$	72/28 (78)	79/21 (86)	83/17 (89)		87/13 (89)	74/26 (87)	51/49 (76)
4-*t*-Bu	$(CH_2)_5$		86/14 (75)	89/11	85/15	91/9	88/12	
4-*t*-Bu	$[(CH_2)_2]_2O$	79/21 (84)	89/11	84/16 (83)		86/14 (85)	86/14 (90)	54/46
4-CH_3	$(CH_2)_4$		84/16 (80)	80/20 (60)	78/22	82/18 (84)	71/29 (50)	
4-CH_3	$(CH_2)_5$	79/21	77/23	84/16	81/19	86/14 (80)	82/18	
3-CH_3	$(CH_2)_5$	86/14	83/17	88/12	87/13	92/8	88/12	
3-CH_3	$(CH_2)_4$		74/26 (86)	86/14 (87)	82/18 (86)	89/11 (84)	81/19 (78)	
4-*tert*-butylcyclohexanone		26/74 (90)	23/77 (95)	16/84 (99)		16/84 (87)		
				9/91[c] (99)		8/92[c] (99)		

[a] Reductions were conducted under Ar or N_2 at 25 °C in acetic acid for 24 h in which the acetoxyboron hydride was preformed prior to addition of the substrate. All reactions were 0.167 M in substrate and 0.33 M in hydride reagents. Ratios of isomers were determined by GLC. [b] All new products gave spectral data and elemental analyses consistent with the assigned structures. [c] Reference 7, in methanol (Experimental Section).

Chart II

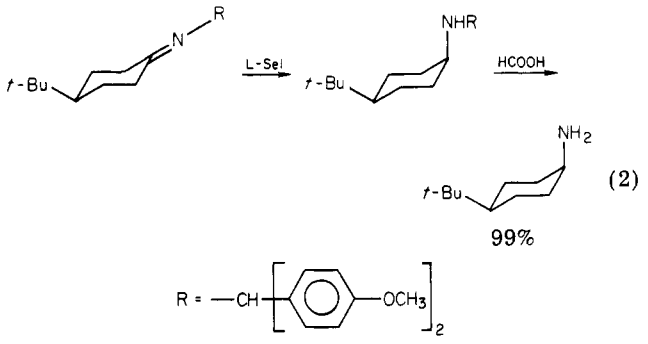


2

perienced by incoming reagents which depend on the conformation of the hetereocyclic ring. This is illustrated by a consideration of the conformers available to the 4-*tert*-butylpiperidinium ion (**2**) and an analysis of the preferred direction of attack. Chart II presents the two conformational possibilities for **2**. In both forms A and B, equatorial attack with respect to the cyclohexyl ring leads to the cis stereoisomer which is the observed major isomer. Inspection shows that in axial approach to both A and B additional interactions are expected for the incoming reagent with the piperidine C_2 and C_6 axial hydrogens in A and the C_2–C_3 and C_5–C_6 bonds in B. Equatorial attack of the carbon end of A is not additionally encumbered and may be regarded as an axial approach to the piperidine ring. Equatorial approach toward B experiences a similar steric environment as axial approach toward A. Overall then, the least congested direction of attack appears to be from the bottom side of A, giving the cis isomer. Apparently smaller, unsubstituted reagents such as BH_4^- and AlH_4^- are less significantly influenced by the above additional interactions, but even moderately substituted reagents such as acetoxyboranes (and dialkoxyalumium hydrides) cannot avoid the congestion by rotating away from offending repulsions, as is possible in ketones.

Reductions of the 3,3,5-trimethylcyclohexyl imine (Table I) illustrate that imposition of an axial methyl at C_3 decreases axial approach as expected, but the effect is much more severe than in ketones.[2] Thus, all tested reagents including $NaBH_4$ favored equatorial approach with high stereoselectivity (88–99%) in contrast to 3,3,5-trimethylcyclohexanone which suffers only 52–62%[2,3a,b,16] equatorial attack with $NaBH_4$.

Reductions of imines and iminium ions as described provide synthetically useful, stereoselective procedures for preparation of cis or trans secondary or tertiary amines, respectively. Reduction of benzyl anils,[17] followed by catalytic debenzylation, provides primary amines. Alternatively, a mild noncatalytic hydrogenolysis cleavage process was developed which involved reduction of imines from *p,p'*-dimethoxybenzhydrylamine[17b] and subsequent cleavage with warm formic acid to the primary amines[17c] (eq 2). The scope of this process is presently being explored.

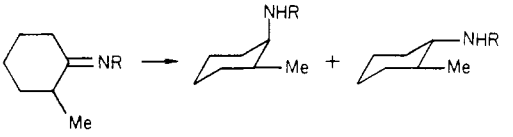


(2)

2-Substituting Cyclic Carbon–Nitrogen Systems. Turning to 2-alkyl cyclic systems, Tables III and IV present reduction results for several imines, iminium ions and enamines with hydride reagents. Included for comparisons are results or reported values for 2-methylcyclohexanone and 2-methylcyclopentanone. Significantly, with all reagents the predominant products were the cis isomers resulting from net equatorial attack on the conformers with equatorial 2-alkyl groups. These results are not, at first glance, unexpected when compared to similar situations observed in the 3- and 4-alkyl systems discussed above.

(16) (A) Wigfield, D. C.; Phelps, D. J. *J. Org. Chem.* **1976**, *41*, 2396. (b) Rickborn, B.; Wuesthoff, M. T. *J. Am. Chem. Soc.* **1970**, *92*, 6894.
(17) (a) Ctvernik, J.; Mayer, J. *Czech. Pat.* 91167, 1959; *Chem. Abstr.* **1961**, *55*, 1536g. (b) Mandel, L.; Piper, J. U.; Peterfield, C. E. *J. Org. Chem.* **1963**, *28*, 574. (c) Trost, B. M.; Keinan, E. *Ibid.* **1979**, *44*, 3451.

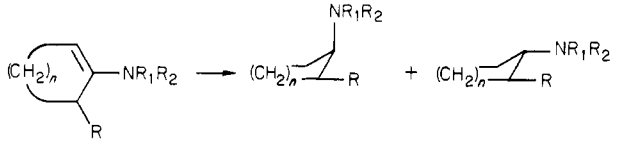
Table III. Reduction of 2-Methylcyclohexyl Imines with Hydride Reagents[a]



R	$NaBH_4$ i-C_3H_7OH 25 °C	$NaBH_3CN$, H^+ CH_3OH 25 °C	$(CH_3)_3CNH_2BH_3$ CH_3COOH[b] 25 °C	$NaAlH_2(OCH_2CH_2OCH_3)_2$ THF 56 °C	$LiBH(sec\text{-}C_4H_9)_3$ THF 56 °C
	ratio of cis/trans product (% yield)				
C_6H_5	75/25 (93)	71/29 (93)	89/11 (76)	76/24 (92)	93/7 (76)
c-C_6H_{11}	74/26 (94)	73/27 (46)	83/17 (63)	72/28 (85)	99/1 (58)
$C_6H_5CH_2$	85/15 (90)	76/24 (92)		78/22 (81)	99/1[d] (78)
2-methylcyclohexanone	25/75[e]	28/72	49/51		99.3/0.7[f]

[a] The reductions were conducted under Ar or N_2 for 20–24 h, with solutions being 0.167 M in imine and 0.50 M in hydride unless specified otherwise. Ratio of isomers were determined by GLC. All new products gave spectral data and elemental analyses consistent with the assignments (Experimental Section). [b] Hydride stirred in CH_3COOH to ensure formation of diacetoxyborane. [c] The concentration of hydride was 0.835 M. [d] Reference 7e reports no reaction. [e] Reference 3a. [f] Reference 6a; conducted at 0 °C.

