A Highly Concise Synthesis of Lavendamycin Methyl Ester

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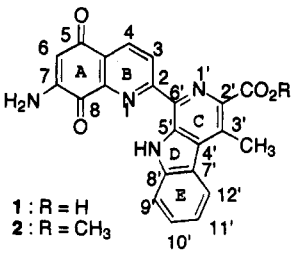
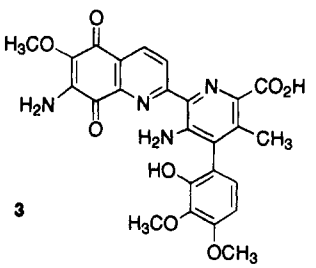
Lavendamycin methyl ester (2), an antitumor antibiotic, was synthesized by a practical and short route in an excellent overall yield of 33% from known starting materials. Pictet–Spengler condensation of 7-acetamido-2-formylquinoline-5,8-dione (4) with the methyl ester of (2*RS*,3*SR*)-β-methyltryptophan (5) followed by hydrolysis afforded 2. Aldehyde 4 was prepared by the oxidation of 7-acetamido-2-methylquinoline-5,8-dione (9). Dione 9 was obtained via the Diels–Alder condensation of the novel 1-[(*tert*-butyldimethylsilyl)oxy]-2-methyl-1-aza-1,3-butadiene (7) with 2-acetamido-6-bromobenzene-1,4-dione (8).

Lavendamycin (1), an antitumor antibiotic, was isolated from the fermentation broth of *Streptomyces lavendulae* by Doyle and co-workers in 1981.[1] In structure as well as in bioassays, lavendamycin was similar to streptonigrin (3), another potent antitumor antibiotic.[2-6] The first total synthesis of lavendamycin methyl ester (2) was reported by Kende and Ebetino in 1984.[7] They accomplished the





synthesis of 2 through a Bischler–Napieralski condensation of a substituted quinaldic acid with β-methyltryptophan methyl ester followed by cyclization and functionalization of the A ring. Boger and co-workers[8] have synthesized 2 by a Friedlander condensation of a functionalized amino aldehyde with a β-carboline followed by other transformations. Formal syntheses of 2 have also been reported by Hibino[9] and Rao.[10,11] Hibino has also reported the synthesis of demethyllavendamycin methyl ester in 1983.[12]

We now wish to report a practical five-step regioselective synthesis of lavendamycin methyl ester which proceeds with an overall yield of 33% from the known starting materials 5[13] and 8.[14] This synthesis is much more concise and practical than the two groundbreaking reported syntheses of Kende[7] and Boger.[8] Our approach is based on the Pictet–Spengler condensation of an aldehyde possessing the AB ring functionalities of lavendamycin (Scheme I). Thus, condensation of 7-acetamido-2-formylquinoline-5,8-dione (4) with the methyl ester of (2*RS*,3*SR*)-β-methyltryptophan (5)[13] in refluxing dry xylene for 23 h gave orange crystals of 7-*N*-acetyllavendamycin methyl ester (6) in 79% yield. Hydrolysis of 6 in a 70% mixture of H_2SO_4–H_2O at 60 °C for 4 h quantitatively gave the dark red crystals of lavendamycin methyl ester (2). Surprisingly, under these severe conditions the C-7 acetamido group was selectively and cleanly hydrolyzed without affecting the C-2′ ester residue.[15] Aldehyde 4 was obtained in 91% yield by the selenium dioxide oxidation of 9 in refluxing dioxane–H_2O for 9 h. 7-*N*-Acetyl-2-methylquinoline-5,8-dione (9) was prepared in 66% yield by the Diels–Alder condensation of the novel 1-azadiene 7 with bromoquinone 8[14] in refluxing chlorobenzene. Azadiene 7 was prepared in 71% yield by the treatment of *o*-(*tert*-butyldimethylsilyl)hydroxylamine (10) with methyl vinyl ketone (11) in dichloromethane at room temperature for 48 h in the presence of molecular sieves.

