Enantioselective Synthesis of Rigid 2-Aminotetralins. Utility of Silicon as an Oxygen and Nitrogen Surrogate in the Tandem Addition Reaction

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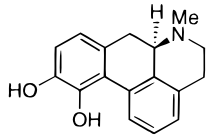
Dimethylphenylsilyllithium undergoes a highly diastereoselective conjugate addition to chiral naphthyloxazoline **11**. Electrophilic trapping of the resulting aza-enolate affords the tandem addition product (**12**) in high yields as a single diastereomer. The silicon, thus incorporated, may be protodesilylated and undergoes a Tamao oxidation to afford the corresponding alcohol. By chemical modification of the oxazoline, both the γ-lactone (**28**) and the δ-lactone (**37**) were prepared. Reduction of each lactone followed by oxidation of the ensuing diol gave the keto aldehyde. Double reductive amination of the 1,4-dicarbonyl (from the γ-lactone) allowed the synthesis of two novel hexahydrobenz[*e*]indoles, **20** and **35**. Double reductive amination of the 1,5-dicarbonyl (from the δ-lactone) gave access to two novel octahydrobenzo[*f*]quinolines, **41** and **43**. An unprecedented rearrangement of nitro alcohol **26** into lactone **28** is described and a reasonable mechanism for its formation postulated.

Reports of the potent anti-Parkinsonian activity of apomorphine (**1**) have triggered research into the development of drugs that mimic this agent.[1] The postulated mechanism of action of **1** involves a selective binding of it to the D-1 and D-2 (dopamine) receptors.[2] Structurally simplified analogues of **1**, 2-aminotetralins (**2**), have been shown to maintain binding affinity to dopamine receptors.[3] Further, through the proper choice of substitution pattern, 2-aminotetralins can show either potent serotonin or dopamine agonist activity. The neurotransmitters dopamine and serotonin have been implicated in many central nervous system related disorders such as anxiety, depression, schizophrenia, and Parkinson's disease.



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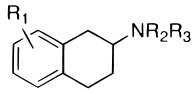

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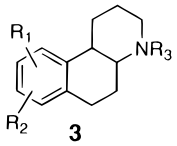

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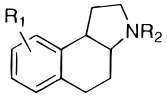

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Cannon et al.[4] synthesized a series of more structurally rigid piperidine-fused tetralins (**3**), formally referred to as octahydrobenzo[*f*]quinolines,[5] and tested them for their ability to bind to dopamine receptors. It was found that most retained good dopamine agonist activity. Wikström[6] later showed that certain analogues of **3** were devoid of dopaminergic activity, yet showed serotonin agonism. Both authors noted increased activity among the trans-fused analogues of **3**.

Later, Lin et al. prepared a series of pyrrolidine-fused tetralins (**4**), formally referred to as hexahydrobenz[*e*]-indoles, and tested them for their ability to bind selectively to dopamine and serotonin receptors.[7] The cis-fused analogues were shown to be more active than the corresponding trans-fused congeners. It was found that analogues with 9-methoxy substitution showed mixed serotonin (5-HT_{1A}) and dopamine (D-2) agonism. In contrast, it was found that analogues with 9-hydroxy substitution showed binding only to 5-HT_{1A} receptors.

The ability to change the binding selectivity to favor one or the other through modification of the substituents present on **3** or **4** poses not only potential medicinal value, but also makes these more rigid ring-fused aminotetralins useful in fundamental research into the mechanism by which neurotransmitters function. Although dopamine and serotonin possess no center of asymmetry, it is apparent from in vivo assays that their respective receptors possess a high degree of chirality, discriminating between enantiomeric dopaminergic and serotoninergic

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(2) Vernier, V. G. *Annu. Rep. Med. Chem.* **1971**, *1970*, 42.
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(5) For other syntheses of octahydrobenzo[*f*]quinolines, see: (a) Ripa, L.; Hallberg, A. *J. Org. Chem.* **1998**, *63*, 84. (b) Tagmatarchis, N.; Katerinopoulos, H. E. *J. Heterocycl. Chem.* **1996**, *33*, 983.
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(7) (a) Lin, C.-H.; Haadsma-Svensson, S. R.; Lahti, R. A.; McCall, R. B.; Piercey, M. F.; Schreur, P. D.; Von Voigtlander, P. F.; Smith, M. W.; Chidester, C. G. *J. Med. Chem.* **1993**, *36*, 1053. (b) Cruse, S. F.; Lear, J.; Klein, C. L.; Andersen, P. H.; Dick, R. M.; Crider, A. M. *J. Pharm. Sci.* **1993**, *82*, 334.

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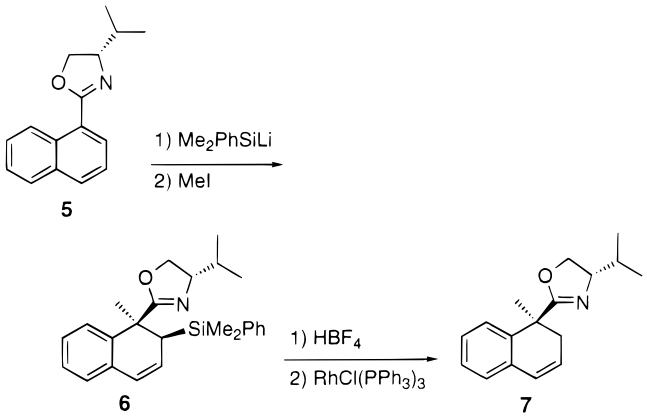
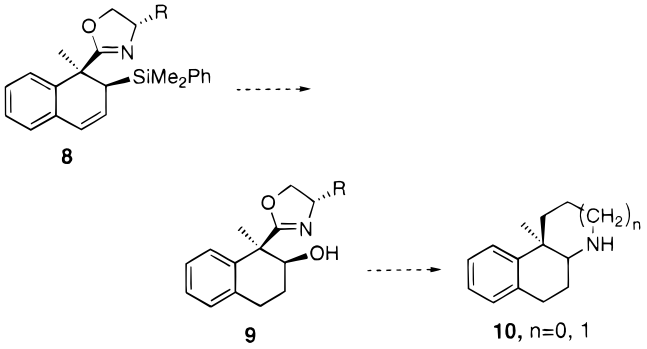
Scheme 1



Scheme 2

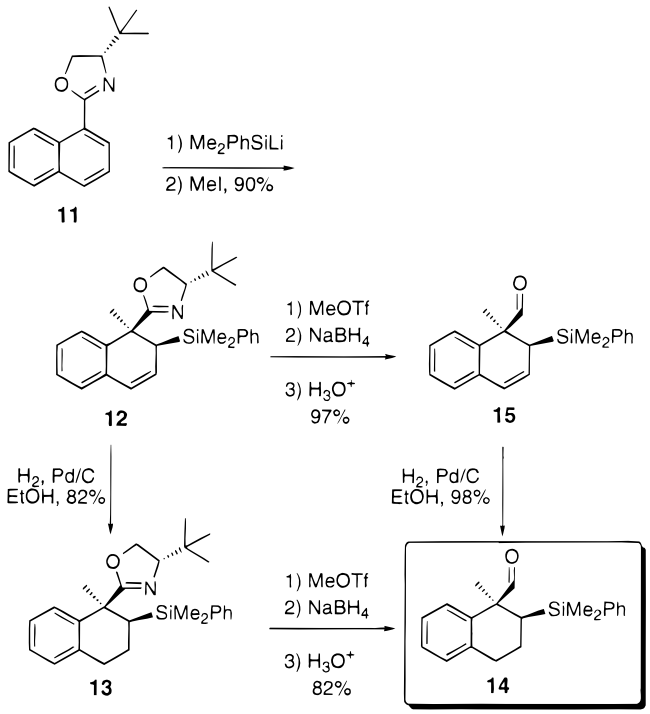


agonists.[8] As such there is a need to synthesize these molecules in a highly enantioselective fashion.

In an earlier report,[9] it was shown that dimethylphenylsilyllithium undergoes conjugate addition[10] to naphthyloxazoline **5** to afford **6** as a single diastereomer (Scheme 1). In that work, the silane was a mere proton surrogate, allowing the creation of chiral 1,1-disubstituted dihydronaphthalenes, **7**. It was anticipated that this same methodology would allow the incorporation of a hydroxyl group via protodesilylation of the phenyl group and subsequent Tamao oxidation[11] of the incorporated silicon (Scheme 2). As oxygen nucleophiles have been found to be unsuitable to undergo the tandem addition reaction, this would represent an expedient entry into chiral 2-hydroxy tetralins, **9**. It was felt that, once installed, the hydroxyl could be elaborated to afford one or more rigid 2-aminotetralins[12] (**10**).

As described in our previous studies,[9] dimethylphenylsilyllithium underwent conjugate addition to oxazoline **11** to afford a single diastereomer[13] of **12** after quenching with methyl iodide (Scheme 3). The oxazoline moiety could then be converted to the tetrahydronaphthylaldehyde **14** in either of two fashions. Hydrogenation of the

Scheme 3



addition product **12** to give **13** followed by quaternization of **13** with methyl triflate, reduction with sodium borohydride, and hydrolysis of the resulting aminal gave aldehyde **14** in 65% overall yield. The two-step process was significantly improved by reversing the catalytic and hydride reduction steps to afford the tetrahydronaphthylaldehyde in 95% overall yield from **12**.

