Asymmetric Tandem Additions to Chiral 2,3-Dihyronaphthyloxazolines: Synthesis of the Triptoquinone/Triptinin A Ring System

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Received 25 April 2002
This is dedicated to Professor Dieter Seebach, an old and dear friend and an excellent scientist, for his outstanding contributions to organic chemistry.

Abstract: A study to reach the diterpenoid (+)-triptoquinone A (3) or its analog (+)-triptinin A (4) via an asymmetric tandem addition to naphthyloxazolines is described. The tandem addition to the chiral dihydronaphthalene 6 resulted in a 70% yield of a single diastereomer 10. Further manipulation gave the natural products’ tricyclic ring system, compounds 20 and 29 via ring-closing metathesis in 90% yield, using the Schrock catalyst. Final assault to the target compounds 3 or 4 fell short due to the failure to either reduce a neopentyl hydroxymethyl group to a methyl or to install the conjugated carboxylic acid present in 3 or 4.

Key words: ring closing metathesis, alkyllithiums, chiral oxazolines, conjugate additions, deoxygenation, triflates, tetralones

Chiral 2-oxazolines, first introduced from this laboratory, have found significant use in asymmetric synthesis for the past three decades.1a The oxazoline functionality has served not only as a carboxylic masking group, but also as a chiral ligand and auxiliary in many carbon–carbon bond-forming reactions,1b,c For the latter, the chiral oxazoline has been used in this laboratory in the total synthesis of several important natural products such as (−)-steganone (an antileukemic),2 (−)-podophyllotoxin (an antitumor agent),3 and (S)-gossypol (an antispermatogenic)4 (Figure 1).

Tandem nucleophilic/electrophilic alkylations on various chiral naphthyloxazolines have, in the past on many occasions, furnished adducts in good to excellent chemical yields and very high stereoselectivity (Scheme 1).5 After the nucleophilic addition by RLi, the subsequently added electrophile was invariably found to enter trans to RLi. This pattern has been observed with numerous examples of tandem intermolecular additions on chiral naphthyl oxazolines and electrophiles.1,5–6 Therefore, in one reaction, two adjacent stereocenters are set very selectively, and furthermore, one center appears as a stereogenic quaternary carbon which historically has been more difficult to access selectively than a tertiary carbon center. We now report an effort to further expand the utility of this asymmetric tandem addition. The target chosen was the tricyclic system present in (+)-triptoquinone A (3) or its closely reduced analog, triptinin A (4) (Figure 2).

Figure 1 The structures of (−)-steganone, (−)-gossypol and (−)-podophyllotoxin

Figure 2 The structures of (+)-triptoquinone A (3) and (+)-triptinin A (4)
(+)-Triptquinone A (3) and (+)-triptinin A (4) are members of a family of structurally related diterpenoid natural products isolated from the plant *Tripterygium wilfordii* var regelii. This plant has been used in traditional Chinese medicine to treat rheumatoid arthritis and spondylitis. Triptquinone A (3) has been shown to inhibit IL-1α and IL-1β release from lipopolysaccharide-stimulated human peripheral mononuclear cells. Also, it has been shown to inhibit the expression of inducible nitric oxide synthase (iNOS) gene with an IC₅₀ = 25.5 μM in rat glial cells. Triptinin A (4) has been indicated as a competitive leukotriene-d₄ (LTD₄) antagonist with guinea pig smooth tracheal muscle. Shishido et al. have recently completed a total synthesis of racemic-3 and (+)-3.

With two adjacent stereocenters, one quaternary, it can be imagined to initiate this study from a naphthalene system. (+)-Triptquinone A (3) appeared to be an ideal target for demonstrating the utility of the tandem addition chemistry mentioned above. It was the goal of this project to first evaluate the behavior to 2,3-dihydronaphthyl rather than the fully aromatic naphthyloxazolines and then secondly to complete the total synthesis of 3 in a more convergent and efficient manner than previously reported.

The retrosynthetic route is shown in Scheme 2. The oxidation of the aromatic ring to the quinone 3 was planned to be delayed until the final step. The C-ring was expected to be introduced by ozonolysis of the olefin 5b to the ketone 5a, followed by an intramolecular aldol condensation. The stereogenic quaternary methyl group in 3 would ultimately arise from transformation of the oxazoline moiety in 5a by reductive methods previously performed in our laboratory. The latter oxazoline ring would be affixed to the tetralone 1, via an earlier procedure also reported from our laboratory, to give 6. It should also be noted that due to the more accessible (S)-tert-leucinol versus (R)-tert-leucinol necessary for constructing the chiral oxazoline, the actual synthetic target would be the (−)-enantiomer of natural triptquinone A (3) or triptinin A (4).

