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Total Synthesis of Lavendamycin Methyl Ester

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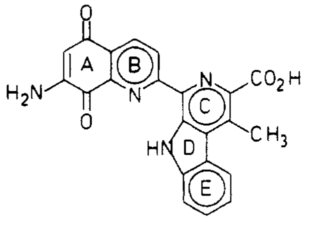
A total synthesis of lavendamycin methyl ester is described and is based on a Friedlander condensation of 2-amino-3-(benzyloxy)-4-bromobenzaldehyde (**11**), a 2-aminobenzaldehyde possessing suitable functionality for introduction of the 7-aminoquinoline-5,8-quinone AB ring system of lavendamycin, with 1-acetyl-3-(methoxycarbonyl)-4-methyl-β-carboline (**10**), a 1-acetyl-β-carboline constituting the fully functionalized CDE ring system of lavendamycin. The 1-acetyl-β-carboline **10** was prepared in a palladium(0)-mediated closure of 2-acetyl-3-amino-4-(2-bromophenyl)-6-(methoxycarbonyl)-5-methylpyridine (**9**), a 4-arylpyridine derived from the product of a regioselective, inverse electron demand [4 + 2] cycloaddition reaction of 3,5,6-tris(ethoxycarbonyl)-1,2,4-triazine with the pyrrolidine enamine of 2-bromopropiophenone.

Lavendamycin (**1**),[2] an antitumor antibiotic[3] isolated from *Streptomyces lavendulae* which is structurally and biosynthetically related to streptonigrin (**2**), was determined to possess the structure **1** through extensive spectroscopic studies on the limited supply of the naturally occurring material in studies which were guided by biosynthetic considerations.[4] A recent total synthesis of lavendamycin methyl ester unambiguously confirmed the structural assignment and provided material identical with that derived from natural lavendamycin.[5a] This and related synthetic approaches[5] to lavendamycin are based on a Bischler–Napieralski-type cyclodehydration and subsequent in situ dehydrogenation of amides derived from β-methyltrytophan enroute to the construction of the β-carboline CDE ring system of lavendamycin, a process mimicking the transformations involved in the biosynthesis of lavendamycin.[2,4]



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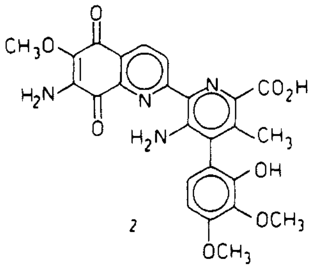

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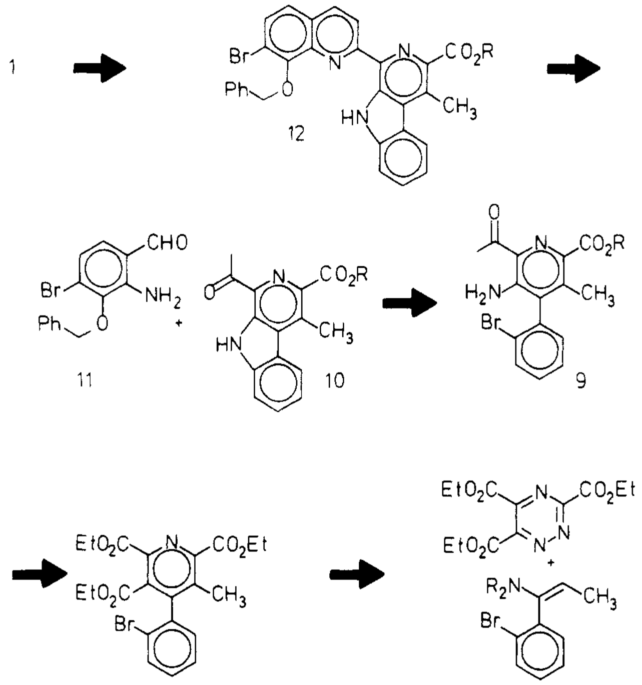
Herein, we describe full details[6] of a complementary approach to the total synthesis of lavendamycin methyl ester which is based on the Friedlander condensation of 2-amino-3-(benzyloxy)-4-bromobenzaldehyde (**11**), a 2-aminobenzaldehyde possessing suitable functionality for introduction of the lavendamycin 7-aminoquinoline-5,8-quinone AB ring system, with 1-acetyl-3-(methoxycarbonyl)-4-methyl-β-carboline (**10**), a fully elaborated 1-acetyl-β-carboline constituting the CDE ring system of lavendamycin, Scheme I. The 1-acetyl-β-carboline **10** was prepared in a palladium(0)-mediated closure of 2-acetyl-3-amino-4-(2-bromophenyl)-6-(methoxycarbonyl)-5-methylpyridine which in turn was derived from the product of a regioselective [4 + 2] cycloaddition of 3,5,6-tris(ethoxycarbonyl)-1,2,4-triazine with the pyrrolidine enamine of 2-bromopropiophenone.[7]

Scheme I



Preparation of 1-Acetyl-3-(methoxycarbonyl)-4-methyl-β-carboline: CDE Ring System of Lavendamycin. In studies described in the accompanying report[7a] we detailed the preparation of 1,3-bis(methoxycarbonyl)-4-methyl-β-carboline from triethyl 4-(2-bromophenyl)-5-methylpyridine-2,3,6-tricarboxylate, the product of a regioselective inverse electron demand [4 + 2] cycloaddition reaction of 3,5,6-tris(ethoxycarbonyl)-1,2,4-triazine, eq 1. A key to the implementation of this approach to the functionalized 4-aryl-3-aminopyridine **3** utilized in the β-carboline preparation was the effective differentiation of the hindered C-3 carboxylate from the less hindered

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[1] Searle scholar recipient, 1981–1985. National Institutes of Health research career development award recipient, 1983–1988 (CA 00898/01134). Alfred P. Sloan Research Fellowship recipient, 1985–1989. Correspondence regarding this work should be addressed to this author at Department of Chemistry, Purdue University, West Lafayette, IN, 47907.

[2] Doyle, T. W.; Balitz, D. M.; Grulich, R. E.; Nettleton, D. E.; Gould, S. J.; Tann, C.-H.; Meows, A. E. *Tetrahedron Lett.* **1981**, *22*, 4595. For a recent review, see: Gould, S. J.; Weinreb, S. M. *Fortschr. Chem. Org. Natur.* **1982**, *41*, 77.

[3] Balitz, D. M.; Bush, J. A.; Bradner, W. T.; Doyle, T. W.; O'Herron, F. A.; Nettleton, D. E. *J. Antibiot.* **1982**, *35*, 259.

[4] Gould, S. J.; Cane, D. E. *J. Am. Chem. Soc.* **1982**, *104*, 343. Erickson, W. R.; Gould, S. J. *Ibid.* **1985**, *107*, 5831.

