at δ 84.36 (s), 67.8 (d), 31.4 (t), 31.2 (s), 30.8 (t), 25.77 (q), 25.4 (t), 22.45 (t), and 13.9 (q) are assigned to *anti,anti*-**24**, those at δ 84.43 (s), 68.3 (d), 59.9 (d), 31.6 (t), 31.1 (s), 29.7 (t), 25.76 (q), 25.2 (t), 22.43 (t), and 13.9 (q) to *anti,anti*-**24**. This material was not further characterized.

Synthesis of Allenes. Applications of literature methods were used.

4,5-Nonadiene (16a).[24] A solution of *n*-propylmagnesium bromide was prepared from 11 g (89 mmol) of 1-bromopropane and 2.2 g (89 mmol) of Mg turnings in 80 mL of ether. This was added to a stirred mixture of 4.0 g (22 mmol) of the tetrapyranyl ether of 1-hexyn-3-ol (prepared from the commercially available alcohol)[25] and 1.7 g (5.6 mmol) of cuprous bromide in 30 mL of ether at −78 °C. The reaction mixture was allowed to warm to 0 °C over 3 h and hydrolyzed by the addition of NH_4Cl solution. The organic layer was washed with water and brine, dried ($MgSO_4$), concentrated by simple distillation of solvent, and eluted through a column of silica gel with pentane. The allene-containing fractions were concentrated and distilled to give 1.7 g (60%) of **16a** as a clear liquid: bp 52–55 °C (11 Torr); IR 1969, 880 cm^{-1}; ^1H NMR δ 5.09 (m, 2), 1.95 (m, 4), 1.43 (m, 4), 0.95 (t, 3, J = 7 Hz); ^{13}C NMR δ 204.0, 90.6, 31.1, 22.4, 13.6. The following allenes were prepared in a similar manner.

2,6-Dimethyl-3,4-heptadiene (16b):[26] bp 56–59 (38 Torr); IR 1965, 1385, 1368, 878, 740 cm^{-1}; ^1H NMR δ 5.16 (t, 2, J = 5 Hz), 2.34–2.2 (m, 2), 1.0 (d, 6, J = 7 Hz), 0.99 (d, 6, J = 7 Hz); ^{13}C NMR δ 200.8 (s), 99.7 (d, J = 150 Hz), 28.0 (d), 22.6 (q), 22.5 (q).

4,4-Dimethyl-1,2-pentadiene (11a).[27] A sample of **11a** was purified by preparative GC: IR 1965, 1352, 1260, 1198, 870, 840 cm^{-1}; ^1H NMR δ 5.09 (t, 1, J = 7 Hz), 4.06 (d, 2, J = 7 Hz), 1.02 (s, 9); ^{13}C NMR δ 205.9 (s), 102.0 (d), 76.3 (t), 31.2 (s), 30.1 (q).

1,2-Tridecadiene (11b).[28] A sample of **11b** was purified by preparative GC: IR 2940, 2860, 1964, 1460, 840 cm^{-1}; ^1H NMR δ 5.07 (quint, 1, J = 7 Hz), 4.62 (dt, 2, J = 7, 3 Hz), 1.97 (qt, 2, J = 7, 3 Hz), 1.38 (quint, 2, J = 7 Hz), 1.33–1.20 (m, 14), 0.86 (t, 3, J = 7 Hz); ^{13}C NMR δ 208.5 (s), 90.1 (d), 74.4 (t), 31.9 (t), 29.62 (t), 29.61 (t), 29.4 (t), 29.3 (t), 29.14 (t), 29.09 (t), 28.3 (t), 22.7 (t), 14.1 (q).

3-Butyl-1,2-heptadiene (14).[29] A solution of *n*-butylmagnesium bromide prepared from 27.4 g (0.2 mol) of *n*-butyl bromide and 4.8 g (0.2 mol) of magnesium turnings in 150 mL of THF was transferred over 15 min by cannula to a well-stirred slurry of 28 g (0.15 mol) of CuI and 13 g (0.15 mol) of LiBr in 120 mL of THF at −5 °C for 15 min before 10 g (0.07 mol) of 2-heptyn-1-yl acetate[30] in 40 mL of THF was added rapidly. The mixture was stirred at −5 °C for 2 h before hydrolysis by the addition of NH_4Cl solution. The organic layer was diluted with pentane, washed with NH_4Cl solution and brine, dried ($MgSO_4$), and concentrated to give a yellow liquid. Distillation gave a yellow liquid (bp 55–73 °C, 5 Torr). Column chromatography on silica gel using pentane provided 3.5 g (36%) of **14** as a colorless liquid: IR 3046, 2928, 2859, 1960, 1456, 841 cm^{-1}; ^1H NMR δ 4.63 (pentet, 2, J = 3 Hz), 1.94 (m, 4), 1.5–1.2 (m, 8), 0.91 (t, 6, J = 7 Hz).

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Supplementary Material Available: NMR spectra of new compounds (49 pages). Ordering information is given on any current masthead page.

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Synthesis of the Vinblastine-like Antitumor Bis-Indole Alkaloid Navelbine Analogue Desethyldihydronavelbine

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(*R*)-(−)-Ethyl nipecotate **6** was converted into the *N*-allyl bromide **10** whose derived Grignard reagent **11** was added to *N*-(phenylsulfonyl)-2-(methoxyoxalyl)indole **12** to give the diastereomeric alcohols **13**. Removal of the indole protecting group from **13** and coupling with vindoline gave the separable diastereomers **15**(*S*) and **17**(*R*). Deprotection of **15**/**17** and treatment with formaldehyde/acetic acid gave desethyldihydronavelbine **5**, and its 18′-epimer **19**. Only the natural 18′-epimer exhibited any antitumor activity.