The starting material, 5,8-dimethoxy substituted oxazoline 6b was derived from the known 5,8-dimethoxy-6-isopropyl-α-tetralone via its triflate (cf. vide supra, Scheme 4, see preparation of 6a). It was readily apparent, after early attempts at tandem additions, that there was something unusual about additions to the dihydronaphthoyl oxazoline compared to the corresponding naphthyloxazolines reported earlier from our laboratory. Where previous examples of alkylithium additions followed by electrophiles gave essentially one *trans*-disposed diastereomer (>30:1), the stereoselective addition affording 9 proceeded in relatively poor diastereomeric ratio (4:1, Scheme 3). Furthermore, conversion of the oxazoline moiety to a carbinol by many earlier utilized acidic and basic routes was unsuccessful, yielding mainly the starting material or decomposition products. At this stage it seemed that the steric crowding between the oxazoline ring and the peri-positioned methoxyl group in 6b may be contributing to both lack of stereoselectivity in the tandem addition and hindering smooth removal of the oxazoline ring. This notion was verified when the less encumbered des-methoxyoxazoline derivative 6a was examined, and the high *trans*-diastereoselectivity was once again observed (>95%). Thus, adduct 10 was now obtained as a single diastereomer in 76% yield. After several attempts, a modification of earlier procedures, requiring heating in a sealed tube followed by acidic hydrolysis and reduction, led to the carbinol 11a. Protection of the hydroxyl group as the tert-butyldimethylsilyl (TBDMs) ether, or methyl ether, followed by ozonolysis of both double bonds provided the requisite dicarbonyl groups as an aldol precursor, 11b. However, after numerous attempts, no satisfactory aldol condensation products were observed from 11b, and this route to the construction of the C-ring was eventually abandoned.

The synthesis of the requisite chiral oxazoline 6a began with 2-bromo-6-isopropylanisole (12) (Scheme 4). Metal-halogen exchange with butyllithium gave the oxygen-sensitive aryllithium which was then treated with BF₃·Et₂O followed by ethylene oxide, yielding phenethyl alcohol 13, which was transformed into the iodide 14, by triphenylphosphine and iodine. To this was added the lithium enolate of tert-butyl acetate in the presence of HMPA affording the homologated ester 15. Cyclization of the ester using polyphosphoric acid furnished tetralone 7. Hav-
ing the acid labile tert-butyl ester in 15 allowed for direct conversion to the tetralone, without the necessity of a separate saponification step. The tetralone 7 was transformed to vinyl triflate 16 (KHMDS, PhNTf₂) which underwent a palladium-catalyzed amidation 11 to yield the chiral amide alcohol (+)-17. Cyclization, using thionyl chloride, gave the chiral 2,3-dihyronaphthyloxazoline (−)-6a.

After the unsuccessful attempts to cyclize the diketone 11b, via aldol methodology, a ring-closing metathesis of the diolefin 11a was considered. Furthermore, use of the diolefin would simplify the synthesis and eliminate the ozonolysis steps of 11a to 11b. In the event, adduct 19 was acquired as a single diastereomer in 87% yield, after addition of propenyllithium to 6a followed by but-3-enyl bromide. Treatment of 19 with 20% catalyst A and heat resulted in a good yield (90%) of cyclized material 20 (Scheme 5). This represented the first example of a ring-closing metathesis being performed in the presence of a chiral basic oxazoline, and not surprisingly, a good yield was obtained. Also, the desired tricyclic ring system 20 of the natural products 3 and 4 had now been constructed from a chiral oxazoline intermediate.

In order to increase the efficiency to 3 and 4 and render the synthesis more convergent, the construction of the appropriate tetrasubstituted olefin, such as 21 (R = protecting group), was considered (Figure 3). Because a carboxylic acid or its ester would not be compatible with the organolithium reagent during the tandem addition or with the removal of the oxazoline moiety, a functional group was required that could withstand these conditions, and also be readily converted to the carboxylic acid found in the targeted products 4. Therefore, it was felt that the protected MEM alcohol 21 might serve the purpose at hand. 14

The synthesis of 21 required an appropriately protected vinyl halide 22 to be utilized as the electrophile in the diastereoselective tandem addition step. Due to the synthetic constraints mentioned above, the protecting group chosen for this task was a 2-methoxyethoxy methyl (MEM) ether. The synthetic sequence to reach the desired electrophile is summarized in Scheme 6. The vinyl bromide 22 (from 3-bromobut-3-en-1-ol) was converted to the methyl ester 23 by metal-halogen exchange to form the organolithium species, and this was followed by the
addition of methyl chloroformate. Ester reduction of 23 with DIBAL-H gave the allylic alcohol 24, which was then treated with MEMCl to give the MEM-ether 25. The TBS group was removed and the resulting alcohol 26 was converted to the requisite protected alkyl iodide 27.