A distinct difference between our approach and those of the previous investigators is the construction of the quinolinedione AB-ring system with the protected C-7 NH_2 group prior to the CDE ring formation. The advantage of this strategy is that all of the intermediates involved are stable and are obtained reproducibly in high yields. In contrast, a serious drawback of the previous methods[7-11] is that all involve the unstable and highly reactive intermediates bromo- and azidoquinolinediones ediones 12 and 13.[7,8,16]

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(13) β-Methyltryptophan methyl ester (5) was prepared in an overall yield of 71% according to the procedure described in Behforouz, M.; Zarrinmayeh, H.; Ogle, M. E.; Riehle, T. J.; Bell, F. W. *J. Heterocycl. Chem.* **1988**, *25*, 1627.

(14) 2-Acetamido-2-bromobenzoquinone (8) was prepared in an overall yield of 50% following the procedure described in (a) Kelly, T. R.; Echavarren, A.; Behforouz, M. *J. Org. Chem.* **1983**, *48*, 3849. (b) Kelly, T. R.; Behforouz, M.; Echavarren, A.; Vaya, J. *Tetrahedron Lett.* **1983**, 2331.

(15) Initial attempts to hydrolyze 6 to 2 in methanol or THF using bases such as Na_2CO_3, NaOH, and tetraethylammonium hydroxide or acids such as hydrochloric or sulfuric were unsuccessful.

(16) Our own work on the chemistry of some bromolavendamycin analogs and their intermediates also shows that these compounds are highly unstable and result in complex mixtures and low product yields.

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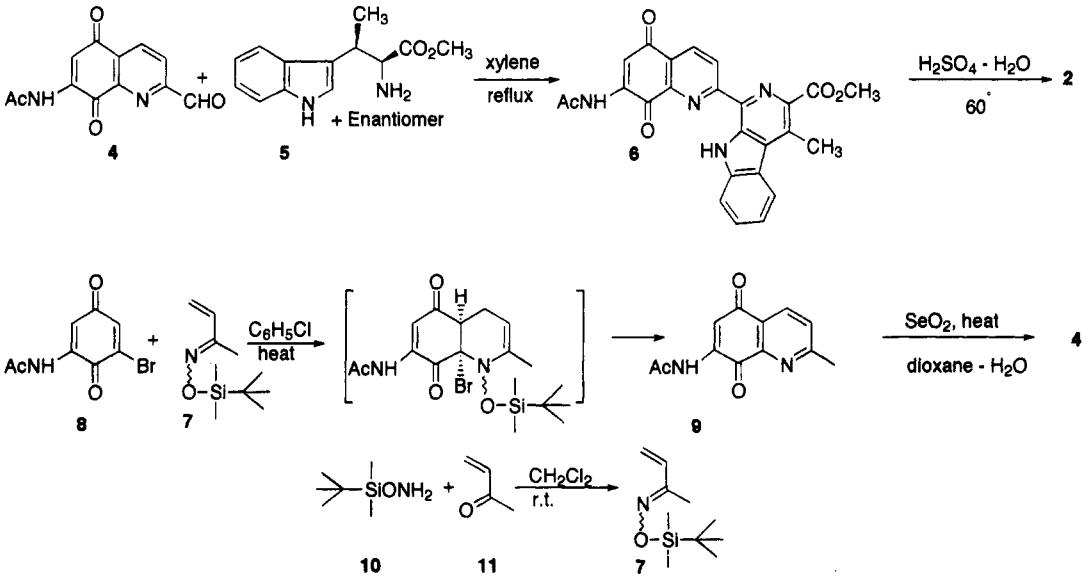
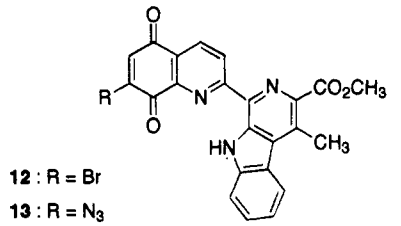
Scheme I