The ring-contracted bis-indole alkaloid navelbine **4** (or 7′-noranhydrovinblastine) inhibits the in vitro assembly of the microtubule system and is currently in phase II clinical trials.[1] Navelbine is synthesized from anhydrovinblastine **1** by oxidation to the *N*-oxide **2** and Polonovski rearrangement, induced by trifluoroacetic anhydride to the putative bisiminium ion **3**, which upon hydration, loss of formaldehyde, and addition of the piperidine nitrogen to the gramine-type iminium ion results in **4** (27%)[2] (Scheme I). The excision of one carbon from the tryptamine bridge has precedent in the chemistry of vallesamine and apparicine.[3]

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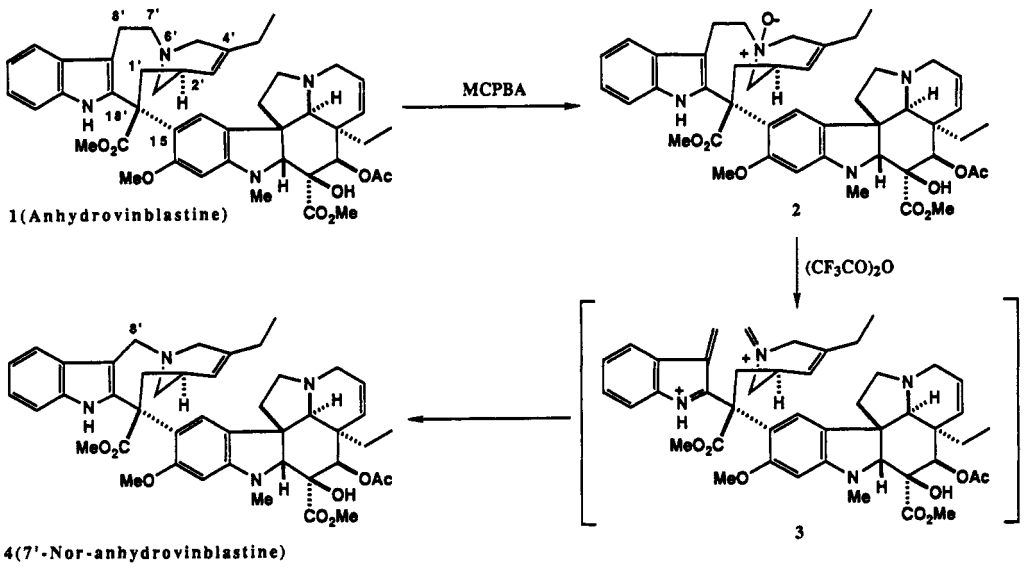
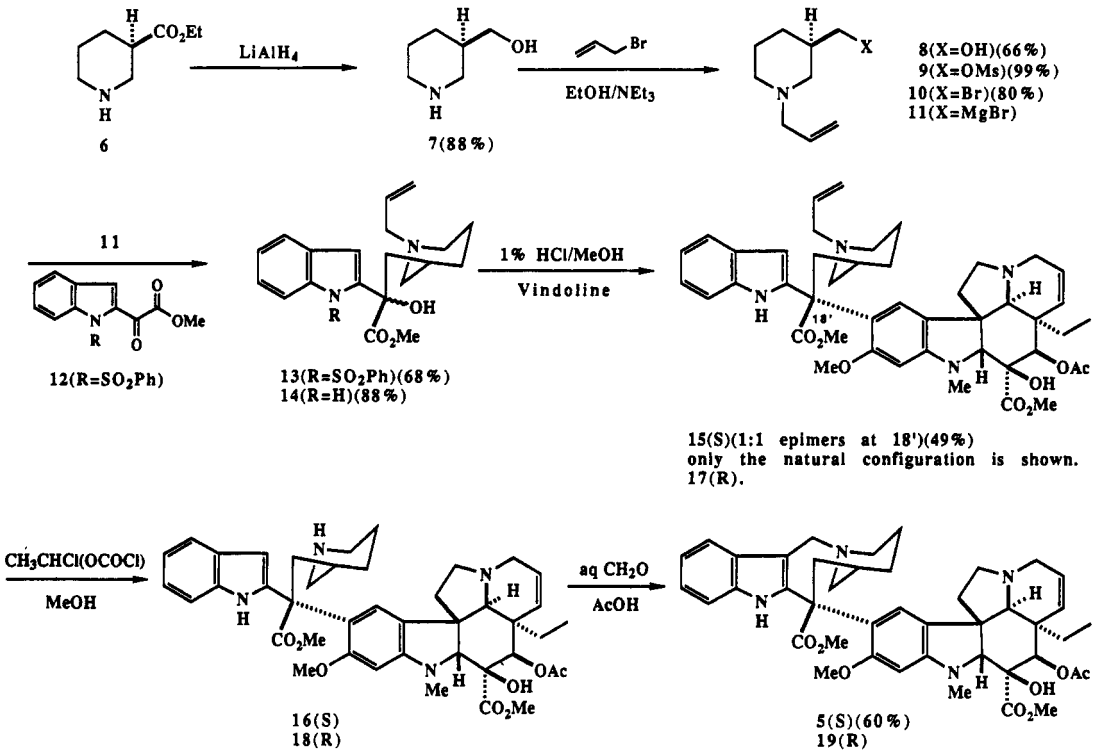
Scheme I



Scheme II



It is somewhat surprising that there have been no reports of the total synthesis of any navelbine-like analogues in view of the promising antitumor activity of **4**. As a further continuation of our studies on the construction of bisindole alkaloids of the vinblastine-type we report the synthesis of desethyldihydronavelbine **5**.[4]

(±)-Ethyl nipecotate was resolved using L-(+)-tartaric acid, and the (+)-tartrate salt was recrystallized from 95% ethanol to give (*R*)-(−)-ethyl nipecotate **6** (after liberation of the free base with aqueous sodium hydroxide).[5] Treatment of **6** with (+)-α-1-naphthyl ethyl isocyanate gave the desired urea, whose diastereomeric purity (^{1}H NMR) indicated that **6** is at least 90% enantiomerically pure. Reduction of **6** by treatment with $LiAlH_4$/THF at reflux for 1 h gave (*R*)-(+)-3-piperidine methanol **7** (89%).[6] After examining the *N*-carbobenzyloxy and *N*-benzyl groups for amine protection, the *N*-allyl group was found to be most compatible with subsequent transformations and readily removed under mild conditions. Treatment of **7** with allyl bromide in ethanol containing triethylamine, heated at reflux, gave **8** (66%). Mesylation of **8** (MsCl/Et_3N/CH_2Cl_2) gave **9** (99%), which was directly converted into the bromide **10** (80%) by treatment with lithium bromide in acetone at reflux.

