Direct, highly efficient synthesis from (S)-(+)-phenylglycine of the taxol and taxotere side chains

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(DMSO-d_6, 300 MHz) δ 1.20 (s, 9 H), 11.07 (s, 1 H), 12.19 (s, 1 H), 13.8 (br s, 1 H). Anal. Calcd for $C_{10}H_{12}BrN_5O_2$: C, 38.23; H, 3.85; N, 22.29; Br, 25.44. Found: C, 38.08; H, 4.04; N, 22.01; Br, 25.68.

Dimethyl [4-[(2-Pivaloylguanin-8-yl)ethynyl]benzoyl]glutamate (7). To a solution of 1.1 g (3.5 mmol) of **5a** in 20 mL of CH_3CN and 2 mL of Et_3N was added a mixture of 82 mg (0.36 mmol) of $Pd(OAc)_2$, 108 mg (0.57 mmol) of CuI, and 213 mg (0.81 mmol) of Ph_3P followed by a solution of 2.02 g (6.6 mmol) of dimethyl [4-ethynylbenzoyl]glutamate (**6**)[6] in 20 mL of CH_3CN. The resulting solution was heated at 70–80 °C for 6 h and then concentrated under reduced pressure, and the resulting solid was purified by flash chromatography with 145 g of silica gel, using 3% MeOH in CH_2Cl_2 as the eluting solvent, to give 0.91 g of a solid which (by NMR) consisted of 60% of 2-pivaloyl-8-bromoguanine **5a** and 40% of **7**: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.22 (s, 9 H), 2.0 (m, 1 H), 2.1 (m, 1 H), 2.48 (t, 2 H, J = 7.3 Hz, CH_2CH_2CH), 3.57 (s, 3 H, CH_3), 3.64 (s, 3 H, CH_3), 4.45 (m, 1 H, $CHCH_2$), 7.74 (d, 2 H, J = 8.0 Hz, C_6H_4), 7.96 (d, 2 H, J = 8.0 Hz, C_6H_4), 8.92 (d, 1 H, J = 7.3 Hz, $NHCH$), 11.09 (s, 1 H), 12.21 (s, 1 H), 13.68 (br s, 1 H, 9-NH).

Dimethyl [4-[2-(2-Pivaloylguanin-8-yl)ethyl]benzoyl]glutamate (8). A suspension of 0.5 g of 3% palladium-on-charcoal and 0.7 g (1.30 mmol) of the above mixture of **5b** and **7** in 40 mL of MeOH was stirred at rt under 50 psi of hydrogen for 16 h. The catalyst was removed by filtration through a pad of Celite, which was washed with 25 mL of 5% MeOH in CH_2Cl_2. The filtrate was concentrated to give a solid which was dissolved in 5% MeOH in CH_2Cl_2. Filtration removed a small amount of a white solid (2-pivaloylguanine), and concentration of the filtrate then gave 0.58 g of an orange solid which was purified by flash chromatography (5% MeOH in CH_2Cl_2) through 86 g of silica gel, yield 0.22 g (31%) of **8** as a yellow solid. The analytical sample, mp 175–176 °C, was prepared by recrystallization from ethyl acetate: IR (KBr) 3140, 2940, 1735, 1660, 1400, 1155 cm^{-1}. For the major tautomer: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.22 (s, 9 H), 2.0 and 2.1 (2m, 2 H, CH_2CH), 2.42 (t, 2 H, J = 7.3 H, CH_2CH_2CH), 3.06 (m, 4 H, CH_2CH_2), 3.55 (s, 3 H, CH_3), 3.61 (s, 3 H, CH_3), 4.41 (m, 1 H, $CHNH$), 7.29 (d, 2 H, J = 8.0 Hz, C_6H_4), 7.75 (d, 2 H, J = 8.0 Hz, C_6H_4), 8.66 (d, 1 H, J = 7.3 Hz, $CHNH$), 11.02 (s, 1 H), 12.16 (s, 1 H), 13.08 (s, 1 H). For the minor tautomer, the upper field region (lower than 7 ppm) is the same as that of the major tautomer: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.31 (d, 2 H, J = 6.1 Hz, C_6H_4), 7.77 (d, 2 H, J = 6.1 Hz, C_6H_4), 8.67 (d, 2 H, J = 7.0 Hz, $CHNH$), 10.93 (s, 1 H), 12.03 (s, 1 H), 12.60 (s, 1 H). MS (FAB, m/e), 541 (MH^+), 366; exact mass (FAB) calcd for $C_{26}H_{33}N_6O_7$ (MH^+) 541.2410, found 541.24049. Anal. Calcd for $C_{26}H_{32}N_6O_7$: C, 57.77; H, 5.97; N, 15.55. Found: C, 57.56; H, 5.78; N, 15.32.

