***trans*-4-Phenyl-5-methylcyclopentenone (3f)**: purified by flash chromatography (10% ethyl acetate in hexanes); IR 1715, 1595, 1495, 1455, 1180, 850, 700 cm^{-1}; ^1H NMR δ 7.70 (1 H, dd, J = 5.73, 2.66 Hz), 7.32 (3 H, m), 7.03 (2 H, m), 6.41 (1 H, dd, J = 5.71, 1.97 Hz), 4.31 (1 H, m), 2.73 (1 H, dt, J = 7.0, 7.50 Hz), 0.70 (3 H, d, J = 7.50 Hz), (3 H, s); high-resolution mass spectrum calcd for $C_{12}H_{12}O$ (M^+) 172.0888, found 172.0888.

***cis*-4,5,6,6a-Tetrahydro-1(3a*H*)-pentalenone (3g)**:[7b,7d,8h] purified by flash chromatography (15% ethyl acetate in hexanes); IR 1710, 1585, 1450, 1345, 840 cm^{-1}; ^1H NMR δ 7.54 (1 H, dd, J = 5.50, 2.68 Hz), 6.15 (1 H, dd, J = 5.75, 1.77 Hz), 3.36 (1 H, m), 2.73–2.67 (1 H, m), 1.95–1.55 (5 H, m), 1.32–1.13 (1 H, m).

***cis*-3a,4,5,6,7,7a-Hexahydro-1*H*-inden-1-one (3h)**:[7b,7d,8h] purified by flash chromatography (15% ethyl acetate in hexanes); IR 2950, 1703, 1580, 1550 cm^{-1}; ^1H NMR δ 7.66 (1 H, dd, J = 5.73, 2.85 Hz), 6.16 (1 H, dd, J = 5.30, 1.55 Hz), 2.96 (1 H, m), 2.41 (1 H, q, J = 6.17 Hz), 1.82–2.05 (2 H, m), 1.63–1.80 (1 H, m), 1.45–1.60 (2 H, m), 1.05–1.45 (3 H, m).

***cis*/*trans*-4,5,6,7,8,8a-Hexahydro-1(3a*H*)-azulenone (3i)**:[7b,7d] purified by flash chromatography (10% ethyl acetate in hexanes); IR 2940, 2370, 1700, 1595, 1455, 1185 cm^{-1}; ^1H NMR δ 7.55 (1 H, dd, J = 5.67, 2.50 Hz), 6.15 (1 H, dd, J = 5.70, 2.20 Hz), 3.06–2.15 (1 H, m), 2.55–2.44 (1 H, m), 2.10–1.85 (4 H, m), 1.85–1.65 (4 H, m), 1.55–1.35 (4 H, m).

5-Chloro-2,3,5-trimethyl-2-cyclopentenone (7). A solution of 1.05 g of freshly distilled methacryloyl chloride (10 mmol) in 2 mL of 1,2-dichloroethane was cooled to 0 °C, and 1.5 g of anhydrous aluminum chloride (12 mmol) was added. The reaction mixture was stirred at 0 °C for 15 min, warmed to room temperature for 30 min, cooled to 0 °C, and then 3.62 g of 2-butyne (67 mmol; Farchan) was added dropwise via syringe. The reaction, which was immediately exothermic, was complete within 10 min. The mixture was then carefully added to ice and diluted with ether. The organic phase was separated, and the aqueous phase was extracted with ethyl acetate. The combined organic fractions were then washed with saturated brine, dried over magnesium sulfate, and filtered, and the solvent was removed in vacuo. Purification by flash column chromatography (silica gel, 10% ether in pentane) afforded 1.07 g (65%) of 5-chloro-2,3,5-trimethyl-2-cyclopentenone: IR 3020, 2915, 1715, 1650, 1435, 1390, 1335 cm^{-1}; ^1H NMR δ 3.05 (d, 1 H, J = 18.8 Hz), 2.81 (d, 1 H, J = 18.8 Hz), 2.05 (s, 3 H), 1.77 (s, 3 H), 1.64 (s, 3 H); high resolution mass spectrum calcd for $C_8H_{12}OCl$ (M + H) 159.0577, found 159.0600.