The tandem addition was undertaken with oxazoline 6a (Scheme 7) and the olefin halide 27 as the electrophile. The addition of HMPA and a cold temperature (−78 °C) were the keys to achieve consistently high yields of the chiral adduct (−)-28, which was invariably obtained as a single diastereomer. In the subsequent ring-closing metathesis, the more reactive catalyst B15 (Scheme 5) was found to be necessary to form the cyclic tetrasubstituted olefin of 29.16 The structure of 28 and 29 were supported by 1H NMR, 13C NMR and HRMS (see Experimental). The synthesis of the tricycle (−)-29 efficiently puts in place not only the ring system of 3 and 4 but all the requisite carbon atoms. Only the transformation of the oxazoline to a methyl group and conversion of the protected primary alcohol remained to complete the synthesis.

In order to achieve these goals, the oxazoline of 29 was converted to a carbinol following the earlier procedures, with slight modifications (Scheme 8). These conditions led to the neopentyl carbinol (+)-30 with the MEM group intact. No isomerization of the olefin linkage was observed during the course of removing the oxazoline ring. Using a variety of analogous model compounds, many

Scheme 5

Scheme 6 Reagents and conditions: (a) t-BuLi, Et2O, CICO2CH3, 50%; (b) DIBAL-H, THF, 90%; (c) MEMCl, Hunig’s base, CH2Cl2, 85%; (d) TBAF, THF, 94%; (e) I2, Ph3P, imidazole, 91%

Scheme 7
deoxygenation conditions were attempted to obtain the quaternary methyl group (Table 1). Conversion of the hindered neopentyl hydroxyl to leaving groups such as halides, mesylates, and xanthate esters did not lead to the desired methyl group. When the phosphorodiamidate (Table 1, entry 4) was formed from the primary alcohol and reductively cleaved by lithium naphthalenide,17 54% of the desired material was obtained. The phosphorodiamidate (–)-31 was subsequently prepared using conditions reported for sterically encumbered alcohols.18 Reductive cleavage of the phosphorodiamidate 31, containing all the rings and carbons in place, was initially attempted in the presence of the allylic MEM-ether 31. The reaction was performed with both lithium naphthalenide and lithium 4,4′-di-tert-butylbiphenyl under various reaction concentrations, molar equivalents of reductant, and temperatures. Unfortunately, only a very small amount of angular methyl derivative 32 was obtained19 (Scheme 9). The deoxygenated derivatives 33 and 34 were also isolated; this allylic deoxygenation has been previously observed with ethers using these reducing agents.20

In the anticipation that the MEM ether was responsible for the poor reductive cleavage of the phosphorodiamidate 31, the MEM group was removed using BBr3, CaH2 in CH2Cl2 at –78 °C affording the desired allylic alcohol (compound 36 in Scheme 10). In this fashion, only the MEM group was cleaved, leaving the aromatic methoxy group intact. Unfortunately, after treatment with 4,4′-di-tert-butylbiphenyl and lithium (or Li-naphthalenide), the resulting allylic alcohol 32a was too unstable to purify and proceed further.

By changing the order of functional group manipulation, the phosphorodiamidate 31 was left intact, while removal of the MEM-ether moiety was performed (Scheme 10). Conversion of 31 to the unstable allylic alcohol 36 (used crude and never subjected to any acidic conditions), was followed by oxidation to the aldehyde 37. Subsequent oxidation to the carboxylic acid, 38 was also successful in the presence of the phosphorodiamidate group. Reductive cleavage of the phosphoramide group of the alcohol, alde-

Table 1  Summary of Deoxygenation Attempts

<table>
<thead>
<tr>
<th>Entry</th>
<th>LG</th>
<th>Conditions</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>OTs, OMs</td>
<td>LiBHEt2, NaBH4/DMSO, LiAlH4</td>
<td>either starting material or complex mixtures</td>
</tr>
<tr>
<td>2</td>
<td>I, Br</td>
<td>as above</td>
<td>unable to convert hydroxyl to halide</td>
</tr>
<tr>
<td>3</td>
<td>C(=S)Me, C(=S)Imid.</td>
<td>LiNp</td>
<td>either starting material or complex mixtures</td>
</tr>
<tr>
<td>4</td>
<td>P(=O)(NM-2)2</td>
<td>LiNp, LiDBB</td>
<td>54% desired deoxygenated product</td>
</tr>
<tr>
<td>5</td>
<td>SCH2CH2S-NNH2</td>
<td>NA</td>
<td>unable to form thioketal or hydrazone</td>
</tr>
</tbody>
</table>
hyde, or acid, 36–38, respectively, did not produce any of the desired corresponding products 40a–c. While we have demonstrated the synthetic versatility of the phosphoroamidate moiety as a hydroxyl-masking and potential methyl group, it seemed apparent that efficient reductive cleavage to a methyl group could not be achieved in the presence of an allylic ether or conjugated carbonyl groups, 40 in this particular ring system.