Table IV. Reduction of 2-Alkylcycloalkyl Enamines and Iminium Salts[a]



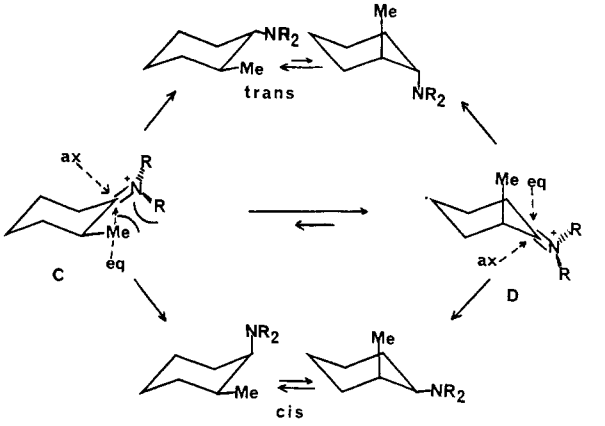
n	R	R_1 and R_2	$NaBH_4$	$NaBH_3CN$	NH_3BH_3	$(CH_3)_3CNH_2BH_3$	$(i\text{-}C_3H_7)_2NHBH_3$
			ratio of cis/trans amines (% yield)				
3	CH_3	$(CH_2)_4$		66/34 (75)	66/34 (59)	68/32 (73)	70/30 (85)
3	CH_3	$(CH_2)_5$	82/18	79/21	80/20	80/20	72/18
3	CH_3	$[(CH_2)_2]_2O$	82/18 (63)	82/18 (82)	80/20 (84)	80/20 (85)	74/26 (70)
3	CH_3CH_2	$[(CH_2)_2]_2O$		82/18	81/19	82/18 (60)	68/32
3	cyclohexyl	$(CH_2)_4$			72/28	94/6	96/4
2	CH_3	$(CH_2)_4$	98/2 (80)		97/3 (92)	98/2 (82)	
2	CH_3	$[(CH_2)_2]_2O$	98/2 (93)		95/5 (84)	97/3 (82)	

compd	$NaBH_4$	$NaBH_3CN$	$(CH_3)_3CNH_2BH_3$	$LiBH(sec\text{-}C_4H_9)_3$[b]
	ratio of cis/trans amines (% yield)			
3			79/21	48/52 (60)
4		83/17 (70)		62/38
5			82/18	68/32
2-methylcyclohexanone	55/45	48/52	49/51	99.3/0.7[c]
2-methylcyclopentanone			38/62	98/2[c]

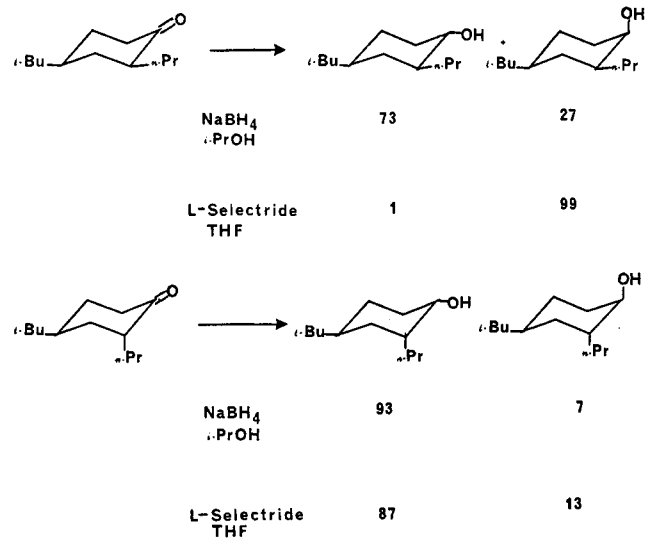
[a] The reductions were conducted under Ar or N^2 for 20–24 h in acetic acid at 25 °C. Solutions were 0.167 M in substrate and 0.33 M in hydride reagent. Hydrides were stirred in CH_3COOH prior to addition of substrate to ensure formation of acetoxyboron species. Ratios of isomers were determined by GLC. All new products gave spectral data and elemental analyses consistent with the assignments (Experimental Section). [b] Conducted in THF. [c] Reference 6a; conducted at 0 °C.

However, the similarity of results with unhindered reagents (i.e. $NaBH_4$, 2-propanol), in contrast to the 3- and 4-alkyl systems, suggested that additional influences must be considered involving conformational changes induced by the proximate alkyl groups. Thus, an equatorial alkyl substituent suffers a severe eclipsing interaction (i.e., C, Scheme I) with any nitrogen attachment (1,3-allylic strain)[4] which can only be relieved by escape to the axial alkyl conformer D, thereby shifting the equilibria to favor, or at least enhance, this latter form. This situation has been observed to a lesser extent in the reduction of 2-alkylcyclohexanones with complexing hydrides such as $ClMgAlH_4$ and $Mg(AlH_4)_2$.[3d] The effect with carbon–nitrogen π systems is probably augmented since iminium ions from enamines cannot avoid allylic strain and since imines complex more readily than carbonyls. Then equatorial attack of C and/or axial approach of D leads to the ob-

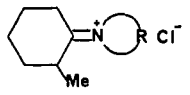
Scheme I. Allylic Strain Increases Population and Axial 2-Alkyl Decreases Equatorial Approach



Scheme II



served preferred cis products. The results suggest either that a 2-axial alkyl group retards equatorial attack forcing axial attack on D or that equatorial approach of C is significantly faster than axial or equatorial attack of D. This question was probed in two ways. First, the intermediate 2-methylcyclohexyl iminium salts **3–5** were prepared.[18]



3 R = $(CH_2)_4$

4 R = $(CH_2)_5$

5 R = $[(CH_2)_2]_2O$

Reductions of **3–5** are presented in Table IV and show that *tert*-butylamine–borane and $NaBH_3CN$ in acetic acid afforded similar product profiles as obtained with the enamines, namely, high cis/trans ratios. However, reduction with LiBH (*sec*-Bu)$_3$ gave mixtures containing substantial quantities of both cis and trans isomers in contrast to the usual extreme stereoselectivity observed with ketones,[6] 3- and 4-substituted imines,[7f,1,m] and unhindered iminium ions. These results provide compelling evidence that axial 2-alkyl groups do retard equatorial attack for moderate to highly hindered reducing agents and force more axial attack. If such were not the case, L-Selectride would have provided high predominances of the trans isomer via equatorial attack of D, the vastly predominate conformer.[19] Evidently, with small to moderately bulky reagents such as diacetoxyborane and diacetoxycyanoborane, the encumberance is sufficient to overcome interference toward axial attack introduced by the nitrogen substituents, and preference reverts to axial favoring.[20] With the very bulky L-Selectride either equatorial approach of C competes with equatorial attack of D even though the population of the latter is much higher (i.e. $k_{eC} > k_{eD}$) or the cis isomer results from axial approach to D. In either case, an axial 2-alkyl group must retard attack from the same side by bulky hydrides. This was confirmed by the reductions of *cis*- and *trans*-4-*tert*-butyl-2-propylcyclohexanones[22] with $NaBH_4$ and LiBH(*sec*-Bu)$_3$ shown in Scheme II. Significantly, both reagents afforded a high predominance of axial attack on the trans isomer. This is expected with $NaBH_4$[2] but is a dramatic reversal of the unusual equatorial approach observed with L-Selectride[6] and shows that increased congestion flanking the system alters the direction of attack by bulky reagents.[25]

Reductions of 2-methylcyclopentyl enamines are exceptionally stereoselective leading almost entirely to cis isomers (95–98%, Table IV) with acetyoxyborn hydrides. This was in contrast to the results for 2-methylcyclopentanone which gave a predominance of the trans isomer (62%, Table IV). This has been observed with other relatively unhindered reagents and attributed to a pseudoequatorial disposition of the methyl group, causing hindrance toward trans attack by the C_2 hydrogen.[2b] In the iminium ion, however, inspection of models indicate that 1,3-allylic strain pushes the methyl into a pseudoaxial orientation which blocks an approaching reagent, and entrance is favored from the opposite face, giving the cis isomers.[26]

Summary and Conclusions

The results presented suggest that additional factors must be considered in defining stereochemical consequences of carbon–nitrogen π bond reduction compared to corresponding ketones. For 3- and 4-alkyl cyclic systems, augmented steric interactions introduced by N substituents enhance attack from the equatorial direction for even moderately substituted hydride reagents, resulting

(18) Via treatment of the enamines with HCl in dry ether. Attempts to prepare **3–5** directly from the ketone and amine salts[8b] failed.

