Concise and Efficient Synthesis of Bioactive Natural Products Pegamine, Deoxyvasicinone, and (−)-Vasicinone†

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Large numbers of quinazolinone alkaloids have been isolated from a number of plants, animals, and microorganisms and synthesized in view of their well-established pharmacological activities.[1] Development of new elegant synthetic strategies to these bioactive quinazolinone alkaloids and their precursors is a challenging task of current interest.[2] Pegamine [2-(3-hydroxypropyl)-quinazolin-4(1*H*)-one, **7a**], deoxyvasicinone [2,3-dihydropyrrolo[2,1-*b*]quinazolin-9(1*H*)-one, **1a**], and (−)-vasicinone [2,3-dihydro-3(*S*)-hydroxypyrrolo[2,1-*b*]quinazolin-9(1*H*)-one, **1b**] have been isolated as bioactive natural products. Pegamine (**7a**) has been isolated from *Peganum harmala* and exhibits cytotoxic activity.[3] Deoxyvasicinone (**1a**) and (−)-vasicinone (**1b**) have been isolated from aerial parts of an evergreen subherbaceous bush *Adhatoda vasica*.[4] Deoxyvasicinone (**1a**) possesses antimicrobial, antiinflammatory, and antidepressant acitivities.[5] Several synthetic routes to deoxyvasicinone (**1a**) are known in the literature.[6] (−)-Vasicinone (**1b**) exhibits antitumor,[7] bronchodilating,[8] hypotensive,[8] anthelmintic,[9] and antianaphylactic[10] activities. It is used in *The Indian Ayurvedic System of Medicine* as a remedy for cold, cough, bronchitis, rheumatism, phthisis, and asthma.[4,11] Very recently, Joshi and co-workers[12,13] reversed the previously assigned[14] 3(R)-configuration of **1b** on the basis of X-ray crystallographic analysis[12a] and by using the Mosher ester analysis method.[12b] Three synthetic routes to vasicinone are known; (±)-vasicinone has been obtained from deoxyvasicinone via NBS-bromination,[15] while (−)-vasicinone has been synthesized[16] from deoxyvasicinone via asymmetric oxidation using (1*R*)-(−)-(10-camphorsulfonyl)oxaziridine with 62% enantiomeric excess (ee). (±)-Vasicinone and (−)-vasicinone have been also synthesized[16] by coupling *o*-azidobenzoyl chloride with O-protected 3-hydroxy γ-lactam and 3(*S*)-hydroxy γ-lactam (derived from L-aspartic acid in six steps),[17] respectively, via the tandem Staudinger/intramolecular aza-Wittig reaction. Recently, Kamal et al. have reported[18] an efficient enzymatic resolution of (±)-vasicinone and its acetyl derivative. For the past several years, we have been using cyclic anhydrides and imides as potential starting materials for the synthesis of structurally interesting and biologically important heterocycles[19] and bioactive natural products.[20] We reasoned and planned to use succinic anhydride (**3a**) for the synthesis of pegamine (**7a**) and deoxyvasicinone (**1a**) and (*S*)-acetoxysuccinic anhydride (**3b**) for the synthesis of (−)-vasicinone (**1b**), and we herein report a new, concise, and convenient synthetic route to these natural products (Scheme 1).

The reaction of anthranilamide (**2**) with succinic anhydride (**3a**) furnished the *o*-amidosuccinanilic acid (**4a**) in quantitative yield, while it reacted in a 100% regioselective[21] fashion with (*S*)-acetoxysuccinic anhydride (**3b**)[22]