Nonaqueous reactions were performed under argon with flame-dried glassware. EtO, THF, and benzene were dried by distillation over sodium-benzophenone. CH₂Cl₂, diisopropylamine, Et₃N, toluene, DMSO, and HMPT were distilled over CaH₂. Thin layer and flash chromatography were performed with E. Merck Kieselgel silica gel 60 (230–400 mesh ASTM). Unless otherwise stated, Schrock catalyst was purchased from Strem Chemical, Inc. and was washed with hexane under argon prior to use. N,N-Dimethylphosphorodiamidic dichloride was purchased from Lancaster Synthesis, Microlab, Inc., Norcross, Georgia.

(4S)-4-tert-Butyl-2-(6-isopropyl-5,8-dimethoxy-3,4-dihydro-naphthalen-1-yl)oxazoline (6a)

To a solution of the amide alcohol 17 (500 mg, 1.45 mmol) in CH₂Cl₂ (15 mL) at 0 °C was slowly added SOCl₂ (0.23 mL, 3.19 mmol). After stirring for 2 h, the solvent was removed. The residue was dissolved in MeCN (8 mL) and sat. aq K₂CO₃ (5 mL) and the solution was refluxed for 6 h. Upon cooling, the solvent was removed and the residue was dissolved in EtOAc (100 mL) and washed with brine (2 × 50 mL). The EtOAc solution was dried (Na₂SO₄), filtered, and concentrated. Flash chromatography (15% EtOAc–hexane) of the crude, yellow residue gave 1.19 (80%) g of 6a.

1H NMR (CDCl₃, 300 MHz): δ = 0.97 (s, 9 H), 1.20 (d, J = 6.9 Hz, 6 H), 2.17–2.14 (m, 2 H), 2.73 (t, J = 7.8 Hz, 2 H), 3.20 (sept, J = 6.9 Hz, 1 H), 3.62 (s, 3 H), 3.73 (s, 3 H), 3.91 (t, J = 9.2 Hz, 1 H), 4.09 (t, J = 8.5 Hz, 1 H), 4.25 (t, J = 9.1 Hz, 1 H), 6.62 (s, 1 H), 6.68 (t, J = 5.0 Hz, 1 H).

IR (film): 1657, 1478 cm⁻¹.

13C NMR (CDCl₃, 75 MHz) δ = 17.4 (C₅), 21.6 (C₄), 26.1 (C₁₀), 26.8 (C₁₁), 26.9 (C₁), 27.2 (C₈), 28.0 (C₁₂), 28.4 (C₇), 28.7 (C₉), 28.9 (C₆), 61.3 (C₁₃), 68.9 (C₂), 75.6 (C₃), 107.9 (C₄₄), 119.9 (C₄₂), 126.6 (C₃₉), 131.0 (C₇₃), 134.5 (C₃₈), 142.0 (C₄₁), 148.1 (C₄₃), 152.2 (C₄₄), 166.5. HRMS (FAB+): m/z Calcd for C₁₄H₁₉O₂ (M + H)⁺ 219.1385. Found 219.1386.

HRMS (FAB+): m/z Calcd for C₂₁H₃₀NO₂ (M + H)⁺ 328.2286. Found 328.2281.

6-Isopropyl-5-methoxy-3,4-dihydro-2H-naphthalen-1-one (7)

Using a mechanical stirrer and an oil bath that had been equilibrated to 95 °C, ester 15 (2 g, 6.85 mmol) was heated in methylphosphonic acid (20 mL) for 2 h. The red reaction mixture was cooled, diluted with H₂O (100 mL), and extracted with EtOAc (3 × 50 mL). The EtOAc solution was washed with sat. aq NaHCO₃ (2 × 75 mL) and brine (100 mL). The solution was dried (MgSO₄), filtered, and concentrated. Flash chromatography (5% EtOAc–hexane) of the crude, yellow residue gave 1.19 (80%) g of 7 as an off-white solid (80%); mp 102–104 °C.

IR (film): 1681, 1416 cm⁻¹.

1H NMR (CDCl₃, 300 MHz): δ = 1.24 (d, J = 6.6 Hz, 6 H), 2.11 (dd, J = 6.3, 6.3, 6.3, 6.3 Hz, 2 H), 2.62 (dd, J = 7.0, 6.0 Hz, 2 H), 2.98 (dd, J = 6.0, 6.0 Hz, 2 H), 3.37 (sept, J = 6.6 Hz, 1 H), 3.75 (s, 3 H), 7.23 (d, J = 8.2 Hz, 1 H), 7.82 (d, J = 8.2 Hz, 1 H).

13C NMR (CDCl₃, 75 MHz): δ = 23.7, 25.4, 26.9, 26.9, 26.9, 33.9, 61.1, 73.9, 123.2, 124.6, 131.2, 153.7, 147.7, 154.5, 198.1.


Anal. Calcd for C₇H₁₀O₂: C, 76.96; H, 8.33.