[5] For the total synthesis of lavendamycin methyl ester and comparison with that derived from natural material, see: (a) Kende, A. S.; Ebetino, F. H. *Tetrahedron Lett.* **1984**, *25*, 923. Kende, A. S.; Ebetino, F. H.; Battista, R.; Lorah, D. P.; Lodge, E. *Heterocycles* **1984**, *21*, 91. Hibino, S.; Okazaki, M.; Ichikawa, M.; Sato, K.; Ishizu, T. *Heterocycles* **1985**, *23*, 261. For the preparation of desmethyllavendamycin and related studies, see: (b) Hibino, S.; Okazaki, M.; Sato, K.; Morita, I. *Heterocycles* **1983**, *20*, 1957. (c) Rao, A. V. R.; Chavan, S.; Sivadasan, L. *Indian J. Chem. Sect. B* **1984**, *23B*, 496.

[6] Boger, D. L.; Panek, J. S. *Tetrahedron Lett.* **1984**, *25*, 3175.

[7] Boger, D. L.; Duff, S. R.; Panek, J. S.; Yasuda, M. *J. Org. Chem.*, preceding paper in this issue.

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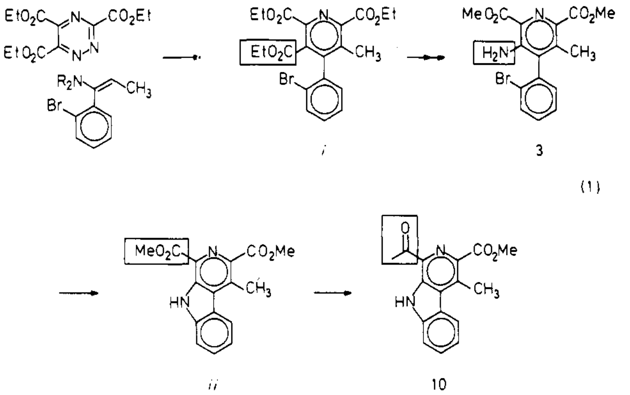
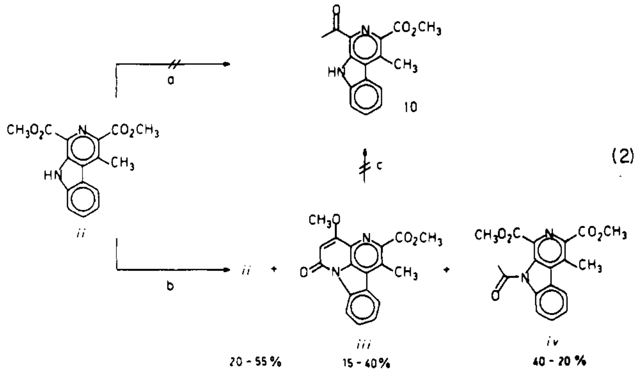


(1)

C-2/C-6 carboxylates in i, an approach adopted from the work detailed in studies on streptonigrin.[2,8] A final differentiation of the remaining C-1/C-3 carboxylates of the 1,3-bis(methoxycarbonyl)-4-methyl-β-carboline (ii) was anticipated to provide the final stage of the CDE ring construction necessary for a total synthesis of lavendamycin.

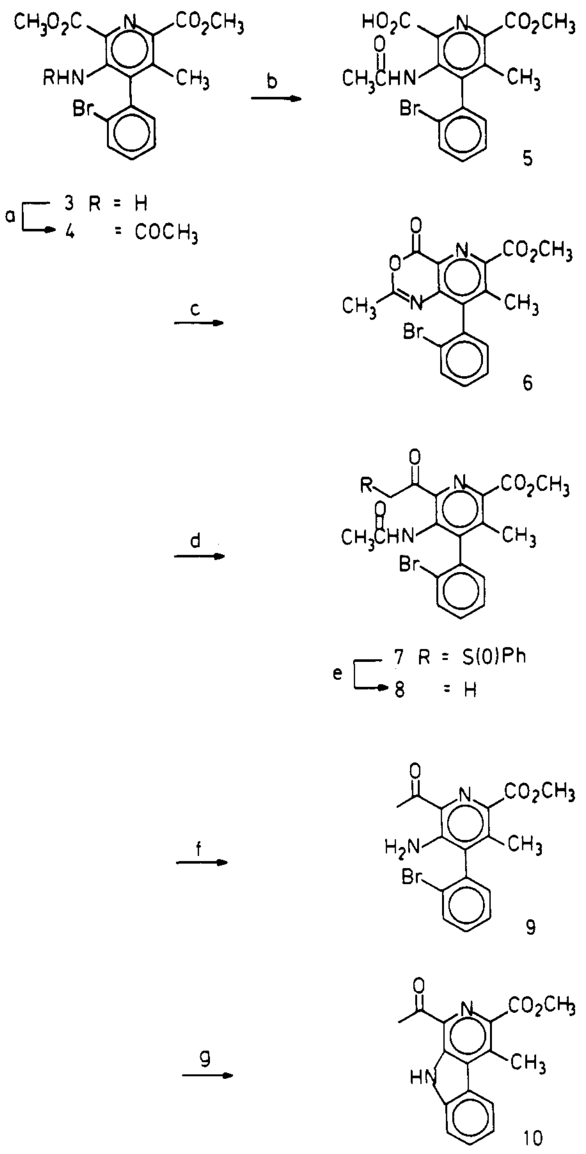
Initial efforts to convert 1,3-bis(methoxycarbonyl)-4-methyl-β-carboline (ii) to **10** directly or with the aid of functionalization of the β-carboline nitrogen to direct selective attack to the C-1 carboxylate proved unsuccessful, eq 2. No satisfactory reagent was found to successfully complex with the β-carboline nitrogen and selectively deliver attack to the proximal C-1 carboxylate.[9] Similar efforts to functionalize the β-carboline nitrogen with derivatives capable of directing selective, intramolecular attack to the C-1 carboxylate were not encouraging.[10] These and related results in simple systems[11] suggested that the differentiation of the carboxylates may be best conducted at the stage of the amino diester **3** (C-2/C-6 carboxylates) in which the amino group could serve as the necessary functionality to direct reactions to the C-2 carboxylate.



(2)

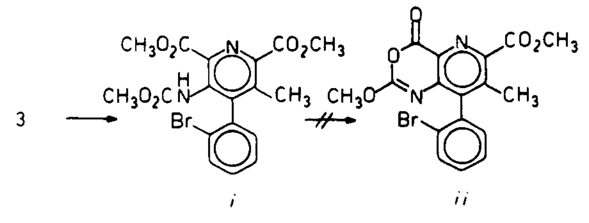
(a) Reference 9. (b) 1.1 equiv of NaH, 15 min, 25 °C; 1.1 equiv of CH_3COCl, THF, 25 °C, 24 h, 41% iii.[10] (c) Excess LiOH, H_2O-(THF), 25-100 °C; 1 N aqueous HCl or 1 N aqueous HCl-dioxane (1:1)

Scheme II[a]



[a] (a) 6 equiv of CH_3COCl, 8 equiv of K_2CO_3, THF, 50 °C, 22 h, 88%. (b) 1.2 equiv of NaH, THF, reflux, 4 h; H_2O, 98%. (c) 1 equiv of DCC, CH_2Cl_2, 0 °C, 7 h, 95-100% from 4. (d) 2.6 equiv, $LiCH_2S(O)Ph$, THF, −78 °C, 40 min; Al(Hg), THF-H_2O, −15 to −10 °C, 41% overall from 4. (e) 10% HCl-MeOH, 60 °C, 6 h, 76%. (f) 1.5 equiv of $(Ph_3P)_4Pd$, dioxane, 100 °C, 36 h, 89%.

