1.75 equiv of acetic acid, which could not be removed without decomposition of **7a**: ^{1}H NMR (CF_3COOD)[24] δ 8.28 (d, 1 H, $J_{1,2}$ = 7.2 Hz, H-1), 7.6–7.7 (m, 3 H, H-2, H-3, H-4), 7.5–7.6 (m, 1 H, H-7), 7.3–7.45 (m, 1 H, H-10), 7.05–7.25 (m, 2 H, H-8, H-9). ESR: The paramagnetism of solutions of **7a** was demonstrated unambiguously by ESR. A solution of **7a** in chloroform or toluene shows an ESR signal of low intensity without hyperfine splitting, indicating low radical concentration and rapid exchange processes between the monomer radical and the disulfide dimer. MW determination: MW (chloroform) 495 g/mol (expected 476 g/mol for the dimer). MS (70 eV), m/z (relative intensity) 238 (100, $C_{13}H_8N_3S^+$), 122 (11, $C_6H_4NS^+$), 119 (14, $C_{13}H_8N_3S^{2+}$), 78 (28%, $C_5H_4N^+$); UV (chloroform) λ_{max} 510 nm (ϵ 7000), 422 (7800), 264 (42 800); based on MW 476. Anal. Calcd for $C_{26}H_{16}N_6S_2 \cdot 1.75$ HOAc: C, 60.91; H, 3.98; N, 14.44; S, 11.02. Found: C, 60.98; H, 4.15; N, 14.67; S, 11.04.

(24) Neutral solvents gave pronounced signal broadening due to the accompanied sulfenyl radical. **7a** is believed to be protonated in CF_3COOD solution, forming the corresponding bis cation of **7a**. This is indicated by the low field lying shifts of the C-1 proton signals. The assignment is analogous to **3b**.

Acknowledgment. We would like to thank Mr. J. S. Dawborne for initial mass spectroscopic studies and Mrs. D. Müller and Mr. N. Oppe for their skillful technical assistance in the preparative work. We are also indebted to Professors R. Gompper, Universität München, and R. R. Schmidt, Universität Konstanz, for critical and fruitful discussions.

Asymmetric Additions to Chiral Naphthalenes. 4. An Asymmetric Synthesis of the AB-Ring of Aklavinone

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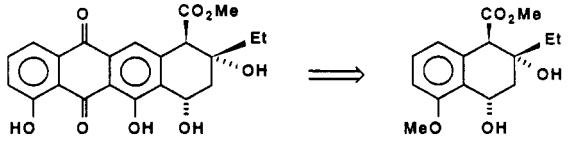
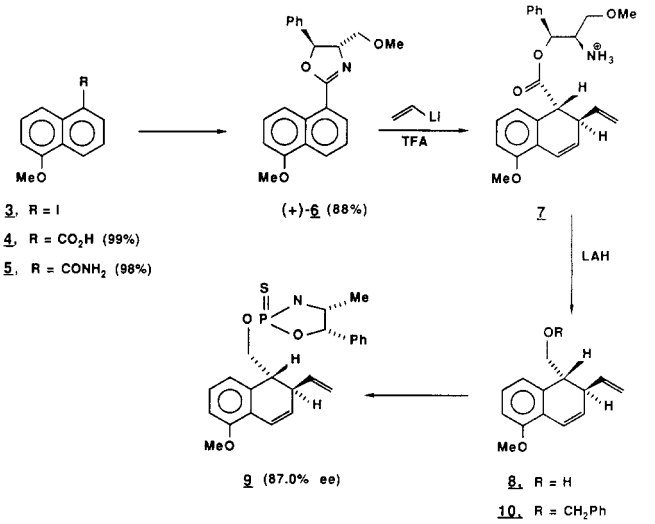
The chiral 1-naphthyloxazoline (+)-**6**, prepared from known 1-iodo-5-methoxynaphthalene, was treated with vinyllithium to afford the dihydronaphthalene **8**, after quenching and reductive removal of the chiral auxiliary. Introduction of the tertiary hydroxyl group followed by bromination–hydrolysis gave the appropriately substituted AB-ring of aklavinone **2** in 84–88% ee. The absolute configuration and relative configuration were confirmed by X-ray single-crystal analysis.

The extensive effort to reach the anthracycline antitumor antibiotics by total synthesis has culminated in a number of efficient and sometimes elegant routes to aklavinone and 11-deoxyanthracyclinones.[1] Our recent studies involving chiral naphthalenes have opened an asymmetric route to a variety of dihydronaphthalenes containing two simultaneously introduced stereocenters,[2] and it is the application of this methodology to the anthracyclinones we now wish to describe. Our approach to the problem addresses the stereochemically endowed AB-ring of aklavinone (**1**) which, if simplified into the bicyclic system **2**, becomes the objective of our chiral naphthalene methodology. Once accomplished, with hopefully high enantiomeric excess, **2** can be appropriately substituted to allow annulation[3] to the final anthracyclinone alkavinone.



1 **2**

Our synthetic sequence leading to the AB-ring **2**, anticipated to provide the correct absolute stereochemistry, began with transforming the known 5-methoxy-1-iodonaphthalene (**3**)[4] into the carboxylic acid **4** (*n*-BuLi, THF, CO_2) in 99% yield. Transformation to the amide **5** was accomplished by using oxalyl chloride, CH_2Cl_2, and ammonia affording the product in 98% yield. The chiral oxazoline (+)-**6** was formed from the amide **5** by first converting it into the imidate (Meerwein's reagent, 1,2-dichloroethane), followed by addition of (*S*,*S*)-(+)-1-methoxy-2-amino-3-phenyl-3-hydroxypropane.[5] Thus, the requisite starting material **6** was prepared from **3** in three steps in 85% yield. The crucial asymmetric addition was



performed by using vinyllithium (THF, –60 °C), which added from the top (*re*) face[2] of **6**, and the resulting adduct was quenched with trifluoroacetic acid. In this manner, the oxazoline ring opened, affording the dihydro-

(1) Bauman, J. G.; Hawley, R. C.; Rappaport, H. *J. Org. Chem.* **1985**, *50*, 1569. A complete list of references to earlier synthetic work is given.
(2) Meyers, A. I.; Barner, B. A. *J. Org. Chem.* **1986**, *51*, 120 and earlier references cited.
(3) Kende, A. S.; Rizzi, J. P. *J. Am. Chem. Soc.* **1981**, *103*, 4247.
(4) Teuber, H.; Lindner, H. *Chem. Ber.* **1959**, *92*, 921.
(5) Meyers, A. I.; Knaus, G.; Kamata, K.; Ford, M. E. *J. Am. Chem. Soc.* **1976**, *98*, 567.