2,3-Dimethyl-5-methylene-2-cyclopentenone (Methylenomycin B). A solution of 383 mg of 5-chloro-2,3,5-trimethyl-2-cyclopentenone (2.41 mmol), 1.26 g of triethylamine (12.5 mmol) in 5 mL of methylene chloride was cooled to 0 °C, whereupon 678 mg of silver perchlorate monohydrate (3.0 mmol; Alfa) was added. The solution was then stirred at 0 °C for 20 min and warmed to ambient temperature for an additional 2 h, during which time a dark precipitate formed. The reaction mixture was then filtered through a short plug of Celite, the solvent was removed in vacuo, and the residue was purified by flash chromatography (silica gel, eluted with 10% ether in pentane) to yield 140 mg (47%) of methylenomycin B (**8**) and 119 mg (40%) of 2,5-dimethyl-3-methylene-2-cyclopentenone (**9**). **8**:[13] IR 3010, 1690, 1665, 1630, 1405, 1390, 1340, 1035, 940 cm^{-1}; ^1H NMR δ 6.05 (br s, 1 H), 5.34 (br s, 1 H), 3.09 (br s, 2 H), 2.09 (s, 3 H), 1.79 (s, 3 H); ^{13}C NMR (62.5 MHz) 164.1, 141.5, 138.1, 114.9, 36.8, 16.6, 8.2 (carbonyl carbon not reported); high-resolution mass spectrum calcd for $C_8H_{11}O$ (M + H) 123.0810, found 123.0798. **9**: IR 3005, 2985, 1705, 1640, 1605, 1325, 910 cm^{-1}; ^1H NMR δ 7.41 (br s, 1 H), 5.24 (br s, 1 H), 5.12 (br s, 1 H), 2.79 (qdd, 1 H, J = 7.60, 1.25, 1.36 Hz), 1.88 (s, 3 H), 1.24 (d, 3 H, J = 7.60 Hz); UV λ_{max} 273 (CH_3CN, $\epsilon = 1.07 \times 10^4$);[20] high-resolution mass spectrum calcd for $C_8H_{11}O$ (M + H) 123.0810, found 123.0817.[20]

Acknowledgment. Support for this investigation was provided by the National Institutes of Health (Grant GM-19033) and by Merck Sharp and Dohme Research Laboratories.

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Selectively Protected L-Dopa Derivatives: Application of the Benzylic Hydroperoxide Rearrangement

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Bouvardin (**1**, NSC 259968) and deoxybouvardin (**2**), bicyclic hexapeptides isolated initially from *Bouvardia ternifolia* (Rubiaceae) and unambiguously identified by single-crystal X-ray structure analysis (bouvardin) and chemical correlation (deoxybouvardin),[2] are the initial members of a growing class of selective, exceptionally potent antitumor antibiotics,[2-4] now including the additional, provisionally named, bicyclic hexapeptides RA-I–RA-VII.[3,4] The unusual 14-membered para- and metacyclophane unit of the naturally occurring materials has been postulated to arise from the oxidative coupling of two adjacent L-tyrosine residues in cyclic hexapeptide precursors[2,3] and has been suggested to be responsible for attainment and/or maintenance of the active, normally inaccessible, conformation of the parent, cyclic hexapeptides necessary for inhibition of protein synthesis.[5,6] The parent 14-membered para- and metacyclophane has been recently disclosed in the characterization and structure determination of piperazinomycin (**9**),[7] an an-

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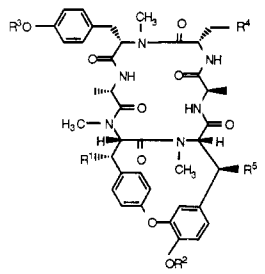
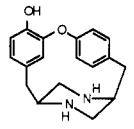


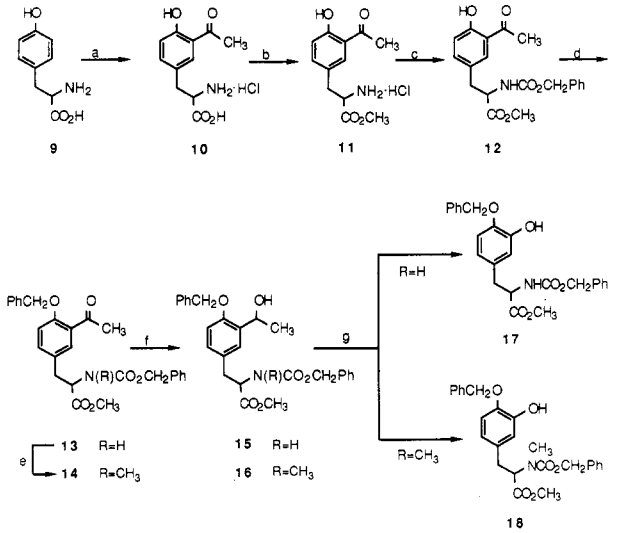


9 Piperazinomycin

	R^1	R^2	R^3	R^4	R^5	
1	OH	H	CH_3	H	H	bouvardin
2	H	H	CH_3	H	H	deoxybouvardin (RA-V)
3	H	H	CH_3	OH	H	RA-I
4	H	CH_3	H	H	H	RA-II
5	H	CH_3	CH_3	OH	H	RA-III
6	H	CH_3	CH_3	H	OH	RA-IV
7	H	CH_3	CH_3	H	H	*O*-methyldeoxybouvardin (RA-VII)
8	OH	CH_3	CH_3	H	H	*O*-methylbouvardin