At this point, it was necessary to plan a sequence that would incorporate the requisite C−N tether by condensing **15** with nitromethane[14] to furnish the nitroolefin, **16** (Scheme 4). The latent hydroxyl group, present as the silyl substituent, would be liberated, by protodesilylation and subsequent Tamao oxidation, to give the intermediate nitro alcohol, which would be oxidized to the nitro ketone **17**. It was initially anticipated that treatment of **17** with H_2−Pd/C would introduce 5 mol of hydrogen to produce the intermediate **18**, which would be expected to undergo intramolecular condensation to imine **19**. Under the hydrogenation conditions, it was thought that this would be further reduced to liberate the target compound **20**. *Thus, the latter, in enantiomerically pure form, could hopefully be accessed in a single hydrogenation step by reduction of nitroketone* ***17****.*

In actuality, the Henry reaction proceeded smoothly affording a quantitative yield of nitro alkene **16** (Scheme 5). However, all attempts to desilylate this material to **21** were unsuccessful, giving rise to heavy decomposition. This was not wholly unexpected as allyl silanes can themselves be protodesilylated to give desilylated material (as seen in Scheme 1). Furthermore, allyl silanes are known to undergo conjugate addition reactions with α,β-unsaturated nitro compounds.[15] It was felt that these obstacles could be bypassed by reduction of one or both of the olefinic linkages present in **16**.

Attention was then focused on the analogous saturated silyl aldehyde, **14**, wherein the styrene double bond had

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(9) (a) Hulme, A. N.; Meyers, A. I. *J. Org. Chem.* **1994**, *59*, 952. (b) Hulme, A. N.; Henry, S. S.; Meyers, A. I. *J. Org. Chem.* **1995**, *60*, 1265.
(10) For reviews on the use of chiral oxazolines in synthesis, see: (a) Meyers, A. I. *J. Heterocycl. Chem.* **1998**, *35*, 991. (b) Gant, T. G.; Meyers, A. I. *Tetrahedron*, **1994**, *50*, 2297. (c) Reuman, M.; Meyers, A. I. *Tetrahedron* **1985**, *41*, 837.
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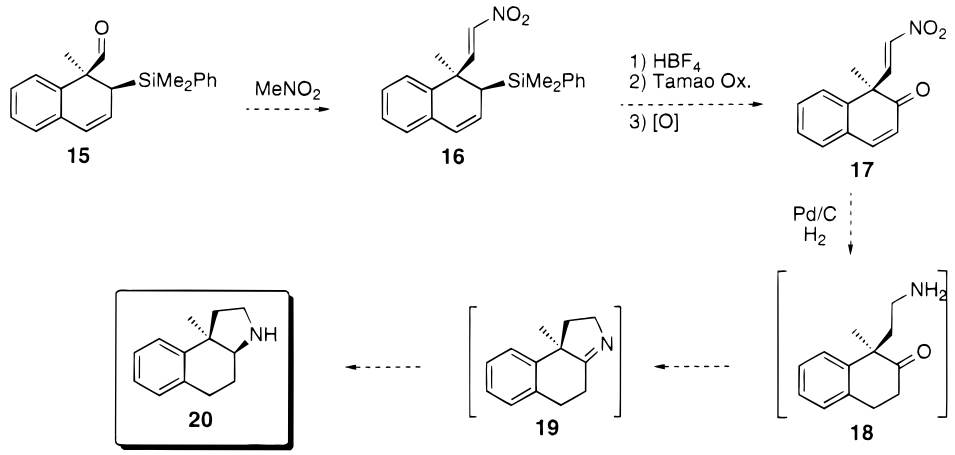
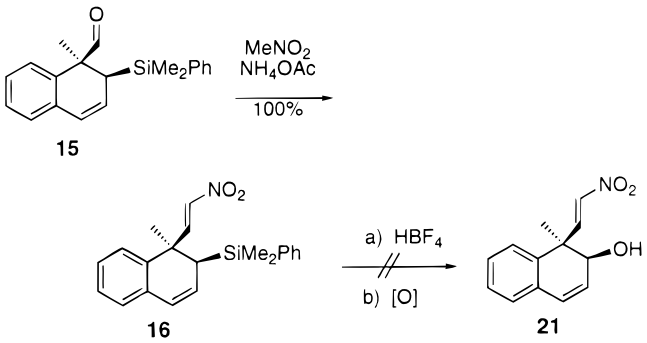
(12) For an earlier report of a naphthyloxazoline-based sythesis of 2-aminotetralins, see: Shimano, M.; Meyers, A. I. *J. Org. Chem.* **1995**, *60*, 7445.
(13) Determined by ^{1}H NMR.
(14) Henry, L. *C. R. Hebd. Seances Acad. Sci.* **1895**, *120*, 1265.
(15) Ochiai, M.; Arimoto, M.; Fujita, E. *Tetrahedron Lett.* **1980**, 4557.

Scheme 4



Scheme 5



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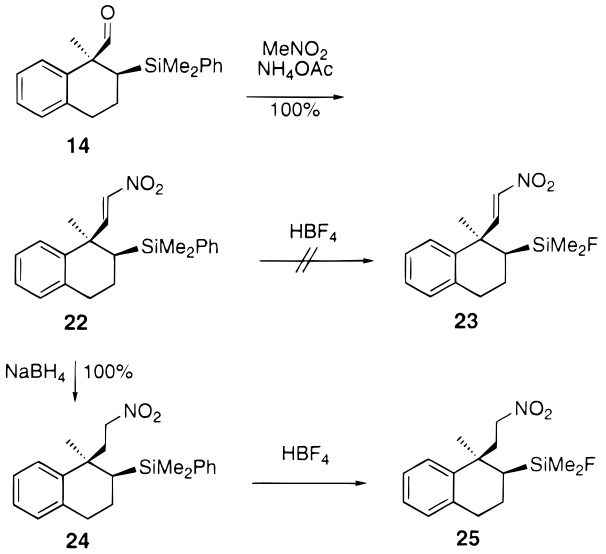

been reduced (Scheme 6). This material also underwent the Henry reaction to give a quantitative yield of nitro olefin **22**. Subjection of **22** to HBF_4 to introduce the fluoride, **23**, also gave rise to decomposition products. Finally, the double bond adjacent to the nitro group was quantitatively reduced by a method reported[16] years ago from these laboratories. Subjection of this fully saturated nitro compound **24** to HBF_4 gave clean conversion to the silylfluoride **25**, which underwent the Tamao oxidation to give hydroxy nitro compound **26** (Scheme 7). Although well precedented[17] in the literature, all attempts to

Scheme 7

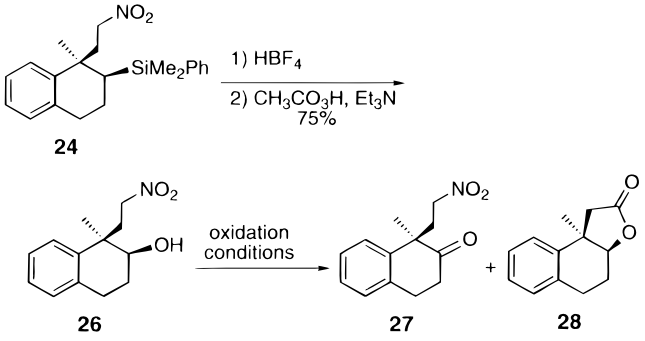

Table 1. Attempts to Oxidize Nitro Alcohol 26 to Nitroketone 27

oxidation conditions	ratio[a] of **27**:**28**
$(COCl)_2$, DMSO (Swern oxid)	1:3.0
PCC, CH_2Cl_2	1:1.8
PDC, CH_2Cl_2	1:1.8
Dess−Martin periodinane, CH_2Cl_2	1:2.8
Jones reagent	1:3.5
TPAP, NMO, mole sieves, CH_2Cl_2	1:19

[a] Determined by ^1H NMR.

oxidize alcohol **26** to the corresponding nitro ketone (Table 1) surprisingly gave mixtures of the desired product (**27**) and a new lactone **28**.

Generation of the lactone **28** from nitro alcohol **26** came unexpectedly since a search of the literature revealed no precedents for this transformation. In fact, there are several reports of the expected oxidation of hydroxy nitro compounds to nitro ketones.[17] It is believed that the lactone formation (to **28**) occurs via the pathway shown in Scheme 8. It seems reasonable that the electrophilic center of the oxidant coordinates to the nitro group rather than the neopentyl alcohol of **26**, activating it toward tautomerization to the aci-nitro form **30**. The hydroxyl group is then in a position to add intramolecularly to the aci-nitro group, furnishing **31**. This intermediate can, in turn, eliminate the coordinated oxygen of the nitro group to afford the *N*-hydroxyimidate **32**. Hydrolysis of the latter completes the formation to the observed lactone **28**. This transformation may not be very general, and occurs in this specific case because of two factors. First, the sterically demanding nature of the neopentyl alcohol in **26** inhibits the coordination of the electrophile to the