(19) (a) Johnso, F.; Whitehead, A. *Tetrahedron Lett* **1964**, 3825. (b) Johnson, F.; Malhotra, S. K. *J. Am. Chem. Soc.* **1965**, *87*, 5492. (c) Malhotra, S. K.; Johnson, F. *Ibid.* **1965**, *87*, 5493. (d) Johnson, F. *Chem. Rev.* **1968**, *68*, 375. (e) Johnson, F.; Dix, D. T. *J. Am. Chem. Soc.* **1971**, *93*, 593. (f) The intensity of 1,3-allylic strain is illustrated by the finding that *cis*-2,6-dimethylcyclohexanone oxime adopts the conformation with the methyls axial, see: Durand, R.; Geneste, P.; Moreau, C.; Pavia, A. A. *Org. Magn. Reson.* **1974**, *6*, 73. Other, sometimes spectacular examples of the effects of allylic strain on conformation preferences include: Geneste, P.; Kamenka, J. M.; Hugon, I.; Graffin, P. *J. Org. Chem.* **1976**, *41*, 3637. Chandrasekrar, N.; Ramalingan, K.; Herd, M. D.; Berlin, K. D. *Ibid.* **1980**, *45*, 4352. Chandrasekara, N.; Ramalingam, K.; Berlin, K. D. *Spectrosc. Lett.* **1981**, *14*, 11. Tourwe, D.; DeCock, E.; Van Binst, G. *J. Org. Chem.* **1981**, *46*, 5321.

(20) Electronic, antiperiplaner effects[21] also predict enhanced axial attack of D since the axial substituent is anti to the incoming hydride; see ref 2b for a discussion of such effects.

(21) Klein, J. *Tetrahedron* **1974**, *30*, 3349. Anh, N. T.; Eisenstein, O.; Lefour, J. M.; Tran Huu Dau, M. R. *J. Am. Chem. Soc.* **1973**, *95*, 6146.

(22) The cis isomer was prepared by alkylation of 2-carbethoxy-4-*tert*-butylcyclohexanone and decarboxylation;[23] the trans isomer was obtained via alkylation of the pyrrolidine enamine of 4-*tert*-butylcyclohexanone and mild hydrolysis.[24]

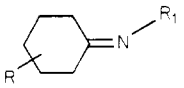
(23) Allinger, N. S.; Blatter, J. M.; Freiberg, L. A.; Karkowski, F. M. *J. Am. Chem. Soc.* **1966**, *88*, 2999.

(24) Karady, S.; Lenfant, M.; Wolff, R. W. *Bull. Soc. Chim. Fr.* **1965**, 2472. Malhotra, S. K.; Johnson, F. *Tetrahedron Lett.* **1965**, 4027.

(25) The retarding influence of axial 2-substituents in cyclohexanones is also consistant with the nearly total production of *cis*-2-methylcyclohexanol (>99%) from the ketone with trialkylborohydrides[6] even though the conformational equilibria contains significant quantities (ca. 5%) of the axial 2-methyl conformer. In this case, equatorial attack on the equatorial methyl conformer must be substantially faster than equatorial attack on the axial methyl isomer, and, in fact, any attack of the axial methyl conformer occurs from the axial (opposite) direction. See also: Hutchins, R. O. *J. Org. Chem.* **1977**, *42*, 920. The retarding effect of an axial 2-alkyl group is quite dependent on the reducing agent since the rate of equatorial attack on 2,2-dimethyl-4-*tert*-butylcyclohexanone[3a] is only slightly diminished compared to 4-*tert*-butylcyclohexanone, a result attributed to similar eclipsing interactions between the incoming hydride with the C_2 and C_6 axial hydrogens or methyl.[3a,4b] Apparently only when the reagent bulk is clustered close to the core atom (as in tri-*sec*-butylborohydride) does the additional steric interaction become dominant and overcome the syn-axial repulsions encountered by axial attack. Noteworthy is the fact that LiAlH(O-*t*-Bu)$_3$ behaves as a "small" reagent, giving a 9:1 ratio of axial/equatorial attack with 4-*tert*-butylcyclohexanone.[3a]

(26) This also has been observed in the reduction of iminium salts of 17-keto steroids containing an adjacent methyl with $LiAlH_4$. The cis isomers were the only reported products: Scribner, R. M. *J. Org. Chem.* **1965**, *30*, 3203.

Table V. Imine and Iminium Salts Physical Data



R	R_1	bp, °C (torr)	% yield isolated	IR, cm^{-1} (C=N)
2-CH_3	C_6H_5	95 (0.25)	83	1650
2-CH_3	C_6H_{11}	142 (4)	84	1660
2-CH_3	$C_6H_5CH_2$	98 (0.5)	80	1660
4-CH_3	C_6H_5	110 (2)	85	1650
4-CH_3	C_6H_{11}	120 (4)	83	1655
4-*t*-C_4H_9	C_6H_5	110 (0.05)	82	1650
4-*t*-C_4H_9	C_6H_{11}	131 (0.1)	81	1660
4-*t*-C_4H_9	$C_6H_5CH_2$	154 (0.5)	73	1660
3,3,5-$(CH_3)_3$	$C_6H_5CH_2$	121 (0.5)	75	1660
4-*t*-C_4H_9	$(CH_2)_4$	258-260[a]	92	1660
4-*t*-C_4H_9	$(CH_3)_2$	243-244 dec[a]	33	1680

[a] Melting point of the perchlorate salt.

in much higher amounts of axial amines compared to ketones. With 2-alkyl systems, all reagents afford *cis*-2-alkyl cyclic amines which suggests that (1) increased steric interactions between N substituents and equatorial 2-alkyl groups (1,3-allylic strain) induce conformation changes in favor the axial 2-alkyl conformer and that (2) hinderances to equatorial approach by reagents induced by axial alkyl substituents combine to favor net formation of cis products.

Experimental Section

Melting points were obtained on a Mel-Temp apparatus and are uncorrected as are boiling points. Infrared spectra were recorded on a Perkin-Elmer 457 or 200 spectrophotometer. NMR spectra were obtained on Varian A60, JEOL FX-90Q, or IBM 200 spectrometers with Me_4Si as a standard. Analtical gas chromatography was performed by using a Varian 3700 (FID) instrument coupled to a Varian CDS III electronic integrator. The columns utilized were one of the following: (A) 10% sp2250 on 100/120 Supelcoport; (B) 15% THEED on 100/120 Supelcoport; (C) capillary Carbowax 20M; (D) 10% Carbowax 20M on 100/120 Supelcoport. Preparative GC was conducting by using a Hewlett-Packard Model 5200 instrument (TC). Elemental analyses were performed by Micro-Analysis, Inc., Wilmington, DE.

The hydride reagents were commercial products used without further purification although purity was routinely monitored by hydrogen evolution.[27] Solvents were dried by storage over 4A molecular sieves (2-propanol, methanol) or distillation from Na/benzophenone (THF, ether). Glacial acetic acid was used as received from freshly opened bottles. Trans-rich mixtures of 3- and 4-methylcyclohexylamines were commercial products from Aldrich Chemical Co.

Preparation of Reactants. (a) Iminium Perchlorates. The general procedure of Leonard[8b] was employed and involved treatment of amine perchlorates[8b] with ketones in ethanol followed by recrystallization from 2-propanol. Data for the derivatives are listed in Table V.

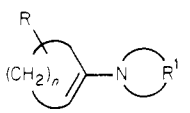
(b) Imines. Standard procedures for imine preparations were employed and involved refluxing the ketone, primary amine (25–100% excess), and a small quantity of *p*-toluenesulfonic acid in benzene until the theoretical amount of water had collected in a Dean–Stark apparatus. Solvent was then removed and the residue fractionated under vacuum. The products were stored under Ar at 0 to −20 °C. Data are listed in Table V.

(c) Enamines. In a related fashion as for imines, the ketone, secondary amine (25–100% excess), and *p*-toluenesulfonic acid were refluxed in benzene until the expected quantity of water was removed. The products were fractionated stored under Ar at 0 or −20 °C. Data are listed in Table VI.

