Hz), 3.86 (dd, 1 H, J = 4, 12.5 Hz), 3.96 (ddd, 1 H, J = 5, 6, 8 Hz), 4.21 (dddd, 1 H, J = 5.5, 5.5, 8, 8 Hz); MS (SIMS) 194 $(M + H)^+$; HRMS (FAB) m/z calcd for $C_7H_{16}O_5N$ $(M + H)^+$ 194.1028, found 194.1029.

General Procedure for the Acid-Catalyzed Cyclization of Galantinic Acid and Its Analogues. Acid Treatment of Galantinic Acid. Galantinic acid (**20a**) (4 mg, 0.02 mmol) was dissolved in 6 N aqueous HCl and heated (110 °C) in a sealed tube. After 14 h, the solution was concentrated in vacuo. The residue was passed through a column of Dowex 50Wx4 (100-200 mesh) ion exchange resin (H_2O, then 1 N aqueous NH_3) to give a mixture of **3a** and **3b** (2.8 mg, 77%). The mixture was dissolved in 1 N HCl and concentrated in vacuo to give a mixture of **3a** and **3b** as hydrochlorides. Using these hydrochlorides, the product ratio (**3a**/**3b**) was calculated from the integration of the ^1H NMR (D_2O, 270 MHz) spectrum of the mixture of **3a** and **3b**: the signal of 3βH of **3a** appeared at δ 2.20 (ddd, 1 H, J = 2.4, 5.3, 12.5 Hz) and that of 3αH and 3βH of **3b** appeared at δ 1.85 (m, 2 H).[4] The ratio of **3a**/**3b** was 9/1.

Acid Treatment of 3-*epi*-Galantinic Acid (20b). According to the general procedure, **20b** (5.5 mg, 0.03 mmol) gave a mixture of **3a** and **3b** (2.1 mg, 42%). The ratio of **3a**/**3b** was 11/1.

Acid Treatment of 3a. According to the general procedure, **3a** (4 mg, 0.02 mmol) gave a mixture of **3a** and **3b** (4 mg, 100%). The ratio of **3a**/**3b** was 8/1.

Acid Treatment of 3b. *N*-(*tert*-Butoxycarbonyl)-**3b** (5 mg, 0.02 mmol) was exposed to 6 N aqueous HCl for 14 h at 110 °C in a sealed tube. The solution was concentrated in vacuo. The residue was dissolved in dioxane (0.5 mL) and H_2O (0.5 mL). The solution was adjusted to pH 8 by adding Et_3N. To this solution was added Boc_2O (10 μL, 0.04 mmol). The solution was stirred for 3 h at room temperature and then adjusted to pH 2 with 1 N aqueous HCl. The resulting solution was extracted with ethyl acetate several times, and the combined organic phase was dried ($MgSO_4$) and concentrated in vacuo. To a solution of the residue in Et_2O was added diazomethane in Et_2O. The solution was concentrated in vacuo to give an oily residue, which was chromatographed on silica gel to give a mixture of **3a'** and **3b'** (2 mg, 38%; **3a'**/**3b'** = 2/7 by ^1H NMR analysis).

Acid Treatment of *E* Unsaturated Acid 46. Protected *E* α,β-unsaturated acid **46** (17 mg, 0.06 mmol), which was prepared from **40a** by hydrolysis (0.5 N NaOH, room temperature, 4 h), was treated with 6 N aqueous HCl according to the general procedure to give a mixture of **3a** and **3b** (8.4 mg, 88%). The ratio of **3a**/**3b** was 2/1.

Acid Treatment of *Z* Unsaturated Acid 47. α,β-Unsaturated δ-lactone **39** (17 mg, 0.06 mmol) was hydrolyzed with 0.5 N aqueous NaOH (140 μL) for 4 h at 0 °C in THF (280 μL). The solution was adjusted to pH 2 with 1 N aqueous HCl, extracted with ethyl acetate, and washed with water. The organic phase was dried ($MgSO_4$) and concentrated in vacuo to give the N-protected form of the *Z* unsaturated acid **47**. This was treated with 6 N aqueous HCl according to the general procedure to give a mixture of **3a** and **3b** (8.4 mg, 85%). The ratio of **3a**/**3b** was 9/1.

Acid Treatment of α,β-Unsaturated Lactone 48. α,β-Unsaturated δ-lactone **39** (10 mg, 0.03 mmol), which was used as an equivalent compound of **48**, was treated with 6 N aqueous HCl according to the general procedure to give a mixture of **3a** and **3b** (4.7 mg, 80%). The ratio of **3a**/**3b** was 10/1.

Acid Treatment of 3(*S*)-Hydroxy δ-Lactone 49. A solution of **45b** (10 mg, 0.02 mmol) in methylene chloride (100 μL) and TFA (100 μL) was stirred for 20 min at room temperature. The solution was concentrated in vacuo to give **49** as the corresponding TFA salt. This was treated with 6 N aqueous HCl according to the general procedure to give a mixture of **3a** and **3b** (4 mg, 98%). The ratio of **3a**/**3b** was 11/1.

Acid Treatment of 3(*R*)-Hydroxy δ-Lactone 50. 3(*R*)-Hydroxy lactone **42a** (10 mg, 0.03 mmol), which was used as an equivalent compound of **50**, was treated with 6 N aqueous HCl according to the general procedure to give a mixture of **3a** and **3b** (5.5 mg, 99%). The ratio of **3a**/**3b** was 11/1.

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Supplementary Material Available: Detailed description of syntheses and spectral data of compounds **1a**, **4a**, and **4b** and ^1H NMR spectra of **1a**, **4a**, **4b**, **5c**, **20a**, **20b**, and other key synthetic intermediates (12 pages). Ordering information is given on any current masthead page.

Regiospecific Synthesis of Polysubstituted Naphthalenes via Oxazoline-Mediated Nucleophilic Aromatic Substitutions and Additions

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Abstract: An efficient procedure for the selective functionalization of several positions of 2-methoxynaphthalene is described. Nucleophilic aromatic substitutions were carried out by displacing both a methoxy group and a neutral amine ortho to an oxazoline **6**. 4-Substituted naphthalenes **8** were obtained from nucleophilic aromatic addition of an allyllithium species to a position para to the oxazoline **6**. The resultant dihydronaphthalenes were converted to the fully aromatic systems **9** or alternatively substituted in the 2-position to form **10**. Reductive cleavage of the oxazoline moities in **7** and **9** proceeded smoothly, producing the substituted naphthaldehydes **11**.

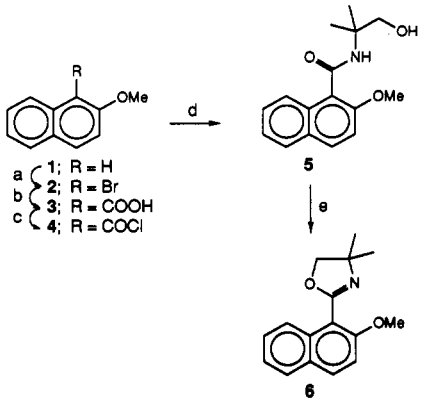
The functionalization of naphthalenes has become a prominent route by which many important organic compounds are accessed. In view of a recent report[1] describing substitution in the naphthalene series via aryne intermediates wherein a single substituent is introduced, we are prompted to disclose our own efficient effort in performing multiple selective substitutions.[2] The widespread use of naphthalenes as a starting material in synthesis stems from the ubiquitous nature of fused 6,6-ring systems in naturally-occurring compounds, including saturated as well as unsaturated variants. Unfortunately, substituted naphthalenes have often

(1) Buchwald, S. L.; King, S. M. *J. Am. Chem. Soc.* **1991**, *113*, 258-265.

(2) For our previous contributions, see: (a) Pansegrau, P. D.; Rieker, W. F.; Meyers, A. I. *J. Am. Chem. Soc.* **1988**, *110*, 7178-7184 (aryne chemistry). (b) Robichaud, A. J.; Meyers, A. I. *J. Org. Chem.* **1991**, *56*, 2607-2609 and references cited therein (naphthalene substitutions).