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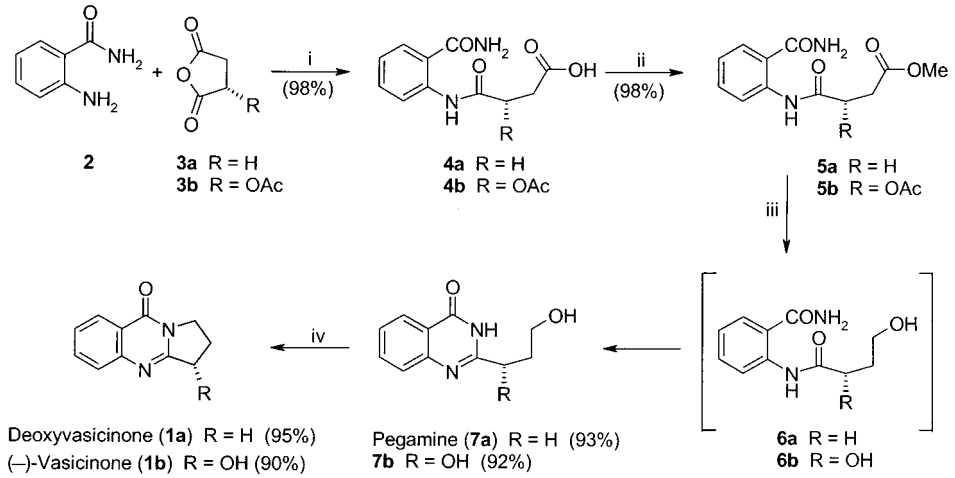
Scheme 1[a]



[a] Key: (i) Et_2O/C_6H_6/1,4-dioxane (2:2:1), room temperature, 2 h; (ii) CH_2N_2, Et_2O, room temperature, 1 h; (iii) LAH, THF, 90 min, aqueous workup; (iv) DEAD, PPh_3, THF, room temperature, 1 h.

at the more reactive electron-deficient carbonyl to yield the ring-opened product *β* (*S*)-acetoxy-*o*-amidosuccinanilic acid (**4b**) in quantitative yield; such a regioselectivity on **3b** with carbon, nitrogen, and oxygen nucleophiles is known.[21] The reaction of succinanilic acids **4a**,**b** with diazomethane in ether at room temperature furnished the corresponding esters **5a**,**b** in quantitative yields, respectively. The esters **5a**,**b** on chemoselective reduction with 2 equiv of LAH in THF at room temperature formed the reduced intermediate compounds **6a**,**b**, which during the aqueous workup underwent a smooth in situ LiOH-catalyzed[23] dehydrative ring closure to yield quinazolinone derivatives **7a**,**b** in 93% and 92% yields, respectively, completing the first synthesis of bioactive natural product pegamine (**7a**) in three steps with 89% overall yield. The analytical and spectral data obtained for **7a** were in complete agreement with reported data.[3] It may also be possible to obtain compounds **6a**,**b** or **7a**,**b** directly from the reaction of anthranilamide (**2**) with *γ*-lactone and (*S*)-hydroxy *γ*-lactone. We feel that readily available cyclic anhydrides **3a**,**b** are better starting materials as these lactone preparations require a number of steps; nucleophilic ring opening using primary aromatic amines is relatively more easy with cyclic anhydrides than lactones, and these lactones have well-proven tenacities for polymerization reactions. The reaction of pegamine (**7a**) with DEAD-TPP reagent gave the deoxyvasicinone (**1a**) in 95% yield, completing the four step synthesis of **1a** with 85% overall yield. The (*S*)-hydroxypegamine (**7b**) on treatment with DEAD-TPP reagent in THF at room temperature underwent a selective facile intramolecular Mitsunobu ring-closure reaction[24] with primary alcohol to furnish the desired naturally occurring linear tricyclic system (−)-vasicinone (**1b**) in 90% yield. The overall yield of (−)-vasicinone (**1b**) in four steps was 80%, and the analytical and spectral data obtained for **1b** were in complete agreement with reported data.[12,13,16,18] The specific rotation of **1b** and ^{1}H NMR spectra of MTPA-ester[25] of **1b** revealed that it possesses 97−98% ee. Our synthesis with a chiral pool directly proves that naturally occurring (−)-vasicinone (**1b**) has the (S)-configuration. The conversion of deoxyvasicinone (**1a**) to bioactive natural products (−)-vasicinone (**1b**),[16] rutecarpine,[26] and isaindigotone,[27] and the conversion of vasicinone to luotonin A[28] and luotonin B[29] are known.

