Highly Stereoselective Syntheses Involving *N*-Alkyl-4,4,7α-trimethyl-*trans*-octahydro-1,3-benzoxazine Intermediates. 2[1]

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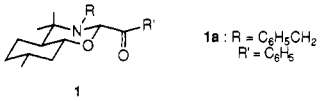
Previously studied highly stereoselective additions of Grignard, organolithium, and hydride reagents to the 2-benzoyl derivative of compound **1a** have been extended to other 2-alkanoyl derivatives (**1**, R′ = methyl, ethyl, isopropyl) and to the 2-benzoyl derivative with R = methyl. High diastereoselectivity is attained in most of the products.

In the previous publication[1] we have described the synthesis of benzoxazine **1a** (**1**, R = benzyl, R′ = phenyl) and the nucleophilic addition of Grignard, organolithium, and hydride reagents to **1a**. Carbon-13 and/or proton NMR spectra of the products suggested that the resulting carbinols were highly diastereomerically pure, and hydrolysis followed by oxidation yielded α-hydroxy acids, PhR″C(OH)CO_2H, whose enantiomeric excess generally exceeded 95% although in two cases (R″ = H and α-naphthyl) racemization during hydrolysis reduced the enantiomeric excess to about 80%.



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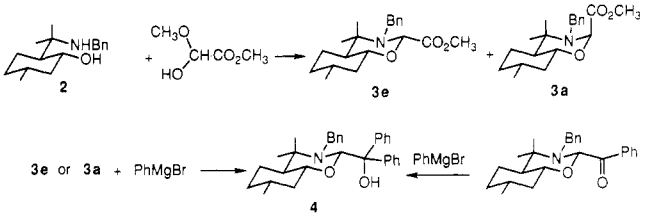
We have now studied structural modifications in **1** to investigate if stereoselectivity would be high even if R′ = alkyl or hydrogen and if it would be affected by replacing the *N*-benzyl by an *N*-methyl group. Incidentally, these experiments led to the diastereomers (with Ph and R″ interchanged) of some of the compounds included in the previous study.

In the previous investigation, **1a** was synthesized by condensation of the amino alcohol **2** precursor (cf. Scheme I) with phenylglyoxal, PhCOCHO. Since the corresponding reaction with methylglyoxal hydrate was not successful, an indirect approach was used, as shown in Scheme I. The amino alcohol **2** was condensed with the methyl hemiacetal of methyl glyoxylate to produce a mixture of equatorial (**3e**) and axial (**3a**) methyl esters which could be separated by silica column chromatography. However, **3a** is quite configurationally unstable: Treatment of either **3e** or **3a** with phenylmagnesium bromide gave the same (equatorial) diphenylcarbinol **4** which was also obtained by similarly treating the previously described[1] phenyl ketone **1a**.

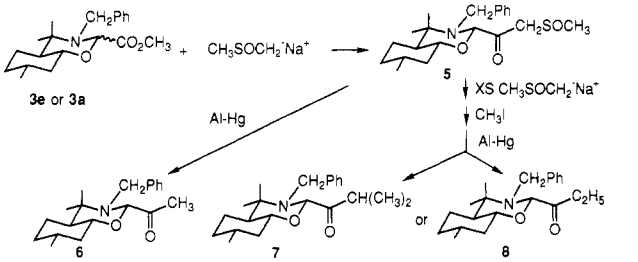
Treatment of **3** (diastereomer mixture) with dimsyl sodium gave equatorial keto sulfoxide **5** (equilibration apparently led to the thermodynamically more stable equatorial product); upon reduction with aluminum amalgam[2] crude **5** yielded the equatorial methyl ketone **6** (Scheme II).

Treatment of **3** (isomer mixture) with an excess of dimsyl sodium followed by alkylation with excess methyl iodide and aluminum amalgam reduction[3] yielded the isopropyl ketone **7**. Attempts to obtain the ethyl ketone **8** by using the appropriate equivalent amount of methyl iodide were less successful; after aluminum amalgam reduction the product was contaminated with either methyl ketone **6** or isopropyl ketone **7**, depending on the amount of methyl iodide used. Compound **8** was separated from

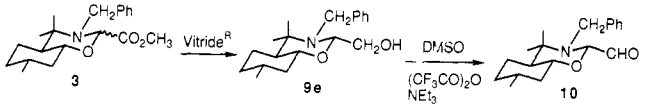
Scheme I



Scheme II



Scheme III



6 by silica gel column chromatography with some difficulty; separation from **7** failed altogether.

Attempts to obtain aldehyde **10** (Scheme III) by DIBAL reduction[4] of esters **3** proved unsuccessful. Therefore **3** (either isomer; see Experimental Section) was reduced[5] with sodium bis(2-methoxyethoxy)aluminum hydride (Vitride), $NaAlH_2(OCH_2CH_2OCH_3)_2$ (which was superior in this reduction to lithium aluminum hydride), to carbinol **9** which, in turn, was oxidized to **10** by Swern's reagent[6] (DMSO–TFFA–Et_3N).

Ketones **6**, **7**, and **8** were treated with various Grignard reagents and (in the case of **6**) sodium borohydride and DIBAL with the results shown in Table I.

The major product, **11a**, from **6** and phenylmagnesium bromide (Table I, entry 1) differed in spectral characteristics from the adduct **11b** previously obtained[1] from **1a** and methylmagnesium bromide; **11b** was the minor product obtained along with **11a**. Accordingly hydrolysis and oxidation of **11a**[1] yielded (*R*)-atrolactic acid of 91% ee. Thus, as previously observed for methyl Grignard additions to **1a**, the PhMgBr addition to **6** proceeds according to

(1) He, X.-C.; Eliel, E. L. *Tetrahedron* **1987**, *43*, 4979.
(2) Corey, E. J.; Chaykovsky, G. D. *J. Am. Chem. Soc.* **1965**, *87*, 1345.
(3) Gassman, P. G.; Richmond, G. D. *J. Org. Chem.* **1966**, *31*, 2355.
(4) Muraki, M.; Mukaiyama, T. *Chem. Lett.* **1974**, 1447; **1975**, 215.
(5) Černý, M.; Málek, J.; Capka, M.; Chvalovský, V. *Collect. Czech. Chem. Commun.* **1969**, *34*, 1025.
(6) Huang, S. L.; Omura, K.; Swern, D. *J. Org. Chem.* **1976**, *41*, 3329.

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Table I. Reaction of Ketones 6–8 with Nucleophiles

entry	ketone	reagent	temp, °C	yield, %	diastereoselectivity	major product
1	**6**	C_6H_5MgBr	5	81[a]	95.5:4.5	**11a**
2	**6**	C_2H_5MgBr	5	97[b]	92:8	**12a**
3	**6**	$(CH_3)_2CHMgCl$	5	100[b]	96:4	**13a**
4	**6**	$NaBH_4$/95% EtOH	5	85–100[b]	95.5:4.5	**14a**
5	**6**	DIBAL	−70	79[a]	ca. 50:50	**14a,b**
6	**8**	CH_3MgBr	5	93[b]	96:4	**12b**
7	**7**	CH_3MgBr	5	100[b]	93.5:6.5	**13b**

[a] Of isolated material. [b] Crude product containing only minor impurities.

Table II. Addition of Grignard Reagents to Aldehyde 10

entry	reagent	temp, °C	yield,[a] %	diastereomer ratio
1	CH_3MgBr	5	81	94.5:5.5[b]
2	CH_3MgBr	−70	95	91:9[b]
3	C_6H_5MgBr	5	100	83.5:16.5[c]
4	C_6H_5MgBr	5	100	82:18[c]
5	C_6H_5MgBr	−70	100	85:15[c]
6	C_6H_5MgBr[d]	−70	100	86:14[c]

[a] Of crude product. [b] Major product is **14b**. [c] Major product has *R* configuration. [d] Inverse addition of aldehyde to Grignard reagent.