(d) 2-Methylcyclohexyl Iminium Hydrochlorides. The pyrrolidine, piperidine, or morpholine enamine of 2-methylcyclohexanone (4 mmol) was dissolved in 15 mL of dry ether and dry HCl bubbled in for a few minutes. Solvent was decanted from the resulting precipitating hydrochloride salt and tested for completion of reaction with additional HCl. The salts were washed with four portions of ether by decantation and then dried under vacuum. Yields for the pyrrolidine (**3**), piperidine (**4**) and morpholine (**5**) hydrochloride were 87%, 89%, and 95%, respectively. The extreme sensitivity to moisture precluded further characterization, and the salts were reduced directly as described below.

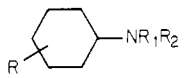
General Reduction and Product Analysis Procedures. The reactant and hydride reagent concentrations along the solvents, reaction temperatures, and times are listed in Tables I–IV with deviations noted. In general a 3:1 ratio of hydride was employed for iminium ion and imine reductions while 2:1 ratios were sufficient for enamines. Less than these ratios generally gave inferior yields while higher ratios showed no improvement in yields or change in product isomer ratios. Higher hydride to substrate ratios were used in alcohol solvents to minimize reduction by intermediate alkoxy hydrides. Workup procedures varied with the solvent empolyed, and representative methods are presented below. The isomer compositions of the products were determined by GC using the columns listed in Table VII. Analysis were performed before and after purification by flash distillation to ensure that selective concentration did not alter compositions. In no case was a significant difference detected. With all 3- and 4-alkyl cases, the cis isomer eluted from the GC columns prior to the trans, but this consistancy was not noted for the 2-alkyl examples; this is indicated in Table VII. Assignments of cis and trans isomers were accomplished by the initial assumption that

Table VI. Enamine Physical Data



n	R	R^1	bp, °C (torr)	% yield isolated	IR, cm^{-1} (CH=CH—N)
3	2-CH_3	$(CH_2)_4$	53-54 (2)	78	1620
3	2-CH_3	$(CH_2)_5$	63-64 (1)	74	1630
3	2-CH_3	$(CH_2CH_2)_2$	72-74 (2)	73	1630
3	2-C_2H_5	$(CH_2CH_2)_2O$	76-77 (1)	71	1635
3	2-C_6H_{11}	$(CH_2)_4$	134-135 (1.5)	80	1630
2	2-CH_3	$(CH_2)_4$	73-74 (3.5)	70	1633
2	2-CH_3	$(CH_2)_5$		83	1632
2	2-CH_3	$(CH_2CH_2)_2O$	86-87 (3.5)	86	1635
3	3-CH_3	$(CH_2)_4$	77-80 (2)	66	1638
3	3-CH_3	$(CH_2CH_2)_2O$	114-115 (2)	56	1630
3	4-CH_3	$(CH_2)_4$	67-68 (2)	85	1630
3	4-CH_3	$(CH_2)_5$	71-73 (2)	81	1640
3	4-*t*-C_4H_9	$(CH_2)_4$	134-135 (3)	78	1640
3	4-*t*-C_4H_9	$(CH_2)_5$	147-148 (4)	56	1640
3	4-*t*-C_4H_9	$(CH_2CH_2)_2O$	155-156 (5.5)	79	1640

Table VII. Physical Data of Amine Products



R	R_1	R_2	GC analysis	isomer	mp, °C	analysis: calcd C	analysis: calcd H	analysis: found C	analysis: found H
4-CH_3	$(CH_2)_4$		A	cis	137-137.5[a]	51.51	6.10	51.72	6.10
4-CH_3	$(CH_2)_4$			trans	190-192[a]	51.51	6.10	51.62	6.25
4-CH_3	$(CH_2)_5$		A	cis	120-121[a]	52.68	6.39	52.27	6.22
4-CH_3	$(CH_2)_5$			trans	155.5-156.5[a]	52.68	6.39	52.52	6.51
4-CH_3	C_6H_5	H	B	cis	130-131[b]	81.87	7.90	81.62	7.97
4-CH_3	C_6H_5	H		trans	97-98[c]	69.93	7.34	70.09	7.25
4-CH_3	C_6H_{11}	H	B	cis	260-262[d]	67.36	11.30	67.84	12.63
4-CH_3	C_6H_{11}	H		trans[e]		79.93	12.90	79.73	13.00
3-CH_3	$(CH_2)_4$		A	trans	150-151[a]	51.51	6.10	51.36	6.21
3-CH_3	$(CH_2)_4$			cis	185-187[a]	51.51	6.10	51.09	5.93
3-CH_3	$(CH_2)_5$		A	trans	130-132[a]	52.68	6.39	52.70	6.17
3-CH_3	$(CH_2)_5$			cis	143-144[a]	52.68	6.39	52.39	6.42
2-CH_3	$(CH_2)_4$		A[h]	cis	111-112[a]	51.51	6.10	51.45	6.11
2-CH_3	$(CH_2)_4$			trans	112-114[a]	51.51	6.10	51.13	6.24
2-CH_3	$(CH_2)_5$		A[h]	cis	156-157[a]	52.68	6.39	52.61	6.22
2-CH_3	$(CH_2)_5$			trans	116-117[a]	52.68	6.39	52.71	6.73
2-CH_3	$(CH_2CH_2)_2O$		A[h]	cis	175-174[a]	49.51	5.87	49.83	5.98
2-CH_3	$(CH_2CH_2)_2O$			trans		72.08	11.55	72.27	11.57
2-CH_3	$C_6H_5CH_2$	H	B	cis	190-191[d]	70.12	9.25	69.86	9.10
2-CH_3	$C_6H_5CH_2$	H		trans	70-72	70.55	7.61	70.29	7.70
2-CH_3	C_6H_5	H	A[h]	cis[e]		82.48	10.12	82.21	10.05
2-CH_3	C_6H_5	H		trans	106-107[c]	69.93	7.34	69.98	7.39
2-CH_3	C_6H_{11}	H	C	cis[e]		79.93	12.90	79.81	12.78
2-CH_3	C_6H_{11}	H		trans[e]		79.93	12.90	80.30	12.93
2-C_2H_5	$(CH_2CH_2)_2O$		A[h]	cis	183-184[a]	50.70	6.14	50.65	6.44
2-C_2H_5	$(CH_2CH_2)_2O$			trans	115-117[a]	50.70	6.14	50.59	6.08
2-C_6H_{11}	$(CH_2)_4$		A[h]	cis	194-195[a]	56.89	6.94	56.66	6.90
2-C_6H_{11}	$(CH_2)_4$			trans	147-148[a]	56.89	6.94	56.68	7.07
2-CH_3[f]	$(CH_2)_4$		C	cis	107-108[a]	50.26	5.80	50.15	5.77
2-CH_3[f]	$(CH_2)_4$			trans	130-131[a]	50.26	5.80	50.24	5.71
2-CH_3[f]	$(CH_2)_5$		A[h]	cis	121-122[a]	51.51	6.10	51.42	6.39
2-CH_3[f]	$(CH_2)_5$			trans	131-132[a]	51.51	6.10	51.88	6.09
2-CH_3[f]	$(CH_2CH_2)_2O$		A[h]	cis	145-146[a]	48.24	5.57	47.92	5.30
2-CH_3[f]	$(CH_2CH_2)_2O$			trans	154-156[a]	48.24	5.57	48.27	5.63
4-*t*-C_4H_9	$(CH_2)_4$		A	cis	139-140[a]	54.78	6.90	54.48	6.97
4-*t*-C_4H_9	$(CH_2)_4$			trans	71-73[g]	80.31	13.00	80.11	13.18
4-*t*-C_4H_9	$(CH_2)_5$		A	cis	120-123[a]	55.74	7.13	55.76	7.30
4-*t*-C_4H_9	$(CH_2)_5$			trans[e]		80.65	13.09	80.84	13.18
4-*t*-C_4H_9	$(CH_2CH_2)_2O$		A	cis	161-163[a]	52.74	6.86	52.45	6.72
4-*t*-C_4H_9	$(CH_2CH_2)_2O$			trans	186-187[a]	52.74	6.86	52.40	6.72
4-*t*-C_4H_9	$C_6H_5CH_2$	H	A, B	cis[e]		83.20	11.09	82.91	11.10
4-*t*-C_4H_9	$C_6H_5CH_2$	H		trans[e]		83.20	11.09	83.01	10.92
4-*t*-C_4H_9	C_6H_5	H	A, B	cis	195-196[d]	71.75	9.41	71.70	9.80
4-*t*-C_4H_9	C_6H_5	H		trans	141-142[c]	71.65	8.10	71.64	8.17
4-*t*-C_4H_9	C_6H_{11}	H	B	cis	261-262[d]	70.17	11.41	70.60	12.17
4-*t*-C_4H_9	C_6H_{11}	H		trans	131-133[b]	80.88	10.53	80.86	10.26
3,3,5-$(CH_3)_3$	$C_6H_5CH_2$		B	trans	185-186[d]	71.75	9.78	71.50	9.75
3,3,5-$(CH_3)_3$	$C_6H_5CH_2$			cis[e]		83.05	10.89	83.13	10.91
4-*t*-C_4H_9	H	H	A	trans	137-140[c]				
				cis	184-185[c]	65.98	8.79	66.01	8.82
2-C_2H_5	H	H	A	trans	115-116.5[c]	64.02	8.2	64.16	8.05
3,3,5-$(CH_3)_3$	H	H	A	cis	119-120[c]	65.04	8.53	65.03	8.44

