Syntheses of Agelasin B and its Analogues

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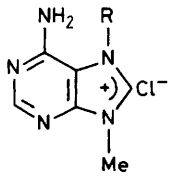
Agelasin B and its analogues with various terpenoid chains have been synthesized by the alkylation of N^6-methoxy-9-methyladenine with the appropriate alkyl bromides followed by treatment of the products with zinc dust–aqueous acetic acid.

Agelasins (**1**) are mono- or bi-cyclic diterpenoids isolated from sea sponges of Pacific *Agelas* species.[1—4] They are distinctive both in their unique structures with a 9-methyl-7-adenylium moiety and in their marked physiological activities including inhibitory effect on the enzymic reaction of Na, K-ATPase.[1,2] The most direct synthesis of agelasins involves the regioselec-

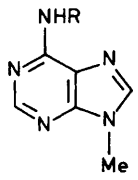
Table 1. Syntheses of agelasin B and its analogues.

	Alkylation				Demethoxylation		
Alkyl bromide R	Product, yield (%)[a]				Product	Yield (%)	M.p., *t*/°C
Prenyl	(**7a**),	55	(**8a**),	36	(**1a**)	66	164—169
Geranyl	(**7b**),	73	(**8b**),	16	(**1b**)	69	145—150
Farnesyl	(**7c**),	53	(**8c**),	17	(**1c**)	67	156—160
Geranylgeranyl	(**7d**),	75	(**8d**),	10	(**1d**)	57	158—162
Kolavenyl	(**7e**),	64	(**8e**),	15	(**1e**)	78	167—170
Methyl[b]	(**7f**),	59	(**8f**),	24			

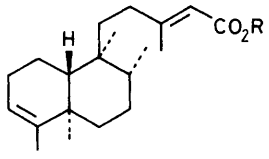
[a] The yields are for products isolated after chromatographic separation. [b] Data from ref. 8.



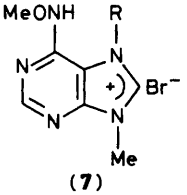
(1)



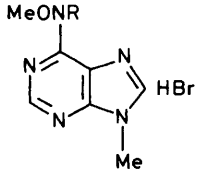
(2) R = H
(3) R = COPh
(4) R = OMe



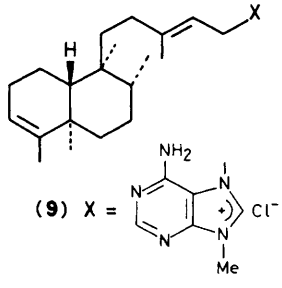
(5) R = H
(6) R = Me



(7)



(8)



(9) X =

(10) X = Br

tive alkylation of 9-methyladenine (**2**) with appropriate terpenoid units. We report here our investigations on such reactions, which have culminated in the synthesis of agelasin B (**9**).

For the synthesis of agelasin B (**9**), which is most abundant in *A. nakamurai* Hoshino and shows marked physiological activity,[2] we noted that its terpenoid unit has a similar structure, including absolute configuration, to that of kolavenic acid (**5**), a *trans*-clerodane diterpene. The latter is plentifully available from the roots of *Solidago* species.[5] The reduction of the corresponding methyl ester (**6**) with Bu^i_2AlH followed by bromination with PBr_3 afforded the allylic bromide (**10**), which could be used for the alkylation.

To study the selective alkylation of (**2**) at N^7, we examined first the reaction[6] of the N^6-benzoylated derivative (**3**). However treatment of (**3**) in dimethylacetamide with (**10**) as well as with prenyl bromide did not give rise to the desired products, presumably owing to the steric hindrance of the benzoyl group. We thus resorted to Fujii's procedure, which uses N^6-methoxy-9-methyladenine (**4**).[7] The reaction of (**4**) with prenyl bromide in dimethylacetamide at 60 °C for 1 h or at room temperature for 12 h proceeded smoothly to furnish the 7-alkylated product (**7a**), $\nu_{max.}$ (Nujol) 1670, 1590, 1550, 1140, 1040, and 870 cm^{-1}; ^1H n.m.r. (CD_3OD) δ 7.76 (1H, s) and 9.06 (1H, s), together with the N^6-alkylated compound (**8a**), $\nu_{max.}$ (Nujol) 1640, 1580, 1550, 1340, and 970 cm^{-1}; ^1H n.m.r. ($CDCl_3$) δ 7.93 (1H, s) and 8.54 (1H, s), in a 2.2 : 1 ratio in >95% yield. The ratio (**7a**) to (**8a**) varied with solvent over the range 1—2.5 : 1, the reaction in hexamethylphosphoramide being the most selective. However, dimethylacetamide was used for convenience during work-up. Treatment of (**4**) with (**10**) likewise yielded the desired 7-adenylium compound (**7e**), m.p. 192—196 °C; $[\alpha]_D^{21}$ − 26.2° (*c* 1.00, MeOH), $\nu_{max.}$ ($CHCl_3$) 3360, 2960, 1670, 1590, 1550, 1050, and 880 cm^{-1}; ^1H n.m.r. ($CDCl_3$) δ 7.97 (1H, s) and 9.83 (1H, s), with even better selectivity (4.4 : 1) with respect to the by-product (**8e**), $\nu_{max.}$ ($CHCl_3$) 2690, 1630, 1580, 1380, 1330, and 950 cm^{-1}; ^1H n.m.r. ($CDCl_3$) δ 7.73 (1H, s) and 8.39 (1H, s). The alkylation of (**4**) with other acyclic terpenoid bromides could be effected in the same way and the results are in Table 1.

A new procedure for the removal of the N^6-methoxy group was required since the original procedure using catalytic reduction[7,8] could not be used for the present examples. Various metal reductions were studied, treatment with zinc dust in aqueous acetic acid giving the most satisfactory results. Thus the reaction of (**7e**) at 60 °C for 18 h followed by treatment with saturated aqueous sodium chloride afforded the demethoxylated product (**1e**) as the chloride,† m.p. 167—170 °C, $[\alpha]_D^{21}$ − 34.8° (*c* 1.00, MeOH) in 78% yield. The identity of this product with agelasin B (**9**), {m.p. 167—170 °C, $[\alpha]_D^{25}$ − 21.5° (*c* 1.00, MeOH)}[1] was confirmed by spectroscopic (u.v., i.r., ^1H and ^{13}C n.m.r.) and t.l.c. comparison with the authentic sample.‡ Deprotection of the alkylated products (**7a—d**) was performed in the same way yielding the corresponding agelasin analogues (**1a—d**).§

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† Confirmed by ion-exchange chromatography.

‡ This constitutes a formal total synthesis of agelasin B (**9**) since we have recently completed the synthesis of (−)-kolavenic acid (**5**); to be published.

§ Our synthetic agelasins were tested for inhibitory activity against Na,K-ATPase reactions and found to exhibit the following activity relative to that of natural agelasin B at 10^{-4} M: (**1a**), 0%; (**1b**), 14%; (**1c**), 36%; (**1d**), 100%; (**7e**), 100%; (**1e**), 100% (H. Nakamura and Y. Ohizumi, unpublished results).