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

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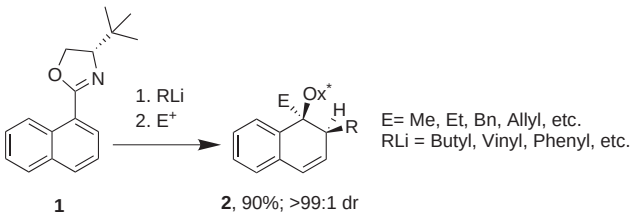
This is dedicated to Professor Dieter Seebach, an old and dear friend and an excellent scientist, for his outstanding contributions to organic chemistry.

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 dihydronophthalene **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**.

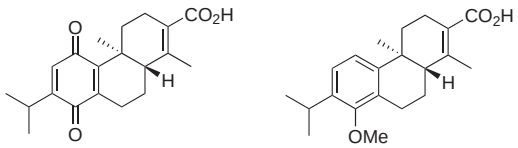
Key words: ring closing metathesis, alkyllithiums, chiral oxazolines, conjugate additions, deoxygenation, triflates, tetralones

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).

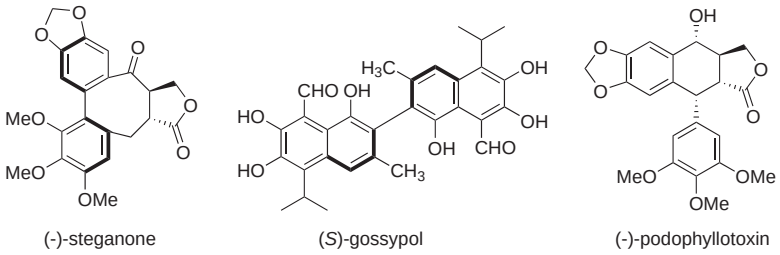


Scheme 1



3 (+)-triptoquinone A **4** (+)-triptinin A

Figure 2 The structures of (+)-triptoquinone A (**3**) and (+)-triptinin (**4**)



(-)-steganone (*S*)-gossypol (-)-podophyllotoxin

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

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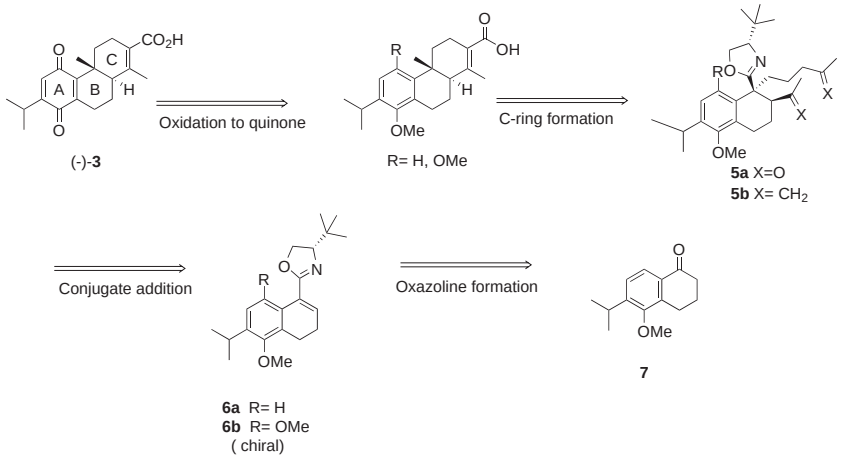
(+)-Triptoquinone A (**3**) and (+)-triptinin A (**4**) are members of a family of structurally related diterpenoid natural products isolated from the plant *Tripterygium wilfordii* var regelii.[7,8] This plant has been used in traditional Chinese medicine to treat rheumatoid arthritis and spondylitis. Triptoquinone A (**3**) has been shown to inhibit IL-1α and IL-1β release from lipopolisaccharide-stimulated human peripheral mononuclear cells.[7] Also, it has been shown to inhibit the expression of inducible nitric oxide synthase (iNOS) gene with an IC_{50} = 25.5 μM in rat glial cells.[9] Triptinin A (**4**) has been indicated as a competitive leukotriene-d_4 (LTD_4) antagonist with guinea pig smooth tracheal muscle.[8] Shishido et al.[10] 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. (+)-Triptoquinone 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.[10]

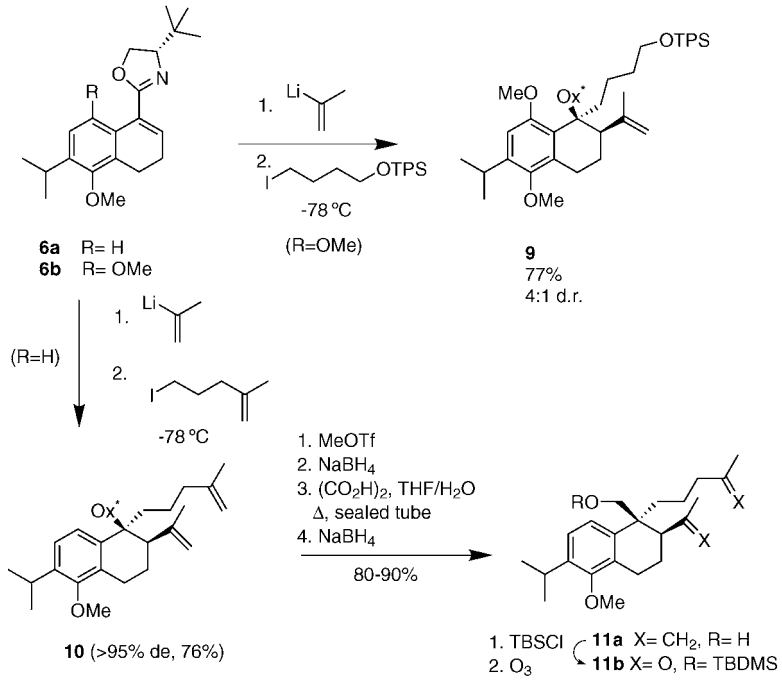
The retrosynthetic route is shown in Scheme 2. The oxidation of the aromatic ring to the quinone **3** was planned to be delayed until the final step. The C-ring was expected to be introduced by ozonolysis of the olefin **5b** to the ketone **5a**, followed by an intramolecular aldol condensation. The 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,[11] 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 triptoquinone 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[10] 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 dihydronaphthyloxazoline compared to the corresponding naphthyloxazolines reported earlier from our laboratory.[5,6] Where previous examples of alkyllithium 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[2–4] 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**.[6c] Protection of the hydroxyl group as the *tert*-butydimethylsilyl (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).[12] Metal-halogen exchange with butyllithium gave the oxygen-sensitive aryllithium which was then treated with $BF_3{\cdot}Et_2O$ 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-