0002-7863/92/1514-1010$03.00/0

Scheme I[a]



[a] (a) Br_2, HOAc. (b) (i) *t*-BuLi (2 equiv), THF; (ii) CO_2(s). (c) Oxalyl chloride, methylene chloride. (d) Triethylamine, amino alcohol, 1,2-dichloroethane. (e) Thionyl chloride, benzene, methylene chloride.

proven difficult to obtain by efficient and general methods. Many substitution patterns are still virtually inaccessible by expedient chemical routes. The importance of developing methods for performing these transformations is well-supported by the steadily increasing activity in this area. A number of research groups, with widely varying interests, have made recent contributions to this field.[3] Our own contributions to the development of this chemistry have centered around the versatile oxazoline moiety.[4] Aromatic oxazolines possess five features important to our purposes: (a) a strongly activating inductive effect which allows displacement of methoxy and fluorine groups,[4] (2) an ortho-directing effect,[5] (3) relative inertness toward reaction at the oxazoline ring,[6] (4) facile preparation and removal,[4] and (5) applicability to optically active systems through incorporation of an enantiomerically pure amino alcohol.[7] The utilization of aromatic oxazolines has resulted in the total syntheses of a number of natural products by us and others.[8]

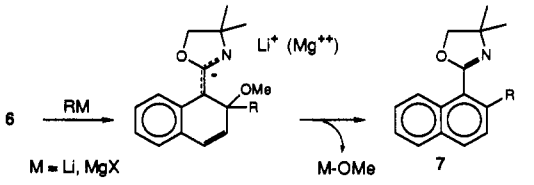
In pursuit of further elaborating the basic features, advantages, and limitations of this group, we have developed the related 2-(2-methoxy-1-naphthyl)oxazoline **6**. In exploring this system, we have encountered expected as well as unexpected behavior, and thus we report herein a higly efficient route to 1,2-disubstituted naphthalenes via nucleophilic aromatic substitution as well as an unprecedented addition of allyllithiums to yield 1,2,4-trisubstituted dihydronaphthalenes.

The requisite naphthyloxazoline, **6**, was prepared as illustrated in Scheme I. The bromination/lithiation/carboxylation sequence is a slight modification of the procedures utilized by Fuson.[9] The bromide, **2**, was metalated via lithium–halogen exchange with 2 equiv of *t*-BuLi in THF followed by quenching with solid CO_2 to yield, upon workup, the acid **3**. Alternatively, this transformation could be accomplished by way of the Grignard reaction as previously published. The lithiation sequence was, however, found to be more reliable and higher yielding, applicable to small (<1 mmol) as well as large (~200 mmol) scale reactions. Conversion of the acid to the acid chloride, **4**, was accomplished with thionyl chloride followed by condensation with an amino alcohol to give the hydroxy amide **5**. The hydroxy amide was then cyclized with either thionyl chloride or oxalyl chloride to afford oxazoline **6**. The overall yield of **6** from **1** was 73%. Alternatively, an overall yield of 77% was achieved by the omission of rigorous purification in steps a and b.

Table I. (2-Substituted-1-naphthyl)oxazolines

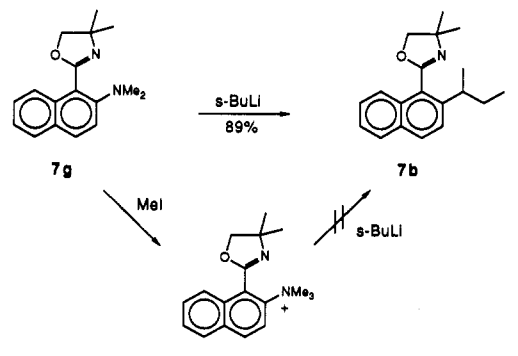
entry	R	M	7, % yield
a	*n*-Bu	Li	94
b	*s*-Bu	Li	98
c	*t*-Bu	Li	98
d	*syn*-propenyl	Li	64
e	Ph	Li	85
f	Ph	MgBr	100
g	Me_2N	Li	98
h	*i*-Pr_2N	Li	86
i	*O*-methylephedrinyl	Li	99

The disubstituted naphthalenes were obtained via a pathway analogous to an earlier reported and complementary system.[10] Naphthyloxazoline **6** was treated with a variety of nucleophiles in THF to give products of ipso substitution. Alkyllithium



reagents typically gave good to excellent results (Table I), whether primary (**7a**), secondary (**7b**), tertiary (**7c**), vinyl (**7d**), or aromatic (**7e**). Grignard reagents also gave excellent results (**7f**) though longer reaction times were required. Lithio amides were found to give high yields regardless of steric considerations (**7g** and **7h**) or chelating ligands (**7i**).

With the purpose of exploring the possible utility of other leaving groups (fluoride and alkoxide being the only two nucleofuges used previously in nucleophilic aromatic substitution of aromatic oxazolines[4]), we sought to methylate the amine or oxazoline nitrogen of **7g** and subsequently add *s*-BuLi to obtain the product of either 1,4- or 1,2-addition. Methylation of **7g** with methyl triflate did give a quaternary salt, presumed to be **7j**, but upon treatment with *s*-BuLi gave only the product of demethylation, i.e., **7g**. On the other hand, when the dimethylamino derivative **7g** was treated directly with *s*-BuLi, workup gave the 2-*sec*-butyl derivative **7b** in 89% yield. This transformation



ostensibly proceeds through an SN_{Ar} mechanism, whereby the

(3) In addition to ref 1, see: (a) Tada, M.; Hiratsuka, M.; Goto, H. *J. Org. Chem.* **1990**, *55*, 4364–4370. (b) Tomioka, K.; Shindo, M.; Koga, K. *J. Org. Chem.* **1990**, *55*, 2276–2277. (c) Zoeller, J. R.; Sumner, C. E., Jr. *J. Org. Chem.* **1990**, *55*, 319–324. (d) Seko, S.; Tanabe, Y.; Suzukamo, G. *Tetrahedron Lett.* **1990**, *31*, 6883–6886. (e) Gatti, N. *Tetrahedron Lett.* **1990**, *31*, 3933–3936. (f) Deluca, M. E.; Hudlicky, T. *Tetrahedron Lett.* **1990**, *31*, 13–16. (g) Suzuki, T.; Hotta, H.; Hattori, T.; Miyano, S. *Chem. Lett.* **1990**, 807–810. (h) Bringmann, G.; Walter, R.; Weirich, R. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 977–991 (review).

(4) For a review of earlier studies, see: Reuman, M.; Meyers, A. I. *Tetrahedron* **1985**, *41*, 837–860 and references cited therein.

(5) (a) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879–933 and references cited therein. (b) Beak, P.; Meyers, A. I. *Acc. Chem. Res.* **1986**, *19*, 356–363.

(6) For a concise tabulation of the reactivity of oxazolines, see: Greene, T. W. *Protective Groups in Organic Synthesis*; J. Wiley and Sons: New York, 1981; pp 315–318.

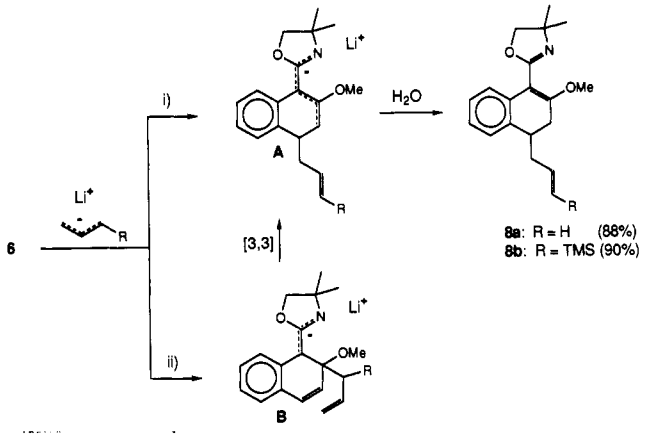
(7) Rawson, D. J.; Meyers, A. I. *J. Org. Chem.* **1991**, *56*, 2292–2294 and references cited therein.