N-Acylation of dimethyl-3-amino-4-(2-bromophenyl)-5-methylpyridine-2,6-dicarboxylate (**3**),[7] prepared in the four-step sequence utilizing a regioselective inverse electron demand [4 + 2] cycloaddition reaction of 3,5,6-tris(ethoxycarbonyl)-1,2,4-triazine, followed by base-catalyzed closure of **4** to the oxazinone **6** and aqueous workup afforded **5**, Scheme II. This sequence did permit selective hydrolysis of the C-2 methyl ester and thus effective differentiation of the C-2/C-6 carboxylates.[12] Reclosure of



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[8] (a) Weinreb, S. M.; Basha, F. Z.; Hibino, S.; Khatri, N. A.; Kim, D.; Pye, W. E. *J. Am. Chem. Soc.* **1982**, *104*, 536. Basha, F. Z.; Hibino, S.; Kim, D.; Pye, W. E.; Wu, T.-T.; Weinreb, S. M. *Ibid.* **1980**, *102*, 3962. (b) Kende, A. S.; Lorah, D. P.; Boatman, J. *Ibid.* **1981**, *103*, 1271. (c) Boger, D. L.; Panek, J. S. *J. Org. Chem.* **1983**, *48*, 621. Boger, D. L.; Panek, J. S. *J. Am. Chem. Soc.* **1985**, *107*, 5745. (d) Martin, J. C. *J. Org. Chem.* **1982**, *47*, 3761.

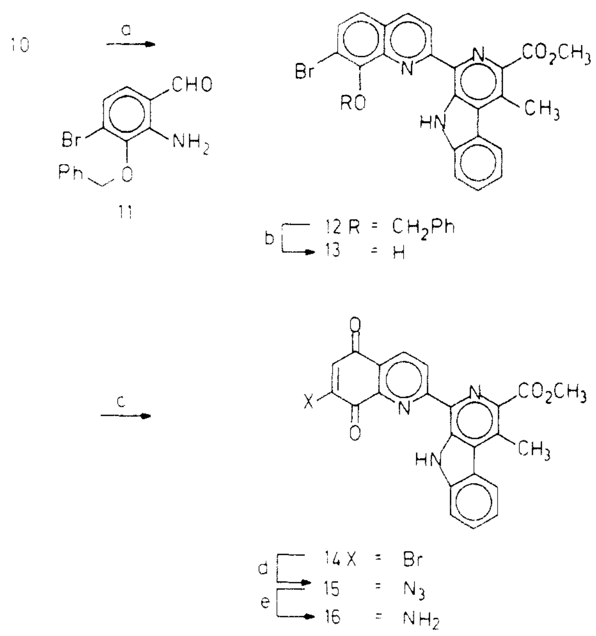
[9] For example, no reaction was observed upon treatment of 1,3-bis(methoxycarbonyl)-4-methyl-β-carboline (ii) with 1.2–3.5 equiv of $(CH_3)_2Al(CH_2)(Cl)Ti(Cp)_2$ (THF–toluene/or pyridine, 11–36 h, 0–65 °C), cf. Pine, S. H.; Zahler, R.; Evans, D. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **1980**, *102*, 3270. Nonselective reactions were observed upon treatment of ii with other reagents including $LiBH_4$, Redal-H, and MeMgBr.

[10] Compound iii was formed in variable yields as detailed (6–24 h). These and additional studies are provided as supplementary material.

[11] Details of related efforts are provided as supplementary material.

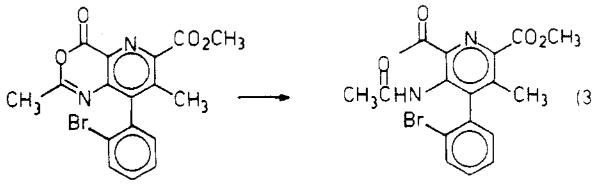
[12] A related effort to prepare and utilize the oxazinone ii was unsuccessful. Details of this and related efforts to selectively direct attack to the C-2 carboxylate of 3 are detailed in supplementary material.

Scheme III[a]



[a] (a) 2.0–4.0 equiv of $PhCH_2(Me)_3NOH$, THF, 25 °C, 18 h, 52–58%. (b) HBr(g), CH_2Cl_2, 0 °C, 20 min, 85%. (c) 5.0–20.0 equiv of $\cdot ON(SO_3K)_2$, 1:1 CH_2Cl_2:0.05 M KH_2PO_4, 1.0 equiv $(n\text{-}Bu)_4NHSO_4$, 25 °C, 4 h, 50–72% (50–72% overall from **12**). (d) 1.1 equiv of NaN_3, THF–H_2O, 25 °C, 21 h. (e) 1.1 equiv of Ph_3P, CH_2Cl_2, 25 °C, 2 h. HOAc:H_2O:THF (3:2:1), 25 °C, 3 h, 31–42% from **14**.

5 to the oxazinone **6** under strict anhydrous conditions followed by treatment with α-lithiomethyl phenyl sulfoxide and subsequent reductive desulfinylation[13] of the β-keto sulfoxide **7** afforded **8**. A number of direct alternatives to the two-step conversion of oxazinone **6** to methyl ketone **8** were investigated and proved to be less successful, eq 3.[14]

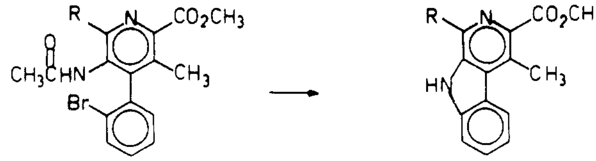


(3)

6 8

$CH_3(CN)CuLi$ THF–Et_2O (2:1), −78 to 0 °C, 2h, no reaction
$(CH_3)_2CNCuLi_2$ THF–Et_2O (1:1), −25 °C, 1 h, complex mixture

Selective amide hydrolysis and subsequent palladium(0)-promoted closure[7,15] of the liberated free amine **9** provided 1-acetyl-3-(methoxycarbonyl)-4-methyl-β-carboline (**10**), constituting the CDE ring system of lavendamycin. Representative results of an investigation of this palladium(0)-promoted β-carboline closure are detailed in the accompanying work,[7] and the study revealed that the reaction does require the use of stoichiometric palladium(0).[15] The *N*-acetyl amide **8** could be employed in the β-carboline closure and provided 1-acetyl-β-carboline **10** directly presumably with the hydrolysis of the sensitive β-carboline amide occurring upon workup and purification, eq 4. This presented no advantage over the initial two-step sequence, and the former process was utilized to prepare material for the synthesis of lavendamycin.