[a] Picrate salt. [b] Benzamide derivative. [c] *p*-Toluenesulfonamide derivative. [d] Hydrochloride salt. [e] Collected by preparative GC (OV-1). [f] Cyclopentyl derivative. [g] Picrate mp 178–181 °C. [h] Trans isomer eluted prior to cis.

$LiBH(i\text{-}C_4H_9)_3$ reductions of 3- and 4-alkyl cases afford the axial amine isomers in predominance, and this was confirmed by independent syntheses. 2-Alkyl isomer assignments were confirmed by alternate syntheses. Examples are presented below. Isolations of individual isomers were accomplished in several manners. Reductions with $LiBH(i\text{-}C_4H_9)_3$ provided mixtures highly rich in the cis diastereomers (Tables I–III) while independent syntheses (see below) gave trans-rich compositions. Final purifications were successful by column (silica gel) or preparative GC chromatography or by conversions of cis- or trans-rich mixtures to solid derivatives which were purified by recrystallization. Data are listed in Table VII.

Reduction of *N*-(4-*tert*-Butylcyclohexylidene)-pyrrolidinium Perchlorate. (a) $NaBH_4$. A solution of the perchlorate (1.54 g, 5mmol) and $NaBH_4$ (0.95 g, 25 mmol) in 30 mL of 2-propanol was refluxed under Ar for 20 h, cooled diluted with 50 mL or water, and acidified with HCl to pH ca. 1. The solution was then made basic with 50% aqueous NaOH and extracted with three 50-mL portions of CH_2Cl_2. The combined extract was dried (K_2CO_3), filtered and, after GC analysis (GC column A, Table VII), concentrated under reduced pressure. The residue was flash distilled in a Kugelrohr apparatus to afford cis and *trans*-*N*-4-*tert*-butylcyclohexyl)pyrrolidine (1.0 g, 97%). The trans isomer was isolated by fractional crystallization from acetone; mp 71–73 °C (Table VII). The picrate had a melting point of 178–181 °C.

(b) $LiBH(i\text{-}C_4H_9)_3$. A solution of the perchlorate (1.54 g, 5 mmol) in 15 mL of dry THF under Ar was cooled in an ice bath

and LiBH(*sec*-$C_4H_9)_3$ (15 mL, of a 1 M solution, 15 mmol) added. The solution was refluxed for 1.5 h and then quenched by slow addition of 2 mL of water. Ethanol (15 mL) and KOH (0.86 g) were added, the mixture was cooled to 0 °C, and 30% H_2O_2 (6 mL) was slowly added (30 min). The reaction was stirred at ambient temperature for 1 h and then for 1 h at 60 °C, cooled, poured into 150 mL of ice–water, and extracted thoroughly with ether. The ether phase was washed with brine, dried (K_2CO_3), and, after GC analysis (column A, Table VII), concentrated at reduced pressure. The residue was flash distilled (Kugelrohr apparatus) to afford a mixture of cis and trans amine isomers (936 mg, 90%) which contained 94% of the cis isomer (GC, Table I). Recrystallization from acetone provided pure *cis*-*N*-(4-*tert*-butylcyclohexyl)pyrrolidine: mp 48–50 °C; characterized as the picrate, mp 139–140 °C (Table VII).

Reduction of *N*-Benzyl-3,3,5-trimethylcyclohexanimine with $NaBH_3CN$. To a solution of the imine (1.14 g, 5 mmol) and $NaBH_3CN$ (0.96 g, 15 mmol) in dry methanol (30 mL) under Ar was added a small amount of bromocresol green indicator. Concentrated HCl was added dropwise to maintain the pH below 4 (yellow), and the reaction mixture was stirred at room temperature for 20 h. The solution was then diluted with 50 mL of water, made basic with KOH, and extracted thoroughly with CH_2Cl_2. After the mixture was dried (K_2CO_3), the solvent was removed at reduced pressure and the residue flash distilled to give 1.04 g (94%) of 3,3,5-trimethyl-*N*-benzylcyclohexylamine isomers which contained 94% of the trans isomer (GC Table I) which was characterized as the HCl salt, mp 185–86 °C (Table VII).

Reduction of *N*-Benzyl-4-*tert*-butylcyclohexanimine with $NaAlH_2(OCH_2CH_2OCH_3)_2$. A solution containing the imine (1.22 g, 5 mmol) and $NaAlH_2(OCH_2CH_2OCH_3)_2$ (4.33 mL of a 70% solution in C_6H_6, 15 mmol) in 30 mL of dry THF was refluxed under Ar for 20 h, cooled, and then poured into 50 mL of 20% NaOH. The mixture was extracted thoroughly with CH_2Cl_2, the combined extract was dried (K_2CO_3) and concentrated, and the residue flash distilled on a Kugelrohr apparatus to yield 1.14 g (94%) of *cis*- and *trans*-4-*tert*-butylcyclohexylamines. Separation was accomplished via preparative GC (OV-1 column).

Reduction of 4-*tert*-Butyl-1-(1-pyrrolidinyl)cyclohexene with $(CH_3)_3CNH_2BH_3$ (Reverse). The amine–borane (0.87 g, 10 mmol) was stirred with 30 mL of glacial acetic acid under Ar for 12 h, the enamine (1.04 g, 5 mmol) was then added, and the solution was stirred at room temperature for 16 h. Concentrated HCl (4 mmL) was added, and the solution was stirred for 1 h, poured onto ice, and made basic with 50% aqueous NaOH. The mixture was thoroughly extracted with ether, and the organic phase was dried (K_2CO_3), concentrated after GC analysis (Table VII), and flash distilled on a Kugelrohr apparatus to afford 0.93 g (89%) of the *cis*- and *trans*-*N*-(4-*tert*-butylcyclohexyl)-pyrrolidines. GC analysis indicated an 87/13 cis/trans ratio (Table II). For examples not conducted under reverse conditions (Tables I and III), the above procedure was modified only in that the enamine was dissolved in acetic acid followed by the amine–borane.

Reduction of Ketones in Acetic Acid. The above reaction conditions were employed by substituting 4-*tert*-butylcyclohexanone or 2-methylcyclohexanone for the enamines. GC analyses were performed on the following columns: (1) 4-*tert*-butylcyclohexanols; (2) 2-methylcyclohexanols, 10% TCEP on 100/120 Chromosorb W AW; (3) 4-*tert*-butyl-2-*n*-propylcyclohexanols, GC column C; (4) 2-methylcyclopentanols, GC column C; (5) 2-*n*-propyl-4-*tert*-butylcyclohexanols, GC column C.

Alternate Preparations of Amine Isomers. As discussed in the text, mixtures rich in trans amine were prepared via reduction of the oximes via Na/ethanol followed by conversion to the tertiary or secondary amines by cyclization with an appropriate dibromide or by reductive amination, respectively. Since the *N*-phenyl derivatives could not readily be prepared from trans-rich amines, identification was accomplished by catalytic hydrogenation to the *N*-cyclohexyl systems. Representative procedures are presented to illustrate the processes.