1-Bromo-3-isopropyl-2-methoxybenzene (12)

To a solution of 2-isopropylphenol (18.3 g, 0.13 mmol) in CS₂ (500 mL) was added solid N-bromosuccinimide (24 g, 0.13 mmol) over 1 h. The reaction mixture was stirred at r.t. for 12 h and an off-white precipitate was formed. The solvent was removed, and the residue was dissolved in Et₂O (350 mL). The Et₂O solution was washed with 10% aq Na₂SO₄ (2 × 50 mL) and brine (100 mL). After drying (MgSO₄), the solution was filtered and concentrated. Flash chromatography (5% EtOAc–hexane) of the crude material produced 2.5 g of the desired 1-bromo-3-isopropyl-2-hydroxybenzene (86%). Following the procedure of McKillop et al., a领先istic mixture of the preceding phenol (15.8 g, 17.6 mmol), dimethyl sulfate (14 g, 111 mmol), LiOH·H₂O (4.9 g, 118 mmol), and benzyltributylammonium chloride (2.3 g, 7.3 mmol) in CH₂Cl₂–H₂O (1:1, 600 mL) was stirred at r.t. for 12 h. The phases were separated, and the aqueous phase was extracted with CH₂Cl₂ (2 × 100 mL). The CH₂Cl₂ extracts were combined and stirred with 10% NH₄OH solution (300 mL) for 5 h. The phases were separated and the organic phase was dried (Na₂SO₄) and concentrated. Flash chro-
matography (1% EtOAc–hexanes) gave 15.5 g (92%) of 12 as a clear liquid; bp 120–125 °C/20 mmHg.

\[ ^1H \text{ NMR (CDCl}_3, 300 MHz)\]: \( \delta = 1.23 \) (d, \( J = 6.9 \) Hz, 6 H), 3.36 (sept, \( J = 6.9 \) Hz, 1 H), 3.83 (s, 3 H), 6.97 (t, \( J = 7.8 \) Hz, 1 H), 7.2 (dd, \( J = 7.8, 1.5 \) Hz, 1 H), 7.37 (dd, \( J = 7.8, 1.5 \) Hz, 1 H).

\[ ^1C \text{ NMR (CDCl}_3, 75 MHz)\]: \( \delta = 23.7, 27.2, 62.1, 113.7, 125.6, 125.9, 130.8, 144, 154.2 \).

MS: \( m/z = 228/230 \) (M⁺).


2-(3-Isopropyl-2-methoxyphenyl)ethanol (13)

A solution of 12 (3 g, 13.1 mmol) in anhyd THF (10 mL) (compound dried over NaH in THF and decanted) at –78 °C was degassed by evacuating the system under vacuum until the solvent bubbled by purging the system with argon. This process was repeated 5 times. The solution was then slowly added via cannula to a solution of BuLi (2.4 M in hexane, 13.7 mmol) in anhyd THF (30 mL) at 0 °C. The reaction mixture was allowed to warm to r.t. slowly.

To CH₂Cl₂ (40 mL) at 0 °C was added Ph₃P (2.76 g, 10.5 mmol) and the reaction mixture was bubbled by purging the system with argon. This process was repeated 3 times. Ethylene oxide (5.5 mL, 2.75 mmol) was added and the reaction mixture was stirred for 30 min at –78 °C. In a separate flask, iodide 14 (500 mg, 2.29 mmol) in THF (8 mL) at –78 °C was stirred for 30 min. In a separate flask, iodide 14 (500 mg, 2.29 mmol) in THF (8 mL) at –78 °C was stirred for 30 min. The reaction mixture was added to vinyl triflate (810 mg, 350.08 mmol), 1,3-bis(diphenylphosphino)propane (48 mg, 0.12 mmol), and anhyd HMPA (982 mg, 5.48 mmol) were mixed in THF (5 mL) and cooled to –78 °C. The acetate anion was then added dropwise via cannula into the iodide 14/HMPA solution. After stirring for 5 h at –78 °C, the solution was quenched with sat. aq NH₄Cl (20 mL) and allowed to warm to r.t. The mixture was extracted with EtOAc (3 × 25 mL), the combined organic phases were washed with brine (50 mL), dried (Na₂SO₄), filtered, and concentrated. \( \text{HRMS (FAB+): } m/z \text{ Calcd for C}_{18}H_{28}O₃ (M⁺) } 292.2038. \) Found 292.2040.


Trifluoromethanesulfonic Acid 6-Isopropyl-5-methoxy-3,4-dihydropyridin-1-yl Ester (16)

To a solution of 7 (500 mg, 2.29 mmol) in THF (8 mL) at –78 °C was slowly added potassium bis(trimethylsilyl)amide (0.5 M in toluene, 5.5 mL, 2.75 mmol). The reaction mixture was stirred for 1 h, till it became homogeneous. To this was added N-phenyltriflimide (1.0 g, 3 mmol) in THF (3 mL). After stirring for 1 h at –78 °C, the mixture was allowed to warm to r.t. The mixture was extracted with EtOAc (3 × 20 mL). The EtOAc solution was dried (Na₂SO₄), filtered and concentrated. The crude residue was purified by flash chromatography (2.5% EtOAc–hexanes) to yield 16 as a light brown oil (800 mg, 99%). The material could be stored at –18 °C under argon for several days. After that, significant decomposition was noted.