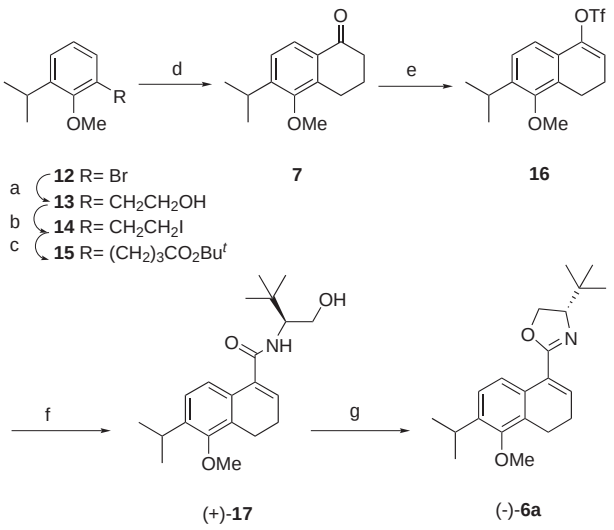
Scheme 2



Scheme 3

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, $PhNTf_2$) which underwent a palladium-catalyzed amidation[11] to yield the chiral amide alcohol (+)-**17**. Cyclization, using thionyl chloride, gave the chiral 2,3-dihydronaphthyloxazoline (–)-**6a**.

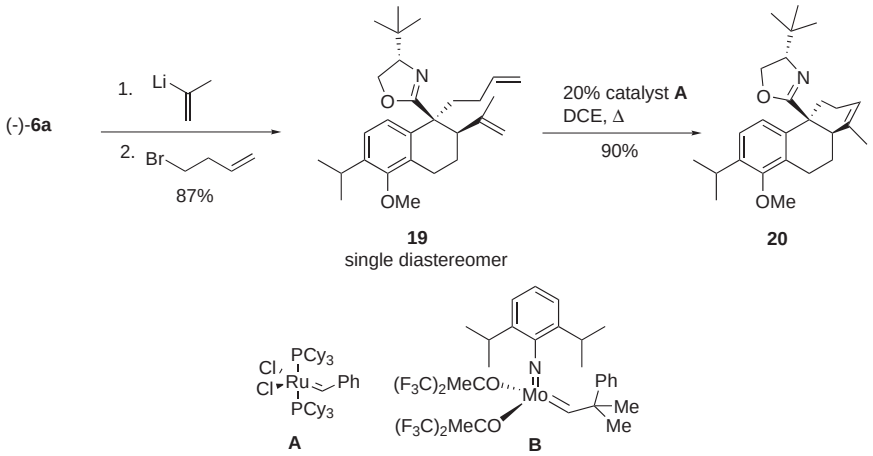
After the unsuccessful attempts to cyclize the diketone **11b**, via aldol methodology, a ring-closing metathesis of the diolefin **11a** was considered. Furthermore, use of the diolefin would simplify the synthesis and eliminate the ozonolysis steps of **11a** to **11b**. In the event, adduct **19** 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**[13] 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.



Scheme 4 *Reagents and conditions*: (a) BuLi, $BF_3{\cdot}Et_2O$, ethylene oxide, 80%; (b) I_2, Ph_3P, imidazole; (c) LDA, $MeCO_2Bu$-*t*, HMPA, 72% (two steps); (d) PPA, 75–85%; (e) KHMDS, $PhNTf_2$, quantitative; (f) $Pd(OAc)_2$, dppp, CO, Et_3N, DMSO, (*S*)-*tert*-leucinol, 78%; (g) $SOCl_2$, sat. aq K_2CO_3, MeCN, 83%

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



Scheme 5

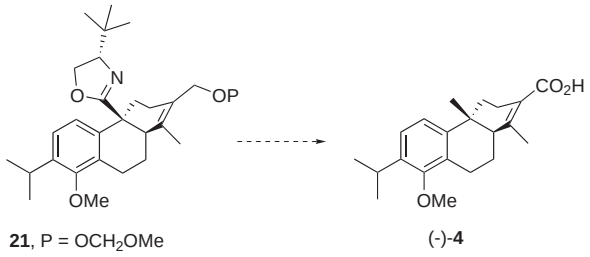
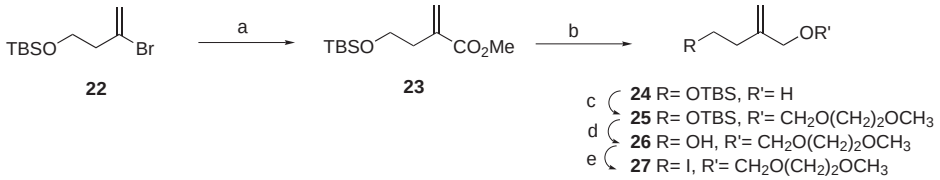


Figure 3 The structures of compounds **21** and **4**

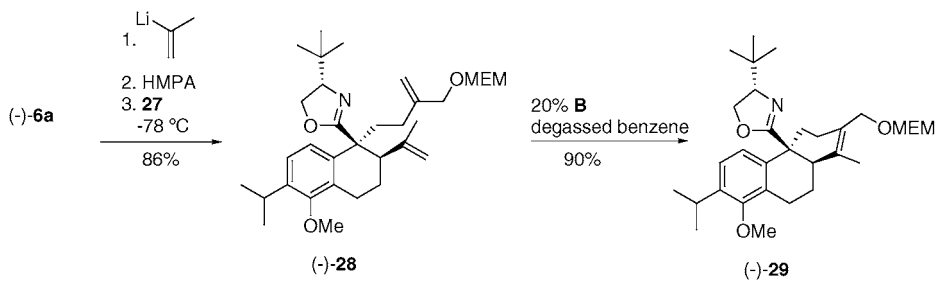
addition of methyl chloroformate. Ester reduction of **23** with DIBAL-H gave the allylic alcohol **24**, which was then treated with MEMCl to give the MEM-ether **25**. The TBS group was removed and the resulting alcohol **26** was converted to the requisite protected alkyl iodide **27**.

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 **B**[15] (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 ^{1}H NMR, ^{13}C 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.

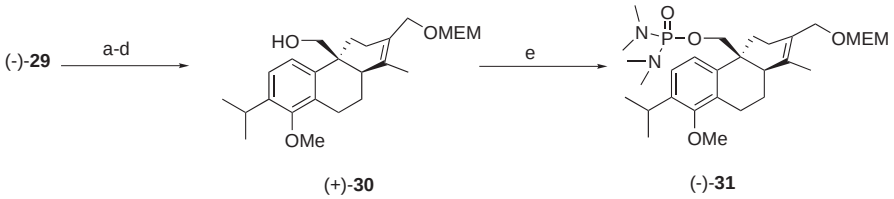
In order to achieve these goals, the oxazoline of **29** was converted to a carbinol following the earlier procedures, with slight modifications (Scheme 8). These conditions led to the neopentyl carbinol (+)-**30** with the MEM group intact. No isomerization of the olefin linkage was observed during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