(8) (a) Rizzacasa, M. A.; Sargent, M. V. *J. Chem. Soc., Chem. Commun.* **1991**, 278–280. (b) Comber, M. F.; Sargent, M. V. *J. Chem. Soc., Chem. Commun.* **1991**, 190–192. (c) Warshawsky, A. M.; Meyers, A. I. *J. Am. Chem. Soc.* **1990**, *112*, 8090–8099 and references cited therein. (d) Patten, A. D.; Nguyen, N. H.; Danishefsky, S. J. *J. Org. Chem.* **1988**, *53*, 1003–1007. (e) Andrews, R. C.; Teague, S. J.; Meyers, A. I. *J. Am. Chem. Soc.* **1988**, *110*, 7854–7858. (f) Findlay, J. A.; Daljeet, A.; Murray, P. J.; Rej, R. N. *Can. J. Chem.* **1987**, *65*, 427–431.

(9) (a) Fuson, R. C.; Chadwick, D. H. *J. Org. Chem.* **1949**, *13*, 484–488. (b) Fuson, R. C. *J. Am. Chem. Soc.* **1956**, *78*, 5409–5413.

(10) Meyers, A. I.; Lutomski *Synthesis* **1983**, 105–107.

Scheme II



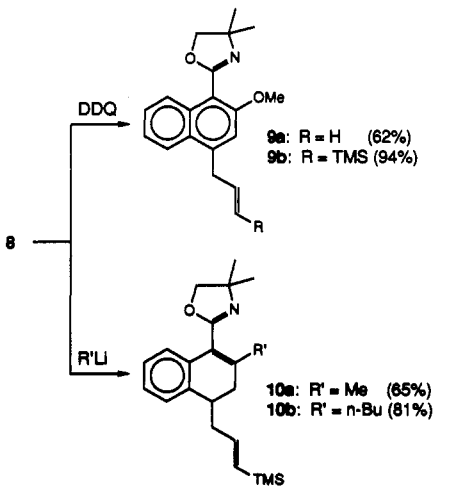
nucleophilic addition to form the σ complex is the rate-determining step, i.e., leaving group ability is relatively unimportant. However, this mechanism does require that the bond to be broken (the C–N bond in this case) have a reasonable degree of polarization, and as a consequence, only cationic nitrogen species are typically displaced from aromatic systems. It is, therefore, uncommon to observe the displacement of a neutral amine moiety as in this instance.[11] We are currently investigating the possibility of utilizing this characteristic to impart axial chirality via the displacement of optically active amines from aromatic oxazolines using aryl metallics.[12]

Unexpected results were obtained upon addition of two separate allyllithium species to **6**. Rather than obtaining the 2-substituted naphthalenes, **7**, a high yield of addition, *not* substitution, products **8** was observed upon quenching. Scheme II illustrates the two likely pathways to 4-substituted adducts **8a** and **8b**. In path i, 1,6-addition[13] takes place giving rise to aza dienolate A.[14] An alternative mechanism is shown in path ii. In this scenario, a more typical 1,4-addition takes place to give aza enolate B, but instead of the usual methoxide elimination taking place, B may undergo a rate-competitive, carbanion-accelerated Cope rearrangement[15] to give A. The latter intermediate, common to both pathways, must either be quenched at the α position followed by allylic rearrangement to give the styrenyl product **8** *or* may be quenched at the γ position directly. In either case, this useful synthetic result now opens up a variety of pathways to polysubstituted derivatives.

The dihydronaphthalenes **8** above were found to readily oxidize to the fully aromatic systems (Scheme III). For example, **8a** was oxidized with DDQ in benzene overnight to yield **9a** in 62% yield. For reasons which are not clear, the oxidation of **8b** to **9b** required only 20 min and proceeded in considerably higher yield (94%). In neither case was the resultant allyl system observed to rearrange into conjugation with the naphthalene ring system;[16] thus a great deal of flexibility is preserved with respect to potential manipulation of the versatile allyl and (trimethylsilyl)allyl groups in **9a** and **9b**, respectively.

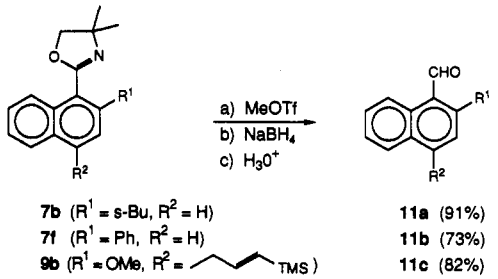
Further synthetic manipulations were accomplished by subjecting **8b** to organolithium reagents (MeLi, *n*-BuLi), resulting

Scheme III



in methoxide displacement (**10a**, **10b**) in satisfactory yields. In addition to the substitution products, starting materials were recovered (10–20%), reflecting competitive deprotonation of the C-3 allylic proton in **8b**. Nevertheless, the additional synthetic parameter introduced by methoxyl substitution (to **10**) further demonstrates the versatility of these systems.

Several of the naphthyloxazolines were converted by methods previously reported[4] to the corresponding naphthaldehydes **11a–c** in good yields. The procedure involved methylation of the oxazoline nitrogen, with methyl triflate furnishing the iminium salt, followed by reduction with sodium borohydride. The resulting oxazolidine may be isolated but was typically hydrolyzed under mildly acidic conditions, affording aldehyde **11**.



In summary, the naphthyloxazoline **1**[17] is a highly versatile precursor to a number of selectively substituted naphthaldehydes, and this method can take its place among other recent efforts[1] to reach these important systems.[18]

Experimental Section

General. Reaction solvents were purified according to standard procedures.[19] All reactions were carried out under dry argon in oven-dried glassware. Temperatures are reported as bath temperatures. Organic layers from extractive workups were dried over $MgSO_4$. Rotary evaporation was used to concentrate dried extractants. Chromatographic solvents were distilled prior to use without further drying.

Radial chromatography was carried out on a Harrison Research Chromatotron 7924 and silica gel plates (No. 7749, Kieselgel 60 PF_{254}, Merck). Flash column chromatography was carried out with Grace 951 silica gel (58 μm, Aldrich).

Melting points are uncorrected. ^1H NMR were recorded at 300 MHz, and ^{13}C NMR were recorded at 75.5 MHz. Carbon multiplicities were obtained from DEPT experiments. Deuteriochloroform was used as the NMR solvent unless otherwise noted. Chemical shifts are expressed in

(11) March, J. *Advanced Organic Chemistry*; J. Wiley and Sons: New York, 1985; pp 576–607 and references cited therein.

(12) Wilson, J. W.; Cram, D. J. *J. Org. Chem.* **1984**, *49*, 4930–4943. Wilson and Cram showed that chiral alkoxy groups acting as leaving groups in oxazoline-mediated substitution (to binaphthyls) were responsible for inducing a high degree of axial chirality.

(13) For examples of early 1,6-conjugate additions, see: (a) Ralls, J. W.; Dodson, R. M.; Riegel, B. *J. Am. Chem. Soc.* **1949**, *71*, 3320–3325. (b) Fuson, R. C.; Tull, R. *J. Am. Chem. Soc.* **1949**, *71*, 2543–2546. (c) Abe, Y.; Harukawa, T.; Ishikawa, H.; Miki, T.; Sumi, M.; Toga, T. *J. Am. Chem. Soc.* **1956**, *78*, 1422–1426.

(14) The possibility of *E* and *Z* isomers exists for the aza enolate A, as well as for the dienolate B. Only the *E* isomer has been illustrated in Scheme II.

(15) For a review of the related oxy-Cope reaction, see: Paquette, L. A. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 609–626.

(16) The styrenyl compound is potentially accessible via a metal-catalyzed rearrangement to the more stable conjugated system. As a consequence, ozonolysis would allow entry into a variety of 4-substituted compounds if desired.

(17) A new procedure has recently been developed in our laboratory for the production of aryl- and vinyloxazolines based on Pd-catalyzed vinyl triflate–amide couplings. This chemistry will be published in due course.

(18) After this manuscript was completed, we became aware of a patent (Sandoz, A.-G. *Chem. Abstr.* **1985**, *102*, 61957p) which reports aryl Grignard substitution of (2-methoxy-1-naphthyl)oxazoline to ultimately produce mevalonolactone analogues with excellent cholesterol biosynthesis inhibition properties.

