Asymmetric Tandem Addition to Chiral 1- and 2-Substituted Naphthalenes. Application to the Synthesis of (+)-Phyltetralin

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Abstract: A series of chiral naphthyloxazolines (**1–4**) have been subjected to addition reactions with a variety of organolithium and organostannane reagents. The intermediate azaenolates **5** were trapped with various electrophiles, including proton, affording the dihydronaphthalenes **6** and **15**. These were transformed into the trisubstituted dihydronaphthalenes **7**, **9**, **10**, and **13** in 80–100% ee's. For proton-quenched azaenolates, the 1,1-disubstituted dihydronaphthalenes **17** were obtained with pure trans stereochemistry. The stereochemistry of the tandem addition adducts was verified by single-crystal X-ray analyses. This method of naphthalene addition was applied to the asymmetric total synthesis of the lignan (+)-phyltetralin (**22**). Studies on the mechanism of this process and the effect of different chiral auxiliaries were also performed, and it was found that the absolute stereochemistry observed is a function of the C-4 stereocenter in the oxazoline, whereas the C-5 stereocenter has little effect.

We have recently described[1] the use of 1- and 2-naphthyloxazolines as precursors to substituted dihydronaphthalenes. Thus, addition of alkyl-, aryl-, or alkenyllithium reagents to the naphthalene systems followed by electrophilic (E^+) trapping gives rise to stereospecifically substituted dihydronaphthalenes. Proton or methyl iodide quenching leads exclusively to the trans 1,2-disubstituted or the 1,1,2-trisubstituted derivatives, respectively (Scheme I).

In view of the dearth of methods[2-5] to introduce substituents directly into the naphthalene nucleus, this simple procedure becomes one of considerable importance. Furthermore, prior to the initial report on this work,[6] *there were no routes to introduce substituents into naphthalenes with any level of enantioselectivity.* In 1982, we reported, along with Cram,[7] the enantioselective addition to a naphthyloxazoline, producing binaphthyls, a process that provides chiral aromatic products by an addition–elimination sequence and therefore passes through a transient dihydronaphthalene.

It became obvious during the course of these studies that the process described in Scheme I might achieve even greater importance if a chiral nonracemic oxazoline was used to mediate naphthalene additions. If this were successfully implemented, a route to highly substituted dihydronaphthalenes in high enantiomeric excess and predictable absolute configuration would be available.

This paper describes our studies which have allowed this asymmetric addition to naphthalenes to reach fruition. Using a series of naphthalenes substituted with a chiral oxazoline **1–4**, we have introduced a variety of organolithium reagents furnishing, initially, the azaenolate **5** (Scheme II). The latter was then quenched with various electrophiles to give the tandem addition products **6a–s**. The latter are formed in generally good chemical yields with diastereofacial selectivity in the satisfactory category. Table I summarizes the examples evaluated with the four different naphthalenes (**1–4**) and a number of different organolithium reagents. In every case, quenching of the azaenolate **5** occurred with an electrophile, E. Proton quenches were also performed, but these will be discussed later.

The absolute stereochemistry of the major products **6** were determined by performing a single-crystal X-ray analyses on the crystalline adduct **6d** (Figure 1A). This, therefore, also establishes the absolute stereochemistry of the aldehyde **7d**, and on the basis of this, we have assigned all the adducts **6** and aldehydes **7** and **10** as well as lactone **9** as having the same absolute configurations. Several other adducts whose X-ray structure has been determined are consistent with these assignments (vide infra).

From Table I, the addition of *n*-butyllithium to **1** followed by trapping with the electrophile shown gives the adducts **6a–c** in 16–30:1 diastereoselectivity. The use of methyllithium, however, proceeds very sluggishly to **5** and after trapping with diphenyl disulfide gave only a 56% yield of **6d** as an 86:14 mixture of diastereomers. In no instance was a cis addition product observed. This was confirmed in several cases (**6j** and **6q**) where poor selectivity allowed meaningful quantities of diasteromeric products to be separated and carried on to enantiomeric aldehydes **7** (see Table II). Had the mixtures in **6** been those derived from cis and trans additions of the organolithium and the electrophile, the aldehydes **7**, ultimately formed, would *not* have been enantiomers. The fact that methyllithium addition to **1** proceeded slowly turned out to be rather advantageous. It was observed during the early stages of this work that vinyl-, isopropenyl-, and cyclopentenyllithium reagents added very slowly or not at all. Furthermore, we observed that as these organolithium reagents aged they lost their ability to add to **1** even under prolonged contact, yet simple addition to benzaldehyde produced high yields of the carbinols. In order to prepare organolithium of this type (vinyl, isopropenyl, 1-cyclopentenyl) as fresh as possible, we first prepared the tetrasubstituted stannanes, added them to **1**, and treated the mixture with methyllithium. In contrast to the traditional organolithium behavior, those produced by transmetalation proceeded smoothly to give the adducts **6** in good yield (**6g**, **6h**, **6i**; 73–79%) and diastereoselectivities in the 9:1 ratio range. This behavior of organolithium reagents, generated in situ via their stannane analogues has recently been noted in this laboratory.[1] The addition of cyclopentenyllithium to oxazoline **3** was also carried out via transmetalation of the stannane and gave **6o** as an 85:15 mixture of diastereomers. Our current assessment of this reactivity enhancement by organolithium reagents generated in situ by the transmetalation procedure is that the extent of aggregation is playing a significant role. Thus, organolithium reagents generated in the presence of the naphthalene reacts as a different species since it does not appear to have the opportunity to form normal aggregates under these conditions.

A number of adducts **6** were transformed into the corresponding aldehydes **7** by using a mild efficient procedure. The addition

(1) Meyers, A. I.; Lutomski, K. A.; Laucher, D. *Tetrahedron*, in press. For earlier studies, see Lutomski, K. A. Ph.D. Dissertation, Colorado State University, 1982.

(2) Fuson, R. C.; McKusick, B. C.; Spangler, F. W. *J. Am. Chem. Soc.* **1945**, *67*, 597. Fuson, R. C.; Gaertner, R.; Sheeley, Y. F. *J. Org. Chem.* **1952**, *17*, 881.

(3) Dixon, J. A.; Fishman, D. H. *J. Am. Chem. Soc.* **1963**, *85*, 1356. Dixon, J. A.; Eppley, R. L. *J. Am. Chem. Soc.* **1968**, *90*, 1606.

(4) Kuendig, E. P. *Pure Appl. Chem.* **1985**, *57*, 1855.

(5) Negishi, E.-I.; Merrill, R. E. *Chem. Commun.* **1974**, 860.

(6) For preliminary disclosure of this methodology, see: (a) Meyers, A. I.; Barner, B. A. *J. Am. Chem. Soc.* **1984**, *106*, 1865. (b) Meyers, A. I.; Hoyer, D. *Tetrahedron* Lett. **1984**, *25*, 3667. (c) Meyers, A. I.; Barner, B. A. *J. Org. Chem.* **1986**, *51*, 120.

(7) (a) Meyers, A. I.; Lutomski, K. A. *J. Am. Chem. Soc.* **1982**, *104*, 879.. (b) Wilson, J. M.; Cram, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 881.

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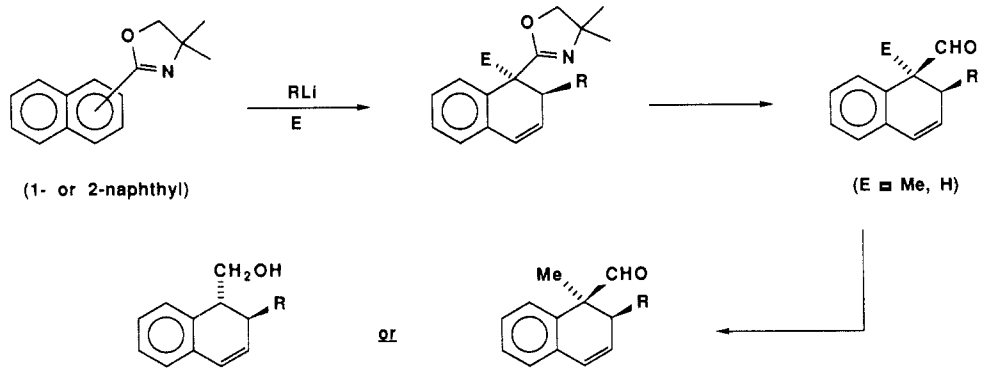
Scheme I



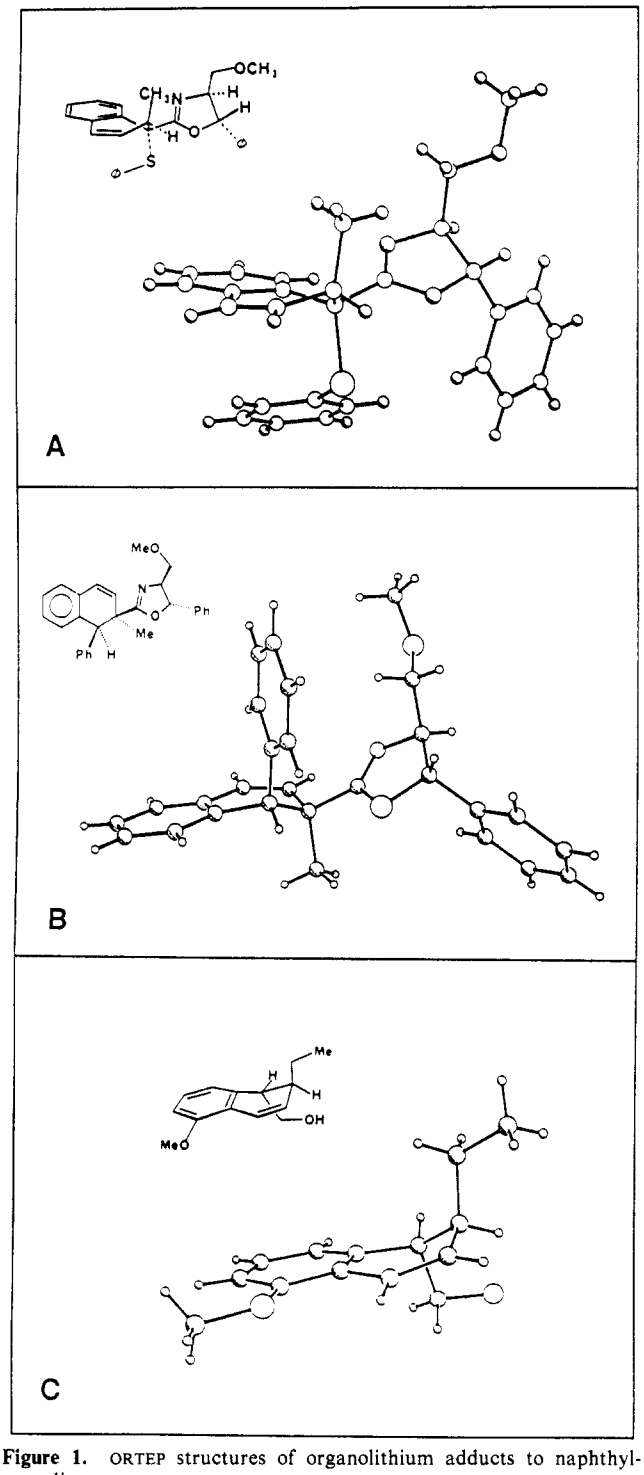
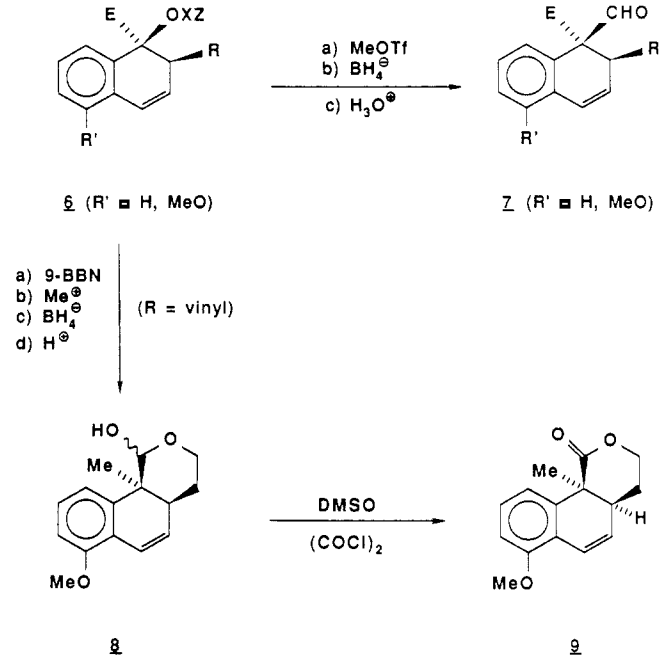


Figure 1. ORTEP structures of organolithium adducts to naphthyloxazolines.

of methyl triflate to the adducts **6**, followed by reduction of the iminium salt and hydrolysis with oxalic acid, gave the aldehydes **7** in generally good overall yields as seen in Table II. In some



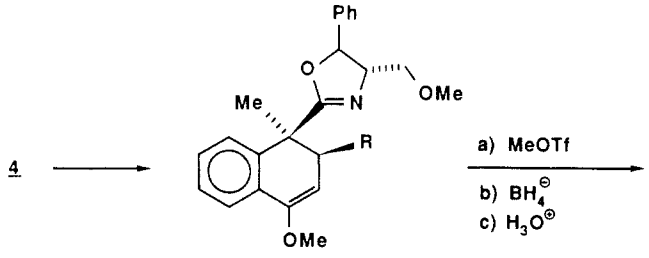
6 (R' ◻ H, MeO) 7 (R' ◻ H, MeO)

8 9

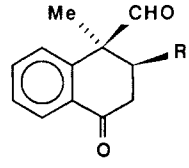
instances, the diastereomers in **6** were readily separated by chromatographic means, and thus cleavage to the aldehydes resulted in pure enantiomers (**7d**, **7f**, **7j**). In the case of the 2-vinyl adduct **6l**, the double bond was hydroborated prior to cleavage and on hydrolysis gave the lactol **8**, which was readily oxidized with DMSO/oxalyl chloride to the lactone **9** in 70% yield. The latter was obtained in 60% ee since no separation of the initial diastereomeric mixture (80:20) in **6l** was performed.

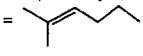
Another series of adducts, **6p–s** (Table I) were also converted to the aldehydes **10** by use of the procedure described above. In this series, since the tandem addition products **6** were enol ethers, the oxazoline removal provided the chiral tetralones. The chemical and enantiomeric yields in this series were generally excellent as seen from three examples, **10a**, **10c**, and **10d**, which were all formed in 94% ee. The *tert*-butyl adduct **6q** was poorly selective and gave a 65:35 ratio of diastereomers. However, these were cleanly separated via radial chromatography and each separately cleaved to the enantiomerically pure aldehydes **10b** with equal and opposite signs of rotation ($[\alpha]_D$ +- or −145.5°).

In a similar fashion, 2-oxazolinylnaphthalene **11** was investigated to provide a route to the chiral dihydronaphthalenes **12** and **13**. The introduction of various organolithium reagents to **11**, usually at low temperatures, led, after methyl iodide trapping of the intermediate azaenolate, to the dihydronaphthalene **12** in generally good yields and high diastereomeric ratios (Table III). The diastereomeric products obtained were all due to trans tandem alkylation, thus reflecting only facial selectivity of the organo-

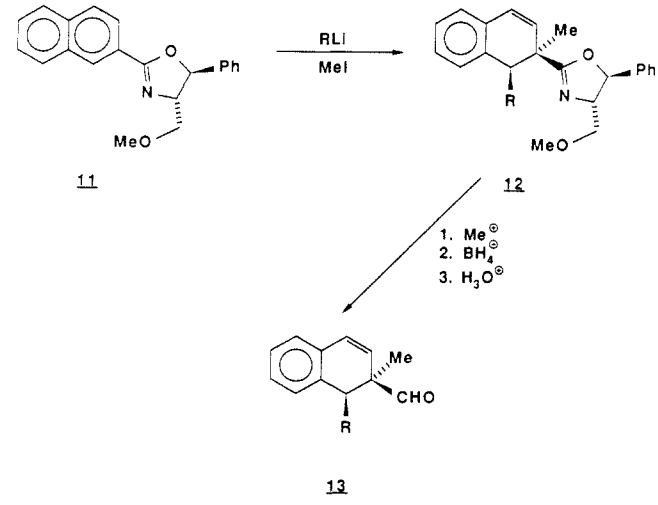


6p-6s



(-) **10a**, R = n-Bu (94% ee)
(-) **10b**, R = t-Bu (100% ee)
(+) **10b**, R = t-Bu (100% ee)
(-) **10c**, R = 1-pentenyl (94% ee)
10d, R =  (94% ee)

lithium step. No cis addition products were observed, and this was again confirmed when the aldehydes **13** were collected showing only enantiomeric impurities. It was quite easy to purify the diastereomers **12** via radial chromatography and then proceed to remove the oxazoline moiety. In this way, enantiomerically pure aldehydes **13** were obtained (Table IV).