[4-(2-Guanin-8-ylethyl)benzoyl]glutamic Acid (2). A suspension of 0.14 g (0.26 mmol) of the ester **8** in 2.5 mL of 1 N NaOH was stirred at rt for 3 days. The resulting clear solution was neutralized with acetic acid until pH 6 and then diluted with 10 mL of water, and the resulting solid was collected by filtration, washed throughly with water, MeOH, and ether, and finally dried to give 50 mg (48%) of a yellow solid, mp 200–230 °C dec: IR (KBr) 3350 (br), 1690, 1630 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.95 and 2.05 (2m, 2 H, CH_2CH), 2.32 (s, 2 H, CH_2CH_2CH), 2.9 and 3.34 (2 br s, 4 H, CH_2CH_2), 4.37 (m, 1 H, $CHNH$), 6.23 (s, 2 H, NH_2), 7.29 (d, 2 H), 7.70 (d, 2 H), 8.51 (d, 1 H, $NHCH$), 10.5 (s, 1 H), 12.1 (s, 1 H), 12.5 (s, 2 H, 2 COOH); mass (FAB, m/e), 429.5 (MH^+) 282.4; exact mass (FAB) calcd for $C_{19}H_{21}N_6O_6$ (MH^+) 429.1522, found 429.15107. Anal. Calcd for $C_{19}H_{20}N_6O_6 \cdot {}^1/_2H_2O$: C, 52.17; H, 4.84; N, 19.21. Found: C, 52.44; H, 4.60; N, 18.98.

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Registry No. **2**, 136675-81-5; **5a**, 136675-83-7; **6**, 135352-72-6; **7**, 136675-84-8; **8**, 136675-85-9; guanine, 73-40-5; 2-pivaloylguanine, 136675-82-6.

Direct, Highly Efficient Synthesis from (*S*)-(+)-Phenylglycine of the Taxol and Taxotere Side Chains

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Taxol (**3a**, Chart I), a natural product obtainable in only low yield from yew bark,[1] and taxotere (**3b**), a semisynthetic analogue,[2] are very exciting antileukemic and tumor-inhibiting agents.[3] Each of these substances, fortunately, can now[4] be secured in good yield from the appropriate hydroxyl-protected side chain (**1a,b**)[5] and naturally abundant 10-desacetyl baccatin III (**2**, in protected form).[6]

The increasingly apparent cancer chemotherapeutic potential of these compounds has generated the need for a highly efficient enantioselective synthesis of the required side chains **1a,b**. In this note we wish to disclose a particularly effective approach to these side chains from inexpensive, enantiomerically pure (*S*)-(+)-phenylglycine.

The synthetic strategy was based on the assumption that the aldehydes derived from alcohols **5a,b** (Scheme I) would, under the proper conditions, undergo chelation-controlled carbonyl addition[7] and provide preferentially the desired threo amino alcohol derivatives **6a,b**. It was, of course, presupposed that the aldehydes would have the necessary configurational stability for this approach.[8]

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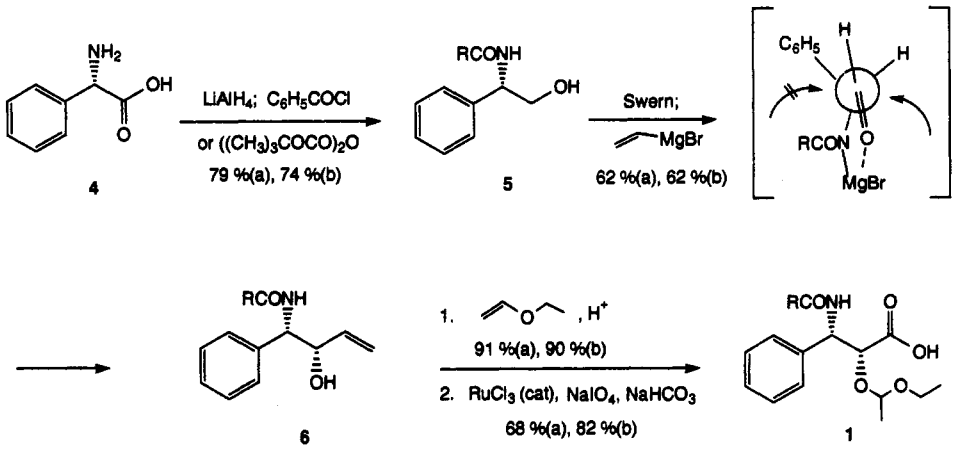
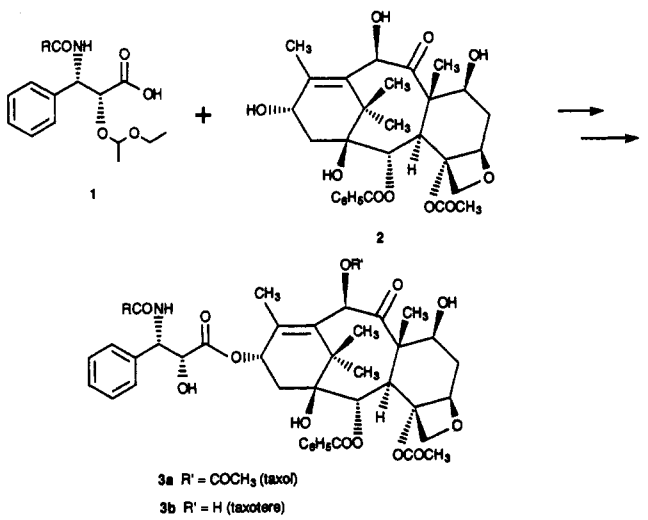
Scheme I[a]