(19) Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*; Pergamon Press: New York, 1988.

parts per million (ppm) downfield from tetramethylsilane in most cases. In instances where TMS was obscured by molecular components, the chloroform peak was set to 7.24 ppm.

1-Bromo-2-methoxynaphthalene (2) was prepared as described previously:[9a] ^{1}H NMR 4.02 (s, 3 H), 7.26 (d, J = 9.1 Hz, 1 H), 7.36–7.42 (m, 1 H), 7.53–7.59 (m, 1 H), 7.79 (t, J = 9.1 Hz, 2 H), 8.22 (d, J = 8.4 Hz, 1 H).

2-Methoxy-1-naphthoic Acid[9b] (3). To a stirred solution of bromide **2** (2.65 g, 11.18 mmol) in THF (125 mL) cooled to −78 °C was added t-BuLi (13.5 mL, 22.92 mmol, 1.7 M in pentane) dropwise. After the mixture was stirred for 1 h at −78 °C, dry ice (4 g, large excess) was added and the mixture warmed to ambient temperature. After 1 h of additional stirring, 2 N NaOH (50 mL) was added. The organic layer was further extracted with saturated aqueous $NaHCO_3$ (4 × 40 mL). The combined water layers containing the carboxylate product were then washed with ether (50 mL), cooled to 0 °C, and acidified (6 N HCl). Extraction of the carboxylic acid by ether (5 × 100 mL) followed by drying of the combined organic layers and subsequent concentration yielded white crystals (2.088 g, 10.33 mmol, 92%): mp 177–179 °C; IR (KBr pellet) 3300–2500, 1686, 1255 cm^{-1}; ^{1}H NMR (acetone-d_6) 3.97 (s, 3 H), 7.40 (ddd, J = 1.1, 6.8, 6.9 Hz, 1 H), 7.47 (d, J = 9.2 Hz, 1 H), 7.54 (ddd, J = 1.3, 6.8, 8.5 Hz, 1 H), 7.85–7.93 (m, 2 H), 8.00 (d, J = 9.2 Hz, 1 H), 9.30–12.80 (br s, 1 H); ^{13}C NMR (acetone-d_6) 57.09 (q), 114.48 (d), 119.29 (s), 124.69 (d), 124.83 (d), 128.21 (d), 128.96 (d), 129.48 (s), 131.64 (s), 132.12 (d), 155.05 (s), 168.66 (s). Anal. Calcd for $C_{12}H_{10}O_3$: C, 71.28; H, 4.98. Found: C, 71.34; H, 4.92.

2-(2-Methoxy-1-naphthyl)oxazoline 6. To a stirred solution of 2-methoxy-1-naphthoic acid (**3**) (1.52 g, 7.52 mmol) in CH_2Cl_2 (100 mL) at ambient temperature was added oxalyl chloride (0.85 mL, 9.78 mmol). Stirring was continued for 5 h. The solvent and excess oxalyl chloride were then removed by rotary evaporation. Next was added 1,2-dichloroethane (15 mL) followed by additional rotary evaporation (to remove trace oxalyl chloride). The crude 2-methoxy-1-naphthoyl chloride (**4**) was then dissolved in 1,2-dichloroethane (30 mL), treated successively with triethylamine (1.2 mL, 8.65 mmol) and amino alcohol (0.83 mL, 8.65 mmol), and stirred overnight. Next were added saturated aqueous NH_4Cl (10 mL) and water (10 mL). The entire mixture was then added to a separatory funnel containing ether (600 mL). The organic layer was separated and washed with water (30 mL). The aqueous layers were combined and extracted with ether (150 mL). The combined organic layers were dried and concentrated to yield crude hydroxy amide **5**. After redissolving **5** in CH_2Cl_2 (120 mL) and benzene (30 mL), thionyl chloride (2.19 mL, 30.1 mmol) was added at 0 °C followed by warming to ambient temperature and stirring for 4 h. Solvent and excess thionyl chloride were removed by rotary evaporation. Next were added ether (400 mL), saturated aqueous $NaHCO_3$ (35 mL), water (35 mL), and 2 N NaOH (35 mL). After the solution was stirred for 0.5 h, the organic layer was removed and the aqueous layer re-extracted with ether (200 mL). The combined organic layers were dried, concentrated, and chromatographed on silica gel (120 g) using hexanes/ethyl acetate (2:1 to 1:1) to afford white crystals (1.75 g, 6.85 mmol, 91%): mp 100–101 °C; IR (CCl_4) 2966, 1666, 1513, 1264, 1007 cm^{-1}; ^{1}H NMR 1.50 (s, 6 H), 3.92 (s, 3 H), 4.19 (s, 2 H), 7.25 (d, J = 9.1 Hz, 1 H), 7.30–7.35 (m, 1 H), 7.44–7.49 (m, 1 H), 7.73–7.77 (m, 1 H), 7.85–7.90 (m, 2 H); ^{13}C NMR 28.44 (q), 56.75 (q), 68.03 (s), 78.86 (t), 112.52 (s), 113.00 (d), 123.77 (d), 123.86 (d), 127.26 (d), 127.82 (d), 128.46 (s), 131.56 (d), 132.54 (s), 155.79 (s), 159.73 (s). Anal. Calcd for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71; N, 5.49. Found: C, 75.18; H, 6.74; N, 5.44.

(2-Substituted-1-naphthyl)oxazolines 7a–c,e,f,h. General Procedure. A stirred solution of 2-(2-methoxy-1-naphthyl)oxazoline **6** in THF (10 mL/mmol of **6**) was cooled to −78 °C (0 °C for **7f**) and treated with a nucleophile (1.2 equiv based on **6**). After warming to ambient temperature, the reaction was monitored by TLC (hexanes/ethyl acetate, 1:1) until complete. The solution was then quenched (saturated aqueous NH_4Cl) and diluted with ether. The organic layer was separated, dried, concentrated, and chromatographed via radial chromatography using hexanes/ethyl acetate (4:1) as eluent to yield pure material.

2-(2-*n*-Butyl-1-naphthyl)oxazoline 7a was obtained as a clear colorless oil (207 mg, 0.74 mmol, 94%): IR (neat) 2961, 1665, 1461, 1199, 1006 cm^{-1}; ^{1}H NMR 0.94 (t, J = 7.3 Hz, 3 H), 1.33–1.46 (m, 2 H), 1.51 (s, 6 H), 1.62–1.72 (m, 2 H), 2.82 (app t, J = 7.9 Hz, 2 H), 4.20 (s, 2 H), 7.34 (d, J = 8.5 Hz, 1 H), 7.39–7.51 (m, 2 H), 7.76–7.81 (m, 2 H), 7.89 (app d, J = 8.5 Hz, 1 H); ^{13}C NMR 13.92 (q), 22.75 (t), 28.58 (q), 33.67 (t), 33.82 (t), 68.25 (s), 78.98 (t), 124.66 (d), 124.85 (s), 125.21 (d), 126.62 (d), 127.37 (d), 127.82 (d), 129.61 (d), 131.65 (s), 131.70 (s), 140.25 (s), 161.56 (s). Anal. Calcd for $C_{19}H_{23}NO$: C, 81.10; H, 8.24; N, 4.98. Found: C, 81.17; H, 8.24; N, 4.95.

2-(2-*sec*-Butyl-1-naphthyl)oxazoline 7b was obtained as white crystals (215 mg, 0.76 mmol, 98%): IR (CCl_4) 2965, 1665, 1461, 1198, 1005 cm^{-1}; ^{1}H NMR 0.83 (t, J = 7.4 Hz, 3 H), 1.31 (d, J = 6.9 Hz, 3 H), 1.516 (s, 3 H), 1.523 (s, 3 H), 1.60–1.82 (m, 2 H), 2.99 (hex, J = 7.0 Hz, 1 H), 4.21 (s, 2 H), 7.40–7.51 (m, 3 H), 7.77–7.80 (m, 1 H), 7.84–7.87 (m, 2 H); ^{13}C NMR 12.39 (q), 21.71 (q), 28.61 (q), 28.64 (q), 30.72 (t), 38.44 (d), 68.33 (s), 79.04 (t), 123.35 (d), 124.82 (d), 124.94 (s), 125.33 (d), 126.66 (d), 127.79 (d), 129.96 (d), 131.56 (s), 131.71 (s), 144.42 (s), 161.59 (s). Anal. Calcd for $C_{19}H_{23}NO$: C, 81.10; H, 8.24; N, 4.98. Found: C, 81.18; H, 8.27; N, 4.92.