Herein, we detail an effective approach to the preparation of selectively protected derivatives of L-Dopa [L-3-(3,4-dihydroxyphenyl)alanine] suitable for incorporation into efforts on the total synthesis[8] of bouvardin (1), deoxybouvardin (2), RA-I–RA-VII, and piperazinomycin (9) that is based on the application of the benzylic hydroperoxide rearrangement of *secondary* benzylic alcohols for controlled, selective phenol introduction.[9] Comparative, past efforts on the preparation of L-Dopa derivatives bearing a selectively protected catechol have been based on the nonselective monoprotection of the unsymmetrical catechol of L-Dopa and derivatives (10–30%),[10,12] diazotization of *O*-methyl/*O*-benzyl-3-amino-L-tyrosine derivatives and subsequent copper(I)-promoted phenol introduction (*O*-methyl, ca. 10%; *O*-benzyl, 0%),[11,12] or Baeyer–Villiger oxidation of 3-acetyl-L-tyrosine derivatives (ca. 30%).[12,13]

Scheme I[a]



[a] (a) 3.0 equiv of $AlCl_3$, 1.2 equiv of CH_3COCl, $PhNO_2$, 100 °C, 6 h, 77%; (b) HCl(g), MeOH, 25 °C, 1 h, 90% (74%, recrystallized); (c) 1.0 equiv of benzyl chloroformate, 3.0 equiv of sodium carbonate, Et_2O–H_2O (1:1), 25 °C, 3 h, 90%; (d) 1.0 equiv of benzyl bromide, 2.0 equiv of potassium carbonate, cat. tetra-*n*-butylammonium iodide, DMF, 25 °C, 6 h, 93%; (e) 3.0 equiv of methyl iodide, 1.0 equiv of sodium hydride, THF–DMF (10:1), 85 °C, 20 h, 97%; (f) 1.5 equiv of $NaBH_4$, MeOH, 25 °C, 1 h, 99% for **15**, 95% for **16**; (g) 10.0 equiv of 30% aq. H_2O_2, 30 mol % *p*-TsOH·H_2O, THF, 23 °C, 24 h, 60% for **17**, 61% for **18**.

Friedel–Crafts acylation ($AlCl_3$, CH_3COCl, $PhNO_2$, 77%) of L-tyrosine[12,14,15] followed by Fischer esterification (HCl(g), CH_3OH, 90%) and subsequent protection of the free amine ($PhCH_2OCOCl$, Et_2O–H_2O, 90%)[16] provided **12**. Protection of the free phenol as its benzyl ether under conditions which minimize the extent of observed racemization[17] provided **13** (1.0 equiv of $PhCH_2Br$, 2.0 equiv of K_2CO_3, 0.1 equiv of $(n\text{-}Bu)_4NI$, DMF, 25 °C). N-Methylation of **13** under the conditions detailed by Coggins and Benoiton[18] (1.0 equiv of NaH, 3.0 equiv of CH_3I, THF–DMF) provided **14** with little or no observable racemization. Conversion of **13**/**14** to the corresponding *secondary* benzylic alcohols **15**/**16** ($NaBH_4$) and subsequent room temperature, acid-catalyzed benzylic hydroperoxide formation and rearrangement provided the L-Dopa derivatives **17** and **18** bearing the selectively protected, unsymmetrical catechols.

Efforts on the incorporation of the selectively protected L-Dopa and *N*-methyl-L-Dopa derivatives **17** and **18** into synthetic approaches to piperazinomycin (**9**) and bouvardin (**1**), deoxybouvardin (**2**), and RA-I–RA-VII (**2**–**8**), respectively, are in progress.

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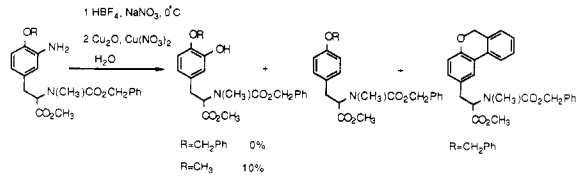

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(17) Protection of the free phenol under more vigorous reaction conditions (1.0 equiv of benzyl bromide, 2.0 equiv of potassium carbonate, acetone, 60 °C) results in substantial racemization (15–20%). See also ref 12.

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Experimental Section[19]