\[ ^1H \text{ NMR (CDCl}_3, 300 MHz)\]: \( \delta = 1.23 \) (d, \( J = 6.9 \) Hz, 6 H), 2.48 (dd, \( J = 8.4, 4.2, 2.2 \) Hz, 2 H), 2.9 (dd, \( J = 8.1, 1.8 \) Hz, 2 H), 3.32 (sept, \( J = 6.8 \) Hz, 1 H), 3.71 (s, 3 H), 5.96 (dd, \( J = 4.6, 4.6 \) Hz, 1 H), 7.12 (d, \( J = 8.4 \) Hz, 1 H), 7.16 (d, \( J = 8.4 \) Hz, 1 H).

\[ ^1C \text{ NMR (CDCl}_3, 75 MHz)\]: \( \delta = 20.4, 22.1, 23.7, 26.7, 61.2, 116.8, 117.5, 124.6, 127.6, 128.9, 130 \) [q, \( J = 15.7 \) Hz], 143.4, 146.2, 152.4.

HRMS (FAB+): \( m/z \text{ Calcd for C}_{18}H_{17}F₃O₄S (M⁺) } 530.0800. \) Found 530.0801.

6-Isopropyl-5-methoxy-3,4-dihydropyridin-1-yl carbonyl Acid (15)-2Hydroxy-1-tert-butyl)lelamide (17)

The following were combined in order: vinyl triflate 16 (810 mg, 2.34 mmol), (S)-tert-leucinol (548 mg, 4.68 mmol), Et₃N (0.82 mL, 5.88 mmol), 1,3-bis(diphenylphosphino)propane (48 mg, 0.12 mmol), and Pd(OAc)₂ (16 mg, 0.07 mmol). After diluting with anhyd DMSO (2 mL), the reaction was aerated with CO from a balloon for 15 min, and then heated at 65 °C for 12 h under a CO atmosphere. After cooling to r.t., the mixture was diluted with EtOAc (75 mL) and washed with brine (50 mL). The EtOAc solution was dried (Na₂SO₄), filtered, and concentrated. The crude residue was purified by flash chromatography (15% EtOAc–hexanes and 45% EtOAc–hexanes) to give 624 mg (77%) of 15 as a colorless foam; \( \delta_{19}^D = 13.7 \) (c = 0.54, CHCl₃).

IR (film): 1644, 1610 cm⁻¹.

\[ ^1H \text{ NMR (CDCl}_3, 300 MHz)\]: \( \delta = 1.02 \) (s, 9 H), 1.23 (d, \( J = 7.2 \) Hz, 6 H), 2.31–2.42 (m, 2 H), 2.85 (ddd, \( J = 7.5, 3.3, 2.8 \) Hz, 2 H), 3.33 (sept, \( J = 6.9 \) Hz, 1 H), 3.57–3.74 (m, 2 H), 3.7 (s, 3 H), 3.94–4.06
[3-Bromobut-3-enyloxy]-tert-butyl(dimethyl)silane (22)

To a solution of 3-bromobut-3-en-1-ol (Aldrich) (860 mg, 5.7 mmol) in DMF (4 mL) was added tert-butyl(dimethyl)silyl chloride (1.12 g, 7.4 mmol), imidazole (582 mg, 8.55 mmol) and a catalytic amount of 4,4-dimethylaminopyridine. The reaction mixture was allowed to stir at r.t. for 12 h, and then was diluted with Et2O (50 mL). The solution was washed with brine (3 x 150 mL), dried (Na2SO4), filtered, and concentrated. Flash chromatography (25% EtOAc–hexanes) gave 22 as a clear liquid.

IR (neat): 1652, 1455 cm–1.

1H NMR (CDCl3, 300 MHz): δ = 0.07 (s, 6 H), 0.89 (s, 9 H), 2.62 (t, J = 6.3 Hz, 2 H), 3.79 (t, J = 6.3 Hz, 2 H), 5.45 (s, 1 H), 5.63 (s, 1 H).

13C NMR (CDCl3, 75 MHz): δ = –5.3, 18.3, 25.9, 44.8, 60.8, 118.4, 130.8.


3-(2-Methoxyethoxymethyl)but-3-en-1-ol (26)

To a solution of allylic MEM-ether 25 (2 g, 6.58 mmol) in THF (20 mL) at r.t. was added tetrabutylammonium fluoride (1 M in THF, 8.6 mL) and the reaction mixture was stirred for 3 h. The solvent was removed and the residue was dissolved in EtOAc (75 mL). The EtOAc solution was washed with brine (2 x 50 mL), dried (Na2SO4), filtered, and concentrated. Flash chromatography (25% EtOAc–hexanes and 50% EtOAc–hexanes) gave 26 as a clear oil.