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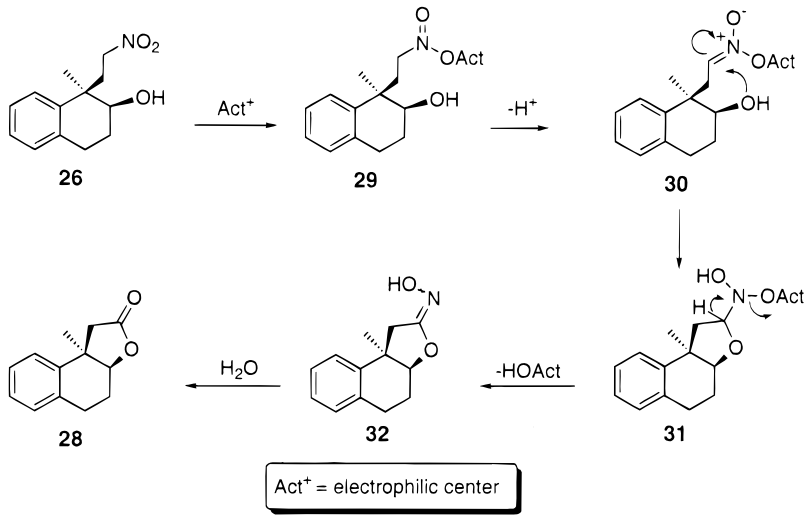
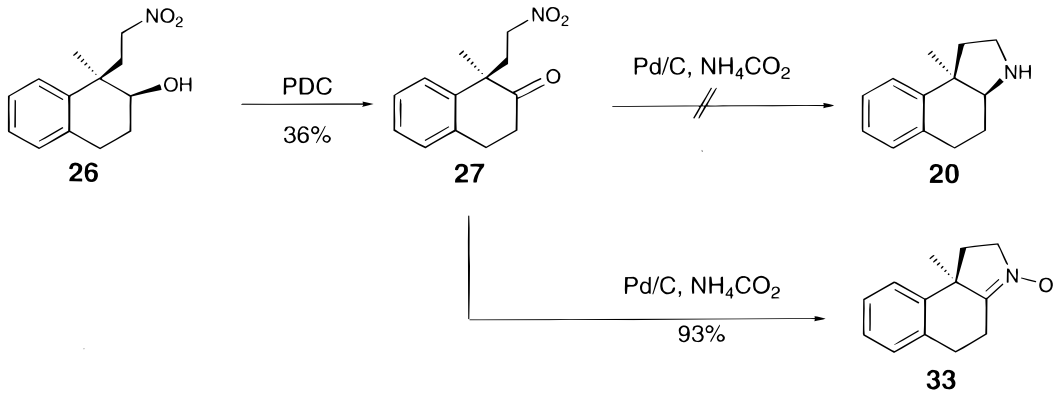
(17) Shvekhgeimer, M.-G. A. *Russ. Chem. Rev.* **1998**, *67*, 35.

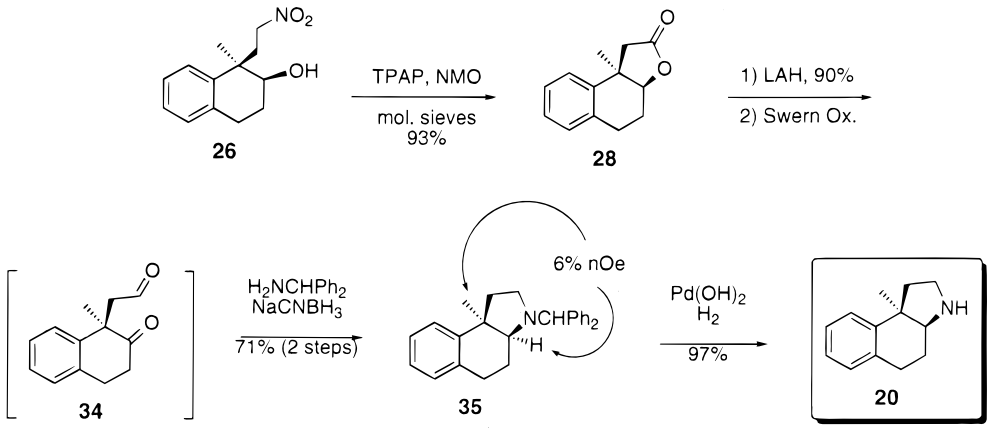
Scheme 8



Scheme 9



Scheme 10



hydroxyl lone pairs. Second, the close proximity of the hydroxyl group to the α-carbon of the nitro group leads to facile cyclization affording "aminal" **31**.

Although oxidation yields to nitroketone **27** could not be improved beyond 36%, the process was continued by reduction of **27** gave nitrone **33** as the sole product under transfer hydrogen conditions. No trace of the tricyclic pyrrolidine **20** was detected (Scheme 9). The nitrone arises from the previously reported[18] intramolecular cyclization of the hydroxylamine before hydrogenation of the nitro group could be completed.

Since the nitro ketone **27** was obtained in poor yield and only led to the nitrone **33**, which still required a second reduction step[19] to the corresponding pyrrolidine, this route was abandoned. The unexpectedly efficient conversion of the nitro ketone to lactone **28**, suggested that this intermediate may, in fact, be a suitable precursor to the aminotetralin **20** (Scheme 10). In this regard, reduction of the lactone **28** with LAH produced the corresponding diol in 90% yield which was immediately oxidized to keto aldehyde **34**. The latter proved to be highly unstable and was utilized directly without puri-

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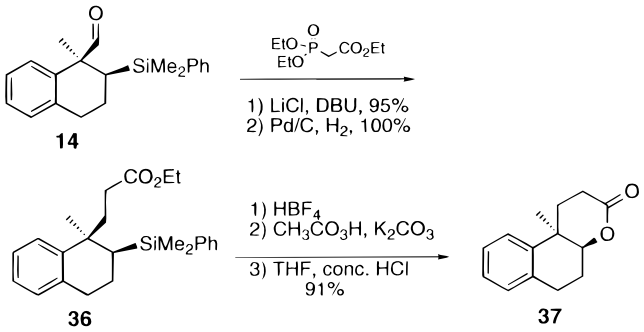
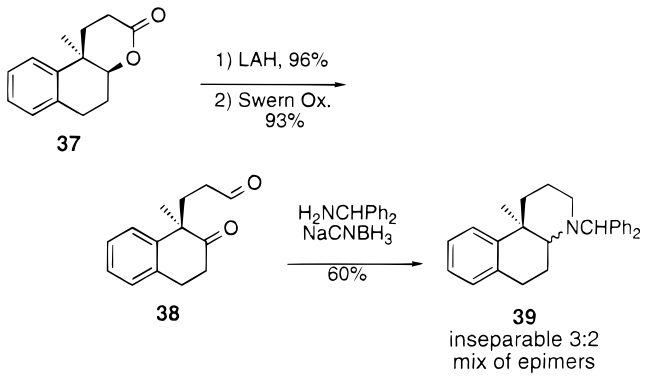
(19) Sar, C. P.; Kalai, T.; Baracz, N. M.; Jerkovich, G.; Hideg, K. *Synth. Commun.* **1995**, *25*, 2929.

Scheme 11



Scheme 12



fication in a double reductive amination.[20] This was accomplished by treatment of keto aldehyde **34** with benzhydrylamine and sodium cyanoborohydride and gave a 71% yield of the desired ring system, **35**, as a 9:1 ratio of diastereomers[13] that were readily separable by column chromatography. The relative stereochemistry of the major diastereomer (**35**) was unambiguously established by NOE studies of the quaternary methyl with the α-hydrogen, which confirmed the cis-fused ring system. Removal of the benzhydryl group was readily accomplished under hydrogenolysis conditions to afford aminotetralin **20**—*the primary target of this study*.

Since the γ-lactone, **28**, was smoothly converted to the pyrrolidine-fused tetralin **20**, it was expected that elaboration of aldehyde **14** to the analogous δ-lactone **37** would provide the corresponding piperidine-fused tetralin, **41**. Horner−Wadsworth−Emmons olefination[21] proceeded smoothly on the saturated aldehyde **14**, affording the unsaturated ester exclusively as the *E* isomer[13] in 95% chemical yield (Scheme 11), which was cleanly reduced (H_2−Pd/C) to give a quantitative yield of the γ,γ-disubstituted butanoic ester **36**. Treatment of the arylsilane with HBF_4 gave the silyl fluoride, which was taken on directly, via the Tamao oxidation (utilizing excess peracetic acid and K_2CO_3 in acetic acid), to the hydroxy ester—the precursor to lactone **37**. Although most of the hydroxy ester spontaneously cyclized to lactone **37**, it was found beneficial to include a separate acid-catalyzed lactonization step to furnish the lactone **37**, which was produced in 91% yield over three steps (**36** → **37**).

The δ-lactone **37** was reduced with LAH to afford the corresponding diol in 96% yield which, in turn, was directly oxidized, under Swern conditions, furnishing 93% of keto aldehyde **38** (Scheme 12). The latter proved to be much more stable than its related keto-aldehyde **34**, thus allowing purification by column chromatography and complete characterization. Double reductive amination of **38** with benzhydrylamine and $NaCNBH_3$ proceeded in good chemical yield, but gave the piperidine **39** as a 3:2 ratio of cis and trans diastereomers.[13] Attempts to completely separate the epimers met with failure.

To assess whether the use of a chiral nonracemic amine may direct the reductive amination to favor either of the diastereomers of the cis- or trans-fused derivative, keto aldehyde **38** was condensed, separately, with each enantiomer of α-methylbenzylamine (Scheme 13). Furthermore, introduction of an additional stereocenter might be expected to further bias the reduction leading to the cis- and trans-fused product, respectively. When (*S*)-α-methylbenzylamine was used, the double reductive amination proceeded with complete diastereoselectivity,[13] affording only the cis-fused ring system (**40**) as determined by an NOE analysis. Treatment of this compound with Pearlman's catalyst ($Pd(OH)_2$) in the presence of H_2 gave rise to the single enantiomer of the *cis*-piperidine-fused tetralin **41**.

Alternately, when (*R*)-α-methylbenzylamine was reductively condensed with keto aldehyde **38**, only the trans-fused enantiomer **42** was observed.[13] This was supported by the absence of an NOE response between the angular methyl and the adjacent methine. Subsequently, this assignment was confirmed by hydrogenolysis of the benzylamine **42** to give aminotetralin **43**, which clearly differed from cis-fused aminotetralin **41**, prepared above.