L-3-(3-Acetyl-4-hydroxyphenyl)alanine Hydrochloride (10). Anhydrous aluminum chloride (42.4 g, 0.315 mol, 3.94 equiv) was added to a solution of L-tyrosine (14.5 g, 0.080 mol) in 350 mL of dry nitrobenzene at 25 °C. The slightly exothermic reaction was stirred at 25 °C until homogeneous. Acetyl chloride (7.50 g, 0.095 mol, 1.2 equiv) was added in one portion and was accompanied by an immediate color change from red to yellow. The reaction mixture was warmed at 100 °C with stirring (6 h). The reaction mixture was cooled to room temperature and was poured over a mixture of 500 g of ice and 80 mL of concentrated HCl. The nitrobenzene layer was separated and the aqueous phase was washed with ethyl acetate (2 × 200 mL). The aqueous mixture was concentrated in vacuo to ca. a 200-mL volume and the concentrated solution was allowed to stand at 0 °C for 12 h. The precipitated solid was collected by filtration and recrystallized (5 N aqueous HCl) to afford **10** (16.0 g, 20.8 g theoretical yield, 77%) as yellow needles: mp 220–224 °C dec (lit.[12] mp 221–225 °C); $[\alpha]^{22}_D$ −3.1° (*c* 1.0, H_2O) [lit.[12] $[\alpha]^{25}_D$ −3.2° (*c* 1, H_2O)]; ^1H NMR (D_2O, 200 MHz, ppm) 7.60 (d, 1 H, *J* = 3 Hz, C2-H), 7.23 (dd, 1 H, *J* = 9, 3 Hz, C6-H), 6.84 (d, 1 H, *J* = 9 Hz, C5-H), 4.24 (t, 1 H, *J* = 7 Hz, CH_2CHNH_2), 3.33 and 3.20 (two dd, 1 H each, *J* = 16, 7 Hz, $CHHCHNH_2$ and $CHHCHNH_2$), 2.51 (s, 3 H, CH_3); IR (KBr) ν_{max} 2965, 2645, 2498, 2046, 1744, 1643, 1586, 1518, 1495, 1446, 1420, 1364, 1324, 1305, 1251, 1210, 1192, 1147, 1134, 1057, 1022, 967, 930, 906, 829, 774, 759 cm^{-1}; EIMS, *m/e* (relative intensity) 223 (M^+, 1), 149 (23), 131 (9), 107 (2), 77 (2), 44 (base); CIMS (isobutane), *m/e* (relative intensity) 224 (M^+ + H, base); HRMS, *m/e* 223.0846 ($C_{11}H_{13}NO_4$ requires 223.0844).

L-3-(3-Acetyl-4-hydroxyphenyl)alanine Methyl Ester Hydrochloride (11). A steady stream of HCl gas was passed through a suspension of **10** (9.5 g, 43 mmol) in 100 mL of dry methanol until the solution reached saturation (ca. 0.5 h). After stirring at 25 °C for 1 h, the volatiles were removed in vacuo to afford a flaky, yellow solid (10.5 g, 90%). Recrystallization from MeOH–CH_2Cl_2 (1:4) afforded **11** (8.5 g, 11.6 g theoretical yield, 74%) as crystalline, yellow needles: mp 180–183 °C; $[\alpha]^{22}_D$ −3.3° (*c* 1.0, MeOH); ^1H NMR (D_2O, 200 MHz, ppm) 7.80 (d, 1 H, *J* = 3.4 Hz, C2-H), 7.45 (dd, 1 H, *J* = 9.3, 3.4 Hz, C6-H), 7.00 (d, 1 H, *J* = 9.3 Hz, C5-H), 4.42 (t, 1 H, *J* = 7 Hz, CH_2CHNH_2), 3.85 (s, 3 H, OCH_3), 3.35 and 3.22 (two dd, 1 H each, *J* = 16, 7 Hz, $CHHCHNH_2$ and $CHHCHNH_2$), 2.67 (s, 3 H, $ArCOCH_3$), IR (KBr) ν_{max} 3128, 2956, 2622, 2005, 1752, 1639, 1598, 1572, 1504, 1490, 1446, 1373, 1325, 1304, 1286, 1253, 1226, 1128, 1090, 1062, 1029, 969, 890, 849, 811, 763, 642 cm^{-1}; EIMS, *m/e* (relative intensity) 237 (M^+, 3), 178 (16), 150 (42), 149 (base), 131 (30), 107 (14), 88 (49), 82 (14), 77 (11); CIMS (isobutane), *m/e* (relative intensity) 238 (M^+ + H, base); HRMS, *m/e* 237.1006 ($C_{12}H_{15}NO_4$ requires 237.1001).

