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TOTAL SYNTHESES OF THE DITERPENOIDS (-)-KOLAVENOL AND (-)-AGELASINE B

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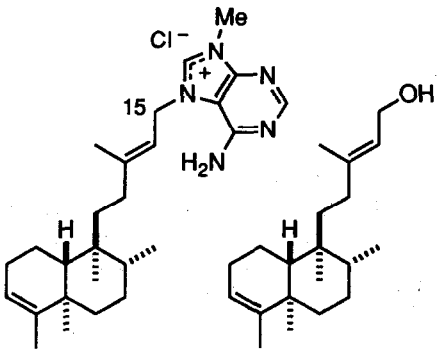
Summary: *The* trans*-clerodane diterpenoids (-)-kolavenol (**2**) and (-)-agelasine B (**1**) have been prepared from the enantiomerically pure decalone **3**. The key steps of the syntheses involve the stereoselective alkylation of the nitrile **4** (to give **5**), the efficient coupling of the iodides **10** and **11** to produce the clerodane skeleton **12**, and the electrochemical reduction of **16** to provide (-)-**1**.*

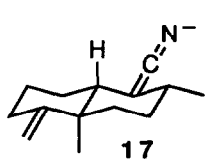
The natural product (-)-agelasine B (**1**) is a structurally unusual compound of mixed biogenesis. Isolated from the Okinawan marine sponge *Agelas nakamurai* Hoshino,[1] this substance contains a 9-methyl-7-adeninium moiety attached to C-15 of a *trans*-clerodane diterpenoid skeleton and, interestingly, has been shown to possess a variety of biological activities, including antimicrobial activity and inhibitory effects on Na,K-ATPase.[1] We report herein a total synthesis of (-)-**1** and of (-)-kolavenol (**2**), a *trans*-clerodane diterpenoid isolated from the oleoresin of *Hardwickia pinnata* Roxb.[2]