(4)

4, R = CO_2CH_3, 50%[7a]
8, R = $COCH_3$, 54%[15b]

Introduction of the Lavendamycin 7-Aminoquinoline-5,8-quinone AB Ring System: Total Synthesis of Lavendamycin Methyl Ester. In preceding work[7] we investigated the potential for introduction of the lavendamycin AB ring system, a 7-aminoquinoline-5,8-quinone, utilizing a Friedlander condensation[16] of 2-amino-3-(benzyloxy)-4-bromobenzaldehyde (**11**).[7] The basis for the selection of **11** as the 2-aminobenzaldehyde component for use in a Friedlander condensation for the lavendamycin AB ring introduction rested on the anticipation that it could be expected to participate well in a Friedlander condensation and it possessed suitable functionality for conversion to the 7-aminoquinoline-5,8-quinone.

Consistent with these expectations, Friedlander condensation of 1-acetyl-3-(methoxycarbonyl)-4-methyl-β-carboline (**10**) with 2-amino-3-(benzyloxy)-4-bromobenzaldehyde [**11**, 2.0–4.0 equiv of benzyltrimethylammonium hydroxide (Triton B), THF, 25 °C, 52–58%] afforded **12** and completed the assemblage of the carbon skeleton of lavendamycin, Scheme III. Debenzylation of **12**, which was most effectively accomplished with HBr(g) in methylene chloride at 0 °C (85%), provided **13**.[17] The subsequent *p*-quinone formation,[18] which could be effected only by direct oxidation with potassium nitrosodisulfonate (5.0–25.0 equiv, Fremy's salt)[18] and with the adoption of Kende's[5a] two-phase reaction system (1:1 CH_2Cl_2:0.05 M KH_2PO_4, 25 °C, 4 h) in the presence of a phase-transfer catalyst [1.0 equiv of $(n\text{-}Bu)_4NHSO_4$],[5a] provided the red, crystalline 7-bromoquinoline-5,8-quinone **14** (50–72%)[19] identical with authentic material previously described. In practice, the execution of these last two steps without the purification of **13** and with rapid purification of the sensitive bromoquinone provided **14** in yields up to 72% for the combined two steps. Conversion of **14** to lavendamycin methyl ester **16** was accomplished[20] employing the protocol

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(13) Corey, E. J.; Chaykovsky, M. J. *J. Am. Chem. Soc.* **1965**, *87*, 1345. Meyers, A. I.; Durandetta, J. L.; Marava, R. *J. Org. Chem.* **1975**, *40*, 2025.

(14) Studies on simple, related oxazinones which provided comparable findings are detailed in supplementary material.

(15) (a) Occasional isolation of trace (0–10%) amounts of 2-acetyl-3-amino-4-phenyl-6-(methoxycarbonyl)-5-methylpyridine [^1H NMR ($CDCl_3$, ppm) 7.53–7.35 (3 H, m, Ar), 7.17–7.03 (2 H, m, Ar), 6.45 (2 H, br s, NH_2), 3.94 (3 H, s, CO_2CH_3), 2.76 (3 H, S, $COCH_3$), 2.22 (3 H, s, $ArCH_3$); EIMS, *m/e* (relative intensity) 284 (M^+, 83), 43 (100)] accompanied the isolation of **10** in the palladium(0)-promoted closure of **9**. (b) Cyclization of **8** [1.5 equiv of $(Ph_3P)_4Pd$, 100 °C, dioxane, 18 h] and chromatography (SiO_2) of the crude product provided **10** (54%).

(16) Cheng, C. C.; Yan, S. J. *Org. React.* (*N.Y.*) **1982**, *28*, 37.

(17) Deprotection at 25 °C or for longer periods of reaction time leads to a diminished yield of product.

(18) (a) Zimmer, H.; Lankin, D. C.; Horgan, S. W. *Chem. Rev.* **1971**, *71*, 229. (b) Fremy's salt oxidations in a single phase (5–20 equiv, acetone–0.05 M KH_2PO_4, 1–4 h; 2–20 equiv, MeOH–0.05 M KH_2PO_4, 1–18 h) were unsuccessful.

(19) ^1H NMR, IR, HRMS of **14** are in agreement with that previously disclosed for synthetic material.[5a] A direct comparison of copies of the ^1H NMR (400-MHz) spectrum of authentic material[5a] with that of **14** (300 MHz) confirmed that the materials are identical.

described in prior work[5a] implementing the modifications detailed in the accompanying report.[7] Carefully controlled conditions for azide displacement, a reaction which is sensitive to the presence of excess azide,[20b] provided the 7-azidoquinoline-5,8-quinone **15** cleanly and subsequent utilization of triphenylphosphine for reduction of the azide, a reduction process which does not proceed with competing quinone to hydroquinone reduction and with the generation of the corresponding stable and isolatable phosphine imine,[20c] cleanly converted **15** to lavendamycin methyl ester (**16**).[21]

Experimental Section[21]

3-Acetamido-4-(2-bromophenyl)-2,6-bis(methoxycarbonyl)-5-methylpyridine (4). A solution of 3-amino-4-(2-bromophenyl)-2,6-bis(methoxycarbonyl)-5-methylpyridine[7] (**3**; 250 mg, 0.66 mmol) in dry THF (2.5 mL) was treated with anhydrous potassium carbonate (730 mg, 5.27 mmol, 8 equiv) and acetyl chloride (310 mg, 3.95 mmol, 6 equiv) at 25 °C under nitrogen. The resulting reaction mixture was warmed at 50 °C (22 h). The reaction mixture was poured onto water (10 mL) and extracted with EtOAc (2 × 15 mL, 1 × 10 mL), the organic phase was washed with saturated aqueous NaCl (1 × 10 mL), dried (Na_2SO_4), and filtered, and the solvent was removed in vacuo. Chromatography (SiO_2, 1.5 × 21 cm, 75–100% EtOAc–hexane; gradient elution) afforded 244 mg (278 mg theoretical, 88%) of pure **4** as a white solid: mp 212–214 °C (EtOAc–hexane); ^1H NMR ($CDCl_3$, ppm) 7.74 (1 H, br s, NH), 7.78–7.64 (1 H, m, Ar), 7.45–7.15 (3 H, m, Ar), 3.98 (6 H, s, two CO_2CH_3), 2.24 (3 H, s, $ArCH_3$), 1.87 (3 H, s, $NHCOCH_3$); IR (KBr) ν_{max} 3335, 2953, 1732, 1701, 1491, 1358, 1260, 1235, 1113, 1070, 1028, 779 cm^{-1}; EIMS, *m/e* (relative intensity) 421/423 (M + 1, 1/1, 1), 405/407 (1), 389/391 (4), 377/379 (2), 342 (20), 341 (85), 320 (14), 309 (91), 288 (24), 267 (16), 239 (45), 209 (32), 179 (31), 153 (30), 115 (17), 59 (38), 43 (base).

Anal. Calcd for $C_{18}H_{17}BrN_2O_5$: C, 51.32; H, 4.06; N, 6.65. Found: C, 51.60; H, 4.20; N, 6.52.