0022-3263/87/1952-4592$01.50/0

Table I. Effect of Temperature and Time on Vinyllithium Addition to (+)-6

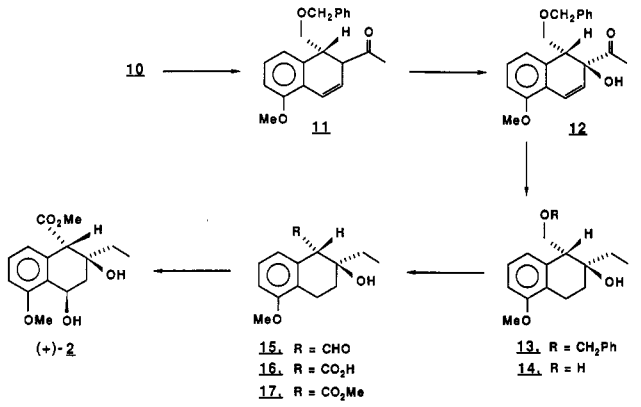
addn T, °C[a]	time, h[a]	% yield[b]	diastmr ratio[c]	%ee
0	4	72.4	77.3:22.7	54.6
−20	12	60.0	88.2:11.8	76.4
−40	21	65.6	89.6:10.4	79.2
−60	44	64.1	91.2:8.8	82.4
−60	72	73.1	93.5:6.5	87.0

[a] Vinyllithium added to (+)-6 at the temperature indicated and allowed to stir at this temperature for the time indicated. Quenching with trifluoroacetic acid was done by cooling first to −75–78 °C in all cases. [b] Isolated yield of alcohol 8. [c] Determined by ^{31}P NMR on the thiophosphonamide 9.

naphthalene 7. The latter was directly reduced ($LiAlH_4$–Et_2O, 25 °C) to crystalline alcohol 8 ($[\alpha]_D$ 405° ($CHCl_3$)) in 73% yield for the two steps. At this stage, the enantiomeric excess was determined by transforming the alcohol 8 to its thiophosphonamide ester 9 according to Johnson.[6] Integration of the ^{31}P NMR spectrum showed the enantiomers in a ratio of 93.6:6.4 (87% ee).

With a viable method in hand to assess the stereoselectivity of the vinyl addition to the chiral naphthalene 6, a temperature vs. ee study was carried out, and the results are presented in Table I. It is clear that the stereoselectivity increases with decreasing temperature; however, the rate of addition begins to slow considerably as the temperature is lowered such that the reaction reaches completion after ~70 h. At lower temperatures (e.g., −78 °C) there is virtually no addition occurring after 72 h. Thus, optimum conditions were set at −60 °C for 48–72 h, giving rise to 65–73% yield of material with an enantiomeric excess of 87%.

Proceeding on to the target 2, the alcohol 8 was converted to the benzyl ether, 10 (90%, benzyl bromide, PTC, CH_2Cl_2–NaOH) and then subjected to the Wacker procedure ($PdCl_2(CH_3CN)_2$, CuCl, O_2, MeOH) to form 11 in 81% yield. Introduction of the tertiary hydroxyl required



enolization of the ketone 11 and hydroxylation by an electrophilic oxygen source. The excellent studies in this regard by Davis[7] provided the necessary solution. Treatment of 11 with sodium hexamethyldisilazane followed by 2-(phenylsulfonyl)-3-phenyloxaziridine gave the hydroxy ketone 12 (54%) *as a single diastereomer*. The relative configuration, however, was not known since NMR studies were unable to distinguish whether the hydroxyl had entered from the β- or α-face. An X-ray structure would be required to confirm this point. However, the synthetic plan continued by forming dihydro-12 by reduction of the double bond (Pd/C, MeOH) followed by conversion of the methyl ketone to the ethyl group 13 ($NaBH_4$–MeOH; MsCl–Et_3N; $LiAlH_4$–Et_2O, 62% overall). The debenzylation took place quantitatively using Pd-reductive cleavage and afforded the diol 14 as a crucial intermediate in this projected route to aklavinones. In order to reach the C-10 carboxyl function, the Sharpless procedure[8] ($RuCl_3$, $NaIO_4$) for oxidizing primary alcohols 14 to aldehydes 15 proceeded quantitatively, and Jones oxidation, followed by diazomethane furnished the ester 17 in 75% yield (from 14). The last event to be addressed was the introduction of the 7-hydroxyl group, which was performed by using *N*-bromosuccinimide under irradiation conditions furnishing 2 as a single product (86%, $[\alpha]_D$ +85° ($CHCl_3$)). As stated earlier, the absolute configuration was not known with certainty, and therefore, the urethane (18) was prepared[9] from (*S*)-(+)-1-(1-naphthyl)ethyl isocyanate for X-ray purposes. The single-crystal structure of 18

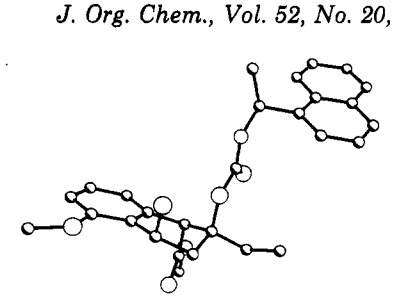
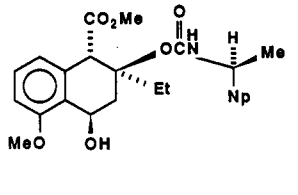
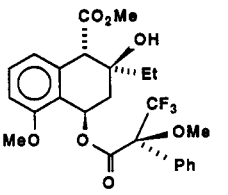


Figure 1. X-ray structure of 18.

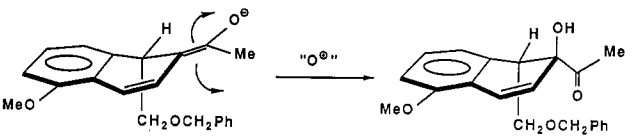


18



19

confirmed that all the relative configurations of the stereocenters were correct, and the product possessed the absolute configuration shown 18 (Figure 1). This represented the unnatural enantiomer for aklavinone. It is quite reasonable to assume that the introduction of the hydroxyl group in 12 proceeded via the enolate A entering from the sterically most accessible top face. Bottomside oxygen



A 12

entry would be rather restricted, especially when the oxygen electrophile is part of a bulky oxaziridine system. The topside oxygen entry fixes two stereocenters for the AB-ring set up to produce the unnatural enantiomer. The hydroxylation at C-7 to give (+)-2 is dictated by the stereocenters already in place, and this has also been noted earlier by Kende,[3] Confalone,[10] and Li.[11]

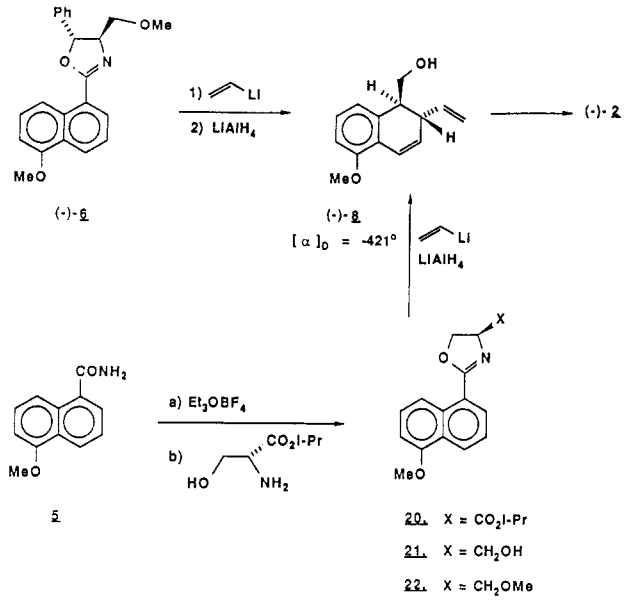
It was important to evaluate the enantiomeric excess of (+)-2 in view of the number of events during the synthesis which could have resulted in racemization. The Mosher ester[12] 19 was prepared and subjected to ^{19}F NMR studies.