Given this apparent directing affect associated with the use of chiral α-methylbenzylamines in the double reductive amination, it was felt that the same directing effect may be observed in the preparation of the pyrrolidine-fused tetralins **44** and **45**. It might also serve to improve the earlier synthesis, which gave a 9:1 ratio of **36**, *epi*-**35**, respectively. If this was to hold true, it was expected that use of (*S*)-α-methylbenzylamine would give rise to the cis-fused aminotetralin (**20**) as a single enantiomer. Alternately, it was hoped that use of (*R*)-α-methylbenzylamine would overcome the internal preference to form the cis-fused ring system, affording the trans-fused aminotetralin (**47**) preferentially.

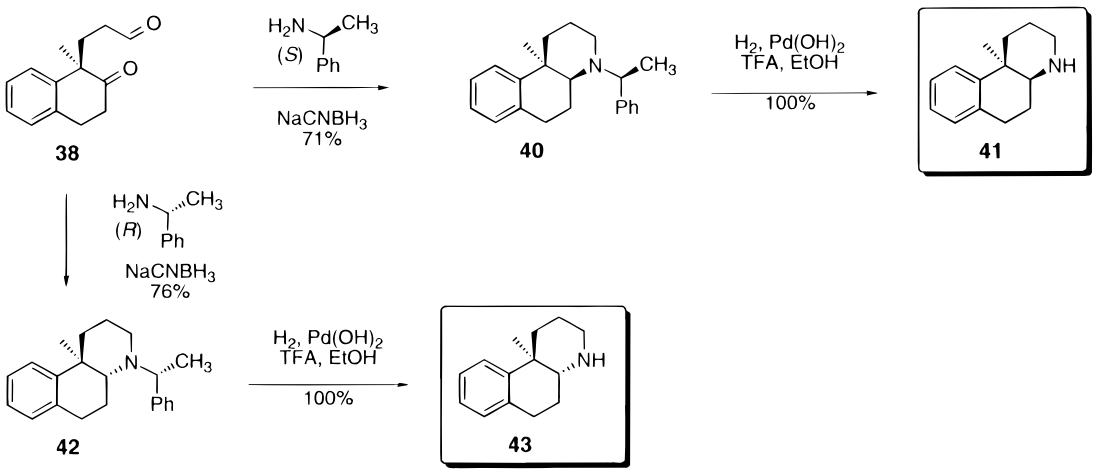
Unfortunately, condensation of keto aldehyde **34** with (*S*)-α-methylbenzylamine gave rise to a mixture of **44** and **45** as a 3:1 ratio of diastereomers (Scheme 14).[13] As this was well below the diastereoselectivity observed earlier with benzyhydrylamine, attempts to improve the diastereomeric ratio above 9:1 in favor of the *cis*-fused aminotetralin were considered unlikely.

Even with the poor diastereoselectivity observed above, it still seemed worthwhile to condense the keto aldehyde **34** with the (*R*)-enantiomer of α-methylbenzylamine in the hopes of exceeding the 10−12% of the trans-fused aminotetralin (**48**), obtained from the benzhydryl reductive amination. Condensation of the keto aldehyde **34** with (*R*)-α-methylbenzylamine gave rise to a 1:1 mixture of **46** and **47**.[13] This finding was consistent with the earlier result in the piperidine series (**41**, **43**) that (*R*)-α-methylbenzylamine appears to favor the formation of

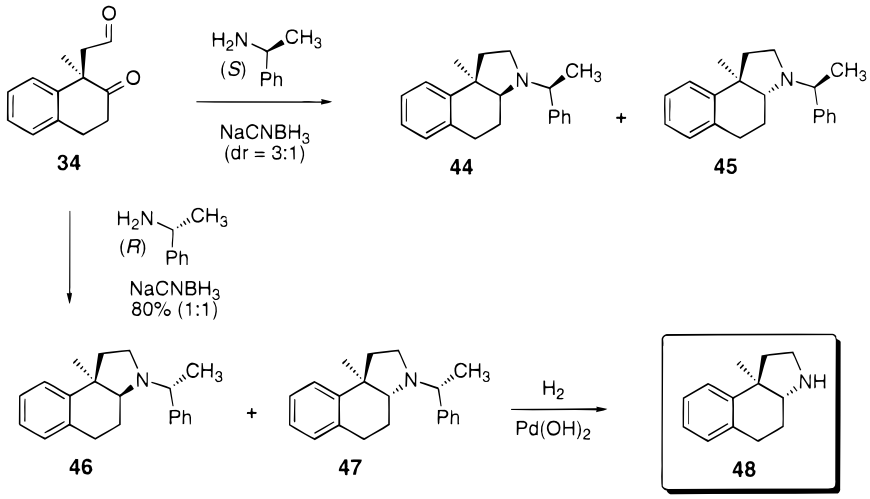
(20) For other syntheses of pyrrolidines and piperidines using a double reductive amination, see: (a) Barili, P. L.; Berti, G.; Catelani, G.; D'Andrea, F.; De Rensis, F.; Puccioni, L. *Tetrahedron* **1997**, *53*, 3407. (b) Solé, D.; Bosch, J.; Bonjoch, J. *Tetrahdron* **1996**, *52*, 4013. (c) Baxter, E. W.; Reitz, A. B. *J. Org. Chem.* **1994**, *59*, 3175 and references therein.

(21) For a review of phosphorous-based olefinations, see: Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863.

Scheme 13

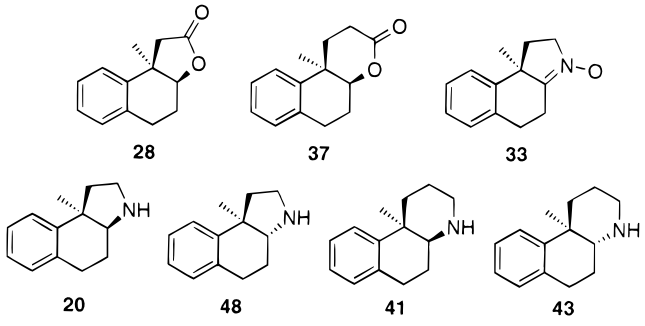


Scheme 14



the trans-fused ring system. Given the considerable bias for **34** to form the cis-fused ring juncture (9:1), the formation of a 1:1 mixture of epimers represents a significant increase in selectivity, 11% to 50%. The epimers **46** and **47** were separated via column chromatography, and their structures were assigned on the basis of the presence or absence of an NOE interaction between the angular methyl and the adjacent methine. Reductive removal of the chiral auxiliary of **47** gave the trans-fused pyrrolidine (**48**) which, as expected, differed spectroscopically from the cis-fused pyrrolidine (**20**). Any attempts to rationalize the stereo results of the reductive amination leading to **41**, **43** and **44**, **45** would be purely speculative at this time.

In conclusion, dimethylphenylsilyllithium underwent the tandem addition reaction to naphthyloxazoline **11** with complete diastereoselectivity to afford **12**. The silicon served as a surrogate first for oxygen and later for nitrogen. As oxygen anions are not sufficiently nucleophilic to undergo the tandem addition reaction to naphthyl oxazolines this represents a convenient entry into this important class of compounds. As a result of this investigation a series of enantiomerically pure oxygen and nitrogen heterocycles have been cleanly accessed. Furthermore, all seven contain quaternary stereocenters in fused tetralin systems (**20**, **28**, **33**, **37**, **41**, **43**, **48**).



Experimental Section

Thin-layer chromatography (TLC) and flash chromatography were performed with E. Merck silica gel (230−400 mesh). NMR coupling constants (*J*) are reported in hertz.All reagents were purchased from Aldrich. All nonaqueous reactions were conducted under an argon atmosphere in oven or flame-dried apparatus. Microanalyses were performed by Atlantic Microlab, Inc., Norcross, GA.

Tandem Addition Product, 12. To a stirred suspension of lithium wire (1.1 g, 159 mmol) in THF (20 mL) at room temperature was added chlorodimethylphenylsilane (7.6 mL, 45 mmol). The flask was sonicated for 2 h to give a very

reddish-brown suspension and was stirred an additional 1.5 h without sonication. The solution was added dropwise via a very fine cannula over 30 min to a stirred solution of naphthyloxazoline **11**[12] (5.7 g, 23 mmol) in ether (80 mL, −72 °C) and stirred for 87 h. MeI (2.8 mL, 45 mmol) was added via syringe and the reaction allowed to warm to −20 °C before quenching with MeOH and concentration in vacuo. The residue was partitioned between water and ether (3×), washed with brine, dried over Na_2SO_4, and concentrated. The crude oil was filtered through a plug of silica gel using 10% EtOAc/Hex. The material was recrystallized from ether to give 8.2 g (90%) diastereomerically pure **12** as large cubes: $[\alpha]^{25}_D = +309$ (c = 1.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.02 (s, 3H), 0.08 (s, 3H), 0.86 (s, 9H), 1.60 (s, 3H), 2.50 (dd, J = 6.0, 0.9, 1H), 2.84 (dd, J = 10.5, 8.4, 1H), 3.18 (dd, J = 10.5, 8.7, 1H), 3.67 (dd, J = 8.7, 8.4, 1H), 5.90 (dd, J = 9.6, 6.3, 1H), 6.41 (d, J = 9.9, 1H), 6.80−7.50 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.6, −0.7, 26.2, 29.1, 33.6, 37.2, 44.2, 68.0, 75.7, 124.3, 126.3, 126.5, 126.9, 127.3, 127.9, 128.5, 129.6, 132.8, 133.0, 138.9, 140.1, 170.3; IR (thin film) 1654 cm^{-1}. Anal. Calcd for $C_{26}H_{33}NOSi$: C, 77.37; H, 8.24; N, 3.47. Found: C, 77.23; H, 8.29; N, 3.51.