Preparation of Oximes. (a) 2-Methylcyclopentanone. A solution of NH_2OH HCl (10.4 g, 0.15 mol) and sodium acetate (13.6 g, 0.1 mol) in 50 mL of water and 10 mL of ethanol was warmed to 60 °C and 2-methylcyclopentanone (9.8 g, 0.1 mol) added with swirling. The flask was stirred and ethanol added until the solution was homogeneous (ca. 50 mL). The solution was heated on a steam bath for 1–5 h, kept at ambient temperature overnight, and poured onto ice. The mixture was extracted thoroughly with ether, the organic phase dried (Na_2SO_4) and concentrated, and the residue distilled to yield the oxime: 8.23 g (72%); bp 82–83 °C (3 mm); IR ca. 3260 (br, OH), 1680 cm^{-1} (C=N).

(b) 2-Methylcyclohexanone Oxime. In a similar fashion the oxime was obtained in 93% yield: bp 65–66 °C (2 mm) (lit.[28b] bp 117–118 °C (22 mm)); IR 3280 (br, OH), 1665 cm^{-1} (C=N).

(c) 2-Cyclohexylcyclohexanone oxime: obtained in 85% yield; mp 100–101 °C (lit.[28a] mp 98–99 °C); IR 3260 (br, OH), 1665 cm^{-1} (C=N).

(d) 2-Ethylcyclohexanone oxime: obtained in 89% yield; bp 67–69 °C (3 mm) (lit.[28c] bp 120 °C (20 mm)); IR 3280 (br, OH), 1665 cm^{-1} (C=N).

(e) 4-*tert*-Butylcyclohexanone oxime: obtained in 87% yield; mp 138–139 (lit.[28b] mp 137.5–138.5 °C); IR 3260 (br, OH), 1677 cm^{-1} (C=N).

(f) 3,3,5-Trimethylcyclohexanone oxime: obtained in 62% yield; mp 86–87 °C (lit.[28b] mp 72–73 °C); IR 3240 (br, OH), 1670 cm^{-1} (C=N).

Preparation of Trans-Rich Primary Amines. Reduction of Oximes. (a) 2-Methylcyclopentylamines. The oxime (8.2 g, 0.072 mol) was dissolved in 160 mL of dry ethanol and the solution heated to reflux. The heat was removed and Na(20 g, 0.87 mol) added in small pieces to maintain reflux. An additional 100 mL of ethanol was added to maintain solution. The solution was diluted with water (ca. 200 mL) and steam distilled into 20% HCl. The distillate was evaporated to dryness, and the residue was made basic with 50% NaOH and extracted thoroughly with ether. The ether solution was dried ($MgSO_4$), concentrated, and distilled to yield the amine isomers: 3.28g (46%); bp 68–69 °C (90 mm); GC analysis (GC column C) indicated the cis/trans isomer ratio to be 14/86.

(b) 2-Methylcyclohexylamines. Oxime reduction as above gave the amine: 60% yield; bp 78 °C (100 mm) [lit.[28] bp 150 °C (760 mm)]; 20/80 cis/trans mixture of isomers (GC, column A). A commercial sample (Aldrich) was an 8/92 mixture of cis and trans isomers: IR 3340, 3280 cm^{-1} (d).

(c) 2-Cyclohexylcyclohexylamines: obtained from the oxime in 56% yield; bp 96 °C (8 mm); separation by GC was not successful; Ir 3370, 3290 cm^{-1} (d); characterized as the benzamide, mp 155–56 °C (lit.[28b] mp 157–158 °C).

(d) 2-Ethylcyclohexylamines: obtained from the oxime in 75% yield; bp 99–100 °C (70 mm); cis/trans ratio was 10/90 (GC column A); IR 3370, 3290 cm^{-1} (d); characterized as the *p*-toluenesulfonamide (Table VII).

(e) 3,3,5-Trimethylcyclohexylamines: obtained from the oxime in 83% yield; cis/trans ratio was 86–14 (GC column A); IR 3360, 3290 cm^{-1} (d); characterized as the *p*-toluenesulfonamide (Table VII).

(f) 4-*tert*-Butylcyclohexylamines: obtained from the oxime in 73% yield; flash distilled on a Kugelrohr apparatus; cis/trans ratio was 6/94 (GC, column B); IR 3350, 3280 cm^{-1} (d); characterized as the benzamide, mp 178–79 °C (lit.[29] mp 179–80 °C).

Bis(2-bromoethyl) Ether. A modified version of the procedure described by Harrison and Diehl[30] was utilized. To diethylene glycol (9.28 g, 0.0875 mol) was added dropwise with stirring PBr_3 (15 g, 0.055 mol) over a 1.5-h period. The mixture was stirred for 8 h and distilled at reduced pressure, and the distillate was collected in a flask cooled with dry ice. The distillate was diluted with water, and the organic phase was separated, dried ($CaCl_2$), and distilled to afford 6.7 g (33%) of colorless product, bp 44–45

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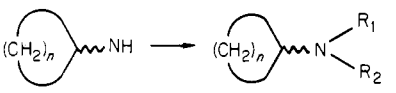
Table VIII. Preparation of Trans-Rich Amine Isomers



n	R	R_1 and R_2	% yield	ax/eq ratio primary amine	ax/eq ratio product
3	2-CH_3	$(CH_2)_4$	57	20/80	25/75
3	2-CH_3	$(CH_2)_5$	52	20/80	24/76
3	2-CH_3	$(CH_2CH_2)_2O$	55	10/80	22/78
2	2-CH_3	$(CH_2)_4$	34	14/86	13/87
2	2-CH_3	$(CH_2)_5$	48	14/86	15/85
2	2-CH_3	$(CH_2CH_2)_2O$	50	14/86	16/84
3	2-C_2H_5	$(CH_2CH_2)_2O$	47	10/90	13/87
3	2-C_6H_{11}		68		
3	3-CH_3	$(CH_2)_4$	53	28/72	30/70
3	3-CH_3	$(CH_2)_5$	49	29/72	30/70
3	4-CH_3	$(CH_2)_4$	53	35/65	34/66
3	4-CH_3	$(CH_2)_5$	48	35/65	35/65
3	3,3,5-$(CH_3)_3$	$(CH_2)_4$	63	14/86	
3	4-*t*-C_4H_9	$(CH_2)_4$		6/94	6/94
3	4-*t*-C_4H_9	$(CH_2)_5$	70	6/94	5/95
3	4-*t*-C_4H_9	C_6H_{11}	54	36/64	32/68
3	4-CH_3	C_6H_{11}	47	35/65	24/76
3	2-CH_3	C_6H_{11}	51	20/80	23/77
3	2-CH_3	$C_6H_5CH_2$	48	8/92	10/90
3	3,3,5-$(CH_3)_3$	$C_6H_5CH_2$	46	14/86	15/85

°C (0.5 mm). The IR and NMR spectra were consistent with the dibromo ether.

Tertiary Amines. Trans-Rich *N*-(2-Methylcyclopentyl)morpholine. A solution of trans-rich 2-methylcyclopentylamine (990 mg, 10 mmol; cis/trans ratio 14/86), bis(2-bromoethyl) ether (2.32 g, 10/mmol), and triethylamine (10 mL) in 50 mL of ethanol was refluxed for 4 days. The solvent was then removed at reduced pressure, 50% NaOH added, and the mixture extracted thoroughly with ether. The organic phase was dried (Na_2SO_4), concentrated, and flash distilled on a Kugelrohr apparatus to afford 847 mg (50%) of isomeric *N*-(2-methylcyclopentyl)morpholines. Analysis by GC (Column A) indicated a cis/trans ratio of 16/84 and confirmed the assignments of the isomers obtained by reduction. Several recrystallizations of the picrate from ethanol afforded the analytical sample for the trans isomer, mp 154.5–156 °C (Table VII). In the same fashion, trans-rich mixtures of *N*-(2-methylcyclopentyl)pyrrolidine (cis/trans ratio 13/87, column C) and *N*-(2-methylcyclopentyl)piperidine (cis/trans ratio 15/85, column C) were obtained by cyclization with 1,4-dibromobutane and 1,5-dibromopentane, respectively. These were characterized as the picrates (Table VII). The results of cyclizations are summarized in Table VIII.