(6) Johnson, C. R.; Elliot, R. C.; Penning, T. D. *J. Am. Chem. Soc.* **1984**, 106, 5019.
(7) Davis, F. A.; Vishwarama, L. C.; Billmers, J. M.; Finn, J. *J. Org. Chem.* **1984**, *49*, 3241.
(8) Carlsen, H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936.
(9) Pirkle, W. H.; Hauske, J. R. *J. Org. Chem.* **1977**, *42*, 1839.
(10) Confalone, P. N.; Pizzolato, G. *J. Am. Chem. Soc.* **1981**, *103*, 4251.
(11) Li, T.; Wu, Y. L.; Walsgrove, T. C. *Tetrahedron* **1984**, *40*, 4701.
(12) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512.

The ratio of ^{19}F signals at −71.8 and −71.9 ppm was 92:8 ± 2 (80–88% ee), which agrees fairly well with the ^{31}P spectrum of **9** described earlier. Thus, no significant racemization occurred in the latter half of the synthesis.

Since the preceding synthetic route was carried on to the unnatural AB-ring, it was desirable to perform some experiments to demonstrate that the natural enantiomer could also be reached with similar yields and enantiomer excess.

The options open to prepare the natural enantiomer were either to use the antipodal[13] amino diol (*R,R* rather than *S,S*) and prepare the oxazoline, (−)-**6**, or utilize (−)-serine as its isopropyl ester to generate the oxazoline **20**. The latter would have the same sense of chirality as (−)-**6** and should, therefore, lead to the same sense of vinyl introduction. It was a relatively simple task to prepare the necessary chiral oxazoline, **22**, by treatment of the naphthamide **5** with the Meerwein's reagent followed by (−)-isopropyl serinate. This gave the oxazoline ester **20** in 94% yield, which was reduced with lithium aluminum hydride to the hydroxy methyl derivative **21** in 82% yield. The methyl ether **22** was then obtained (74%) by the use of potassium *tert*-butoxide–methyl iodide. When vinyllithium was added to the naphthalene **22** at the conditions considered to be optimum (−60 °C, THF, 48–72 h), there was obtained, after acidic quench and lithium aluminum hydride reduction, the vinyldihydronaphthalene (−)-**8** in a pure isolated yield of 54%. However, the $[\alpha]_D$ value showed −277° as compared to +405° obtained earlier for (+)-**8**. On the basis of the rotation, the asymmetric addition proceeded in a disappointing 57% ee. This was also confirmed by using the Mosher ester of (−)-**8** and determining via ^{19}F NMR that (−)-**8** was indeed only 57% ee. The fact that **22** may have undergone some racemization during its preparation via **20** and **21** such that the % ee of **22** is less (~10–20%) than expected cannot be discounted at this time.



The scheme, therefore, was repeated by using the antipodal (*R,R*)-(−)-1-methoxy-2-amino-3-phenyl-3-hydroxypropane,[13] and in the same manner used to prepare (+)-**6**, the antipodal naphthyl oxazoline (−)-**6** was prepared. As expected, vinyllithium addition at −60 °C for 70 h gave, after acidic quench and lithium aluminum hydride reduction, a 68–70% yield of (−)-**8** with a specific rotation of −421° or within 3% of the rotation of the previously prepared (+)-enantiomer. Confirmation of the enantiomeric purity was again gained via ^{31}P NMR of its thiophosphonamide derivative **9** and was measured at 87–88%. In order to confirm the validity of the ee determination, it was necessary to prepare racemic material (±)-**8** and examine the ^{31}P NMR spectrum of the corresponding thiophosphonamide.[14]

In conclusion, we have demonstrated the viability of the asymmetric addition to chiral naphthalene derivatives and have also shown that they can be elaborated to either enantiomer. Although we did not carry the precursor to the natural enantiomer (−)-**8** on to the appropriate AB-ring (−)-**2**, there is no reason to expect that the sequence would not be successful. Future goals are now focusing on introducing an appropriate substituent (e.g., formyl, bromo, etc.) onto the naphthalene nucleus, ortho to the methoxyl in (−)-**6**, such that the CD-rings can be fused onto the system.[3]

Experimental Section[15]

5-Methoxy-1-naphthoic Acid (4). To a stirred solution of 1-iodo-5-methoxynaphthalene (**3**) (10.7 g, 37.6 mmol) in 100 mL of dry THF (under argon) at −78 °C was added *n*-BuLi (23.8 mL, 1.58 M in hexane, 37.6 mmol) over a period of 5 min, and the resulting mixture was further stirred for 8 min at the same temperature. Crushed solid CO_2 (3 g) was then added in one portion at −78 °C, the reaction mixture was warmed up to room temperature, and most of the THF was evaporated. After the addition of water (50 mL), the resulting mixture was washed with ether (30 mL), and the ether washes were discarded. The aqueous solution was acidified with 5% HCl, and the solid precipitate was collected by filtration. Recrystallization from ethanol afforded the naphthoic acid **4** (7.5 g, 98.5%) as colorless needles: mp 227–229 °C (lit.[12] mp 229–228 °C); ^1H NMR (DMSO) δ 11.15 (br s, 1 H, COOH), 8.44 (d, 2 H, J = 8.4 Hz), 8.17 (d, 1 H, J = 7.5 Hz), 7.58 (t, 1 H, J = 7.5 Hz), 7.57 (t, 1 H, J = 8.4 Hz), 7.05 (d, 1 H, J = 7.5 Hz), 4.00 (s, 3 H).

5-Methoxy-1-naphthamide (5). To a stirred suspension of naphthoic acid **4** (6.7 g, 33.1 mmol) in dry dichloromethane (90 mL) was added oxalyl chloride (5.05 g, 39.8 mmol) at 0 °C, the reaction mixture was warmed to room temperature and stirred for 12 h at room temperature. Evaporation of the solvent afforded a solid residue, which was dissolved in dry chloroform (20 mL) and cooled to 0 °C. Concentrated ammonia (20 mL) was added dropwise with stirring, and the resulting precipitate was collected by filtration. Recrystallization from methanol gave the amide **5** (6.5 g, 97.5%) as colorless needles: mp 225–226 °C; ^1H NMR ($CDCl_3$) δ 8.41 (d, 1 H, J = 8.3 Hz), 7.97 (d, 1 H, J = 8.6 Hz), 7.72 (d, 1 H, J = 7.8 Hz), 7.54–7.43 (m, 2 H), 6.88 (d, 1 H, J = 7.8 Hz), 6.13 (br d, 2 H, $CONH_2$), 4.02 (s, 3 H).

Anal. Calcd for $C_{10}H_{11}NO_2$: C, 71.63; H, 5.51; N, 6.96. Found: C, 71.44; H, 5.42; N, 6.83.

1-[(*S,S*)-4-(Methoxymethyl)-5-phenyl-2-oxazolinyl]-5-methoxynaphthalene [(+)-6]. The amide **5** (6.0 g, 29.8 mmol) in 100 mL of dichloromethane was treated with triethyloxonium tetrafluoroborate (7.93 g, 41.7 mmol) at room temperature under argon. The initial cloudy solution clarified after 1 h and was stirred for 20 h at ambient and then 5 h at reflux. The *S,S*-methoxyamino alcohol[5] (13.5 g, 74.5 mmol) was added in a single portion and the mixture heated to reflux for 24 h. The cooled mixture was then poured in 60 mL of saturated $NaHCO_3$ and the organic layer removed, washed with brine (20 mL), and dried over K_2CO_3. Evaporation of the solvents left a yellow gummy material, which was passed through a silica gel column with hexane–ethyl acetate

(13) The *R,R*-amino diol is available from Sigma Chemical Company and may be transformed into its methyl ether as described in ref 5 above.