Scheme 6 *Reagents and conditions*: (a) *t*-BuLi, Et_2O, $ClCO_2CH_3$, 50%; (b) DIBAL-H, THF, 90%; (c) MEMCl, Hunig's base, CH_2Cl_2, 85%; (d) TBAF, THF, 94%; (e) I_2, Ph_3P, imidazole, 91%



Scheme 7

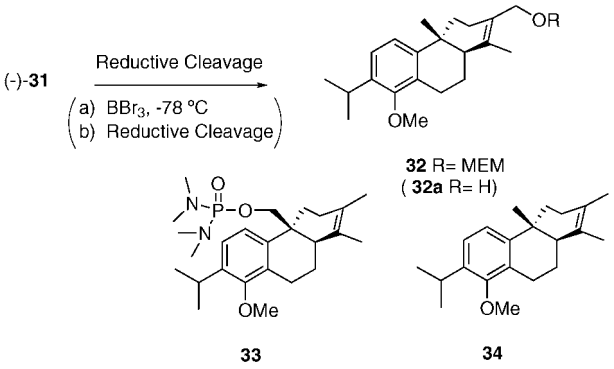


Scheme 8 *Reagents and conditions*: (a) MeOTf, CaH_2, CH_2Cl_2; (b) $NaBH_4$, THF, H_2O; (c) oxalic acid, THF, H_2O, 70 °C (d) $NaBH_4$, THF, H_2O, 75% over four steps; (e) $P(=O)Cl_2N(CH_3)_2$, Me_2NH, 85%

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 obtained[19] (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 BBr_3, CaH_2 in CH_2Cl_2 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-

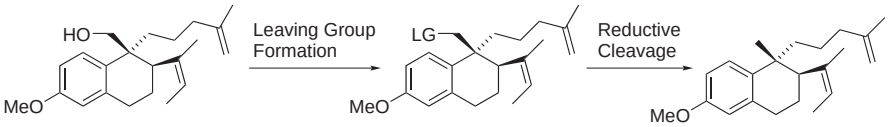


Scheme 9

tert-butylbiphenyl and lithium (or Li-naphthalenide), the resulting allylic alcohol **32a** was too unstable to purify and proceed further.

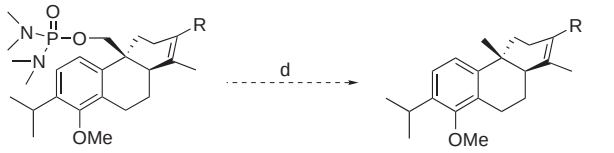
By changing the order of functional group manipulation, the phosphorodiamidate **31** was left intact, while removal of the MEM-ether moiety was performed (Scheme 10). Conversion of **31** to the unstable allylic alcohol **36** (used crude and never subjected to any acidic conditions), was followed by 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



Entry	LG	Conditions	Results
1	OTs, OMs	$LiBHEt_2$, $NaBH_4$/DMSO, $LiAlH_4$	either starting material or complex mixtures
2	I, Br	as above	unable to convert hydroxyl to halide
3	C(=S)SMe, C(=S)Imid.	LiNp	either starting material or complex mixtures
4	$P(=O)(NMe_2)_2$	LiNp, LiDBB	54% desired deoxygenated product
5	SCH_2CH_2S, $=NHNH_2$	NA	unable to form thioketal or hydrazone

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 phosphorodiamidate 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.



a **31** R= CH_2OMEM
b **36** R= CH_2OH
c **37** R= CHO
38 R= CO_2H
39 R= H

40a-d (R - CH_2OH, CHO, CO_2H, H)

Scheme 10 *Reagents and conditions*: (a) BBr_3, CaH_2, CH_2Cl_2, –78 °C; (b) MnO_2, CH_2Cl_2, r.t., 60% over 2 steps; (c) $NaClO_2$, NH_2SO_3H, aq dioxane, r.t., 80%; (d) Li-naphthalenide (or LDBB): unsatisfactory with **31**,**36**–**38**, 54% with **39**

Nonaqueous reactions were performed under argon with flame-dried glassware. Et_2O, THF, and benzene were dried by distillation over sodium-benzophenone. CH_2Cl_2, diisopropylamine, Et_3N, toluene, DMSO, and HMPA were distilled over CaH_2. Thin layer and flash chromatography were performed with E. Merck Kieselgel silica gel 60 (230–400 mesh A.S.T.M.) unless otherwise stated. Schrock catalyst was purchased from Strem Chemical, Inc. and was washed with hexane under argon prior to use. *N*,*N*-Dimethylphosphoroamidic dichloride was purchased from Lancaster Synthesis, Inc. and used without further purification. All other commercial compounds were purchased from Aldrich Chemical Co. and unless otherwise indicated, used without further purification. Melting points are uncorrected. Microanalyses were performed by Atlantic Microlab, Inc., Norcross, Georgia.

(4*S*)-4-*tert*-Butyl-2-(6-isopropyl-5-methoxy-3,4-dihydronaphthalen-1-yl)oxazoline (6a)

To a solution of the amide alcohol **17** (500 mg, 1.45 mmol) in CH_2Cl_2 (15 mL) at 0 °C was slowly added $SOCl_2$ (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 K_2CO_3 (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 (Na_2SO_4), filtered, and concentrated. The crude material was purified by flash chromatography (5% EtOAc–hexanes and 10% EtOAc–hexanes) to yield (–)-**6a** as a slow-forming, cream colored solid. The product could be stored under argon at –18 °C for several weeks; however, at r.t., decomposition began to occur within 24 h; mp 78–80 °C; $[\alpha]_D^{25}$ –149 (*c* = 0.55, $CHCl_3$).

IR (film): 1650, 1482 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 1.21 (d, *J* = 2.25 Hz, 3 H), 1.24 (d, *J* = 2.25 Hz, 3 H), 2.66 (ddd, *J* = 15.3, 11.7, 6.4 Hz, 1 H), 2.94 (ddd, *J* = 15.2, 6.6, 6.6 Hz, 1 H), 3.32 (ddd, *J* = 13.8, 6.8, 6.8 Hz, 1 H), 3.67 (s, 3 H), 4.04 (dd, *J* = 10.1, 7.7 Hz, 1 H), 4.13 (dd, *J* = 8.1, 8.1 Hz, 1 H), 4.24 (dd, *J* = 10.1, 8.4 Hz, 1 H), 6.88 (dd, *J* = 5.4, 4.35 Hz, 1 H), 7.14 (d, *J* = 8.1 Hz, 1 H), 7.74 (d, *J* = 8.1 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 20.5, 23, 23.7, 26, 26.5, 33.9, 61.1, 67.5, 77.6, 122.6, 124, 127.5, 128.9, 130.6, 135.1, 141, 153.9, 162.3.

HRMS (FAB+): *m*/*z* Calcd for $C_{21}H_{30}NO_2$ $(M + H)^+$ 328.2276. Found 328.2281.

(4*S*)-4-*tert*-Butyl-2-(6-isopropyl-5,8-dimethoxy-3,4-dihydronaphthalen-1-yl)oxazoline (6b)

Oxazoline **6b** was obtained in a similar manner as **6a** starting from 5,8-dimethoxytetralone;[10] $[\alpha]_D^{25}$ –67.5 (*c* = 0.79, MeOH).