8-(2-Bromophenyl)-2,7-dimethyl-6-(methoxycarbonyl)-4-oxopyridyl[3,2-*d*]-1,3-oxazine (6). A solution of 3-acetamido-4-(2-bromophenyl)-2,6-bis(methoxycarbonyl)-5-methylpyridine (**4**; 198 mg, 0.47 mmol) in dry THF (10 mL) was treated with sodium hydride (23.0 mg, 0.56 mmol, 1.2 equiv) at 25 °C under N_2. The reaction mixture was warmed at reflux (4 h). The cooled reaction mixture was treated with saturated ammonium chloride (2 mL), and the resulting solution was diluted with H_2O (10 mL), acidified to pH 2–3 with 1 N HCl, and extracted with EtOAc (1 × 30 mL). The organic phase was washed with saturated NaCl and dried (Na_2SO_4), and the solvent was removed in vacuo. The crude product was triturated with hexane (2 × 5 mL), affording 187 mg (191 mg theoretical, 98%) of 3-acetamido-4-(2-bromophenyl)-6-(methoxycarbonyl)-5-methylpyridine-2-carboxylic acid (**5**) as a white foam: mp 171–174 °C (Et_2O); ^1H NMR ($CDCl_3$, ppm) 8.86 (1 H, br s, CO_2H), 7.61–7.41 (1 H, m, Ar), 7.36–7.26 (3 H, m, Ar), 4.00 (3 H, s, CO_2CH_3), 2.30 (3 H, s, $ArCH_3$), 1.92 (3 H, s, $NHCOCH_3$); IR (KBr) ν_{max} 3424, 2953, 2930, 1730, 1499, 1437, 1368, 1316, 1279, 1111, 756 cm^{-1}; CIMS (NH_3), *m/e* (relative intensity) 407/409 (M + 1, 1/1, base), 363/365 (90), 327 (33), 283 (30), 209 (12).

The carboxylic acid **5** (190 mg, 0.467 mmol) was dissolved in dry CH_2Cl_2 (30 mL) and cooled to 0 °C. Dicyclohexylcarbodiimide (97 mg, 0.467 mmol, 1.0 equiv) was added (0 °C), and the reaction mixture was stirred at 0 °C (12 h). The reaction mixture was filtered through Celite, and the solvent was removed in vacuo. The crude product was triturated with hexane (4 × 2 mL) to remove unreacted DCC and afforded 182 mg (182 mg theoretical, 100%) of **6** as a white solid: ^1H NMR ($CDCl_3$, ppm) 7.68 (1 H, dd, J = 8.1 Hz, Ar), 7.47–7.28 (2 H, m, Ar), 7.15–6.98 (1 H, m, Ar), 4.02 (3 H, s, CO_2CH_3), 2.35 (3 H, s, CH_3), 2.32 (3 H, s, CH_3); IR (KBr) ν_{max} 2930, 1784, 1734, 1645, 1559, 1437, 1348, 1287, 1236, 1211, 1150, 1021 cm^{-1}; CIMS (NH_3), *m/e* (relative intensity) 389/391 (M + 1, 1/1, 70), 309 (base), 281 (15).

Anal. Calcd for $C_{17}H_{13}BrN_2O_4$: C, 52.45; H, 3.36; N, 7.19. Found: C, 52.22; H, 3.31; N, 7.10.

3-Acetamido-2-acetyl-4-(2-bromophenyl)-6-(methoxycarbonyl)-5-methylpyridine (8). Methyl phenyl sulfoxide (41 mg, 0.287 mmol, 2.6 equiv) in THF (0.5 mL) was added to a solution of freshly generated lithium diisopropylamide (0.287 mmol, 1.0 equiv) in 0.5 mL of THF at −78 °C under N_2. The reaction was stirred for 20 min (−78 °C) before being added dropwise (5 min) to a stirred solution of **6** (40 mg, 0.102 mmol) in dry THF (1.0 mL) at −78 °C under N_2. The reaction mixture was allowed to stir at −78 °C (40 min) before saturated ammonium chloride (1.0 mL) was added. The mixture was diluted with H_2O (15 mL), acidified to pH 2–3 with 1 N HCl, and extracted with EtOAc (1 × 25 mL). The organic phase was washed with saturated NaCl, dried (Na_2SO_4), and filtered, and the solvent was removed in vacuo. The crude product was triturated with 20% ether–hexane (2 × 5 mL) to remove excess methyl phenyl sulfoxide. Crude β-keto sulfoxide **7** was dissolved in 10% H_2O–THF (10 mL) and cooled to −15 °C. The reaction mixture was treated with freshly prepared aluminum amalgam[13] (7 wt equiv) for 15 min (−15 to −10 °C). The reaction mixture was filtered, the filtrate was diluted with CH_2Cl_2 (20 mL) and dried (Na_2SO_4), and the solvent was removed in vacuo. Chromatography (SiO_2, 40% EtOAc–hexane eluant) afforded 17 mg (41 mg theoretical, 41%) of pure **8** as a pale white solid: ^1H NMR ($CDCl_3$, ppm) 8.27 (1 H, br s, $NHCOCH_3$), 7.61 (1 H, dd, J = 8, 1 Hz, Ar), 7.48–7.08 (3 H, m, Ar), 4.00 (3 H, s, CO_2CH_3), 2.76 (3 H, s, $COCH_3$), 2.22

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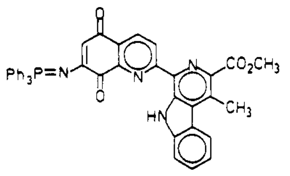
[20] (a) Treatment of 7-bromoquinoline-5,8-quinone **14** with sodium azide (1.5 equiv, THF–H_2O, 25 °C, 3 h) followed by reduction with excess sodium hydrosulfite (THF–H_2O, reflux, 3 h) and subsequent air oxidation has been previously described and provides lavendamycin methyl ester (30%).[5a] (b) The sodium azide displacement is sensitive to the presence of excess reagent and can lead to the predominant formation of 6-azido-7-aminoquinoline-5,8-quinone.[7] Small amounts of lavendamycin methyl ester (**16**, 0–10%) can be isolated directly from this reaction mixture (1.1 equiv of sodium azide, THF–H_2O, 25 °C), and on one occasion the treatment of 7-bromoquinoline-5,8-quinone **14** with sodium azide (1.1 equiv, THF–H_2O, 25 °C, 4 h) provided lavendamycin methyl ester (**16**) (42%) directly. (c) The triphenylphosphine reduction,[7] which proceeds at 25 °C without competing quinone/hydroquinone reduction and with the generation of a stable, isolatable triphenylphosphine imine, provides lavendamycin methyl ester (**16**) under controlled and reproducible conditions. Details of these and related studies are provided in the accompanying account. The phosphine imine was characterized as described in the Experimental Section. (d) Synthetic **16** displayed spectroscopic properties identical with those reported for authentic material. A direct comparison of a copy of the ^1H NMR (300 MHz) of authentic material with that of **16** (300 MHz) confirmed that the materials are identical.