Cram's chelate rule[7,8] with chelation to the oxygen rather than the nitrogen of the oxazane ring. By analogy it was assumed that this is true also of the remaining Grignard additions in Table I (entries 2, 3, 6, 7); in any case, interchanging the alkyl groups of the ketone and Grignard reagent (entries 2 vs 6 and 3 vs 7) produced as major products species which, according to their proton and ^{13}C spectra were diastereomeric. The spectra also suggested that **12b** and **13b** were the minor contaminants in the synthesis of **12a** and **13a** and vice versa.

Reduction of **6** with sodium borohydride (Table I, entry 4) gave largely one diastereomeric alcohol, similarly to what had been previously observed in the corresponding reduction of the phenyl ketone **1a**. In contrast (and again as previously observed[1]), reduction with DIBAL (diisobutylaluminum hydride, entry 5) gave an almost equal mixture of the two possible diastereomeric alcohol products, even though the reaction was carried out at −70 °C. By analogy with the previous result[1] and in view of the stereochemical outcome of the addition of methylmagnesium bromide to **10** which gave largely **14b**, the diastereomer of **14a**, we again assume that borohydride reduction gives the oxygen-chelated product predicted by Cram's rule.[7,8]

Addition of methyl and phenyl Grignard reagents to aldehyde **10** is summarized in Table II. Stereoselectivity in the addition of CH_3MgBr (entries 1, 2) is comparable to that shown in Table I but that in the addition of phenylmagnesium bromide (entries 3–6) is surprisingly lower. Lowering the temperature or reversing the order of addition did not improve the selectivity substantially.

The major product of the phenylmagnesium bromide addition (entries 3–6, Table II) differed from the borohydride reduction product of phenyl ketone **1a**.[1] Since the latter reaction has been shown—by hydrolysis and oxidation of the product to mandelic acid of known absolute configuration—to follow Cram's chelate rule (oxygen chelation), the same must be true of the addition of C_6H_5MgBr (and, by inference, also CH_3MgBr) to **10**. The CH_3MgBr adduct is therefore **14b**, diastereomeric to **14a** (Table I, entry 4).

Chart I

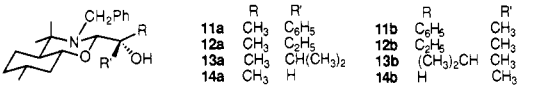
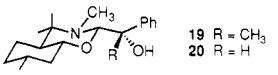


Chart II



Scheme IV

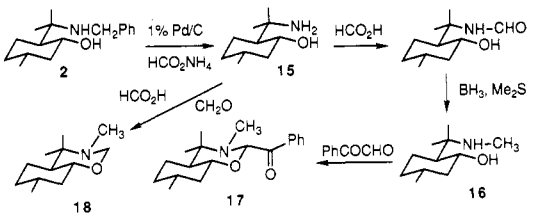


Table III. Hydrolysis/Oxidation Products of 19[a]

starting material	yield,[b] %	ee,[c] %	ref
19 from CH_3MgBr[d]	26	92	*e*
19 from CH_3Li[f]	30	96	*e*

[a] Hydrolysis of **19** requires longer HCl refluxing time than the corresponding *N*-benzyl compound.[1] [b] From ketone **17**, based on chromatographically purified methyl atrolactate. [c] For determination, see ref 1. [d] Addition at 20 °C. [e] Meyers, A. I.; Slade, J. *Synth. Commun.* **1976**, *6*, 601. [f] Addition at 5 °C.

From these considerations it may be inferred (cf. Chart I) that **11a**, **12a**, **13a**, and **14b** have the *R* configuration at the carbinol chiral center whereas the configuration at that center of **11b**, **12b**, **13b**, and **14a** is *S*.

In this study, as in the previous one,[1] chelation of the organometallic (including, in the previous study, methyllithium) seems to occur very largely with the oxygen rather than the nitrogen of the oxazane ring in **1**. In order to investigate whether this was, in any way, related to the presence of the *N*-benzyl substituent, we synthesized the corresponding *N*-methyl compound **17** (**1**, R = Me, R′ = Ph). Unfortunately, synthesis of **2** with methyl instead of benzyl analogous to that previously described[1] (addition of amine to (+)-pulegone followed by sodium borohydride reduction) was not successful, and so **16** (and **17**) had to be synthesized by a longer route from **2**[1] as shown in Scheme IV.

Debenzylation of **2** with palladium on charcoal in the presence of either hydrazine or (better) ammonium formate[9] gave the debenzylated amine **15**, which was methylated to amino alcohol **16** by treatment with formic acid followed by diborane–methyl sulfide.[10] (Treatment of **15**

(7) Cram, D. J.; Kopecky, K. R. *J. Am. Chem. Soc.* **1959**, *81*, 2748.
(8) Eliel, E. L. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1983; Vol. 2, p 125.
(9) Adger, B. M.; Farrell, C. O.; Lewis, N. J.; Mitchell, M. B. *Synthesis* **1987**, 53.
(10) Brown, H. C.; Choi, Y. M.; Narasimhan, S. *J. Org. Chem.* **1982**, *47*, 3153.

with formaldehyde/formic acid yielded the very stable ring-closed oxazane **18**. Attempts to ring open **18** by refluxing with concentrated hydrochloric acid were unsuccessful.) Ketone **17** was obtained as before[1] by treatment of **16** with phenylglyoxal.

The *N*-methyl compound **17** was treated with methylmagnesium bromide, methyllithium and sodium borohydride. In all three cases, the NMR spectra of the products suggested that diastereoselectivity was very high. The methyl addition products (**19**, Chart II) were hydrolyzed and oxidized to (*S*)-atrolactic acid, as previously described[1] with the results shown in Table III. The high enantiomeric excess of the (*S*)-(−)-atrolactic acid obtained confirms the high diastereoselectivity of the methylmagnesium bromide and methyllithium addition to **17** which thus behaves entirely analogously[1] to **1a**. The diastereomeric purity of the sodium borohydride reduction product was 85 ± 1%, as inferred from the proton NMR spectrum of the crude reduction product (integration of *N*-methyl signals). Thus, the nature of the *N*-methyl substituent does not affect the stereoselectivity of addition in these cases.

Discussion

The experiments described here extend the previously described[1] highly stereoselective addition of Grignard reagents, methyllithium, and sodium borohydride to phenyl ketone **1a** to the corresponding methyl ketone **6** and isopropyl ketone **7** as well as to aldehyde **10**. Other ketone starting materials can undoubtedly be synthesized from keto sulfoxide **6** by alkylation followed by reduction. It has also been shown that **17**, the *N*-methyl analogue of **1a**, reacts as stereoselectively as **1a** itself.

In analogous reactions of 2-acyloxathianes (S instead of NR)[11] we had ascribed the high diastereoselectivity in nucleophilic additions to chelation of the Grignard addend (hard acid at the MgX site) with the hard base O in preference to the soft base S. It therefore came as a surprise that the present work suggests chelation with oxygen to be also greatly preferred over chelation with nitrogen. This is true whether the substituent at nitrogen is benzyl or methyl. We thought at first that this might be a consequence of the equatorial position of the *N*-alkyl group, on the assumption that chelation would involve the equatorial rather than the axial lone pair on the heteroatom. However, for a variety of reasons, this hypothesis does not seem viable. In the first place, it is not clear that only the equatorial pair can engage in chelation; it is in principle possible to engage the axial lone pair although it would then not be obvious why the resulting chelate reacts so predominantly by addition to the *Re* face of the carbonyl, as in fact it does in all cases. Experimentally we were unable to glean evidence, from either proton or carbon-13 NMR spectra, that the *N*-alkyl group was greatly biased toward either the equatorial or the axial configuration. Other experiments in simpler *N*-methyloxazanes[12] suggest a nearly 1:1 ratio of axial to equatorial *N*-methyl; it is, of course, possible that this proportion may be changed by the carbonyl substituent at C(2).