2-(2-*tert*-Butyl-1-naphthyl)oxazoline 7c was obtained as white crystals (216 mg, 0.76 mmol, 98%): IR (CCl_4) 2966, 1665, 1550, 1220, 1002 cm^{-1}; ^{1}H NMR 1.52 (br s, 15 H), 4.24 (v br s, 2 H), 7.38–7.49 (m, 2 H), 7.63 (d, J = 9.0 Hz, 1 H), 7.74–7.82 (m, 3 H); ^{13}C NMR 27–30 (br), 31.80 (q), 36.85 (s), 68.33 (s), 78.95 (t), 124.09 (s), 124.54 (d), 125.18 (d), 125.38 (d), 126.50 (d), 127.46 (d), 129.31 (d), 131.41 (s), 132.68 (s), 146.61 (s), 162.74 (s). Anal. Calcd for $C_{19}H_{23}NO$: C, 81.10; H, 8.24; N, 4.98. Found: C, 80.75; H, 8.29; N, 4.80.

2-(2-Phenyl-1-naphthyl)oxazoline 7e was obtained as white crystals (199 mg, 0.66 mmol, 85%): mp 97–99 °C; IR (CCl_4) 2968, 1664, 1496, 1201, 998 cm^{-1}; ^{1}H NMR 1.31 (s, 6 H), 3.95 (s, 2 H), 7.33–7.61 (m, 8 H), 7.86–7.89 (m, 1 H), 7.95 (d, J = 8.5 Hz, 1 H), 8.08 (dd, J = 0.8, 8.2 Hz, 1 H); ^{13}C NMR 28.10 (q), 68.13 (s), 79.07 (t), 125.10 (s), 125.15 (d), 126.04 (d), 127.15 (d), 127.28 (d), 127.38 (d), 127.92 (d), 127.97 (d), 128.94 (d), 129.79 (d), 131.55 (s), 132.29 (s), 139.93 (s), 141.17 (s), 161.26 (s). Anal. Calcd for $C_{21}H_{19}NO$: C, 83.69; H, 6.35; N, 4.65. Found: C, 83.57; H, 6.32; N, 4.30.

7f was obtained as white crystals (153 mg, 0.508 mmol, 100%): spectral data matched that obtained for **7e** as described above.

2-[2-(*N*,*N*-Diisopropylamino)-1-naphthyl]oxazoline 7h was obtained as a clear colorless oil (561 mg, 1.73 mmol, 86%): IR (CCl_4) 2969, 1669, 1383, 1012 cm^{-1}; ^{1}H NMR (1.06 (d, J = 6.5 Hz, 12 H), 1.52 (s, 6 H), 3.53 (hep, J = 6.5 Hz, 2 H), 4.16 (s, 2 H), 7.39–7.47 (m, 3 H), 7.77–7.82 (m, 2 H), 7.87–7.91 (m, 1 H); ^{13}C NMR 21.69 (q), 28.48 (q), 50.03 (d), 68.00 (s), 78.77 (t), 125.12 (d), 125.36 (d), 126.53 (d), 127.31 (d), 127.52 (d), 128.67 (s), 129.10 (d), 131.34 (s), 132.23 (s), 145.97 (s), 161.76 (s). Anal. Calcd for $C_{21}H_{28}N_2O$: C, 77.74; H, 8.70; N, 8.63. Found: C, 77.80; H, 9.03; N, 8.73.

2-[2-(*cis*-Propenyl)-1-naphthyl]oxazoline 7d. A stirred solution of (*Z*)-1-(tributylstannyl)propene[20] (806 mg, 2.43 mmol) in THF (10 mL) was cooled to −78 °C and treated with *n*-BuLi (1.29 mL, 2.43 mmol, 1.89 M in hexanes) dropwise. The mixture was warmed to −50 °C over 1 h followed by the dropwise addition of a solution of 2-(2-methoxy-1-naphthyl)oxazoline **6** (518 mg, 2.03 mmol) in THF (5 mL). Stirring was continued at −50 °C for 1 h followed by quenching (saturated aqueous NH_4Cl) and diluting with ether. The organic layer was separated, dried, concentrated, and chromatographed on silica gel (45 g) using hexanes/ethyl acetate (4:1) as the eluent, yielding a clear colorless liquid (411 mg, 1.55 mmol, 64%): IR (neat) 2965, 1661, 1199, 1120, 1006, cm^{-1}; ^{1}H NMR 1.49 (s, 6 H), 1.80 (dd, J = 1.8, 7.2 Hz, 3 H), 4.16 (s, 2 H), 5.89 (dq, J = 11.5, 7.2 Hz, 1 H), 6.70 (dd, J = 1.8, 11.5 Hz, 1 H), 7.40–7.53 (m, 3 H), 7.78–7.86 (m, 2 H), 7.98 (app d, J = 8.2 Hz, 1 H); ^{13}C NMR 14.61 (q), 28.38 (q), 68.16 (s), 78.87 (t), 124.84 (d), 125.24 (s), 125.66 (d), 126.71 (d), 126.81 (d), 127.76 (d), 127.91 (d), 128.28 (d), 129.03 (d), 131.43 (s), 131.88 (s), 135.14 (s), 161.15 (s).

2-[2-(*N*,*N*-Dimethylamino)-1-naphthyl]oxazoline 7g. A suspension of dimethylamine hydrochloride (204 mg, 2.5 mmol) in THF (10 mL) was cooled to −78 °C and treated with *s*-BuLi (3.46 mL, 1.3 M in cyclohexane, 4.5 mmol). The reaction mixture was allowed to warm to −50 °C over 3 h and was treated with **6** (255 mg, 1.0 mmol). Stirring was continued at −50 °C for 3 h and at ambient temperature for 1 h. Saturated aqueous NH_4Cl was added, followed by ether. The organic layer was separated, dried, concentrated, and purified via radial chromatography using hexanes/ethyl acetate (1:1) as eluent to yield 264 mg (0.98 mmol, 98%) of a clear colorless oil: IR (neat) 2966, 1659, 1620, 1598, 1509, 1008 cm^{-1}; ^{1}H NMR 1.49 (s, 6 H), 2.95 (s, 6 H), 4.18 (s, 2 H), 7.21–7.30 (m, 2 H), 7.40–7.46 (m, 1 H), 7.69 (d, J = 8.0 Hz, 1 H), 7.74 (d, J = 9.0 Hz, 1 H), 7.95 (d, J = 8.5 Hz, 1 H); ^{13}C NMR 28.47 (q), 43.53 (q), 67.79 (s), 78.59 (t), 113.29 (s), 118.19 (d), 123.19 (d), 123.32 (d), 126.87 (d), 127.65 (d), 128.22 (s), 130.54 (d), 133.03 (s), 150.03 (s), 161.73 (s).

7b (as derived from 7g). A solution of 2-[2-(*N*,*N*-dimethylamino)-1-naphthyl]oxazoline **7g** (454 mg, 1.69 mmol) in THF (10 mL) was cooled to −78 °C and treated with *s*-BuLi (1.95 mL, 2.54 mmol, 1.3 M in cyclohexane). Stirring was continued for 8 h at −78 °C followed by gradual warming to ambient temperature. After stirring at ambient temperature for 8 h, the mixture was quenched (NH_4Cl) and diluted (ether). The organic layer was separated, dried, concentrated, and chromatographed on silica gel (15 g) using hexanes/ethyl acetate (4:1)

(20) (*Z*)-(Tributylstannyl)propene was kindly supplied by Bristol-Myers/Squibb.

as the eluent to yield white crystals (424 mg, 1.51 mmol, 89%): spectral data matched that previously described for **7b**.