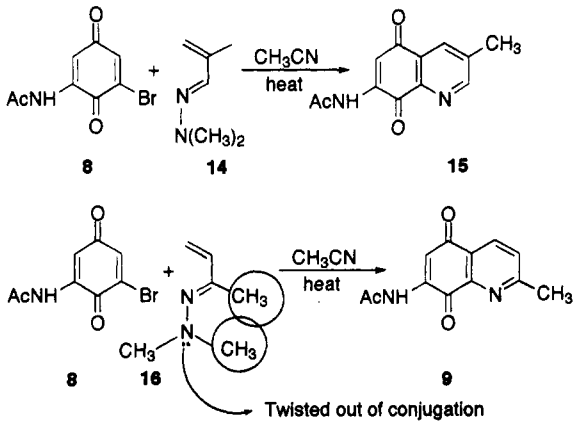


Another unique feature of this route is the application of a novel intermolecular Diels–Alder condensation of a siloxy-activated 1-azadiene in the synthesis of a key intermediate such as quinolinedione **9**.

1-Azadienes are known to be electron poor and consequently unreactive toward dienophiles.[17,18] It has been reported that placement of an electron-releasing group such as a nitrogen atom at position 1 of 1-azadienes increases their reactivity in the Diels–Alder condensations and gives fair to good yields of adducts.[18] Our original choice of such an activated azadiene for the Diels–Alder preparation of **9** was the known diene **16**, the dimethylhydrazone of methyl vinyl ketone.[19]

Although the condensation of methacrolein hydrazone[20] (**14**) with 2-acetamido-6-bromobenzene-1,4-dione (**8**) in acetonitrile (120 °C, sealed) gave a 64% yield of the aromatized adduct **15**,[21] the Diels–Alder condensation of azadiene **16** with quinone **8** failed to produce **9** (Scheme II). It appears that the interference of the methyl groups on N and C-2 prevents the nitrogen nonbonding electrons from activating the azadiene system and consequently hinders the Diels–Alder reaction.[18b]

Scheme II



Based on the above facts, it was anticipated that an azadiene possessing a silyloxy group on N-1 (**7**) would be free of steric hindrance and activated toward the Diels–Alder reaction. As stated previously, this azadiene was prepared and was successfully used in the synthesis of intermediate **9**.

Work on this unique Diels–Alder condensation and its application as a general method for the synthesis of quinoline and pyridine derivatives is being continued in our laboratory and will be the subject of future reports.

Experimental Section

General Procedures. Melting points are uncorrected. Proton magnetic resonance spectra were obtained in $CDCl_3$ or DMSO-d_6 with TMS as internal standard. Elemental analyses were performed by Midwest Microlabs, Ltd.

***1*-[(*tert*-Butyldimethylsilyl)oxy]-2-methyl-1-aza-1,3-butadiene (7).** To 2.85 g of dry 4-Å molecular sieves[22] was added 0.525 g (7.52 mmol) of freshly distilled methyl vinyl ketone in 5 mL of dry CH_2Cl_2. A solution of *o*-(*tert*-butyldimethylsilyl)-hydroxylamine (Aldrich)[23] in 2.5 mL of dry CH_2Cl_2 was added. The mixture was stirred at rt under Ar for 70 h and then filtered.

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(21) The structure of compound **15** was confirmed by spectroscopic methods.

(22) Molecular sieves were dried for 48 h at 150 °C under vacuum.

(23) Siloxy amine **10** can also be prepared by a procedure similar to that of Bottaro, J. C.; Bedford, C. D.; Dodge, A. *Synth. Commun.* **1985**, *15*, 1333: To a magnetically stirred solution of dry ethylenediamine (6.0 g, 0.1 mol) in 25 mL of CH_2Cl_2 was added 7.0 g (0.1 mol) of dry hydroxylamine hydrochloride. The reaction flask was stoppered and stirred at rt for 6 h. A solution a *tert*-butyldimethylsilyl chloride (15.1 g, 0.1 mol)