13

From Table III, it can be seen that the temperature of addition has a minimal effect upon the degree of diastereoselectivity. Thus, *n*-butyllithium added at −78 or 25 °C, a difference of 103 °C, resulted in a loss of diastereoselectivity of only 10–12%. Furthermore, addition of HMPA at −78 °C (third entry in Table III) was virtually without effect. The oxazoline is apparently a much better ligand for *n*-butyllithium than HMPA. This result also suggests that the organolithium is reacting as a monomer since it is unlikely it could aggregate in the presence of HMPA. The inability of higher temperature to lower the diastereoselection indicates the difference in ΔS for the diastereomeric transition states is relatively small compared to their difference in ΔH, at least within the temperature range indicated for *n*-butyllithium.

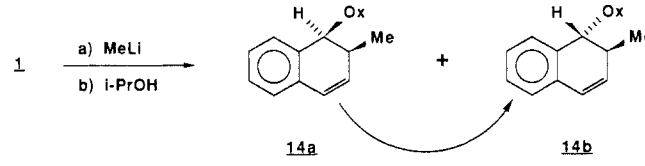
Methyllithium added rather slowly, and much higher temperatures were required for longer periods of time to effect addition (Table III). It is likely that the tetrameric nature of methyllithium[8] in THF was slowing the addition. Performing the addition in the presence of 1 equiv of TMEDA accelerated the addition but did not change the diastereoselection observed.

(8) West, P.; Waack, R. *J. Am. Chem. Soc.* **1967**, *89*, 4395.

Phenyllithium showed a diastereoselectivity comparable to methyllithium but added over a shorter time. The lower degree of aggregation (dimeric in THF[9a]) may facilitate the addition. The diastereomeric mixture was chromatographed to obtain pure material. The major diastereomer **12** (R = Ph) was crystallized from hexane and subjected to single-crystal X-ray analysis. The ORTEP structure (Figure 1B) indicated a trans 1*S*,2*S* configuration for the phenyl and methyl, respectively, relative to the known 4*S*,5*S* stereochemistry of the oxazoline ring. The absolute sense of addition is therefore the same as seen for the products derived by additions to the 1-naphthyloxazolines **1**–**4**. This again implies that the mechanism of addition is probably related (vide infra).

Tandem Additions Involving Proton Quench. Having established the utility of the tandem-addition process to reach trisubstituted 1,2-dihydronaphthalene systems **7** with good to excellent enantiomeric purity, three questions were addressed: (a) Could the azaenolate **5** formed from the nucleophilic-addition step be quenched with a proton source, thus giving access to the fragile 1,2-disubstituted 1,2-dihydronaphthalenes? (b) Would these addition products be stable to aromatization? (c) Could the chiral auxiliary be removed to provide the enantiomerically enriched substrates without aromatization? The feasibility of this process appeared to be quite good, and thus, studies were initiated to answer these questions. If successful, the results would be of considerable significance since the new studies would provide chiral substrates potentially useful for reaching a variety of natural-product systems.

The initial experiments attempted involved addition of methyllithium to naphthalene **1** at −45 °C in THF, followed by quenching with 3 equiv of 2-propanol. Two products were formed in a total of 56% yield after flash chromatography. On attempting

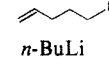
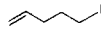
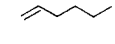
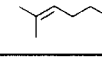


purification of these products, with column or radial chromatography, extensive decomposition occurred along with aromatization to the naphthalene derivatives. This behavior was observed earlier[1] in these laboratories in the achiral oxazoline series. However, ^{1}H NMR data (360 MHz) was obtained on the separated adducts, and interestingly, the pure diastereomers exhibited a C-1(H)/C-2(H) coupling constant of 7 and 9 Hz. Since it was known that methyllithium gives facial selectivity on **1** of approximately 86:14 (Table I) and the minor isomer **14b** amounted to at least 33% of the product mixture, it was therefore speculated that the two adducts observed (**14a** and **14b**) were C-1 epimers resulting from a nonselective quench *or* from epimerization under the reaction conditions.

In an attempt to suppress the formation of the minor epimer, a stronger protic acid, trifluoroacetic acid, was used in the quenching step, the rationale being that the weak conjugate acid, trifluoroacetate, would not cause epimerization. Addition of organolithium reagents to **1**, followed by trifluoroacetic acid led, not to the expected dihydronaphthyl salt **16**, but to the ester ammonium salt **15** (Scheme III). Thus, the workup conditions (NH_4Cl–H_2O; ether extraction; Na_2SO_4 drying) produced the opened oxazoline in the form of the amino ester salt. It was soon discovered that the use of finely powdered Na_2SO_4, with a few drops of water added, substantially enhanced the rate of formation of **15** during the drying procedure. It is believed that this process is surface catalyzed by the sodium sulfate since neither magnesium sulfate nor molecular sieves (4A) were able to cause amino ester formation. Thus, initially **1** is formed as its TFA salt **16**, which under the controlled delivery of water from the sodium sulfate is efficiently transformed into the amino ester salt **15**. The latter was directly reduced with lithium aluminum hydride to the pure

(9) (a) Jackman, L. M.; Scarmoutzos, L. M. *J. Am. Chem. Soc.* **1984**, *106*, 4627. (b) Hay, D. R.; Song, Z.; Smith, S. G.; Beak, P. *J. Am. Chem. Soc.*, in press.

Table I. Addition of Organolithiums to Naphthyloxazolines **1–4**

				dihydronaphthyloxazolines **6**			
oxazoline	RLi	*t*, °C	E[d]	**6** (% yield)	R	E	diastereomeric ratio[c]
1	*n*-BuLi	−45	MeI	**6a** (97)	*n*-Bu	Me	94:6
1	*n*-BuLi	−45	$(PhS)_2$	**6b** (91)	*n*-Bu	SPh	94:6
1	*n*-BuLi	−45	$ClCO_2Me$	**6c** (99)	*n*-Bu	CO_2Me	97:3
1	MeLi	−20	$(PhS)_2$	**6d** (56)	Me	SPh	86:14
1	*t*-BuLi	−78	MeI	**6e** (98)	*t*-Bu	Me	74:26
1	PhLi	−45	MeI	**6f** (99)	Ph	Me	83:17
1		−80	MeI	**6g** (75)		Me	88:12
1		−80	MeI	**6h** (79)		Me	90:10
1		−80	MeI	**6i** (73)		Me	89:11
1	Me_3SiLi	−78	MeI	**6j** (70)	Me_3Si	Me	60:40[b]
1	EtLi	−45	MeI	**6k** (92)	Et	Me	94:6
2		0	MeI	**6l** (80)		Me	80:20
2		−78	MeI	**6m** (80)	1-pentenyl	Me	95:5
2	*n*-BuLi	−78	MeI	**6n** (95)	*n*-Bu	Me	97:3
3		−80	MeI	**6o** (50)		Me	85:15
4	*n*-BuLi	−80	MeI	**6p** (95)	*n*-Bu	Me	97:3
4	*t*-BuLi	−80	MeI	**6q** (95)	*t*-Bu	Me	65:35[b]
4		−80	MeI	**6r** (90)		Me	97:3
4		−90	MeI	**6s** (90)		Me	97:3

[a] Generated from the tetrasubstituted stannane with MeLi, in situ. [b] Both diastereomers separated and cleaved to aldehyde 7. Each showed equal but opposite rotations (See Table II). [c] Determined by HPLC and NMR spectroscopy. [d] The electrophiles were added 2–4 h after the organolithium was introduced.

Table II. Cleavage of Dihydronaphthyloxazolines **6** to Aldehydes **7**

oxazoline	R	R′	E	**7**	aldehyde, %	% ee
6d[a]	Me	H	PhS	**7d**	62	~100
6c	*n*-Bu	H	MeO_2C	**7c**	88	88
6f[a]	Ph	H	Me	**7f**	89	~100
6g		H	Me	**7g**	70	~100
6h		H	Me	**7h**	70	~100
6i		H	Me	**7i**	65	~100
6m	5-hydroxypentyl	MeO	Me	**7m**	97	~100
6j[a]	Me_3Si	H	Me	(+)-**7j**	85[b]	~100
6j[a]	Me_3Si	H	Me	(−)-**7j**	58[b]	~100
6l		MeO	Me	**7l**	80	60[c]
6n	*n*-Bu	MeO	Me	**7n**	79	94

[a] Oxazolines **6** were separated to pure diastereomers by flash chromatography on silica gel 60 H (Merck) prior to cleavage to aldehydes. [b] Based on 60% of (+)-enantiomer and 40% of (−)-enantiomer. [c] Unstable substance, reduced to carbinol.

Table III. Tandem Additions to Naphthalene **11**

				dihydronaphthalene **12**	
RLi	equiv	addn *T*, °C	addn time[a]	% yield	% de
n-BuLi	1.1	−78	2 h	85	96[b]
n-BuLi	1.1	25	5 min	70	84[b,d]
n-BuLi	1.1	−78	2 h	92	96[b,e]
MeLi	2.0	−30	15 h	67	82[b,c,e]
PhLi	2.0	−30	5 h	89	80[c,d]
t-BuLi	2.0	−100	1.5 h	74	46[b,d]

[a] Time required for addition of organolithium to react completely with **11** as determined by NMR spectroscopy, HPLC, or TLC. MeI quench was virtually instantaneous. [b] Determined by HPLC. [c] Mass of isolated diastereomers. [d] Determined by ^1H NMR spectroscopy. [e] HMPA (1.0 equiv) added.

trans 1,2-carbinol **17** in good overall yields based on **1** (Table V). The NMR spectrum of **17** showed a C-1 to C-2 proton–proton coupling constant near zero, and we were not convinced that the configuration was unambiguously assigned. A single-crystal X-ray study (Figure 1C) confirmed that indeed the configuration of **17** was trans diaxial; the expected most favorable conformation in a ring system with four sp^2 centers. Thus, it may be concluded that the proton quench follows from the side opposite the alkyllithium addition and epimerization to the trans 1,2-disubstituted product occurs during the workup and/or the hydride reduction.

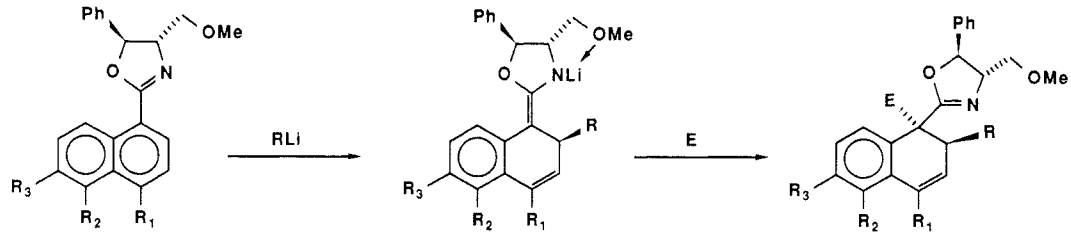
Table IV. Cleavage of Dihydronaphthyloxazine **12** to Aldehydes **13**

	aldehyde **13**		
R in **12**	% yield	$[\alpha]_D$ (*c*(mg/mL), $CHCl_3$)	% ee
n-Bu	81	+190.8° (1.0)	>99
Me	65	−85.8° (0.5)	>99
Ph	89	−333.6° (0.5)	>99
t-Bu	70	+244.4° (0.7)	>99

All the carbinols **17** in Table V were stable, highly viscous oils, which were readily purified by standard chromatographic techniques. For the example with isopropyllithium, this was prepared[10]

(10) Glaze, W. H.; Lin, J.; Felton, E. G. *J. Org. Chem.* **1965**, *30*, 1258.

Scheme II



1, $R_1 = R_2 = R_3 = H$
2, $R_2 = OMe$, $R_1 = R_3 = H$
3, $R_1 = R_2 = H$, $R_3 = OMe$
4, $R_1 = MeO$, $R_2 = R_3 = H$

5

6a-6s

Scheme III

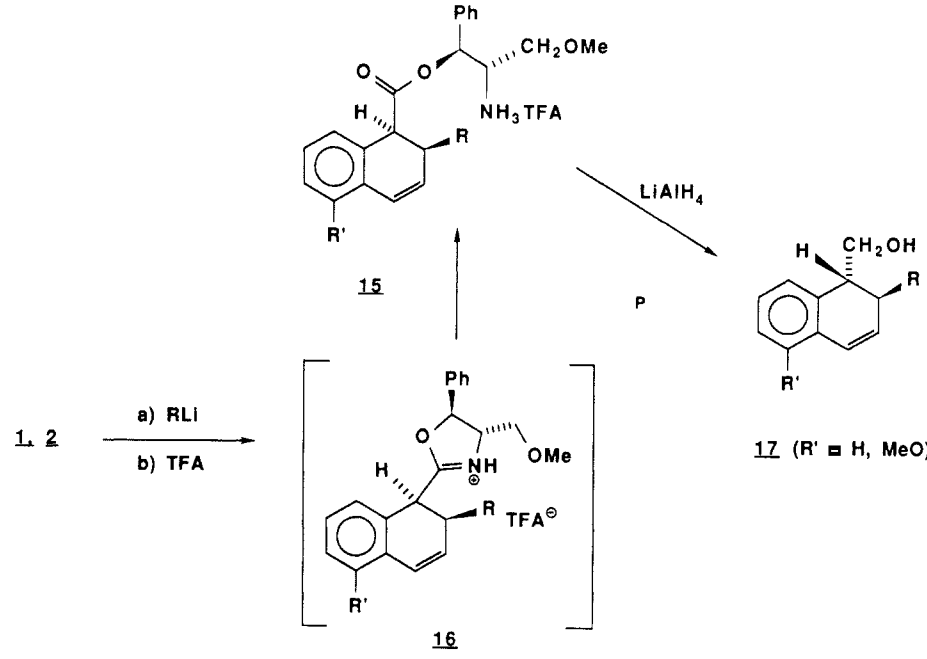


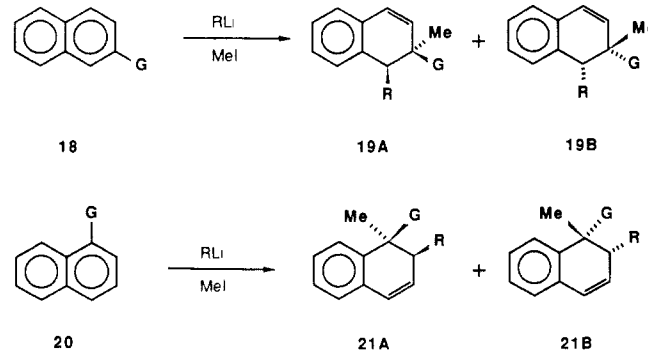
Table V. Addition of Organolithiums–Proton Quench to **1**. Formation of Dihydronaphthalene Carbinols (+)-**17**

			(+)-17		
oxazoline	RLi	*t*, °C	% yield	R	% ee
(+)-**1**	*n*-BuLi	−78	73	Bu	88[a]
(+)-**1**	PhLi	−45	62	Ph	70[b]
(+)-**1**	MeLi	−45	42	Me	70[b]
(+)-**2**	EtLi	−78	85	Et	94[b]
(+)-**1**	*i*-PrLi	−78	73	*i*-Pr	92[b]

[a] Determined via ^{31}P NMR spectroscopy on the thiophosphonate ester (see ref 11). [b] Determined via ^{19}F NMR spectroscopy on the Mosher ester (se ref 12).

from isopropyl chloride and lithium metal in pentane. This reagent exhibited a rapid and clean reaction with (+)-**1** at −78 °C after 3 h. The enantiomeric excess of the carbinols in Table V were determined by using either the Johnson thiophosphonate ester[11] or the Mosher ester[12] and were in excellent agreement (±1%) with the ratio obtained on the diastereomeric adducts **6** from HPLC data. Thus, the facial selectivity of organolithiums to **1** or **2** were virtually identical regardless of the nature of the quenching electrophile (proton or other) so that the percent ee in Table V matches those in Table I for the same organolithium reagent utilized.

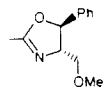
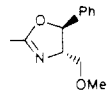
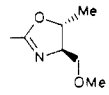
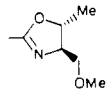
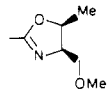
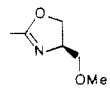
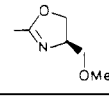
Mechanistic Considerations. This generally useful stereoselective process that was initially observed with simple achiral naphthyloxazolines[1] has now developed into a potentially powerful process and will be featured in an asymmetric synthesis of (+)-phyltetralin (vide infra). We attempted to gain further insight into this asymmetric tandem addition by focusing on the nature of the chiral auxiliary, namely the oxazoline. The oxazolines derived from threonine (Table VI, entries 3–5 and 11), which were reported earlier,[13] were subjected to organolithium additions followed by methyl iodide quench. The major difference observed with the threonine-derived auxiliary is the reversal in stereochemistry of addition products. Thus, the addition to oxazoline **18** (entries 1 and 2) gives 90% **19A** while addition to oxazoline **18** (entries 3, 4, 6, and 7) gives greater than 90% of **19B**. The

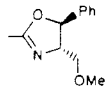
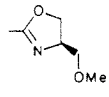
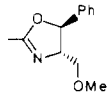
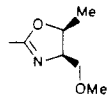


only factor, therefore, that determines the facial selectivity is the

(11) Johnson, C. R.; Elliot, R. C.; Penning, T. D. *J. Am. Chem. Soc.* **1984**, *106*, 5019.
(12) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512.
(13) Meyers, A. I.; Hoyer, D. *Tetrahedron Lett.* **1985**, *26*, 4687.