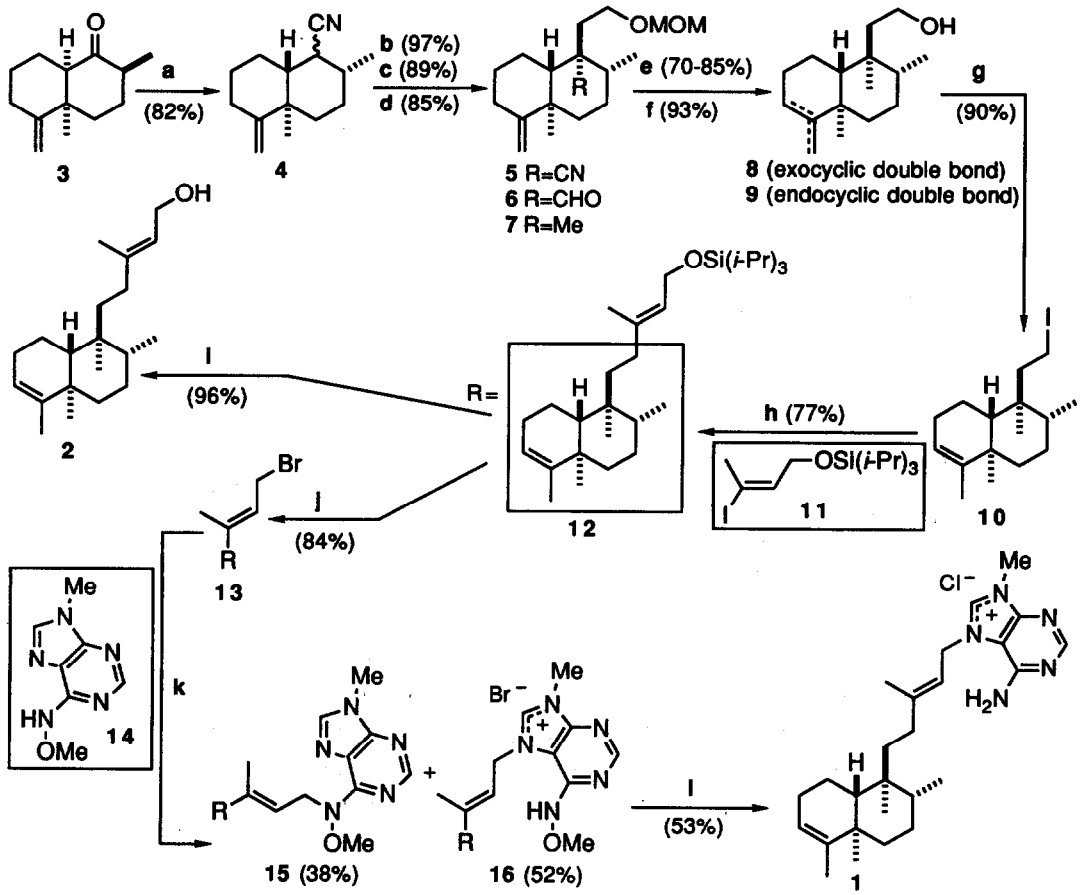
1 **2**

Reaction of the enantiomerically pure *cis*-fused decalone **3**[3] (see **Scheme 1**) with (*p*-tolylsulfonyl)methyl isocyanide (TosMIC) in 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) in the presence of base provided the nitrile **4** (mixture of epimers).[4] Under these reaction conditions, the process that introduced the necessary nitrile function was preceded by a thermodynamically favored, base-promoted equilibration (epimerization) of the two carbon centers adjacent to the carbonyl group in **3**. Thus, compound **4**, which possesses three of the four stereogenic centers with the correct absolute configuration for the eventual syntheses of **1** and **2**, was readily obtained.

Alkylation of the anion **17** derived from **4** with $ICH_2CH_2OCH_2OMe$ is expected to occur, for steric reasons, from the side of the molecule opposite to the angular methyl group. Indeed, this process gave a single product **5** ($[\alpha]_D^{25}$ +56.9°) in high yield. Reduction of **5** with *i*-Bu_2AlH in 1,2-dimethoxyethane (DME), followed by acid hydrolysis of the resulting imine, gave the somewhat unstable aldehyde **6**, which upon subjection to a modified Huang-Minlon reduction procedure, gave **7** ($[\alpha]_D^{25}$ +75.7°). Thus, the final stereogenic (quaternary) center was installed stereoselectively and efficiently.



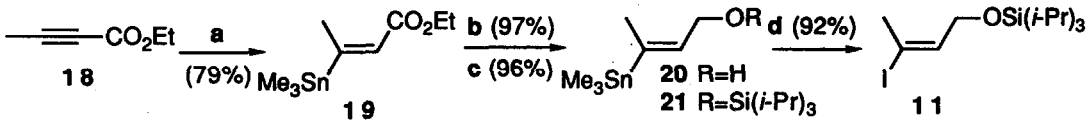
17



Scheme 1 **a**: TosMIC, *t*-BuOK, *t*-BuOH, DMPU, 45°C, 95 h; **b**: *i*-Pr_2NLi, HMPA, THF, -78°C to 0°C; $ICH_2CH_2OCH_2OMe$; **c**: *i*-Bu_2AlH, DME, 60°C, 6 h; AcOH, THF, H_2O, r.t., 12 h; **d**: H_2NNH_2 (anhydrous), $(HOCH_2CH_2)_2O$, 120-150°C, 4.5 h; remove H_2O, excess H_2NNH_2 (vacuum pump); add KOH (10 equiv), heat 230°C, 10 h; **e**: Me_2BBr, CH_2Cl_2, -78°C, 3 h; $NaHCO_3$, Na_2CO_3, H_2O, DME, r.t., 6 h; **f**: *p*-TsOH, $CHCl_3$, r.t., 24 h; **g**: I_2, Ph_3P, imidazole, CH_2Cl_2, r.t., 24 h; **h**: *t*-BuLi (2.3 equiv), Et_2O, -78°C to r.t.; recool to -78°C; add $ZnBr_2$ (1.5 equiv) in THF, -78°C to r.t.; add $Pd(dba)_2$ (0.03 equiv), Ph_3As (0.12 equiv), and **11** (1.5 equiv), stir r.t., 21 h; **i**: Bu_4NF, THF; **j**: Ph_3PBr_2, CH_2Cl_2; **k**: **14** (2 equiv), Bu_4NI, DMA, 60°C; **l**: -1.0 V, Hg(*vs.* Ag/AgCl), divided cell, NaOAc buffer, pH 4.5, H_2O; NaCl, H_2O.

Sequential treatment of **7** with Me_2BBr in CH_2Cl_2[5] and $NaHCO_3$-Na_2CO_3 in aqueous DME[6] provided a mixture of the alkenes **8** and **9** and, therefore, it was clear that during the Me_2BBr-mediated removal of the MOM group, partial isomerization of the exocyclic double bond had occurred.[7] Treatment of **8** with *p*-TsOH in $CHCl_3$ completed the rearrangement process and provided an excellent yield of the alcohol **9** ($[\alpha]_D^{25}$ -48.7°), which was readily transformed[8] into the corresponding iodide **10**.