[a] Series a: R = C_6H_5. Series b: R = $(CH_3)_3CO$.

Chart I[a]



[a] Series a: R = C_6H_5. Series b: R = $(CH_3)_3CO$.

(*S*)-(+)-Phenylglycine (4) was conveniently and efficiently converted to the amino alcohol derivatives **5a,b** in a one-pot operation that involved lithium aluminum hydride reduction[9] followed by in situ derivatization. The in situ treatment obviated the need to isolate the polar amino alcohol intermediate, and the yields of **5a,b** were thereby substantially improved.[10]

Although α-amino aldehyde derivatives are known to be configurationally labile,[8] it was felt that the tandem Swern oxidation–carbonyl addition sequence developed by Ireland and Norbeck[11] might be employed successfully to effect a nonracemizing conversion of **5a,b** to **6a,b**. It was thus initially quite disheartening to find that the syn product that resulted from in situ treatment of the aldehyde from **5b** with excess vinylmagnesium bromide was essentially racemic. Reasoning that the initially produced carbamate anion, formed in the presence of unreacted aldehyde, might be responsible for this result, we added the Swern oxidation[12] mixture to the vinylmagnesium bromide in tetrahydrofuran–dichloromethane at room temperature. Much to our satisfaction, we found that the reaction, when carried out in this way, proceeded with good syn diastereoselection (9:1) *and with complete retention of enantiomeric purity*[13] to give **6b** in 62% yield after purification. The pure amino alcohol derivative **6a** could be obtained in an analogous manner, also in 62% yield.

In anticipation of both the double bond oxidation and the ultimate esterification reaction (Chart I), the hydroxyls of **6a,b** were protected by reaction with ethyl vinyl ether in the presence of pyridinium *p*-toluenesulfonate.[14] Of the several oxidation procedures examined, the combination of ruthenium chloride (catalytic) and sodium periodate[15] in the presence of sodium bicarbonate[5a] proved clearly the best and delivered pure **1a,b** in high yields. The enantiomeric purity (≥99%) of these substances was readily confirmed by ^1H and ^{19}F NMR analysis of the Mosher esters[13] of the alcohols derived from the methyl esters.

In summary, the pure hydroxyl-protected side chains of taxol and taxotere *can now be easily obtained in only four steps from inexpensive (S)-(+)-phenylglycine, with overall yields of 30 and 34%, respectively.* It is particularly significant that the approach is well-suited for large-scale work.

Experimental Section[16]

(−)-*N*-((*S*)-2-Hydroxy-1-phenylethyl)benzamide (5a). (*S*)-(+)-Phenylglycine (5.00 g, 33.1 mmol) was carefully added portionwise from the top of the condenser to a stirred mixture

(8) For a discussion of the configurational stability of N-protected α-amino aldehydes, see: Jurczak, J.; Golebiowski, A. *Chem. Rev.* **1989**, *89*, 149–164. Phenylglycine derivatives are particularly racemization prone. See, for example: Burgess, K.; Ohlmeyer, M. J. *Tetrahedron Lett.* **1989**, *30*, 5857–5860. Evans, D. A.; Ellman, J. A.; DeVries, K. M. *J. Am. Chem. Soc.* **1989**, *111*, 8912–8914. It should be noted, however, that carbamate anion formation can render subsequent α-proton abstraction difficult, and thereby slow racemization. See: Coppola, G. M.; Schuster, H. F. *Asymmetric Synthesis. Construction of Chiral Molecules using Amino Acids*; Wiley Interscience: New York, 1987; Chapter 1, p 14.