[21] Proton (^1H) and carbon (^{13}C) nuclear magnetic resonance spectra (NMR) were recorded on Varian FT-80A/XL-300 instruments. Infrared spectra (IR) were recorded on an IBM FTIR 32 or Beckmann IR-32 spectrophotometer. Electron impact (EI), chemical ionization (CI) mass spectra (MS) and high resolution mass spectra (HRMS) were recorded on a Varian CH-5 or Ribermag R10-10 spectrometer by Dr. Charles Judson and Robert Drake. Microanalyses were performed by Tho I. Nguyen on a Hewlett-Packard Model 185 analyzer at the University of Kansas. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Medium-pressure liquid chromatography (MPLC) was performed on Merck silica gel 60 (230–400 mesh).[22a] Preparative centrifugal thin-layer chromatography (PCTLC)[22b] was performed on a Chromatotron Model 7924 (Harrison Research, Palo Alto, CA) on Kieselgel 60 $PF_{254}/CaSO_4\cdot{}^1/_2H_2O$ (Merck, D6100 Darmstadt, FGR). All dry solvents were distilled under argon, nitrogen, or vacuum. Tetrahydrofuran (THF), ether (Et_2O), and benzene were distilled immediately prior to use from benzophenone ketyl. Methylene chloride (CH_2Cl_2) was distilled from phosphorus pentoxide. Dioxane, toluene, diisopropylamine, and hexamethylphosphoramide (HMPA) were distilled from powdered calcium hydride. Triethylamine was distilled from calcium hydride and stored over potassium hydroxide. Ethanol (EtOH) and methanol (MeOH) were distilled from their respective magnesium alkoxides. Extraction and chromatographic solvents (CH_2Cl_2, EtOAc, Et_2O, pentane, and hexane) were distilled before use. All reactions requiring anhydrous or inert conditions were run under a positive pressure of argon, and reagent was introduced by syringe through a septum. Syringes and reaction flasks were oven dried.

[22] (a) Meyers, A. I.; Slack, J.; Smith, R. K.; Mihelich, E. D.; Hershenson, F. M.; Liang, C. D. *J. Org. Chem.* **1979**, *44*, 2277. (b) Stahl, E.; Mueller, J. *Chromatographia* **1982**, *15*, 493.

(3 H, s, $ArCH_3$), 1.86 (3 H, s, $NHCOCH_3$); IR (KBr) ν_{max} 3299, 2928, 2855, 1732, 1700, 1578, 1541, 1437, 1221, 1102, 1028 cm^{-1}; EIMS, *m/e* (relative intensity) 404/406 (M^+, 1/1, 0.2), 373/375 (3), 361/363 (30), 325 (base), 304 (14), 251 (20), 223 (38); HRMS, *m/e* for $C_{18}H_{17}BrN_2O_4$ requires 404.0370, found 404.0373.

This sequence consistently provided **8** (30–41% overall) from **4**.

2-Acetyl-3-amino-4-(2-bromophenyl)-6-(methoxycarbonyl)-5-methylpyridine (9). A solution of **8** (30 mg, 0.074 mmol) in absolute MeOH (0.5 mL) was added to a solution of 10% HCl–MeOH (4 mL) at 25 °C under N_2, and the reaction mixture was warmed at 60 °C (6 h). The reaction mixture was allowed to cool to 25 °C, and the solvent was removed in vacuo. Chromatography (SiO_2, 25% EtOAc–hexane eluant) afforded 20.5 mg (27 mg theoretical, 76%) of pure **9** as a pale white solid: ^1H NMR ($CDCl_3$, ppm) 7.76 (1 H, dd, *J* = 7, 1 Hz, Ar), 7.38 (2 H, dt, *J* = 8, 2 Hz, Ar), 7.25–7.05 (1 H, m, Ar), 6.21 (2 H, br s, $ArNH_2$), 3.95 (3 H, s, CO_2CH_3), 2.77 (3 H, s, $COCH_3$), 2.39 (3 H, s, $ArCH_3$); IR (KBr) ν_{max} 3470, 3447, 1732, 1229, 1198, 1151, 1098 cm^{-1}; EIMS, *m/e* (relative intensity) 362/364 (M^+, 1/1, 13), 330/332 (5), 302/304 (5), 251 (12), 223 (20), 209 (5), 195 (10), 181 (15), 154 (14), 127 (18), 115 (18), 77 (12), 43 (base); HRMS, *m/e* for $C_{16}H_{15}BrN_2O_3$ requires 362.0265, found 362.0269.

1-Acetyl-3-(methoxycarbonyl)-4-methyl-β-carboline (10). A solution of 2-acetyl-3-amino-4-(2-bromophenyl)-6-(methoxycarbonyl)-5-methylpyridine (**9**, 19.2 mg, 0.053 mmol) in dioxane (0.65 mL) was treated with tetrakis(triphenylphosphine)palladium(0) (92 mg, 0.079 mmol, 1.5 equiv) at 25 °C under argon in a resealable Kontes vial. The reaction mixture was warmed at 100 °C (36 h), and cooled, and the solvent was removed in vacuo. Chromatography (SiO_2, 10–15% EtOAc–hexane, gradient elution) afforded 13.4 mg (14.9 mg theoretical, 89%) of pure **10** as a white solid: ^1H NMR ($CDCl_3$, ppm) 10.41 (1 H, br s, NH), 8.30 (1 H, d, *J* = 7 Hz, Ar), 7.65–7.42 (3 H, m, Ar), 4.05 (3 H, s, CO_2CH_3), 3.17 (3 H, s, $ArCH_3$), 2.90 (3 H, s, $COCH_3$); IR (KBr) ν_{max} 3376, 2951, 2926, 1738, 1719, 1665, 1620, 1586, 1437, 1420, 1337, 1239, 1207, 1091 cm^{-1}; EIMS, *m/e* (relative intensity) 282 (M^+, 69), 251 (12), 250 (93), 223 (23), 222 (70), 208 (18), 181 (11), 180 (26), 179 (15), 43 (base); HRMS, *m/e* for $C_{16}H_{14}N_2O_3$ requires 282.1004, found 282.1013.

