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A Concise Total Synthesis of (±)-Ipalbidine by Application of the Aldimine–Diene Cyclocondensation Reaction

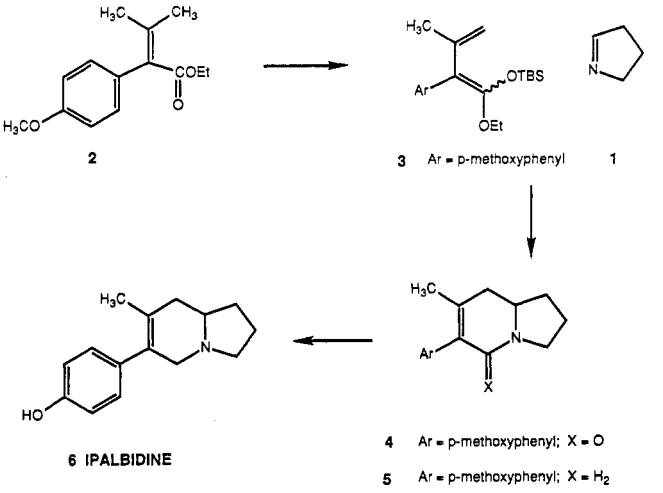
Summary: The scope of the diene–imine cyclocondensation reaction has been extended to the unstable Δ^1-pyrroline. Cyclocondensation of this compound with the silylketene acetal derived from ethyl 2-*p*-anisyl-3-methylcrotonate provides the basis for a rapid synthesis of (±)-ipalbidine.

Sir: Recently we described the Lewis acid catalyzed cycloaddition of siloxydienes with aldimines.[1] Prior to our work, examples of such reactions had been restricted to specially activated imines.[2,3] The use of highly nucleophilic dienes and Lewis acid catalysts allowed for extension of the process to a broad range of imines,[1] including dihydro-β-carboline.[4]

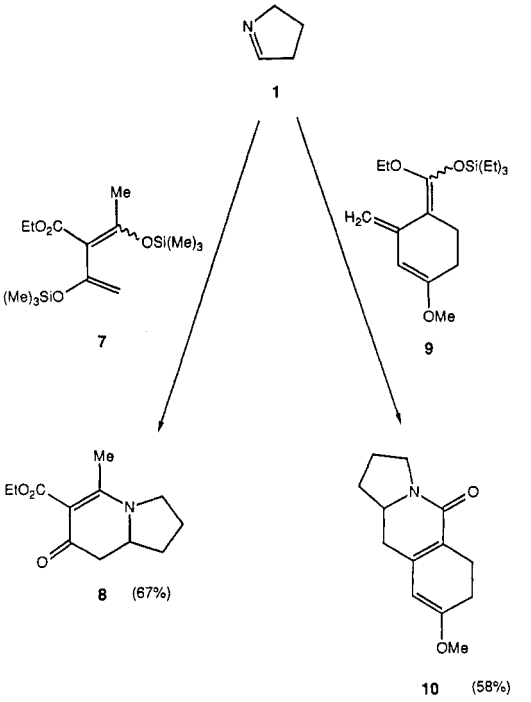
It was of interest to learn whether the parent Δ^1-pyrroline (**1**)[5] could participate in such cyclocondensations. If the reaction could be applied to imines of this type, it could have a major impact in the synthesis of various alkaloidal systems, many of which are of considerable current biological interest.[6] We report an affirmative finding regarding this question, in the context of a particularly straightforward synthesis of ipalbidine (**6**).[7]

Reaction of the known α-aryl-β-methylcrotonate derivative **2**[8] with lithium diisopropylamide in THF in the presence of HMPA, followed by quenching of the resultant ester enolate with *tert*-butyldimethylsilyl chloride afforded the silylketene acetal **3** in near quantitative recovery. Reaction of **3** with **1** in methylene chloride under the influence of BF_3 etherate (−78 °C → room temperature) affords a 40–45% yield of unsaturated lactam **4**, mp 141–142 °C. Reduction of this lactam to the hexahydroindolizine **5** was accomplished (73%) through reaction with $LiAlH_4$–$AlCl_3$. Demethylation of **5** via boron tribromide in methylene chloride afforded a 78% yield of (±)-ipalbidine (**6**), mp 149–150 °C (lit.[7] mp 149–150 °C). The assignment of the ipalbidine structure to the synthetic compound follows from comparison of its spectral properties with those previously reported.[7]

Compound **1** participates as the aldimine component with a variety of other activated dienes under Lewis acid catalysis. Two particularly interesting cases are shown.



Reaction of **1** with **7**[4,9] under the influence of zinc chloride in acetonitrile at room temperature produces vinylogous lactam **8**, mp 93–95 °C in 67% yield. Similarly, reaction of **1** with silylketene acetal **9**[4,10] in chloroform at room temperature (no catalysis) gives rise to lactam **10**, mp 126–128 °C in 58% yield.



These results are suggestive of a broad potential of the cyclic aldimine–diene cyclocondensation process. We are currently exploring its stereochemical ramifications in situations with substituents at the 4-position of the diene. We are also investigating the applicability of the reaction to more complex variations of compound **1**. It now seems likely that this reaction will play an important role in heterocyclic synthesis.

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Supplementary Material Available: All experimental procedures and full spectral characterizations of the material described herein (3 pages). Ordering information is given on any current masthead page.