Tetrahydronaphthyloxazoline, 13. A 250 mL flask was charged with dihydronaphthyloxazoline **12** (1.0 g, 2.5 mmol), palladium (100 mg, 10% on carbon), and absolute ethanol (90 mL). The flask was flushed with argon and then H_2, before finally affixing a balloon of H_2. The suspension was stirred overnight, filtered through silica gel (eluting with EtOAc), and concentrated. Column chromatography (2−4% EtOAc/Hex) gave 0.82 g (82%) as an oil: $[\alpha]^{25}_D = -142$ (c = 1.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.36 (s, 3H), 0.40 (s, 3H), 0.86 (s, 9H), 1.29 (dd, J = 12.9, 2.7, 1H), 1.65 (s, 3H), 1.88 (m, 1H), 2.03 (m, 1H), 2.62 (m, 1H), 2.78 (m, 1H), 3.66 (m, 3H), 6.97−7.60 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −3.5, −0.7, 23.0, 26.3, 31.5, 32.0, 34.0, 35.4, 41.7, 68.4, 75.4, 126.0, 126.0, 127.6, 127.7, 128.9, 129.4, 134.1, 136.8, 139.8, 141.6, 171.2; IR (thin film) 1654 cm^{-1}.

Unsaturated Aldehyde, 15. To a solution of oxazoline **12** (2.03 g, 5.03 mmol) in CH_2Cl_2 (2.5 mL) was added MeOTf (1.15 mL, 10.2 mmol) at 0 °C. The ice bath was removed and the solution stirred overnight at room temperature. This solution was transferred dropwise via cannula into a 250 mL round-bottom flask containing $NaBH_4$ (0.80 g, 21 mmol) in MeOH (5 mL) and THF (20 mL) at 0 °C. There was rapid evolution of gas. Upon completion of addition, the ice bath was removed, and stirring was continued 30 min. The solution was concentrated and the residue partitioned between ether and saturated $NaHCO_3$. The aqueous was washed twice more with ether. The organics were combined, concentrated, and treated with oxalic acid (1.25 g, 14 mmol), THF (30 mL), and water (6 mL). The flask was heated at reflux for 4 h and concentrated and the residue partitioned between ether and water. The aqueous was washed twice more with ether. The organics were combined, dried over Na_2SO_4, and concentrated to give 1.49 g (97%) of **15** as a white solid: mp 49.9−51.5 °C; $[\alpha]^{25}_D = +658$ (c = 4.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.07 (s, 3H), 0.10 (s, 3H), 1.25 (s, 3H), 2.02 (dd, J = 6.3, 1.2, 1H), 5.73 (dd, J = 9.6, 6.3, 1H), 6.35 (d, J = 9.9, 1H), 6.69 (dd, J = 7.8, 0.9, 1H), 6.95−7.40 (m, 8H), 9.87 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −2.87, −2.64, 23.3, 36.1, 53.6, 124.4, 125.8, 126.8, 127.8, 127.9, 128.0, 128.8, 129.5, 133.2, 133.7, 135.5, 137.8, 203.4; IR (thin film) 1724 cm^{-1}.

Saturated Aldehyde, 14. A flask was charged with aldehyde **15** (1.91 g, 6.23 mmol), Pd/C (300 mg, 0.28 mmol, 10%), and EtOH (40 mL) and was purged with hydrogen. A hydrogen balloon was attached, and the reaction was allowed to stir for 10 h. The reaction was filtered through a pad of silica gel, eluting with EtOAc. Concentration gave 1.88 g of **14** (98%) as an oil: $[\alpha]^{25}_D = -195$ (c = 3.4, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.39 (s, 3H), 0.39 (s, 3H), 1.33 (dd, J = 12.6, 2.4, 1H), 1.40 (s, 3H), 1.75 (m, 1H), 1.98 (m, 1H), 2.78 (m, 1H), 7.10 (m, 4H), 7.45 (m, 5H), 9.61 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −2.7, −1.2, 23.0, 25.3, 31.3, 32.8, 52.4, 126.4, 126.7, 127.8, 128.5, 129.1, 129.7, 133.9, 136.7, 138.4, 138.5, 201.5; IR (thin film) 1716 cm^{-1}. Anal. Calcd for $C_{20}H_{24}OSi$: C, 77.87; H, 7.84. Found: C, 77.74; H, 7.91.

Nitro Olefin, 22. A pressure tube was charged with aldehyde **14** (100 mg, 0.32 mmol), ammonium acetate (100 mg, 1.3 mmol), and nitromethane (2 mL) and purged with argon. A Teflon cap was applied, and the reaction was heated at 120 °C for 24 h. The crude was filtered through cotton and concentrated and the residue partitioned between brine and ether. The water was twice more extracted with ether. The ethereal was combined, dried over Na_2SO_4, and concentrated to give 114 mg (100%) of **22** as an oil: $[\alpha]^{25}_D = +155$ (c = 3.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.38 (s, 3H), 0.39 (s, 3H), 1.41 (dd, J = 12.6, 1.8, 1H), 1.42 (s, 3H), 1.64 (dddd, J = 12.3, 12.3, 11.4, 5.1, 1H), 1.96 (dddd, J = 13.5, 5.1, 3.0, 3.0, 1H), 2.65−2.90 (m, 2H), 6.62 (d, J = 13.5, 1H), 7.00−7.15 (m, 4H), 7.35−7.40 (m, 3H), 7.42 (d, J = 13.2, 1H), 7.50−7.60 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −2.27, −1.63, 22.3, 29.2, 31.7, 36.3, 42.3, 126.5, 126.8, 128.1, 128.4, 129.5, 129.7, 134.0, 137.1, 138.3, 138.6, 140.0, 149.6; IR (thin film) 1348, 1523 cm^{-1}; HRMS (FAB$^+$) for $C_{21}H_{26}NO_2Si$ (M + 1)$^+$ calcd 352.1733, found 352.1728.

Nitroalkane, 24. To a stirred solution of nitro olefin **22** (3.32 g, 9.5 mmol) in acetonitrile (40 mL, 0 °C) was added a solution of $NaBH_4$ (3.0 g, 79 mmol) in water (25 mL) made basic with 10% NaOH in small portions via an addition funnel. The pH was monitored with pH paper and was maintained between 3 and 6 by addition of 1 N HCl as needed. Upon completion of borohydride addition, the ice bath was removed and the reaction stirred for 4 h at room temperature. Excess hydride was destroyed by addition of solid NH_4Cl and the reaction concentrated. The residue was partitioned between ether and water and the aqueous layer twice more extracted with ether. The ethereal was washed with brine, dried over Na_2SO_4, and concentrated to give 3.34 g of **24** (100%) as an oil: $[\alpha]^{25}_D = -82.0$ (c = 2.6, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.47 (s, 3H), 0.52 (s, 3H), 1.34 (dd, J = 13.2, 2.7, 1H), 1.38 (s, 3H), 1.60 (dddd, J = 13.5, 13.5, 11.1, 6.0, 1H), 2.02 (dddd, J = 13.5, 6.3, 3.0, 3.0, 1H), 2.34 (ddd, J = 16.5, 11.4, 5.4, 1H), 2.47 (ddd, J = 17.4, 11.1, 6.3, 1H), 2.72 (ddd, J = 16.8, 10.5, 5.7, 1H), 2.84 (ddd, J = 16.8, 5.7, 3.3, 1H), 3.85−4.05 (m, 2H), 7.00−7.65 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −1.47, −0.76, 22.8, 31.5, 31.8, 36.9, 39.4, 39.5, 73.5, 125.8, 126.3, 126.3, 128.1, 129.4, 129.7, 134.0, 136.9, 138.8, 142.6; IR (thin film) 1379, 1552 cm^{-1}.

Nitro Alcohol, 26. To a stirred solution of nitrosilane **24** (0.50 g, 1.42 mmol) in CH_2Cl_2 (8 mL) at 0 °C was added HBF_4 (2 mL, 54% in ether). The solution was allowed to gradually warm to room temperature and was stirred overnight, and then it was poured over an excess of solid $NaHCO_3$. The suspension was diluted with CH_2Cl_2, filtered, and concentrated to give the crude silylfluoride. The residue was suspended in CH_3CO_3H (2.5 mL, 32% in CH_3CO_2H) at 0 °C and treated with Et_3N (0.5 mL, 3.59 mmol). The solution was allowed to gradually warm to room temperature and was stirred overnight, and the resulting suspension was poured into 20% K_2CO_3 and extracted into ether (3×). The ethereal portion was washed with 20% K_2CO_3 (2×), dried over Na_2SO_4, and concentrated. Column chromatography gave 0.33 g (75%) of **26** as an oil: $[\alpha]^{25}_D = +26.4$ (c = 1.4, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.36 (s, 3H), 1.80−2.10 (m, 2H), 2.22 (bs, 1H), 2.40 (ddd, J = 14.1, 10.2, 6.0, 1H), 2.56 (ddd, J = 14.1, 10.2, 5.4, 1H), 2.70−3.10 (m, 2H), 3.83 (dd, J = 8.1, 3.0, 1H), 4.52 (m, 2H), 7.05−7.30 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.6, 22.7, 23.1, 31.6, 36.6, 69.2, 70.0, 121.8, 122.0, 122.2, 124.7, 130.6, 136.5; IR (thin film) 1383, 1549 cm^{-1}.