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N-(Phenylsulfonyl)-2-(methoxyoxalyl)indole (**12**)[7] was treated with the Grignard reagent **11** at 0 °C to give **13** (68%) as a mixture of diastereomers (1:1). While these diastereomers could be separated it was not necessary since the coupling reaction with vindoline gives a 1:1 mixture at the stereogenic center. Reductive cleavage of the phenylsulfonyl group from the indole nitrogen atom to give **14** was accomplished in 88% yield by treatment of **13** with sodium naphthalenide in dimethoxyethane at −50 °C, followed by quenching with trifluoroacetic acid. Coupling of **14** with vindoline was achieved using conditions analogous to those used by Buchi in the synthesis of the bisindole alkaloid dihydrovoacamine.[8] The *N*-allyl-α-hydroxy ester **14** in 1% HCl/MeOH containing 1.1 equiv of vindoline was heated at reflux for 2 h to give **15** (49%) as a 1:1 diastereomeric mixture at 18′. The diastereomers were separated by preparative HPLC, and the assignment of absolute configuration at 18′ could be made from the comparison of the CD spectra with vinblastine and navelbine (see the Experimental Section).[9] The allyl protecting group was removed by treatment of **15** with 1-chloroethyl chloroformate followed by heating the intermediate carbamate in methanol at reflux to give the secondary amine **16** (74%).[10] An intramolecular Mannich reaction served to form the eight-membered ring of navelbine. A solution of the secondary amine **16** in aqueous formaldehyde and glacial acetic acid was heated at 40 °C for 24 h to provide desethyldihydronavelbine **5** (81%). The CD spectrum of **5** was very similar to navelbine, and the ^{1}H NMR spectrum exhibited an AB quartet for the newly introduced methylene hydrogens at δ 4.70 (J = 13 Hz) and 4.47 (partly resolved) very similar to navelbine itself. Carrying out the same series of transformations with the 18′-epimer, namely **17**, gave, via **18**, the 18′*R* epimer **19**.

The natural 18′S epimer **5** exhibited in vitro antitumor activity comparable to vinblastine, whereas the 18′R epimer **19** was inactive.[11]

Experimental Section

Melting points were obtained on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Optical rotations were recorded using a 10 cm, 1-mL cell on a Perkin-Elmer 241 MC polarimeter. Thin-layer chromatography was performed on Merck silica gel 60 F-254 analytical plates. Flash chromatography was conducted using Merck silica gel 60 (230–400 mesh). Tetrahydrofuran was freshly distilled from sodium benzophenone ketyl under argon. Preparative HPLC was performed on a Rainin Dynamax SiO_2 column (41.4 × 250mm) with a 11-cm guard column, eluting with 81:15:4 ethyl acetate/dichloromethane/methanol (containing 10% NH_4OH) at 40 mL/min, 300 psi. Circular dichroism spectra were recorded on a JASCO J-20A automatic recording spectropolarimeter for solutions in MeOH and reported as λ_{max} and ϵ (differential absorptivity). $[\theta] = [\psi]M/100 = 3300\Delta\epsilon$, where $[\theta]$ = molecular ellipticity, $[\psi]$ = specific ellipticity, and M = molecular weight. Infrared spectra were obtained for solutions in chloroform, or neat, using a Perkin-Elmer 1600 FTIR instrument. Ultraviolet spectra were obtained for solutions in methanol using a Lambda 3B UV/vis spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded using a GE 300 instrument at 300 and 75 MHz, respectively.

(*R*)-(−)-Ethyl Nipecotate (6). (±)-Ethyl nipecotate (70.16 g, 71 mL) and (+)-tartaric acid (67 g) were dissolved in hot 95% ethanol (350 mL). The resulting solution was allowed to slowly cool to room temperature and refrigerated overnight. The crystals were filtered, washed with cold ethanol, and recrystallized from 95% ethanol (550 mL), cooling as before to give the (+)-tartrate salt of (+)-ethyl nipecotate (42.9 g): mp 155–156 °C; $[\alpha]^{21}_D$ = +52.4° (c = 2.0 in 0.2% aqueous ammonium molybdate) (lit.[5] $[\alpha]_D$ +51.0°). The salt (25 g) was dissolved in water (400 mL) and cooled on ice, and 3 N sodium hydroxide was slowly added until the pH reached 11–12. The solution was extracted with chloroform (3 × 100 mL), dried (Na_2SO_4), and evaporated in vacuo to give **6** (9.48 g) as a mobile oil: $[\alpha]^{21}_D$ = −1.4° (c = 5.0 in water) (lit.[5] $[\alpha]_D$ = −1.8°). The enantiomeric purity of **6** was determined to be at least 90% by treatment of **6** with (*S*)-(+)-ethyl naphthylisocyanate to give the urea derivative **6a**: mp 242.5–243.5 °C (MeOH/Et_2O); ^{1}H NMR δ 8.15 (1 H, d, J = 8.3 Hz), 7.81 (2 H, m), 7.50 (4 H, m), 5.8 (1 H, br s), 5.6 (1 H, br), 4.04 (2 H, m), 3.87 (1 H, dd, J = 12 and 2 Hz), 3.51 (1 H, dt, J = 14 Hz), 3.13 (2 H, m), 2.50 (1 H, m), 1.97 (1 H, m), 1.65 (3 H, d, J = 4 Hz), 1.16 (3 H, t, J = 4 Hz), the other diastereomer gives 1.28 (3 H, t, J = 4 Hz); HRMS calcd for $C_{21}H_{26}N_2O_3$ 354.1943, found 354.1948.