L-3-(3-Acetyl-4-hydroxyphenyl)-*N*-(benzyloxycarbonyl)alanine Methyl Ester (12). Amine hydrochloride **11** (5.46 g, 20.0 mmol) in a two-phase mixture of 100 mL of water and 80 mL of Et_2O at 25 °C was treated with sodium carbonate (6.40 g, 60.0 mmol, 3.0 equiv) and benzyl chloroformate (2.9 mL, 20 mmol, 1.0 equiv), and the resulting mixture was stirred for 3 h (25 °C). The ether layer was separated, washed with saturated aqueous NaCl, dried ($MgSO_4$), and concentrated in vacuo to afford a yellow oil. Short column chromatography (SiO_2, 2 × 10 cm, Et_2O) afforded **12** (6.68 g, 7.42 g theoretical yield, 90%) as a clear viscous oil which solidified on standing: mp 94–96 °C; $[\alpha]^{22}_D$ −4.9° (*c* 1.0, MeOH); ^1H NMR ($CDCl_3$, 470 MHz, ppm) 7.47 (d, 1 H, *J* = 2.2 Hz, C2-H), 7.28 (s, 5 H, Ph), 7.20 (dd, 1 H, *J* = 9.5, 2.2 Hz, C6-H), 6.91 (d, 1 H, *J* = 9.5 Hz, C5-H), 5.29 (br d, 1 H, *J* = 8 Hz, NH), 5.16 and 5.08 (two d, 1 H each, *J* = 12 Hz, PhC*H*HO and PhCH*H*O), 4.68 (q, 1 H, *J* = 8 Hz, CH_2CHNH), 3.76 (s, 3 H, OCH_3), 3.18 and 3.08 (two dd, 1 H each, *J* = 16, 8 Hz, C*H*HCHNH and CH*H*CHNH), 2.56 (s, 3 H, $ArCOCH_3$); IR (neat) ν_{max} 3342, 3034, 2954, 1723, 1644, 1619, 1589, 1525, 1488, 1438, 1360, 1324, 1300, 1254, 1287, 1059, 1025, 963, 911, 838, 808, 774, 756, 741, 699, 634 cm^{-1}; EIMS, *m/e* (relative intensity) 371 (M^+, 1), 220 (57), 176 (4), 150 (7), 149 (base), 131 (14), 107 (2), 92 (3), 91 (72), 77 (4); CIMS (isobutane), *m/e* 372 (M^+ + H, 48), 328 (base); HRMS, *m/e* 371.1349 ($C_{20}H_{21}NO_6$ requires 371.1369).

L-3-(3-Acetyl-4-(benzyloxy)phenyl)-*N*-(benzyloxycarbonyl)alanine Methyl Ester (13). A solution of the phenol **12** (0.896 g, 2.41 mmol) in dry *N,N*-dimethylformamide (10 mL) at 23 °C was treated with benzyl bromide (0.287 mL, 2.41 mmol, 1.0 equiv), potassium carbonate (0.666 g, 4.83 mmol, 2.0 equiv), and tetra-*n*-butylammonium iodide (89 mg, 0.242 mmol, 0.1 equiv), and the resulting reaction mixture was stirred at 23 °C (6 h). The reaction mixture was filtered and the filtrate was poured onto 10 mL of water and was extracted with EtOAc (3 × 15 mL). The combined organic extracts were washed with saturated aqueous NaCl and dried ($MgSO_4$), and the solvent was removed in vacuo. Flash chromatography (SiO_2, 3 × 20 cm, 30% EtOAc–hexane eluant) afforded **13** (1.04 g, 1.11 g theoretical yield, 93%) as a colorless oil which solidified on standing to give a white solid: mp 83–85 °C; $[\alpha]^{22}_D$ −3.1° (*c* 1.0, MeOH); ^1H NMR ($CDCl_3$, 200 MHz, ppm) 7.50 (d, 1 H, *J* = 2.4 Hz, C2-H), 7.40 (s, 5 H, Ph), 7.32 (s, 5 H, Ph), 7.17 (dd, 1 H, *J* = 8.6, 2.4 Hz, C4-H), 6.91 (d, 1 H, *J* = 8.6 Hz, C5-H), 5.22 (br d, 1 H, *J* = 8 Hz, NH), 5.12 (s, 2 H, $PhCH_2OAr$), 5.09 (s, 2 H, $PhCH_2O_2C$), 4.64 (q, 1 H, *J* = 8 Hz, CH_2CHNH), 3.74 (s, 3 H, OCH_3), 3.13 and 3.06 (two dd, 1 H each, *J* = 16, 8 Hz, C*H*HCHNH and CH*H*CHNH), 2.57 (s, 3 H, $ArCOCH_3$); IR (neat) ν_{max} 3334, 3064, 3034, 2952, 1958, 1723, 1674, 1608, 1577, 1498, 1455, 1420, 1381, 1356, 1295, 1245, 1218, 1156, 1060, 1022, 915, 848, 819, 801, 778, 741, 698 cm^{-1}; CIMS (isobutane), *m/e* (relative intensity) 462 (M^+ + H, 6), 419 (6), 418 (26), 402 (6), 372 (52), 329 (19), 328 (base), 312 (27), 220 (11); HRMS, *m/e* 462.1890 ($C_{27}H_{27}NO_6$ requires 462.1917). Chiral-phase HPLC analysis[19] revealed a 96:4 ratio of L/D-**13**; t_R 22 min/30 min, 2.0 mL/min, 10% 2-propanol–hexane.