Completion of the synthesis of the *trans*-clerodane carbon skeleton was accomplished *via* an efficient, convergent route involving an overall coupling of **10** with the vinyl iodide **11**. The latter substance was prepared from ethyl 2-butynoate **18** (**Scheme 2**). Reaction of **18** with lithium (trimethylstannyl)(cyano)cuprate in the presence of EtOH[9] provided, stereoselectively, the (*E*)-enoate **19**. Transformation of this material into the required iodo alkene **11** was carried out, *via* the intermediates **20** and **21**, in a straightforward fashion.



18 19 11

Scheme 2 **a:** $(Me_3SnCuCN)Li$, THF, EtOH, -78°C; **b:** *i*-Bu_2AlH, Et_2O, -78°C to 0°C; **c:** $(i\text{-}Pr)_3SiCl$, imidazole, CH_2Cl_2; **d:** I_2, CH_2Cl_2.

Treatment of **10** with *t*-BuLi at low temperature[10] was followed by conversion of the resultant primary alkyl-lithium into the corresponding organozinc reagent. Linking of the latter species with **11** was achieved by use of palladium(0)bis(dibenzylidene)acetone [$Pd(dba)_2$] in the presence of triphenylarsine.[11] This synthetically useful, Pd(0)-catalyzed coupling process provided the silyl ether **12**, which was readily transformed into the natural product (-)-kolavenol (**2**).[12]

Reaction of the silyl ether **12** with Ph_3PBr_2 in CH_2Cl_2[13] provided directly the allylic bromide **13** (unstable on silica gel), which, upon treatment with N^6-methoxy-9-methyladenine (**14**)[14,15] in *N,N*-dimethylacetamide (DMA) gave a mixture of the neutral compound **15** and the desired salt **16**. Analysis of the crude product by ^1H NMR spectroscopy showed that **15** and **16** were formed in a ratio of ~4:5.[16] Separation of these substances by chromatography on silica gel provided homogenous **16** (mp 198-199°C, $[\alpha]_D^{25}$ -24.4°; lit.[15] mp 192-196°C, $[\alpha]_D^{21}$ -26.2°).

Conversion of **16** into (-)-agelasine B (**1**) required reductive cleavage of the N-O bond associated with the methoxyamino group. This transformation was conveniently achieved by use of an electrochemical process.[17] Thus, reduction (0.1 M NaOAc, H_2O, pH 4.5) of **16** at -1.0 V (*vs.* Ag/AgCl) using a mercury electrode, followed by anion exchange with NaCl and careful purification of the product by chromatography on silica gel (4:1 CH_2Cl_2-MeOH) gave (-)-agelasine B (**1**) in 53% yield. This material exhibited $[\alpha]_D^{25}$ -27.2° (lit. -21.5°[1], -34.8°[15]) and displayed spectra (^1H NMR, ^{13}C NMR, IR, UV) identical with those of natural (-)-agelasine B.[18]

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4. All compounds reported herein exhibited spectra in accord with structural assignments and gave satisfactory C and H analyses.

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6. The crude product from the Me_2BBr reaction contained some of the bromomethyl ether of **8**. Aqueous base was employed to convert this material into **8**.

7. It is likely that the presence of traces of acid in the Me_2BBr was responsible for this (partial) isomerization.

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12. Our synthetic material ($[\alpha]_D^{25}$ -56.3°; lit.[2] $[\alpha]_D^{25}$ -45.7°) was spectrally identical with a sample of (-)-kolavenol obtained by reduction of methyl kolavenate. We thank Professor T. Tokoroyama for a sample of this ester. See Iio, H.; Monden, M.; Okada, K.; Tokoroyama, T. *J. Chem. Soc., Chem. Commun.* **1987**, 358.

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16. It has been reported[15] that the reaction of **13** with **14** produces **15** and **16** in a ratio of ~1:4.4. We have been unable to reproduce this claim. Our experiments consistently produced mixtures of **15** and **16** in a ratio of ~4:5.

17. It has been reported[15] that the conversion of **16** into (-)-**1** can be effected by treatment of **16** with zinc dust in aqueous acetic acid at 60°C. In our hands, repeated attempts to carry out this reaction under these (or similar) conditions gave none of the desired product **1**. The reason(s) underlying our inability to achieve the reported result is (are) unclear. In view of these difficulties, the new method involving an electrochemical protocol was developed.

18. Impure samples of (-)-agelasine B were obtained from Dr. D. J. Faulkner and Dr. R. J. Andersen. Purification of this material by reverse phase HPLC (C_{18}) (MeCN-0.2 M aqueous NaCl) provided the pure natural product. We thank Drs. Faulkner and Andersen for their assistance.

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