(*R*)-(+)-3-Piperidinylmethanol (7). Reduction of (−)-ethyl nipecotate (14.1 g, 0.089 mol) with $LiAlH_4$ (3.54 g, 0.093 mol) in THF (200 mL), using the usual protocols associated with this reagent, gave **7** (9.1 g, 0.079 mol, 89%), as a pale yellow oil: $[\alpha]^{21}_D$ = +3.8° (c = 18 in pyridine) (lit.[6] $[\alpha]_D$ +5.8°); ^{1}H NMR ($CDCl_3$) δ 3.50–3.31 (4 H, m), 3.15 (1 H, d, J = 12.0 Hz), 2.98 (1 H, d, J = 12 Hz), 2.53 (1 H, dt, J's = 11.74 and 2.82 Hz), 2.32 (1 H, m), 1.81–1.60 (3 H, m), 1.47 (1 H, m), 1.11 (1 H, m). This material was used directly in the next step.

(*R*)-(+)-*N*-Allyl-3-piperidinomethanol (8). To a solution of **7** (0.23 g, 2 mmol) in ethanol (5 mL) and triethylamine (2.8 mL, 10 equiv) was added allyl bromide (0.35 mL, 2.0 equiv), and the mixture was heated at reflux for 12 h. The mixture was evaporated in vacuo, and the residue was dissolved in chloroform and washed with 5% aqueous K_2CO_3 (5 × 10 mL). The chloroform layer was dried ($MgSO_4$) and evaporated in vacuo to give **8** (0.20 g, 66%): $[\alpha]^{23}_D$ = +19.0° (c = 5 in absolute ethanol); ^{1}H NMR ($CDCl_3$) δ 5.89 (1 H, m), 5.15 (2 H, m), 3.57 (1 H, dd, J's = 10.64 and 4.77 Hz), 3.44 (1 H, dd, J's = 10.71 and 6.21 Hz), 3.38 (1 H, br s), 2.98 (2 H, d, J = 6.55 Hz), 2.93 (1 H, d, J = 8.68 Hz), 2.75 (1 H, m), 2.02 (1 H, m), 1.85–1.57 (5 H, m), 1.04 (1 H, m); ^{13}C NMR ($CDCl_3$) δ 134.5, 117.8, 65.5, 62.0, 57.0, 53.9, 38.4, 27.1, 24.5; HRMS calcd for $C_9H_{17}NO$ 155.1310, found m/e 155.1295.

(*R*)-(+)-*N*-Allyl-3-piperidinylmethanol Methanesulfonate (9). The alcohol **8** (1.3g, 8.38 mmol) was converted into its methanesulfonate ester **9** (1.96 g, 99%), in the standard manner: $[\alpha]^{23}_D$ = +10.02° (c = 5 in absolute ethanol); IR ($CHCl_3$) 2931, 1466, 1334, 1172, 1043, 955, and 820 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.84 (1 H, m), 5.16 (2 H, m), 4.11 (2 H, m), 3.01 (3 H, s), 2.98 (2 H, d, J = 8.1 Hz), 2.87 (1 H, m), 2.77 (1 H, m), 2.09–1.97 (2 H, m), 1.86 (1 H, t, J = 10.3 Hz), 1.77–1.58 (3 H, m), 1.10 (1 H, m); ^{13}C NMR ($CDCl_3$) δ 134.77, 118.03, 72.27, 62.00, 55.91, 53.75, 37.79, 26.49, 24.17; HRMS calcd for $C_{10}H_{19}NO_3S$ 233.1086, found m/e 233.1075.

(*R*)-(+)-*N*-Allyl-3-piperidinylmethyl Bromide (10). To a solution of **9** (9.6 g, 0.04 mol) in acetone (100 mL) was added lithium bromide (6.9 g, 0.08 mol), and the suspension was heated at reflux for 18 h. The acetone was evaporated in vacuo, and the residue was partitioned between chloroform and cold aqueous 5% K_2CO_3 solution. The chloroform layer was dried ($MgSO_4$), filtered, and evaporated in vacuo to give a brown oil. Fractional distillation gave **10** (6.97g, 80%): bp 110 °C (0.1 mm); $[\alpha]^{23}_D$ = +22.3° (c = 10 in chloroform); IR (thin film) 2932, 2789, 1640, 1465, 1451, 1437, 1340, 1295, 1137, 1084, 995, and 918 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.86 (1 H, m), 5.17 (2 H, m), 3.30 (2 H, m), 3.02 (2 H, d, J = 6.5 Hz), 2.98 (1 H, m), 2.80 (1 H, dd, J's = 7.6 and 3.4 Hz), 1.97 (2 H, m), 1.82 (2 H, d, J = 10.8 Hz), 1.65 (2 H, m), 1.08 (1 H, dt, J's = 12.5 and 4.5 Hz); ^{13}C NMR ($CDCl_3$) δ 135.0, 117.4, 61.8, 58.0, 53.6, 38.2, 36.9, 29.3, 24.4. Anal. Calcd for $C_9H_{16}NBr$: C, 49.56; H, 7.39; N, 6.42. Found: C, 49.32; H, 7.43; N, 6.35.