Table VI. Additions as a Function of Oxazoline Structure

entry	RLi	G	t, °C	% yield	ratio 19A	ratio 19B
		2-Naphthyl, **18**				
1	PhLi		−30	89	90[a]	10
2	BuLi		−78	85	98	2
3	PhLi		−78	90	9	91
4	BuLi		−78	87	6	94
5	PhLi		−78	93	25	75
6	PhLi		−78	90	9	91
7	BuLi		−78	96	7	93

entry	RLi	G	t, °C	% yield	ratio 21A	ratio 21B
		1-Naphthyl, **20**				
8	*n*-BuLi		−45	100	94	6
9	*n*-BuLi		−78	93	8	92
10	PhLi		−30	100	86	14
11	PhLi		−45	94	30	70

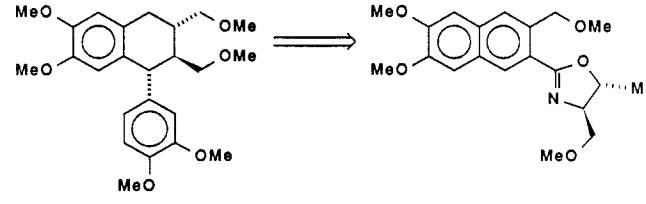
[a] Diastereomeric ratios determined by NMR spectroscopy and/or HPLC, see Figure 1, supplementary material.

stereocenter at C-4 in the oxazolines. The substituents at C-5 apparently have no effect on the major course of facial selectivity as can be seen from entries 3, 4, 6, and 7. The stereochemistry at C-5, however, appears to show some effect since the cis or trans methyl substituent (entry 3 versus 5) loses some selectivity when the methyl is on the same side as the methoxymethyl. Perhaps the cis stereochemistry interfers with the chelate by crowding the bottom side of the oxazoline, thus allowing the random, nonchelating addition to compete more favorably. On the other hand, the C-5 substituent (Ph, Me, H) has no apparent effect on the stereoselectivity (entries 1, 3, and 6). In the 1-naphthyloxazolines **20**, similar behavior is seen, and, once again, the stereochemistry of the C-4 substituent (i.e. the methoxymethyl group) dictates the facial selectivity. Also, the positioning of the C-5 methyl (entry 11) into a cis arrangement with C-4 causes a drop in selectivity over the presence of a trans substituent or no substituent (entries 8 and 9, respectively). On the basis of the above observations, we may describe this process as shown in Scheme IV. The chelate-controlled addition begins by the complexing of the organolithium to the oxazoline (A). The tetracoordinate lithium may undergo a ligand exchange with the solvent (THF) so that an equilibrium is established involving A and B. Only in B is the organolithium bond properly aligned to undergo a 1,5-sigmatropic rearrangement.

Since two of the four binding sites to lithium are taken up by the chelate in A or B, only two are left for exchange. The tighter the solvent binds to the metal the slower would be the exchange between A and B. This was confirmed by using ether as a solvent, which is known to be a poorer ligand than THF. The results of the use of ether showed a severe drop in diastereoselectivity from 95:5 to 70:30. This may be interpreted by assuming a chelate less well-defined than A or B which prefers random addition similar to that observed in the achiral naphthyl oxazoline.[1] Alternatively, the alkyllithium may be considered as an aggregate (C) complexed to the oxazoline, maintaining the same relationship of R to the aromatic π-system. In this case, the proposal that C is the complex may be more consistent with recent results pertaining to aggregates of organolithiums and their reaction with electrophilic sites.[9b]

The results of the 1,5-rearrangement, leading to **5**, can be viewed as a suprafacial sigmatropic process from the HOMO (ψ_3) of the six-electron system. Once **5** is formed, the addition of the electrophile would enter the azaenolate **5** from the more accessible opposite face from which the organolithium initially entered.

Application to the Synthesis of (+)-Phyltetralin. We felt it would be desirable to demonstrate the synthetic utility of this methodology by the total synthesis of some appropriate naturally occurring material. We chose, at this point in the development of this chemistry, the aryl lignan, (+)-phyltetralin (**22**), which would, in a retrosynthetic manner, emanate from the appropriately substituted naphthyloxazoline **23** (Scheme V). Phyltetralin was



(+)-22 23

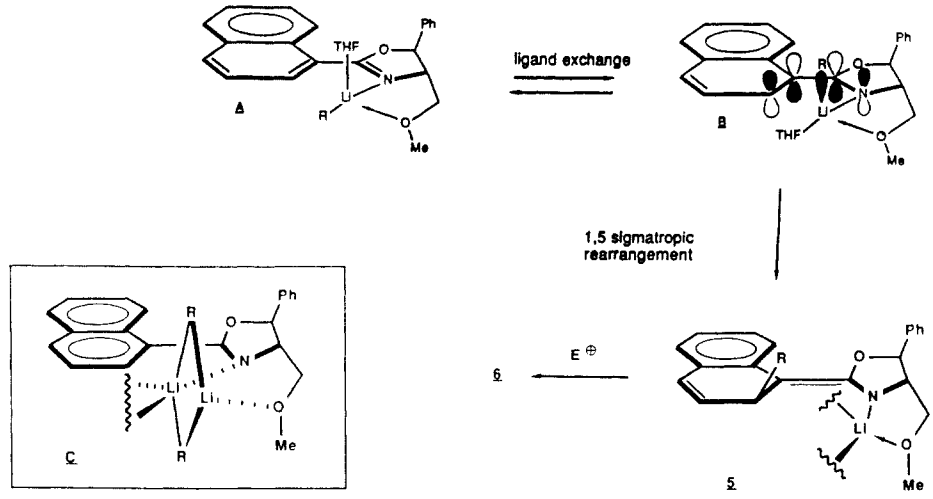
first reported and its structure incorrectly assigned in 1973.[14] It was one of five constituents isolated from *Phyllanthus niruri* Linn. The structure was later corrected by Stevenson who succeeded in the synthesis of racemic phyltetralin[15] and an enantioselective synthesis[16] derived from the related system α-conidendrin. On the basis of the earlier studies, we envisioned that **23**, derived from threonine, would provide the correct absolute configuration to reach the (+)-enantiomer of phyltetralin. On the other hand, the oxazoline derived from the Parke-Davis amino diol (**1–4**) would give the (−)-enantiomer, consistent with the results presented in Table VI.

The synthesis of the starting naphthyloxazoline **23** is outlined in Scheme VI. The requisite naphthalene **25** was prepared in excellent yield via the method of Teague and Roth[17] and the methyl group was smoothly functionalized by initially transforming it to the bromo derivative **26** followed by methanolysis to the methyl ether **27**. Hydrolysis of the ester followed by oxazoline formation[13] by using a modified Vorbruggen procedure,[18] gave the desired starting naphthalene **23**.

Addition of lithio-3,4-dimethoxybenzene to **23** at −20 °C for 15 h followed by quenching the azaenolate with 2-propanol gave as the major product the adduct **28**, which was completely trans with regard to the aryl and oxazoline moieties. Thus, the lithium

(14) Row, L. R.; Rao, K. J.; Anjaneyula, A. S. R. *Tetrahedron* **1973**, *29*, 1291.
(15) Stevenson, R.; Ganeshpare, P. A. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1681.
(16) Stevenson, R.; Williams, J. D. *Tetrahedron* **1977**, *33*, 2913.
(17) Teague, S. J.; Roth, G. P. *Synthesis* **1986**, 427.
(18) Vorbruggen, H.; Krolikiewicz, K. *Tetrahedron Lett.* **1981**, *22*, 4471.

Scheme IV



isopropoxide generated during the proton quench completely epimerized the α-proton to **28**. Attempts to assess the diastereoselectivity of **28** via NMR methods with or without chiral or achiral shift reagents failed to provide any useful information. Further attempts using HPLC, normal-phase or reverse-phase, gave no indication of the percent de in **28**.

The chiral oxazoline was next removed by treating **28** with trifluoroacetic acid in the presence of sodium sulfate monohydrate in THF. The ester amine salt **29** thus obtained was reduced with lithium aluminum hydride at room temperature to the alcohol **30** in high yield. Once again, attempts were made to determine the enantiomeric purity (and thus the percent de in **28**) for the alcohol **30**. Esterification of **30** with racemic Mosher ester[12] or (+)- or (−)-Mosher ester showed no separation or ^{1}H or ^{19}F NMR evaluation; neither did any separation become evident with the Mosher esters with HPLC. The phosphonamides of Johnson[11] also failed to exhibit any diastereotopic signals on the ^{1}H or ^{31}P NMR spectrum. These derivatives were also subjected to normal- or reverse-phase HPLC and once again failed to show diastereomeric ratios.

The next stage in the synthesis of (+)-phyltetralin involved hydrogenation of **30** to give the saturated alcohol **31**. This was readily accomplished by using rhodium on carbon, and **31** was obtained in 80–85% yield. Again, the enantiomeric excess was sought by preparation of the Mosher ester **32**, and the ^{19}F NMR spectrum clearly exhibited two ^{19}F signals in the ratio 86:14 (Figure 2). Thus, the lithio veratrole addition to give **28** was in the same general range of diastereoselectivity as other aryllithium additions to chiral naphthalenes (Tables I and III). Since **28** represents the thermodynamically favored configuration and there is no reason to expect the epimerization of the oxazoline or its subsequently derived substituents in **29**, **30**, and **31**, the percent ee in **31** may be correlated to the percent de of the initial adduct **28**. The sequence to (+)-phyltetralin was completed by treatment of the alcohol **31** with sodium hydride–methyl iodide in DMSO, which provided the natural product in 88% yield. The ^{1}H and ^{13}C NMR data were in complete agreement with published spectra[15,19] and comparison with an authentic sample.[20] The specific rotation of (+)-phyltetralin (**22**) obtained in this study, when compared to (−)-phyltetralin obtained as an authentic sample,[20] gave an ee of 60%. Furthermore, we observed the $[\alpha]_D$ varied with concentration, which made rotation correlations somewhat precarious (Figure 3). This is to be compared with the more reliable 68% ee determined by Mosher ester analysis with ^{19}F NMR spectroscopy.

In summary, the asymmetric tandem addition of organolithium reagents or organostannanes to chiral naphthalenes has been shown to be a fruitful method to reach chiral alicyclic systems.

(19) Snider, B. B.; Jackson, A. C. *J. Org. Chem.* **1983**, *48*, 1471.
(20) We are grateful to Professor Robert Stevenson of Brandeis University for an authentic sample of (−)-phyltetralin.

Although most of the asymmetric additions were carried out on a 1–3-mmol scale (Experimental Section), we have on several occasions performed these additions on a 20–30-mmol scale with comparable results. A recent report from this laboratory exhibited

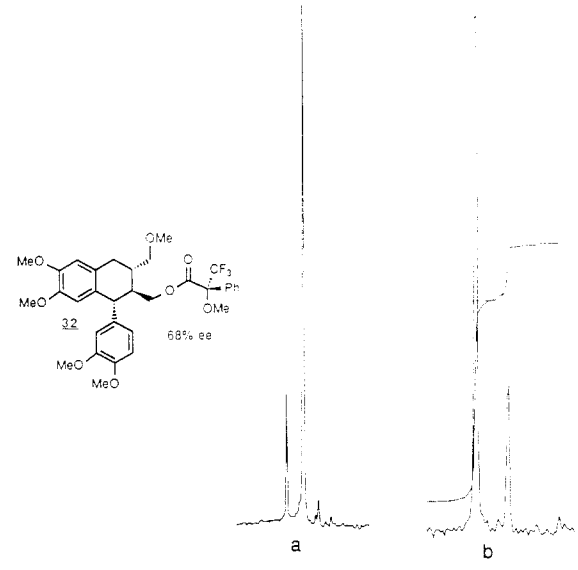


Figure 2. ^{19}F NMR spectra of Mosher esters **32**. (a) Mosher esters prepared from (*R*)-MTPA acid chloride. (b) Mosher esters prepared from (*S*)-MTPA acid chloride.

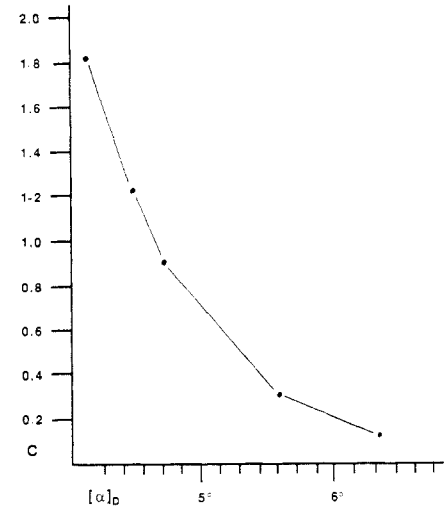
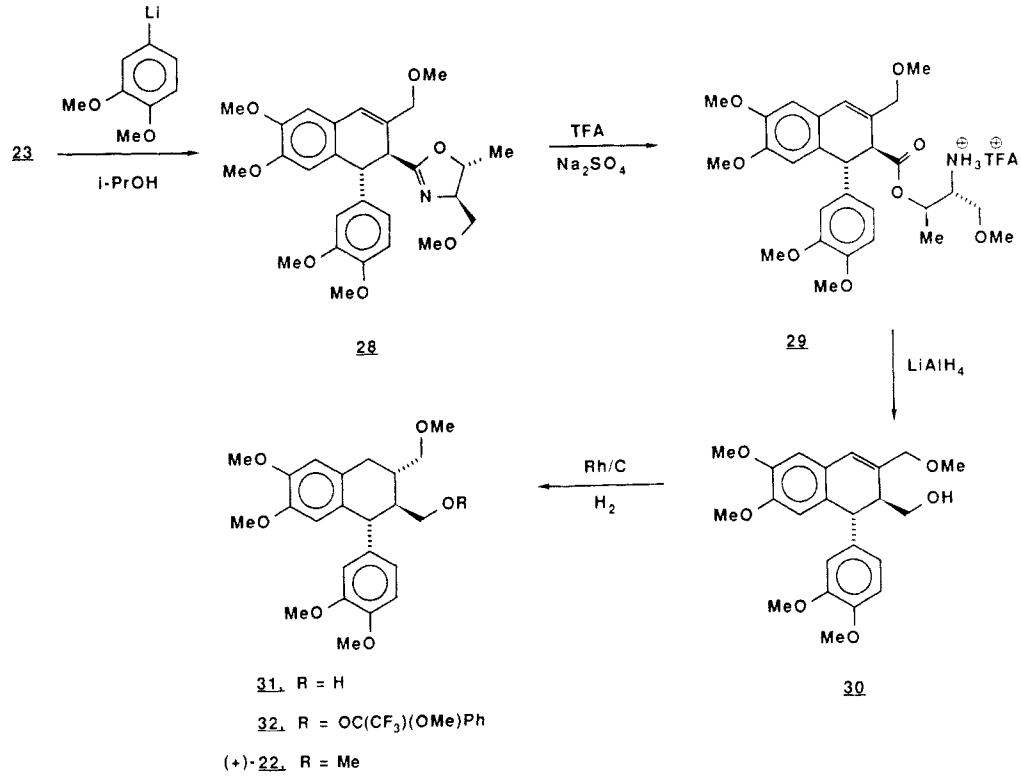
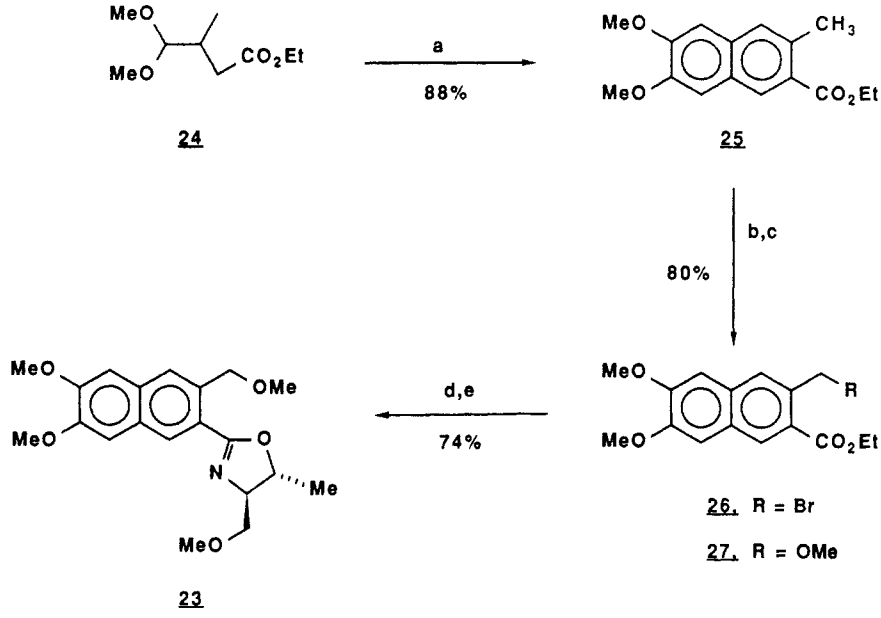


Figure 3. Plot of concentration (g/100 mL) versus $[\alpha]_D$ of (+)-phyltetralin [(+)-**22**].