IR (neat): 3444 (br), 1652 cm–1.

1H NMR (CDCl3, 300 MHz): δ = 2.36 (t, J = 6.6 Hz, 2 H), 3.39 (s, 3 H), 3.55–3.58 (m, 2 H), 3.70–3.73 (m, 4 H), 4.05 (s, 2 H), 4.75 (s, 2 H), 5.03 (br s, 1 H), 5.16 (br s, 1 H).

13C NMR (CDCl3, 75 MHz): δ = 37.1, 59.1, 61.7, 70.4, 71.7, 94.7, 112.5, 142.5.

HRMS (FAB+): m/z Calcd for C15H33O4Si (M+H)+ 219.1283. Found: 219.1282.

4-Iodo-2-(2-methoxyethoxymethyl)but-1-ene (27)

To a solution of Ph3P (497 mg, 1.89 mmol) in CH2Cl2 (6 mL) at 0 °C was added I2 (522 mg, 2.06 mmol), and the mixture was stirred for 30 min. Imidazole (150 mg, 2.2 mmol) was added followed by the alcohol 26 (300 mg, 1.58 mmol) in CH2Cl2 (3 mL). The mixture was heated for 10 h while allowing to warm to r.t., and the insolubles were removed by filtration and washed with EtOAc (50 mL). After concentration of the filtrate, the crude residue was flushed through a plug of basic alumina (30% EtOAc–hexanes) to give 430 mg (91%) of 27 as a yellow oil.

IR (neat): 1652, 1455 cm–1.

1H NMR (CDCl3, 300 MHz): δ = 2.66 (t, J = 7.8 Hz, 2 H), 3.28 (t, J = 7.8 Hz, 2 H), 3.4 (s, 3 H), 3.55–3.58 (m, 2 H), 3.70–3.73 (m, 2 H), 4.04 (s, 2 H), 4.72 (s, 2 H), 4.99 (s, 1 H), 5.16 (s, 1 H).

13C NMR (CDCl3, 75 MHz): δ = 3.2, 37.7, 59.1, 67, 69.5, 71.8, 94.6, 114.3, 143.9.

HRMS (FAB+): m/z Calcd for C19H18O3I (M+H)+ 301.0301. Found: 301.0303.
(4S)-4-tert-Butyl-2-((15Z,2R)-2-isopropenyl-6-isopropyl-5-methoxy-1-[3-(2-methoxyethoxymethyl)but-3-enyl]-1,2,3,4-tetrahydronaphthalen-1-yl)oxazoline (28); Representative Tandem Addition

t-ButLi (1.7 M in pentane, 0.94 mL, 1.59 mmol) was added dropwise to a solution of 2-bromopropene (92 µL, 1.03 mmol) in anhyd THF (6 mL) at –78 °C. After stirring for 15 min, a solution of oxazoline 6a in anhyd THF (2 mL) was added and the reaction mixture was stirred for 15 min at –78 °C. Anhyd HMPA (227 µL, 1.59 mmol) was added and the solution was allowed to stir another 20 min at –78 °C. Isodine 27 (358 mg, 1.19 mmol) was added and after 5 min, the reaction was stopped by addition of sat. aq NH₄Cl (10 mL). After addition of EtOAc (6 mL), the phases were separated. The organic layer was washed with brine, dried (Na₂SO₄), filtered and concentrated. The crude material was purified by flash chromatography (5% EtOAc–hexanes and 15% EtOAc–hexanes) to give 370 mg (86% of 28) as a single diastereomer and as a viscous, light yellow oil; [α]D²⁵ –157 (c = 0.42, CHCl₃).

IR (neat): 1652 cm⁻¹.

¹H NMR (CDCl₃, 300 MHz): δ = 0.92 (s, 9 H), 1.24 (d, J = 6.6 Hz, 3 H), 1.25 (d, J = 6.6 Hz, 3 H), 1.45 (ddd, J = 14.7, 6.6, 6.6 Hz, 1 H), 1.75 (s, 3 H), 1.79–1.84 (m, 1 H), 1.96 (dd, J = 14.7, 6.6, 6.6 Hz, 1 H), 2.35–2.68 (m, 5 H), 3.14 (br d, J = 16.5 Hz, 1 H), 3.31 (sept, J = 6.9 Hz, 1 H), 3.43–3.59 (m, 3 H), 3.69–3.8 (m, 3 H), 3.76 (s, 3 H), 3.92 (app t, J = 8.1 Hz, 1 H), 3.99 (s, 3 H), 4.05 (app t, J = 9.5 Hz, 1 H), 4.7 (s, 2 H), 4.84 (s, 1 H), 4.91 (s, 1 H), 4.95 (s, 1 H), 5.01 (s, 1 H), 6.95 (d, J = 8.4 Hz, 1 H), 7.04 (d, J = 8.4 Hz, 1 H).