***N*-(Phenylsulfonyl)-2-methoxalylindole (12).** To a solution of *N*-(phenylsulfonyl)indole (5.14g, 20 mmol) in dry THF (100 mL) under argon, and cooled to −65 °C, was added *tert*-butyl-

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lithium (13 mL, 22 mmol, 1.7 M in pentane). The solution was allowed to warm to 0 °C and stirred for 1 h. The above solution was added via canula to a stirred solution of dimethyl oxalate (9.5 g, 80 mmol) in THF (250 mL) at 0 °C. After 4 h at 0 °C the mixture was quenched with saturated aqueous NH_4Cl and extracted with ethyl acetate (3 × 100 mL). The dried ($MgSO_4$) extract was evaporated in vacuo, and the residue was purified by chromatography over silica gel, eluting with hexane/ethyl acetate (10:1) to give **12** (2.3 g, 34%): mp 111–112 °C (from ethyl acetate); IR ($CHCl_3$) 3680, 3619, 3415, 3019, 1743, 1692, 1600, 1537, and 1372 cm^{-1}; λ_{max} (ϵ) (MeOH) 208 (23930), 265 (4460), 275 (4170), 312 (10040) nm; ^1H NMR ($CDCl_3$) δ 8.06 (1 H, d, J = 8.5 Hz), 7.78 (2 H, d, J = 7.5 Hz), 7.58 (1 H, d, J = 8 Hz), 7.51–7.37 (5 H, m), 7.29 (1 H, t, J = 7.6 Hz), 3.99 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 177.2, 161.3, 138.5, 136.7, 135.8, 134.1, 129.0, 128.7, 128.5, 127.0, 124.8, 123.4, 122.2, 115.3, 53.3. Anal. Calcd for $C_{17}H_{13}NO_5S$: C, 59.47; H, 3.82; N, 4.08. Found: C, 59.42; H, 3.84; N, 3.99.

Methyl 2-[2-[*N*-(Phenylsulfonyl)indolyl]]-2-hydroxy-3-[3-(*N*-allylpiperidinyl)]propionate (13). To the piperidinomethyl bromide **10** (0.82 g, 3.75 mmol) in a flame-dried flask under argon was added Mg powder (0.10 g, 4.125 mmol, 50 mesh) and dry THF (10 mL). The mixture was heated at reflux, and two drops of 1,2-dibromoethane was added to initiate Grignard reagent formation. After 3 h the turbid suspension was cooled to room temperature and added to a solution of **12** (1.03 g, 3 mmol) in THF (30 mL), at 0 °C under argon. After 30 min the orange solution was quenched with saturated aqueous NH_4Cl solution and diluted with ethyl acetate (50 mL). The dried ($MgSO_4$) extract was evaporated in vacuo to give **13** as an orange oil (1.28 g, 68%) consisting of a mixture of diastereomers at C2 (1:1). For the purpose of characterization, one of the diastereomers was purified by chromatography over silica gel, eluting with hexane/ethyl acetate/10% aqueous NH_4OH/MeOH (15:3:1) to give **13** (unknown C2 configuration): mp 186–187.5 °C (from diethyl ether); $[\alpha]^{23}_D$ = −12.5° (c = 4.4 in $CHCl_3$); IR ($CHCl_3$) 3413, 3013, 2943, 1741, 1653, 1447, 1371, 1202, and 1072 cm^{-1}; λ_{max} (ϵ) (MeOH) 213 (28370), 251 (14700), 339 (1520) nm; ^1H NMR ($CDCl_3$) δ 7.84 (2 H, d, J = 7.4 Hz), 7.48 (2 H, m), 7.40 (2 H, m), 7.22 (2 H, m), 6.90 (1 H, d, J = 5 Hz), 5.88 (1 H, m), 5.14 (2 H, m), 3.78 (3 H, s), 3.02–2.78 (4 H, m), 2.23 (2 H, m), 2.02–1.61 (6 H, m), 1.15 (1 H, m); HRMS calcd for $C_{26}H_{30}N_2O_5S$ 482.1875, found m/e 482.1863.

Methyl 2-(2-Indolyl)-2-hydroxy-3-[3-(*N*-allylpiperidinyl)]propionate (14). To a solution of **13** (a mixture of diastereomers at C-2) (0.265 g, 0.55 mmol) in dry dimethoxyethane (5 mL) at −50 °C under argon was added sodium naphthalenide (1 M solution in THF) until the solution remained pale green. The mixture was quenched with trifluoroacetic acid (0.1 mL), and extracted with ethyl acetate (3 × 10 mL). The extract was washed with saturated aqueous $NaHCO_3$ solution, dried ($MgSO_4$), and evaporated in vacuo to give **14** (0.165 g, 88%). The mixture of diastereomers was not separated but chromatographed over silica gel, eluting with hexane/ethyl acetate/10% aqueous NH_4OH/MeOH (5:1:1) to remove more polar impurities. The purified mixture has $[\alpha]^{23}_D$ = +7.6° (c = 9 in $CHCl_3$); HRMS calcd for $C_{20}H_{26}N_2O_3$ 342.1943, found m/e 342.1942. This material was used directly in the next stage.