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(15) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936–3938.

(16) For general experimental procedures, see ref 5b.

of 2.52 g (66.3 mmol) of $LiAlH_4$ in 120 mL of tetrahydrofuran (THF) at reflux under argon. After the addition, the condenser was rinsed with 7 mL of THF, and the mixture was refluxed for an additional 6 h. The mixture was then allowed to cool to room temperature and was slowly treated with 4.0 mL of 10% aqueous NaOH followed by 5.0 mL of water and was stirred for 5 min. Additional 10% aqueous NaOH (53 mL) and 3.3 mL (4.0 g, 28 mmol) of benzoyl chloride were then introduced at 0 °C, and the resulting mixture was stirred for 30 min at 20 °C, whereupon CH_2Cl_2 and aqueous potassium sodium tartrate (Rochelle salt) were added. The crude product was isolated with CH_2Cl_2 in the usual way and recrystallized from CH_3OH–CH_2Cl_2 to give 4.90 g of **5a**. Silica gel chromatography with 20% $CH_3CO_2C_2H_5$ in CH_2Cl_2 of the residue from the mother liquor yielded an additional 1.42 g (79%) of **5a**: mp 179–180 °C (CH_2Cl_2–cyclohexane); $[\alpha]^{25}_D$ −18° (*c* 1.5, CH_3OH); ^1H NMR (300 MHz) δ 7.73–7.70 (m, 2 H), 7.42–7.16 (m, 8 H), 6.71 (br s, 1 H), 5.18 (dt, *J* = 4.8, 6.5 Hz, 1 H), 3.93 (dd, *J* = 4.8, 5.5 Hz, 2 H), 2.40 (t, *J* = 5.5 Hz, 1 H); ^{13}C NMR (50.3 MHz, $CDCl_3$ + CD_3OD) δ 166.2, 139.2, 134.0, 131.6, 128.5 128.4, 127.5, 127.0, 126.6, 65.3, 55.8; IR 3300, 1630, 1580, 1520, 1075 cm^{-1}; mass spectrum (CI) *m/z* 242 (MH^+), 224, 210, 122, 105. Anal. Calcd for $C_{15}H_{15}O_2N$: C, 74.66; H, 6.27; N, 5.81. Found: C, 74.45; H, 6.10; N, 5.91.

(+)-1,1-Dimethylethyl (*N*-((*S*)-2-Hydroxy-1-phenylethyl)amino)methanoate (5b). (*S*)-(+)-Phenylglycine (9.07 g, 60.0 mmol) was carefully added as above to 4.55 g (120 mmol) of $LiAlH_4$ in 210 mL of THF at reflux under argon. After the addition, the condenser was rinsed with 10 mL of THF, and the mixture was refluxed for an additional 6 h. The mixture was then allowed to cool to room temperature and was slowly treated with 7.3 mL of 10% aqueous NaOH followed by 9.1 mL of water and was stirred for 5 min. A solution of 14.40 g (66.0 mmol) of di-*tert*-butyl dicarbonate and 200 mg (1.64 mmol) of 4-(dimethylamino)pyridine in 80 mL of CH_2Cl_2 was introduced and the resulting mixture was refluxed for 6 h, whereupon it was allowed to cool to room temperature and was filtered through a pad of anhydrous Na_2SO_4, which was then washed with several portions of CH_2Cl_2. The solvents were removed under reduced pressure to give the crude product, which was recrystallized from CH_2Cl_2–cyclohexane to give 7.50 g of **5b**. Silica gel chromatography with 50% ether in hexane provided an additional 2.99 g (74%) of **5b**: mp 136–137 °C (CH_2Cl_2–cyclohexane); $[\alpha]^{24}_D$ +40° (*c* 1.6, $CHCl_3$); ^1H NMR (300 MHz) δ 7.38–7.26 (m, 5 H), 5.20 (br s, 1 H), 4.77 (br s, 1 H), 3.85 (d, *J* = 4.3 Hz, 2 H), 1.99 (br s, 1 H), 1.43 (s, 9 H); ^{13}C NMR (50.3 MHz) δ 156.1, 139.6, 128.6, 127.6, 126.5, 79.9, 66.6, 56.7, 28.2; IR 3250, 1670, 1555, 1365, 1060 cm^{-1}; mass spectrum (CI) *m/z* 295 (M^+ + isobutane), 255 (MH^+ + ammonia), 238 (MH^+, 100), 220, 206, 199, 182, 168, 150, 138, 124, 106. Anal. Calcd for $C_{13}H_{19}O_3N$: C, 65.80; H, 8.07; N, 5.90. Found: C, 65.89; H, 8.02; N, 5.76.