While this work was in progress, Reetz and co-workers[13] published a study of Grignard and methyllithium additions to α-dialkylamino aldehydes, which shows that these reactions proceed contrary to Cram's chelate rule, in contrast to corresponding additions to α-alkoxy aldehydes.[8] Although the reason for this finding is not obvious, it does, by analogy, account for the preferential chelation to oxygen rather than nitrogen which presumably accounts for the stereochemical outcome of the addition reactions to ketones **1a**, **6**, **7**, and **17** and aldehyde **10**.

Experimental Section

Proton and ^{13}C NMR spectra were recorded in $CDCl_3$ at 200 and 50.3 MHz, respectively. The DEPT technique was used to distinguish methyl (Me), methylene (CH_2), methine (CH), and quaternary (C_q) carbons in ^{13}C NMR spectra. IR peak intensities are recorded as s (strong), m (medium), w (weak), or b (broad). The solvent for all NMR spectra was $CDCl_3$ unless otherwise indicated. Melting points are uncorrected. The ^1H NMR spectra of the new compounds reported (with the exception of **4**, **8**, **9a**, **15**, and **21**) suggest that they were over 90% pure except for the presence of diastereomers as noted.

Methyl [2*S*(2α,4aα,7α,8aβ)]-Octahydro-3-(phenylmethyl)-4,4,7-trimethyl-2*H*-1,3-benzoxazine-2-carboxylate and Its Epimer (3). To a solution of 495 mg (1.9 mmol) of **2**[1] in 35 mL of anhydrous benzene was added 550 mg (4.6 mmol) of methyl α-hydroxy-α-methoxyacetate.[14] The solution was heated at reflux with a Dean–Stark trap for 3.5 h and concentrated, and the residue was purified by silica gel chromatography to give 542 mg (86%) of a mixture of diastereomers (**3**).

Careful column chromatography (elution with 1% ethyl acetate in hexanes) gave two isomers, **3a** and **3e**.

3a. ^1H NMR: δ 0.94 (d, J = 6.4 Hz, 3 H), 1.08 (s, 3 H), 1.19 (s, 3 H), 1.4–1.8 (m), 1.9–2.1 (b d, ca. 6 H), 3.71 (s, 3 H), 3.95 (dt, J = 10.5, 4.1 Hz, 1 H), 4.11 (s, 2 H), 4.63 (s, 1 H), 7.1–7.6 (m, 5 H). ^{13}C NMR: δ 19.6 (Me), 22.2 (Me), 24.9 (CH_2), 27.9 (Me), 31.1 (CH), 34.8 (CH_2), 41.3 (CH_2), 47.7 (CH), 50.4 (CH_2), 51.7 (Me), 55.5 (C_q), 71.2 (CH), 83.4 (CH), 126.7 (CH), 128.0 (CH), 128.2 (CH), 140.5 (C_q), 173.1 (C_q). IR (film): 3055 (w), 3020 (m), 1740 (s), 1600 (w), 1490 (m), 1220 (s), 1165 (s), 1135 (s), 1090 (s), 1060 (s), 995 (m), 975 (m), 885 (m), 835 (m), 790 (m), 690 (m) cm^{-1}. $[\alpha]^{21}_D$ +47.3° (c = 0.844, EtOAc).

3e. ^1H NMr: δ 0.95 (d, J = 6.4 Hz, 3 H), 1.10 (s, 3 H), 1.2–1.4 (m), 1.29 (s, 3 H), 1.4–1.8 (m, overlaid by H_2O peak), 1.9–2.1 (b d), 3.28 (s, 3 H), 3.57 (dt, J = 10.5, 4.1 Hz, 1 H), 3.91 (AB, Δ_{AB} = 0.12, J = 17.2 Hz, 2 H), 5.20 (s, 1 H), 7.1–7.5 (m, 5 H). ^{13}C NMR: δ 20.1 (Me), 22.2 (Me), 25.0 (CH_2), 27.0 (Me), 31.3 (CH), 34.9 (CH_2), 41.0 (CH_2), 46.0 (CH), 48.0 (CH_2), 51.7 (Me), 57.5 (C_q), 76.4 (CH), 85.8 (CH), 126.2 (CH), 127.5 (CH), 127.8 (CH), 141.9 (C_q), 169.2 (C_q). IR (film): 3060 (m), 3020 (m), 1760 (s), 1740 (shoulder), 1595 (w), 1495 (m), 1215 (s), 1175 (s), 1140 (m), 1090 (s), 1050 (s), 910 (m), 845 (m), 795 (m), 715 (s), 690 (s) cm^{-1}. $[\alpha]^{21}_D$ −58.3° (c = 0.612, EtOAc).

α,α-Diphenyl-[2*S*(2α,4aα,7α,8aβ)]-octahydro-3-(phenylmethyl)-4,4,7-trimethyl-2*H*-1,3-benzoxazine-2-methanol (4). Ketone **1a**, axial ester **3a**, or equatorial ester **3e** was dissolved in dry ether. An excess of phenylmagnesium bromide was added under a dry nitrogen atmosphere, and the mixture was stirred for 1 h after which time TLC showed the starting material to have disappeared. The reaction mixture was quenched with saturated ammonium chloride, and the product extracted with ether, which was dried and concentrated to give crude **4**. Proton and ^{13}C NMR spectra showed the products from the three sources to be identical. ^1H NMR: δ 0.70 (s, 3 H), 0.87 (d, J = 6.5 Hz, 3 H), 1.30 (s, 3 H), 3.64 (d, J = 17.7 Hz, 1 H), 3.69 (dt, J = 10.5, 4 Hz, 1 H), 4.60 (d, J = 17.7 Hz, 1 H), and others, including peaks due to olefinic impurities. ^{13}C NMR: δ 22.2, 22.8, 24.9, 27.1, 31.5, 35.1, 41.3, 44.0, 47.0, 58.8, 77.8, 78.4, 88.2, also numerous aromatic carbon signals and signals of an olefinic impurity. A small signal at 70.5 ppm may have been due to an impurity or may be the quaternary carbinol signal (in lieu of the 78.4 ppm signal which would then be due to an impurity).

(11) Eliel, E. L.; Morris-Natschke, S. *J. Am. Chem. Soc.* **1984**, *106*, 2937. Lynch, J. E.; Eliel, E. L. *Ibid.* **1984**, *106*, 2943.

(12) Cf.: Riddell, F. G. *The Conformational Analysis of Heterocyclic Compounds*; Academic Press: New York, 1980; p 96.

(13) Reetz, M. T.; Drewes, M. W.; Schmitz, A. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1141.

(14) This ester was prepared by refluxing the hydrate of the acid (Aldrich) with methanol in a round-bottom flask equipped with a Soxhlet extractor charged with 3-Å molecular sieves topped by a reflux condenser. Cf.: Herrmann, J. L.; Kieczykowski, G. R.; Romanet, R. F.; Wepplo, P. J.; Schlessinger, R. H. *Tetrahedron Lett.* **1973**, 4711.

1-[[2*S*(2α,4aα,7α,8aα)]-Octahydro-3-(phenylmethyl)-4,4,7-trimethyl-2*H*-1,3-benzoxazin-2-yl]ethanone (6). To 210 mg of sodium hydride (60% dispersion in mineral oil) was added 6 mL of DMSO (dimethyl sulfoxide) to prepare dimsyl sodium.[2] After cooling with an ice bath, 356 mg (1.08 mmol) of methyl ester **3** (isomer mixture) in 3 mL of dry THF (tetrahydrofuran) was added dropwise with stirring. The ice bath was removed, and the reaction mixture was stirred at room temperature for an additional hour and then poured into 40 mL of saturated aqueous ammonium chloride. The product was extracted with methylene chloride (4 × 20 mL) and the combined organic layer washed with water followed by half-saturated brine (NaCl), dried over Na_2SO_4, and concentrated to give ca. 0.56 g of crude **5**.