(14) The racemic naphthyl oxazolines were prepared by using 2-methyl-2-amino-1-propanol as described: Meyers, A. I.; Avila, W. B. *J. Org. Chem.* **1981**, *46*, 3881.

(15) All ^1H NMR spectra were taken at 270 MHz and all chemical shifts are given in ppm. Elemental analyses were performed by Desert Analytics, Tucson, AZ.

(16) Reynolds, C. F. *J. Am. Chem. Soc.* **1924**, *46*, 2779.

(3:1). The oxazoline (+)-6 was obtained as colorless needles (9.1 g, 87.8%); mp 76–77 °C (hexane); $[\alpha]^{25}_D$ +59.6° (*c* 7.4, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 8.73 (d, 1 H, *J* = 8.8 Hz), 8.47 (d, 1 H, *J* = 8.5 Hz), 8.21 (dd, 1 H, *J* = 7.3 and 1.0 Hz), 7.53–7.31 (m, 7 H), 6.87 (d, 1 H, *J* = 7.7 Hz), 5.54 (d, 1 H, *J* = 6.7 Hz), 4.49 (dt, 1 H, *J* = 6.7 and 4.3 Hz), 4.00 (s, 3 H), 3.84 (dd, 1 H, *J* = 9.7 and 4.3 Hz), 3.70 (dd, 1 H, *J* = 9.7 and 6.7 Hz), 3.47 (s, 3 H); ^{13}C NMR ($CDCl_3$) 164.2, 155.7, 141.4, 132.5, 129.8, 128.8, 128.1, 127.4, 126.3, 125.7, 124.3, 124.0, 119.0, 104.4, 82.9, 75.9, 74.8, 59.3, 55.6 ppm; IR (film) 1645, 1590, 1515, 1465, 1410, 1260, 1015, 785 cm^{-1}.

Anal. Calcd for $C_{22}H_{21}NO_3$: C, 76.06; H, 6.09. Found: C, 75.94; H, 6.04.

Naphthyloxazoline (−)-6. In a manner identical with that above, 0.971 g of (−)-6 was obtained from 0.64 g of amide 5 and 1.73 g of the *R,R*-amino diol. Yield of (−)-6 was 83%, mp 75–77 °C; $[\alpha]^{25}_D$ −60.95° (*c* 7.06, $CHCl_3$).

(+)-*trans*-1-(Hydroxymethyl)-2-vinyl-5-methoxy-1,2-dihydronaphthalene [(+)-8]. Oxazoline 6 (8.68 g, 25.0 mmol) in THF (200 mL) at −60 °C under argon was treated with vinyllithium (21.55 mL, 1.74 M in Et_2O, 37.5 mmol). The solution became deep red and was stirred for 72 h at −60 °C. The deep red mixtue was quenched by the dropwise addition of freshly distilled trifluoroacetic acid (14.25 g, 125.0 mmol) at −78 °C, instantly producing a pale yellow solution. After 1 h, the solution was diluted with ether (300 mL) and was washed twice with brine (25 mL). The combined aqueous layer was back-extracted twice with dichloromethane (20 mL), and the combined extracts were dried by vigorously stirring over 5–7 g of powdered anhydrous Na_2SO_4, to which 20 drops of water had been added. After 3 h, the hydrolysis to the ester–ammonium salt 7 was complete (TLC gave only baseline material) and removal of the sodium sulfate left a solution, which, after concentration, gave a viscous yellow oil, 7. The latter was directly used for the next step.

To a suspension of lithium aluminum hydride (2.37 g, 62.5 mmol) in dry ether (20 mL) under argon at room temperature was added, dropwise, a solution of the crude ester–ammonium salt 7 in 75 mL of ether over a 30-min period. After the mixture was stirred 1 h, the excess hydride was decomposed by the slow addition of water (0.2 mL) and the mixture filtered through Celite. Evaporation of the solvent gave a pale yellow gum, which was subjected to column chromatography (silica gel; hexane–ethyl acetate, 3:1) to give the vinyl alcohol 8 as colorless needles (3.95 g, 73.1%): mp 57.5–58.0 °C (*n*-hexane); $[\alpha]^{25}_D$ +405° (*c* 0.885, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.12 (t, 1 H, *J* = 7.9 Hz), 6.87 (d, 1 H, *J* = 9.9 Hz), 6.74 (d, 2 H, *J* = 7.9 Hz), 5.83 (dd, 1 H, *J* = 9.7 and 5.9 Hz), 5.71 (ddd, 1 H, *J* = 17.2, 10.0, and 7.3 Hz), 5.06 (dd, 1 H, *J* = 17.2 and 1.2 Hz), 4.90 (dd, 1 H, *J* = 10.0 and 1.2 Hz), 3.81 (s, 3 H), 3.61 (d, 2 H, *J* = 7.3 Hz), 2.88 (t, 1 H, *J* = 7.3 Hz), 1.68 (br s, 1 H, OH); ^{13}C NMR ($CDCl_3$) 154.9, 138.6, 135.2, 127.7, 126.9, 121.9, 121.6, 120.4, 114.1, 109.6, 64.6, 55.4, 46.3, 38.9 ppm; IR (film) 3370, 1645, 1605, 1585 cm^{-1}; ^{31}P NMR ($CDCl_3$) of thiophosphonamide ester 9, minor product 83.8 ppm (6.6%), major product 83.6 ppm (93.4%).

(−)-*trans*-1-(Hydroxymethyl)-2-vinyl-5-methoxy-1,2-dihydronaphthalene [(−)-8]. (a) From (−)-6. In exactly the same manner as above, the addition product (−)-8 was formed in 68% yield from 593 mg of (−)-6; mp 57.5–58.5 °C (*n*-hexane); $[\alpha]^{25}_D$ −421.06° (*c* 0.85, $CHCl_3$); ^{31}P NMR of 9, 83.8 (94.6%), 83.6 ppm (5.4%).

(b) From (+)-22. In the same manner, the addition product (−)-8 was formed in 54% yield from 525 mg of (+)-22: mp 55.0–56.0 °C (*n*-hexane); $[\alpha]^{25}_D$ −277° (*c* 0.85, $CHCl_3$); ^{31}P NMR of 9, 83.8 (78.5%), 83.6 ppm (21.5%).