2-[2-(*O*-Methylephedrinyl)-1-naphthyl]oxazoline 7i. A stirred solution of ephedrine methyl ether[21] (0.886 g, 4.94 mmol) in THF (100 mL) was cooled to −70 °C and treated with *n*-BuLi (2.61 mL, 4.94 mmol, 1.89 M in hexanes). The solution was warmed to 0 °C and stirred for 0.5 h. To this was added 2-(2-methoxy-1-naphthyl)oxazoline **6** (766 mg, 3.00 mmol) as a solid. After stirring for an additional 2 h, the mixture was quenched with water (30 mL) and diluted with ether (150 mL). The organic layer was separated, dried, concentrated, and chromatographed through a plug of silica gel (30 g) using hexanes/ethyl acetate (1:1) as the eluent to yield a clear, light-golden oil (1.20 g, 2.98 mmol, 99%): $[\alpha]^{20}_D$ +78.5° (*c* = 1.0, MeOH anhyd); IR (CCl_4) 2976, 1658, 1597, 1508, 1008 cm^{-1}; ^1H NMR 1.28 (d, *J* = 6.8 Hz, 3 H), 1.44 (s, 3 H), 1.51 (s, 3 H), 3.01 (s, 3 H), 3.24 (s, 3 H), 3.90 (dq, *J* = 4.5, 6.8 Hz, 1 H), 4.11 (A of AB, *J* = 8.2 Hz, 1 H), 4.16 (B of AB, *J* = 8.2 Hz, 1 H), 4.32 (d, *J* = 4.5 Hz, 1 H), 7.06 (d, *J* = 9.0 Hz, 1 H), 7.15–7.21 (m, 5 H), 7.25–7.32 (m, 1 H), 7.40–7.46 (m, 1 H), 7.63–7.69 (m, 2 H), 7.98 (d, *J* = 8.5 Hz, 1 H); ^{13}C NMR 12.37 (q), 28.68 (q), 28.76 (q), 34.84 (q), 56.74 (q), 62.94 (d), 68.04 (s), 78.71 (t), 86.23 (d), 115.06 (s), 121.19 (d), 123.56 (d), 123.65 (d), 126.77 (d), 126.90 (d), 127.14 (d), 127.64 (d), 128.06 (d), 128.60 (s), 130.29 (d), 133.13 (s), 140.13 (s), 149.98 (s), 161.84 (s).

4-Substituted Dihydronaphthalenes 8a and 8b. General Procedure. A stirred solution of allyltributyltin or allyltrimethylsilane[22] (2.3 equiv based on **6**) and TMEDA (2 equiv based on **6**) in THF (5 mL/mmol of **6**) was cooled to −78 °C and treated with BuLi (2 equiv based on **6**, *n*-BuLi used with allyltributyltin, *s*-BuLi used with allyltrimethylsilane) dropwise over 10 min. Stirring was continued for 1 h at −78 °C and for an additional hour at −40 °C. Oxazoline **6** in THF (6 mL/mmol of **6**) was added dropwise over 5 min. The solution was allowed to warm to ambient temperature over 16 h, recooled to −78 °C, and quenched with saturated aqueous NH_4Cl. The suspension was warmed to ambient temperature followed by sequential addition of water and ether. The organic layer was dried, filtered, and concentrated. Chromatography with hexanes/ethyl acetate (4:1) yielded pure material.

8a was obtained as a clear oil (262 mg, 0.88 mmol, 88%): IR (CCl_4) 2969, 1668, 1640, 1487, 1250, 1001 cm^{-1}; ^1H NMR 1.41 (s, 3 H), 1.42 (s, 3 H), 2.36 (app t, *J* = 7.6 Hz, 2 H), 2.54 (dd, *J* = 4.3, 16.5 Hz, 1 H), 2.64 (dd, *J* = 6.5, 16.5 Hz, 1 H), 2.92 (m, 1 H), 3.75 (s, 3 H), 4.05 (A of AB, *J* = 8.1 Hz, 1 H), 4.08 (B of AB, *J* = 8.1 Hz, 1 H), 5.03–5.05 (m, 1 H), 5.09 (s, 1 H), 5.72–5.85 (m, 1 H), 7.03–7.27 (m, 4 H); ^{13}C NMR 27.77 (t), 28.39 (q), 28.46 (q), 38.00 (d), 38.27 (t), 55.97 (q), 67.55 (s), 78.36 (t), 117.01 (t), 123.70 (d), 125.45 (d), 126.71 (d), 126.80 (d), 128.06 (s), 132.62 (s), 134.99 (s), 136.53 (d), 157.74 (s), 159.93 (s).

8b was obtained as a white oily solid (996 mg, 2.69 mmol, 90%): IR (neat) 2956, 1666, 1632, 1247, 1000 cm^{-1}; ^1H NMR 0.021 (s, 9 H), 1.39, 1.40 (two unresolved singlets of equal intensity, 6 H total), 2.34–2.41 (m, 2 H), 2.48–2.65 (m, 2 H), 2.88–2.97 (m, 1 H), 3.71 (s, 3 H), 4.02 (A of AB, *J* = 8.1 Hz, 1 H), 4.06 (B of AB, *J* = 8.1 Hz, 1 H), 5.67 (dt, *J* = 18.5, 1 Hz, 1 H), 5.96 (dt, *J* = 18.5, 6.7 Hz, 1 H), 7.01–7.21 (m, 4 H); ^{13}C NMR −1.22 (q), 27.53 (t), 28.45 (q), 28.54 (q), 37.90 (d), 41.28 (t), 55.85 (q), 67.58 (s), 78.37 (t), 105.32 (s), 123.75 (d), 125.42 (d), 126.82 (d), 126.87 (d), 132.65 (s), 133.32 (d), 135.06 (s), 144.56 (d), 157.75 (s), 159.95 (s). Anal. Calcd for $C_{22}H_{31}NO_2Si$: C, 71.50; H, 8.45; N, 3.79. Found: C, 71.18; H, 8.18; N, 3.45.

4-Substituted Naphthalenes 9a and 9b. General Procedure. A stirred solution of dihydronaphthalene **8** in dry benzene (15 mL/mmol of **8**) was treated with DDQ (1.05 equiv based on **8**) at ambient temperature. Stirring was continued (overnight for **8a**, 20 min for **8b**) followed by rotary evaporation of benzene. Ether was added, followed by successive washes with saturated aqueous $NaHCO_3$, saturated aqueous $NaHSO_4$, and 2 N NaOH. After drying, filtration, and concentration of the organic layer, the resultant oil was chromatographed on silica gel with hexanes/ethyl acetate/triethylamine (7:3:0.5) to yield pure material.

9a was obtained as white crystals (54 mg, 0.183 mmol, 62%): mp 65–66 °C; IR (CCl_4) 2967, 1665, 1596, 1005 cm^{-1}; ^1H NMR 1.49 (s, 6 H), 3.83 (app d, *J* = 6.1 Hz, 2 H), 3.94 (s, 3 H), 4.19 (s, 2 H), 5.04 (ddd, *J* = 1.6, 3.3, 17.1 Hz, 1 H), 5.11 (ddd, *J* = 1.4, 3.0, 11.6 Hz, 1 H), 6.00–6.14 (m, 1 H), 7.13 (s, 1 H), 7.32–7.37 (m, 1 H), 7.43–7.49 (m, 1 H), 7.91 (app t, *J* = 7.7 Hz, 2 H); ^{13}C NMR 28.54 (q), 37.52 (t), 56.85 (q), 68.09 (s), 78.93 (t), 111.42 (s), 113.89 (d), 116.75 (t), 123.79 (d), 124.09 (d), 124.67 (d), 127.05 (d), 127.22 (s), 133.10 (s), 136.16 (d), 140.47 (s), 155.43 (s), 159.99 (s). Anal. Calcd for $C_{19}H_{21}NO_2$: C, 77.26; H, 7.17; N, 4.74. Found: C, 77.31; H, 7.42; N, 4.65.