This material was dissolved in 28 m L of 10% aqueous THF and reduced by addition of 0.61 g of freshly prepared[2] aluminum amalgam. The suspension was heated to mild reflux with efficient stirring until the amalgam was converted to a black powder (≥90 min). The suspension was cooled to room temperature, solid sodium sulfate was added, the suspension was filtered, and the solid residue was washed with ethyl acetate (ca. 80 mL). The combined filtrate was washed with brine (2 × 15 mL), dried over Na_2SO_4, and concentrated to give 0.46 g of crude **6**.

Purification by silica gel chromatography (eluent: 2% ethyl acetate in hexanes) yielded 258 mg (76% overall) of **6**, which was further purified for analysis by Kugelrohr distillation (bath temperature 180–185 °C/1 mm). ^{1}H NMR: δ 0.95 (d, J = 6.4 Hz, 3 H), 1.10 (s, 3 H), 1.0–1.2 (m), 1.27 (s, 3 H), 1.4–1.8 (m), 1.86 (s, 3 H), 1.95–2.05 (b d), 3.51 (dt, J = 10.4, 4.0 Hz, 1 H), 3.78 (s, 2 H), 4.93 (s, 1 H), 7.1–7.6 (m, 5 H). ^{13}C NMR: δ 19.4 (Me), 22.1 (Me), 24.8 (CH_2), 26.0 (Me), 26.8 (Me), 31.1 (CH), 34.8 (CH_2), 41.1 (CH_2), 46.1 (CH), 48.1 (CH_2), 57.4 (C_q), 75.8 (CH), 90.8 (CH), 126.1 (CH), 127.5 (CH), 127.8 (CH), 141.5 (C_q), 205.4 (C_q). IR film: 3060 (w), 3020 (w), 1730 (s), 1605 (w), 1495 (m), 1200 (m), 1160 (m), 1050 (m), 730 (m), 690 (m) cm^{-1}. $[\alpha]^{21}_D$ −32.9° (c = 0.453, EtOAc). Anal. Calcd for $C_{20}H_{29}NO_2$: C, 76.15; H, 9.29. Found: C, 76.18; H, 9.33.

2-Methyl-1-[[2*S*(2α,4aα,7α,8aβ)]-octahydro-3-(phenylmethyl)-4,4,7-trimethyl-2*H*-1,3-benzoxazin-2-yl]propan-1-one (7). Dimsyl sodium was prepared as above from 240 mg sodium hydride (60% oil dispersion) and 6.5 mL of DMSO. After cooling, 3 mL of dry THF and a solution of 290 mg (0.88 mmol) of **3** in 3 mL of THF was added dropwise. The ice bath was removed, and the mixture stirred for 40 min; then 0.3 mL of iodomethane was added, and stirring was continued for 1.5 h at room temperature. Workup was as described for **6** above and yielded 0.50 g of crude sulfoxide. Aluminum foil (0.70 g) was used to prepared aluminum amalgam,[2] which was added to the above sample of sulfoxide dissolved in ca. 30 mL of 10% aqueous THF. The mixture was heated for 2 h and then worked up as described for **4** to give crude **7**, which was purified by silica gel chromatography (eluent: 1.5–2% EtOAc in hexanes) to give 208 mg (69%) of **7**. ^{1}H NMR: δ 0.65 (d, J = 6.7 Hz, 3 H), 0.95 (d, J = 6.4 Hz, 3 H), 0.97 (d, J = 7.0 Hz, 7 H), 1.06 (s, 3 H), 1.23 (q, 1 H), 1.36 (s, 3 H), 1.4–1.8 (m, 4 H), 1.95–2.05 (b d, 1 H), 2.91 (septet, J = 6.9 Hz, 1 H), 3.55 (dt, J = 10.5, 4.0 Hz, 1 H), 3.83 (AB, Δ_{AB} = 0.16, J = 17.7 Hz, 2 H), 5.27 (s, 1 H), 7.0–7.5 (m, 5 H). ^{13}C NMR: δ 17.1 (Me), 19.3 (Me), 21.3 (Me), 22.2 (Me), 25.0 (CH_2), 26.9 (Me), 31.4 (CH), 35.0 (CH_2), 36.5 (CH), 41.1 (CH_2), 45.3 (CH), 48.2 (CH_2), 57.7 (C_q), 76.5 (CH), 88.5 (CH), 126.2 (CH), 127.2 (CH), 128.0 (CH), 140.1 (C_q), 211 (C_q). IR (film): 3080 (w), 3060 (w), 3025 (m), 1725 (s), 1605 (w), 1495 (m), 1195 (m), 1170 (s), 1025 (s), 715 (s), 690 (s) cm^{-1}. $[\alpha]^{21}_D$ −49.7° (c = 0.6335, EtOAc).

1-[[2*S*(2α,4aα,7α,8aβ)]-Octahydro-3-(phenylmethyl)-4,4,7-trimethyl-2*H*-1,3-benzoxazin-2-yl]propan-1-one (8). Attempts to optimize preparation of this material by using the above procedure with 4 mol equiv of dimsyl sodium and 1 mol equiv of methyl iodide always led to mixtures of **6** and **8** from which **8** was isolated in low yield by silica gel column chromatography. Lesser amounts of dimsyl sodium led to more of **6** and less of **8**. Use of an excess of methyl iodide (3.4 mmol equiv) led to mixtures of **7** and **8**, which were not separable in our hands. ^{1}H NMR: δ 0.59 (t, J = 7.3 Hz, 3 H), 0.95 (d, J = 6.4 Hz, 3 H), 1.12 (s, 3 H), 1.26 (s, 3 H), 1.0–1.05 (m), 1.15–1.25 (m), 1.4–1.8 (m), 1.9–2.1 (b d) (total 8 H), 2.2–2.5 (m, 2 H), 3.51 (dt, J = 10.4, 4.1 Hz, 1 H), 3.76 (AB, Δ_{AB} = 0.06, J = 17.3 Hz, 2 H), 4.93 (s, 1 H), 7.0–7.6 (m, 5 H). ^{13}C NMR: δ 6.7 (Me), 19.2 (Me), 2.22 (Me), 25.0 (CH_2), 27.0 (Me), 31.3 (CH), 31.9 (CH_2), 34.9 (CH_2), 41.2 (CH_2), 46.6 (CH), 48.1 (CH_2), 57.5 (C_q), 75.9 (CH), 90.5 (CH), 126.2 (CH), 127.7 (CH), 127.9 (CH), 141.7 (C_q), 208 (C_q). IR (film): 3050 (w), 3005 (m), 1725 (s), 1595 (w), 1495 (m), 1110 (m), 1025 (m), 690 (m) cm^{-1}.

α-Methyl-[2*S*(2α,4aα,7α,8aβ)]-octahydro-α-phenyl-3-(phenylmethyl)-4,4,7-trimethyl-2*H*-1,3-benzoxazine-2-methanol (11a). To a stirred solution of 75 mg (0.24 mmol) of **6** in 10 mL of anhydrous ether was added 0.36 mL of 3 M ethereal phenylmagnesium bromide (Aldrich) under a nitrogen atmosphere with the temperature maintained near 5 °C with an ice bath. Stirring was continued for 1 h after which TLC showed absence of starting ketone.