(+)-(18′*S*)-4′-Desethyl-4′-deshydroxy-6′-allyl-7′,8′-bisnorvinblastine (15). A solution of **14** (0.468 g, 1.368 mmol, mixture of diastereomers) and vindoline (0.686 g, 1.50 mmol, 1.1 equiv) in 1% HCl/MeOH (50 mL) was heated at reflux for 2 h. The solution was evaporated in vacuo, and the residue was dissolved in chloroform and washed with saturated aqueous $NaHCO_3$ solution. The chloroform layer was dried ($MgSO_4$), filtered, and evaporated to give a foam consisting of a mixture of (18′*S*)-**15** and (18′*R*)-**17** (ca. 1:1, 0.524 g, 49%). The diastereomeric mixture was separated by preparative HPLC, eluting with hexane/CH_2Cl_2/MeOH (10% aqueous NH_4OH) to give (18′*S*)-**15**, R_f (TLC, silica gel) 0.38 (5:5:1 hexane/EtOAc/MeOH, 10% NH_4OH): t_R (HPLC) 43 min (81:15:4, the above solvent system); mp 155–157 °C; $[\alpha]^{23}_D$ = 24.8° (c = 1.65 in $CHCl_3$); CD (MeOH) λ_{max} ($\Delta\epsilon$) 210 (−66.3), 222 (+43.2), 256 (+19.5), 305 (+3.1), 312 (+2.8); IR ($CHCl_3$) 3452, 2936, 1740, 1611, 1502, 1456, 1435, 1373, 1235, and 1041 cm^{-1}; UV (MeOH) λ_{max} (ϵ) 213 (48300), 264 (16800), 308 (5940) nm; ^1H NMR ($CDCl_3$) δ 9.65 (1 H, br s, NH), 8.90 (1 H, br s, OH), 7.49 (1 H, d, J = 7.6 Hz), 7.20 (1 H, d, J = 7.8 Hz), 7.06 (2 H, m), 6.51 (1 H, s), 6.29 (1 H, s), 6.03 (1 H, s), 5.84 (2 H, m), 5.40 (1 H, s), 5.27 (1 H, d, J = 10.3 Hz), 5.13 (2 H, m), 3.77 (3 H, s), 3.71 (3 H, s), 3.67 (3 H, s), 3.34 (2 H, m), 2.95 (2 H, d, J = 6.3 Hz), 2.69 (3 H, s), 2.56 (1 H, s), 2.41 (1 H, m), 2.26 (2 H, m), 2.08 (3 H, s), 2.05–1.63 (5 H, m), 1.41 (1 H, m), 1.24 (4 H, m), 0.86–0.72 (2 H, m), 0.56 (3 H, t, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 175.16, 171.54, 170.73, 158.33, 152.57, 138.89. 135.72, 130.11, 127.73, 124.29, 123.12, 122.14, 121.84, 121.45, 120.17, 119.27, 110.81, 102.44, 93.63, 83.08, 79.73, 76.37, 65.46, 62.14, 55.71, 53.80, 53.15, 52.83, 52.24, 52.12, 50.56, 50.44, 44.42, 42.60, 38.25, 32.49, 31.97, 30.59, 21.06, 7.90, and four tertiary carbons too weak; HRMS (FAB) calcd for $C_{45}H_{57}N_4O_8$ (M^+ + 1) 781.4176, found m/e 781.4235.

(18′*R*)-**17**: R_f (TLC, silica gel) 0.5; t_R (HPLC) 49 min; mp 173–174 °C; $[\alpha]^{23}_D$ = −8.56° (c = 1.8 in $CHCl_3$); CD (MeOH) λ_{max} ($\Delta\epsilon$) 210 (+61.7), 222 (−69.9), 269 (+11.3), 305 (−2.6), 312 (−2.6); IR ($CHCl_3$) 3436, 3001, 2931, 1739, 1616, 1502, 1454, 1434, 1372, 1243, and 1041 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.71 (1 H, s), 9.44 (1 H, s), 7.47 (1 H, d, J = 7.66 Hz), 7.31 (1 H, d, J = 8.0 Hz), 7.13–7.00 (2 H, m), 6.70 (1 H, s), 6.16 (1 H, s), 6.01 (1 H, s), 5.85 (1 H, dd, J's = 10.0 and 3.77 Hz), 5.63 (1 H, m), 5.40 (1 H, s), 5.24 (1 H, d, J = 10.1 Hz), 4.99–4.88 (2 H, m), 3.77 (3 H, s), 3.75 (1 H, s), 3.64 (3 H, s), 3.62 (3 H, s), 3.48–3.36 (2 H, M0, 2.87–2.65 (5 H, m), 2.68 (3 H, s), 2.61–2.46 (2 H, m), 2.34–2.00 (5 H, m), 2.06 (3 H, s), 1.83 (1 H, m), 1.65–1.40 (5 H, m), 1.12–1.09 (2 H, m), 0.50 (3 H, t, J = 7.25 Hz); ^{13}C NMR ($CDCl_3$) δ 175.45, 171.68, 170.63, 158.25, 152.52, 140.79, 135.44, 130.32, 127.67, 124.18, 123.34, 123.10, 121.10, 120.70, 119.88, 119.12, 110.87, 100.75, 93.96, 83.24, 79.60, 76.30, 62.05, 60.26, 55.65, 53.99, 53.16, 52.14, 52.09, 51.91, 50.66, 44.08, 42.73, 38.31, 32.71, 31.83, 30.66, 21.00, 16.35, 7.62, and four tertiary carbons too weak; HRMS (FAB) calcd for $C_{45}H_{57}N_4O_8$ (M^+ + 1) 781.4176, found m/e 781.4199.