L-3-(3-Acetyl-4-(benzyloxy)phenyl)-*N*-(benzyloxycarbonyl)-*N*-methylalanine Methyl Ester (14). A solution of carbamate **13** (6.36 g, 18.8 mmol) in 100 mL of THF/DMF (10:1) at 0 °C under N_2 was treated with methyl iodide (2.58 mL, 41.4 mmol, 3.0 equiv) and sodium hydride (50% oil dispersion, 0.662 g, 13.8 mmol, 1.0 equiv) and stirred at 0 °C (10 min). The reaction mixture was warmed at reflux (85 °C bath temperature, 20 h) under N_2. The cooled reaction solution was poured onto 10% aqueous HCl (100 mL) and the mixture was extracted with EtOAc (3 × 100 mL). The combined extracts were washed with saturated aqueous NaCl, dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (SiO_2, 5 × 20 cm, 30% EtOAc–hexane eluant) afforded **14** (6.35 g, 6.55 g theoretical yield, 97%) as a colorless, viscous oil: $[\alpha]^{22}_D$ −9.2° (*c* 1.0, MeOH); ^1H NMR ($CDCl_3$, 200 MHz, ppm), 7.50 (d, 1 H, *J* = 2.4 Hz, C2-H), 7.39 (s, 5 H, Ph), 7.29 (m, 5 H, Ph), 7.17 (dd, 1 H, *J* = 8.6, 2.4 Hz, C6-H), 6.91 (d, 1 H, *J* = 8.6 Hz, C5-H), 5.12 (s, 2 H, $PhCH_2OAr$), 5.09 (s, 2 H, $PhCH_2O_2C$), 4.64 (t, 1 H, *J* = 8 Hz, CH_2CHN), 3.74 (s, 3 H, OCH_3), 3.17 and 3.07 (two dd, 1 H each, *J* = 16, 8 Hz, C*H*HCHN and CH*H*CHN), 2.82 (s, 3 H, NCH_3), 2.57 (s, 3 H, $ArCOCH_3$) IR (neat) ν_{max} 3338, 3033, 2952, 1720, 1674, 1608, 1577, 1498, 1455, 1420, 1381, 1356, 1295, 1245, 1218, 1154, 1060, 1021, 915, 818, 740 cm^{-1}; CIMS (isobutane), *m/e* 476 (M^+ + H, 16), 432 (base); HRMS, *m/e* 476.2047 ($C_{28}H_{29}NO_6$ requires 476.2073). Chiral-phase HPLC analysis[19] revealed a 95:5 ratio of L/D-**14**; t_R 14 min/20 min, 2.0 mL/min, 10% 2-propanol–hexane.

(19) (a) Proton nuclear magnetic resonance spectra (^1H NMR) were recorded on a Varian FT-80, Varian XL-200, Nicolet NT-200, or Nicolet NT-470 spectrometer. Infrared spectra (IR) were recorded on a Perkin-Elmer 1710 Fourier transform spectrophotometer. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Electron-impact mass spectra (EIMS) and chemical ionization mass spectra (CIMS) were recorded on a Finnigan 4000 spectrometer. High-resolution mass spectra (HRMS) were recorded on a Kratos MS-50 spectrometer. Chiral-phase HPLC analysis was determined on a Gilson Model 320 dual pump chromatograph equipped with a ISCO V^4 variable wavelength absorbance detector (254 nm) employing a J. T. Baker Bakerbond DNBPG (covalent) chiral column. Flash chromatography[19b] was performed on silica gel 60 (240–400 mesh) and preparative centrifugal thin-layer chromatography (PCTLC)[19c] was performed on a Harrison Model 7924 chromatotron (Harrison Research, Palo Alto, CA) using Merck silica gel 60 PF_{254} containing $CaSO_4 \cdot {}^1/_2H_2O$ binder. Diethyl ether (Et_2O) and tetrahydrofuran (THF) were distilled from sodium benzophenone ketyl, methylene chloride (CH_2Cl_2) was distilled from P_2O_5, benzene was distilled from CaH_2, and methanol (MeOH) was distilled from magnesium prior to use. All extraction and chromatographic solvents (CH_2Cl_2, Et_2O, EtOAc, hexane) were distilled before use. L-Tyrosine was obtained from the Aldrich Chemical Company. All other reagents were used as received from commercial sources. (b) Still, W. C.; Khan, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923. (c) Stahl, E.; Müller, J. *Chromatographia* **1982**, *15*, 493.

L-*N*-(Benzyloxycarbonyl)-3-(3-hydroxy-4-(benzyloxy)-phenyl)alanine Methyl Ester (17). Sodium borohydride (324 mg, 8.64 mmol, 1.5 equiv) was added to a solution of ketone **13** (2.70 g, 5.87 mmol) in dry methanol (27 mL) at 10 °C, and the reaction mixture was stirred for 2 h (25 °C). The reaction mixture was poured onto 5% aqueous HCl and was extracted with CH_2Cl_2 (3 × 50 mL). The organic extracts were washed with saturated aqueous sodium chloride, dried ($MgSO_4$), and concentrated in vacuo to afford the alcohol **15** as a colorless oil which was used directly in the following reaction. For **15**: ^1H NMR ($CDCl_3$, 200 MHz, ppm) 7.85 (d, 1 H, J = 8 Hz, OH), 7.26 (br s, 10 H, two Ph), 6.80 (dd, 1 H, J = 8, 3 Hz, C6-H), 6.68 (d, 1 H, J = 8 Hz, C5-H), 6.62 (d, 1 H, J = 3 Hz, C2-H), 5.23 (br d, 1 H, J = 8 Hz, NH), 5.09 (s, 2 H, PhCH_2O), 5.06 (s, 2 H, PhCH_2O_2C), 4.92 (p, 1 H, J = 8 Hz, ArC(OH)HCH$_3$), 4.61 (q, 1 H, J = 8 Hz, CH$_2$CHNH), 3.73 (s, 3 H, OCH$_3$), 3.19 and 3.05 (two dd, 1 H each, J = 16, 8 Hz, CHHCHNH and CHHCHNH), 1.51 (d, 3 H, J = 8 Hz, ArCHCH_3).