(−)-*N*-((1*S*,2*S*)-2-Hydroxy-1-phenyl-3-butenyl)benzamide (6a). To a stirred solution of 1.05 mL (1.52 g, 12.0 mmol) of oxalyl chloride in 16 mL of CH_2Cl_2 at −78 °C under argon was added 908 μL (1.00 g, 12.8 mmol) of dimethyl sulfoxide (DMSO). After being stirred for 5 min at −78 °C, the reaction mixture was allowed to warm to −60 °C over 20 min, whereupon 1.88 g (7.79 mmol) of alcohol **5a** suspended in 25 mL of CH_2Cl_2–DMSO (24:1) was added over 15 min. The flask containing the suspension was rinsed with 5 mL of CH_2Cl_2, which was then added to the reaction mixture. The mixture was allowed to warm to −35 °C over 20 min, stirred for 5 min at this temperature, and then treated over 4 min with 8.36 mL (6.20 g, 48.0 mmol) of diisopropylethylamine. The cooling bath was removed for 5 min, and then at −78 °C the mixture was added with a double-tipped needle to a room temperature solution (104 mL, 0.5 M, 52 mmol) of vinylmagnesium bromide in 1:1 THF–CH_2Cl_2 (exothermic!). After being stirred for 1 h, the mixture was treated with 8 mL of C_2H_5OH and 12 mL of saturated aqueous NH_4Cl. CH_2Cl_2 and aqueous HCl were then added and the crude reaction product was isolated with CH_2Cl_2 in the normal way. Purification of this material by silica gel chromatography with 5% $CH_3CO_2C_2H_5$ in CH_2Cl_2 gave 169 mg of **5a**, 280 mg of anti product, and 1.17 g (62% based on consumed **5a**) of **6a**: mp 135–136 °C (CH_2Cl_2–cyclohexane); $[\alpha]^{23}_D$ −50° (*c* 1.0, $CHCl_3$); ^1H NMR (200 MHz) δ 7.83–7.80 (m, 2 H), 7.54–7.24 (m, 8 H), 6.98 (d, *J* = 7.6 Hz, 1 H), 5.94 (ddd, *J* = 5, 10.5, 17.1 Hz, 1 H), 5.40 (dt, *J* = 1.5, 17.1 Hz, 1 H), 5.26 (dd, *J* = 3.5, 7.6 Hz, 1 H), 5.23 (dt, *J* = 1.5, 10.5 Hz, 1 H), 4.55 (ddd, *J* = 3.5, 3.5, 5.0 Hz, 1 H), 2.40 (d, *J* = 3.9 Hz, 1 H); ^{13}C NMR (50.3 MHz) δ 167.5, 139.6, 137.4, 134.3, 131.6, 128.7, 128.6, 127.7, 127.0, 126.9, 116.6, 75.3, 57.7; IR 3300, 1620, 1525, 1120, 1080, 995, 920 cm^{-1}; mass spectrum (CI) *m/z* 268 (MH^+), 250, 210, 105. Anal. Calcd for $C_{17}H_{17}O_2N$: C, 76.38; H, 6.41. Found: C, 76.44; H, 6.49.