(+)-*trans*-1-[(Benzyloxy)methyl]-2-vinyl-5-methoxy-1,2-dihydronaphthalene [(+)-10]. A flask was charged with 20 mL of dichloromethane, 20 mL of 40% KOH, 3.9 g (18.03 mmol) of alcohol 8, and 4.0 g (23.44 mmol) of benzyl bromide. To this two-phase solution was added 0.41 g (1.8 mmol) of benzyltriethylammonium chloride, and the mixture was stirred vigorously for 20 h at room temperature. Dichloromethane (20 mL) was added, and the phases were separated. The upper aqueous phase was extracted with dichloromethane (10 mL × 3), and the combined extracts were washed with brine and dried (Na_2SO_4) and concentrated to give a colorless oil. After column chromatography (silica gel, CH_2Cl_2) the benzyl ether 10 (4.97 g, 89.9%) was obtained as a colorless oil: $[\alpha]_D$ +255.2° (*c* 0.98, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.36–7.23 (m, 5 H), 7.10 (t, 1 H, *J* = 7.8 Hz), 6.86 (d, 1 H, *J* = 9.8 Hz), 6.73 (d, 1 H, *J* = 7.8 Hz), 6.72 (d, 1 H, *J* = 7.8 Hz), 5.82 (dd, 1 H, *J* = 9.8, 5.8 Hz), 5.71 (ddd, 1 H, *J* = 17.2, 10.0, 7.3 Hz), 5.06 (d, 1 H, *J* = 17.2 Hz), 4.89 (d, 1 H, *J* = 10.0 Hz), 4.49 (d, 1 H, *J* = 12.1 Hz), 4.48 (d, 1 H, *J* = 12.1 Hz), 3.80 (s, 3 H), 3.51 (t, 1 H, *J* = 9.5 Hz), 3.41 (dd, 1 H, *J* = 9.5, 5.3 Hz), 3.29 (br t, 1 H, *J* = 6.6 Hz), 3.07 (dd, 1 H, *J* = 9.8, 5.3 Hz); IR (film) 1635, 1595, 1575 cm^{-1}; ^{13}C NMR ($CDCl_3$) 154.9, 138.9, 138.6, 135.5, 128.3 (×2), 127.8, 127.5 (×2), 127.2, 127.0, 122.1, 121.7, 120.6, 114.3, 109.4, 72.9, 72.0, 55.4, 44.0, 38.8 ppm.

Anal. Calcd for $C_{21}H_{22}O_2$: C, 82.32; H, 7.24. Found: C, 82.25; H, 7.04.

(+)-*trans*-1-[(Benzyloxy)methyl]-2-acetyl-5-methoxy-1,2-dihydronaphthalene [(+)-11]. Oxygen gas was bubbled into a mixture of benzyl ether 10 (4.9 g, 160 mmol), $PdCl_2(MeCN)_2$ (0.41 g, 1.6 mmol), and CuCl (4.75 g, 48.0 mmol) in methanol (50 mL) with stirring for 20 h at 45 °C. The reaction mixture was poured into 10% HCl (50 mL), and most of the methanol was evaporated in vacuo, followed by extraction with ether (20 mL × 3). The combined extracts were washed with brine (20 mL), dried (Na_2SO_4), and concentrated to give a pale yellow gum, which was subjected to column chromatography (silica gel; CH_2Cl_2–MeOH, 99:1). The ketone 11 (4.19 g, 81.2%) was obtained as a yellowish viscous oil, which was not very stable; $[\alpha]_D$ +320° (*c* 0.845, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.34–7.23 (m, 5 H), 7.12 (t, 1 H, *J* = 7.9 Hz), 6.95 (d, 1 H, *J* = 9.9 Hz), 6.78 (d, 1 H, *J* = 7.9 Hz), 6.69 (d, 1 H, *J* = 7.9 Hz), 5.94 (dd, 1 H, *J* = 9.9, 6.5 Hz), 4.50 (d, 1 H, *J* = 12.0 Hz), 4.47 (d, 1 H, *J* = 12.0 Hz), 3.78 (s, 3 H), 3.68 (br t, 1 H, *J* = 7.1 Hz), 3.53 (d, 1 H, *J* = 6.6 Hz), 3.45–3.42 (m, 2 H), 2.12 (s, 3 H); IR (film) 1720, 1635, 1600, 1585 cm^{-1}; ^{13}C NMR ($CDCl_3$) 206.4, 155.1, 138.3, 135.6, 128.6 (×2), 128.3 (×2), 127.6 (×2), 123.0, 121.3 (×2), 121.1, 109.5, 72.8, 71.6, 55.4, 49.1, 39.1, 28.1 ppm.

Anal. Calcd for $C_{21}H_{22}O_3$: C, 78.23; H, 6.89. Found: C, 78.46; H, 6.90.

1-[(Benzyloxy)methyl]-2-acetyl-2-hydroxy-5-methoxy-1,2-dihydronaphthalene [(−)-12]. A stirred solution of 11 (4.03 g, 12.5 mmol) in dry THF (50 mL) was cooled to −78 °C under argon and treated with sodium bis(trimethylsilyl)amide (1.0 equiv, in THF). After the mixture was stirred for 30 min at −78 °C, a solution of oxaziridine[7] (4.90 g, 18.7 mmol) in THF (10 mL) was added dropwise. The solution was stirred for 40 min at −78 °C and then quenched with triethylamine (0.2 mL) followed by saturated NH_4Cl solution. After the mixture had been diluted with ether (50 mL), the phases were separated, and the aqueous phase was extracted with ether (10 mL × 3). The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated to give a yellow gum. Column chromatography (silica gel; CH_2Cl_2–MeOH, 99:1) gave the α-hydroxy ketone 12 (2.26 g, 53.5%) as a colorless oil; $[\alpha]^{25}_D$ −264.2° (*c* 0.79, $CHCl_3$); IR (film) 3440, 1705, 1635, 1600, 1580 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.36–7.24 (m, 5 H), 7.19 (t, 1 H, *J* = 8.0 Hz), 7.03 (d, 1 H, *J* = 10.0 Hz), 6.94 (d, 1 H, *J* = 8.0 Hz), 6.87 (d, 1 H, *J* = 8.0 Hz), 5.65 (d, 1 H, *J* = 10.0 Hz), 4.62 (s, 1 H, OH), 4.39 (d, 1 H, *J* = 11.6 Hz), 4.37 (d, 1 H, *J* = 11.6 Hz), 3.79 (dd, 1 H, *J* = 10.1, 3.6 Hz), 3.87–3.79 (m, 1 H), 3.84 (s, 3 H), 3.58 (br t, 1 H), 1.98 (s, 3 H); ^{13}C NMR ($CDCl_3$) 208.3, 155.3, 137.7, 135.8, 130.4, 129.0, 128.3 (×2), 127.9 (×2), 127.6, 124.4, 121.7, 118.5, 109.7, 79.6, 73.5, 65.6, 55.6, 49.0, 25.2 ppm.

1-[(Benzyloxy)methyl]-2-acetyl-2-hydroxy-5-methoxy-1,2,3,4-tetrahydronaphthalene (Dihydro-12). To a solution of α-hydroxy ketone 12 (2.2 g, 6.5 mmol) in methanol (40 mL) was added a catalytic amount of 10% Pd/C. The mixture was stirred under 40 psi of hydrogen for 4 h at room temperature. The resulting mixture was passed through a Celite pad, and the filtrate was concentrated to a residue, which was recrystallized from hexane–ether to afford dihydro-12 (2.15 g, 97.2%) as colorless needles: mp 94–95 °C (ether–hexane); $[\alpha]^{25}_D$ +61.7° (*c* 0.82, $CHCl_3$); ^1H NMR ($CDCl_3$) 7.37–7.26 (m, 5 H), 7.15 (t, 1 H, *J* = 7.9 Hz), 6.79 (d, 1 H, *J* = 7.9 Hz), 6.72 (d, 1 H, *J* = 7.9 Hz), 4.39 (s, 2 H), 3.85–3.80 (m, 1 H), 3.82 (s, 3 H), 3.64 (t, 1 H, *J* = 9.3 Hz), 3.49 (br s, 1 H, OH), 3.28 (dd, 1 H, *J* = 8.7, 4.3 Hz), 2.89–2.65 (m, 2 H), 2.23–2.09 (m, 1 H), 2.18 (s, 3 H); ^{13}C NMR ($CDCl_3$) 211.1, 156.9, 137.6, 136.1, 128.4 (×2), 127.9 (×2), 127.8, 126.7, 125.2, 120.7, 108.0, 78.6, 73.4, 72.1, 55.3, 49.0, 28.2, 25.8, 19.7 ppm; IR (film) 3490, 1720, 1605 cm^{-1}.

