Studies Towards Streptonigrinoids: Formal Synthesis of Lavendamycin Methyl Ester

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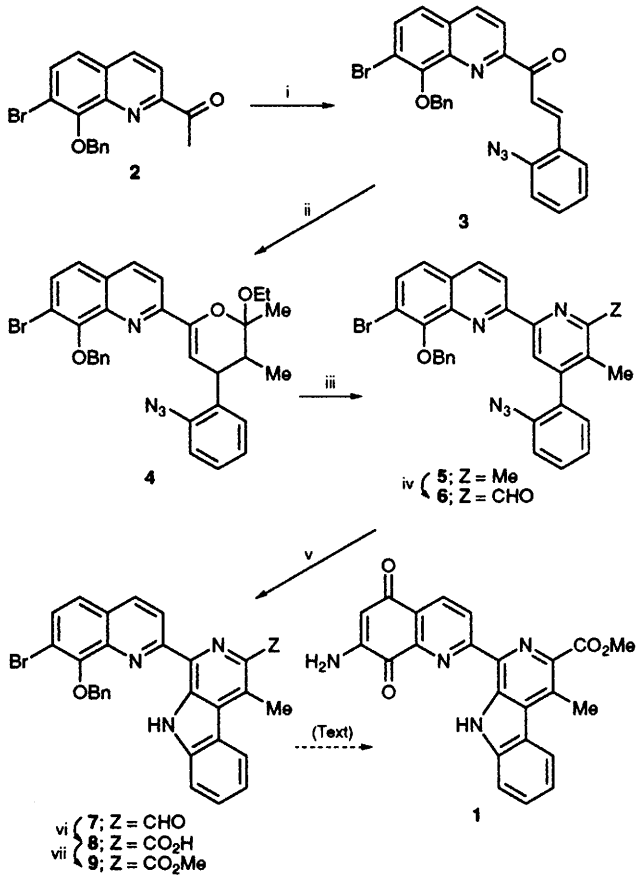
A modified Knoevenagel–Stobbe pyridine formation and a thermolytic nitrene insertion are the key steps in a practical new synthesis of lavendamycin methyl ester.

The discovery that streptonigrin and congeners are inhibitors of HIV reverse transcriptase[1] has renewed interest in these compounds, and has reinforced the need for additional investigation of their medicinal chemistry. Syntheses of both streptonigrin and of its biogenetic precursor, lavendamycin (as the methyl ester), have been described,[2] but despite these important developments, a practical avenue to streptonigrinoids remains elusive. We recently conceived the possibility of creating the complex framework of these molecules by our two-step pyridine synthesis.[3] Results of a feasibility-level investigation are described herein in the form of an efficient formal synthesis of lavendamycin methyl ester, **1**.†

Condensation of quinoline **2**‡ with 2-azidobenzaldehyde[4] in an aqueous medium provided chalcone **3** (93%; decomp. 158 °C, EtOH–H_2O). Reaction of this enone with a 2:1 mixture of 2-ethoxybut-1-ene and 2-ethoxybut-2-ene (mixture of *E*- and *Z*-isomers)[5] in the presence of Yb(fod)$_3$, Hfod = 1,1,1,2,2,3,3-heptafluoro-7,7-dimethyloctane-4,6-dione, proceeded with exclusive formation of adduct **4** as a mixture of diastereoisomers in essentially quantitative yield. In the course of this reaction, rapid equilibration of the various isomers of the ethers occurs under the influence of the lanthanide complex, and the isomer of the vinyl ether that possesses the highest-lying HOMO is the one that reacts

† All compounds described herein were characterized by ^1H and ^{13}C NMR, IR, and low- and high-resolution mass spectra, and were essentially pure as judged by analytical TLC, by the appearance of NMR spectra, and by the sharpness of melting points of solid substances (uncorrected).

‡ M.p. 140–141 °C. Prepared from 2-nitro-3-benzyloxy-4-bromobenzaldehyde [ref. 2(*d*)] by reaction with the Wadsworth–Emmons reagent obtained from methyl pyruvate dimethyl acetal (*cf.* E. J. Corey and G. T. Kwiatkowski, *J. Am. Chem. Soc.*, 1966, **88**, 5654), followed by Friedländer cyclization ($Na_2S_2O_4$) and acidic workup of the intermediate dimethyl acetal (41% overall yield).