9b was obtained as a clear colorless oil (526 mg, 1.43 mmol, 94%): IR (neat) 2959, 1664, 1595, 1248 cm^{-1}; ^1H NMR −0.009 (s, 9 H), 1.49 (s, 6 H), 3.88 (dd, *J* = 5.6, 1.3 Hz, 2 H), 3.94 (s, 3 H), 4.20 (s, 2 H), 5.64 (dt, *J* = 18.6, 1.3 Hz, 1 H), 6.22 (dt, *J* = 18.6, 5.6 Hz, 1 H), 7.11 (s, 1 H), 7.31–7.36 (m, 1 H), 7.43–7.48 (m, 1 H), 7.87–7.91 (m, 2 H); ^{13}C NMR −1.30, 28.57, 40.41, 56.76, 68.09, 78.96, 111.19, 114.01, 123.71, 124.34, 124.58, 127.07, 127.32, 132.54, 133.10, 140.62, 143.70, 155.39, 160.05. Anal. Calcd for $C_{22}H_{29}NO_2Si$: C, 71.89; H, 7.95; N, 3.81. Found: C, 71.91; H, 7.97; N, 3.82.

Methoxide Displacement Products 10a and 10b. General Procedure. To a stirred solution of methoxy compound **8b** in THF (10 mL/mmol of **8b**), cooled to 0 °C for MeLi addition and −78 °C for *n*-BuLi addition, was added the nucleophile (1 equiv). After the mixture was stirred (45 min at 0 °C for MeLi addition, overnight for *n*-BuLi addition) and allowed to warm to ambient temperature, saturated aqueous NH_4Cl was added, followed by water and ether. The organic layer was separated, dried, and concentrated. Purification via radial chromatography using hexanes/ethyl acetate (4:1) as the eluent yielded pure material.

10a was obtained as a clear colorless oil (144 mg, 0.41 mmol, 65%): IR (CCl_4) 2960, 1668, 1637, 1615, 1247, 993 cm^{-1}; ^1H NMR 0.02 (s, 9 H), 1.41, 1,43 (2 singlets, 6 H total), 1.99 (s, 3 H), 2.18 (dd, *J* = 3.6, 16.7 Hz, 1 H), 2.23–2.39 (m, 2 H), 2.49 (ddd, *J* = 1.0, 6.7, 16.7 Hz, 1 H), 2.77–2.87 (m, 1 H), 4.04 (A of AB, *J* = 8.2 Hz, 1 H), 4.07 (B of AB, *J* = 8.2 Hz, 1 H), 5.59 (d, *J* = 18.5 Hz, 1 H), 5.94 (ddd, *J* = 6.2, 7.2, 18.5 Hz, 1 H), 7.04–7.15 (m, 4 H); ^{13}C NMR −1.22 (q), 21.67 (q), 28.52 (q), 28.62 (q), 34.37 (t), 37.12 (d), 41.46 (t), 67.71 (s), 78.46 (t), 122.24 (s), 124.24 (d), 126.53 (d), 126.59 (d), 127.22 (d), 132.11 (s), 132.64 (d), 137.66 (s), 139.29 (s), 144.62 (d), 161.32 (s). Anal. Calcd for $C_{22}H_{31}NOSi$: C, 74.73; H, 8.84; N, 3.96. Found: C, 74.61; H, 8.96; N, 3.95.

10b was obtained as a clear colorless oil (181 mg, 0.457 mmol, 81%): IR (neat) 2958, 1667, 1631, 1616, 1247, 995 cm^{-1}; ^1H NMR 0.046 (s, 9 H), 0.92 (t, *J* = 7.2 Hz, 3 H), 1.30–1.55 (m, 4 H), 1.42 (s, 3 H), 1.44 (s, 3 H), 2.17–2.54 (m, 6 H), 2.79–2.89 (m, 1 H), 4.05 (A of AB, *J* = 8.1 Hz, 1 H), 4.08 (B of AB, *J* = 8.1 Hz, 1 H), 5.62 (d, *J* = 18.5 Hz, 1 H), 5.97 (ddd, *J* = 18.5, 7.3, 5.9 Hz, 1 H), 7.05–7.18 (m, 4 H); ^{13}C NMR −1.21, 13.94, 22.83, 28.47, 28.59, 30.10, 32.12, 34.87, 37.28, 41.18, 67.73, 78.50, 122.29, 124.25, 126.56, 126.61, 127.26, 132.13, 132.62, 137.72, 142.96, 144.92, 161.36. Anal. Calcd for $C_{25}H_{37}NOSi$: C, 75.89; H, 9.43; N, 3.54. Found: C, 75.93; H, 9.45; N, 3.53.

Naphthaldehydes 11a–c. General Procedure. A solution of substituted naphthyloxazoline in CH_2Cl_2 (10 mL/mmol of oxazoline) was cooled to 0 °C and treated with methyl triflate (1.1 equiv based on oxazoline). After the mixture was stirred for 7 h, a 0 °C solution of THF/MeOH (4:1) was added, followed immediately by sodium borohydride (2–3 g atom equiv of sodium based on oxazoline, hydrogen gas evolution). After stirring for an additional 20 h at ambient temperature, the reaction was quenched with saturated aqueous NH_4Cl (hydrogen gas evolution). The biphasic mixture was diluted with ether, and the organic layer was removed, dried, and concentrated. The residue was taken up in THF/water (4:1) and treated with oxalic acid (5 equiv). After the solution was stirred for 2 days at ambient temperature (or 2 h at reflux), ether was added and the organic layer washed with saturated aqueous NH_4Cl, saturated aqueous $NaHCO_3$, and water, followed by drying and concentration. Chromatography using hexanes/ethyl acetate (4:1) yielded pure material.

11a was obtained as a clear colorless oil (104 mg, 0.490 mmol, 91%): IR (neat) 2965, 2929, 2872, 2771, 1682, 1062; ^1H NMR 0.85 (t, *J* = 7.4 Hz, 3 H), 1.36 (d, *J* = 6.9 Hz, 3 H), 1.75 (pent, *J* = 7.4 Hz, 2 H), 3.64 (hex, *J* = 7.0 Hz, 1 H), 7.47–7.52 (m, 2 H), 7.56–7.62 (m, 1 H), 7.82 (d, *J* = 8.0 Hz, 1 H), 7.99 (d, *J* = 8.6 Hz, 1 H), 8.80 (d, *J* = 8.6 Hz, 1 H), 10.99 (s, 1 H); ^{13}C NMR 12.21 (q), 21.98 (q), 30.96 (t), 35.23 (d), 123.89 (d), 124.66 (d), 125.97 (d), 128.20 (d), 128.36 (d), 129.33 (s), 130.77 (s), 131.90 (s), 134.02 (d), 150.55 (s), 194.10 (d). Anal. Calcd for $C_{15}H_{16}O$: C, 84.87; H, 7.60. Found: C, 84.86; H, 7.88.

11b was obtained as white crystals (90 mg, 0.387 mmol, 73%): mp 83–86 °C; IR (CCl_4) 3057, 2875, 2788, 1680, 1060 cm^{-1}; ^1H NMR 7.41–7.53 (m, 6 H), 7.55–7.61 (m, 1 H), 7.66–7.72 (m, 1 H), 7.90 (d, *J* = 8.1 Hz, 1 H), 8.06 (d, *J* = 8.4 Hz, 1 H), 9.27 (d, *J* = 8.4 Hz, 1 H), 10.19 (s, 1 H); ^{13}C NMR 125.42 (s), 125.72 (d), 126.72 (d), 128.21 (d), 128.26 (d), 128.28 (d), 128.78 (s), 129.16 (d), 130.27 (d), 130.50 (d), 132.91 (s), 133.84 (d), 138.64 (s), 147.84 (s), 194.57 (d). Anal. Calcd for $C_{17}H_{12}O$: C, 87.91; H, 5.21. Found: C, 87.82; H, 5.44.

11c was obtained as white crystals (223 mg, 0.747 mmol, 82%): mp 89–90 °C; IR (CCl_4) 2956, 2897, 2806, 1672, 1590, 1249 cm^{-1}; ^1H NMR 0.04 (s, 9 H), 3.88 (d, *J* = 5.8 Hz, 2 H), 3.99 (s, 3 H), 5.78 (dt, *J* = 18.6, 1.5 Hz, 1 H), 6.22 (dt, *J* = 18.6, 5.9 Hz, 1 H), 7.10 (s, 1 H), 7.37–7.43 (m, 1 H), 7.56–7.62 (m, 1 H), 7.93 (d, *J* = 8.4 Hz, 1 H), 9.35 (d, *J* =

(21) For ephedrine methyl ether preparation, see: (a) Tameo, K. *Tetrahedron Lett.* **1984**, *25*, 1913–1916. (b) Meyers, A. I.; Poindexter, G. S.; Brich, Z. *J. Org. Chem.* **1978**, *43*, 892–898.