A solution of alcohol **15** (2.72 g, 5.87 mmol) in 11.5 mL of THF was treated at 23 °C with 30% H_2O_2 (6.02 mL, 58.7 mmol, 10.0 equiv) and p-TsOH·H_2O (345 mg, 1.75 mmol, 30 mol %). The reaction mixture was stirred at 23 °C (24 h), diluted with half-saturated $NaHCO_3$ (10 mL), and extracted with Et_2O (3 × 15 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (SiO_2, 5 × 25 cm, 20% EtOAc–hexane eluant) afforded **17** (1.53 g, 2.55 g theoretical yield, 60%) as a colorless oil: $[\alpha]^{22}_D$ −15.1° (c 1.0, MeOH); ^1H NMR ($CDCl_3$, 200 MHz, ppm) 7.39 (br s, 5 H, Ph), 7.33 (br s, 5 H, Ph), 6.80 (d, 1 H, J = 8.2 Hz, C5-H), 6.69 (d, 1 H, J = 2 Hz, C2-H), 6.55 (dd, 1 H, J = 8.2, 2 Hz, C6-H), 5.62 (br s, 1 H, OH), 5.23 (br d, 1 H, J = 8 Hz, NH), 5.09 (s, 2 H, PhCH_2O), 5.06 (s, 2 H, PhCH_2O_2C), 4.61 (q, 1 H, J = 8 Hz, CH$_2$CHNH), 3.72 (s, 3 H, OCH$_3$), 3.18 and 3.09 (two dd, 1 H each, J = 16, 8 Hz, CHHCHNH and CHHCHNH); IR (neat) ν_{max} 3854, 3838, 3816, 3807, 3745, 3676, 3347, 2954, 1719, 1696, 1685, 1646, 1590, 1576, 1539, 1507, 1457, 1432, 1341, 1275, 1215, 1129, 1061, 739, 697 cm^{-1}; EIMS, m/e (relative intensity) 435 (M^+, 4), 303 (5), 284 (4), 213 (7), 158 (9), 156 (31), 141 (9), 139 (33), 111 (11), 91 (base); HRMS, m/e 436.1736 ($C_{25}H_{29}NO_6$ requires 436.1760). Chiral-phase HPLC analysis[19] revealed a 95:5 ratio of L/D-**17**; t_R = 18 min/28 min, 2.0 mL/min, 10% 2-propanol–hexane.

L-*N*-(Benzyloxycarbonyl)-3-(3-hydroxy-4-(benzyloxy)-phenyl)-*N*-methylalanine Methyl Ester (18). Sodium borohydride (20 mg, 0.51 mmol, 1.5 equiv) was added to a solution of the ketone **14** (164 mg, 0.34 mmol) in 1.5 mL of MeOH at 25 °C and the reaction mixture was stirred at 25 °C (1 h). The reaction mixture was poured onto 5% aqueous HCl and was extracted with CH_2Cl_2 (3 × 2 mL). The organic extracts were dried ($MgSO_4$) and concentrated in vacuo to afford alcohol **16** as a colorless oil which was used without purification. For **16**: ^1H NMR ($CDCl_3$, 200 MHz, ppm) 7.85 (d, 1 H, J = 8 Hz, OH), 7.26 (br s, 10 H, two Ph), 6.80 (dd, 1 H, J = 8, 3 Hz, C6-H), 6.68 (d, 1 H, J = 8 Hz, C5-H), 6.62 (d, 1 H, J = 3 Hz, C2-H), 5.09 (s, 2 H, PhCH_2O), 5.06 (s, 2 H, PhCH_2O_2C), 4.92 (p, 1 H, J = 8 Hz, ArC(OH)HCH$_3$), 4.61 (q, 1 H, J = 8 Hz, CH$_2$CHN), 3.73 (s, 3 H, OCH$_3$), 3.19 and 3.05 (two dd, 1H each, J = 16, 8 Hz, CHHCHN and CHHCHN), 2.82 (s, 3 H, NCH$_3$), 1.51 (d, 3 H, J = 8 Hz, ArCHCH_3).