Evaporation of the solution under reduced pressure and silica gel flash chromatography on a 1.5 cm diameter column using hexane as the solvent gave 1.06 g (71%) of azadiene **7**.[24]

NMR showed the product to be an *E*/*Z* mixture (7:3) which was used as such in the next reaction. An analytical sample of the major isomer was obtained by silica gel column chromatography using petroleum ether and then petroleum ether + EtOAc (200:1) as solvents: IR (liquid film) 2959, 2931, 2890, 2860, 1630, 1462, 1363, 1251, 1061, 983, 948, 808, 787 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.15 (s, 6 H), 0.91 (s, 9 H), 1.95 (s, 3 H), 5.35–5.57 (m, 2 H), 6.38–6.52 (m, 1 H); MS, *m*/*z* (rel inten) 199 (M^+, 0.3), 142 (100), 75 (68), 68 (97), 42 (20); Anal. Calcd for $C_{10}H_{21}NOSi$: C, 60.24; H, 10.62; N, 7.03. Found: C, 60.22; H, 10.56; N, 7.10.

7-Acetamido-2-methylquinoline-5,8-dione (9). A solution of bromoquinone **8** (317 mg, 1.3 mmol)[14] and azadiene **7** (130 mg, 0.65 mmol) in 28 mL of dry chlorobenzene was heated at reflux under Ar for 22 h. Chlorobenzene (10 mL) was added and the mixture was heated at reflux for another 2 h. The reaction mixture was allowed to cool and was added to a silica gel column (2 × 9.5 cm). The column was eluted with EtOAc–petroleum ether (2:1), EtOAc, and then EtOH. The solvent was removed, benzene was added, and the resulting mixture was heated and filtered. Evaporation of the filtrate gave 99 mg of yellow solid **9** (66%). An analytical sample recrystallized from $CHCl_3$: mp 217 °C dec; IR (KBr) 3339, 1750, 1714, 1679, 1651, 1609, 1588, 1510 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.30 (s, 3 H), 2.75 (s, 3 H), 7.55 (d, *J* = 8.0 Hz, 1 H), 7.90 (s, 1 H), 8.29 (d, *J* = 8.0 Hz, 1 H), 8.38 (br s, 1 H); MS, *m*/*z* (rel inten) 230 (M^+, 69), 188 (81), 161 (100), 132 (20), 93 (15), 43 (31). Anal. Calcd for $C_{12}H_{10}N_2O_3$: C, 62.61; H, 4.38; N, 12.17. Found: C, 62.52; H, 4.28; N, 11.93.

7-Acetamido-2-formylquinoline-5,8-dione (4). A stirred mixture of 7-acetamido-2-methylquinoline-5,8-dione (**9**, 230 mg, 1 mmol) and SeO_2[25] (139 mg, 1.25 mmol) in dry dioxane (3.5 mL)[25] and water (0.13 mL) under Ar was heated at reflux for 9 h. Dioxane (7 mL) was added, and the mixture was refluxed for 10 min and then was filtered hot. The residue on the filter paper was added to the reaction flask containing 20 mL of CH_2Cl_2, and the mixture was refluxed for 5 min and filtered. This process was repeated four more times. The filtrates were combined and evaporated to give 222 mg (91%) of the yellow solid **4**. An analytical sample was obtained by sublimation (150–180 °C/0.5 mm): mp 225 °C dec; IR (KBr) 3346, 3085, 1721, 1687, 1652, 1609, 1504 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.33 (s, 3 H), 8.05 (s, 1 H), 8.31 (d, *J* = 8.0 Hz,1 H), 8.43 (br s, 1 H), 8.62 (d, *J* = 8.0 Hz,1 H), 10.29 (s, 1 H); MS, *m*/*z* (rel inten) 244 (M^+, 81), 216 (19), 202 (51), 175 (37), 174 (21), 97 (19), 85 (20), 71 (30), 68 (18), 57 (34), 43 (100). Anal. Calcd for $C_{12}H_8N_2O_4$: C, 59.02; H, 3.30; N, 11.47. Found: C, 58.99; H, 3.38; N, 11.22.