Scheme V



Scheme VI[a]



[a] (a) LDA, −78 °C; THF; 3,4-$(MeO)_2C_6H_3CHO$; 3 M H_2SO_4; (b) *N*-Bromosuccinimide, CCl_4, 75 °C; (c) K_2CO_3, MeOH; (d) 2 M NaOH, 90 °C, 4 h; (e) PPh_3, CCl_4, pyridine, Et_3N, CH_3CN, $MeCH(OH)CH(NH_2)CH_2OMe$.

further the use of this methodology in a route to alklavinone.[21] Progress toward other enantiomeric natural products has been made and will be described in due course.

Experimental Section

Chiral Naphthalenes 1–4 and 11. A typical procedure for **4** is given, which is identical with the procedures that produce **1–3** and **11**.

1-[(*S*,*S*)-4-(Methoxymethyl)-5-phenyl-2-oxazolinyl]-4-methoxynaphthalene (4). To a slurry of 4-methoxy-1-naphthamide[23] (4.23 g, 15 mmol) in 100 mL of dry 1,2-dichloroethane was added triethyloxonium tetrafluoroborate (3.47, 18 mmol), and the reaction mixture was allowed to stir for 20 h at ambient temperature. The resulting orange solution was then treated with (1*S*,2*S*)-(+)-1-phenyl-2-amino-3-methoxy-1-propanol (4.0 g, 22 mmol)[24] and heated to reflux for 16 h. The reaction mixture was then cooled and poured into 60 mL of water. The organic fraction was removed, dried ($MgSO_4$), and concentrated to give a yellow oil. The crude product was purified by flash chromatography (EtOAc/hexane, 20%) to give 4.9 g (94%) of the desired product as a colorless oil: $[\alpha]_D$ 75.0° (*c* 1.19, $CHCl_3$); IR (film) 2920, 1630, 1575, 1505, 1455, 1235, 1080, 990, 855 cm^{-1}; ^1H NMR δ 9.27 (d, 1 H, *J* = 8.4 Hz), 8.32 (d, 1 H, *J* = 8.2 Hz), 8.19 (d, 1 H, *J* = 8.2 Hz), 7.62 (t,

(21) Meyers, A. I.; Higashiyama, K. *J. Org. Chem.* **1987**, *52*, 4592.
(22) Watson, S. C.; Eastman, J. *J. Organomet. Chem.* **1967**, *7*, 165.
(23) Prepared from 4-methoxy-1-naphthonitrile (Aldrich) by KOH hydrolysis in *tert*-butyl alcohol according to Hall, J. H.; Gisler, M. *J. Org. Chem.* **1976**, *41*, 3769 (mp 238–239 °C).
(24) Meyers, A. I.; Kamata, K.; Ford, M. E. *J. Am. Chem. Soc.* **1976**, *98*, 567. Commercially available from Fluka, A. G.

1 H, J = 7.1 Hz), 7.48 (t, 1 H, J = 7.1 Hz), 7.40–7.31 (m, 5 H), 6.28 (d, 1 H, J = 8.2 Hz), 5.48 (d, 1 H, J = 6.5 Hz), 4.50–4.40 (m, 1 H), 4.04 (s, 3 H), 3.84 (dd, 1 H, J = 4.3, 9.6 Hz), 3.68 (dd, 1 H, J = 6.8, 9.6 Hz), 3.47 (s, 3 H); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 158.39, 142.59, 141.53, 132.59, 130.54, 128.74, 128.00, 127.90, 126.52, 125.68, 122.18, 118.23, 102.79, 82.44, 75.73, 74.93, 68.87, 59.34. Anal. Calcd for $C_{22}H_{21}NO_3$: C, 76.06; H, 6.09. Found: C, 76.64; H, 6.11.

1-[(*S*,*S*)-4-(Methoxymethyl)-5-phenyl-2-oxazolinyl]naphthalene (1). This was prepared as described above, with use of 1-naphthamide: mp 49–50 °C; $[\alpha]^{22}_D$ 53.0° (c 7.5, $CHCl_3$); IR (film) 1650, 1625, 1595, 1517, 1460, 1130, 995 cm^{-1}; ^{1}H NMR δ 9.20 (d, 1 H, J = 8.4 Hz), 8.21 (dd, 1 H, J = 7.3 Hz, 1.3 Hz), 7.99 (d, 1 H, J = 8.2 Hz), 7.89 (d, 1 H, J = 8.3 Hz), 7.6–7.3 (m, 8 H), 5.55 (d, 1 H, J = 6.6 Hz), 4.5 (m, 1 H), 3.85 (m, 1 H), 3.70 (m, 1 H), 3.48 (s, 3 H); t_R (20% THF/hexane, 1 mL/min) 6.54 min. Anal. Calcd for $C_{21}H_{19}NO_2$: C, 79.47; H, 6.03. Found: C, 79.57; H, 5.96.

1-[(*S*,*S*)-4-(Methoxymethyl)-5-phenyl-2-oxazolinyl]-5-methoxynaphthalene (2). This has been prepared as above and has previously been described.[21]

1-[(*S*,*S*)-4-(Methoxymethyl)-5-phenyl-2-oxazolinyl]-6-methoxynaphthalene (3). This was prepared from 6-methoxy-1-naphthonitrile[25] and transforming[23] it into the naphthamide, mp 199–200 °C. The latter was then utilized in the procedure given above: mp 103–104 °C; $[\alpha]^{22}_D$ 54.6° (c 6.0, $CHCl_3$); IR (film) 1650, 1630, 1600, 1520, 1260, 1120, 980 cm^{-1}; ^{1}H NMR δ 9.1 (d, 1 H, J = 9.5 Hz), 8.07 (d, 1 H, J = 6.1 Hz), 7.87 (d, 1 H, J = 7.8 Hz), 7.30 (m, 8 H), 5.54 (d, 1 H, J = 6.7 Hz), 4.49 (m, 1 H), 3.92 (s, 3 H), 3.85 (m, 1 H), 3.72 (m, 1 H), 3.47 (s, 3 H). Anal. Calcd for $C_{22}N_{21}NO_3$: C, 76.06; H, 6.09. Found: C, 76.32; C, 6.05.

2-[(*S*,*S*)-4-(Methoxymethyl)-5-phenyl-2-oxazolinyl]naphthalene (11) was prepared from 2-naphthamide by the procedure described for **4**: mp 64–66 °C; $[\alpha]^{22}_D$ 124.2° (c 2.8, $CHCl_3$); ^{1}H NMR δ 3.45 (s, 3 H), 3.68 (dd, 1 H), 3.79 (dd, 1 H), 4.40 (m, 1 H), 5.55 (d, 1 H), 7.25–8.55 (m, 9 H); IR (film) 2935, 1655, 1647 cm^{-1}. Anal. Calcd for $C_{21}H_{19}NO_2$ (317.4): C, 79.47; H, 6.03. Found: C, 79.35; H, 6.03.

Addition of Organolithium Reagents to Naphthalenes 1–4. General Procedure. A flame-dried flask under Ar containing a 0.08 M THF solution of 317 mg (1.0 mmol) of 1–4 (Table I) was cooled to the indicated temperature and was treated with 1.5–2.0 equiv of the alkyllithium listed for each example. The solution became deep red over 2–4 h and was quenched by the dropwise addition of 1.5 equiv of electrophile (either neat or as a THF solution). The temperature was maintained for 1 h before the solution was warmed gradually to 0 °C. The solution was diluted with 100 mL of ether and washed with 5 mL of saturated aqueous NH_4Cl, followed by 3 mL of saturated aqueous NaCl. The combined aqueous layers were back-extracted with 10 mL of CH_2Cl_2, and the combined extracts were dried over Na_2SO_4. Concentration of the filtrate in vacuo provided a yellow oil, which was flash chromatographed over silica gel (1–10% EtOAc in hexane) to yield the desired adducts, shown in Table I. The diastereomeric ratios were determined with HPLC (Zorbax Sil column, Du Pont, 4.6 mm × 25 cm). The solvent system utilized was 20% THF/hexane at 1 mL/min. No further purification on **6** was attempted, and a representative number of examples (Table II) were carried on to aldehydes **7**.

General Procedure for 6g–h,o. Additions via Organostannanes (Table I). The tetrasubstituted stannanes were all prepared from the appropriate Grignard reagent and $SnCl_4$ in benzene after being heated to reflux overnight according to Seyferth.[26] To a solution of the naphthyloxazoline **1** or **3** (1.0 mmol) and tetrasubstituted stannane (0.4 mmol) in 20 mL of THF, cooled to −78 °C, was added dropwise a solution of methyllithium (1.2 mmol) in dry ether. The resulting red mixture was stirred for 16–20 h at the temperature indicated in Table I, and then methyl iodide (2.0 mmol) was added. The mixture was allowed to warm slowly to room temperature and then poured into 20 mL of saturated ammonium chloride. The layers were separated, and the organic phase was washed with brine, dried ($MgSO_4$), and concentrated to give a yellow oil. The mixture of diastereomers were analyzed by HPLC (hexane/ethyl acetate, 9:1) to give the ratios shown in Table I. In the case of **6g**, the isopropenyllithium/methyl iodide adduct was completely characterized. The two diastereomers were separated by medium-pressure liquid chromatography on silica gel (hexane/ethyl acetate, 9:1), giving 228 mg (61%) of pure diastereomer **6g**: $[\alpha]^{22}_D$ 368.3° (c 3.0, $CHCl_3$); IR (neat) 3060, 3020, 2980, 2920, 2880, 2820, 1650 (C=N), 1600 (C=C), 1480, 1450, 1370, 1190, 1120, 1100, 1070, 980, 890, 780, 750 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.54 (d, 1 H, J = 7.18 Hz), 7.2 (m, 8 H), 6.53 (d, 1 H, J = 9.6 Hz), 5.76 (dd, 1 H, J = 6.0 and 9.6 Hz), 5.31 (d, 1 H, J = 7.6 Hz), 4.89 (s, 1 H), 4.62 (s, 1 H), 4.24 (m, 1 H), 3.69 (dd, 1 H, J = 4.4, 9.7 Hz), 3.5 (dd, 1 H, J = 9.8, 7.3 Hz), 3.41 (s, 3 H), 3.29 (d, 1 H, J = 5.9 Hz), 1.62 (s, 3 H), 1.43 (s, 3 H). Anal. Calcd for $C_{25}H_{27}O_2N$: C, 80.40; H, 7.28; N, 3.75. Found: C, 80.56; H, 7.17; N, 3.74.

General Procedure for Cleavage to Aldehydes 7 (Table II). To a flame-dried flask under Ar containing a 0.08 M CH_2Cl_2 solution of **6** was added 2.0 equiv of methyl trifluoromethanesulfonate,[27] and the solution was stirred at ambient temperature until TLC indicated complete conversion of **6** into base-line salts (1–4 h). The solution (usually colorless) was cooled to 0 °C and treated with a solution of 2.0 equiv of $NaBH_4$ in THF/MeOH, 4:1. After 30 min at 0 °C, the solution was quenched by the addition of a 50% saturated solution of aqueous NH_4Cl and diluted with ether.

The organic layer was washed with a few milliliters of saturated aqueous NaCl, and the combined aqueous layers were back-extracted with 10 mL of CH_2Cl_2. The combined extracts were dried over Na_2SO_4 before concentration in vacuo. Flash filtration through a small bed of silica gel provided the diastereomeric oxazolidines.

The oxazolidine mixture was taken up in a solution of THF/H_2O, 4:1 (0.1 M), and treated with 5.0 equiv of oxalic acid dihydrate. The solution was stirred at ambient temperature until TLC indicated complete conversion into aldehyde (15–20 h). The conversion may be monitored by the use of Dragendorff's reagent for TLC staining, as the R_f's of oxazolidine and aldehyde are often the same. The solution was diluted with Et_2O and washed with a small amount of saturated aqueous $NaHCO_3$, followed by 3 mL of saturated aqueous NaCl. The extract was dried over Na_2SO_4 before concentration in vacuo. Chromatography, flash or radial, with hexane–ethyl acetate (9:1) provided pure aldehyde **7**.

Aldehydes 7 (Table II). 7d (R = Me, R′ = H, E = PhS). The corresponding oxazoline **6d** was separated via flash chromatography (silica gel 60 H, E. Merck) prior to cleavage. The aldehyde **7d** was, therefore, obtained as a pure enantiomer: mp 47–48 °C (from pentane); $[\alpha]^{25}_D$ 747° (c 4.35, $CHCl_3$); IR (film) 2740, 1715, 1492, 1450, 750 cm^{-1}; ^{1}H NMR δ 9.75 (s, 1 H), 7.3–6.9 (m, 9 H), 6.59 (d, 1 H, J = 9.5 Hz), 6.12 (dd, 1 H, J = 9.5, 6.1 Hz), 2.66 (m, 1 H), 0.97 (d, 3 H, J = 6.9 Hz). Anal. Calcd for $C_{18}H_{16}OS$: C, 77.11; H, 5.75. Found: C, 76.94; H, 5.80.

7c (R = *n*-Bu, R′ = H, E = MeO_2C). The oxazoline **6c** was not separated into pure diastereomers; thus **7c** represents an 94:6 ratio (88% ee) of enantiomers: oil from silica gel; IR (film) 1730, 1740, 1725, 1240 cm^{-1}; ^{1}H NMR δ 9.69 (s, 1 H), 7.3–7.1 (m, 4 H), 6.40 (dd, 1 H, J = 9.6, 2.3 Hz), 6.02 (dd, 1 H, J = 9.7, 3.3 Hz), 3.83 (s, 3 H), 3.26 (m, 1 H), 1.8–0.9 (m, 9 H).

7f (R = Ph, R′ = H, E = Me). The oxazoline **6f** was purified via flash chromatography (silica gel 60 H, ethyl acetate/hexane) to give a single diastereomer prior to cleavage. The aldehyde **7f** was obtained as a pure diastereomer: mp 112.5–113.5 °C (from pentane); $[\alpha]^{25}_D$ 201° (c 3.60, $CHCl_3$); IR ($CHCl_3$) 2730, 1720, 1600 cm^{-1}; ^{1}H NMR δ 9.52 (s, 1 H), 7.3–7.0 (m, 9 H), 6.67 (dd, 1 H, J = 9.7, 1.6 Hz), 6.07 (dd, 1 H, J = 9.6, 4.7 Hz), 3.71 (dd, 1 H, J = 4.6, 1.8 Hz), 1.42 (s, 3 H). Anal. Calcd for $C_{18}H_{16}O$: C, 87.06; H, 6.50. Found: C, 86.44; H, 6.58.

(+)-7j and (−)-7j (R = Me_3Si, R′ = H, E = Me). The diastereomeric mixture in **6j** (60:40) was separated by flash chromatography (silica gel 60 H, E. Merck, hexane/ethyl acetate, 9:1), and each diastereomer was cleaved separately to (+)- and (−)-**7j**. Except for specific rotations, $[\alpha]^{25}_D$ 634° (η 0.58, $CHCl_3$) and $[\alpha]^{25}_D$ −638° (c 0.85, $CHCl_3$), all other physical data were identical: mp 45–47 °C; IR (film) 2710, 1728, 1623, 1250, 840 cm^{-1}; ^{1}H NMR δ 10.11 (s, 3 H), 7.3–6.8 (m, 4 H), 6.42 (d, 1 H, J = 9.5 Hz), 5.95 (dd, 1 H, J = 9.6, 6.3 Hz), 1.78 (d, 1 H, J = 6.3 Hz), 1.35 (s, 3 H), −0.07 (s, 9 H).

7g (R = isopropenyl, R′ = H, E = Me). The diastereomeric mixture (88:12) was separated via MPLC (silica gel 60, hexane/ethyl acetate, 9:1) to give pure **6g**. The aldehyde **7g** was obtained as a pure enantiomer: oil (46% overall yield from **1**); $[\alpha]^{22}_D$ 355° (c 3.3, $CHCl_3$); IR (neat) 1730 (C=O), 1650 (C=C), 1490, 1450, 1380, 1160, 900 cm^{-1}; ^{1}H NMR δ 9.83 (s, 1 H), 7.19 (m, 3 H) 6.96 (m, 1 H), 6.58 (d, 1 H, J = 9.6 Hz), 5.8 (dd, 1 H, J = 5.3, 9.6 Hz), 4.85 (s, 1 H), 4.80 (d, 1 H, J = 1.3 Hz), 3.14 (dd, 1 H, J = 5.3, 0.8 Hz), 1.52 (s, 3 H), 1.35 (s, 3 H). Anal. Calcd for $C_{15}H_{16}O$: C, 84.86; H, 7.63. Found: C, 84.85; H, 7.68.