Nitro Ketone, 27. To a solution of alcohol **26** (20 mg, 0.085 mmol) in CH_2Cl_2 (1.5 mL) was added PDC (55 mg, 0.15 mmol). After 4 h, another portion of PDC was added (55 mg, 0.15 mmol) and stirring continued overnight. The reaction was diluted with ether and filtered through silica gel. Column chromatography gave 7 mg (36%) of **27** as an oil: $[\alpha]^{25}_D = +75.5$ (1.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.53 (s, 3H), 2.47 ddd, J = 15.3, 10.2, 5.1, 1H), 2.63 (ddd, J = 14.7, 5.7, 5.7, 1H), 2.80−2.95 (m, 2H), 3.00−3.20 (m, 2H), 3.96 (ddd, J = 13.2, 10.2, 5.1, 1H), 4.17 (ddd, J = 12.9, 10.2, 5.7, 1H), 7.20−7.40 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.5, 28.9, 35.7, 37.5,

50.0, 72.0, 126.3, 127.4, 127.8, 128.8, 135.8, 139.7, 212.8; IR (thin film) 1383, 1552, 1712 cm^{-1}.

Nitrone, 33. To a stirred solution of nitro ketone **27** (5 mg, 0.020 mmol) in THF/MeOH (1 mL, 1:1) were added NH_4HCO_2 (20 mg, 0.32 mmol) and Pd/C (2 mg, 10%). After being overnight, the solution was diluted with ether (6 mL), filtered through Celite, and concentrated. Column chromatography (5% MeOH/CH_2Cl_2) gave 4 mg (93%) of **33** as a solid: mp 147−149 °C; $[\alpha]^{25}_D$ +99.8 (*c* = 1.9, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.43 (s, 3H), 2.40−2.50 (m, 2H), 2.70−2.80 (m, 1H), 2.90−3.15 (m, 3H), 3.90−4.00 (m, 1H), 4.25−4.40 (m, 1H), 7.05−7.30 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.0, 26.4, 27.3, 34.1, 48.0, 61.4, 124.7, 127.0, 127.5, 128.7, 134.8, 143.1, 151.1; IR (thin film) 1622, 1198 cm^{-1}. Anal. Calcd for $C_{13}H_{15}NO\cdot{}^1/_8H_2O$: C, 76.72; H, 7.55. Found: C, 76.82; H, 7.56.

***γ*-Lactone, 28.** A flask was charged with nitro alcohol **26** (18 mg, 0.08 mmol), NMO (18 mg, 0.15 mmol), molecular sieves (45 mg, 3 Å, powdered), and CH_2Cl_2 (0.75 mL). To this was added TPAP (4 mg, 0.01 mmol) at 0 °C. The ice bath was removed, and stirring was continued 30 min. The suspension was diluted with ether and filtered through silica gel to give 14 mg (93%) of **28** as a white solid: mp 99.1−101 °C; $[\alpha]^{25}_D$ +164 (*c* = 1.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.50 (s, 3H), 2.00−2.20 (m, 2H), 2.70 (ddd, *J* = 16.5, 5.7, 5.7, 1H), 2.73 (d, *J* = 17.1, 1H), 2.81 (d, *J* = 17.1, 1H), 2.93 (ddd, *J* = 16.5, 9.9, 5.7, 1H), 4.54 (dd, *J* = 6.6, 3.3, 1H), 7.00−7.25 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.4, 24.8, 28.5, 42.5, 45.1, 85.1, 126.7, 127.2, 127.9, 128.9, 135.0, 139.7, 175.7; IR (thin film) 1780 cm^{-1}. Anal. Calcd for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 76.93; H, 6.95.

Keto Aldehyde, 34. To a solution of lactone **28** (50 mg, 0.25 mmol) in THF (3 mL) at 0 °C was added LAH (30 mg, 0.79 mmol). After 15 min, the ice bath was removed, and stirring was continued for 30 min. The suspension was diluted with THF and was quenched by dropwise addition of saturated Na_2SO_4 in 20% KOH, until a filterable white solid formed. The suspension was filtered and concentrated. Column chromatography (50% EtOAc/Hex) gave 46 mg (90%) of the 1,4-diol as a white solid: mp 78.8−79.8 °C; $[\alpha]^{25}_D$ +12.3 (*c* = 1.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.32 (s, 3H), 1.84 (ddd, *J* = 15.0, 5.7, 2.4, 1H), 1.95−2.05 (m, 2H), 2.12 (ddd, *J* = 15.3, 9.0, 3.3, 1H), 2.78 (ddd, *J* = 17.4, 6.6, 6.6, 1H), 3.01 (ddd, *J* = 16.8, 6.9, 6.9, 1H), 3.63 (ddd, *J* = 11.1, 6.0, 3.3, 1H), 3.70−3.85 (m, 2H), 4.00−4.50 (bs, 2H), 7.00−7.25 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.8, 26.9, 27.1, 41.9, 42.0, 58.8, 73.6, 125.7, 126.2, 126.8, 129.0, 135.2, 144.0; IR (thin film) 3297 (br) cm^{-1}.

To a stirred solution of oxalyl chloride (0.38 mL, 0.75 mmol, 2 M in CH_2Cl_2) in CH_2Cl_2 (4.5 mL) at −78 °C was added DMSO (0.1 mL, 1.4 mmol). The resulting solution was stirred for 15 min and treated with the diol described above (40 mg, 0.19 mmol) in CH_2Cl_2 (1 mL). The solution was stirred for 30 min at −78 °C, allowed to warm to −50 °C in the dewar, and recooled to −78 °C. It was treated with triethylamine (0.3 mL, 2.2 mmol) and stirred for 5 min before removing the ice bath and allowing it to reach rt. The solution was poured into saturated $NaHCO_3$, extracted with CH_2Cl_2 (3×), dried over Na_2SO_4, and concentrated to give 40 mg of **34** (100%) as an oil which was used without purification.

***cis*-*N*-Benzhydrylpyrrolidine-Fused Tetralin, 35.** A flask was charged with keto aldehyde **34** (40 mg, 0.19 mmol), benzhydrylamine hydrochloride (44 mg, 0.20 mmol), and MeOH (2 mL). The solution was cooled to −78 °C and treated with $NaCNBH_3$ (20 mg, 0.32 mmol). After 1 h, an additional portion of $NaCNBH_3$ (20 mg, 0.32 mmol) was added, and the solution was allowed to warm slowly to room temperature overnight (Dewar flask). The suspension was treated with solid $NaHCO_3$ and K_2CO_3, stirred 15 min and diluted with ether, filtered through silica, and concentrated. Column chromatography (2% EtOAc/Hex) gave 49 mg (71%, 2 steps) of a 9:1 mixture of *cis*- and *trans*-**35**. Column chromatography (100% toluene) gave complete separation of the two diastereomers. Major (cis): $[\alpha]^{25}_D$ +3.57 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.38 (s, 3H), 1.50−1.75 (m, 2H), 1.85−2.10 (m, 2H), 2.41 (ddd, *J* = 16.2, 9.3, 3.9, 1H), 2.58 (ddd, *J* = 9.3, 6.9, 6.9, 1H), 2.70−2.85 (m, 3H), 4.91 (s, 1H), 6.95−7.50 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.5, 27.9, 31.0, 40.4, 44.9, 48.7, 67.3, 70.8, 125.2, 126.3, 126.9, 126.9, 127.5, 128.1, 128.2, 128.3, 128.7, 136.7, 142.2, 143.9, 145.8.

Minor (trans): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.29 (s, 3H), 1.45−1.65 (m, 2H), 1.76 (ddd, *J* = 11.4, 11.4, 7.8, 1H), 1.96 (ddd, *J* = 11.7, 8.4, 3.0, 1H), 2.46 (ddd, *J* = 11.1, 11.1, 3.3, 1H), 2.57 (dd, *J* = 12.3, 3.6, 1H), 2.71 (ddd, *J* = 18.0, 9.0, 9.0, 1H), 2.87 (dd, *J* = 18.0, 8.1, 1H), 3.19 (ddd, *J* = 9.9, 8.1, 8.1, 1H), 4.76 (s, 1H), 6.95−7.50 (m, 14H); HRMS (FAB$^+$) for $C_{26}H_{27}N$ $(M)^+$ calcd 353.2144, found 353.2138.

***cis*-Pyrrolidine-Fused Tetralin, 20.** A flask was charged with benzhydryl-protected aminotetralin **35** (15 mg, 0.05 mmol), $Pd(OH)_2$ (5 mg, 20% on carbon), TFA (0.2 mL, 2.6 mmol), and EtOH (5 mL). The atmosphere was flushed with hydrogen, and a balloon was attached. After 4 h, the suspension was concentrated, made basic with a mixture of 10% NaOH and EtOH, filtered, and concentrated. The residue was partitioned between water and ether. The aqueous was further washed twice with ether, dried over Na_2SO_4, and concentrated. Column chromatography (neutral alumina, 1, 5% MeOH/CH_2Cl_2) gave 7.7 mg (97%) of **20** as an oil. $[\alpha]^{25}_D$ +86 (0.4, $CHCl_3$); ^{1}H NMR (300 MHz, C_6D_6) δ 1.16 (s, 3H), 1.60−1.90 (m, 4H), 2.40 (ddd, *J* = 16.2, 6.9, 4.8, 1H), 2.70−3.20 (m, 4H), 4.59 (bs, 1H), 6.80−7.10 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.2, 26.5, 29.3, 41.2, 44.2, 45.2, 64.4, 126.2, 126.9, 127.5, 128.8, 135.4, 142.0; IR (thin film) 3322(br) cm^{-1}; HRMS (FAB$^+$) for $C_{13}H_{18}N$ $(M + H)^+$ calcd 188.1439, found 188.1437.