(+)-1,1-Dimethylethyl (*N*-((1*S*,2*S*)-2-Hydroxy-1-phenyl-3-butenyl)amino)methanoate (6b). To a reaction mixture prepared as above for **6a** (but with 24 mL of CH_2Cl_2) was added over 15 min a solution of 1.90 g (8.01 mmol) of **5b** in 26 mL of CH_2Cl_2. The mixture was allowed to warm to −35 °C over 20 min, stirred for 5 min at this temperature, and then treated over 4 min with 8.36 mL (6.20 g, 48.0 mmol) of diisopropylethylamine. The reaction mixture was allowed to warm to −5 to 0 °C over 10 min and was then added with a double-tipped needle to a room temperature solution (104 mL, 0.5 M, 52 mmol) of vinylmagnesium bromide in 1:1 THF–CH_2Cl_2 (exothermic!). After being stirred for 1 h, the mixture was treated with 8 mL of C_2H_5OH and 12 mL of saturated aqueous NH_4Cl. CH_2Cl_2 and aqueous HCl were then added, and the crude reaction product was isolated with CH_2Cl_2 in the usual manner (ca. 87:13 syn–anti by ^1H NMR). Chromatography of this material on silica gel with 5% ether in CH_2Cl_2 gave 1.70 g (81%) of a 94:6 syn–anti mixture of products. Rechromatography of the mixture with 5% ether–45% CH_2Cl_2–50% hexane yielded 1.30 g (62%) of pure **6b**: mp 56–57 °C; $[\alpha]^{25}_D$ +0.3° (*c* 1.6, $CHCl_3$); ^1H NMR (300 MHz) δ 7.37–7.24 (m, 5 H), 5.86 (ddd, *J* = 5.4, 10.5, 17.2 Hz, 1 H), 5.34 (dt, *J* = 1.4, 17.2 Hz, 1 H), 5.26 (br s, 1 H), 5.20 (dt, *J* = 1.4, 10.5 Hz, 1 H), 4.70 (br s, 1 H), 4.38 (pseudo t, *J* = 4.6, 4.8 Hz, 1 H), 1.90 (br s, 1 H), 1.40 (s, 9 H); ^{13}C NMR (50.3 MHz) δ 155.9, 140.0, 137.2, 128.3, 127.3, 126.7, 116.4, 79.6, 75.3, 58.7, 28.1; IR 3400, 1690, 1500, 1365, 1250, 1175, 1050, 920 cm^{-1}; mass spectrum (CI) *m/z* 321 (M^+ + isobutane), 281 (MH^+ + ammonia), 264 (MH^+, 100), 246, 225, 208, 190, 164, 124, 106. Anal. Calcd for $C_{15}H_{21}O_3N$: C, 68.41; H, 8.04; N, 5.32. Found: C, 68.15; H, 7.98; N, 5.34.

(2*R*,3*S*)-(−)-2-(1-Ethoxyethoxy)-3-phenyl-3-(phenylmethanamido)propanoic Acid (1a). A solution of 708 mg (2.65 mmol) of **6a** and 66.5 mg (0.26 mmol) of pyridinium *p*-toluenesulfonate in 2.53 mL (1.91 g, 26.5 mmol) of ethyl vinyl ether and 13.5 mL of CH_2Cl_2 under argon was stirred at room temperature for 4 h. One drop of pyridine was added to the reaction mixture, which was then processed with CH_2Cl_2 in the normal manner. The crude product was purified by silica gel chromatography with 40% ether in hexane to provide 818 mg (91%) of *N*-((1*S*,2*S*)-2-(1-ethoxyethoxy)-1-phenyl-3-butenyl)benzamide: mp 85.5–87 °C; $[\alpha]^{22}_D$ −34° (c 1.6, $CHCl_3$); ^1H NMR (200 MHz) δ 7.92–7.74 (m, 2 H), 7.55–7.15 (m, 8 H), 7.05 (d, *J* = 8 Hz, 1 H), 5.99 and 5.81 (2ddd, *J* = 6.5, 10.4, 17.1 Hz, 1 H), 5.46–5.12 (m, 3 H), 4.43–4.29 (m, 1 H), 4.66–4.36 (2q, *J* = 5.3 Hz, 1 H), 3.56–2.98 (m, 2 H), 1.29 and 1.09 (2d, *J* = 5.3 Hz, 3 H), 1.08 and 1.00 (2t, *J* = 7.0 Hz, 3 H); IR 3300, 1630, 1600, 1580, 1520, 1125, 1030, 920 cm^{-1}; mass spectrum (CI) *m/z* 340 (MH^+), 294, 268, 250, 211, 105.

To a stirred mixture of 254 mg (0.75 mmol) of the above acetal in 1.5 mL of CH_3CN, 1.5 mL of CCl_4, and 2.25 mL of H_2O at room temperature under argon were added 409.5 mg (4.88 mmol) of $NaHCO_3$ and, in small portions, 882 mg (4.12 mmol) of $NaIO_4$. After being stirred for 5 min following completion of the addition, the mixture was treated with 25.4 mg (0.12 mmol) of $RuCl_3$, and stirring was allowed to continue for 48 h. The reaction mixture was extracted with ether and then carefully acidified with aqueous HCl, and the product was isolated with CH_2Cl_2 to give 183 mg (68%) of pure **1a** (as a ca. 1:1 mixture of methyl epimers): mp 93–94 °C; $[\alpha]^{25}_D$ −21° (*c* 0.7, CH_3OH); ^1H NMR (300 MHz) δ 7.80–7.00 (br s, 1 H), 7.83–7.78 (m, 2 H), 7.52–7.26 (m, 9 H), 5.80–5.74 (m, 1 H), 4.81 and 4.60 (2q, *J* = 5.3 Hz, 1 H), 4.63 and 4.50 (2d, *J* = 2.4 Hz, 1 H), 3.45–3.24 and 2.99–2.88 (2m, 2 H), 1.24 (d, *J* = 5.3 Hz, 3 H), 1.07 and 0.90 (2t, *J* = 7 Hz, 3 H); IR 3425, 3600–2100, 3060, 3025, 1740, 1640, 1600, 1580, 1520, 1480, 1075 cm^{-1}. The methyl ester of **1a** (CH_2N_2) was identical with material previously prepared by an alternative synthesis.[5a] ^1H and ^{19}F NMR analysis of the Mosher esters of the alcohols derived from the methyl esters of (±)-**1a** and (−)-**1a** (aqueous HCl; (*R*)-(−)-2-methoxy-2-phenyl-2-trifluoromethylacetyl chloride, pyridine) confirmed the enantiomeric purity (≥99%) of (−)-**1a**.