7h (R = vinyl, R′ = H, E = Me). The diastereomeric mixture (90:10) for **6h** was separated via MPLC (silica gel 60 H, hexane–ethyl acetate, 10:1), and the pure diastereomer was cleaved to the aldehyde **7h**: col-

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(26) Seyferth, D.; Weiner, M. A. *J. Am. Chem. Soc.* **1961**, *83*, 3583; *J. Org. Chem.* **1959**, *24*, 1395. Seyferth, D.; Stone, F. G. H. *J. Am. Chem. Soc.* **1957**, *79*, 515.

(27) In our preliminary communication on this subject, ref 6a, we utilized "magic methyl" FSO_3Me for quaternizing the oxazoline **6**. We noted in this paper the quaternization was also efficient with trimethyloxonium fluoborate. However, in later studies, it was found that methyl triflate, as described in the Experimental Section, is far superior and safer to use than the previously employed methylating reagents.

orless oil (46% overall yield from **1**); $[\alpha]^{22}_D$ 85.90° (*c* 2.4, $CHCl_3$); ^1H NMR δ 9.78 (s, 1 H), 7.17 (m, 4 H), 6.50 (d, 1 H, *J* = 9.2 Hz), 5.8 (m, 2 H), 5.18 (d, 1 H, *J* = 9.1 Hz), 5.13 (m, 1 H), 3.13 (dd, 1 H, *J* = 4.2, 8.5 Hz), 1.39 (s, 3 H); IR (neat) 3060, 3040, 2980, 2920, 2820, 2720, 2720, 1720 (C=O), 1640 (C=C), 1480, 1450, 1030, 980, 920 cm^{-1}. Anal. Calcd for $C_{14}H_{14}O$: C, 84.81; H, 7.21. Found: C, 80.95; H, 6.24 (the product is unstable, turning very dark after 1–2 days precluding a satisfactory analysis).

7i (R = 1-cyclopentenyl, R′ = H, E = Me). The diastereomeric mixture (89:11) of **6i** was purified by MPLC (silica gel 60 H, E. Merck, hexane–ethyl acetate, 9:1) prior to cleavage furnishing **7i** as a pure enantiomer: colorless oil (55% overall from **1**); $[\alpha]^{22}_D$ 432° (*c* 2.7, $CHCl_3$); IR (neat) 3040, 2940, 2920, 2880, 2840, 2720, 1720 (C=O), 1480, 1440, 1390, 1135, 920, 780 cm^{-1}; ^1H NMR δ 9.79 (s, 1 H), 7.10 (m, 4 H), 6.53 (d, 1 H, *J* = 9.6 Hz), 5.79 (dd, 1 H, *J* = 5.2, 9.6 Hz, 5.54 (t, 1 H, *J* = 1.8 Hz), 3.34 (d, 1 H, *J* = 5.2 Hz), 2.23 (m, 2 H), 2.1 (m, 2 H), 1.8 (m, 2 H), 1.35 (s, 3 H). Anal. Calcd for $C_{17}H_{18}O$: C, 85.67; H, 7.61. Found: C, 85.61; H, 7.58.

7m (R = 5-hydroxyamyl, R′ = MeO, E = Me). This procedure describes the entire sequence from **2** to the aldehyde **7m**. A flame-dried flask was charged with 1-iodo-4-pentene (423.2 mg, 2.1 mmol) and 5 mL of pentane/ether (3:2) followed by cooling to −85 °C in a controlled temperature bath. *tert*-Butyllithium (2.5 mL, 4.3 mmol; 1.7 M in pentane) was added dropwise over a 5-min period, and the resulting suspension was allowed to stir for 15 min. A solution consisting of the naphthyloxazoline **2** (500 mg, 1.43 mmol) in 10 mL of THF was then added via cannula, and the deep red solution was allowed to stir for 4 h at that temperature before being quenched with an excess of iodomethane. The quenched reaction was allowed to warm to ambient temperature and diluted with 5 mL of water, and the solvent was evaporated. The resulting yellow slurry was taken up in CH_2Cl_2 and washed with water, and the organic fraction was dried ($MgSO_4$) and then concentrated to give 668 mg of a crude oil. HPLC analysis of the product (Zorbax; hexane/THF, 10%) shows it to contain 80% of the desired addition product **6m** in a diastereomeric ratio of 95:5: ^1H NMR δ 7.35–7.19 (m, 5 H), 7.16 (t, 1 H, *J* = 7.7 Hz), 6.86 (dd, 1 H, *J* = 7.7, 1.0 Hz), 6.75 (dd, 1 H, *J* = 7.7, 1.5 Hz), 6.01 (dd, 1 H, *J* = 9.9, 4.7 Hz), 5.76–5.70 (m, 1 H), 5.27 (d, 1 H, *J* = 6.8 Hz), 4.98–4.87 (m, 1 H), 4.24–4.17 (m, 1 H), 3.82 (s, 3 H), 3.67 (dd, 1 H, *J* = 9.6, 4.1 Hz), 3.49–3.42 (m, apparent dd, 1 H), 3.39 (s, 3 H), 2.46–2.42 (br s, 1 H), 2.01–1.25 (m, 6 H), 1.64 (s, 3 H); IR (film) 2970, 1645, 1570, 1470, 1260, 1050, 750 cm^{-1}.

A solution of crude **6m** (558 mg, 1.29 mmol) in THF (20 mL) was cooled to 0 °C in a ice water bath and then treated with 9-BBN (5.2 mL, 2.58 mmol; 0.5 M in THF). The resulting solution was allowed to warm to ambient temperature and stir overnight. The resulting mixture was again cooled to 0 °C and treated with 2 mL of 3 N NaOH solution followed by 2 mL of 30% aqueous H_2O_2. The reaction mixture was allowed to stir for 30 min as it warmed to ambient temperature, and then the solvent was evaporated. The residue was taken up in $CHCl_3$ and washed with water. The organic fraction was dried ($MgSO_4$), and the crude oil was chromatographed (hexane/ethyl acetate, 1:1) to give 402 mg (80%) of a colorless oil, $[\alpha]_D$ +159.37° (*c* 0.48, $CHCl_3$) for pure diastereomer, as determined by HPLC (Zorbax column, hexane/ethyl acetate, 1:1, 2 mL/min flow rate). Major isomer: t_R 11.56 min, 95%. Minor isomer: t_R 16.43 min, 5%. The latter was absent (<0.1%) after chromatography: ^1H NMR δ 7.36–7.18 (m, 5 H), 7.15 (t, 1 H, *J* = 7.7 Hz), 6.86 (dd, 1 H, *J* = 7.7, 1.0 Hz), 6.75 (dd, 1 H, *J* = 7.7, 1.5 Hz), 6.01 (dd, 1 H, *J* = 9.9, 4.7 Hz), 5.28 (d, 1 H, *J* = 6.8 Hz), 4.22–4.17 (m, 1 H), 3.79 (s, 3 H), 3.68–3.40 (m, 4 H), 3.37 (s, 3 H), 2.44–2.40 (br s, 1 H), 2.27 (br s, exch with D_2O, 1 H), 1.64 (s, 3 H), 1.75–1.14 (m, 8 H); ^{13}C NMR δ 170.18, 154.87, 141.01, 139.52, 129.27, 128.43, 127.72, 125.62, 125.09, 122.08, 119.85, 119.59, 109.29, 83.07, 82.86, 74.40, 74.09, 62.57, 59.02, 55.54, 44.74, 43.54, 32.54, 31.17, 27.15, 26.44, 25.76; IR (film) 3400, 2920, 1730, 1630, 1565, 690, 640 cm^{-1}.

A solution consisting of the above oxazoline (539.5 mg, 1.19 mmol) in dry CH_2Cl_2 (10 mL) was treated with a catalytic amount of DMAP, followed by addition of *tert*-butyldimethylchlorosilane (217.2 mg, 1.44 mmol) and triethylamine (0.23 mL, 1.6 M). The resulting solution was allowed to stir overnight and then quenched with water. After being stirred for 20 min, the organic fraction was dried ($MgSO_4$) and concentrated to give 631.2 mg (94%) of a colorless oil. The protected *O*-silyloxazoline (132 mg, 0.23 mmol) was taken up in 5 mL of dry CH_2Cl_2 and cleaved according to the general procedure for oxazoline removal to give a crude oil. The product **7m** was purified by chromatography (hexane/ethyl acetate, 1:1) to give 64.0 mg (97%) of a colorless oil: $[\alpha]_D$ 95° (*c* 1.47, $CHCl_3$) for the pure enantiomer **7m**; ^1H NMR δ 9.83 (s, 1 H), 7.19 (t, 1 H, *J* = 8.0 Hz), 6.88 (dd, 1 H, *J* = 9.9, 1.6 Hz), 6.81 (d, 1 H, *J* = 8.0 Hz), 6.75 (d, 1 H, *J* = 8.0 Hz), 3.85 (s, 3 H), 3.61 (t, 2 H, *J* = 6.5 Hz), 2.53–2.39 (br s, 1 H), 1.64–1.42 (env, 8 H), 1.37 (s, 3 H); ^{13}C NMR δ 204.06, 155.39, 136.77, 129.06, 128.63, 120.65, 118.85, 110.19, 77.21, 62.78, 55.64, 52.57, 42.59, 32.60, 29.95, 27.31, 25.78, 19.54; IR (film) 3320, 2920, 1700, 1560, 1450, 1250, 1030, 730 cm^{-1}; high-resolution mass spectrum for $C_{18}H_{24}O_3$ *m/e* 288.172, found 288.171.

7l (R = vinyl, R′ = MeO, E = Me). The mixture of oxazoline diastereomers **6l** was not separated and cleaved to the aldehyde **7l** as an 80:20 mixture (60% ee) of enantiomers. The aldehyde was obtained as a yellow oil in 80% yield from **6l** and was quite unstable, turning dark on standing after 1–2 days. Thus, no satisfactory elemental analysis could be obtained. However, this product was taken on to the lactone **9** (see below).

7n (R = *n*-Bu, R′ = MeO, E = Me). The diastereomeric oxazolines **6n** (97:3 ratio) was cleaved according to the general procedure to give aldehyde **7n** in 79% yield as a pale yellow oil, after flash chromatography on silica gel, hexane/ethyl acetate (9:1): $[\alpha]^{25}_D$ −9.79° (*c* 0.95, $CHCl_3$); ^1H NMR δ 9.83 (s, 1 H), 7.19 (t, 1 H, *J* = 8.0 Hz), 6.88 (dd, 1 H, *J* = 1.6, 10.0 Hz), 6.81 (d, 1 H, *J* = 8.2 Hz), 6.75 (d, 1 H, *J* = 7.7 Hz), 5.97 (dd, 1 H, *J* = 4.0, 10.0 Hz), 3.85 (s, 3 H), 2.42 (m, 1 H), 1.38 (s, 3 H), 1.58–1.22 (complex m, 6 H), 0.87 (t, 3 H, *J* = 6.9 Hz); IR (film) 2910, 2820, 1720, 1560, 1460, 1250, 1030, 760 cm^{-1}. Anal. Calcd for $C_{17}H_{22}O_2$: C, 79.03; H, 8.57. Found: C, 79.28; H, 8.72.

Lactol 8. A solution of **6l** (4.9 g, 24 mmol) in 75 mL of THF was cooled to 0 °C in an ice water bath and a solution of 9-BBN in THF (50.4 mL, 24 mmol) was added via syringe. The reaction mixture was allowed to warm to ambient temperature and stir overnight. The solution was again cooled to 0 °C and treated with 30 mL of 3 N NaOH solution, followed by 25 mL of 30% aqueous H_2O_2. Workup consisted of extraction with CH_2Cl_2 followed by chromatography to give 4.3 g (90%) of a pale yellow oil. The exocyclic alcohol was then protected with the *tert*-butyldimethylchlorosilane to give 5.6 g (98%) of a yellow oil. A solution of the crude oxazoline (3.0 g) in dry CH_2Cl_2 was cleaved by the standard procedure to give 1.7 g of **8** as a yellow oil. Purification by flash chromatography (hexane/ethyl acetate, 3:1–1:1) afforded 1.0 g (70%) of a colorless solid, mp 30–35 °C, as a diastereomeric mixture (80:20): ^1H NMR (270 MHz) δ 7.18 (t, 1 H, *J* = 7.9 Hz), 6.99 (d, 1 H, *J* = 7.9 Hz), 6.89 (dd, 1 H, *J* = 9.8, 1.3 Hz), 6.74 (d, 1 H, *J* = 7.9 Hz), 5.80 (dd, 1 H, *J* = 9.8, 4.3 Hz), 5.26 (d, 1 H, *J* = 3.7 Hz), 4.06–3.67 (m, 2 H), 3.81 (s, 3 H), 3.10 (d, ex, 1 H, *J* = 3.7 Hz), 2.69 (br s, 1 H), 1.98–1.79 (m, 1 H), 1.35–1.25 (m, 1 H), 1.31 (s, 3 H); ^{13}C NMR (67.9 MHz) δ 155.23, 140.36, 129.9, 128.06, 122.18, 121.50, 119.76, 118.64, 109.37, 94.75, 61.05, 55.74, 36.93, 27.63, 19.92; IR (film) 3400, 2925, 1570, 1470, 1260, 750 cm^{-1}.

Lactone (−)-9. A solution of oxalyl chloride (250 μL, 2.9 mmol) in dry CH_2Cl_2 (5 mL) was cooled to −78 °C in a dry ice/acetone bath and treated with DMSO (406 μL, 5.72 mmol) dropwise via syringe. The reaction mixture was allowed to stir for 2 min, and then a solution of the lactol **8** (647 mg, 2.6 mmol) in CH_2Cl_2 (5 mL) was added over a 10-min period. The reaction mixture was allowed to stir for 15 min, and then triethylamine (2 mL) was added and the reaction mixture was warmed to ambient temperature. After 30 min the solution was diluted with 25 mL of water, and the organic fraction was collected, dried ($MgSO_4$), and concentrated to give a yellow oil. Flash chromatography (hexane/ethyl acetate 1:1) afforded 444 mg (70%) of a white solid, mp 64–65 °C, with some crystals melting at 76–77 °C: $[\alpha]^{22}_D$ −11.9° (*c* 1.17, $CHCl_3$); 60% ee; ^1H NMR δ 7.17 (t, 1 H, *J* = 8 Hz), 6.91 (d, 1 H, *J* = 9.8 Hz), 6.82 (d, 1 H, *J* = 8 Hz), 6.78 (d, 1 H, *J* = 8 Hz), 5.96 (dd, 1 H, *J* = 9.8, 6.0 Hz), 4.26–4.09 (m, 2 H), 3.84 (s, 3 H), 2.64 (dd, 1 H, *J* = 13.3, 6.7 Hz), 2.04–1.91 (m, 1 H), 1.83–1.73 (m, 1 H), 1.50 (s, 3 H); ^{13}C NMR δ 174.38, 155.38, 136.88, 129.22, 127.53, 120.50, 119.97, 118.17, 110.35, 68.44, 55.79, 47.40, 38.46, 28.05, 25.57; IR (KBr) 3000, 1740, 1590, 1485, 1280, 770 cm^{-1}. Anal. Calcd for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60. Found: C, 73.77; H, 6.66.

2,3,3-Trisubstituted 1-Tetralones 10. By use of the general procedure for tandem alkylation, additions of organolithium reagents to **4** were performed. Cleavage of the oxazolines **6p–s** with methyl triflate and the general procedure given earlier furnished the following chiral 1-tetralones.

Repeated attempts at obtaining elemental analyses on this and the other 1-tetralones **10b–d** failed due to decomposition over 1–2 days. The 270-MHz ^1H and ^{13}C spectra of the freshly prepared material were totally consistent with pure material.

3-*n*-Butyl-4-formyl-4-methyl-1-tetralone [(−)-10a]. A solution of tandem addition adduct **6p** (115.3 mg; 0.3 mmol) in dichloromethane was treated as described in the general procedure for oxazoline removal, followed by flash chromatography (10% THF/hexane) to give 64.6 mg (98%) of the desired product as a colorless oil: $[\alpha]^{25}_D$ −102.0° (*c* 1.6, $CHCl_3$); 94% ee; IR (film) 2945, 2920, 1720, 1690, 1595, 1290, 750 cm^{-1}; ^1H NMR δ 9.84 (s, 1 H), 8.12 (dd, 1 H, *J* = 1.0, 7.8 Hz), 7.59 (dt, 1 H, *J* = 1.0, 6.3 Hz), 7.42 (dt, 1 H, *J* = 1.0, 6.6 Hz), 7.28 (d, 1 H, *J* = 7.8 Hz), 2.92 (dd, 1 H, *J* = 4.7, 17.1 Hz), 2.77 (dd, 1 H, *J* =

10.1, 17.1 Hz), 2.27–2.19 (m, 1 H), 1.61 (s, 3 H), 1.74–1.18 (m, 6 H), 0.88 (t, 3 H, J = 6.7 Hz); ^{13}C NMR δ 201.53, 196.30, 134.14, 132.81, 128.27, 127.96, 127.80, 126.47, 53.32, 43.06, 29.95, 29.80, 22.51, 21.55.