7-*N*-Acetyllavendamycin Methyl Ester (6). A stirred mixture of aldehyde **4** (12.0 mg, 0.05 mmol) and amino acid ester **5**[13] (11.6 mg, 0.05 mmol) in dry xylene (16 mL) under argon was slowly warmed (3 h) to reflux and then refluxed for 19 h. The solution was concentrated to 5 mL and then cooled. The pure orange crystals of **6** were filtered (17.8 mg, 79%): mp > 300 °C; IR (KBr) 3473 (br), 3310, 3121, 1728, 1708, 1680, 1645, 1588, 1504, 1398 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.35 (s, 3 H), 3.19 (s, 3 H), 4.07 (s, 3 H), 7.39 (t, *J* = 8.0 Hz, 1 H), 7.65 (t, *J* = 8.0 Hz, 1 H), 7.74 (d, *J* = 8.0 Hz, 1 H), 8.00 (s, 1 H), 8.35 (d, *J* = 8.0 Hz,1 H), 8.41 (br s,1 H), 8.5 (d, *J* = 7.0 Hz,1 H), 9.1 (d, *J* = 7.5 Hz, 1 H), 11.85 (br s, 1 H); MS, *m*/*z* (rel inten) 454 (M^+, 68), 396 (14), 394 (25), 352 (17), 106 (36), 91 (100), 77 (14), 54 (14); HRMS calcd for $C_{25}H_{18}N_4O_5$ 454.1277, found 454.1277.

Lavendamycin Methyl Ester (2). To an ice-cooled *N*-acetyllavendamycin methyl ester (**6**, 23.0 mg, 0.05 mmol) was added 2.4 mL of H_2SO_4–H_2O (v/v = 4:3) dropwise with stirring over a period of 10 min and the mixture was then warmed under argon at 60 °C for 4 h. The red reaction mixture was neutralized with 20% NaOH solution to pH = 8 and then evaporated under reduced pressure. The solid residue was extracted with 150 mL of $CHCl_3$ for 4 h using a Soxhlet extractor. Evaporation of the resulting extract gave 20.5 mg (99.5%) of lavendamycin methyl ester (**2**) as a red solid: ^1H NMR ($CDCl_3$) δ 3.2 (s, 3 H), 4.07 (s, 3 H), 5.31 (br s, 2 H), 6.11 (s, 1 H), 7.38 (t, *J* = 7.0 Hz,1 H), 7.64 (t, *J* = 7.0 Hz,1 H), 7.72 (d, *J* = 8.0 Hz, 1 H), 8.36 (d, *J* = 8.4 Hz, 1 H), 8.52 (d, *J* = 8.4 Hz, 1 H), 9.07 (d, *J* = 8.4 Hz, 1 H), 11.97 (br s, 1H). The NMR spectrum was identical to the spectrum of lavendamycin methyl ester provided by Professor Boger of Scripps Institute: MS *m*/*z* (rel inten) 412 (M^+, 100), 352 (43), 335 (16), 255 (9), 206 (8); HRMS calcd for $C_{23}H_{16}N_4O_4$ 412.1171, found 412.1170.

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in 15 mL of dry CH_2Cl_2 was added dropwise over 1 h and the mixture was stirred for 38 h at rt. The mixture was filtered and CH_2Cl_2 was distilled off to give white crystals of **10** (10.3 g, 70%): mp 62–64 °C, bp 70 °C/9 mm; ^1H NMR ($CDCl_3$) δ 0.09 (s, 6 H), 0.86 (s, 9 H), 5.05 (br s, 2 H).

(24) Azadiene **7** can also be purified by fractional distillation (bp 67–71 °C/8 mm) but with a yield of 51%.

(25) A fresh bottle of 99.9+% of SeO_2 (Aldrich) was used. Dioxane was purified and distilled according to the procedure in Perrin, D. D.; Perrin, D. R.; Armarego, W. L. F. *Purification of Laboratory Chemicals*; Pergamon Press: Oxford, 1980.