1-(8-(Benzyloxy)-7-bromo-2-quinolinyl)-3-(methoxycarbonyl)-4-methyl-β-carboline (12). A solution of β-carboline **10** (20 mg, 0.071 mmol) in dry THF (5.0 mL) was treated sequentially with benzyltrimethylammonium hydroxide (Triton B, 23.7 mg, 0.064 mL of 40% solution in MeOH, 0.14 mmol, 2.0 equiv) and 2-amino-3-(benzyloxy)-4-bromobenzaldehyde (**11**)[7] (21.7 mg, 0.071 mmol) in 1.0 mL of THF at 25 °C under N_2, and the reaction mixture was allowed to stir at 25 °C (18 h). The reaction mixture was diluted with saturated ammonium chloride (5.0 mL) and extracted with EtOAc (1 × 20 mL). The organic phase was washed with saturated NaCl (1 × 10 mL), dried (Na_2SO_4), and concentrated in vacuo. Chromatography (SiO_2, 10–20% EtOAc–hexane gradient elution) afforded 20.5 mg (39.1 mg theoretical, 52%, 52–58%) of pure **12** as a pale white solid: ^1H NMR ($CDCl_3$, ppm) 11.92 (1 H, br s, NH), 8.79 (1 H, d, *J* = 8 Hz, C-4 H), 8.26 (1 H, d, *J* = 8 Hz, C-3 H), 7.63 (1 H, d, *J* = 8 Hz, C-6 H), 7.72–7.22 (10 H, m, Ar), 5.38 (2 H, s, CH_2Ph), 4.08 (3 H, s, CO_2CH_3), 3.19 (3 H, s, $ArCH_3$); IR (KBr) ν_{max} 3347, 2952, 1719, 1440, 1337, 1242, 1223, 1084 cm^{-1}; EIMS, *m/e* (relative intensity) 551/553 (M^+, 1/1, 1), 491/493 (1), 474/476 (2), 460/462 (2), 402/404 (4), 305 (5), 293 (5), 292 (7), 291 (4), 251 (6), 250 (1), 179 (5), 167 (6), 153 (10), 149 (8), 127 (5), 91 (base); HRMS, *m/e* for $C_{30}H_{22}BrN_3O_3$ requires 551.0843, found 551.0853.

Similar reactions (2–4.0 equiv of Triton B) provided **12** (52–58%).

1-(8-Hydroxy-7-bromo-2-quinolinyl)-3-(methoxycarbonyl)-4-methyl-β-carboline (13). The benzyl ether **12** (4.0 mg, 0.0072 mmol) was treated with a precooled (0 °C) solution of CH_2Cl_2 (0.5 mL) saturated with HBr(g). The reaction mixture was allowed to stir at 0 °C (20 min) during which time a yellow precipitate formed. The reaction mixture was diluted with H_2O (0.5 mL), and the yellow precipitate was dissolved with the addition of 5% aqueous $NaHCO_3$ until the aqueous phase was at a pH of 7. The resulting solution was extracted with CH_2Cl_2 (3 × 5 mL), and the combined organic phase was dried (Na_2SO_4) and concentrated in vacuo. Chromatography (SiO_2, 50% EtOAc–hexane eluant) afforded 2.8 mg (3.3 mg theoretical, 85%) of pure **13** as a yellow solid: ^1H NMR ($CDCl_3$, ppm) 11.16 (1 H, s, NH), 8.60 (1 H, d, *J* = 8.7 Hz, C-4 H), 8.25 (1 H, d, *J* = 7.9 Hz, C-9′ H), 7.99 (1 H, d, *J* = 8.7 Hz, C-3 H), 7.64–7.60 (2 H, m, C-11′ H and C-12′ H), 7.61 (1 H, d, *J* = 8.6 Hz, C-6 H), 7.38 (1 H, dd, *J* = 7.9, 4.1 Hz, C-10′ H), 7.17 (1 H, d, *J* = 8.6 Hz, C-5 H), 4.13 (3 H, s, CO_2CH_3), 2.87 (3 H, s, $ArCH_3$); IR (KBr) ν_{max} 3400, 3055, 2949, 1711, 1622, 1556, 1496, 1454, 1338, 1279, 1223, 1080, 744 cm^{-1}; EIMS, *m/e* (relative intensity) 463/461 (M^+, 1/1, 5), 447/445 (6), 431/429 (8), 403 (29), 401 (20), 262 (65), 183 (100), 108 (58); HRMS, *m/e* for $C_{23}H_{16}BrN_3O_3$ requires 461.03736, found 461.03714.

1-(7-Bromoquinoline-5,8-quinon-2-yl)-3-(methoxycarbonyl)-4-methyl-β-carboline (14). A solution of the bromophenol **13** (5.0 mg, 0.0108 mmol) in CH_2Cl_2 (2.5 mL) was added dropwise to a solution of potassium nitrosodisulfonate (Fremy's salt, 58.0 mg, 0.216 mmol, 20 equiv) and tetra-*n*-butylammonium hydrogen sulfate (3.7 mg, 0.0108 mmol, 1 equiv) in 0.05 M KH_2PO_4 buffer (2.5 mL) at 25 °C. The two-phase reaction mixture was stirred vigorously at 25 °C (4.5 h). The reaction mixture was diluted with water (5.0 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. Rapid chromatography (SiO_2, 100% ethyl acetate eluant) afforded 3.7 mg (5.1 mg theoretical, 72%) of **14** as a red solid:[19] mp 284–287 °C (lit.[5a] mp 285–287 °C); ^1H NMR ($CDCl_3$, ppm) 11.84 (1 H, br s, NH), 9.06 (1 H, d, *J* = 8.3 Hz, C-4 H), 8.47 (1 H, d, *J* = 8.3 Hz, C-3 H), 8.35 (1 H, d, *J* = 7.8 Hz, C-12′ H), 7.80 (1 H, d, *J* = 7.8 Hz, C-9′ H), 7.65 (1 H, t, *J* = 7.8 Hz, C-10′ H), 7.61 (1 H, s, C-6 H), 7.41 (1 H, t, *J* = 7.3 Hz, C-11′ H), 4.09 (3 H, s, CO_2CH_3), 3.20 (3 H, s, $ArCH_3$); IR (KBr) ν_{max} 2926, 2855, 1714, 1691, 1662, 1578, 1334, 1298, 1275 cm^{-1}; EIMS, *m/e* (relative intensity) 477/475 (M^+, 1/1, 7), 445 (6), 417 (16), 336 (9), 308 (10), 282 (11), 222 (9), 179 (12), 149 (17), 91 (73), 71 (32), 69 (47), 57 (70), 55 (57), 43 (100), 41 (63); HRMS, *m/e* for $C_{23}H_{14}BrN_3O_4$ requires 475.01663, found 475.01663.

Carrying out the two-step sequence, conversion of **12** (10 mg) to **14**, without purification of **13** and with 20.0–25.0 equiv of Fremy's salt (25 °C, 4–4.5 h) as described above provided **14** (50–72% overall).

1-(7-Azidoquinoline-5,8-quinon-2-yl)-3-(methoxycarbonyl)-4-methyl-β-carboline (15). A stirred solution of 1-(7-bromoquinoline-5,8-quinon-2-yl)-3-(methoxycarbonyl)-4-methyl-β-carboline (**14**; 2.5 mg, 0.0053 mmol) in 0.06 mL of THF was treated with a solution of sodium azide (0.38 mg, 0.0058 mmol, 1.1 equiv) in 0.015 mL of H_2O at 25 °C under a N_2 atmosphere, and the mixture was stirred at 25 °C (21 h). Chromatography (SiO_2, 1 × 15 cm, EtOAc eluant) afforded 2.3 mg (2.3 mg theoretical, 100%) of **15** as a red-orange solid: ^1H NMR ($CDCl_3$, ppm) 8.97 (1 H, d, *J* = 8 Hz, C-4 H), 8.37 (1 H, d, *J* = 8 Hz, C-3 Hz), 8.30 (1 H, d, *J* = 8 Hz, C-12′ H), 7.50–7.78 (2 H, m, C-9′ H and C-10′ H), 7.35 (1 H, dd, *J* = 8,4 Hz, C-11′ H), 6.47 (1 H, s, C-6 H), 4.03 (3 H, s, CO_2CH_3), 3.16 (3 H, s, $ArCH_3$).