Anal. Calcd for $C_{21}H_{24}O_4$: C, 74.09; H, 7.11. Found: C, 73.92; H, 7.03.

1-[(Benzyloxy)methyl]-2-ethyl-2-hydroxy-5-methoxy-1,2,3,4-tetrahydronaphthalene [(+)-13]. To a stirred room temperature solution of the dihydro α-hydroxy ketone (2.1 g, 6.17 mmol) in methanol (50 mL) was added $NaBH_4$ (0.7 g, 18.4 mmol) in small portions over 30 min. After 1.5 h, the methanol was removed by evaporation, and the mixture was dissolved in water (50 mL) and extracted with dichloromethane (20 mL × 3). The combined extracts were washed with brine, dried (Na_2SO_4), and concentrated to give a diastereomeric mixture of alcohols as a colorless viscous oil (2.05 g, 97.1%).

To a stirred solution of the alcoholic mixture (2.05 g, 5.99 mmol) and triethylamine (0.91 g, 7.0 mmol) in dry dichloromethane (50 mL) was added dropwise methanesulfonyl chloride (0.755 g, 6.59 mmol) at 0 °C. After being stirred for 1 h at 0 °C, the resulting solution was diluted with dichloromethane (40 mL), and the organic layer was washed with brine, dried (Na_2SO_4), and evaporated to give the mesylate as a yellow viscous oil.

To a stirred suspension of lithium aluminum hydride (0.568 g, 15.0 mmol) in dry ether (20 mL) under argon at room temperature was added dropwise a solution of crude mesylate in dry ether (40 mL) over a period of 20 min. After heating at reflux for 2 h, the excess hydride as decomposed by addition of water, and the resulting mixture was passed through a Celite pad. The filtrate was dried (Na_2SO_4) and evaporated to a residue, which was subjected to column chromatography (silica gel; hexane–ethyl acetate, 3:1), furnishing the alcohol **13** (1.31 g, 65.1%) as a colorless oil: $[\alpha]_D$ +5.69° (*c* 1.16, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.37–7.25 (m, 5 H), 7.12 (t, 1 H, *J* = 8.0 Hz), 6.81 (d, 1 H, *J* = 8.0 Hz), 6.70 (d, 1 H, *J* = 8.0 Hz), 4.52 (s, 2 H), 3.90 (dd, 1 H, *J* = 9.6, 5.5 Hz), 3.81 (s, 3 H), 3.74 (dd, 1 H, *J* = 9.6, 8.0 Hz), 3.19 (br t, 1 H, *J* = 6.6 Hz), 2.85–2.55 (m, 2 H), 2.02–1.92 (m, 1 H), 1.79–1.68 (m, 1 H), 1.65–1.43 (m, 2 H), 1.00 (t, 3 H, *J* = 7.4 Hz); ^{13}C NMR ($CDCl_3$) 157.2, 138.1, 137.7, 128.4 (×2), 127.6 (×2), 126.4, 125.3, 120.9, 107.7, 73.5, 73.0, 72.6, 55.2, 48.9, 30.9, 28.8, 20.8, 7.0; IR (film) 3470, 1585 cm^{-1}.

Anal. Calcd for $C_{21}H_{26}O_3$: C, 77.27; H, 8.03. Found: C, 77.23; H, 8.19.

1-(Hydroxymethyl)-2-ethyl-2-hydroxy-5-methoxy-1,2,3,4-tetrahydronaphthalene [(+)-14]. To a solution of tertiary alcohol (+)-**13** (1.3 g, 3.98 mmol) in methanol (50 mL) was added a catalytic amount of 10% Pd/C. The mixture was stirred under 40 psi of hydrogen for 8 h at room temperature. The mixture was passed through a Celite pad and the solution concentrated to give a residue, which was chromatographed (silica gel; dichloromethane–MeOH, 98:2) to give the diol **14** (925 mg, 98.3%) as a colorless viscous oil: $[\alpha]^{25}_D$ +7.82° (*c* 0.66, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.13 (t, 1 H, *J* = 7.9 Hz), 6.78 (d, 1 H, *J* = 7.9 Hz), 6.71 (d, 1 H, *J* = 7.9 Hz), 3.90–3.83 (m, 2 H), 3.81 (s, 3 H), 2.94 (d, 1 H, *J* = 6.1 Hz), 2.75–2.69 (m, 2 H), 2.22 (s, 2 H, OH × 2), 1.96–1.86 (m, 1 H), 1.80–1.70 (m, 1 H), 1.69–1.48 (m, 2 H), 1.01 (t, 3 H, *J* = 7.4 Hz); ^{13}C NMR ($CDCl_3$) 157.3, 136.9, 126.5, 125.4, 121.2, 107.9, 72.7, 64.5, 55.2, 50.5, 31.0, 29.5, 20.4, 6.8 ppm; IR (film) 3370, 1585, 1460 cm^{-1}.

Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 70.96; H, 8.53.

1-Carbomethoxy-2-ethyl-2-hydroxy-5-methoxy-1,2,3,4-tetrahydronaphthalene [(+)-17]. (a) Aldehyde (+)-15. A flask was charged with CCl_4 (7 mL), CH_3CN (7 mL), H_2O (11 mL), diol **14** (824 mg, 3.52 mmol), and $NaIO_4$ (2.26 g, 10.55 mmol). To this two-phase solution was added $RuCl_3 \cdot H_2O$ (20.2 mg, 0.077 mmol), and the entire mixture was stirred vigorously for 1 h at room temperature. Dichloromethane (50 mL) was added, and the phases were separated. The upper aqueous phase was extracted with dichloromethane (10 mL × 3), and the combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was diluted with ether (20 mL), filtered through a Celite pad, and concentrated to give the crude aldehyde **15** as a viscous oil, which was not sufficiently stable to give a satisfactory microanalysis and was therefore used in the next step without further purification; $[\alpha]^{25}_D$ +274.6° (*c* 0.8, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 9.51 (d, 1 H, *J* = 4.4 Hz), 7.18 (t, 1 H, *J* = 8.0 Hz), 6.78 (d, 1 H, *J* = 8.0 Hz), 6.68 (d, 1 H, *J* = 8.0 Hz), 3.85 (s, 3 H), 3.65 (d, 1 H, *J* = 4.4 Hz), 2.92 (ddd, 1 H, *J* = 3.2, 6.7, and 18.5 Hz), 2.75 (ddd, 1 H, *J* = 6.8, 10.5, and 18.5 Hz), 2.04–1.95 (m, 1 H), 1.88 (ddd, 1 H, *J* = 6.8, 10.5, and 14.1 Hz), 1.76 (s, 1 H, OH), 1.65 (q, 2 H, *J* = 7.5 Hz), 1.06 (t, 3 H, *J* = 7.5 Hz); ^{13}C NMR ($CDCl_3$) 199.0 157.8, 130.7, 127.3, 125.6, 122.8, 109.1, 71.0, 62.7, 55.4, 32.4, 31.0, 19.9, 6.6 ppm; IR (film) 3450, 2925, 2830, 2710, 1720, 1585, 1465, 1435 cm^{-1}.