A solution of alcohol **16** (154 mg, 0.32 mmol) in 1 mL of THF at 23 °C was treated with 30% H_2O_2 (0.33 mL, 3.2 mmol, 10 equiv) and p-TsOH·H_2O (19 mg, 0.10 mmol, 30 mol %). The reaction mixture was stirred at 23 °C (24 h), diluted with half-saturated $NaHCO_3$ (0.5 mL), and extracted with Et_2O (3 × 1 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (SiO_2, 1 × 25 cm, 20% EtOAc–hexane eluant) afforded **18** (88 mg, 143 mg theoretical yield, 61%) as a colorless oil: $[\alpha]^{22}_D$ −7.0° (c 1.0, MeOH); ^1H NMR ($CDCl_3$, 200 MHz, ppm) 7.39 (br s, 5 H, Ph), 7.33 (br s, 5 H, Ph), 6.80 (d, J = 8.2 Hz, C5-H), 6.69 (d, 1 H, J = 2 Hz, C2-H), 6.55 (dd, 1 H, J = 8.2, 2 Hz, C6-H), 5.62 (br s, 1 H, OH), 5.09 (s, 2 H, PhCH_2O), 5.06 (s, 2 H, PhCH_2O_2C), 4.61 (t, 1 H, J = 8 Hz, CH$_2$CHN), 3.72 (s, 3 H, OCH$_3$), 3.17 and 3.07 (two dd, 1 H each, J = 16, 8 Hz, CHHCHN and CHHCHN), 2.82 (s, 3 H, NCH$_3$); IR (neat) ν_{max} 3372, 3065, 3033, 2592, 1741, 1703, 1592, 1511, 1455, 1403, 1382, 1320, 1274, 1217, 1130, 1011, 914, 855, 795, 766, 740, 699 cm^{-1}; CIMS (isobutane), m/e 450 (M^+ + H, base), 406 (M^+ + H − CO_2, 81); HRMS, m/e 449.1839 ($C_{26}H_{27}NO_6$ requires 449.1838). Chiral-phase HPLC analysis[19] revealed a 95:5 ratio of L/D-**18**; t_R 16 min/25 min, 2.0 mL/min, 10% 2-propanol–hexane.

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Registry No. **1**, 64755-14-2; **2**, 64725-24-2; **3**, 106283-67-4; **4**, 106235-26-1; **5**, 70840-66-3; **6**, 86849-13-0; **7**, 86229-97-2; **8**, 70840-66-3; **9**, 83858-82-6; **10**, 32404-28-7; **11**, 57085-32-2; **12**, 110774-03-3; **13**, 105205-69-4; **14**, 110774-04-4; **15**, 105205-68-3; **16**, 110774-05-5; **17**, 105229-41-2; **18**, 110774-06-6; H-Tyr-OH, 60-18-4; AcCl, 75-36-5; PhCH$_2$OCOCl, 501-53-1; PhCH$_2$Br, 100-39-0.

Angoluvarin, an Antimicrobial Dihydrochalcone from *Uvaria angolensis*

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The genus *Uvaria* is a member of the plant family Annonaceae and has been a rich and varied source of new natural products, several of which have interesting biological activity.[1] *Uvaria angolensis* has previously yielded dihydrochalcones, flavanones, and benzylated indole alkaloids.[2] An investigation of another active column fraction[2a] has resulted in the isolation of an antimicrobially active dihydrochalcone for which the name angoluvarian has been chosen. It represents the most complex of the active dihydrochalcones yet isolated.

Angoluvarin (**1**) has molecular formula $C_{30}H_{28}O_6$ as determined by mass spectroscopy and combustion analysis. The 60-MHz ^1H NMR (acetone-d_6) data showed the characteristic A_2B_2 pattern for dihydrochalcones, five aromatic protons as a broad singlet (δ 7.20), one aromatic proton at δ 6.15 as a singlet, seven additional aromatic protons as a complex multiplet (δ 6.5–7.1), seven protons as a broad singlet at δ 3.80 (1 OCH$_3$ and 2 ArCH$_2$Ar), and four D_2O exchangeable signals at δ 14.70, 4.80 (2 H), and 4.50. The low resolution mass spectrum shows a fragment ion peak at m/z 379 (M^+ − 105), consistent for an unsubstituted B ring. These data suggest that angoluvarian (**1**) is a dibenzylated dihydrochalcone methyl ether. The 15-MHz ^{13}C NMR (acetone-d_6) data further support this conclusion with key signals located at δ 56.0 (q), 46.3 (t), 35.4 (t), 31.5 (t), 22.9 (t). The signal resonating at δ 35.4 (t) seems characteristic of the C-30 benzylic carbon of uvarinol, a tribenzylated flavanone previously isolated from *Uvaria chamae*.[3] The upfield signals at δ_C 92.1 (d) and δ_H 6.15 (1 H, s) suggest that they must be located ortho to a methoxyl group and therefore angoluvarin is benzylated at C-3′ and not C-5′. On the basis of previous

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