The mixture was worked up as previously described,[1] and the product was purified by silica gel chromatography (elution by 1–2% EtOAc in hexanes) to yield 76 mg (81%) product. ^{1}H NMR: δ 0.90 (d, J = 6.6 Hz, 3 H), 0.92 (s, 3 H), 1.05–1.35 (m, 3 H), 1.35 (s, 3 H), 1.47 (s, 3 H), 1.55–1.75 (m, 3–4 H), 1.8–2 (b d, 1–2 H), 3.3 (s, 1 H), 3.44 (dt, J = 10.5, 3.9 Hz, 1 H), 3.77 (d, J = 18.5 Hz, 1 H), 4.40 (d, J = 18.5 Hz, 1 H), 4.95 (s, 1 H), 7.0–7.5 (m, 10 H). ^{13}C NMR: δ 22.2 (Me), 23.0 (Me), 24.9 (CH_2), 26.6 (Me), 28.1 (Me), 31.4 (CH), 35.1 (CH_2), 41.2 (CH_2), 44.3 (CH), 46.6 (CH_2), 58.4 (C_q), 75.1 (C_q), 78.0 (CH), 92.0 (CH), 125.2 (CH), 125.5 (CH), 126.2 (CH), 126.5 (CH), 127.6 (CH), 127.8 (CH), 143.9 (C_q), 147.9 (C_q). IR (film): 3540 (b, m), 3050 (m), 3020 (m), 1600 (w), 1495 (s), 1195 (s), 1170 (s), 1085 (s), 1045 (s), 1020 (s), 945 (s), 750 (m), 710 (s), 690 (s) cm^{-1}. Several of the NMR peaks of **11b**[1] as a minor component appeared in the NMR spectrum of crude **11a**. Integration of the proton peak at 0.57 ppm[1] relative to the methyl proton peaks of the major component indicated a ratio of 4.5:95.5 of **11b**:**11a**.

α-Ethyl-α-methyl-[2*S*(2α,4aα,7α,4aβ)]-octahydro-3-(phenylmethyl)-4,4,7-trimethyl-2*H*-1,3-benzoxazine-2-methanol (12a). Ethylmagnesium bromide[15] was added to ketone **6** similarly as described above. The crude addition product was characterized by NMR spectroscopy. ^{1}H NMR (CD_2Cl_2): δ 0.87 (s, 3 H), 0.89 (t, J = 7.9 Hz, 3 H), 0.94 (d, J = 6.6 Hz, 3 H), 1.06 (s, 3 H), 1.28 (s, 3 H), 1.0–1.25 (m), 1.4–1.8 (m), 1.85–2 (b d) (total 10 H), 2.4 (s, 1 H), 3.55 (dt, J = 10.6, 4.0 Hz, 1 H), 3.88 (d, J = 18.5 Hz, 1 H), 4.50 (s, 1 H), 4.84 (d, J = 18.5 Hz, 1 H), 7.0–7.6 (m, 5 H). ^{13}C NMR: δ 8.1 (Me), 21.2 (Me), 22.3 (Me), 23.0 (Me), 24.9 (CH_2), 26.8 (Me), 31.5 (CH), 35.0 (CH_2), 35.2 (CH_2), 41.5 (CH_2), 44.0 (CH), 47.0 (CH_2), 58.0 (C_q), 74.4 (C_q), 77.5 (CH), 89.3 (CH), 125.3 (CH), 126.8 (CH), 127.7 (CH), 144.4 (C_q). Minor peaks of **12b** (see below) indicated a ratio of **12a**:**12b** of ca. 92:8.

Diastereomer 12b. Excess methylmagnesium bromide (3 M solution in diethyl ether, Aldrich) was added to ethyl ketone **8** in ether at 5 °C. The crude product, characterized by NMR, was different from **12a** (above) but appeared to contain ca. 4% **12a** as minor component. ^{1}H NMR: δ 0.85 (s, 3 H), 0.95 (d, J = 5.8 Hz, 3 H), 0.96 (t, J = 7.4 Hz, 3 H), 1.14 (q, 2 H), 1.22 (s, 3 H), 1.28 (s, 3 H), 1.3–1.8 (m) and 1.9–2.0 (b d) (total 8 H), 2.45 (s, 1 H), 3.55 (dt, J = 10.5, 4.0 Hz, 1 H), 3.86 (d, J = 18.4 Hz, 1 H), 4.47 (s, 1 H), 4.93 (d, J = 18.4 Hz, 1 H), 7.0–7.6 (m, 5 H). ^{13}C NMR: δ 8.5 (Me), 22.3 (Me), 22.7 (Me), 25.0 (Me), 26.7 (Me), 26.9 (Me), 29.9 (CH_2), 31.5 (CH), 35.2 (CH_2), 41.5 (CH_2), 43.9 (CH), 46.7 (CH_2), 58.1 (C_q), 74.8 (C_q), 77.7 (CH), 89.3 (CH), 125.3 (CH), 126.5 (CH), 127.8 (CH), 144.8 (C_q).

α-Methyl-α-(1-methylethyl)-[2*S*(2α,4aα,7α,8aβ)]-octahydro-3-(phenylmethyl)-4,4,7-trimethyl-2*H*-1,3-benzoxazine-2-methanol (13a). Isopropylmagnesium chloride (Aldrich, 2.0 M solution in diethyl ether) was added to ketone **6** at 5 °C as described above, except that the reaction time was extended to 5.5 h after which time NMR showed absence of starting material. The crude addition product was characterized by NMR spectroscopy. No reduction seems to have occurred. ^{1}H NMR (CD_2Cl_2): δ 0.86 (s, 3 H), 0.88 (d, J = 7.0 Hz, 3 H), 0.91 (d, J = 7.0 Hz, 3 H), 0.94 (d, J = 6.4 Hz, 3 H), 0.99 (s, 3 H), 1.0–1.25 (m), 1.29 (s, 3 H), 1.4–1.8 (m), 1.8–2.0 (b d), 2.4 (s, 1 H), 3.55 (dt, J = 10.6, 3.9 Hz, 1 H), 3.88 (d, J = 18.4 Hz, 1 H), 4.68 (s, 1 H), 4.86 (d, J = 18.4 Hz, 1 H), 7.0–7.6 (m, 5 H). ^{13}C NMR: δ 16.9 (Me), 17.8 (Me), 18.4 (Me), 22.3 (Me), 23.0 (Me), 24.9 (CH_2), 26.8

(15) Cf.: Eliel, E. L.; Hartmann, A. A.; Abatjoglou, A. G. *J. Am. Chem. Soc.* **1974**, *96*, 1807. Abatjoglou, A. G.; Eliel, E. L.; Kuyper, L. F. *Ibid.* **1977**, *99*, 8262.

(Me), 31.5 (CH), 35.2 (CH_2), 37.0 (CH), 41.5 (CH_2), 43.8 (CH), 47.2 (CH_2), 58.4 (C_q), 76.4 (C_q), 77.5 (CH), 87.2 (CH), 125.3 (CH), 126.8 (CH), 127.6 (CH), 144.4 (C_q).

The spectra suggested the presence of a minor amount (ca. 4%) of **13b** (see below).

Diastereomer 13b. Addition of excess methylmagnesium bromide (cf. **12b**) to isopropyl ketone **7** yielded largely **13b** which, by NMR characterization, was diastereomeric to **13a** but contained about 6.5% of the latter. ^1H NMR: δ 0.81 (s, 3 H), 0.81 (d, J = 6.8 Hz, 3 H), 0.95 (d, J = 6.5 Hz, 3 H), 1.03 (d, J = 6.8 Hz, 3 H), 1.11 (s, 3 H), 1.27 (s, 3 H), 1.1–1.25 (m), 1.4–1.8 (m), 1.9–2.1 (b m) (total 8–9 H), 2.5 (s, 1 H), 3.56 (dt, J = 10.6, 4.0 Hz, 1 H), 3.84 (d, J = 18.2 Hz, 1 H), 4.48 (s, 1 H), 4.99 (d, J = 18.2 Hz, 1 H), 7.0–7.6 (m, 5 H). ^{13}C NMR: δ 16.5 (Me), 18.1 (Me), 21.0 (Me), 22.3 (Me), 22.4 (Me), 24.9 (CH_2), 27.1 (Me), 31.4 (CH), 31.5 (CH), 35.2 (CH_2), 41.5 (CH_2), 43.6 (CH), 47.2 (CH_2), 58.3 (C_q), 76.4 (C_q), 77.7 (CH), 89.2 (CH), 125.3 (CH), 126.4 (CH), 127.8 (CH), 145.2 (C_q).