(b) Acid (+)-16. To a stirred solution of crude aldehyde **15** in acetone (30 mL) was added an excess of Jones' reagent dropwise at 0 °C. After the mixture was stirred for 3 h at 0 °C, the solvent was evaporated, and the resulting mixture was dissolved in water (20 mL) and extracted with dichloromethane (10 mL × 3). The combined extracts were washed with brine, dried (Na_2SO_4), and evaporated to give the crude acid, which was chromatographed (silica gel; CH_2Cl_2–MeOH, 98:2) to give **16** as a viscous oil (652 mg, 74.8%): $[\alpha]^{25}_D$ +126.0° (*c* 0.42, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.14 (t, 1 H, *J* = 7.9 Hz), 6.81 (d, 1 H, *J* = 7.9 Hz), 6.75 (d, 1 H, *J* = 7.9 Hz), 3.82 (s, 4 H, OMe and 1-CH), 2.87 (ddd, 1 H, *J* = 1.6, 6.7, and 18.4 Hz), 2.68 (ddd, 1 H, *J* = 7.2, 10.3, and 18.4 Hz), 2.23 (ddd, 1 H, *J* = 7.4, 10.3, and 13.5 Hz), 1.86–1.77 (m, 1 H), 1.74–1.58 (m, 2 H), 1.05 (t, 3 H, *J* = 7.4 Hz); ^{13}C NMR ($CDCl_3$) 177.4, 157.6, 132.7, 126.7, 125.2, 122.1, 108.2, 71.8, 55.3 (×2), 32.0, 29.0 19.5, 6.8 ppm; IR (film) 3200–2400 (COOH), 1700, 1585, 1465, 1250 cm^{-1}.

(c) Methyl Ester (+)-17. To a stirred solution of **16** (652 mg, 2.50 mmol) in ether (20 mL) was added an excess of diazomethane in ether at 0 °C for 1 h. After evaporation of the solvent and excess reagent, the residue was chromatographed (silica gel; hexane–ethyl acetate, 3:1) to give the methyl ester **17** (682 mg, 99.0%) as a colorless viscous oil; $[\alpha]^{25}_D$ +114° (*c* 0.9, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.11 (t, 1 H, *J* = 8.0 Hz), 6.75 (d, 1 H, *J* = 8.0 Hz), 6.72 (d, 1 H, *J* = 8.0 Hz), 3.83 (s, 1 H), 3.81 (s, 3 H), 3.66 (s, 3 H), 2.88 (ddd, 1 H, *J* = 2.7, 7.0, and 18.4 Hz), 2.67 (ddd, 1 H, *J* = 7.1, 10.6, and 18.4 Hz), 2.26 (ddd, 1 H, *J* = 7.1, 10.6, and 13.8 Hz), 1.85–1.71 (m, 1 H), 1.75 (br s, 1 H, OH), 1.63 (dq, 1 H, *J* = 7.4 and 14.7 Hz), 1.53 (dq, 1 H, *J* = 7.4 and 14.7 Hz), 1.03 (t, 3 H, *J* = 7.4 Hz); ^{13}C NMR ($CDCl_3$) 172.8, 157.6, 133.3, 126.6, 125.2, 122.0, 108.7, 71.7, 55.7, 55.3, 51.8, 32.1, 29.1, 19.6, 6.9 ppm; IR (film) 3520, 1730, 1590 cm^{-1}.

Anal. Calcd for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 68.08; H, 7.81.

1-Carbomethoxy-2-ethyl-2,4-dihydroxy-5-methoxy-1,2,3,4-tetrahydronaphthalene [(+)-2] (AB-Ring of Aklavinone). To a stirring solution of methyl ester **17** (13.6 mg, 0.0515 mmol) in dry CCl_4 was added *N*-bromosuccinimide (9.2 mg, 0.0517 mmol) in one portion and then irradiated for 30 min with a sun lamp at 10 °C. The solution was diluted with dichloromethane (20 mL), washed with brine (10 mL), dried (Na_2SO_4), and concentrated to give a residue, which was dissolved in 20 mL of THF–H_2O (1.2:1) and stirred at 25 °C for 2 h. The reaction mixture was diluted with CH_2Cl_2 (20 mL), the organic phase was washed with brine (10 mL), dried (Na_2SO_4), and concentrated in vacuo to give a yellow oil, which was chromatographed (silica gel; hexane–ethyl acetate, 3:1). There was obtained 12.4 mg (86.0%) of (+)-**2** as a colorless viscous oil: $[\alpha]^{25}_D$ +85.6° (*c* 0.96, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.25 (t, 1 H, *J* = 7.9 Hz), 6.86 (d, 1 H, *J* = 7.9 Hz), 6.84 (d, 1 H, *J* = 7.9 Hz), 5.28 (d, 1 H, *J* = 5.2 Hz), 3.97 (s, 1 H), 3.90 (s, 3 H), 3.65 (s, 3 H), 2.54 (dd, 1 H, *J* = 14.8 and 5.2 Hz), 2.18 (d, 1 H, *J* = 14.8 Hz), 1.70–1.45 (m, 2 H), 1.60 (br s, 2 H, OH × 2), 1.08 (t, 3 H, *J* = 7.4 Hz); ^{13}C NMR ($CDCl_3$) 172.7, 157.9, 134.0, 129.3, 126.1, 122.3, 109.5, 71.6, 63.4, 56.1, 55.6, 51.8, 35.4, 32.6, 6.7 ppm; IR ($CHCl_3$) 3600–3350 (OH), 3002, 1732, 1595, 1472, 1460, 1436, 1260, 1160, 1022 cm^{-1}.

Anal. Calcd for $C_{15}H_{20}O_5$: C, 64.27; H, 7.19. Found: C, 63.97; H, 6.90.

Preparation of Mosher Ester 19. To a solution of alcohol (+)-**2** (22.4 mg, 0.08 mmol) in dry dichloromethane (1.5 mL) was added successively Et_3N (13.7 mg, 0.135 mmol), DMAP (2.0 mg, 0.016 mmol), and Mosher acid chloride (26.3 mg, 0.104 mmol) at room temperature. After the mixture was stirred for 30 min, two drops of 10% $NaHCO_3$ and ether (2 mL) were added, and stirring was continued for 10 min. The reaction mixture was filtered through a Celite pad and concentrated, to give the diastereomeric esters which were analyzed without further purification by ^{19}F NMR: ^{19}F NMR ($CDCl_3$) −71.8 (9.0%), −71.9 ppm (91.0%).

Preparation of X-ray Sample 18. To a solution of alcohol (+)-**2** (13.7 mg, 0.049 mmol) in benzene (3 mL) was added (*S*)-(+)-1-(1-naphthyl)ethyl isocyanate (11.6 mg, 0.059 mmol) in one portion. The reaction mixture was heated to reflux for 2 days.

After concentration of the solvent, the residue was recrystallized from *n*-hexane–ether (three times) to give **18** as colorless prisms, mp 182–184 °C.