3-*tert*-Butyl-4-formyl-4-methyl-1-tetralone [(+)- and (−)-10b]. Both pure diastereomers of **6q** were treated separately according to the general procedure for oxazoline removal to give identical enantiomers in 98% yield: $[\alpha]^{24}_D$ −145.5° (c 0.46, $CHCl_3$, major isomer); $[\alpha]_D$ 145° (c 0.75, $CHCl_3$, minor isomer); IR (film) 2960, 1720, 1685, 1595, 1450, 1395, 1365, 1290, 1110, 1025, 905, 720 cm^{-1}; ^{1}H NMR δ 10.01 (s, 1 H), 8.05 (dd, 1 H, J = 1.1, 7.7 Hz), 7.58 (dt, 1 H, J = 1.3, 7.7 Hz), 7.40 (t, 1 H, J = 7.7 Hz), 7.18 (d, 1 H, J = 7.8 Hz), 2.98 (dd, 2 H, J = 1.5, 7.1 Hz), 2.27 (t, 1 H, J = 6.5 Hz), 1.68 (s, 3 H), 0.96 (s, 9 H); ^{13}C NMR δ 201.65, 197.40, 129.43, 128.76, 128.05, 127.58, 127.48, 126.96, 54.37, 54.27, 38.73, 30.90, 30.00, 29.54, 26.47.

3-(1-Pentenyl)-4-formyl-4-methyl-1-tetralone [(−)-10c]. A solution of tandem addition adduct **6r** (262 mg, 0.6 mmol) in dichloromethane was treated as described in the general procedure for oxazline removal, followed by flash chromatography (10% THF/hexane) to give 145.9 mg (95%) of the desired product as a colorless oil: $[\alpha]^{25}_D$ −52.9° (c 0.95, $CHCl_3$); 94% ee; IR (film) 2940, 1720, 1685, 1590, 1450, 1300, 910, 760 cm^{-1}; ^{1}H NMR δ 9.83 (s, 1 H), 8.11 (dd, 1 H, J = 1.5, 7.7 Hz), 7.60 (dt, 1 H, J = 1.4, 7.6 Hz), 7.42 (dt, 1 H, J = 1.4, 7.6 Hz), 7.28 (d, 1 H, J = 8.0 Hz), 5.31–5.70 (m, 1 H), 5.03–4.93 (m, 2 H), 2.92 (dd, 1 H, J = 4.8, 17.2 Hz), 2.77 (dd, 1 H, J = 10.2, 17.2 Hz), 2.27–1.39 (m, 7 H), 1.61 (s, 3 H); ^{13}C NMR δ 201.53, 196.32, 137.89, 134.19, 132.65, 127.95, 127.84, 127.3, 115.06, 53.27, 42.83, 39.73, 33.34, 29.58, 26.78, 21.50.

3-(2-Methyl-2-pentenyl)-4-formyl-4-methyl-1-tetralone [(−)-10d]. A solution of tandem addition adduct **6s** (100 mg, 0.22 mmol) in dichloromethane was treated as described in the general procedure for oxazoline removal, followed by flash chromatography (10% THF/hexane) to give 53.5 mg (90%) of the desired product as a colorless oil: $[\alpha]^{25}_D$ −89.26° (c 0.8, $CHCl_3$); IR (film) 2950, 2900, 1710, 1680, 1590, 1440, 1295, 755 cm^{-1}; ^{1}H NMR δ 9.82 (s, 1 H), 8.11 (dd, 1 H, J = 1.5, 7.8 Hz), 7.59 (dt, 1 H, J = 1.5, 7.6 Hz), 7.41 (dt, 1 H, J = 1.5, 7.6 Hz), 7.28 (d, 1 H, J = 7.8 Hz), 5.03 (br t, 1 H), 2.92 (dd, 1 H, J = 4.8, 17.1 Hz), 2.77 (dd, 1 H, J = 10.3, 17.1 Hz), 2.30–1.41 (env, 5 H), 1.66 (s, 3 H), 1.60 (s, 3 H), 1.59 (s, 3 H); ^{13}C NMR δ 201.42, 196.24, 134.14, 132.81, 128.21, 127.79, 127.69, 126.68, 123.03, 53.26, 42.48, 39.78, 30.37, 25.88, 25.52, 21.50, 17.64.

General Procedure for the Addition of Organolithiums to 2-Naphthyloxazoline 11. A solution of the oxazoline **11** (ca. 100 mg, 0.30 mmol) in 3 mL of dry THF under argon was cooled to the indicated temperature and treated with 1.2–2.0 equiv (0.36–0.6 mmol) of the organolithium. A deep red color developed within several hours. After the specified time, the solution was cooled to −78 °C and quenched with an excess of methyl iodide. After the mixture was slowly warmed to room temperature, the THF was removed in vacuo, and the residue was taken up in dichloromethane and washed with water. The water wash was extracted with additional dichloromethane, and the organic phases were combined and dried ($MgSO_4$), and the solvent was removed in vacuo to provide the two diastereomeric products as an oil.

HPLC of the crude diastereomeric mixture was performed on a normal-phase silica column (Du Pont Zorbax, 20% ethyl acetate/hexane, 1 mL/min). The diastereomers were detected by UV absorbance at 254 nm. The diastereomers were separated by radial chromatography on a silica gel rotor (Merck no. 7747) eluted with 20% ethyl acetate/hexane.

Tandem Addition Product 12 (R = *n*-Bu). Treatment of 101 mg (0.318 mmol) of **11** with 0.36 mmol (1.2 equiv) of *n*-butyllithium in THF at −78 °C for 2 h, followed by quenching with methyl iodide (0.45 mL, 0.72 mmol) and standard workup, provided 105.9 mg (0.272 mmol) of two diastereomers. HPLC indicated a diastereomeric ratio of 98:2. Radial chromatography provided 101 mg (0.265 mmol, 85%) of the major diastereomer **12** as an oil: $[\alpha]^{22}_D$ 177.7° (c 4.4, $CHCl_3$); IR (film) 3100, 2900, 1650, 1620 cm^{-1}; ^{1}H NMR δ 0.74 (t, 3 H), 0.9–1.2 (m, 4 H), 1.25 (s, 3 H), 1.4 (m, 2 H), 2.75 (t, 1 H), 3.33 (s, 3 H), 3.49 (dd, 1 H), 3.59 (dd, 1 H), 4.10 (m, 1 H), 5.31 (d, 1 H, J = 6.8 Hz), 6.34 (s, 2 H), 6.9–7.3 (m, 9 H); ^{13}C NMR δ 13.8, 22.7, 23.8, 29.7, 30.7, 43.1, 47.2, 59.2, 74.5, 74.8, 83.4, 125.5, 125.7, 126.5, 128.0, 128.7, 129.5, 131.8, 132.5, 137.1, 141.4, 171.4. Anal. Calcd for $C_{26}H_{31}NO_2$: C, 80.17; H, 8.02; N, 3.60. Found: C, 79.77; H, 8.00; N, 3.41.

Tandem Addition Product 12 (R = Me). Treatment of 48 mg (0.152 mmol) of **11** in 3 mL of THF with 0.32 mmol (2 equiv) of methyllithium in hexane at −30 °C for 15 h, followed by quenching with 0.019 mL (0.304 mmol) of methyl iodide and normal workup, gave 35.6 mg (0.123 mmol) of two diastereomers in a yield of 67%. HPLC indicated a diastereomeric ratio of 91:9. Radial chromatography provided the pure major diastereomer **12** as an oil: $[\alpha]^{22}_D$ 151.6° (c 1.2, $CHCl_3$); IR (film) 3020, 2980, 1665, 1630, 1600, 1490, 1450 cm^{-1}; ^{1}H NMR δ 1.05 (d, 3 H, J = 7 Hz), 1.27 (s, 3 H), 3.00 (m, 1 H), 3.31 (s, 3 H), 3.42 (dd, 1 H), 3.59 (dd, 1 H), 4.10 (m, 1 H), 5.29 (d, 1 H, J = 7 Hz), 6.28 (d, 1 H, J = 9.7 Hz), 6.38 (d, 1 H, J = 9.7 Hz), 6.95–7.30 (m, 9 H). The minor diastereomer showed the following: ^{1}H NMR δ 1.05 (d, 3 H, J = 7 Hz), 1.33 (s, 3 H), 2.06 (q, 1 H), 3.31 (s, 3 H), 3.42 (dd, 1 H), 3.59 (dd, 1 H), 4.10 (m, 1 H), 4.54 (d, 1 H, J = 7 Hz), 6.28 (d, 1 H, J = 9.7 Hz), 6.38 (d, 1 H, J = 9.7 Hz), 6.95–7.30 (m, 9 H); ^{13}C NMR (diastereomeric mixture) δ 18.17, 24.00, 35.56, 42.00, 42.64, 59.14, 66.74, 74.57, 74.71, 81.11, 83.49, 124.41, 124.42, 124.67, 125.42, 125.57, 125.90, 126.21, 126.42, 126.63, 127.54, 127.64, 127.96, 128.28, 128.70, 131.70, 139.26, 170.97. Anal. Calcd for diastereomeric mixture $C_{23}H_{25}NO_2$: C, 79.51; H, 7.25; N, 4.03. Found: C, 79.69; H, 7.39; N, 3.95.

Tandem Addition Product 12 (R = Ph). Treatment of 75.8 mg (0.239 mmol) of **11** in 3 mL of THF at −30 °C with 0.478 mmol of phenyllithium in ether for 15 h, followed by quenching with 0.30 mL (0.478 mmol) of methyl iodide and normal workup, provided two diastereomers as an oil. Radial chromatography of the mixture provided two pure diastereomers with a combined mass of 87.2 mg (0.213 mmol) for a yield of 89%. The major diastereomer **12** crystallized on standing: mp 133–134 °C; $[\alpha]^{22}_D$ +423° (c 0.33, $CHCl_3$); IR (film) 3300, 2930, 1665, 1600, 1490, 1450 cm^{-1}; ^{1}H NMR δ 1.59 (s, 3 H), 2.26 (t, 1 H, J = 9 Hz), 3.00 (d, 1 H), 6.45 (d, 1 H), 6.62 (d, 1 H), 7.05–7.45 (m, 14 H); ^{13}C NMR δ 25.35, 43.76, 53.79, 58.79, 73.77, 74.67, 83.87, 125.31, 126.43, 126.69, 126.79, 127.11, 127.99, 128.54, 128.75, 129.65, 131.60, 132.18, 136.20, 141.07, 141.80, 170.07.

Minor diastereomer: ^{1}H NMR δ 1.52 (s, 3 H), 3.34 (s, 3 H), 3.38 (dd, 1 H), 3.53 (dd, 1 H), 3.87 (m, 1 H), 4.15 (s, 1 H), 4.98 (d, 1 H), 6.59 (s, 1 H), 6.72 (dd, 1 H), 7.20–7.45 (m, 14 H). No elemental analysis was recorded since this was the X-ray sample (Figure 1B).

Tandem Addition Product 12 (R = *t*-Bu). A solution of 68.6 mg (0.216 mmol) of **11** and 3 mL of THF at −100 °C was treated with 0.432 mmol (2 equiv) of *tert*-butyllithium in pentane and held for 1.5 h. The deep red solution was slowly warmed to −78 °C and quenched with 0.864 mmol (0.054 mL) of methyl iodide and allowed to warm to room temperature. Normal workup provided two diastereomers as an oil. HPLC analysis indicated a diastereomeric ratio of 73:27. Radial chromatography provided the pure major diastereomer **12** and the minor diastereomer contaminated with the major diastereomer. The two diastereomers had a combined mass of 62.6 mg (0.161 mmol) for a yield of 74%. The major diastereomer exhibited the following physical and spectral characteristics: ^{1}H NMR δ 0.84 (s, 9 H), 1.27 (s, 3 H), 3.34 (s, 3 H), 3.53 (dd, 1 H), 3.70 (dd, 1 H), 4.10 (m, 1 H), 5.22 (d, 1 H, J = 8.4 Hz), 6.32 (d, 1 H, J = 9.7 Hz), 6.57 (d, 1 H, J = 9.7 Hz), 6.9–7.3 (m, 9 H); IR (film) 2900, 1645, 1600, 1470, 1440; $[\alpha]^{22}_D$ 208.2° (c 1.1, $CHCl_3$); ^{13}C NMR δ 27.7, 30.5, 36.3, 56.7, 59.2, 74.1, 74.9, 83.9, 125.7, 126.0, 126.5, 126.8, 128.0, 128.7, 131.6, 133.6, 134.4, 135.5, 141.1, 172.7. Anal. Calcd for diastereomeric mixture $C_{21}H_{30}NO_2$ (389.5): C, 80.17; H, 8.02; N, 3.60. Found: C, 80.05; H, 8.01; N, 3.63.

(*S*)-1-*n*-Butyl-2-methyl-2-formyl-1,2-dihydronaphthalene [13 (R = *n*-Bu)]. The pure diastereomer **12** (82.9 mg, 0.213 mmol) was dissolved in 2 mL of dichloromethane and treated with 2 equiv (0.060 mL, 0.74 mmol) of methyl triflate and allowed to stir at room temperature for 15 h. The solution was then cooled to 0 °C and treated with a solution of 4.0 equiv (32 mg, 0.850 mmol) of sodium borohydride in 2 mL of ethanol at 0 °C. Normal hydrolysis and workup followed by radial chromatography provided 39.4 mg (0.172 mmol) of the pure aldehyde as an unstable oil in 81% yield: $[\alpha]^{22}_D$ 190.8° (c 0.98, $CHCl_3$); ^{1}H NMR δ 0.80 (t, 3 H), 1.08 (s, 3 H), 1.2–1.6 (m, 6 H), 2.80 (d, 1 H), 6.52 (d, 1 H), 7.05–7.30 (m, 4 H), 9.65 (s, 1 H). Instability of the aldehyde prevented elemental analysis.

(*S*)-1,2-Dimethyl-2-formyl-1,2-dihydronaphthalene [13 (R = Me)]. Use of procedure above provided 25.4 mg (0.136 mmol) of the pure aldehyde as an unstable oil in 65% yield: $[\alpha]^{22}_D$ −85.83° (c 0.51, $CHCl_3$); IR (film) 2960, 2705, 1725; ^{1}H NMR δ 1.09 (d, 3 H), 1.11 (s, 3 H), 3.06 (q, 1 H), 6.00 (d, 1 H), 6.58 (d, 1 H), 7.05–7.25 (m, 4 H), 9.60 (s, 1 H). Instability of the aldehyde prevented elemental analysis.

(*S*)-1-Phenyl-2-methyl-2-formyl-1,3-dihydronaphthalene [13 (R = Ph)]. Use of the procedure above provided 25.9 mg (0.104 mmol) of the pure aldehyde as an unstable oil in 83% yield as a solid: mp 98–101 °C; $[\alpha]^{22}_D$ −333.59° (c 0.52, $CHCl_3$); ^{1}H NMR δ 1.20 (s, 3 H), 4.30 (s, 1 H), 6.00 (d, 1 H), 6.80 (d, 1 H), 7.00 (d, 1 H), 7.1–7.4 (m, 8 H), 9.65 (s, 1 H). Instability of the aldehyde prevented elemental analysis.

(*S*)-1-*tert*-Butyl-2-methyl-2-formyl-1,2-dihydronaphthalene [13 (R = *t*-Bu)]. From the procedure above was obtained 19.6 mg (0.086 mmol) of the pure aldehyde as an unstable oil in 70% yield: $[\alpha]^{25}_D$ +244.4° (c 0.66, $CHCl_3$); IR (film) 2955, 2705, 1725; ^{1}H NMR δ 0.83 (s, 3 H), 0.84 (s, 9 H), 2.76 (s, 1 H), 6.45 (s, 2 H), 7.0–7.3 (m, 4 H). Instability prevented elemental analysis.

General Procedure for Tandem Addition–Proton Quench to Carbinols 17. A flame-dried flask under Ar containing a well-stirred 0.08 M THF

solution of 317 mg (1.0 mmol) of **1**, or 347 mg (1.0 mmol) of **2** for ethyllithium addition, was cooled to the indicated temperature and treated with the equivalents of alkyllithium shown (with MeLi, 3 equiv of HMPA was added prior to alkyllithium addition). The solutions became deep red over the time period indicated and were quenched by the dropwise addition of 4–5 equiv of distilled trifluoroacetic acid in 3 mL of dry THF, producing a pale yellow solution instantly. After 20 min, the solutions were diluted with 60 mL of ether and washed with 5 mL of saturated aqueous NH_4Cl, followed by 3 mL of saturated of aqueous NaCl. The combined aqueous layers were back-extracted with 120 mL of CH_2Cl_2, and the combined extracts were dried as a vigorously stirred solution over powdered anhydrous Na_2SO_4, to which 10 drops of water had been added. Hydrolysis of the oxazoline to the ester ammonium salt **15** occurred within 2–4 h, as evidenced by TLC base-line salts. Concentration of the filtrate in vacuo gave a yellow, viscous oil.