In summary, we have demonstrated a most concise, efficient, and practical total synthesis of naturally occurring bioactive quinazolinone alkaloids pegamine (**7a**), deoxyvasicinone (**1a**), and (−)-vasicinone (**1b**), for the first time starting from succinic anhydride (**3a**) and (*S*)-acetoxysuccinic anhydride (**3b**). The present approach also provides a new general method for designing several quinazolinone derivatives using a variety of cyclic anhydrides for structure activity relationship studies.

Experimental Section

Melting points are uncorrected. Column chromatographic separations were carried out on ACME silica gel (60−120 mesh). Anthranilamide, (*S*)-malic acid, lithium aluminum hydride (LAH), triphenylphosphine (TPP), and diethyl azodicarboxylate (DEAD) were obtained from Aldrich Chemical Co.

2(*S*)-Acetoxysuccinic Anhydride (3b). A mixture of (*S*)-malic acid (8.04 g, 60 mmol) and freshly distilled acetyl chloride (60 mL) was heated to 40 °C with stirring for 2 h. An excess of acetyl chloride and acetic acid/acetic anhydride formed were distilled off in vacuo. The obtained solid residue was used for the next step without any further purification. The analytically pure sample was obtained by recrystallization from benzene. **3b**: 9.28 g (98% yield); mp 56 °C (lit.[22] 55 °C); $[\alpha]^{20}_D = -26.4$ (*c* 5.0, $CHCl_3$) [lit.[22] −26.0 (*c* 5.0, $CHCl_3$)]; ^{1}H NMR ($CDCl_3$, 200 MHz) *δ* 2.20 (s, 3H), 3.04 (dd, *J* = 18 and 8 Hz, 1H), 3.40 (dd, *J* = 20 and 8 Hz, 1H), 5.55 (dd, *J* = 8 and 6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) *δ* 20.0, 34.8, 67.7, 167.0, 168.3, 170.0. MS (*m*/*e*) 158, 131, 116, 104, 99, 88, 70, 55. IR (Nujol) ν_{max} 1877, 1796, 1749, 1738 cm^{-1}. Anal. Calcd for $C_6H_6O_5$: C, 45.58; H, 3.83. Found: C, 45.69; H, 3.99.

***β* (*S*)-Acetoxy-*o*-amidosuccinanilic Acid (4b).** To a solution of **3b** (7.90 g, 50 mmol) in ether (50 mL) was added a

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solution of anthranilamide (**2**, 6.80 g, 50 mmol) in benzene-1,4-dioxane mixture (75 mL, 2:1) in a dropwise fashion with constant stirring at room temperature. The reaction mixture was further stirred for 2 h, and the formed precipitate was filtered under vacuum and washed with ether (50 mL). The obtained compound **4b** was used for the next step without any further purification. Analytically pure **4b** was obtained by recrystallization from ethyl acetate. **4b**: 14.4 g (98% yield); mp 152−153 °C; $[\alpha]^{20}_D = -88.7$ (*c* 0.6, acetone); ^{1}H NMR (CD_3OD, 200 MHz) δ 2.26 (s, 3H), 2.92 (d, $J = 6$ Hz, 1H), 2.95 (d, $J = 2$ Hz, 1H), 5.53 (dd, $J = 8$ and 4 Hz, 1H), 7.16 (t, $J = 8$ Hz, 1H), 7.49 (t, $J = 8$ Hz, 1H), 7.76 (d, $J = 8$ Hz, 1H), 8.51 (d, $J = 8$ Hz, 1H); ^{13}C NMR (CD_3OD, 75 MHz) δ 20.9, 37.5, 71.8, 121.7, 122.0, 124.7, 129.5, 133.6, 139.8, 169.8, 171.6, 173.0, 173.3. MS (*m*/*e*) 294, 277, 259, 235, 216, 198, 163, 146, 136, 119, 92, 71, 65. IR (Nujol) ν_{max} 3445, 3396, 3336, 3188, 1747, 1693, 1666, 1660 cm^{-1}. Anal. Calcd for $C_{13}H_{14}N_2O_6$: C, 53.06; H, 4.80; N, 9.52. Found: C, 53.13; H, 4.71; N, 9.74.