α-Methyl-[2*S*(2α,4aα,7α,8aβ)]-octahydro-3-(phenylmethyl)-4,4,7-trimethyl-2*H*-1,3-benzoxazine-2-methanol (14a). The reduction was carried out with sodium borohydride as previously described[1] for the phenyl analogue. The major product was **14a**; the NMR spectra below suggested the presence of ca. 4.5% of **14b** (see below). ^1H NMR: δ 0.94 (d, J = 6.5 Hz, 3 H), 1.11 (d, J = 6.0 Hz, 3 H), 1.20 (s, 3 H), 1.33 (s, 3 H), 1.0–1.9 (m), 2.0 (s), 3.4–3.7 (overlap m, 2 H), 3.99 (AB, Δ_{AB} = 0.19, J = 17.6 Hz, 2 H), 4.39 (d, J = 8.0 Hz, 1 H), 7.1–7.6 (m, 5 H). ^{13}C NMR: δ 18.6 (Me), 22.1 (Me), 22.2 (Me), 25.0 (CH_2), 27.4 (Me), 31.4 (CH), 35.1 (CH_2), 41.3 (CH_2), 45.6 (CH_2), 46.0 (CH), 57.3 (C_q), 65.9 (CH), 77.0 (CH), 91.5 (CH), 126.6 (CH), 128.7 (CH), 143.3 (C_q).

Reduction with Diisobutylaluminum Hydride (DIBAL). Methyl ketone **6** (63 mg, 0.2 mmol) was reduced by excess DIBAL (hexane solution, Aldrich) in 9 mL of toluene at −70 °C to give a mixture of two diastereomeric carbinols, as evident from NMR spectra. Separation by silica gel chromatography gave 24 mg (38%) of **14a**, 9 mg of a mixture, and 26 mg (41%) of a more polar diastereomer (**14b**). The separation was followed by proton NMR. The NMR spectra of the first fraction were identical with those of **14a** (vide supra) while those of the third fraction suggested that it was the isomer of **14b**. ^1H NMR: δ 0.94 (d, J = 6.5 Hz, 3 H), 0.98 (d, J = 6.2 Hz, 3 H), 1.06 (s, 3 H), 1.27 (s, 3 H), 1.1–1.25 (m), 1.4–1.8 (m), and 1.9–2.0 (b d) (total 7–8 H), 2.6 (1 H), 3.53 (dt, J = 10.5, 4.0 Hz, 1 H), 3.70 (quintet, J = 6.4 Hz, 1 H), 3.92 (AB, Δ_{AB} = 0.17, J = 17.8 Hz, 2 H), 4.38 (d, J = 6.9 Hz, 1 H), 7.1–7.6 (m, 5 H). ^{13}C NMR: δ 18.5 (Me), 21.3 (Me), 22.3 (Me), 25.0 (CH_2), 27.0 (Me), 31.4 (CH), 35.1 (CH_2), 41.3 (CH_2), 45.8 (CH), 47.0 (CH_2), 57.4 (C_q), 67.4 (CH), 76.6 (C_q), 92.0 (CH), 126.1 (CH), 126.9 (CH), 128.1 (CH), 143.2 (C_q).

α-Phenyl-[(2*S*(2α,4aα,7α,8aβ)]-octahydro-3-(phenylmethyl)-4,4,7-trimethyl-2*H*-1,3-benzoxazine-2-methanol (Chart I, R,R′ = Ph, H). The reduction of 189 mg (0.5 mmol) of phenyl ketone **1a** with excess DIBAL in 25 mL of toluene at 20 °C yielded a crude carbinol mixture, which was separated by silica gel chromatography (eluent methylene chloride). After 46 mg (24%) of product identical with that of borohydride reduction[1] (Chart I, R = Ph, R′ = H) followed by some ring-opened product, there was obtained 10 mg (5%) of a more polar diastereomer (Chart I, R = H, R′ = Ph, **21**). ^1H NMR: δ 0.95 (d, J = 6.4 Hz, 3 H), 0.96 (s, 3 H), 1.0–1.3 (m), 1.19 (s, 3 H), 1.4–1.8 (m), 1.9–2.05 (b d), 3.06 (d, J = 2.9 Hz, 1 H), 3.59 (dt, J = 10.5, 4.0 Hz, 1 H), 4.00 (AB, Δ_{AB} = 0.38, J = 17.8 Hz, 2 H), 4.55 (dd, J = 5.6, 2.8 Hz, 1 H), 4.85 (d, J = 5.6 Hz, 1 H), 7.0–7.6 (m, 5 H). ^{13}C NMR: δ 20.2 (Me), 22.2 (Me), 25.0 (CH_2), 26.9 (Me), 31.3 (CH), 35.0 (CH_2), 41.2 (CH_2), 46.0 (CH), 47.5 (CH_2), 57.6 (C_q), 73.8 (CH), 76.5 (CH), 90.7 (CH), 125.9 (CH), 126.9 (CH), 127.5 (CH), 127.6 (CH), 127.9 (CH), 128.0 (CH), 140.6 (C_q), 142.9 (C_q).

[2*S*(2α,4aα,7α,8aβ)]-Octahydro-3-(phenylmethyl)-4,4,7-trimethyl-2*H*-1,3-benzoxazine-2-methanol (9e). To a solution of 103 mg (0.31 mmol) of equatorial methyl ester **3e** in 10 mL of dry benzene under a nitrogen atmosphere 0.4 mL of Vitride [70% solution of $NaAlH_2(OCH_2CH_2OCH_3)_2$ in toluene] was added dropwise with stirring. Stirring was continued for 3.5 h when TLC (CH_2Cl_2 development) showed disappearance of the methyl ester. The reaction was quenched with 10 mL of water-saturated ether followed by 0.1 mL of 10% aqueous sodium hydroxide. The suspension was filtered, and the solids were washed with ethyl acetate. The combined organic layer was dried over sodium sulfate and concentrated to give crude carbinol **9e**. Proton NMR indicated this to be pure enough for the subsequent oxidation. A sample was purified by silica gel chromatography (elution with 4% EtOAc in hexanes). ^1H NMR: δ 0.94 (dt, J = 6.4 Hz, 3 H), 1.16 (s, 3 H), 1.24 (s, 3 H), 1.0–1.15 (m) and 1.4–2.0 (m) (total 8 H), 3.33 (d, J = 5.5 Hz, 2 H), 3.54 (dt, J = 10.6, 4.1 Hz, 1 H), 3.84 (AB, Δ_{AB} = 0.165, J = 17.4 Hz, 2 H), 4.69 (t, J = 5.5 Hz, 1 H), 7.1–7.6 (m, 5 H). ^{13}C NMR: δ 19.2 (Me), 22.2 (Me), 25.1 (CH_2), 27.1 (CH_2), 31.3 (CH), 34.9 (CH_2), 41.2 (CH_2), 46.6 (CH_2), 47.6 (CH), 57.0 (C_q), 64.0 (CH_2), 75.9 (CH), 87.6 (CH), 126.3 (CH), 126.7 (CH), 128.3 (CH), 143.1 (C_q). IR (film): 3450 (b s), 3080 (w), 3060 (w), 3025 (w), 1605 (w), 1490 (m), 1050 (s), 1020 (m), 1000 (m), 940 (m), 860 (m), 725 (m), 685 (w) cm^{-1}.

Diastereomer 9a was similarly obtained from axial ester **3a**. The NMR data recorded below are based on the crude product since attempted purification by silica gel chromatography led to conversion to the more stable equatorial isomer **9e**. **9a.** ^1H NMR δ 0.94 (d, J = 6.5 Hz, 3 H), 1.08 (s, 3 H), 1.0–1.2 (m), 1.20 (s, 3 H), 1.4–1.6 (m), 1.6–1.8 (m), 1.85–2.0 (b d), 3.61 (dt, J = 10.5, 4.4 Hz, 1 H), 3.65–3.9 (m, 2 H), 3.90 (AB, Δ_{AB} = 0.165, J = 15.5 Hz, 2 H), 4.48 (dd, J = 8.4, 4.8 Hz), 7.0–7.6 (m, 5 H). ^{13}C NMR: δ 22.0 (Me), 22.1 (Me), 25.3 (CH_2), 28.0 (Me), 31.1 (CH), 34.7 (CH_2), 41.7 (CH_2), 48.6 (CH), 49.3 (CH_2), 55.1 (C_q), 60.1 (CH_2), 69.0 (CH), 86.4 (CH), 126.7 (CH), 127.5 (CH), 128.4 (CH), 141.4 (C_q).