IR (film): 1657, 1478 cm^{-1}.

^1H NMR ($CDCl_3$, 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), 3.30 (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).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 21.6, 22.4, 23.7, 26.1, 26.8, 33.6, 56.4, 61.3, 68.9, 75.6, 107.9, 119.9, 126.6, 131.0, 134.5, 142.0, 148.1, 152.2, 166.5.

HRMS (FAB+): *m*/*z* Calcd for $C_{22}H_{32}NO_3$ $(M + H)^+$ 358.2382. Found 358.2386.

6-Isopropyl-5-methoxy-3,4-dihydro-2*H*-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 polyphosphoric acid (20 mL) for 2 h. The red reaction mixture was cooled, diluted with H_2O (100 mL), and extracted with EtOAc (3 × 50 mL). The EtOAc solution was washed with sat. aq $NaHCO_3$ (2 × 75 mL) and brine (100 mL). The solution was dried ($MgSO_4$), 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 ($CDCl_3$, 300 MHz): δ = 1.24 (d, *J* = 6.6 Hz, 6 H), 2.11 (dddd, *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).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 22.9, 23.5, 26.9, 38.8, 61.1, 123. 2, 124.6, 131.9, 137.7, 147.7, 154.5, 198.1.

HRMS (FAB+): *m*/*z* Calcd for $C_{14}H_{19}O_2$ $(M + H)^+$ 219.1385. Found 219.1382.

Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: 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 CS_2 (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 Et_2O (350 mL). The Et_2O solution was washed with 10% aq $Na_2S_2O_3$ (2 × 150 mL), and brine (100 mL). After drying ($MgSO_4$), the solution was filtered and concentrated. Flash chromatography (0.5% EtOAc–hexanes) of the crude material produced 24.9 g of the desired 1-bromo-3-isopropyl-2-hydroxybenzene (86%). Following the procedure of McKillop et al.,[21] a biphasic mixture of the preceding phenol (15.8 g, 17.6 mmol), dimethyl sulfate (14 g, 111 mmol), $LiOH·H_2O$ (4.9 g, 118 mmol), and benzyltributylammonium chloride (2.3 g, 7.3 mmol) in CH_2Cl_2–H_2O (1:1, 600 mL) was stirred at r.t. for 12 h. The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 100 mL). The CH_2Cl_2 extracts were combined and stirred with 10% NH_4OH solution (300 mL) for 5 h. The phases were separated and the organic phase was dried (Na_2SO_4) 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.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 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).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 23.7, 27.2, 61.3, 117.4, 125.6, 125.9, 130.8, 144, 154.2.

MS: *m*/*z* = 228/230 (M^+).

Anal. Calcd for $C_{10}H_{13}BrO$: C, 52.42; H, 5.72. Found: C, 52.13; H, 5.90.

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, 5.7 mL, 13.7 mmol) at –78 °C, which had also been degassed as described above. After stirring 15 min, $BF_3{\cdot}Et_2O$ (2.04 g, 14.4 mmol) was added and the reaction mixture was stirred for 30 min, which became brightly yellow over time. Ethylene oxide (~1 mL) was condensed into the reaction mixture. After stirring for 2 h at –78 °C, sat. aq NH_4Cl (30 mL) was added and the mixture was allowed to warm to r.t. and extracted with EtOAc (3 × 50 mL). The combined extracts were dried (Na_2SO_4), filtered, and concentrated. Flash chromatography (gradient from 10 to 25% EtOAc–hexanes) gave 2.03 g (80%) of **13** as a light yellow oil.

IR (neat): 3358 (br), 1462 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.24 (d, *J* = 6.9 Hz, 6 H), 1.98 (t, *J* = 5.4 Hz, 1 H), 2.93 (t, *J* = 6.6 Hz, 2 H), 3.33 (sept, *J* = 6.9 Hz, 1 H), 3.77 (s, 3 H), 3.87 (q, *J* = 6 Hz, 2 H), 7.02–7.10 (m, 2 H), 7.17 (dd, *J* = 6.6, 2.8 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 24, 26.3, 33.9, 61.7, 63.5, 124.6, 128.1, 131.7, 142.1, 155.8.

HRMS (FAB+): *m*/*z* Calcd for $C_{12}H_{18}O_2$ $(M)^+$ 194.1307. Found 194.1289.

1-(2-Iodoethyl)-3-isopropyl-2-methoxybenzene (14)

To CH_2Cl_2 (40 mL) at 0 °C was added Ph_3P (2.76 g, 10.5 mmol) and I_2 (2.89 g, 11.38 mmol). After stirring for 20 min, imidazole (835 mg, 12.3 mmol) was added, followed by a solution of **13** in CH_2Cl_2 (10 mL). The reaction mixture was allowed to warm to r.t. slowly. After 12 h, the mixture was diluted with EtOAc (100 mL), washed with 10% aq $Na_2S_2O_3$ (2 × 75 mL) and brine (50 mL). The EtOAc solution was dried (Na_2SO_4), filtered, and concentrated. The crude residue was flushed through a plug of silica gel with 10% EtOAc–hexanes gave 2.49 g (94%) of **14** as a light yellow oil.

IR (neat): 1463 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.23 (d, *J* = 7.5 Hz, 6 H), 3.21 (t, *J* = 7.5 Hz, 2 H), 3.32 (sept, *J* = 6.6 Hz, 1 H), 3.37 (t, *J* = 7.5 Hz, 2 H), 3.76 (s, 3 H), 7.01 (dd, *J* = 10.5, 2.1 Hz, 1 H), 7.07 (t, *J* = 7.5 Hz, 1 H), 7.2 (dd, *J* = 10.5, 2.1 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 4.6, 24, 26.4, 35.5, 61.9, 124.5, 125.7, 127.3, 133.6, 142.2, 155.4.

4-(3-Isopropyl-2-methoxyphenyl)butyric Acid *tert*-Butyl Ester (15)

To a solution of anhyd diisopropylamine (0.31 g, 3.01 mmol) in anhyd THF (6 mL) at –78 °C was added BuLi (1.95M in hexane, 2.74 mmol, 1.4 mL). After stirring for 15 min, *tert*-butyl acetate (315 mg, 2.74 mmol) was added dropwise, and the reaction mixture was stirred for 30 min at –78 °C. In a separate flask, iodide **14** (1g, 3.29 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 NH_4Cl (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 (Na_2SO_4), filtered and concentrated. Flash chromatography (step gradient: hexanes to 2% EtOAc–hexanes) gave 685 mg (85%) of **15** as a colorless oil.