Similarly, the reaction of succinic anhydride (**3a**) with anthranilamide (**2**) furnished *o*-amidosuccinanilic acid (**4a**): 98% yield; mp 197−198 °C (MeOH); ^{1}H NMR (CD_3OD, 200 MHz) δ 2.68 (s, 4H), 7.13 (t, $J = 8$ Hz, 1H), 7.47 (t, $J = 8$ Hz, 1H), 7.73 (d, $J = 8$ Hz, 1H), 8.37 (d, $J = 8$ Hz, 1H); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 28.9, 32.2, 119.7, 120.2, 122.3, 128.5, 132.1, 139.6, 169.9, 170.8, 173.5. MS (*m*/*e*) 236, 218, 202, 174, 146, 136, 119, 107, 101, 90, 73, 65, 55. IR (Nujol) ν_{max} 3414, 3346, 3242, 3217, 3165, 1709, 1680, 1659, 1616 cm^{-1}. Anal. Calcd for $C_{11}H_{12}N_2O_4$: C, 55.93; H, 5.12; N, 11.86. Found: C, 56.21; H, 5.29; N, 12.01.

Methyl β (*S*)-Acetoxy-*o*-amidosuccinanilate (5b). To a solution of diazomethane in ether (50 mL) was added acid **4b** (5.0 g, 17 mmol) at 0 °C, and the reaction mixture was further stirred at room temperature until the starting acid was completely consumed (1 h). An excess of diazomethane was quenched with acetic acid, and the organic layer was washed with water, brine, and dried over Na_2SO_4. The organic layer was concentrated in vacuo followed by silica gel column chromatographic purification of the residue using a petroleum ether and ethyl acetate mixture (3:1) to give pure **5b**: 5.13 g (98% yield); mp 80−82 °C (C_6H_6); $[\alpha]^{20}_D = -65.7$ (*c* 1.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.30 (s, 3H), 2.90−3.10 (m, 2H), 3.71 (s, 3H), 5.68 (dd, $J = 9$ and 6 Hz, 1H), 5.57−6.00 (bs, 1H), 6.00−6.50 (bs, 1H), 7.11 (t, $J = 6$ Hz, 1H), 7.50 (t, $J = 9$ Hz, 1H), 7.55 (d, $J = 9$ Hz, 1H), 8.64 (d, $J = 9$ Hz, 1H), 11.94 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 20.7, 36.4, 51.9, 70.0, 119.0, 121.0, 123.2, 127.5, 133.0, 138.9, 167.6, 169.9, 170.1, 171.1. MS (*m*/*e*) 277, 180, 147, 131, 107, 93, 81, 59. IR (Nujol) ν_{max} 3448, 3340, 1740, 1737, 1662 cm^{-1}. Anal. Calcd for $C_{14}H_{16}N_2O_6$: C, 54.54; H, 5.23; N, 9.09. Found: C, 54.33; H, 5.09; N, 9.14.

Similarly, **4a** furnished **5a**: 98% yield; mp 133−135 °C (C_6H_6); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.75 (s, 4H), 3.71 (s, 3H), 5.50−6.00 (bs, 1H), 6.00−6.50 (bs, 1H), 7.08 (t, $J = 8$ Hz, 1H), 7.40−7.60 (m, 2H), 8.61 (d, $J = 10$ Hz, 1H), 11.25 (bs, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 29.1, 32.6, 51.8, 118.8, 121.6, 122.6, 127.4, 133.1, 140.0, 170.2, 171.4, 173.1. MS (*m*/*e*) 250, 219, 202, 174, 146, 136, 119, 100, 92, 72, 55. IR (Nujol) ν_{max} 3358−3192, 1745, 1682, 1666 cm^{-1}. Anal. Calcd for $C_{12}H_{14}N_2O_4$: C, 57.59; H, 5.64; N, 11.19. Found: C, 57.49; H, 5.60; N, 11.32.