[2*S*(2α,4aα,7α,8aβ)]-Octahydro-3-(phenylmethyl)-4,4,7-trimethyl-2*H*-1,3-benzoxazine-2-carboxaldehyde (10). To a solution of 0.1 mL of dry DMSO and 2.5 mL of methylene chloride injected by syringe into a flask under dry nitrogen and cooled with a dry ice–acetone bath was added 0.08 mL of trifluoroacetic anhydride dropwise with stirring. After 20 min a solution of 100 mg of crude **9e** in 2 mL of CH_2Cl_2 was added dropwise, stirring was continued for 1 h, and then 0.1 mL triethylamine was added and the cooling bath was removed. After the mixture had warmed to 0 °C, 25 mL of CH_2Cl_2 and 10 mL of 2% aqueous Na_2CO_3 were added. The organic layer was separated, washed with brine, dried over sodium sulfate, and concentrated. Silica gel chromatography (elution with 2% EtOAc in hexanes) yielded 64 mg (68% in two steps) of **10**. ^1H NMR: δ 0.96 (d, J = 6.5 Hz, 3 H), 1.09 (s, 3 H), 1.28 (s, 3 H), 1.0–1.05 (m), 1.15–1.22 (m), 1.55–1.6 (m), 1.8–2.0 (b d) (total 8 H), 3.57 (dt, J = 10.5, 4.1 Hz, 1 H), 3.86 (AB, Δ_{AB} = 0.05, J = 17.4 Hz, 2 H), 4.96 (s, 1 H), 7.1–7.6 (m, 5 H), 9.19 (d, J = 0.5 Hz, 1 H). ^{13}C NMR: δ 19.9 (Me), 22.2 (Me), 25.0 (CH_2), 26.6 (Me), 31.3 (CH), 34.9 (CH_2), 41.1 (CH_2), 46.4 (CH), 48.5 (CH_2), 57.1 (C_q), 76.1 (CH), 90.1 (CH), 126.6 (CH), 127.5 (CH), 128.2 (CH), 141.5 (C_q), 197.4 (CH). IR (film): 3060 (w), 3025 (m), 2750 (w), 1740 (s), 1600 (m), 1170 (m), 1085 (m), 1020 (s), 715 (m), 685 (m) cm^{-1}. $[\alpha]^{22}_D$ −37.9° (c = 0.2845, EtOAc).

Grignard Additions to 10 (Table II). To a solution of **10** in dry diethyl ether at the temperature indicated (Table II) an excess of Grignard reagent in ether was added dropwise. The reaction was followed by TLC (CH_2Cl_2 development). The reaction mixture was quenched with aqueous ammonium chloride and worked up as described above for ketones.

Diastereomer analysis was affected by proton and ^{13}C NMR spectroscopy. The major product from addition of PhMgBr had the opposite configuration as that obtained by sodium borohydride reduction of **1a** (vide supra).

[1*R*(1α,2β,5α)]-5-Methyl-2-(1-methyl-1-aminoethyl)cyclohexanol (15). To a stirred solution of 0.522 g (2 mmol) of *N*-benzylamino alcohol **2** in 5 mL of methanol was added 0.05 g of 10% Pd-on-charcoal followed by 1.0 g of ammonium formate in 3 mL of water. The suspension was heated at reflux with stirring for 2.5 h, cooled, and filtered through a short Celite column. The solids were washed with ca. 40 mL of EtOAc, and the filtrate was extracted with 2 × 15 mL of water. The aqueous layer was made alkaline with aqueous sodium carbonate to pH ~12 and back-extracted with ethyl acetate (2 × 20 mL).

The combined organic layer was cleared once with brine, dried over sodium sulfate, and concentrated to give 0.35 g (~100%) of crude debenzylated amino alcohol **15** which was pure enough for the following methylation step. ^1H NMR: δ 0.91 (d, J = 6.4 Hz, 3 H), 1.0–1.15 (m), 1.15 (s, 3 H), 1.20 (s, 3 H), 1.25–1.6 (b m), 1.65 (d), 1.95–2.1 (dm), 3.64 (dt, J = 10.5, 4.2 Hz, 1 H). ^{13}C NMR: δ 22.0 (Me), 22.2 (Me), 26.1 (CH_2), 31.0 (CH), 33.8 (Me), 34.9 (CH_2), 44.3 (CH_2), 52.2 (CH), 53.3 (C_q), 72.4 (CH). IR (Nujol): 3500–2600

(b m), 3340 (w), 3270 (m), 3170 (w), 1595 (w), 1190 (m), 1030 (m), 715 (m) cm^{-1}.

[1*R*(1α,2β,5α)]-5-Methyl-2-(1-methyl-1-(methylamino)-ethyl)cyclohexanol (16). A solution of 0.63 g (3.7 mmol) of **15** in 16 mL of 95–97% formic acid (Aldrich) was heated at 80–85 °C for 36 h. Water (30 mL) was added, and the solution was concentrated at aspirator pressure to remove formic acid and then made alkaline (pH ~12) by addition of sodium carbonate monohydrate. The basic water layer was extracted with EtOAc (3 × 25 mL), and the combined organic layer was washed once with brine, dried over sodium sulfate, and concentrated to give 0.74 g of crude formylamino alcohol. NMR showed the presence of cis and trans rotamers.

To a refluxing solution of the formylamino alcohol in 9 mL of THF under a nitrogen atmosphere was added, dropwise, 9 mL of BH_3·Me_2S in THF (2 N, Aldrich), and dimethyl sulfide was distilled out (hood!). Reflux was continued for 50 min, the solvent was removed at reduced pressure, and about 1 mL of methanol was added to destroy excess borane, followed by 8 mL of 6 N aqueous hydrochloric acid. The mixture was heated at ca. 100 °C for 0.6 h. On cooling a clear solution resulted which was diluted with 20 mL of water and extracted with hexanes. The aqueous layer was made alkaline (pH 12) by addition of sodium carbonate monohydrate saturated with sodium chloride and extracted with EtOAc (3 × 25 mL). The combined organic layer was washed once with brine, dried over sodium sulfate, and concentrated to give 0.63 g (92% in two steps) of pure **16**, mp 84.5–85 °C (recrystallized from pentane). ^1H NMR: δ 0.91 (d, J = 6.5 Hz, 3 H), 0.9–1.1 (m, 2 H), 1.08 (s, 3 H), 1.10 (s, 3 H), 1.15–1.3 and 1.3–1.5 (broad) (m's ca. 3 H), 1.6–1.7 (m, 2–3 H), 1.85–2 (m, 1–2 H), 2.32 (s, 3 H), 3.61 (dt, J = 10.2, 4.1 Hz, 1 H). ^{13}C NMR: δ 21.2 (Me), 22.0 (Me), 25.3 (Me), 25.9 (CH_2), 27.4 (Me), 30.9 (CH), 35.0 (CH_2), 44.4 (CH_2), 49.0 (CH), 56.4 (C_q), 72.5 (CH). IR (Nujol): 3260 (m), 1170 (m), 1080 (m), 1050 (m), 1025 (m) cm^{-1}. $[\alpha]^{22}_D$ −23.1° (c = 0.436, EtOAc). Anal. Calcd for $C_{11}H_{23}NO$: C, 71.30; H, 12.51. Found: C, 71.41; H, 12.02.