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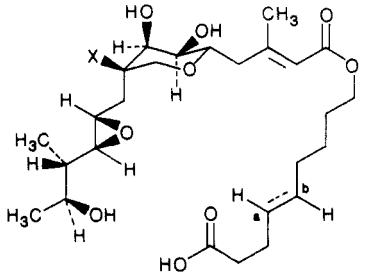
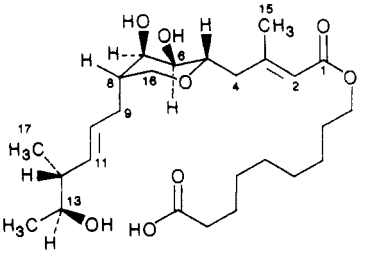
Total Synthesis of (+)-Pseudomonic Acid C†

Summary: The convergent enantiospecific total synthesis of (+)-pseudomonic acid C (**1c**) has been completed from D-glucose.

Sir: The pseudomonic acids consist of a small group of four related metabolites, originally isolated from submerged cultures of *Pseudomonic fluorescens* NCIB 10586.[2] Detailed studies of structural and chemical characterizations of the major component pseudomonic acid A (**1a**) and the lesser components B, C, and D have been reported in a series of papers.[3] In 1982, X-ray crystallography established the absolute configuration of the monate skeleton of pseudomonic acid C (**1c**).[4] The therapeutic value of



1a, X = H; C_a-C_b = C_2H_4
1b, X = OH; C_a-C_b = C_2H_4
1d, X = H; C_a-C_b = *E*-CH=CH

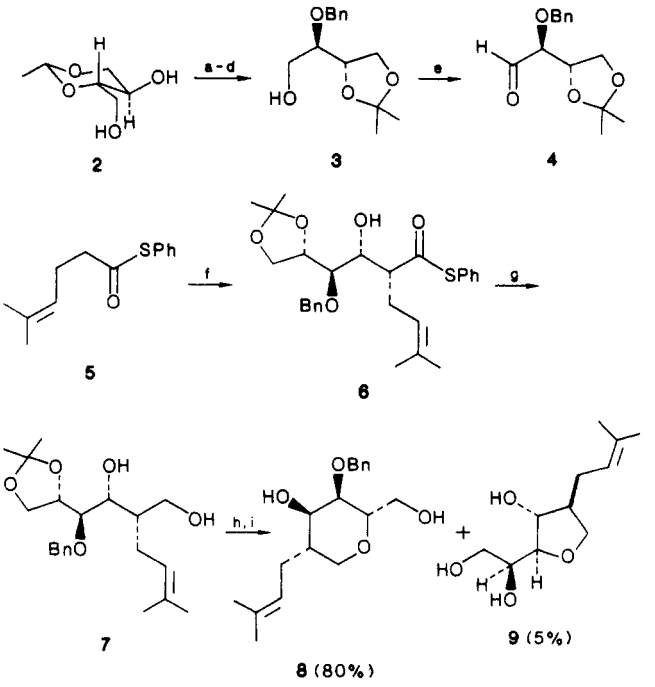


1c (pseudomonic acid C)

these antibiotics has been clinically developed in the Beecham Laboratories.[5] Several chemical investigations have documented strategies for the total synthesis of pseudomonic acid C, and numerous approaches have been published. The conversion of pseudomonic acid C (**1c**) to the major metabolite **1a** has also been reported.[7] Herein, we communicate our recent efforts affording a convergent total synthesis of (+)-pseudomonic acid C.

Construction of a chiral tetrahydropyran, bearing four contiguous asymmetric centers (C_5 through C_8; **1c** numbering), suggested use of a reduced (at C_{16}) carbohydrate precursor. However, the necessary absolute configuration at C_5 was directly apparent only in the series of L-hexoses.

Scheme I



[a] (a) Trityl chloride (1.1 equiv), DMAP (1.1 equiv), DMF (80%); (b) NaH dispersion, THF, benzyl bromide (83%); (c) 40% concentrated HCl in methanol, 22 °C, 14 h (84%): (d) PPTs (0.1 equiv), acetone, 18 h (78%); (e) ClCOCOCl (1.5 equiv), Me_2SO (2.4 equiv), CH_2Cl_2, -78 °C; then Et_3N (2.4 equiv), -78 °C → 0 °C (87%); (f) 9-BBN triflate, Et_2O, thio ester **5** (1 equiv), diisopropylethylamine (1.4 equiv); add **4** at -78 °C → 0 °C (79%); (g) $LiAlH_4$, ether, 0 °C → 22 °C, 1 h (85%); (h) TsCl (1.4 equiv), CH_2Cl_2, DMAP (1.1 equiv), Et_3N (2.5 equiv), 22 °C, 4 h; (i) TsOH (1.1 equiv), MeOH, 16 h, 22 °C; add $NaOCH_3$ in methanol (80% yield of **8**).

Our introduction of the desired absolute stereochemistry at C_5, as well as C_6, was accomplished by D-glucose, as illustrated in Scheme I. A classical three-step sequence provided the known diol **2**,[8] and arrangement of appropriate protection gave the optically pure primary alcohol **3**. Swern oxidation provided aldehyde **4**, which was used immediately for condensation at -78 °C in anhydrous ether with the preformed *Z*(O)-boron enolate derived from thio ester **5**.[9,10] High stereocontrol was observed with formation

† Dedicated to Professor George Büchi on the occasion of his 65th birthday.

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