To a well-stirred suspension of 76 mg (2.0 mmol) of lithium aluminum hydride in 10 mL of dry ether under Ar at 23 °C was added dropwise a solution of crude ester ammonium salts **15** in 10 mL of dry ether over a period of 20 min, producing vigorous gas evolution (H_2). After 45 min, the mixture was quenched by the slow, dropwise addition of 76 μL of water, followed by 76 μL of 10% aqueous NaOH and 3 × 76 μL of water. The resulting suspension was stirred for 3 h and then filtered through a $^1/_2$-in. bed of Celite. Concentration in vacuo gave a pale yellow, viscous oil. Flash filtration through silica gel (hexane/EtOAc, 4:1) followed by radial chromatography (Chromatotron, hexane/EtOAc, 4:1) provided pure primary alcohols **17**. Aliquots of **17** were further purified by PLC (0.25 mm silica gel plates, E. Merck) for elemental analysis[28] and optical rotation determinations. For percent ee determination, the Mosher esters[12] or thiophosphonate derivatives[11] were prepared according to the published procedures, and analyses were performed by ^{19}F or ^{31}P NMR spectroscopy, respectively.

(+)-*trans*-1-(Hydroxymethyl)-2-*n*-butyl-1,2-dihydronaphthalene [17 (R = *n*-Bu, R′ = H)]. Addition of 1.2 equiv of *n*-butyllithium at −78 °C or 2.5 h prior to quenching with TFA gave the product as an oil, after silica gel chromatography: $[\alpha]^{22}_D$ 366° (*c* 1.23, $CHCl_3$); 90% ee; IR (film) 3500–3200 (br –OH), 1485, 1450, 1050, 785, 745 cm^{-1}; ^1H NMR δ 7.2–7.0 (m, 4 H), 6.36 (d, 1 H, *J* = 9.7 Hz), 5.94 (dd, 1 H, *J* = 9.6, 6.1 Hz), 3.56 (m, 2 H), 2.80 (t, 1 H, *J* = 7.4 Hz), 2.38 (m, 1 H), 1.6 (br s, 1 H, OH), 1.4–1.2 (m, 6 H), 0.85 (t, 3 H, *J* = 6.9 Hz); ^{13}C NMR (68 MHz) δ 134.6, 133.2, 131.6, 129.4, 127.2, 126.4, 125.8, 65.9, 46.2, 35.6, 33.8, 29.2, 22.8, 13.8; ^{31}P NMR (81 MHz, of thiophosphonate derivative) minor δ 83.73 (5%), major δ 83.58 (95%). Anal. Calcd for $C_{15}H_{20}O$: C, 83.28,; H, 9.32. Found: C, 82.81; H, 9.52.

(+)-*trans*-1-(Hydroxymethyl)-2-phenyl-1,2-dihydronaphthalene [17 (R = Ph, R′ = H)]. Addition of 2.2 equiv of phenyllithium at −45 °C for 3 h prior to quenching with TFA gave the product as a glass after silica gel chromatography: $[\alpha]^{26}_D$ +392° (*c* 1.1, $CHCl_3$); 70% ee; IR (film) 3500–3200 (br, –OH), 1595, 1490, 1445, 1045, 1020, 770, 745, 690 cm^{-1}; ^1H NMR δ 7.3–7.1 (m, 8 H), 6.98 (d, 1 H, *J* = 7.3 Hz), 6.57 (d, 1 H, *J* = 9.5 Hz), 5.94 (dd, 1 H, *J* = 9.5, 5.7 Hz), 3.95 (d, 1 H, *J* = 5.6 Hz), 3.64 (m, 2 H), 3.03 (t, 1 H, *J* = 7.1 Hz), 2.04 (br s, 1 H, OH); ^{13}C NMR (68 MHz) δ 143.2, 133.3, 129.4, 129.0, 128.5, 128.1, 127.5, 127.3, 127.0, 126.5, 66.0, 48.8, 41.7; ^{19}F NMR (188 MHz, of Mosher ester) minor δ −71.71 (15%), major δ −71.80 (85%). Anal. Calcd for $C_{17}H_{16}O$: C, 86.40; H, 6.82. Found: C, 85.43; H, 6.31.

(+)-*trans*-1-(Hydroxymethyl)-2-methyl-1,2-dihydronaphthalene [17 (R = Me, R′ = H)]. Addition of 3.0 equiv of methyllithium and 3.0 equiv of HMPA at −45 °C for 3 h prior to quenching with TFA gave the product as an oil after silica gel chromatography: $[\alpha]^{24}_D$ 307° (*c* 0.68, $CHCl_3$); 72% ee; IR (film) 3600–3100 (br, –OH), 1485, 1450, 1365, 1030, 780, 750 cm^{-1}; ^1H NMR δ 7.2–7.0 (m, 4 H), 6.35 (d, 1 H, *J* = 9.6 Hz), 5.91 (dd, 1 H, *J* = 9.7, 5.9 Hz), 3.58 (d, 2 H, *J* = 7.3 Hz), 2.74 (t, 1 H, *J* = 7.4 Hz), 2.53 (m, 1 H), 1.4 (br s, 1 H, OH), 1.00 (d, 3 H, *J* = 7.0 Hz); ^{13}C NMR (68 MHz) δ 134.1, 132.6, 129.5, 127.3, 126.5, 125.5, 65.7, 48.1, 30.4, 19.2; ^{19}F NMR (188 MHz, of Mosher ester) major δ −71.92 (86%), minor δ −72.02 (14%).

(+)-*trans*-1-(Hydroxymethyl)-2-ethyl-6-methoxy-1,2-dihydronaphthalene [17 (R = Et, R′ = MeO)]. Addition of 1.5 equiv of ethyllithium at −78 °C for 3 h prior to quenching with TFA gave needles from pentane: mp 59–61 °C; $[\alpha]^{26}_D$ 250° (*c* 0.66, $CHCl_3$); 94% ee. This sample was subjected to single-crystal X-ray analysis (Figure 1C): IR (film) 3600–3100 (br, –OH), 1560, 1455, 1255, 1030, 750 cm^{-1}; ^1H NMR δ 7.12 (t, 1 H, *J* = 7.9 Hz), 6.8–6.7 (m, 3 H), 5.95 (dd, 1 H, *J* = 9.8, 6.1 Hz), 3.82 (s, 3 H), 3.57 (m, 2 H), 2.80 (t, 1 H, *J* = 7 Hz), 2.27 (m, 1 H), 1.4 (br s, 1 H, –OH), 1.4–1.2 (m, 2 H), 0.90 (t, 3 H, *J* = 7.5 Hz); ^{13}C NMR (68 MHz) δ 136.0, 130.1, 127.7, 122.1, 119.6, 109.9, 65.8, 55.6, 46.1, 37.0, 26.9, 11.4; ^{31}P NMR (81 MHz, of thiophosphonate derivative) minor δ 83.73 (<3%), major δ 83.54 (>97%).

(+)-*trans*-1-(Hydroxymethyl)-2-isopropyl-1,2-dihydronaphthalene [17 (R = *i*-Pr, R′ = H)]. Addition of 1.2 equiv of isopropyllithium at −78 °C for 2.5 h prior to quenching with TFA gave an oil, after silica gel chromatography: $[\alpha]^{23}_D$ 372° (*c* 1.0, $CHCl_3$); 92% ee; IR (film) 3600–3100 (br, –OH), 1485, 1460, 1380, 1360, 1045, 775, 740 cm^{-1}; ^1H NMR δ 7.15–6.95 (m, 4 H), 6.42 (d, 1 H, *J* = 9.7 Hz), 5.87 (dd, 1 H, *J* = 9.7, 6.0 Hz), 3.50 (m, 2 H), 2.90 (t, 1 H, *J* = 7.3 Hz), 2.16 (t, 1 H, *J* = 6.1 Hz), 2.0 (br s, 1 H, OH), 1.7–1.55 (m, 1 H), 0.84 (d, 3 H, *J* = 6.8 Hz), 0.83 (d, 3 H, *J* = 6.7 Hz); ^{13}C NMR (68 MHz) δ 135.3, 133.4, 129.6, 128.9, 127.1, 127.0, 126.6, 126.3, 66.4, 43.8, 42.1, 32.5, 20.0, 19.6; ^{31}P NMR (81 MHz, of thiophosphonate derivative) minor δ 83.77 (4%), major δ 83.61 (96%). Anal. Calcd for $C_{14}H_{18}O$: C, 83.12; H, 8.97. Found: C, 82.39; H, 9.54.

Threonine-Based Oxazolines Synthesis of 18 (Entries 3 and 5) and 20 (Entry 11). (4*R*,5*R*)-2-(2-Naphthyl)-4-(methoxymethyl)-5-methyl-2-oxazoline (18) (Entry 3, Table VI). β-Cyanonaphthalene (0.310 g, 2.02 mmol) was dissolved in 20 mL of absolute ethanol and sparged with dry HCl gas until the solution boiled. The flask was sealed and allowed to stand for 15 h after which the ethanol was removed by distillation at atmospheric pressure. The oil remaining was triturated with ether to precipitate the imino ester hydrochloride, and the slurry was filtered to remove ether and unreacted β-cyanonaphthalene. The crude imino ester hydrochloride was dissolved in 25 mL of chloroform containing 240 mg (2.02 mmol) of (2*R*,3*R*)-1-(methoxymethyl)-2-amino-3-hydroxybutane-,[13,29] and the solution was heated to reflux and held at this temperature for 24 h. The mixture was cooled and filtered to remove precipitated ammonium chloride. The chloroform solution was washed with brine and dried ($MgSO_4$), and the solvent was removed by rotary evaporation and then high vacuum to provide 0.515 g (2.0 mmol) of product as an oil in 96% yield: $[\alpha]^{22}_D$ 50.0° (*c* 0.72, $CHCl_3$); ^1H NMR δ 1.48 (d, 3 H, *J* = 6.3 Hz), 3.41 (s, 3 H), 3.48 (dd, 1 H), 3.69 (dd, 1 H), 4.03 (m, 1 H), 4.68 (d, 1 H, *J* = 6.3 Hz), 7.53–8.45 (m, 7 H); ^{13}C NMR δ 20.87, 59.14, 73.29, 74.83, 79.57, 124.89, 125.00, 126.36, 127.32, 127.64, 127.85, 132.76, 134.77, 164.06. Anal. Calcd for $C_{16}H_{17}NO_2$ (255.3): C, 75.27; H, 6.71; N, 5.49. Found: C, 75.39; H, 6.00; N, 5.49.

(4*R*,5*S*)-2-(2-Naphthyl)-4-(methoxymethyl)-5-methyl-2-oxazoline (18) (Entry 5, Table VI). A solution of 2-naphthoic acid (290 mg, 1.68 mmol), carbon tetrachloride (0.53 mL, 5 mmol), triethylamine (0.70 mL, 5 mmol), and amino alcohol[13,29] (0.200 g, 1.68 mmol) in 8 mL of 50% pyridine/acetonitrile was treated dropwise with 1.32 g (5.00 mmol) of triphenylphosphine dissolved in 10 mL of pyridine. After being stirred for 15 h, the dark mixture was filtered to remove precipitated triphenylphosphine oxide, and the filtrate was concentrated by rotary evaporation. The black resin was dissolved in a minimum amount of chloroform and added dropwise to a rapidly stirred slurry of 2 g of Celite in 50 mL of ether. The suspension was filtered and the Celite washed with an additional 20 mL of ether. The filtrate was concentrated by rotary evaporation, and the light brown oil was chromatographed (Merck no. 7747, 30% ethyl acetate/hexane) to provide 0.320 g (1.25 mmol) as an oil in 75% yield: $[\alpha]^{22}_D$ 80.54° (*c* 1.5, $CHCl_3$); ^1H NMR δ 1.46 (d, 3 H), 3.41 (s, 3 H), 3.59 (dd, 1 H), 3.72 (dd, 1 H), 4.45 (m, 1 H), 5.00 (m, 1 H), 7.53–8.45 (m, 7 H); IR (film) 3060, 2920, 1645, 1625, 740 cm^{-1}; ^{13}C NMR δ 14.60, 20.82, 58.87, 59.11, 67.58, 71.45, 74.72, 78.59, 79.69, 124.83, 125.20, 126.37, 127.37, 127.64, 127.90, 128.81, 132.70, 134.82, 164.27. Anal. Calcd for $C_{16}H_{17}NO_2$ (255.3): C, 75.27; H, 6.71; N, 5.49. Found: C, 75.18; H, 6.58; N, 5.89.

(4*R*,5*S*)-2-(1-Naphthyl)-4-(methoxymethyl)-5-methyl-2-oxazoline (20) (Entry 11, Table VI). A solution of 1-naphthoic acid (0.500 g, 2.90 mmol), carbon tetrachloride (0.92 mL, 8.70 mmol), triethylamine (1.21 mL, 8.70 mmol), and amino alcohol[13,29] (0.346 g, 2.90 mmol) in 10 mL of 50% pyridine/acetonitrile was treated dropwise with 2.28 g (8.70 mmol) of triphenylphosphine dissolved in 15 mL of pyridine. After being stirred for 15 h, the dark mixture was filtered to remove precipitated triphenylphosphine oxide, and the filtrate was concentrated by rotary evaporation. The black resin was dissolved in a minimum amount of chloroform and added dropwise to a rapidly stirred slurry of 3 g of Celite in 100 mL of ether. The suspension was filtered and the Celite washed with an additional 50 mL of ether. The filtrate was concentrated by rotary evaporation, and the light brown oil was chromatographed (Merck no. 7747, 30% ethyl acetate/hexane) to provide 0.577 g (2.26 mmol) of **20** as an oil in 78% yield: $[\alpha]^{22}_D$ 22.34° (*c* 1.0, $CHCl_3$); IR (film) 3015, 2900, 1700, 1630, 1605, 1580 cm^{-1}; ^1H NMR δ 9.03 (d, 1 H, *J* = 7.8 Hz), 8.06 (dd, 1 H, *J* = 1.1, 7.2 Hz), 7.93 (d, 1 H, *J* = 8.2 Hz), 7.85

(28) The chiral carbinols **17** (R′ = H) were all highly viscous oils, approaching a glass, and could not be completely freed of traces of trapped solvents even after extensive evacuation. Heating during evacuation was precluded due to oxidation to naphthalenes. Because of this, the elemental analyses are slightly out of the range of acceptable values.

(29) Details for the preparation of the methoxyamino alcohol are available in the Ph.D. Thesis of D. Hoyer, Colorado State University, 1988.

(d, 1 H, J = 7.3 Hz), 7.61–7.44 (m, 3 H), 5.03–4.97 (m, 1 H), 4.59–4.54 (m, 1 H), 3.79 (dd, 1 H, J = 4.7, 9.7 Hz), 3.64–3.61 (m, apparent dd, 1 H), 3.42 (s, 3 H), 1.49 (d, 3 H, J = 6.6 Hz); ^{13}C NMR δ 14.53, 58.84, 68.22, 71.50, 124.47, 124.93, 125.89, 126.47, 127.05, 128.22, 128.85, 131.23, 131.66, 133.76, 164.11. Anal. Calcd for $C_{16}CH_{17}NO_2$ (255.3): C, 75.27; H, 6.71; N, 5.49. Found: C, 75.39; H, 6.89; N, 5.49.

(+)-Phyltetralin. Ethyl 3-Methyl-4,4-dimethoxybutyrate (24). Triethyl phosphonoacetate (27.37 g, 122 mmol, Aldrich) was added dropwise to a slurry of 3.0 g (125 mmol) of sodium hydride in 250 mL of THF, resulting in vigorous hydrogen evolution. After stirring 2 h, 14.42 g (122 mmol) of freshly distilled pyruvic aldehyde dimethyl acetal (Aldrich) was added dropwise with vigorous stirring. At the end of the addition, the solution turned to a gel. The flask was shaken and allowed to stand 15 h. Water (2 mL) was added, causing a phase separation. The THF was removed by rotary evaporation, and the resultant oil was diluted with ether and washed with dilute aqueous sodium bicarbonate. The ether layer was dried (K_2CO_3), and the solvent was removed by rotary evaporation to give an oil. The crude product was dissolved in 250 mL of absolute ethanol and hydrogenated over 450 mg of 10% Pd on carbon for 10 h. The solution was filtered through Celite and distilled (77–80 °C, 4.2 mm) to give 17.0 g (89 mmol, 71%) of **24** as a colorless oil. This acetal did not store well and was used soon after preparation: ^{1}H NMR δ 0.96 (s, 3 H), 1.26 (t, 3 H), 2.21 (dd, 1 H), 2.31 (m, 1 H), 2.48 (dd, 1 H), 3.35 (s, 3 H), 3.36 (s, 3 H), 4.10 (d, 1 H), 4.13 (q, 2 H).