[2*S*(2α,4aα,7α,8aβ)]-Octahydro-3,4,4,7-tetramethyl-2*H*-1,3-benzoxazine (18). Amino alcohol **15**, 0.35 g, was dissolved in 2 mg of 95–97% formic acid with cooling, and 2.3 mL of 37% aqueous formaldehyde was added. The solution was heated to 80–85 °C overnight. It was then cooled, diluted with 25 mL of water, and concentrated at reduced pressure to remove most of the formic acid. The solution was then made alkaline (pH 12) by addition of sodium carbonate monohydrate and extracted with ethyl acetate (3 × 20 mL).

The combined organic layer was cleared with water and then brine, dried over sodium sulfate, and concentrated to give 0.38 g (97%) of **18** as a colorless oil, which appeared to be pure by NMR analysis. A sample was distilled in a Kugelrohr, bath temperature 140–145 °C/20 mm. ^1H NMR: δ 0.93 (d, J = 6.5 Hz, 3 H), 0.9–1.1 (ca. 1 H), 1.09 (s, 3 H), 1.13 (s, 3 H), 1.4–1.8 (m, ca. 4 H), 1.8–2 (b d, ca. 2 H), 2.44 (s, 3 H), 3.38 (dt, J = 10.4, 4.1 Hz, 1 H), 4.20 (d, J = 10.0 Hz), 4.60 (d, J = 10.0 Hz). ^{13}C NMR: δ 17.2 (Me), 22.2 (Me), 24.9 (CH_2), 26.6 (Me), 31.2 (CH), 34.5 (Me), 34.9 (CH_2), 41.2 (CH_2), 45.9 (CH), 54.7 (C_q), 75.6 (CH), 81.4 (CH_2). IR (film): 2720 (w), 1255 (m), 1230–1210 (b m), 1180 (m), 1165 (m), 1080 (m), 1055 (s), 1000 (s), 960 (s), 900 (m), 690 (m). $[\alpha]^{21}_D$ −73.9° (c = 2.739, EtOAc).

1-Phenyl-1-[[2*S*(2α,4aα,7α,8aβ)]-octahydro-3,4,4,7-tetramethyl-2*H*-1,3-benzoxazin-2-yl]methanone (17). To a solution of 185 mg (1 mmol) of *N*-methylamino alcohol **16** in 20 mL of benzene was added 0.35 g of freshly distilled anhydrous phenylglyoxal, and the solution was heated at reflux for 6 h with water being removed by means of a Dean–Stark trap. After cooling, 10 mL of water and 20 mL of ethyl acetate were added, the layers were separated, and the aqueous phase was extracted with 20 mL more of ethyl acetate. The combined organic layer was cleared with brine, dried over sodium sulfate, and concentrated. The residue was chromatographed on a silica gel column (eluent 1% ethyl acetate–hexanes) to give 191 mg (63.5%) of product **17**. ^1H NMR: δ 0.94 (d, J = 6.4 Hz, 3 H), 1.19 (s, 3 H), 1.32 (s, 3 H), 1.4–1.8 (m) and 1.8–1.95 (m, total 8 H), 2.19 (s, 3 H), 3.56 (dt, J = 10.4, 4.1 Hz, 1 H), 5.57 (s, 1 H), 7.2–7.7 (m, 3 H), 8.2–8.4 (m, 2 H). ^{13}C NMR: δ 18.3 (Me), 22.1 (Me), 25.0 (CH_2), 26.7 (Me), 30.4 (Me), 31.3 (CH), 34.9 (CH_2), 41.1 (CH_2), 45.2 (CH), 56.6 (C_q), 76.3 (CH), 89.4 (CH), 128.1 (CH), 128.5 (CH), 133.2 (CH), 134.7 (C_q), 195.3 (C_q). IR (film): 3060 (m), 1690 (s), 1600 (m), 1580 (m), 1280 (m), 1230 (s), 1215 (m), 1170 (s), 1100 (s), 1060 (m), 1010 (m), 1000 (m), 700 (m), 680 (m) cm^{-1}. $[\alpha]^{22}_D$ −3.1° (c = 0.511, EtOAc).

Addition of Methylmagnesium Bromide to Ketone 17. The addition was carried out as described[1] for ketone **1a** at 20 °C in ether. The crude product (**19**, Chart II) was characterized by NMR spectroscopy. ^1H NMR: δ 0.95 (d, J = 6.4 Hz, 3 H), 1.00 (s, 3 H), 0.9–1.25 (m), 1.17 (s, 3 H), 1.4–1.6 (m), 1.49 (s, 3 H), 1.6–1.75 (m, 1 H), 1.9–2.0 (b d, 1 H), 2.10 (s, 3 H), 3.57 (dt, J = 10.5, 4.0 Hz, 1 H), 4.84 (s, 1 H), 7.0–7.6 (m, 5 H). ^{13}C NMR: δ 20.6, 22.3, 25.1, 27.0, 29.3, 31.4, 32.2, 35.1, 41.3, 44.1, 56.6, 75.0, 76.9, 89.9, 125.0, 125.9, 127.4, 146.2. It was largely one diastereomer. Hydrolysis and oxidation to atrolactic acid was carried out as previously described[1] for the *N*-benzyl analogue (cf. Table III). Similar results were obtained in methyllithium addition at 5 °C in the manner previously described[1] for **1a**.

Sodium Borohydride Reduction of 17. The procedure was analogous to that previously described[1] for the *N*-benzyl analogue **1a**. The crude product (**20**, Chart II) seemed to be largely one diastereomer according to NMR spectroscopy. ^1H NMR: δ 0.87 (d, J = 6.5 Hz, 3 H), 0.9–1.15 (m, 3–4 H), 1.19 (s, ca. 6 H), 1.15–1.8 (m, 3–4 H), 2.46 (s, 3 H), 3.23 (dt, J = 3.8, 10.5 Hz, 1 H), 4.53 (AB, Δ_{AB} = 0.06, J = 8.4 Hz, 2 H), 7.1–7.6 (m, 5 H). ^{13}C NMR: δ 21.9, 22.1, 25.0, 27.4, 27.7, 31.3, 35.0, 40.8, 43.7, 56.6, 71.1, 77.2, 89.9, 127.1, 127.4, 127.8, 142.

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Registry No. **1a**, 115156-57-5; **2**, 115156-56-4; **3a**, 125353-88-0; **3e**, 125353-89-1; **4**, 125251-07-2; **5**, 115156-69-9; **6**, 115156-70-2; **7**, 125250-95-5; **8**, 125250-96-6; **9a**, 125353-90-4; **9e**, 125250-97-7; **10**, 125250-98-8; **11a**, 115224-70-9; **11a** (R = H, 125353-91-5; **11b**, 115156-58-6; **11b** (R′ = H), 115156-62-2; **12a**, 125250-99-9; **12b**, 125353-92-6; **13a**, 125251-00-5; **13b**, 125355-35-3; **14a**, 125251-01-6; **14b**, 125353-93-7; **15**, 55179-51-6; **16**, 125251-02-7; **17**, 125251-03-8; **18**, 125251-04-9; **19**, 125251-05-0; **20**, 125251-06-1; HOCH(OMe)CO_2Me, 109745-70-2; PhMgBr, 100-58-3; MeMgBr, 75-16-1; *i*-PrMgCl, 1068-55-9; 2-methyl-2-(methylsulfonyl)-1-[octahydro-3-(phenylmethyl)-4,4,7-trimethyl-2*H*-1,3-benzoxazin-2-yl]-propan-1-one, 125251-08-3; 5-methyl-2-(1-methyl-1-(formylamino)ethyl)cyclohexanol, 125281-09-6; phenylglyoxal, 1074-12-0; atrolactic acid, 515-30-0.

Supplementary Material Available: Proton NMR spectra of compounds **3a,e**, **4**, **6–8**, **9e,a**, **10**, **11a**, **12a,b**, **13a,b**, **14a,b**, **15–21** (23 pages). Ordering information is given on any current masthead page.