(22) (Lithioallyl)trimethylsilane was prepared according to procedure of Lau, P. W. K.; Chan, T. H. *Tetrahedron Lett.* **1978**, *27*, 2383–2386 and references cited therein.

8.8 Hz, 1 H), 10.84 (s, 1 H); ^{13}C NMR -1.32 (q), 40.97 (t), 56.30 (q), 113.21 (d), 115.49 (s), 124.13 (d), 124.51 (d), 125.50 (d), 127.20 (s), 129.37 (d), 132.10 (s), 133.66 (d), 142.79 (d), 147.17 (s), 163.57 (s), 191.41 (d). Anal. Calcd for $C_{18}H_{22}O_2Si$: C, 72.44; H, 7.43. Found: C, 72.74; H, 7.46.

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Registry No. 1, 93-04-9; **2**, 3401-47-6; **3**, 947-62-6; **4**, 51439-58-8; **5**, 94321-75-2; **6**, 94321-29-6; **7a**, 137869-07-9; **7b**, 137869-12-6; **7c**, 137869-13-7; **7d**, 137869-14-8; **7e**, 137869-15-9; **7g**, 137869-16-0; **7h**, 137869-17-1; **7i**, 137869-18-2; **8a**, 137869-08-0; **8b**, 137869-19-3; **9a**, 137869-09-1; **9b**, 137869-20-6; **10a**, 137869-10-4; **10b**, 137869-21-7; **11a**, 137869-11-5; **11b**, 137869-22-8; **11c**, 137869-23-9; BuLi, 109-72-8; *s*-BuLi, 598-30-1; *t*-BuLi, 594-19-4; (*Z*)-CH_3CH=$CHLi$, 6524-17-0; PhLi, 591-51-5; PhMgBr, 100-58-3; $LiMe_2N$, 3585-33-9; lithium diisopropylamine, 4111-54-0; lithium ephedrine methyl ether, 91525-92-7; allyltributylstannane, 24850-33-7; allyltrimethylsilane, 762-72-1; methyllithium, 917-54-4; 2-amino-2-methyl-1-propanol, 124-68-5.

Aspernomine: A Cytotoxic Antiinsectan Metabolite with a Novel Ring System from the Sclerotia of *Aspergillus Nomius*

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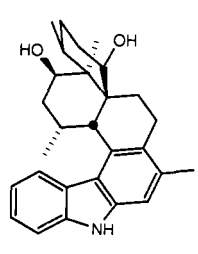
Abstract: Aspernomine (**3**), a new cytotoxic antiinsectan fungal metabolite with a previously undescribed ring system has been isolated from a pentane extract of the sclerotia of *Aspergillus nomius*. The structure of **3** was determined using NMR techniques, including COSY, NOESY, HMBC, and HMQC experiments conducted at 600 MHz.

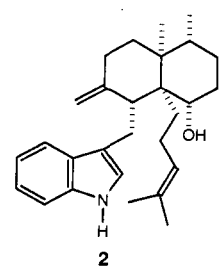
Studies of *Aspergillus* sclerotia as potential sources of new natural products with antiinsectan effects and other bioactivities have afforded a variety of new bioactive metabolites.[2a-f] Most of these compounds are indole diterpenoids (e.g., **1**), and several of them contain previously undescribed or rare ring systems. Our initial studies[2b] of sclerotial metabolites from *A. nomius* Kurtzman, Horn, and Hesseltine[3] led to the isolation of nominine (**2**), a compound exhibiting potent activity against the corn earworm *Helicoverpa zea* (formerly *Heliothis zea*).[4] Further studies of the pentane-soluble metabolites of an isolate of *A. nomius* have now afforded a unique new compound of similar biogenetic origin. This compound, which we have named aspernomine (**3**), possesses a new ring system and exhibits activity against *H. zea*, as well as significant cytotoxicity toward three human solid tumor cell lines. Details of the isolation, structure elucidation, and biological activity of aspernomine are presented here.

Results and Discussion

Pentane extracts were obtained by Soxhlet extraction of the sclerotia of an isolate of *A. nomius* (NRRL 6552)[5] produced by solid substrate fermentation on corn. Silica gel chromatography of the extracts using gradient elution from hexane to ethyl acetate yielded aspernomine, a metabolite with the molecular formula $C_{28}H_{39}NO_2$ as determined by ^{13}C NMR and HREIMS data. This formula differed from that of nominine (**2**) by the addition of one oxygen atom, and NMR data indicated some similarities between the two compounds. However, the appearance of the NH proton chemical shift at 4.35 ppm as compared to 7.88 ppm for nominine, along with other differences in the UV and ^{13}C NMR spectra, indicated the absence of an indole moiety. In addition, IR and ^{13}C NMR data revealed the presence of a ketone functionality (1698 cm^{-1} and 209.2 ppm, respectively). The presence of signals for only eight other sp^2-hybridized carbons indicated that the compound must be pentacyclic. Thus, it is clear that the structure of aspernomine is significantly different from that of **2**. Proton spin systems were determined by analysis of a series of decoupling experiments and a homonuclear proton COSY spectrum recorded at 600 MHz. Shift assignments for carbons bound to hydrogen atoms were established on the basis of HMQC[6] data. The remaining carbon NMR assignments and the connectivity of the spin systems were determined with the aid of long-range C-H correlations obtained through HMBC[7] and selective INEPT[8] experiments. All of these results are summarized in Table I.



1



2

The presence of a 1,2-disubstituted benzene ring and isolated $NHCHCH_2$, $CHCH_2$, and 4-methyl-3-pentenyl units were established from the COSY, decoupling, and HMQC data. Partial structure **a**, a structural subunit found in nominine, was also initially proposed by a comparison of NMR data with those obtained for nominine. HMBC correlation of H_3-28 with C-15, -16, and -17 and correlation of H_3-29 with C-14, -15, -16, and

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(1) Alfred P. Sloan Fellow (1990-1992) and NIH Research Career Development Awardee (1990-1995; K04 CA01571).
(2) (a) Gloer, J. B.; TePaske, M. R.; Sima, J.; Wicklow, D. T.; Dowd, P. F. *J. Org. Chem.* **1988**, *53*, 5457. (b) Gloer, J. B.; Rinderknecht, B. L.; Wicklow, D. T.; Dowd, P. F. *J. Org. Chem.* **1989**, *54*, 2530. (c) TePaske, M. R.; Gloer, J. B.; Wicklow, D. T.; Dowd, P. F. *Tetrahedron* **1989**, *45*, 4961. (d) TePaske, M. R.; Gloer, J. B.; Wicklow, D. T.; Dowd, P. F. *J. Org. Chem.* **1989**, *54*, 4743. (e) TePaske, M. R.; Gloer, J. B.; Wicklow, D. T.; Dowd, P. F. *Tetrahedron Lett.* **1989**, *30*, 5965. (f) TePaske, M. R.; Gloer, J. B.; Wicklow, D. T.; Dowd, P. F. *J. Org. Chem.* **1990**, *55*, 5299.
(3) Kurtzman, C. P.; Horn, B. W.; Hesseltine, C. W. *Antonie van Leeuwenhoek* **1987**, *53*, 147.
(4) Stoetzel, M. B. *Common Names of Insects and Related Organisms*; Entomological Society of America: Lanham, MD, 1989; p 77.
(5) The initial studies of *A. nomius* that led to the isolation of nominine were carried out with NRRL 13137. NRRL 6552 was employed in this study because it afforded a significantly higher yield of **3**.
(6) Bax, A.; Subramanian, S. *J. Magn. Reson.* **1986**, *67*, 565.
(7) Bax, A.; Summers, M. F. *J. Am. Chem. Soc.* **1986**, *108*, 2093.
(8) Bax, A. J. *J. Mag. Reson.* **1984**, *57*, 314.

0002-7863/92/1514-1015$03.00/0