2-(Ethoxycarbonyl)-3-methyl-6,7-dimethoxynaphthalene (25). Lithium diisopropylamide was generated in 100 mL of THF at −78 °C by treating 10.6 mL (75.6 mmol) of diisopropylamine with 63.3 mmol of *n*-butyllithium in 37 mL of hexane. After the mixture was stirred for 1 h, 12.00 g (63.1 mmol) of acetal **24** was added dropwise. After an additional hour at −78 °C, veratraldehyde was added (10.3, 62.0 mmol) dropwise in a minimum amount of THF. The solution was allowed to warm to room temperature and quenched with 1.5 mL of water, and the THF was removed by rotary evaporation. The residue was diluted with ether and washed with brine. The ether was removed by rotary evaporation, the oil was dissolved in a small amount of methanol and added dropwise to 500 mL of 3.6 M sulfuric acid, and the mixture was heated to reflux. After 2 h, the mixture was cooled and extracted with ether. The crude ether extract was washed with 20 mL of 1 M aqueous sodium hydroxide to remove contaminating 3-methyl-6,7-dimethoxynaphthoic acid. The ether was dried ($MgSO_4$), and the solvent was removed by rotary evaporation and then high vacuum to give 13.8 g (50.3 mmol) of the naphthalene **25** in 81% yield: mp 105–106 °C; ^{1}H NMR δ 1.43 (t, 3 H), 2.69 (s, 3 H), 3.99 (s, 3 H), 4.01 (s, 3 H), 4.39 (q, 2 H), 7.04 (s, 1 H), 7.51 (s, 1 H), 8.35 (s, 1 H). Anal. Calcd for $C_{16}H_{18}O_4$ (274.3): C, 70.06; H, 6.61. Found: C, 70.07; H, 6.63.

2-(Ethoxycarbonyl)-3-(bromomethyl)-6,7-dimethoxynaphthalene (26). A solution of 5.0 g (18.2 mmol) of **25** was heated to reflux in 500 mL of 85% carbon tetrachloride/hexane and treated with 3.24 g (18.2 mmol) of *N*-bromosuccinimide added in small portions over 8 h. After being heated to reflux for 24 h, the suspension was cooled and filtered to remove succinimide. The filtrate was concentrated by rotary evaporation and dissolved in 200 mL of methanol, resulting in the precipitation of the bromide. The mixture was filtered to obtain the bromide, and the filtrate was reduced in volume by half and cooled in an ice bath. Filtration gave additional bromide, which was combined with the first crop, washed with a small amount of cold methanol, and dried under vacuum to provide 5.21 g (14.7 mmol) of bromide **26** in 80% yield: mp 133–133.5 °C; ^{1}H NMR δ 1.47 (t, 3 H), 4.01 (s, 3 H), 4.02 (s, 3 H), 4.45 (q, 2 H), 5.13 (s, 2 H), 7.10 (s, 1 H), 7.18 (s, 1 H), 7.74 (s, 1 H), 8.41 (s, 1 H). Anal. Calcd for $C_{16}H_{17}BrO_4$ (353.3): C, 54.40; H, 4.87; Br, 22.60. Found: C, 54.64;, H, 4.75; Br, 22.64.

2-Carboxy-3-(methoxymethyl)-6,7-dimethoxynaphthalene (27). A solution of 607 mg (1.72 mmol) of bromide **26** in 30 mL of dry methanol containing 1.0 g of potassium carbonate was stirred for 24 h. The methanol was removed by rotary evaporation, and the residue was taken up in chloroform and washed with brine. The chloroform was removed by rotary evaporation, and the crude ester was hydrolyzed by being heated to reflux in 20 mL of 2 M aqueous sodium hydroxide for 1 h. The solution was cooled and neutralized with concentrated HCl to precipitate the acid. The suspension was extracted with ethyl acetate, the organic phase was separated and dried (Na_2SO_4), and the solvent was removed by rotary evaporation and then high vacuum to provide 0.466 g (1.67 mmol) of **27** as a white solid in 98% yield. The acid begins subliming at 190 °C: ^{1}H NMR δ 3.55 (s, 3 H), 4.02 (s, 3 H), 4.03 (s, 3 H), 4.94 (s, 2 H), 7.15 (s, 1 H), 7.21 (s, 1 H), 7.83 (s, 1 H), 8.54 (s, 1 H). Anal. Calcd for $C_{15}H_{16}O_5$ (276.28): C, 65.21; H, 5.84. Found: C, 64.92; H, 5.70.

L-*trans*-Threonine Oxazoline 23. A solution of 585 mg (2.10 mmol) of **27**, 1.50 g (6.30 mmol) of carbon tetrachloride, 1.30 mL (9.4 mmol) of triethylamine, and 250 mg (2.10 mmol) of amino alcohol[13,29] was dissolved in 50 mL of pyridine/acetonitrile. Triphenylphosphine (1.65 g, 6.30 mmol) dissolved in 5 mL of pyridine was added over 2 h by syringe pump, giving a dark brown mixture. The mixture was filtered to remove precipitated triphenylphosphine oxide, and the filtrate was concentrated by rotary evaporation to a brown oil. The oil was dissolved in a small amount of chloroform and added dropwise to a rapidly stirred suspension of 10 g of Celite in 200 mL of ether. The ether was filtered to remove Celite and polymer and washed with additional ether. The ether was removed by rotary evaporation, and the light oil was dissolved in a small amount of methanol and added to 100 mL of rapidly stirred 1 M HCl at 0 °C. After being stirred for 10 min, the acid was extracted with three 20-mL portions of ether to remove traces of triphenylphosphine oxide. The acid solution was basified by adding in one portion 5.0 g (100 mmol) of sodium hydroxide, which gave an immediate precipitate of oxazoline as a white oily solid. The oxazoline was extracted with ether, the organic phase was separated and dried ($MgSO_4$), and the ether was removed by rotary evaporation and then high vacuum to provide 566 mg (1.57 mmol) of pure **23** as an oil in 75% yield: $[\alpha]^{22}_D$ 26.34° (c 0.56, $CHCl_3$); ^{1}H NMR δ 1.47 (d, 3 H, 6, J = 3, Hz), 3.42 (s, 3 H), 3.43 (dd, 1 H), 3.50 (s, 3 H), 3.69 (dd, 1 H), 3.99 (s, 3 H), 4.03 (m, 1 H), 4.63 (m, 1 H), 4.94 (s, 2 H), 7.12 (s, 1 H), 7.14 (s, 1 H), 7.85 (s, 1 H), 8.25 (s, 1 H); ^{13}C NMR δ 20.71, 55.68, 58.19, 58.98, 72.93, 73.56, 74.83, 78.59, 106.86, 122.56, 125.04, 127.47, 128.80, 130.38, 133.83, 149.74, 150.00, 151.05, 163.85. Anal. Calcd for $C_{20}H_{25}NO_5$ (359.4): C, 66.84; H, 7.01; N, 3.90. Found: C, 66.81; H, 6.96; N, 3.77.

Veratrole Adduct 28. Generation of 4-lithioveratrole was performed at −78 °C by treatment of 197 mg (0.907 mmol) of 4-bromoveratrole (Aldrich) in 5 mL of THF with 1.81 mmol of *tert*-butyllithium in 1 mL of pentane. The oxazoline **23** (156.9 mg, 0.436 mmol) was dissolved in 2 mL of THF and added dropwise to the cold solution of 4-lithioveratrole. The solution was quickly warmed to −20 °C and held for 15 h, after which time the azaenolate was quenched with 0.10 mL of 2-propanol and allowed to warm to room temperature. After standing for 4 h, the solution was treated with 0.100 mL of water, and the THF was removed by rotary evaporation. The residue was taken up in dichloromethane and washed with brine. The organic phase was separated, dried (Na_2SO_4), and concentrated by rotary evaporation to give a viscous oil. Column chromatography (58 μm large pore silica, Alfa, 4% methanol/dichloromethane) gave 156 mg (0.313 mmol) of **28** as a resin in 72% yield. This material rapidly decomposes on standing and was best stored frozen in benzene: $[\alpha]^{22}_D$ −26.85° (c 0.55, $CHCl_3$); ^{1}H NMR δ 1.19 (d, 3 H, J = 6.3 Hz), 3.04 (s, 3 H), 3.26 (s, 3 H), 3.38 (m, 1 H), 3.57 (d, 1 H, J = 6 Hz), 3.65 (m, 1 H), 3.75 (s, 3 H), 3.81 (s, 3 H), 3.84 (s, 3 H), 3.89 (s, 3 H), 3.90 (d, 1 H), 4.17 (d, 1 H, J = 13 Hz), 4.39 (t, 1 H), 4.46 (d, 1 H, J = 6 Hz), 6.5–6.9 (m, 6 H); ^{13}C NMR δ 20.66, 43.49, 46.76, 55.95, 57.34, 58.95, 72.28, 74.21, 74.41, 79.01, 110.56, 111.09, 111.46, 112.17, 112.39, 120.71, 125.89, 126.16, 128.30, 128.66, 131.60, 135.46, 148.03, 148.72, 149.04, 167.23; IR (film) 2920, 2820, 1650, 1600, 1510 cm^{-1}. Anal. Calcd for $C_{28}H_{35}NO_7$ (497.6): C, 67.59; H, 7.09; N, 2.81. Found: C, 66.45; H, 6.90; N, 2.27. The sensitive nature of this material prevented satisfactory elemental analysis. This material was immediately carried on to the next intermediate, **30**.

Carbinol 30. A solution of 156 mg (0.313 mmol) of **28** in 5 mL of THF was treated with 3 g (21 mmol) of anhydrous sodium sulfate, 0.159 mL (2.01 mmol, 6.6 equiv) of trifluoroacetic acid, and 0.413 mL (23 mmol) of water and stirred rapidly for 4 h. The slurry was then stirred with 1.0 g of anhydrous magnesium sulfate to remove dissolved water, followed by filtration to remove inorganic salts. The salts were washed with additional THF, and the filtrate containing **29** was collected and reduced to ca. 1 mL of a pale yellow solution by rotary evaporation at 20 °C. This solution was added dropwise to a slurry of 88 mg (2.3 mmol) of LAH in 5 mL of THF at 0 °C. The solution was then warmed to room temperature, diluted with 50 mL of ether, and treated sequentially with 0.90 mL of water, 0.90 mL of 15% aqueous sodium hydroxide, and 2.70 mL of water. The suspension was filtered to remove aluminum hydroxide, and the filtrate was concentrated to an oil by rotary evaporation. The oil was taken up in dichloromethane and washed with water to remove the liberated amino alcohol.[13,29] The dichloromethane extract was dried ($MgSO_4$), and the solvent was removed by rotary evaporation and then high vacuum to provide 108 mg (0.269 mmol) of **30** as a colorless resin in 86% yield: $[\alpha]^{22}_D$ −51.78° (c 0.84, $CHCl_3$); ^{1}H NMR δ 2.61 (m, 1 H), 2.68 (br s, 1 H), 3.21 (s, 3 H), 3.60 (m, 1 H), 3.7–3.9 (m, 3 H), 3.79 (s, 3 H), 3.80 (s, 3 H), 3.82 (s, 3 H), 3.90 (s, 3 H), 3.98 (d, 1 H, J = 12 Hz), 4.13 (d, 1 H, J = 2.4 Hz), 6.49–6.71 (m, 6 H); ^{13}C NMR δ 15.16, 45.18, 47.88, 55.94, 56.06, 57.69, 64.32, 75.89, 110.46, 111.47, 111.72, 113.16, 119.98, 125.98, 126.69, 128.64, 133.61, 137.09, 147.72, 148.09, 148.99; IR (film) 3520–3400, 2990, 2930, 2830, 1600, 1585 cm^{-1}.

(−)-Demethylphyltetralin (31). The olefin carbinol **30** (44.4 mg, 0.111 mmol) was dissolved in 6 mL of absolute ethanol containing 25 mg of

5% rhodium on alumina and hydrogenated at 50 psi for 15 h. The solution was filtered through Celite, and the filtrate was concentrated by rotary evaporation to give a colorless resin. The resin was purified by preparative TLC (Merck no. 5715 silica, 1:1 ethyl acetate/1% methanol), and the major of two bands were extracted with wet ethyl acetate. The ethyl acetate extract was dried ($MgSO_4$), and the solvent was removed under high vacuum to provide 36 mg (0.090 mmol) of pure **31** as a resin in 81% yield: $[\alpha]^{22}_D$ −15.8° (*c* 0.23, $CHCl_3$); IR (film) 3520–3400, 2900, 1605, 1585, 1500, 1450 cm^{-1}; ^1H NMR δ 1.65 (m, 1 H), 2.19 (m, 1 H), 2.75 (m, 3 H), 3.36–3.90 (m, 4 H), 3.41 (s, 3 H), 3.58 (s, 3 H), 3.80 (s, 3 H), 3.84 (s, 3 H), 3.88 (s, 3 H), 3.98 (d, 1 H, *J* = 10.9 Hz), 6.22 (s, 1 H), 6.58 (s, 1 H), 6.60 (s, 1 H), 6.74 (d, 1 H, *J* = 8 Hz), 6.81 (d, 1 H, *J* = 8 Hz); ^{13}C NMR δ 33.38, 36.77, 47.77, 49.14, 56.07, 56.18, 58.87, 61.78, 77.20, 111.57, 111.78, 113.10, 113.79, 122.08.

A higher R_f band in amounts less than 5% of the total mass balance consisted of a 3-methyl product resulting from hydrogenolysis of the methyl ether.

The enantiomeric purity of **31** was determined by ^{19}F NMR of the diastereomeric Mosher esters **32**. A solution of 14.4 mg (0.036 mmol) of **31** in 1 mL of chloroform was treated with 23.2 mg (0.120 mmol) of triethylamine and 14.1 mg (0.056 mmol) of (*R*)-MTPA acid chloride. After 15 h, 0.050 mL of 3-(dimethylamino)propylamine (Aldrich) was added to scavenge any remaining acid chloride. The solution was diluted with ether and washed sequentially with dilute HCl and dilute aqueous sodium bicarbonate. The ether was dried (Na_2SO_4), and the solvent was removed under high vacuum to provide the diastereomeric Mosher esters as a colorless resin. The ^{19}F NMR revealed two diastereomeric singlets at −71.70 and −71.46 ppm with an integral ratio of 84:16, respectively (Figure 2).

Treatment of a small sample (ca. 15 mg) of **31** with (*S*)-MTPA acid chloride under identical conditions provided two diastereomeric singlets in the ^{19}F NMR at −71.70 and −71.46 ppm with an exactly reversed integral ratio of 16:84. The ee of **31** was therefore determined to be 68%.

(+)-Phyltetralin (22). Demethylphyltetralin (**31**) (44.3 mg, 0.111 mmol) was dissolved in 1 mL of DMSO containing 15 mg (0.062 mmol) of sodium hydride. After the mixture was stirred for 15 min, 0.050 mL (0.80 mmol) of methyl iodide was added, and the thick solution was stirred for 1 h. An additional 15 mg of sodium hydride was added, and the solution was stirred for 15 min, followed by the addition of 0.050 mL (0.80 mmol) of methyl iodide. After being stirred for 3 h, the solution was diluted with water and extracted with ether. The ether extracts were combined and washed with several portions of water to remove traces of DMSO. The ether was dried ($MgSO_4$), and solvent was removed by rotary evaporation to provide a tan resin. Preparative TLC (Merck no. 5715 silica plates, 50% ethyl acetate/hexane) provided 40.7 mg (0.097 mmol) of (+)-phyltetralin (**22**) in 88% yield as a crystalline solid: mp 100–105 °C (lit.[15] mp 110–111 °C); ^1H NMR δ 1.81 (m, 1 H), 2.17 (m, 1 H), 2.85 (d, 2 H), 3.08 (dd, 1 H), 3.27 (s, 3 H), 3.36 (s, 3 H), 3.46 (m, 2 H), 3.58 (s, 3 H), 3.81 (s, 3 H), 3.85 (s, 3 H), 3.89 (s, 3 H), 3.99 d, 1 H, *J* = 10.2 Hz), 6.22 (s, 1 H), 6.61 (s, 2 H), 6.70 (d, 1 H, *J* = 8 Hz), 6.81 (d, 1 H, *J* = 8 Hz); ^{13}C NMR δ 33.02, 36.72, 45.07, 47.35, 56.13, 56.22, 58.81, 72.03, 75.69, 76.53, 112.00, 113.50, 113.94, 121.98, 129.38, 132.47, 138.47, 147.66, 147.78, 148.04, 149.51. A plot of $[\alpha]^{22}_D$ versus concentration revealed a nonlinear relationship (Figure 3). The following data points were used to construct the plot: $[\alpha]^{22}_D$ 4.03° (*c* 1.81, $CHCl_3$), $[\alpha]^{22}_D$ 4.63° (*c* 0.95, $CHCl_3$); $[\alpha]^{22}_D$ 5.52° (*c* 0.83, $CHCl_3$), $[\alpha]^{22}_D$ 6.31° (*c* 0.19, $CHCl_3$). Anal. Calcd for $C_{24}H_{32}O_6$ (416.5): C, 69.21; H, 7.74. Found: C, 69.07; H, 7.62.

A sample of 8.3 mg of (−)-phyltetralin obtained from Stevenson[16] (enantiomerically pure) showed $[\alpha]^{22}_D$ −7.7° (*c* 0.83, $CHCl_3$), mp 110–111 °C, and an ^1H NMR spectrum identical with (+)-phyltetralin (**22**) obtained from the present work.

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Supplementary Material Available: X-ray data for Figure 1A–C (atomic coordinates, thermal parameters, and bond angles) and general experimental information and Mosher ester preparation and analysis (23 pages). Ordering information is given on any current masthead page.