IR (neat): 1729, 1462 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.23 (d, *J* = 6.6 Hz, 6 H), 1.45 (s, 9 H), 1.9 (q, *J* = 7.5 Hz, 2 H), 2.28 (t, *J* = 7 Hz, 2 H), 2.66 (t, *J* = 7.8 Hz, 2 H), 3.32 (sept, *J* = 6.6 Hz, 1 H), 3.73 (s, 3 H), 7.04–7.02 (m, 2 H), 7.12 (dd, *J* = 6.3, 3.3 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 24.1, 26.2, 26.4, 28.2, 29.3, 35.4, 61.7, 80, 124.2, 124.4, 127.4, 134.4, 141.8, 155.4, 172.8.

HRMS (FAB+): *m*/*z* Calcd for $C_{18}H_{28}O_3$ $(M)^+$ 292.2038. Found 292.2040.

Anal. Calcd for $C_{18}H_{28}O_3$: C, 73.93; H, 9.65. Found: C, 73.98; H, 9.72.

Trifluoromethanesulfonic Acid 6-Isopropyl-5-methoxy-3,4-dihydronaphthalen-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*-phenyltriflamide (1.07 g, 3 mmol) in THF (3 mL). After stirring for 1 h at –78 °C, the mixture was allowed to warm to r.t. Sat. aq NH_4Cl (20 mL) was added, and the mixture was extracted with EtOAc (3 × 20 mL). The EtOAc solution was dried (Na_2SO_4), 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.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.23 (d, *J* = 6.9 Hz, 6 H), 2.48 (ddd, *J* = 8.4, 4.2, 4.2 Hz, 2 H), 2.9 (dd, *J* = 8.1, 8.1 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, 1H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 20.4, 22.1, 23.7, 26.7, 61.2, 116.8, 117.5, 124.6, 127.6, 128.9, 130 [q, *J* (^{13}C,^{19}F) = 75 Hz], 143.4, 146.2, 154.3.

HRMS (FAB+): *m*/*z* Calcd for $C_{15}H_{17}F_3O_4S$ $(M)^+$ 350.0800. Found 350.0801.

6-Isopropyl-5-methoxy-3,4-dihydronaphthalene-1-carboxylic Acid (1*S*)-2Hydroxy-1-*tert*-butylethyl)amide (17)

The following were combined in order: vinyl triflate **16** (810 mg, 2.34 mmol), (*S*)-*tert*-leucinol (548 mg. 4.68 mmol), Et_3N (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 (Na_2SO_4), filtered, and concentrated. The crude residue was purified by flash chromatography (15% EtOAc–hexanes and 45% EtOAc–hexanes) to give 624 mg (77%) of **17** as a colorless foam; $[\alpha]_D^{25}$ +13.7 (*c* = 0.54, $CHCl_3$).

IR (film): 1644, 1610 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 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, 7.5, 3.3 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

(m, 2 H), 5.97 (br d, *J* = 9.3 Hz, 1 H), 6.51 (app t, *J* = 4.6 Hz, 1 H), 7.12 (d, *J* = 8.4 Hz, 1 H), 7.22 (d, *J* = 8.4 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 20.6, 22.6, 23.7, 26.5, 27, 33.6, 59.7, 61.1, 63.3, 121.4, 124.4, 128.8, 130.2, 130.4, 136.5, 141.8, 154.3, 170.2.

HRMS (FAB+): *m*/*z* Calcd for $C_{21}H_{32}NO_3$ $(M + H)^+$ 346.2382. Found 346.2388.

Anal. Calcd for $C_{21}H_{31}NO_3$: C, 73.01; H, 9.04 Found: C, 72.87; H, 9.20.

(3-Bromobut-3-enyloxy)-*tert*-butyldimethylsilane (22)

To a solution of 3-bromobut-3-en-1-ol (Aldrich) (860 mg, 5.7 mmol) in DMF (4 mL) was added *tert*-butyldimethylsilyl 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 Et_2O (50 mL). The solution was washed with brine (3 × 150 mL), dried (Na_2SO_4), and concentrated. The material was purified by flash chromatography (2% EtOAc–hexanes) to give **22** as a clear liquid.

^{1}H NMR ($CDCl_3$, 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).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = –5.3, 18.3, 25.9, 44.8, 60.8, 118.4, 130.8.

Anal. Calcd for $C_{10}H_{21}BrOSi$: C, 45.28; H, 7.98 Found: C, 45.30; H, 8.04.

4-(*tert*-Butyldimethylsilyloxy)-2-methylenebutyric Acid Methyl Ester (23)

t-BuLi (2 M in pentane, 4 mL, 8 mmol) was added slowly to a solution **22** (1 g, 3.77 mmol) in anhyd Et_2O (30 mL). After 15 min, methyl chloroformate (465 mg, 4.92 mmol) was added and the solution was stirred for 30 min. Sat. aq NH_4Cl (15 mL) was added and the mixture was allowed to warm to r.t. The layers were separated and the aqueous layer was extracted with Et_2O (2 × 15 mL). The organic layers were combined, dried (Na_2SO_4), filtered, and concentrated at r.t. (30 mmHg). The crude residue was purified by flash chromatography (2.5% Et_2O–petroleum ether) to give 460 mg (50%) of **23** as a tan oil.

IR (neat): 1723, 1632 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.53 (t, *J* = 6.6 Hz, 2 H), 3.72 (t, *J* = 6.6 Hz, 2 H), 3.74 (s, 3 H), 5.62 (d, *J* = 1.5 Hz, 1 H), 6.2 (d, *J* = 1.5 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = –5.4, 18.3, 25.9, 35.5, 51.8, 61.8, 127, 137.2, 167.5.

4-(*tert*-Butyldimethylsilyloxy)-2-methylenebutan-1-ol (24)

To a solution of **23** (520 mg, 2.13 mmol) in THF (15 mL) at 0 °C was slowly added DIBAL-H (2 M in toluene, 3.2 mL, 6.4 mmol). The reaction mixture was stirred for 3 h, and aq 1 N NaOH (25 mL) was slowly added. The phases were separated and the aqueous phase was extracted with EtOAc (2 × 25 mL). The organic phase was dried (Na_2SO_4), filtered and concentrated. Flash chromatography (5% EtOAc–hexanes and 10% EtOAc–hexanes) gave 414 mg (90%) of **24** as a light yellow oil.

IR (neat): 3357 (br), 1649 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.07 (s, 6 H), 0.9 (s, 9 H), 2.34 (t, *J* = 6 Hz, 2 H), 2.77 (t, *J* = 6 Hz, 1 H), 3.75 (t, *J* = 6 Hz, 2 H), 4.07 (d, *J* = 5.7 Hz, 2 H), 4.9 (br s, 1 H), 5.04 (br s, 1 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = –5.5, 18.3, 25.9, 37.1, 63.4, 66.4, 112.5, 147.2.

Anal. Calcd for $C_{11}H_{24}O_2Si$: C, 61.06; H, 11.18 Found: C, 61.33; H, 11.28.