(2*R*,3*S*)-(+)-3-(*N*-(1,1-Dimethylethoxycarbonyl)-amino)-2-(1-ethoxyethoxy)-3-phenylpropanoic Acid (1b). A

solution of 1.04 g (3.95 mmol) of **6b** and 99 mg (0.40 mmol) of pyridinium *p*-toluenesulfonate in 3.80 mL (2.86 g, 39.7 mmol) of ethyl vinyl ether and 20 mL of CH_2Cl_2 under argon was stirred at room temperature for 4 h. One drop of pyridine was added to the reaction mixture, which was then processed with CH_2Cl_2 in the usual way. The crude product was purified by silica gel chromatography with 20% ether in hexane to provide 1.19 g (90%) of 1,1-dimethylethyl (*N*-((1*S*,2*S*)-2-(1-ethoxyethoxy)-1-phenyl-3-butenyl)amino)methanoate: mp 59–65 °C; $[\alpha]^{25}_D$ +15° (*c* 1.6, $CHCl_3$); ^1H NMR (300 MHz) δ 7.37–7.17 (m, 5 H), 5.91 and 5.77 (2ddd, *J* = 7, 10.5, 17.4 Hz, 1 H), 5.44 and 5.37 (2m, 1 H), 5.30 and 5.25 (2dt, *J* = 1.2, 17.4 Hz, 1 H), 5.23 and 5.22 (2dt, *J* = 1.2, 10.5 Hz, 1 H), 4.73 and 4.71 (2m, 1 H), 4.62 and 4.31 (2q, *J* = 5.4 and 5.3 Hz, 1 H), 4.23 and 4.16 (2 pseudo dd, *J* = 6.6, 7.0 Hz, 1 H), 3.51–3.05 and 2.98–2.90 (2 m, 2 H), 1.40 (s, 9 H), 1.22 and 1.05 (2d, *J* = 5.4 and 5.3 Hz, 3 H), 1.07 and 0.90 (2t, *J* = 7.0 Hz, 3 H); IR 3370, 1680, 1520, 1170, 1080, 1050 cm^{-1}. Anal. Calcd for $C_{19}H_{29}O_4N$: C, 68.03; H, 8.71; N, 4.18. Found: C, 68.00; H, 8.78; N, 4.13.

The above acetal (1.09 g, 3.25 mmol) was treated as was that from **6a** to afford 940 mg (82%) of pure **1b**: mp 33–37 °C; $[\alpha]^{25}_D$ +18° (*c* 1.1, $CHCl_3$); ^1H NMR (300 MHz) δ 8.52 (br s, 1 H), 7.38–7.13 (m, 5 H), 5.72 (br s, 1 H), 5.29 (br s, 1 H), 4.80–4.65 and 4.50–4.35 (2m, 2 H), 3.52–3.15 and 2.88–2.60 (2m, 2 H), 1.42 (s, 9 H), 1.20 and 1.18 (2d, *J* = 5.4 Hz, 3 H), 1.04 and 0.81 (2t, *J* = 7.0 Hz, 3 H); IR 3700–2200, 3060, 1720, 1660, 1370, 1170, 1080, 955 cm^{-1}. The methyl ester of **1b** (CH_2N_2) was identical with material previously prepared by an alternative synthesis.[5b] ^1H and ^{19}F NMR analysis of the Mosher esters of the alcohols derived from the methyl esters of (±)-**1b** and (+)-**1b** (aqueous HCl; (*R*)-(−)-2-methoxy-2-phenyl-2-trifluoromethylacetyl chloride, pyridine) confirmed the enantiomeric purity (≥99%) of (+)-**1b**.