Saturated Ester, 36. To a solution of aldehyde **14** (500 mg, 1.62 mmol), LiCl (400 mg, 9.4 mmol), and triethylphosphonoacetate (0.56 mL, 2.8 mmol) in ether (4 mL) and acetonitrile (4 mL) was added DBU (0.42 mL, 2.8 mmol) and the reaction allowed to stir 24 h at room temperature. After dilution with ether, the solution was filtered through Celite and concentrated. Column chromatography (5−10% EtOAc/Hexanes) gave 596 mg (97%) of the (*E*)-α,*β*-unsaturated ester as an oil: $[\alpha]^{25}_D$ −137 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.34 (s, 3H), 0.37 (s, 3H), 1.28 (t, *J* = 6.9, 3H), 1.32 (dd, *J* = 12.3, 1.8, 1H), 1.39 (s, 3H), 1.63 (dddd, *J* = 23.7, 11.1, 4.5, 2.1, 1H), 1.86 (dddd, *J* = 13.5, 5.1, 3.0, 3.0, 1H), 2.60−2.85 (m, 2H), 4.17 (q, *J* = 6.9, 2H), 5.52 (d, *J* = 15.6, 1H), 7.07 (m, 4H), 7.13 (d, *J* = 15.6, 1H), 7.33 (m, 3H), 7.52 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −2.70, −1.16, 14.5, 22.1, 29.3, 31.9, 36.1, 43.7, 60.5, 119.0, 126.1, 126.2, 128.0, 128.9, 129.1, 129.4, 134.2, 137.3, 139.4, 141.8, 156.1, 167.0; IR (thin film) 1716 cm^{-1}; HRMS (FAB$^+$) for $C_{24}H_{31}O_2Si$ $(M + 1)^+$ calcd 379.2093, found 379.2091.

A pressure tube was charged with the unsaturated ester from above (0.60 g, 1.6 mmol), Pd/C (90 mg, 0.09 mmol, 10%), and EtOH (20 mL). The tube was purged with H_2 and pressurized to 80 psi for 22 h. The reaction was filtered through a pad of silica gel, eluting with EtOAc. Concentration gave 0.60 g (100%) **36** as an oil: $[\alpha]^{25}_D$ −77.2 (*c* = 1.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.42 (s, 3H), 0.44 (s, 3H), 1.16 (t, *J* = 6.9, 3H), 1.30 (s, 3H), 1.31 (dd, *J* = 12.3, 3.0, 1H), 1.75 (dddd, *J* = 12.9, 12.9, 10.5, 5.4, 1H), 1.85−2.10 (m, 5H), 2.60−2.90 (m, 2H), 3.97 (q, 2H), 6.95−7.60 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −1.72, −0.48, 14.3, 22.6, 31.4, 31.6, 31.6, 36.8, 37.1, 39.7, 60.3, 125.6, 125.8, 126.5, 127.9, 128.9, 129.4, 134.1, 137.1, 139.8, 144.1, 173.9; IR (thin film) 1732 cm^{-1}.

***δ*-Lactone, 37.** To a solution of alkylsilane **36** (1.0 g, 2.63 mmol) in CH_2Cl_2 (27 mL, 0 °C) was added HBF_4 (3 mL, 54% in ether). The solution was stirred 15 min at 0 °C, the ice bath was removed, and stirring was continued overnight. The solution was poured over solid $NaHCO_3$ and filtered, and the cake was washed with CH_2Cl_2 and concentrated. The crude silyl fluoride was treated with K_2CO_3 (6.0 g, 43 mmol), cooled to 0 °C, and treated with CH_3CO_3H (21 mL, 32% in CH_3CO_2H). Effervescence was immediate. After 15 min, the ice bath was removed and stirring continued at room temperature for 9 h. The mixture was poured into water and extracted into ether (3×). The ether layers were combined, back-extracted with 20% K_2CO_3 (2×) and brine, dried over Na_2SO_4, and concentrated. The crude mixture was redissolved in THF (12 mL), treated with six Pasteur pipet drops of concentrated HCl, stored in the freezer overnight, and concentrated. Column chromatography neutral alumina 35, 50% EtOAc/Hex) gave 0.53 g (93%)

as a white solid: mp 116−118 °C; $[\alpha]^{25}_D$ +164 (c = 1.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.33 (s, 3H), 1.95−2.25 (m, 4H), 2.33 (ddd, J = 13.2, 5.7, 4.2, 1H), 2.46 (ddd, J = 17.1, 4.8, 3.3, 1H), 2.69 (ddd, J = 16.8, 6.0, 2.4, 1H), 3.04 (ddd, J = 17.7, 12.3, 6.0, 1H), 4.54 (dd, J = 4.5, 1.8, 1H), 7.00−7.30 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.1, 24.4, 27.9, 30.5, 33.2, 35.8, 84.0, 126.0, 126.7, 127.1, 129.6, 136.0, 138.6, 171.7; IR (thin film) 1714 cm^{-1}. Anal. Calcd for $C_{14}H_{20}O_2 \cdot {}^1/_3H_2O$: C, 75.67; H, 7.56. Found: C, 75.36; H, 7.39.

Keto Aldehyde, 38. To a solution of lactone **37** (50 mg, 0.23 mmol) in THF (3 mL) at 0 °C was added LAH (30 mg, 0.79 mmol). After 15 min, the ice bath was removed, and stirring was continued for 30 min. The suspension was diluted with THF and was quenched by dropwise addition of saturated Na_2SO_4 in 20% KOH, until a filterable white solid formed. The suspension was filtered and concentrated. Column chromatography (50% EtOAc/Hex) gave 49 mg (96%) of the 1,5-diol as a white solid: mp 142−145 °C; $[\alpha]^{25}_D$ +17.0 (c = 1.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24 (s, 3H), 1.50−1.70 (m, 2H), 1.70−1.85 (m, 2H), 1.90−2.05 (m, 2H), 2.56 (bs, 2H), 2.75 (ddd, J = 17.1, 6.3, 6.3, 1H), 3.00 (ddd, J = 17.4, 7.2, 7.2, 1H), 3.56 (m, 2H), 3.85 (dd, J = 5.1, 5.1, 1H), 6.95−7.30 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.0, 26.4, 27.2, 27.5, 33.4, 41.2, 63.7, 73.3, 125.8, 126.0, 127.2, 129.1, 135.1, 143.2; IR (thin film) 3307 (br) cm^{-1}.

To a stirred solution of oxalyl chloride (0.43 mL, 0.85 mmol, 2 M in CH_2Cl_2) in CH_2Cl_2 (5 mL) at −78 °C was added DMSO (0.1 mL, 1.4 mmol). The resulting solution was stirred for 15 min and treated with the 1,5-diol from above (60 mg, 0.27 mmol) in CH_2Cl_2 (1 mL). The solution was stirred for 30 min at −78 °C, allowed to warm to −50 °C in a Dewar flask, and recooled to −78 °C. It was treated with triethylamine (0.4 mL, 2.9 mmol) and stirred for 5 min before removing the ice bath and allowing it to reach rt. The solution was poured into saturated $NaHCO_3$, extracted with CH_2Cl_2 (3×), dried over Na_2SO_4, and concentrated. Column chromatography (neutral alumina 20, 40% EtOAc/Hex) gave 55 mg (93%) of **38** as an oil: $[\alpha]^{25}_D$ +51.3 (1.6, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.43 (s, 3H), 1.95−2.10 (m, 2H), 2.16 (m, 1H), 2.41 (m, 1H), 2.57 (ddd, J = 15.0, 5.7, 5.7, 1H), 2.74 (ddd, J = 15.0, 8.4, 8.4, 1H), 3.04 (d, J = 5.4, 1H), 3.06 (d, J = 5.4, 1H), 7.10−7.30 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.8, 28.7, 31.6, 38.1, 40.2, 51.1, 126.5, 126.8, 127.4, 128.4, 136.0, 141.0, 201.3, 213.9; IR (thin film) 1716 cm^{-1}; HRMS (FAB$^+$) for $C_{13}H_{17}O_2$ (M + H)$^+$ calcd 217.1229, found 217.1222.

***cis*-*N*-α-Methylbenzylpiperidine-Fused Tetralin, 40.** A flask was charged with keto aldehyde **38** (25 mg, 0.12 mmol), (*S*)-α-methylbenzylamine hydrochloride (25 mg, 0.15 mmol), and MeOH (1 mL). The solution was cooled to −78 °C and treated with $NaCNBH_3$ (10 mg, 0.16 mmol). After 1 h, an additional portion of $NaCNBH_3$ (10 mg, 0.16 mmol) was added, and the solution was allowed to warm to room temperature. The reaction was treated with molecular sieves (50 mg, 3 Å, powdered) and acetic acid (7 mL, 0.12 mmol) and allowed to stir 3 h. The suspension was treated with solid $NaHCO_3$ and K_2CO_3, stirred 15 min, and then diluted with ether, filtered through silica, and concentrated. Column chromatography (2% EtOAc/Hex) gave 25 mg (71%) of **40** as a white solid: mp 97.7−99.5 °C; $[\alpha]^{25}_D$ −24.5 (c = 1.4, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.31 (d, J = 6.6, 3H), 1.30−1.40 (m, 1H), 1.55−1.75 (m, 2H), 1.67 (s, 3H), 1.80−2.15 (m, 3H), 2.20−2.45 (m, 2H), 2.85 (ddd, J = 16.5, 10.8, 5.4, 1H), 2.97 (ddd, J = 16.5, 4.8, 4.8, 1H), 3.14 (dd, J = 10.8, 2.1, 1H), 3.79 (q, J = 6.6, 1H), 7.05−7.50 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.1, 23.0, 27.0, 29.7, 30.5, 36.4, 38.2, 45.0, 60.0, 60.3, 125.4, 126.1, 126.6, 127.0, 127.2, 128.4, 128.9, 135.3, 147.4, 148.0; HRMS (FAB$^+$) for $C_{22}H_{27}N$ (M)$^+$ calcd 305.2144, found 305.2135.