Lavendamycin Methyl Ester (16). A stirred solution of the 7-azidoquinoline-5,8-quinone **15** (1.7 mg, 0.0039 mmol) in dry CH_2Cl_2 (0.065 mL) under a N_2 atmosphere was treated with a solution of triphenylphosphine (1.13 mg, 0.0043 mmol, 1.1 equiv) in 0.025 mL of CH_2Cl_2, and the resulting mixture was stirred at 25 °C (2 h). The solvent was removed in vacuo to afford the crude phosphine imine (3.2 mg). A solution of the crude phosphine imine (3.2 mg) in 0.03 mL of THF was treated with 0.09 mL of acetic acid and 0.06 mL of H_2O, and the resulting mixture was stirred at 25 °C (3 h). Chromatography (SiO_2, 1 × 18 cm, 50–100% EtOAc–hexane; gradient elution) afforded 0.5 mg (1.6 mg theoretical, 31%, 31–42%) of lavendamycin methyl ester (**16**) as a red solid:[20] ^1H NMR ($CDCl_3$, ppm) 12.00 (1 H, br s, NH), 9.12 (1 H, d, *J* = 8.3 Hz, C-4 H), 8.55 (1 H, d, *J* = 8.3 Hz, C-3 H), 8.38 (1 H, d, *J* = 8.3 Hz, C-12′ H), 7.81 (1 H, d, *J* = 8.8 Hz, C-9′ H), 7.67 (1 H, dd, *J* = 7.3, 7.3 Hz, C-10′ H), 7.41 (1 H, dd, *J* = 7.3, 7.3 Hz, C-11′ H), 6.13 (1 H, s, C-6 H), 5.30 (2 H, br s, NH_2), 4.09 (3 H, s, CO_2CH_3), 3.22 (3 H, s, $ArCH_3$); IR (KBr) ν_{max} 3438, 1717, 1620, 1543, 1491, 1437, 1414, 1339, 1269, 1250, 1221, 1140, 1123, 1075, 1046, 810, 718 cm^{-1}; EIMS, *m/e* (relative intensity) 412 (M^+, 50), 380 (13), 352 (44), 335 (39), 255 (22), 206 (20); HRMS, *m/e* for $C_{23}H_{16}N_4O_4$ requires 412.1170, found 412.1179.

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Supplementary Material Available: Details of work described in ref 10–14 (6 pages) are provided. Ordering information may be found on any current masthead page.

Calixarenes. 16. Functionalized Calixarenes: The Direct Substitution Route

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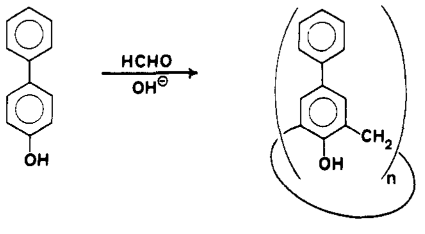
The base-induced condensation of *p*-phenylphenol and formaldehyde is shown to yield *p*-phenylcalix[6]arene **3** and *p*-phenylcalix[8]arene **5** as isolable products but no detectable amount of *p*-phenylcalix[4]arene **1**, contrary to earlier reports. As an alternative to *p*-phenylcalix[4]arene as a "deep cavity" compound, *p*-benzoylcalix[4]arene **27** and *p*-(4′-hydroxybenzoyl)calix[4]arene **29** are proposed, and their syntheses by $AlCl_3$-catalyzed aroylation of the methyl ether of calix[4]arene **14** are described. Methods are given for introducing various groups into the para position of the calix[4]arene ring system, including bromo, lithio, carboxyl, carbomethoxyl, and cyano, thus making available a variety of functionalized calixarene molecules.

The 1944 report by Zinke and Ziegler[1] that *p-tert*-butylphenol and formaldehyde react under certain conditions to form a cyclic tetramer was followed 4 years later by another paper[2] stating that the reaction is a general one and works, inter alia, with *p*-phenylphenol. When we became interested in building enzyme mimics these cyclic oligomers, which we have named calixarenes,[3,4] attracted our attention. The cyclic tetramer that Zinke thought to be the product of condensation of *p*-phenylphenol and formaldehyde seemed particularly intriguing because of its deep cavity. However, when subsequent investigation revealed that the reaction of *p-tert*-butylphenol yields a variety of cyclic oligomers,[5] the cyclic tetrameric structure that had been assigned to the product from *p*-phenylphenol required verification. This provided the starting point for the work reported in the present paper.



1, $n = 4$
2, $n = 5$
3, $n = 6$
4, $n = 7$
5, $n = 8$

***p*-Phenylphenol–Formaldehyde Condensation.** A number of procedures have been described for the preparation of calixarenes via the condensation of phenols and formaldehyde. The original Zinke procedure[1] is a several step process that involves (a) treating a para substituted phenol with aqueous formaldehyde and NaOH at 50–55 °C for 45 h, (b) heating the reaction mixture at 110–120 °C for 2 h, during which time the water evaporates to leave a friable solid, (c) acidifying the residue, and (d) suspending the resin in linseed oil and heating at 220 °C for several hours. A simpler method, which we have referred to as the "Munch procedure" or the "Petrolite procedure"[6] is a one-step process that involves refluxing a mixture of a para substituted phenol, paraformaldehyde, and a very small amount of an alkali hydroxide in xylene for 4 h or more. Several variations on these two themes have been reported, including the substitution of diphenyl ether–biphenyl eutectic (Dowtherm) for linseed oil in the Zinke procedure[7] and the use of a larger amount of base in the Petrolite procedure.[5] In the case of the *p-tert*-butylphenol–formaldehyde condensation previous work in our laboratory has shown[5] that the ring size of the calixarene that is formed is a function of the procedure that is used, viz., the Zinke–Cornforth procedure can yield cyclic tetramer as the major product in some cases, the Petrolite procedure yields cyclic octamer, and a modified Petrolite procedure yields cyclic hexamer. More recent work,[8] however, has revealed that this outcome is far from general and that different para-substituted phenols behave in quite different ways; the behavior of *p-tert*-butylphenol does not necessarily predict that of *p*-phenylphenol, contrary to the inferences in the Zinke papers.

In the present work we use a modified Zinke–Cornforth procedure for synthesizing the *p*-phenylcalixarenes. Chromatographic separation of the $CHCl_3$ soluble fraction of the crude product yielded ca. 10% of *p*-phenylcalix[6]arene **3** as a white powder with a melting point very close to that reported[9] for *p*-phenylcalix[4]arene **1**, and it

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