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Registry No. **1a** (isomer 1), 136778-67-1; **1a** (isomer 2), 136778-69-3; **1a** (methyl ester; isomer 1), 136779-75-4; **1a** (methyl ester; isomer 2), 136778-73-9; **1a** (methyl ester; Mosher ester), 136693-08-8; **1b** (isomer 1), 136778-68-2; **1b** (isomer 2), 136778-70-6; **1b** (methyl ester; isomer 1), 136778-71-7; **1b** (methyl ester; isomer 2), 136778-75-1; **1b** (methyl ester; Mosher ester), 136693-09-9; **2**, 32981-86-5; **3a**, 33069-62-4; **3b**, 114977-28-5; **4**, 2935-35-5; **5a**, 116126-04-6; **5b**, 117049-14-6; **6a**, 136693-02-2; *anti*-**6a**, 136693-06-6; **6a** ((*R*)-ethoxyethyl ether), 136693-04-4; **6a** ((*S*)-ethoxyethyl ether), 136778-72-8; **6b**, 136693-03-3; *anti*-**6b**, 136693-07-7; **6b** ((*R*)-ethoxyethyl ether), 136778-74-0; **6b** ((*S*)-ethoxyethyl ether), 136693-05-5.

Singlet Oxygen Mediated Oxidative Decarboxylation of Pyrrole-2-carboxylic Acids

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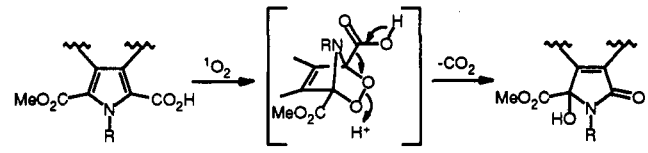
Autoxidation of the chromogen hermidin[1] isolated from *Mercurialis perennis L.*[2] provides isochrysohermidin (1),[3] a functionalized 3,3′-pyrrolin-2-one dimer first isolated from *Mercurialis leiocarpia* and whose structure was unambiguously established by X-ray crystallography. In initial studies directed at the total synthesis of isochrysohermidin,[4] we have examined the singlet oxygen ($^1O_2$) addition[5] to substituted 5-(alkoxycarbonyl)pyrrole-2-carboxylic acids and a subsequent oxidative decarboxylation[6] reaction in efforts to provide direct access to the 5-(alkoxycarbonyl)-5-hydroxy-3-pyrrolin-2-one subunit found in **1**, Scheme I.

Scheme I



Scheme II

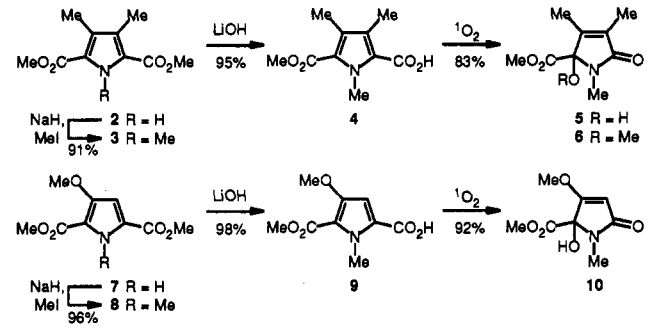
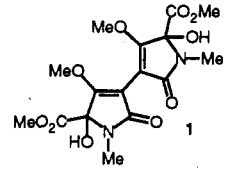


Table I

pyrrole	solvent (0.8 mM)[a]	time (h)	result
4	CH_3OH[b]	5	**5** (20%), **6** (12%)
	CH_3OH	1	**5** (35%), **6** (32%)
	CH_3OH–H_2O (2:1)	1	**5** (37%), **6** (26%)
	^iPrOH–H_2O (2:1)	1	**5** (79%)
	^iPrOH–H_2O (3:1)	1	**5** (83%)
	CH_3CN–H_2O (3:1)	1	**5** (62%)
9	CH_3CN–H_2O (3:1)	1	**10** (92%)
	^iPrOH–H_2O (3:1)	1	**10** (80%)

[a] Rose bengal (8 mequiv), quartz immersion well, Hanovia high-pressure mercury lamp (450 W), uranium yellow glass filter (transmits > 330 nm), O_2, 22 °C. [b] Pyrex reaction vessel, tungsten lamp (500 W), O_2, 22 °C.



1

The substrates employed in the study were derived from the [4 + 2] cycloaddition of 2-[(triethylsilyl)oxy]-2-butene and 1,1-dimethoxyethylene with 3,6-bis(methoxycarbonyl)-1,2,4,5-tetrazine[7] followed by reductive ring contraction (Zn, HOAc) of the resulting 1,2-diazine cycloadducts to provide the substituted pyrroles **2** and **7**.[8] *N*-Methylation of the pyrroles followed by a surprisingly selective monohydrolysis of the symmetrical pyrrole **3** and a well-precedented[9] selective hydrolysis of the sterically

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