***cis*-Piperidine-Fused Tetralin, 41.** A flask was charged with *N*-alkylaminotetralin **40** (15 mg, 0.05 mmol), $Pd(OH)_2$ (5 mg, 20% on carbon), TFA (0.2 mL, 2.6 mmol), and EtOH (5 mL). The atmosphere was flushed with hydrogen, and a balloon was attached. After 4 h, the suspension was concentrated, made basic with a mixture of 10% NaOH and EtOH, filtered, and concentrated. The residue was partitioned between water and ether, and the aqueous phase was washed twice more with ether, dried over Na_2SO_4, and concentrated to give 9.9 mg (100%) of **41** as an oil: $[\alpha]^{25}_D$ +67 (c = 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, C_6D_6) δ 0.68 (bs, 1H), 1.06 (s, 3H), 1.15−1.35 (m, 3H), 1.47 (dddd, J = 13.5, 6.9, 4.5, 2.1, 1H), 1.94 (dddd, J = 13.5, 12.0, 6.6, 2.4, 1H), 2.15−2.30 (m, 1H), 2.45−2.60 (m, 3H), 2.70−2.80 (m, 1H), 3.00 (ddd, J = 16.8, 12.0, 6.9, 1H), 7.00−7.30 (m, 4H); ^{13}C NMR (75 MHz, C_6D_6) δ 23.9, 25.2, 26.3, 30.8, 32.3, 37.5, 37.8, 46.7, 60.4, 125.9, 126.4, 126.7, 130.0, 136.4, 143.4; IR (thin film) 3283(br) cm^{-1}; HRMS (FAB$^+$) for $C_{14}H_{20}N$ (M + H)$^+$ calcd 202.1596, found 202.1596.

***trans*-*N*-α-Methylbenzylpiperidine-Fused Tetralin, 42.** A flask was charged with keto aldehyde **38** (25 mg, 0.12 mmol), (*R*)-α-methylbenzylamine hydrochloride (25 mg, 0.15 mmol), and MeOH (1 mL). The solution was cooled to −78 °C and treated with $NaCNBH_3$ (10 mg, 0.16 mmol). After 1 h, an additional portion of $NaCNBH_3$ (10 mg, 0.16 mmol) was added, and the solution was allowed to warm to room temperature. The reaction was treated with molecular sieves (50 mg, 3 Å, powdered) and acetic acid (7 mL, 0.12 mmol) and allowed to stir 4 h, and then treated with solid $NaHCO_3$ and K_2CO_3 and stirred 15 min. The suspension was diluted with ether, filtered through silica, and concentrated. Column chromatography (2% EtOAc/Hex) gave 27 mg (76%) of **42** as an oil: $[\alpha]^{25}_D$ +39.1 (c = 1.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.32 (d, J = 6.9, 3H), 1.40 (s, 3H), 1.40−1.55 (m, 2H), 1.65−1.90 (m, 2H), 2.14 (ddd, J = 12.3, 12.3, 3.0, 1H), 2.20−2.40 (m, 2H), 2.50−2.60 (m, 1H), 2.63 (dd, J = 12.3, 3.3, 1H), 3.02 (d, J = 4.8, 1H), 3.05 (d, J = 4.8, 1H), 4.45 (q, J = 6.9, 1H), 7.10−7.60 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.1, 21.7, 22.7, 23.7, 29.2, 37.9, 38.7, 46.5, 53.7, 64.1, 125.3, 125.6, 125.9, 126.2, 127.8, 128.0, 134.4, 145.6, 147.0; HRMS (FAB$^+$) for $C_{22}H_{28}N$ (M + H)$^+$ calcd 306.2222, found 306.2225.

***trans*-Piperidine-Fused Tetralin, 43.** A flask was charged with *N*-alkylaminotetralin **42** (15 mg, 0.05 mmol), $Pd(OH)_2$ (5 mg, 20% on carbon), TFA (0.2 mL, 2.6 mmol), and EtOH (5 mL). The atmosphere was flushed with hydrogen, and a balloon was attached. After 4 h, the suspension was concentrated, made basic with a mixture of 10% NaOH and EtOH, filtered, and concentrated. The residue was partitioned between water and ether, and the aqueous phase was washed twice more with ether, dried over Na_2SO_4, and concentrated to give 9.9 mg (100%) of **43** as an oil: $[\alpha]^{25}_D$ +116 (1.0, $CHCl_3$); ^{1}H NMR (300 MHz, C_6D_6) δ 0.83 (bs, 1H), 1.22 (s, 3H), 1.20−1.50 (m, 3H), 1.65−1.90 (m, 2H), 2.05−2.15 (m, 1H), 2.35−2.50 (m, 2H), 2.60−2.85 (m, 2H), 2.89 (dd, J = 11.7, 5.1, 1H), 6.90−7.30 (m, 4H); ^{13}C NMR (75 MHz, C_6D_6) δ 22.6, 23.9, 26.6, 29.7, 30.7, 37.7, 48.4, 62.0, 125.4, 126.2, 126.5, 129.8, 135.2, 147.4; IR (thin film) 3278(br) cm^{-1}; HRMS (FAB$^+$) for $C_{14}H_{20}N$ (M + H)$^+$ calcd 202.1596, found 202.1590.

***trans*-*N*-α-Methylbenzylpyrrolidine-Fused Tetralin, 47.** A flask was charged with keto aldehyde **34** (39 mg, 0.19 mmol), (*R*)-α-methylbenzylamine hydrochloride (40 mg, 0.20 mmol), and MeOH (2 mL). The solution was cooled to −78 °C and treated with $NaCNBH_3$ (10 mg, 0.16 mmol). After 1 h, an additional portion of $NaCNBH_3$ (10 mg, 0.16 mmol) was added, and the solution was allowed to warm to room temperature and stirred overnight when the resulting suspension was treated with solid $NaHCO_3$ and K_2CO_3 and stirred 15 min. The suspension was diluted with ether, filtered through silica, and concentrated. ^{1}H NMR revealed a 1:1 mixture of epimers. Column chromatography (5% EtOAc/Hex) gave 23 mg (41%) of the cis isomer **20** as an oil and then 22 mg (39%) of the trans isomer **48** as an oil. Trans: $[\alpha]^{25}_D$ +66.6 (c = 1.7, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20 (s, 3H), 1.34 (d, J = 6.6, 3H), 1.85 (dddd, J = 11.4, 7.8, 7.8, 7.8, 1H), 1.99 (ddd, J = 11.7, 8.4, 3.0, 1H), 2.55−3.10 (m, 5H), 3.88 (q, J = 6.6, 1H), 7.00−7.50 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.0, 22.3, 25.2, 27.8, 34.6, 44.6, 46.4, 58.2, 66.7, 125.1, 125.6, 125.8, 126.6, 127.5, 128.2, 128.7, 135.5, 146.4, 147.2; HRMS (FAB$^+$) for $C_{21}H_{26}N$ (M + H)$^+$ calcd 292.2065, found 292.2052.

Cis: $[\alpha]^{25}_D$ +78.9 (c = 1.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24 (s, 3H), 1.45 (d, J = 6.6, 3H), 1.69 (dddd, J = 13.2, 9.0, 9.0, 3.9, 1H), 1.80−2.05 (m, 3H), 2.56 (ddd, J = 15.6, 9.6, 3.9, 1H), 2.60−2.70 (m, 2H), 2.75−2.90 (m, 2H), 3.89 (q, J = 6.6, 1H), 7.00−7.40 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ

22.8, 26.9, 27.8, 30.9, 40.0, 44.9, 47.9, 60.9, 66.9, 125.2, 126.4, 126.9, 127.6, 128.0, 128.1, 128.1, 128.2, 128.2, 136.9, 143.8, 146.1; HRMS (FAB$^+$) for $C_{21}H_{26}N$ $(M + H)^+$ calcd 292.2065, found 292.2055.

***trans*-Pyrrolidine-Fused Tetralin, 48.** A flask was charged with *N*-alkylaminotetralin **47** (15 mg, 0.05 mmol), $Pd(OH)_2$ (5 mg, 20% on carbon), TFA (0.2 mL, 2.6 mmol), and EtOH (5 mL). The atmosphere was flushed with hydrogen, and a balloon was attached. After 4 h, the suspension was concentrated, made basic with a mixture of 10% NaOH and EtOH, filtered, and concentrated. The residue was partitioned between water and ether, and the aqueous was washed twice more with ether, dried over Na_2SO_4, and concentrated to give 9.6 mg (100%) of **48** as an oil: $[\alpha]^{25}_D$ +67 (c = 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, C_6D_6) δ 0.93 (s, 3H), 0.97 (bs, 1H), 1.55−1.85 (m, 4H), 2.60−3.05 (m, 4H), 6.95−7.15 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.4, 22.6, 28.1, 30.5, 36.8, 44.5, 63.7, 125.8, 125.8, 126.1, 129.0, 135.5, 146.2; IR (thin film) 3266(br) cm^{-1}; HRMS (FAB$^+$) for $C_{13}H_{18}N$ $(M + H)^+$ calcd 188.1439, found 188.1437.

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Supporting Information Available: Spectral data (^{1}H and ^{13}C) of all key intermediates and final products. This material is available free of charge via the Internet at http://pubs.acs.org.

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