***tert*-Butyl-[3-(2-methoxyethoxymethoxymethyl)but-3-enyloxy]dimethylsilane (25)**

To a solution **24** (2 g, 9.26 mmol) and diisopropylethylamine (5.32 mL, 30.7 mmol) in CH_2Cl_2 (6 mL) at r.t. was added 2-methoxyethoxymethyl chloride (MEM-Cl) (1.6 mL, 14 mmol). After stirring for 24 h, the mixture was diluted with EtOAc (40 mL), and washed with 10% aq $CuSO_4$ (2 × 40 mL) and brine (40 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated. Flash chromatography (10% EtOAc–hexanes) gave 2.4 g (85%) of **25** as an oil.

IR (neat): 1652, 1464 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.04 (s, 6 H), 0.88 (s, 9 H), 2.28 (dd, *J* = 6, 6 Hz, 2 H), 3.39 (s, 3 H), 3.55–3.56 (m, 2 H), 3.69–3.74 (m, 4 H), 4.02 (br s, 2 H), 4.73 (s, 3 H), 4.93 (br s, 1 H), 5.08 (br s, 1 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = –5.3, 18.3, 25.9, 36.7, 59, 62.1, 66.8, 70.4, 71.8, 94.7, 113, 142.8.

HRMS (FAB+): *m*/*z* Calcd for $C_{15}H_{33}O_4Si$ $(M + H)^+$ 305.2148. Found: 305.2143.

3-(2-Methoxyethoxymethoxymethyl)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 × 50 mL), dried (Na_2SO_4), filtered, and concentrated. Flash chromatography (25% EtOAc–hexanes and 50% EtOAc–hexanes) gave 1.18 g (94%) of **26** as a clear oil.

IR (neat): 3444 (br), 1652 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.36 (t, *J* = 6 Hz, 2 H), 3.39 (s, 3 H), 3.55–3.58 (m, 2 H), 3.70–3.77 (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).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 37.1, 59, 61.1, 67, 70.4, 71.7, 94.7, 115, 142.5.

HRMS (FAB+): *m*/*z* Calcd for $C_9H_{18}O_4$ $(M + H)^+$ 191.1283. Found: 191.1282.

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

To a solution of Ph_3P (497 mg, 1.89 mmol) in CH_2Cl_2 (8 mL) at 0 °C was added I_2 (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 CH_2Cl_2 (3 mL). The mixture was stirred for 10 h while allowing to warm to r.t., and the insolubles were removed by filtration and washed with Et_2O (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}.

^{1}H NMR ($CDCl_3$, 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).

^{13}C NMR ($CDCl_3$, 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 $C_9H_{18}O_{3I}$ $(M + H)^+$ 301.0301. Found: 301.0303.

(4*S*)-4-*tert*-Butyl-2-{(1*S*,2*R*)-2-isopropenyl-6-isopropyl-5-methoxy-1-[3-(2-methoxyethoxymethoxymethyl)but-3-enyl]-1,2,3,4-tetrahydronaphthalen-1-yl}oxazoline (28); Representative Tandem Addition

t-BuLi (1.7M 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. Iodide **27** (358 mg, 1.19 mmol) was added and after 5 min, the reaction was stopped by addition of sat. aq NH_4Cl (10 mL). After addition of EtOAc (6 mL), the phases were separated. The organic layer was washed with brine, dried (Na_2SO_4), 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; $[\alpha]_D^{25}$ –157 (*c* = 0.42, $CHCl_3$).

IR (neat): 1652 cm^{-1}.

^1H NMR ($CDCl_3$, 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 (ddd, *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 (s, 3 H), 3.56–3.59 (m, 2 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).

^{13}C NMR ($CDCl_3$, 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, 123.2, 123.9, 131.2, 136.6, 138.7, 145.8, 146, 154.8, 170.7.

HRMS (FAB+): *m*/*z* Calcd for $C_{33}H_{52}NO_5$ $(M + H)^+$ 542.3845. Found: 542.3839.

(4*S*)-4-*tert*-Butyl-2-[(1*S*,2*R*)-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-iodo-4-methylpent-4-ene to give **10** as a single diastereomer; white solid (76%); mp 104–105 °C; $[\alpha]_D^{25}$ –258 (*c* = 0.71, MeOH).

IR (film): 2859, 1651, 1480, 1450 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 0.73–0.93 (m, 1 H), 0.86 (s, 9 H), 1.17 (d, *J* = 6.9 Hz, 3 H), 1.19 (d, *J* = 6.9 Hz, 3 H), 1.20–1.35 (m, 1 H), 1.55 (s, 3 H), 1.64–1.67 (m, 1 H), 1.72 (s, 3 H), 1.91 (m, 2 H), 2.18 (dd, *J* = 9.1, 7.5 Hz, 2 H), 2.29 (qd, *J* = 12.6, 4.46 Hz, 1 H), 2.46–2.62 (m, 2 H), 3.08 (dq, *J* = 10.7, 2.5 Hz, 1 H), 3.27 (hept, *J* = 6.9 Hz, 1 H), 3.68–3.74 (m, 1 H), 3.70 (s, 3 H), 3.86 (t, *J* = 8.1 Hz, 1 H), 3.98 (dd, *J* = 10.3, 8.7 Hz, 1 H), 4.55 (s, 1 H), 4.61 (s, 1 H), 4.76 (s, 1 H), 4.88 (s, 1 H), 6.89 (d, *J* = 8.3 Hz, 1 H), 6.97 (d, *J* = 8.3 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 21.1, 21.7, 22.2, 23.6, 23.9, 24.4, 25.2, 26.0, 26.2, 34.0, 36.6, 38.0, 46.5, 47.5, 60.6, 67.9, 74.9, 109.8, 114.1, 123.3, 123.7, 131.1, 137.0, 138.4, 145.8, 146.1, 154.7, 170.9.

Anal. Calcd for $C_{30}H_{45}NO_2$: C, 79.77; H, 10.04. Found: C, 79.52; H, 10.13.

(4*S*)-4-*tert*-Butyl-2-[(4a*S*,10a*R*)-7-isopropyl-8-methoxy-2-(2-methoxyethoxymethoxymethyl)-1-methyl-3,9,10,10a-tetrahydro-4*H*-phenanthren-4a-yl]oxazoline (29)

The following procedure was performed using standard Schlenk-line techniques. A solution of oxazoline adduct **28** (250 mg, 0.46 mmol) in benzene (5 mL), which had been degassed via freeze/pump/thaw cycles (liquid N_2, 4 ×), was added by cannula to $Mo(CHCMe_2Ph)[N(2,6\text{-}i\text{-}Pr)_2C_6H_3][OCMe(CF_3)_2]_2$ (Schrock catalyst, **B**, ~50 mg). The reaction was stirred for 45 min at r.t., then 1.5 h in a 60 °C oil bath. After cooling, the crude reaction mixture was flushed through a plug of silica gel (1:1 EtOAc–hexanes). The material was concentrated and purified by flash chromatography (5% EtOAc–hexanes, 10% EtOAc–hexanes) to give 210 mg (90%) of **29** as a yellow oil; $[\alpha]_D^{25}$ –146 (*c* = 0.5, $CHCl_3$).