(+)-(18′*S*)-4′-Desethyl-4′-deshydroxy-7′,8′-bisnorvinblastine (16). The *N*-allyl adduct **15** (0.20 g, 0.256 mmol) in 1,2-dichloroethane (15 mL) containing proton sponge (0.060 g, 0.282 mmol) at 25 °C was treated with 1-chloroethyl chloroformate (0.056 mL, 0.512 mmol, 2.0 equiv), and the resulting solution was stirred for 3 h. The mixture was evaporated in vacuo, and the residue was dissolved in methanol and heated at reflux for 3 h. The methanol was evaporated, and the residue was dissolved in chloroform and purified by chromatography over silica gel, eluting with $CHCl_3$/MeOH, 10% aqueous NH_4OH (20:1), to give **16** (0.155 g, 82%): mp 175–177 °C; $[\alpha]^{23}_D$ = +16.25° (c = 0.4 in $CHCl_3$); CD (MeOH) λ_{max} ($\Delta\epsilon$) 211 (−53.3), 222 (+35.9), 256 (+17.4), 305 (+2.8), 312 (+2.8); IR ($CHCl_3$) 3448, 2932, 1740, 1616, 1502, 1457, 1434, 1373, 1235, and 1041 cm^{-1}; UV (MeOH) λ_{max} (ϵ) 215 (51700), 265 (15700), 310 (5480) nm; ^1H NMR ($CDCl_3$) δ 9.70 (1 H, s), 8.97 (1 H, br s), 7.52 (1 H, d, J = 7.60 Hz), 7.23 (1 H, d, J = 7.86 Hz), 7.09 (2 H, m), 6.55 (1 H, s), 6.31 (1 H, s), 6.05 (1 H, s), 5.84 (1 H, dd, J's = 10.1 and 3.8 Hz), 5.41 (1 H, s), 5.28 (1 H, d, J = 10.1 Hz), 3.78 (3 H, s), 3.73 (3 H, s), 3.72 (1 H, s), 3.69 (3 H, s), 3.35 (2 H, m), 2.98 (1 H, dd, J's = 12.1 and 2.7 Hz), 2.88–2.75 (2 H, m), 2.70 (3 H, s), 2.61 (1 H, s), 2.55–2.36 (3 H, m), 2.24 (2 H, m), 2.09 (3 H, s), 2.05 (1 H, d, J = 4.3 Hz), 1.73 (5 H, m), 1.51–1.39 (2 H, m), 1.27 (1 H, m), 0.83 (1 H, m), 0.57 (3 H, t, J = 7.4 Hz); ^{13}C NMR ($CDCl_3$) δ 175.16, 171.54, 170.72, 158.33, 152.59, 138.89, 135.73, 130.09, 127.70, 124.29, 123.09, 122.00, 121.78, 121.52, 120.13, 119.31, 110.82, 102.29, 93.63, 83.07, 79.72, 76.35, 65.45, 53.36, 52.81, 52.24, 50.51, 50.40, 46.60, 44.42, 42.59, 39.17, 38.27, 33.43, 32.51, 30.59, 26.14, 21.04, 7.91; HRMS (FAB) calcd for $C_{42}H_{53}N_4O_8$ (M^+ + 1) 741.3863, found m/e 741.3863.

(−)-(18′*R*)-4′-Desethyl-4′-deshydroxy-7′,8-bisnorvinblastine (18). The 18′-epimer was made as above in 75% yield: mp 203–204 °C; $[\alpha]^{23}_D$ = −93.3° (c = 1.55 in $CHCl_3$); CD (MeOH) λ_{max} ($\Delta\epsilon$) 208 (−23.6), 220 (−26.3), 268 (+3.5), 305 (−1.55), 312 (−1.16); IR ($CHCl_3$) 3436, 3000, 2942, 1737, 1614, 1501, 1454, 1434, 1372, 1240, 1040 cm^{-1}; λ_{max} (ϵ) 212.4 (21700), 265 (6890), 304 (2670) nm; ^1H NMR ($CDCl_3$) δ 9.71 (1 H, br s), 9.29 (1 H, s), 7.51 (1 H, d, J = 7.68 Hz), 7.32 (1 H, d, J = 7.97 Hz), 7.08 (2 H, m), 6.65 (1 H, s), 6.27 (1 H, s), 6.04 (1 H, s), 5.86 (1 H, dd, J's = 10.0 and 3.9 Hz), 5.37 (1 H, s), 5.25 (1 H, d, J = 10.1 Hz), 3.78 (3 H, s), 3.77 (1 H, s), 3.70 (3 H, s), 3.67 (3 H, s), 3.65–3.34 (3 H, m), 2.86 (2 H, d, J = 15.5 Hz), 2.70 (3 H, s), 2.67 (1 H, s), 2.65–2.51 (3 H, m), 2.31–2.02 (5 H, m), 2.07 (3 H, s), 1.91–1.09 (5 H, m), 0.52 (3 H, t, J = 7.18 Hz); ^{13}C NMR ($CDCl_3$) δ 175.17, 171.63, 170.72, 158.18, 152.61, 140.23, 135.53, 130.19, 127.63, 124.35, 123.41, 122.62, 121.31, 121.13, 120.05, 119.24, 110.90, 101.06, 93.71, 83.09, 79.67,

76.29, 65.67, 55.69, 53.18, 52.16, 52.06, 50.80, 50.53, 45.68, 44.00, 42.70, 42.04, 38.23, 32.68, 31.00, 30.65, 25.05, 21.01, 7.61; HRMS (FAB) calcd for $C_{42}H_{53}N_4O_8$ (M^+ + 1) 741.3863, found m/e 741.3863.

(+)-(18'*S*)-4'-Desethyl-4'-deshydroxy-7'-norvinblastine (5). To a solution of (+)-**16** (43 mg, 0.058 mmol) in dioxane (4 mL) and glacial acetic acid (1 mL) was added 37% aqueous formaldehyde (2 mL), and the mixture was stirred at 35 °C for 24 h. The solution was evaporated in vacuo, and the residue was suspended in chloroform and washed with cold aqueous 5% K_2CO_3 solution. The chloroform layer was dried ($MgSO_4$), filtered, and evaporated. The residue was chromatographed, eluting with EtOAc/MeOH, 10% NH_4OH, to give **5** (35 mg, 81%): mp 195-197 °C (MeOH/Et_2O); $[\alpha]^{28}_D$ = +56.7° (c = 1.5 in $CHCl_3$); CD (MeOH) λ_{max} ($\Delta\epsilon$) (MeOH) 209 (-118.9), 221 (+72.3), 255 (+27.7), 298 (+7.9), 309 (+7.8); IR ($CHCl_3$) 3456, 2995, 2940, 1740, 1616, 1505, 1460, 1434, 1373, and 1236 cm^{-1}. λ_{max} (ϵ) 213 (67100), 265 (20920), 310 (6870) nm; ^1H NMR ($CDCl_3$) δ 9.86 (1 H, s), 8.42 (1 H, s), 7.75 (1 H, br d, J = 2.1 Hz), 7.14 (3 H, m), 6.34 (1 H, s), 6.08 (1 H, s), 5.84 (1 H, dd, J's = 4.0 and 10.2 Hz), 5.40 (1 H, s), 5.27 (1 H, d, J = 10.1 Hz), 4.66 (1 H, d, J = 13.0 Hz), 4.42 (1 H, br s), 3.81 (3 H, s), 3.78 (3 H, s), 3.71 (3 H, s), 2.70 (3 H, s), 2.55 (1 H, s), 2.10 (3 H, s), 0,70 (3 H, t, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$) δ 174.9 171.6, 170.9, 157.9, 152.5, 134.6, 129.9, 128.9, 124.6, 123.0, 122.5, 122.4, 121.0, 119.5, 118.4, 111.5, 110.4, 93.8, 83.2, 79.7, 75.1, 65.2, 55.7, 55.5, 53.2, 52.5, 52.1, 51.0, 50.4, 50.2, 48.5, 45.9, 44.4, 42.6, 38.8, 30.9, 30.6, 29.6, 21.1, 14.1, 8.1; HRMS (FAB) calcd for $C_{43}H_{53}N_4O_8$ (M^+ + 1) 753.3863, found m/e 753.3878.