2-[1(*S*),3-Dihydroxypropyl]quinazolin-4(1*H*)-one (7b). To the slurry of LAH (0.76 g, 20 mmol) in THF (20 mL) was added a solution of ester **5b** (3.08 g, 10 mmol) in THF (30 mL) in a dropwise fashion at 0−5 °C over a period of 30 min with continuous stirring. The reaction mixture was further stirred at room temperature for 1 h. The reaction was slowly quenched with water (25 mL) and further stirred for 1 h at room temperature. Saturated NH_4Cl solution (10 mL) was added to the reaction mixture, and then it was completely concentrated under vacuum and dried to the pump. The residue was stirred with THF (75 mL) for 1 h, and the organic layer was filtered through Celite, dried over Na_2SO_4, and concentrated in vacuo. The obtained crude product was purified by silica gel column chromatography using a mixture of ethyl acetate and methanol (99:1) to furnish pegamine derivative **7b**: 2.03 g (92% yield); mp 134−136 °C (ethyl acetate); $[\alpha]^{20}_D = -22.6$ (*c* 1.0, MeOH); ^{1}H NMR (CD_3OD, 200 MHz) δ 1.85−2.25 (m, 2H), 3.78 (t, $J = 6$ Hz, 2H), 4.65−4.85 (m, 1H), 7.49 (t, $J = 8$ Hz, 1H), 7.66 (d, $J = 8$ Hz, 1H), 7.79 (t, $J = 8$ Hz, 1H), 8.18 (d, $J = 8$ Hz, 1H); ^{13}C NMR (CD_3OD, 75 MHz) δ 39.5, 59.4, 70.1, 122.2, 127.2, 127.4, 127.8, 135.9, 149.5, 160.9, 164.3. MS (*m*/*e*) 220, 198, 170, 158, 132, 107, 81, 57. IR (Nujol) ν_{max} 3373, 3276, 3119, 1683, 1613 cm^{-1}. Anal. Calcd for $C_{11}H_{12}N_2O_3$: C, 60.00; H, 5.49; N, 12.72. Found: C, 59.78; H, 5.29; N, 12.83.

Similarly, **5a** gave pegamine (**7a**): 93% yield; mp 163−165 °C (ethyl acetate) (lit.[3b] 160−161 °C); ^{1}H NMR (CD_3OD, 200 MHz) δ 2.00 (quintet, $J = 6$ Hz, 2H), 2.77 (t, $J = 8$ Hz, 2H), 3.66 (t, $J = 6$ Hz, 2H), 7.48 (t, $J = 8$ Hz, 1H), 7.63 (d, $J = 8$ Hz, 1H), 7.79 (t, $J = 8$ Hz, 1H), 8.17 (d, $J = 8$ Hz, 1H); ^{13}C NMR (CD_3OD, 50 MHz) δ 31.3, 33.0, 62.1, 121.8, 127.1, 127.3, 127.4, 127.6, 135.9, 150.0, 159.3. MS (*m*/*e*) 204, 187, 173, 160, 132, 119, 90, 77, 63. IR (Nujol) ν_{max} 3395, 3319, 3173, 3123, 3038, 1695, 1682 cm^{-1}. Anal. Calcd for $C_{11}H_{12}N_2O_2$: C, 64.70; H, 5.92; N, 13.72. Found: C, 64.93; H, 6.11; N, 14.00.