^1H NMR ($CDCl_3$, 300 MHz): δ = 0.75 (s, 9 H), 1.20 (d, *J* = 6.9 Hz, 3 H), 1.22 (d, *J* = 6.9 Hz, 3 H), 1.72 (ddd, *J* = 12.8, 11.1, 7.6 Hz, 1 H), 1.83 (s, 3 H), 2.12–2.49 (m, 4 H), 2.62–2.77 (m, 2 H), 2.86 (dd, *J* = 12.8, 5.6 Hz, 1 H), 2.98–3.10 (m, 1 H), 3.29 (sept, *J* = 6.3 Hz, 1 H), 3.41 (s, 3 H), 3.58 (dd, *J* = 5.6, 2.1 Hz, 2 H), 3.63–3.74 (m, 5 H), 3.72 (s, 3 H), 3.84 (app t, *J* = 8.1 Hz, 1 H), 3.93 (dd, *J* = 10.2, 9 Hz, 1 H), 4.32 (d, *J* = 10.2 Hz, 1 H), 4.72 (s, 2 H), 7.06 (d, *J* = 8.3 Hz, 1 H), 7.34 (d, *J* = 8.3 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 15.5, 21, 23.8, 24.1, 25.8, 26.2, 27.42, 33.5, 34.2, 43.3, 45.1, 59, 60.5, 66.7, 67.3, 67.7, 71.8, 75.8, 94.8, 123.1, 123.4, 125.3, 130.6, 135.1, 138.9, 139.2, 154.7, 167.3.

HRMS (FAB+): *m*/*z* Calcd for $C_{31}H_{47}NO_5$ $(M + H)^+$ 513.3454. Found: 513.3444.

(4*S*)-4-*tert*-Butyl-2-[(4a*S*,10a*R*)-7-isopropyl-8-methoxy-1-methyl-3,9,10,10a-tetrahydro-4*H*-phenanthren-4a-yl]oxazoline (20)

A tandem addition was carried out with oxazoline **6a**, 2-lithiopropene, and 4-bromobut-1-ene to give the adduct **19** in a similar manner as with compounds **10** and **28**. To a degassed solution of oxazoline adduct **19** (60 mg, 0.142 mmol) in CH_2Cl_2 (14 mL) was added Grubbs' catalyst (**A**, 5 mg). The brown solution was refluxed for 24 h adding additional catalyst (3 × 5 mg) every 6–8 h. The solvent was removed and the residue was purified by flash chromatography to give 51 mg (90%) of **20**.

^1H NMR ($CDCl_3$, 300 MHz): δ = 0.84 (s, 9 H), 1.24 (d, *J* = 7.5 Hz, 3 H), 1.27 (d, *J* = 7.5 Hz, 3 H), 1.28–1.33 (m, 1 H), 1.69–1.82 (m, 4 H), 2.05–2.49 (m, 4 H), 2.66–2.86 (m, 2 H), 2.98–3.10 (m, 1 H), 3.30 (sept, *J* = 7.5 Hz, 1 H), 3.66–3.76 (m, 1 H), 3.72 (s, 3 H), 3.88 (app t, *J* = 8.4 Hz, 1 H), 3.94 (app t, *J* = 9.3 Hz, 1 H), 5.28 (br s, 1 H), 7.07 (d, *J* = 8.4 Hz, 1 H), 7.37 (d, *J* = 8.4 Hz, 1 H).

HRMS (FAB+): *m*/*z* Calcd for $C_{26}H_{37}NO_2$ $(M + H)^+$ 396.2902. Found: 396.2896.

[(4a*S*,10a*R*)-7-Isopropyl-8-methoxy-2-(2-methoxyethoxymethoxymethyl)-1-methyl-3,9,10,10a-tetrahydro-4*H*-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 CH_2Cl_2 (1 mL), then chilled to 0 °C, and CaH_2 (~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–H_2O (4:1, 2.5 mL). The mixture was chilled to 0 °C and $NaBH_4$ (15 mg, 0.39 mmol) was added portionwise. After chilling for 30 min, aq 1 N 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 (Na_2SO_4), filtered and concentrated. The crude oxazolidine was dissolved in THF/H_2 (4:1, 2 mL), and oxalic acid dihydrate (82 mg, 0.65 mmol) was added. The solution was refluxed for 6 h. After cooling, sat. aq $NaHCO_3$ (2 mL) was added, and the solution was extracted with EtOAc (3 × 10 mL). The organic phase was washed with brine (10 mL), dried (Na_2SO_4), filtered and concentrated to yield the crude aldehyde which was generally used without further purification. To a solution of the crude aldehyde in THF–H_2O (1:1, 2.5 mL) at 0 °C was slowly added $NaBH_4$ (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 (Na_2SO_4), filtered and concentrated. Flash chromatography (25% and 50% EtOAc–hexanes) gave 42 mg, (75%) of carbinol **30** as a light yellow oil from oxazoline **29**; $[\alpha]_D^{25}$ +4.8 (*c* = 1.2, $CHCl_3$).

IR (neat): 3478 cm^{-1} (br).

^1H NMR ($CDCl_3$, 300 MHz): δ = 1.04 (dd, *J* = 8.7, 5.1 Hz, 1 H), 1.22 (d, *J* = 3 Hz, 3 H), 1.24 (d, *J* = 3 Hz, 3 H), 1.44–1.7 (m, 2 H), 1.78 (s, 3 H), 2.18–2.44 (m, 4 H), 2.65 (br d, *J* = 12 Hz, 1 H), 2.94 (ddd, *J* = 18.3, 18.3, 9.5 Hz, 1 H), 3.01 (ddd, *J* = 18.3, 18.3, 8 Hz, 1 H), 3.31 (sept, *J* = 6.8 Hz, 1 H), 3.41 (s, 3 H), 3.52–3.61 (m, 3 H), 3.67–3.76 (m, 3 H), 3.74 (s, 3 H), 4.00 (d, *J* = 10.8 Hz, 1 H), 4.27 (d, *J* = 10.8 Hz, 1 H), 4.74 (s, 2 H), 7.10 (d, *J* = 8.2 Hz, 1 H), 7.16 (d, *J* = 8.2 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 15.7, 20.3, 23.3, 23.9, 26.2, 28.4, 29.7, 40.5, 43.9, 59, 60.5, 64.6, 66.8, 67.7, 71.8, 94.8, 121.2, 123.5, 127.3, 129.7, 132.9, 139.4, 141.3, 155.6.

HRMS (FAB+): *m*/*z* Calcd for $C_{25}H_{39}O_5$ $(M + H)^+$ 419.2797. Found: 419.2799.