(+)-(18'*R*)-4'-Desethyl-4'-deshydroxy-7'-norvinblastine (19): mp 237 °C dec; $[\alpha]^{23}_D$ = -86.7° (c = 1.5 in $CHCl_3$); CD (MeOH) λ_{max} ($\Delta\epsilon$) 208 (+54.7), 221.5 (-59.2), 271 (+12.9), 294 (-3.0); IR ($CHCl_3$) 3423, 3003, 2931, 1742, 1615, 1498, 1459, 1432, 1372, 1231, and 1039 cm^{-1}; λ_{max} (ϵ) (MeOH) 214 (47600), 267 (14030) nm; ^1H NMR ($CDCl_3$) δ 9.72 (1 H, s), 9.12 (1 H, s), 7.70 (1 H, d, J = 7.15 Hz), 7.22 (1 H, d, J = 7.04 Hz), 7.11 (2 H, m), 6.3 (1 H, s), 6.11 (1 H, s), 5.86 (1 H, dd, J's = 10.17 and 3.67 Hz), 5.34 (1 H, s), 5.25 (1 H, d, J = 10.18 Hz), 4.48 (1 H, d, J = 12.57 Hz), 4.27 (1 H, d, J = 12.57 Hz), 3.91 (3 H, s), 3.77 (6 H, br s), 3.70 (1 H, s), 3.44-3.18 (3 H, m), 2.88-2.53 (5 H, m), 2.70 (3 H, s), 2.45-2.03 (5 H, m), 2.07 (3 H, s), 1.89 (2 H, m), 1.63 (2 H, m), 1.09 (1 H, m), 0.56 (3 H, t, J = 7.28 Hz); ^{13}C NMR ($CDCl_3$) δ 174.77, 171.53, 170.78, 156.51, 152.30, 134.77, 130.16, 128.33, 125.75, 124.51, 123.97, 122.01, 120.76, 119.31, 118.39, 110.43, 94.21, 82.95, 79.68, 76.30, 65.45, 56.02, 54.16, 53.11, 52.18, 52.15, 51.52, 50.55, 50.43, 48.18, 45.35, 43.58, 42.62, 39.40, 38.30, 30.55, 21.04, 13.60, 7.58; HRMS (FAB) calcd for $C_{43}H_{53}N_4O_8$ (M^+ + 1), 753.3863, found m/e 753.3878.

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Supplementary Material Available: NMR spectra for compounds **8**, **13**, **14**, **15**, **16**, **17**, **18**, **19**, and **5** (16 pages). Ordering information is given on any current masthead page.

Chiral Synthesis via Organoboranes. 28. Reaction of α-Chiral Organyldichloroboranes with Organyl Azides Providing a Synthesis of Secondary Amines with Exceptionally High Enantiomeric Purities

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2-Alkyl-1,3,2-dioxaborinanes $R^*BO_2(CH_2)_3$ of essentially 100% enantiomeric purity were prepared by the asymmetric hydroboration of readily available prochiral olefins with mono- or diisopinocampheylboranes, followed by removal of the chiral auxiliary (α-pinene). The intermediate $R^*BO_2(CH_2)_3$ reacts readily with lithium aluminum hydride at 0 °C to give the corresponding lithium monoalkylborohydrides stereospecifically in very good yields and in very high enantiomeric purities. The lithium monoalkylborohydrides, on treatment with hydrogen chloride in dimethyl sulfide, give the corresponding monoalkyldichloroboranes in very high enantiomeric purity. The intermediate monoalkyldichloroboranes react readily with organic azides in 1,2-dichloroethane with evolution of gaseous nitrogen and transfer of the organic group from boron to nitrogen with complete retention of configuration to provide the corresponding secondary amines, either (+)- or (-), in very high yields and exceptionally high enantiomeric purities. The procedure was applied to the synthesis of representative optically active amines of high enantiomeric purities (ee or de ≥99%), including (2*S*,2'*S*)-di-2-butylamine, *N*-[(2*S*)-2-methyl-1-butyl]-(1*S*,2*R*)-*trans*-2-phenylcyclopentylamine, *N*-[(3*S*)-3,7-dimethyloct-6-enyl](1*S*,2*S*)-*trans*-2-methylcyclohexylamine, and the *meso*-di-2-butylamine.

The ready availability of pure enantiomers is vital to modern organic synthesis and much effort has been expended in developing new asymmetric methodologies to meet this requirement.[2] Amines are interesting organic compounds due to their physiological activity and their potential as organic intermediates.[3] For example, C_2-symmetric amines have been used both as enantioselective deprotonating agents[4] and as chiral auxiliaries in a number of asymmetric processes.[5] Generally, optically active secondary amines are prepared either by resolution of racemic amines or by synthesis from optically active pre-

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