¹³C NMR (CDCl₃, 75 MHz): δ = 20.9, 23.7, 23.9, 24.4, 25.1, 26.1, 27.6, 34.1, 35.3, 46.4, 47.4, 59, 60.7, 66.8, 68.1, 70.1, 71.8, 74.9, 94.6, 111.4, 114.4, 123.9, 123.9, 131.2, 136.6, 138.7, 145.8, 146, 154.8, 170.7.

HRMS (FAB⁺): m/z Calcd for C₃₅H₃₅NO₅ (M + H⁺) 542.3845. Found: 542.3839.

(4S)-4-tert-Butyl-2-((15Z,2R)-2-isopropenyl-6-isopropyl-5-methoxy-1-(4-methylpent-4-enyl)-1,2,3,4-tetrahydronaphthalen-1-yl)oxazoline (10)
The compound was obtained in a similar manner to adduct 28 from 1-ido-4-methylpent-4-en-4-ene to give 10 as a single diastereomer; white solid (76%); mp 104–105 °C; [α]D²⁵ –258 (c = 0.71, MeOH).

IR (film): 2859, 1651, 1480, 1450 cm⁻¹.

HRMS (FAB⁺): m/z Calcd for C₃₉H₄₅NO₃ (M + H⁺) 596.3090. Found: 596.3032.

([4aS,10aR]-7-isopropyl-8-methoxy-2-(2-methoxyethoxymethyl)-1-methyl-3,9,10,10a-tetrahydro-4H-phenanthren-4a-yl)methanol (30): Representative Example of Conversion of an Oxazoline to a Carbinol

The oxazoline 29 (69 mg, 0.13 mmol) was dissolved in CH₂Cl₂ (1 mL), then chilled to 0 °C, and CaH₂ (5 mg) was added. To this was added methyl triflate (30 µL, 0.27 mol), and the solution was stirred overnight, and allowed to warm to r.t. After filtration through a plug of cotton, the solution was concentrated and the residue was dissolved in THF–H₂O (4:1, 2.5 mL). The mixture was cooled to 0 °C and NaBH₄ (15 mg, 0.39 mmol) was added portionwise. After chilling for 30 min, aq NaOH (~2 mL) was added and the mixture was stirred for an additional 3 h. The solution was extracted with EtOAc (3 × 10 mL), dried (Na₂SO₄), filtered and concentrated. The crude oxazoline derivative was dissolved in THF–H₂O (4:1, 2 mL), and the solution was reflushed for 6 h. After cooling, sat. aq NaHCO₃ (2 mL) was added, and the solution was extracted with EtOAc (3 × 10 mL). The organic phase was washed with brine (10 mL), dried (Na₂SO₄), filtered and concentrated to yield the crude aldehyde which was generally used without further purification. To a solution of the crude aldehyde in THF–H₂O (1:1, 2.5 mL) at 0 °C was slowly added NaBH₄ (12.5 mg, 0.33 mmol). The reaction mixture was stirred for 30 min at 0 °C and then diluted with aq 1 N NaOH (5 mL). After stirring for 3 h, the mixture was extracted with EtOAc (3 × 8 mL) and washed
with brine (10 mL). The EtOAc solution was dried (Na₂SO₄), filtered and concentrated. Flash chromatography (25% and 50% EtOAc–hexanes) gave 42 mg (75%) of carbinol 31 as a light yellow oil; [α]D²⁵ +4.8 (c = 1.2, CHCl₃).

IR (neat): 3478 cm⁻¹ (br).
IR (neat): 1044, 993 cm⁻¹.

To a solution of the phosphorodiamidate 29 (56 mg, 0.13 mmol) was added and the resulting mixture was extracted with EtOAc (20 mL). The extract was washed with brine (5 mL). The organic layer was dried (Na₂SO₄), filtered and concentrated. The residue was subjected to flash chromatography (C-18 silica gel, MeCN) to give 25 mg (54%) of 40d.

HRMS (FAB+): m/z Calcd for C₉₀H₁₄O₃P (M + H)⁺ 274.2675. Found: 274.2680.

Supplementary Material
See Ref.¹⁹ for information on supplementary material.

Acknowledgment
The authors are grateful to the National Science Foundation (USA) for financial support of this work.

References
(1) For reviews on the use of chiral oxazolines in synthesis, see:
(b) Gant, T. G.; Meyers, A. I. Tetrahedron 1994, 50, 2297.
(12) Compound 12 was prepared as described in the experimental.
(14) Attempts were made to use a vinyl bromide into the tandem product below. However, the electrophilic step in the tandem addition failed. Presumably, the azaenolate, formed upon the addition of the 2-lithiopropene, is too basic and causes elimination of HBr from 1,3-dibromobut-3-ene (Scheme 11).
(16) The yield of this reaction was dependent upon the quality of the catalyst (purchased from Strem Chemical Company) as evidenced by its often dark color.
(19) 300 MHz $^1$H NMR spectra of 32–34 and 38 are included in the supplementary material.

Scheme 11