[(4a*S*,10a*R*)-7-Isopropyl-8-methoxy-2-(2-methoxyethoxymethoxymethyl)-1-methyl-3,9,10,10a-tetrahydro-4*H*-phenanthren-4a-yl]methanol-*N*,*N*,*N*′,*N*′-tetramethylphosphorodiamidate (31); Representative Example of Phosphorodiamidate Formation

To a solution of carbinol **30** (23 mg, 0.055 mmol, dried via toluene azeotrope) in THF (1.2 mL) at 0 °C was added MeLi (0.5 M in Et_2O, 145 μL, 0.072 mmol). After stirring for 10 min, HMPA (15 μL, 0.11 mmol) was added and the solution was stirred for an additional 20 min at 0 °C. To this was added *N*,*N*-dimethylphosphoramidic dichloride (8 μL, 0.067 mmol). The solution was allowed to warm to r.t. and stirred for 30 min. After being rechilled to 0 °C, dimethylamine (~1 mL) was added and the solution was stirred for 30 min. H_2O (5 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 5 mL), then washed with brine (5 mL). Flash chromatography on neutral alumina (EtOAc and 2% MeOH–EtOAc) gave 26 mg (85%) of **31** as a light yellow oil; $[\alpha]_D^{25}$ –8.2 (*c* = 1, $CHCl_3$).

IR (neat): 1044, 993 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 1.14 (d, *J* = 7.2 Hz, 3 H), 1.22 (d, *J* = 7.2 Hz, 3 H), 1.52–1.67 (m, 2 H), 1.74 (s, 3 H), 2.25 (s, 3 H), 2.28 (s, 3 H), 2.20–2.43 (m, 4 H), 2.50 (s, 3 H), 2.53 (s, 3 H), 2.61–2.68 (m, 2 H), 2.85–3.09 (m, 2 H), 3.29 (sept, *J* = 6.8 Hz, 1 H), 3.4 (s, 3 H), 3.56–3.61 (m, 2 H), 3.71 (s, 3 H), 3.69–3.76 (m, 2 H), 3.88 (d, *J* = 11.1 Hz, 1 H), 4.0 (dd, *J* = 9.6, 3 Hz, 1 H), 4.27 (d, *J* = 11.1 Hz, 1 H), 4.73 (s, 2 H), 7.04 (d, *J* = 8.4 Hz, 1 H), 7.15 (d, *J* = 8.4 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 15.7, 20.3, 23, 23.6, 24.3, 25.8, 26.1, 28.5, 36.2, 36.4, 39.4, 43.9, 59, 60.5, 66.8, 67.5, 71.8, 94.8, 122.1, 122.8, 127.2, 129.1, 132.6, 141.4, 155.

HRMS (FAB+): *m*/z Calcd for $C_{29}H_{50}N_2O_6P$ $(M + H)^+$ 553.3407. Found: 553.3393.

(4a*R*,10a*R*)-7-Isopropyl-8-methoxy-1,4a-dimethyl-3,4,4a,9,10,10a-hexahydrophenanthrene (40d)

Oxazoline tricycle **20** (100 mg, 0.25 mmol) was treated in a similar manner as compound **29** to give the required phosphorodiamidate **39** (56 mg, 0.13 mmol), which was then dissolved in THF (1 mL). To this was added a solution of lithium naphthalenide (0.3 M in THF) and the reaction mixture was stirred for 30 min at r.t. H_2O (1 mL) was added and the resulting mixture was extracted with Et_2O (20 mL). The extract was washed with brine, dried ($MgSO_4$), filtered and concentrated. The residue was purified by flash chromatography (2% EtOAc–hexanes) to give 20 mg (54%) of **40d**.

^1H NMR ($CDCl_3$, 300 MHz): δ = 1.04 (s, 3 H), 1.20 (d, *J* = 7 Hz, 3 H), 1.25 (d, *J* = 7 Hz, 3 H), 1.54–1.72 (m, 5 H), 2.10–2.30 (m, 5 H), 2.83 (ddd, *J* = 18.9, 9.9, 8.9 Hz, 1 H), 3.01 (dd, *J* = 17.4, 7.2 Hz, 1 H), 3.30 (sept, *J* = 6.6 Hz, 1 H), 3.74 (s, 3 H), 5.43 (br s, 1 H), 7.07 (d, *J* = 7.8 Hz, 1 H), 7.11 (d, *J* = 7.8 Hz, 1 H).

HRMS (FAB+): *m*/z Calcd for $C_{20}H_{29}O$ $(M + H)^+$ 285.2218, Found: 285.2213.

(4a*S*,10a*R*)-4a-(*N*,*N*,*N*′,*N*′-Tetramethylphosphorodiamidatyl)-7-isopropyl-8-methoxy-1-methyl-3,4,4a,9,10,10a-hexahydrophenanthrene-2-carboxylic Acid (38)

To a solution of the phosphorodiamidate **31** (5 mg, 0.01 mmol) in CH_2Cl_2 (0.8 mL) was added a catalytic amount of CaH_2 and the solution was chilled to –78 °C. BBr_3 (0.3 M in CH_2Cl_2, 40 μL) was slowly added, and the solution was stirred 10 min at –78 °C. The mixture was diluted with aq 1 N NaOH, warmed to r.t., and extracted with CH_2Cl_2 (5 mL). The phases were separated, and the organic layer was dried (Na_2SO_4), filtered and concentrated. The crude alcohol **36** was dissolved in CH_2Cl_2 (1 mL) and MnO_2 (~20 mg) was added. After 2 h, the mixture was filtered through a plug of Celite and concentrated. The crude aldehyde **37** was dissolved in dioxane–H_2O (1:1, 0.8 mL), and sulfamic acid [0.1 M in dioxane–H_2O (1:1), 274 μL] and $NaClO_2$ [0.2 M in dioxane–H_2O (1:1), 144 μL] were added sequentially. After stirring 3 h at r.t., the solvent was removed, and the residue was dissolved in CH_2Cl_2 (5 mL) and washed with brine (5 mL). The organic phase was dried (Na_2SO_4), filtered and concentrated. The residue was subjected to flash chromatography (C-18 silica gel, MeCN) to give **38**, partially purified, (~2.5 mg) as a colorless film.

^1H NMR ($CDCl_3$, 300 MHz).[19]

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 18.3, 20, 23.1, 23.6, 24.1, 26.1, 28.3, 29.7, 36.2, 36.3, 44.9, 60.6, 67.3, 122.1, 123.2, 125.7, 129.1, 139.5, 141, 143.6, 155.1, 171.3.

HRMS (FAB+): *m*/*z* Calcd for $C_{25}H_{40}N_2O_5P$ $(M + H)^+$ 479.2675. Found: 479.2680.

Supplementary Material

See Ref.[19] for information on supplementary material.

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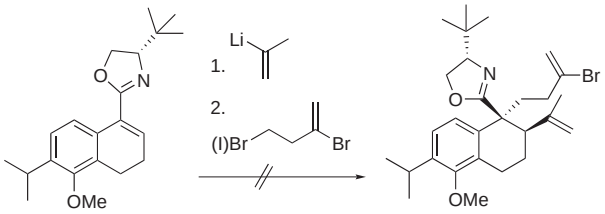

Scheme 11

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