Secondary Amines. (a) *N*-Cyclohexyl-4-*tert*-butylcyclohexylamine. A solution of tans-rich 4-*tert*-butylcyclohexylamine (68% trans; 1.55 g, 10 mmol) and cyclohexanone (2.5 g, 15 mmol) in 50 mL of benzene was refluxed until the theoretical amount of water was collected in a Dean–Stark apparatus. The solvent was evaporated, 30 mL of acetic acid and 1.75 g (20 mmol) of *tert*-butylamine–borane were added, and the solution was stirred for 20 h. The reaction was worked up as previously described for reductions with amine–boranes to yield 1.28 g (54%) of *N*-cyclohexyl-4-*tert*-butylcyclohexylamine. GC analysis (column B) indicated a 36/64 cis/trans ratio. Results of other reductive aminations are summarized in Table VIII.

(b) Conversion of *N*-Phenyl-4-*tert*-butylcyclohexylamine Isomers to *N*-Cyclohexyl-4-*tert*-butylcyclohexylamines. A mixture of phenylamines (cis/trans ratio 44/56; 1.15 g, 5 mmol), 5% rhodium/alumina, 2 drops of acetic acid, and 20 mL of dry methanol was hydrogenated (Parr apparatus, 42 psi, 10 h). The mixture was filtered, diluted with water (50 mL) and 50% NaOH (20 mL), and thoroughly extracted with ether. Concentration and flash distillation yielded *N*-cyclohexyl-4-*tert*-butylcyclohexylamine isomers. GC analysis (column A) indicated a 44/56 cis/trans ratio. Similarly, *N*-phenyl-4-methylcyclohexylamines (69/31 cis/trans ratio) and *N*-phenyl-2-methylcyclohexylamines (74/26 cis/trans ratio) afforded the corresponding cyclohexylamines in 69/31 and 74/26 cis/trans ratios, respectively.

Preparation of *cis*-4-*tert*-Butylcyclohexylamine. (a) *p,p'*-Dimethoxybenzhydrylamine. By use of published procedures,[17] *p,p'*-dimethoxybenzophenone was sequentially converted to the alcohol [$NaBH_4$, ethanol; 91%, mp 67.5–68 °C (lit.[31] mp 69 °C)], the chloride [$SOCl_2$; 99%, mp 81–82 °C (lit.[32] mp 83–84 °C], and the amine [liquid NH_3; 90% yield, mp 58–59 °C (lit.[17c] mp 58–59 °C)].

(b) *cis*-4-*tert*-Butylcyclohexylamine. A solution of 4-*tert*-butylcyclohexanone (3.08 g, 25 mmol) and *p,p'*-dimethoxybenzhydrylamine (6.08 g, 25 mmol) in 80 mL of benzene was refluxed for 48 h while water was collected via a Dean–Stark trap. Solvent was removed under vacuum, $LiBH(i\text{-}C_4H_9)_3$ in THF was added (40 mL, 1 M, 40 mmol), and the solution was refluxed for 24 h and worked up as previously described for $LiBH(sec\text{-}C_4H_9)_3$ reductions. The resulting residue was warmed (80 °C) with 30 mL of formic acid (88%) for 24 h, evaporated to dryness under vacuum, diluted with water (50 mL), and basified with 50% NaOH to pH ca. 12. The mixture was thoroughly extracted with ether, the ether evaporated, aqueous HCl added, and the mixture again extracted with ether. The aqueous phase was basified (NaOH) and thoroughly extracted with ether which was concentrated and distilled on a Kugelrohr apparatus to yield the amine (2.32 g, 59% overall). GC analysis (column B) indicated 99% of the cis isomer. Cyclization with dibromobutane as described above gave a 99/1 cis/trans ratio of 4-*tert*-butylpyrrolidine (GC, column A).

***cis*-2-*n*-Propyl-4-*tert*-butylcyclohexanone** was synthesized in 41% yield (bp 68–70 °C (0.5 mm) from 2-carbethoxy-4-*tert*-butylcyclohexanone as generally described by Allinger.[23] GC analysis (column C) indicated an 82/18 cis/trans mixture. It was characterized as the 2,4-DNP derivative, mp 144–145 °C.

***trans*-2-*n*-Propyl-4-*tert*-butylcyclohexanone** was synthesized via enamine alkylation as described[24] in 36% yield [bp 69–72 °C (0.5 torr), lit.[24] bp 130 °C (10 torr)]. GC analysis (column C) indicated an 11/89 cis/trans ratio of isomers (lit. 10/90).

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Registry No. **1a**, 80516-56-9; **1b**, 777-60-6; **3**, 86822-50-6; **4**, 86822-51-7; **5**, 86822-52-8; $NaBH_4$, 16940-66-2; $NaBH_3CN$, 25895-60-7; $(CH_3)_3CNHBH_3$, 7337-45-3; $(CH_3)_2NHBH_3$, 74-94-2; $(i\text{-}C_3H_7)_2NHBH_3$, 55124-35-1; NH_3BH_3, 13774-81-7; $NaAlH_2(OCH_2CH_2OCH_3)_2$, 22722-98-1; $LiBH(sec\text{-}C_4H_9)_3$, 38721-52-7; *N*-phenyl-4-*tert*-butylcyclohexanimine, 80516-57-0; *N*-benzyl-4-*tert*-butylcyclohexanimine, 27721-51-3; *N*-phenyl-4-methylcyclohexanimine, 51488-27-8; *N*-benzyl-3,3,5-trimethylcyclohexanimine, 80516-58-1; *N*-(4-*tert*-butylcyclohexylidene)pyrrolidinium perchlorate, 67282-73-9; 4-*tert*-butyl-*N,N*-dimethylcyclohexaniminium perchlorate, 14447-55-3; *N*-(4-methylcyclohexylidene)pyrrolidinium perchlorate, 83957-63-5; 4-*tert*-butyl-1-(1-pyrrolidinyl)cyclohexene, 4147-00-6; 4-*tert*-butyl-1-(1-piperidinyl)cyclohexene, 67074-49-1; 4-*tert*-butyl-1-(4-morpholinyl)cyclohexene, 16963-28-3; 4-methyl-1-(1-pyrrolidinyl)cyclohexene, 39716-23-9; 4-methyl-1-(1-piperidinyl)cyclohexene, 31882-35-6; 5-methyl-1-(4-morpholinyl)cyclohexene, 21403-96-3; 5-methyl-1-(1-piperidinyl)cyclohexene, 21403-98-5; 5-methyl-1-(1-pyrrolidinyl)cyclohexene, 17271-84-0; *N*-phenyl-2-methylcyclohexanimine, 13280-22-3; *N*-cyclohexyl-2-methylcyclohexanimine, 20007-02-7; *N*-benzyl-2-methylcyclohexanimine, 31887-88-4; 6-methyl-1-(1-pyrrolidinyl)cyclohexene, 5049-51-4; 6-methyl-1-(1-piperidinyl)cyclohexene, 6127-99-7; 6-methyl-1-(4-morpholinyl)cyclohexene, 5292-69-3; 6-ethyl-1-(4-morpholinyl)-cyclohexene, 86822-53-9; 6-cyclohexyl-1-(1-pyrrolidinyl)cyclohexene, 86822-54-0; 5-methyl-1-(1-pyrrolidinyl)cyclopentene, 69956-37-2; 5-methyl-1-(4-morpholinyl)cyclopentene, 5601-46-7; 5-methyl-1-(1-piperidinyl)cyclopentene, 86822-55-1; *cis*-*N*-(4-methylcyclohexyl)pyrrolidine picrate, 86822-57-3; *trans*-*N*-(4-methylcyclohexyl)pyrrolidine picrate, 86822-59-5; *cis*-*N*-(4-