2,3-Dihydro-3(*S*)-hydroxypyrrolo[2,1-*b*]quinazolin-9(1*H*)-one [(−)-Vasicinone, 1b]. To the solution of **7b** (0.55 g, 2.50 mmol) and TPP (0.85 g, 3.25 mmol) in THF (7 mL) was added a solution of DEAD (0.48 g, 2.75 mmol) in THF (5 mL) in a dropwise fashion with continuous stirring at room temperature, and the reaction mixture was further stirred for 1 h. The reaction mixture was concentrated in vacuo, and the residue was chromatographed on silica gel using petroleum ether and ethyl acetate (1:1) to obtain (−)-vasicinone (**1b**): 0.455 g (90% yield); mp 205−207 °C (EtOH) (lit.[18] 200−201 °C); $[\alpha]^{20}_D = -105.6$ (*c* 1.0, $CHCl_3$) [lit.[18] −105.0 (*c* 1.0, $CHCl_3$)]; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.20−2.45 (m, 1H), 2.60−2.80 (m, 1H), 3.90−4.15 (m, 1H), 4.30−4.50 (m, 1H), 5.27 (t, $J = 6$ Hz, 1H), 7.40−7.60 (m, 1H), 7.65−7.85 (m, 2H), 8.31 (d, $J = 6$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 29.4, 43.5, 72.0, 121.1, 126.7, 126.8, 126.9, 134.4, 148.6, 160.1, 160.6. MS (*m*/*e*) 202, 185, 174, 146, 130, 119, 102, 90, 76, 63, 55. IR (Nujol) ν_{max} 3169, 1683, 1635, 1463 cm^{-1}. Anal. Calcd for $C_{11}H_{10}N_2O_2$: C, 65.34; H, 4.99; N, 13.85. Found: C, 65.24; H, 5.07; N, 13.87.

Similarly, the reaction of **7a** furnished deoxyvasicinone (**1a**): 95% yield; mp 106−108 °C (C_6H_6) (lit.[18] 104−106 °C); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.30 (quintet, $J = 8$ Hz, 2H), 3.19 (t, $J = 8$ Hz, 2H), 4.22 (t, $J = 8$ Hz, 2H), 7.46 (t, $J = 8$ Hz, 1H), 7.55−7.85 (m, 2H), 8.29 (d, $J = 8$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 19.3, 32.3, 46.3, 120.3, 126.0, 126.2, 126.6, 133.9, 149.0, 159.3, 160.7. MS (*m*/*e*) 185, 167, 160, 144, 130, 116, 102, 90, 76, 63. IR (Nujol) ν_{max} 1674, 1620 cm^{-1}. Anal. Calcd for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41; N, 15.04. Found: C, 71.01; H, 5.45; N, 15.14.

MTPA-ester of (±)-Vasicinone. To a solution of (±)-vasicinone (10 mg, 0.05 mmol) and pyridine (0.1 mL) in DCM (1 mL) was added (*S*)-MTPA-Cl solution in DCM (0.08 M, 1 mL), and the reaction mixture was refluxed for 15 h. The reaction mixture was concentrated in vacuo, and the residue was dissolved in diethyl ether (15 mL). The organic layer was washed with $CuSO_4$ solution, water, aqueous bicarbonate, water, and brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo furnished the product as a thick oil (16 mg). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.15−2.55 (m, 2H), 2.60−2.90 (m, 2H), 3.57 (s, 3H), 3.66 (s, 3H), 4.00−4.50 (m, 4H), 6.30−6.55 (m, 2H), 7.20−7.90 (m, 16H), 8.31 (d, $J = 8$ Hz, 2H). MS (*m*/*e*) 418, 388, 359, 201, 189, 184, 119, 105, 91, 77. Anal. Calcd for $C_{21}H_{17}F_3N_2O_4$: C, 60.29; H, 4.09; N, 6.70. Found: C, 60.33; H, 3.97; N, 6.91.

Similarly, the MTPA-ester of (−)-vasicinone (**1b**) was prepared: mp 172−174 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.43 (m, 1H), 2.75 (m, 1H), 3.57 (s, 2.955H), 3.65 (s, 0.045H), 4.22 (m, 1H), 4.30 (m, 1H), 6.37 (m, 0.985H), 6.43 (m, 0.015H), 7.35−7.80 (m, 8H), 8.30 (d, $J = 10$ Hz, 1H). MS (*m*/*e*) 418, 388, 359, 201, 189, 184, 119, 105, 91, 77. Anal. Calcd for $C_{21}H_{17}F_3N_2O_4$: C, 60.29; H, 4.09; N, 6.70. Found: C, 60.12; H, 4.17; N, 6.77.

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Supporting Information Available: ^{1}H NMR spectra of **1**, **4**, **5**, **7**, and MTPA esters of (±)-vasicinone and (−)-**1b**; ^{13}C NMR spectra of **1**, **4b**, **5b**, and **7**; and mass spectra of **1**, **4b**, **5**, and **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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