Scheme 1 *Reagents and conditions*: i, 2-azidobenzaldehyde, EtOH, 10% aq. NaOH, 25 °C, 98%; ii, MeCH=C(Me)OEt + CH_2=C(Et)-OEt (2 : 1 mixture, see text), $(CH_2Cl)_2$, cat. Yb(fod)$_3$, reflux, 98%; iii, $HONH_2$·HCl, MeCN, reflux, 89%; iv, SeO_2; dioxane cat., AcOH, 100 °C, 87%; v, 1,2-$C_6H_4Cl_2$, reflux, 83%; vi, $NaClO_2$, 97%; vii, CH_2N_2, 100%. Bn = benzyl.

fastest with the enone.[6] Smooth formation of pyridine **5** (87%; decomp, 158–160 °C EtOAc–hexanes) occurred upon reaction of **4** with $HONH_2$·HCl in refluxing acetonitrile. Aldehyde **6**, decomp. 155 °C (CH_2Cl_2–hexanes), was readily obtained by oxidation of **5** with SeO_2.[7] Thermolysis of **6** (1,2-$C_6H_4Cl_2$ solution) furnished exclusively carboline **7**, m.p. 232–233 °C (20% EtOAc–hexanes, 83% yield). The complete molecular framework of lavendamycin was thus assembled from three building blocks in just five steps and in 62% overall yield. Oxidation of **7** ($NaClO_2$)[2c] provided acid **8**, m.p. 235–236 °C ($CHCl_3$), which was converted (CH_2N_2) into **9**, m.p. 188 °C (CH_2Cl_2–hexanes). This compound is identical to the Boger lavendamycin intermediate,[2d] and it may be converted into the final product in a straightforward manner. The formal total synthesis of lavendamycin methyl ester was thus accomplished upon reaching **9**, obtained in just 7 steps and in 60% overall yield from **2**. It should be noted that in the cyclocondensation step a vinyl ether is utilized as the synthetic equivalent of a carbonyl enolate, in what is formally a Michael addition. Yet, none of the problems frequently associated with this chemistry, such as retro-Michael reactions followed by cross-condensation,[8] are observed, and no wasteful separations are therefore needed. Our route is entirely regioselective, experimentally simple, and amenable to scale-up to furnish multigram quantities of synthetic materials.

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References

1 Y. Hafuri, E. Takemori, K. Oogose, Y. Inouye, S. Nakamura, Y. Kitahara, S. Nakahara and A. Kubo, *J. Antibiot.*, 1988, **41**, 1471, and references cited therein.
2 For a review of the extensive literature on the chemistry and mode of action of streptonigrinoids see: (*a*) W. A. Remers, *The Chemistry of Antitumor Antibiotics*, Wiley, New York, NY, 1988, vol. 2, ch 7; (*b*) S. J. Gould and S. M. Weinreb, *Fortschr. Chem. Org. Naturst.*, 1982, **41**, 77; (*c*) A. S. Kende and F. H. Ebetino, *Tetrahedron Lett.*, 1984, 903; (*d*) D. L. Boger, S. R. Duff, J. S. Panek and M. Yasuda, *J. Org. Chem.*, 1985, **50**, 5790.
3 M. A. Ciufolini and N. E. Byrne, *J. Chem. Soc., Chem. Commun.*, 1988, 1230.
4 M. A. Ardakani, R. K. Smalley and R. H. Smith, *J. Chem. Soc., Perkin Trans. 1*, 1983, 2501.
5 E. Taskinen, *J. Chem. Thermodyn.*, 1974, **6**, 345.
6 Unpublished work from these laboratories.
7 It is imperative to use SeO_2 freshly sublimed in air: N. Rabjohn, in *Organic Reactions*, ed. R. Adams, Wiley, New York, NY, 1952, vol. 5, ch. 8.
8 See, *e.g.* T. Kametani, S. Tanaka, and A. Kozuka, *Yakugaku Zasshi*, 1971, **91**, 1068.

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