1-[4(*S*)-(Isopropoxycarbonyl)-2-oxazolinyl]-5-methoxynaphthalene [(+)-20]. To a stirred suspension of amide **5** (1.65 g, 8.2 mmol) in dry 1,2-dichloroethane (80 mL) was added triethyloxonium tetrafluoroborate (2.02 g, 10.46 mmol) under argon at room temperature and the mixture stirred for 20 h. (−)-Serine isopropyl ester (2.26 g, 12.3 mmol) was added, in one portion, and the reaction mixture was heated at reflux for 20 h. After cooling, the mixture was poured into brine (50 mL), the organic layer was separated, and the aqueous layer was extracted with dichloromethane (15 mL × 2). The combined extracts were dried (Na_2SO_4) and concentrated to give a residue, which was chromatographed (silica gel; hexane–ethyl acetate, 4:1) to give the oxazoline ester **20** as colorless plates (2.42 g, 94.2%): mp 75.5–76.5 °C (*n*-hexane); $[\alpha]^{25}_D$ +77.14° (*c* 3.4, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 8.63 (d, 1 H, *J* = 8.8 Hz), 8.74 (d, 1 H, *J* = 8.5 Hz), 8.09 (dd, 1 H, *J* = 7.3 and 1.4 Hz), 7.52–7.45 (m, 2 H), 6.85 (d, 1 H, *J* = 7.7 Hz), 5.16 (m, 1 H), 5.04 (dd, 1 H, *J* = 10.5 and 7.6 Hz), 4.68 (br t, 1 H, *J* = 8.1 Hz), 4.60 (dd, 1 H, *J* = 10.5 and 8.7 Hz), 3.98 (s, 3 H), 1.34 (d, 3 H, *J* = 6.8 Hz), 1.33 (d, 3 H, *J* = 6.3 Hz); ^{13}C NMR ($CDCl_3$) δ 170.8, 166.5, 155.6, 132.5, 129.8 (×2), 127.4, 126.2 (×2), 123.8, 118.9, 104.4, 69.8, 69.2, 69.0, 55.6, 21.8 (×2). IR (film): 1735, 1640, 1590, 1516, 1470, 1410 cm^{-1}.

Anal. Calcd for $C_{18}H_{19}NO_4$: C, 68.98; H, 6.11; N, 4.64. Found: C, 69.19; H, 6.08; N, 4.46.

1-[4(*R*)-(Hydroxymethyl)-2-oxazolinyl]-5-methoxynaphthalene [(+)-21]. To a suspension of lithium aluminum hydride (0.363 g, 9.57 mmol) in dry ether (20 mL) at 0 °C under argon was added a solution of **20** (2.0 g, 6.38 mmol) in dry ether (30 mL) over a period of 10 min. After the mixture was stirred for 1 h at 0 °C, the excess reagent was decomposed by the dropwise addition of water and filtered through Celite. Evaporation of the solvent gave a pale yellow gum, which was chromatographed (silica gel; hexane–ethyl acetate–methanol, 15:15:1) to give the oxazoline alcohol **21** as colorless needles (1.34 g, 81.6%): mp 88.0–89.0 °C (*n*-hexane–Et_2O); $[\alpha]^{25}_D$ +9.93° (*c* 3.03, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 8.52 (d, 1 H, *J* = 8.7 Hz), 8.44 (d, 1 H, *J* = 8.3 Hz), 8.04 (dd, 1 H, *J* = 7.3 and 0.7 Hz), 7.50–7.41 (m, 2 H), 6.85 (d, 1 H, *J* = 7.7 Hz), 4.58–4.52 (m, 1 H), 4.88 (br t, 1 H, *J* = 7.4 Hz), 4.30 (br t, 1 H, *J* = 7.4 Hz), 3.99 (s, 3 H), 3.94 (dd, 1 H, *J* = 11.4 and 3.7 Hz), 3.69 (dd, 1 H, *J* = 11.4 and 4.3 Hz), 2.60 (br s, 1 H, OH); ^{13}C NMR ($CDCl_3$) δ 165.7, 155.6, 132.2, 129.6, 127.3, 126.2, 125.9, 124.4, 123.9, 118.7, 104.4, 68.9 (×2), 64.3, 55.6; IR ($CHCl_3$) 3600–3150 (br OH), 1636, 1585, 1502, 1460, 1402, 1348, 1245, 1010 cm^{-1}.

Anal. Calcd for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88; N, 5.44. Found: C, 70.21; H, 5.75; N, 5.33.

1-[4(*R*)-(Methoxymethyl)-2-oxazolinyl]-5-methoxynaphthalene [(+)-22]. To a stirred suspension of potassium *tert*-butoxide (0.63 g, 5.61 mmol) in dry THF (20 mL) was added a solution of **21** (1.2 g, 4.66 mmol) in dry THF (30 mL) under argon at room temperature. After the mixture was stirred for 12 h, iodomethane was added dropwise, and the reaction mixture was stirred for an additional 3 h.

Ether (50 mL) was added, and the organic phase was washed with water and dried (Na_2SO_4). Concentration in vacuo gave a yellow oil, which was chromatographed (silica gel; hexane–ethyl acetate–methanol, 15:10:1) to give the oxazoline **22** (0.934 g, 73.8%) as a colorless oil: $[\alpha]^{25}_D$ +25.76° (*c* 4.53, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 8.61 (d, 1 H, *J* = 8.7 Hz), 8.43 (d, 1 H, *J* = 8.4 Hz), 8.06 (d, 1 H, *J* = 7.2 Hz), 7.50–7.42 (m, 2 H), 6.81 (d, 1 H, *J* = 7.7 Hz), 4.66–4.55 (m, 1 H), 4.48 (t, 1 H, *J* = 8.3 Hz), 4.31 (t, 1 H, *J* = 8.3 Hz), 3.94 (s, 3 H), 3.74 (dd, 1 H, *J* = 9.4 and 4.3 Hz), 3.51 (dd, 1 H, *J* = 9.4 and 6.8 Hz), 3.41 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 165.0, 155.7, 132.5, 129.6, 127.3, 126.3, 125.8, 124.6, 123.9, 119.0, 104.3, 75.1, 69.7, 67.4, 59.3, 55.6; IR (film) 1642, 1587, 1513, 1456, 1408, 1258, 1011, 780 cm^{-1}.

Anal. Calcd for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32; N, 5.16. Found: C, 71.14; H, 6.22; N, 5.15.

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Supplementary Material Available: X-ray data for 18 (6 pages). Ordering information is given on any current masthead page.

Novel Cytotoxic Monoterpenes Having a Halogenated Tetrahydropyran from *Aplysia kurodai*

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The structures of four new halogenated monoterpenes, aplysiapyranoids A, B, C, and D, the constituents of a midgut gland of *Aplysia kurodai*, are presented. They have a 2-(2-chlorovinyl)-2,6,6-trimethyltetrahydropyran skeleton. The conformations of aplysiapyranoids A and B are mobile, and they exhibit only ambiguous NMR signals. The structure of aplysiapyranoid A was deduced from that of aplysiapyranoid B, which has been determined by X-ray analysis. On the contrary, aplysiapyranoids C and D have fixed conformations, and their structures were elucidated by means of conventional spectroscopic analysis.

Since aplysin, the first brominated sesquiterpene, was isolated from *Aplysia kurodai* Baba,[1] the constituents of the mollusc and its congeners have been attracting chemists' interest, and a variety of unique compounds have been isolated from the animals.[2] The types of compounds strongly depend on the places where the molluscs are collected, and therefore, the ingredients isolated from them are considered to originate from the seaweeds on which they feed. This paper describes the structure of a new type

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