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methylcyclohexyl)piperidine picrate, 53635-33-9; *trans*-*N*-(4-methylcyclohexyl)piperidine picrate, 86822-61-9; *cis*-*N*-(4-methylcyclohexyl)-*N*-phenylbenzamide, 86822-62-0; *trans*-*N*-(4-methylcyclohexyl)-*N*-phenyl-*p*-toluenesulfonamide, 86822-63-1; *cis*-*N*-cyclohexyl-4-methylcyclohexylamine hydrochloride, 86822-64-2; *trans*-*N*-cyclohexyl-4-methylcyclohexylamine, 86822-65-3; *trans*-*N*-(3-methylcyclohexyl)pyrrolidine picrate, 86822-67-5; *cis*-*N*-(3-methylcyclohexyl)pyrrolidine picrate, 86822-69-7; *trans*-*N*-(3-methylcyclohexyl)piperidine picrate, 86822-71-1; *cis*-*N*-(3-methylcyclohexyl)piperidine picrate, 86822-73-3; *cis*-*N*-(2-methylcyclohexyl)pyrrolidine picrate, 86822-74-4; *trans*-*N*-(2-methylcyclohexyl)pyrrolidine picrate, 86822-75-5; *cis*-*N*-(2-methylcyclohexyl)piperidine picrate, 86822-76-6; *trans*-*N*-(2-methylcyclohexyl)piperidine picrate, 86822-77-7; *cis*-*N*-(2-methylcyclohexyl)morpholine picrate, 86822-78-8; *trans*-*N*-(2-methylcyclohexyl)morpholine, 64760-75-4; *cis*-*N*-benzyl-2-methylcyclohexylamine hydrochloride, 86822-79-9; *trans*-*N*-(2-methylcyclohexyl)-*N*-benzyl-*p*-toluenesulfonamide, 86822-80-2; *cis*-*N*-phenyl-2-methylcyclohexylamine, 86822-81-3; *trans*-*N*-(2-methylcyclohexyl)-*N*-phenyl-*p*-toluenesulfonamide, 86822-82-4; *cis*-*N*-cyclohexyl-2-methylcyclohexylamine, 86834-27-7; *trans*-*N*-cyclohexyl-2-methylcyclohexylamine, 59083-13-5; *cis*-*N*-(2-ethylcyclohexyl)morpholine picrate, 86822-84-6; *trans*-*N*-(2-ethylcyclohexyl)morpholine picrate, 86822-86-8; *cis*-*N*-(2-cyclohexylcyclohexyl)pyrrolidine picrate, 86834-29-9; *trans*-*N*-(2-cyclohexylcyclohexyl)pyrrolidine picrate, 86822-88-0; *cis*-*N*-(2-methylcyclopentyl)pyrrolidine picrate, 86822-89-1; *trans*-*N*-(2-methylcyclopentyl)pyrrolidine picrate, 86822-90-4; *cis*-*N*-(2-methylcyclopentyl)piperidine picrate, 86822-92-6; *trans*-*N*-(2-methylcyclopentyl)piperidine picrate, 86822-94-8; *cis*-*N*-(2-methylcyclopentyl)morpholine picrate, 86822-96-0; *trans*-*N*-(2-methylcyclopentyl)morpholine picrate, 86822-98-2; *cis*-*N*-(4-*tert*-butylcyclohexyl)pyrrolidine, 67282-82-0; *cis*-*N*-(4-*tert*-butylcyclohexyl)pyrrolidine picrate, 86822-99-3; *trans*-*N*-(4-*tert*-butylcyclohexyl)pyrrolidine, 67282-90-0; *trans*-*N*-(4-*tert*-butylcyclohexyl)pyrrolidine picrate, 86823-00-9; *cis*-*N*-(4-*tert*-butylcyclohexyl)piperidine picrate, 86823-01-0; *trans*-*N*-(4-*tert*-butylcyclohexyl)piperidine, 16499-27-7; *cis*-*N*-(4-*tert*-butylcyclohexyl)morpholine picrate, 86823-02-1; *trans*-*N*-(4-*tert*-butylcyclohexyl)morpholine picrate, 86823-03-2; *cis*-*N*-benzyl-4-*tert*-butylcyclohexylamine, 67498-84-4; *trans*-*N*-benzyl-4-*tert*-butylcyclohexylamine, 67498-86-6; *cis*-*N*-phenyl-4-*tert*-butylcyclohexylamine hydrochloride, 86823-04-3; *trans*-*N*-phenyl-4-*tert*-butylcyclohexylamine, 16622-85-8; *cis*-*N*-cyclohexyl-4-*tert*-butylcyclohexylamine hydrochloride, 86823-05-4; *trans*-*N*-cyclohexyl-*N*-(4-*tert*-butylcyclohexyl)benzamide, 86823-06-5; *trans*-*N*-benzyl-3,3,5-trimethylcyclohexylamine hydrochloride, 86823-07-6; *cis*-*N*-benzyl-3,3,5-trimethylcyclohexylamine, 86823-08-7; *trans*-*N*-(4-*tert*-butylcyclohexyl)-*p*-toluenesulfonamide, 31023-38-8; *cis*-*N*-(4-*tert*-butylcyclohexyl)-*p*-toluenesulfonamide, 31023-37-7; *trans*-*N*-(2-ethylcyclohexyl)-*p*-toluenesulfonamide, 86823-09-8; *cis*-*N*-(3,3,5-trimethylcyclohexyl)-*p*-toluenesulfonamide, 86823-10-1; 4-*tert*-butylcyclohexanone, 98-53-3; 2-methylcyclohexanone, 583-60-8; 2-methylcyclopentanone, 1120-72-5; 2-methylcyclohexanone oxime, 1122-26-5; 2-cyclohexylcyclohexanone oxime, 4575-20-6; 2-ethylcyclohexanone oxime, 86823-11-2; 4-*tert*-butylcyclohexanone oxime, 4701-98-8; 3,3,5-trimethylcyclohexanone oxime, 37694-11-4; *cis*-2-methylcyclopentylamine, 86823-12-3; *trans*-2-methylcyclopentylamine, 6604-07-5; *cis*-2-methylcyclohexylamine, 2164-19-4; *trans*-2-methylcyclohexylamine, 931-10-2; *cis*-2-cyclohexylcyclohexylamine, 2163-28-2; *trans*-2-cyclohexylcyclohexylamine, 2163-29-3; *cis*-2-ethylcyclohexylamine, 24216-90-8; *trans*-2-ethylcyclohexylamine, 2164-24-1; *cis*-3,3,5-trimethylcyclohexylamine, 32158-56-8; *trans*-3,3,5-trimethylcyclohexylamine, 32958-55-7; *cis*-4-*tert*-butylcyclohexylamine, 2163-33-9; *trans*-4-*tert*-butylcyclohexylamine, 2163-34-0; bis(2-bromoethyl) ether, 5414-19-7; diethylene glycol, 111-46-6; *cis*-*N*-phenyl-4-*tert*-butylcyclohexylamine, 86823-13-4; *p,p'*-dimethoxybenzhydrylamine, 19293-62-0; *cis*-2-*n*-propyl-4-*tert*-butylcyclohexanone 2,4-dinitrophenylhydrazone, 86823-14-5.

Intramolecular Cyclopentene Annulation. 3.[1] Synthesis and Carbon-13 Nuclear Magnetic Resonance Spectroscopy of Bicyclic Cyclopentene Lactones as Potential Perhydroazulene and/or Monoterpene Synthons

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The internal cyclopropanation of several diversely substituted dienic diazo esters is described. Thermolysis of the resulting vinylcyclopropanes yielded cyclopentene-annulated lactones in good yields. Depending on the choice of the dienyl unit, either guaiane or pseudoguaiane substitution patterns of the cyclopentene portion were obtained. Stereochemical assignments based on ^{13}C NMR data are provided for all of these lactones. Subsequent transformations of the bicyclic lactones to differentially functionalized cyclopentenes are described. The potential of these synthons in the synthesis of perhydroazulene sesquiterpenes and several monoterpene cyclopentanoid natural products is addressed.

Introduction

The preparation of multiply functionalized cyclopentanes remains near the top margin on the list of synthetic priorities today. We have applied the internal cyclopropanation–rearrangement sequence to the synthesis of cyclopentanoid natural products[3] as well as extended its scope to provide access to cyclopentenecarboxylates via a high-yielding internal cyclopropanation of unsaturated esters.[4]

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