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TOTAL SYNTHESIS OF (±)-AGELINE A, A PHYSIOLOGICALLY ACTIVE CONSTITUENT OF *AGELAS* SPONGES

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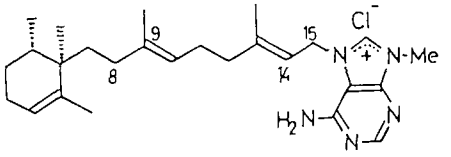
Summary: The monocyclic diterpene moiety of ageline A (**1**) was convergently constructed by the palladium-mediated coupling of C_9-terpenic chain as vinyl bromide **10** and C_{11}-monocyclic segment as alkylzinc compound **16**, which was obtained through a stereoselective cyclization and associated transformations. The appendage of 9-methyladenine ring to the diterpene unit led to the total synthesis of (+)-ageline A.

Recently a number of sesqui- and diterpenes with polar functionalities have been found as the metabolites of sea sponges of the genus *Agelas*[1] and they are featured by prominent bioactivity involving inhibitory effect on Na,K-ATPase.[2,3] In continuation of the synthetic studies on these compounds,[4] we concerned with the synthesis of ageline A[5] (agelasine F[1,3]), (**1**).



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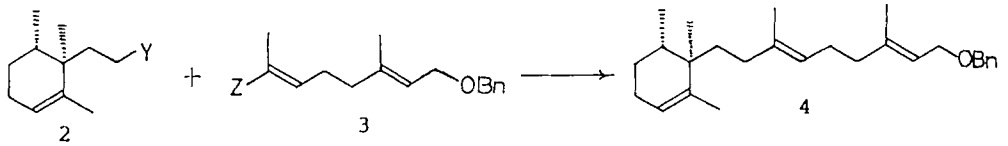
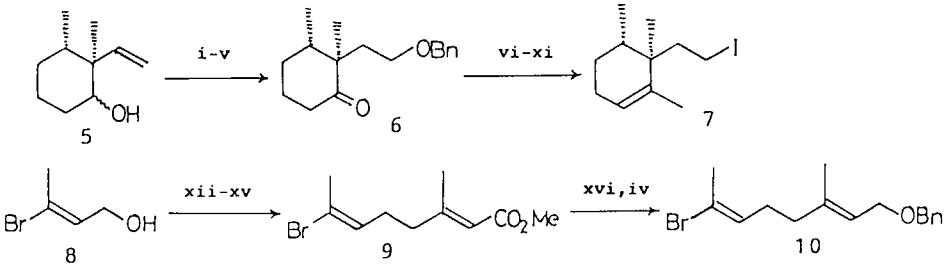
First our attention was focussed on the synthesis of the terpenic unit[6] and we envisaged the application of the folding strain control methodology[7] for the stereoselective construction of the cyclohexane ring with *cis*-dimethyl groups, which was found to be feasible as reported in the preceding report.[8] This synthetic plan necessitated the coupling of the terpenic chains at unprecedented position[9] (Scheme 1). We conceived to solve the problem by the metal-mediated coupling between the synthons **2** and **3**, which would be the most convergent way. With this plan in mind the iodide **7** was derived from the epimeric mixture of the cyclohexanol **5** obtained by the cyclization of (*Z*)-



2 **3** **4**

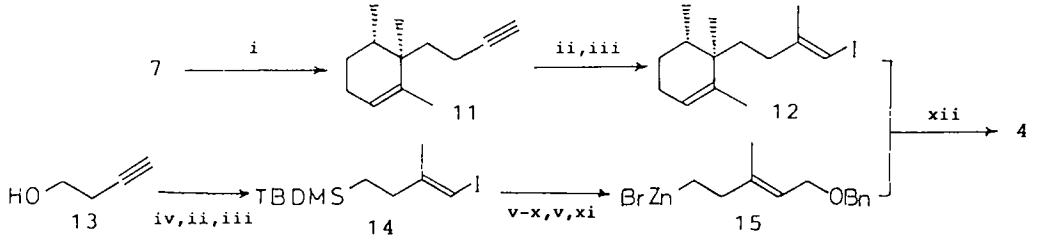
Scheme 1



Scheme 2 Reagents: i, CrO_3, H_2SO_4/Me_2CO; ii, $HOCH_2CH_2OH$, CSA/C_6H_6; iii, B_2H_6/THF, then H_2O_2, NaOH; iv, BnBr, NaH, *n*-Bu_4NI/THF; v, 1M HCl/THF; Vi, $MeMgI/Et_2O$; vii, $SOCl_2$, C_5H_5N/CH_2Cl_2; vii, TsOH/diglyme; vii, Li/NH_3; x, MsCl, Et_3N/CH_2Cl_2; xi, NaI/Me_2CO; xii, PBr_3, C_5H_5N/Et_2O; xiii, $^-CH_2CO^-CHCO_2Me/THF$; xiv, $(EtO)_2POCl$; xv, DIBAL/THF

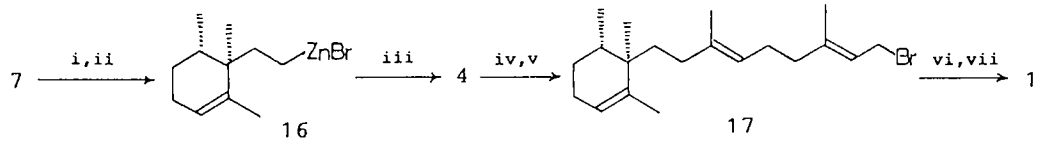
5,6-dimethyl-8-trimethylsilyloctanal[8] and the vinyl bromide **10** was prepared from (*E*)-3-bromo-2-butenol (**8**)[10] as shown in Scheme 2. The coupling of **2** and **3**, which are optional in two modes of polarity combination, was first investigated between the iodide **7** and the cuprate derived from **10**. Among the various modifications[11] of the cuprate used, only the mixed cuprate with 3-methoxy-3-methyl-1-butyne (THF, -20 °C)[12] afforded the coupling product **4** *albeit* in low yield (6.7%). Obviously the cuprate linkage at a non-terminal vinylic position would pose steric drawback for the substitution.

To circumvent this difficulty we searched less convergent route to **4**. The cyclic segment **7** was converted to vinyl iodide **12** by the substitution with lithium acetylide and subsequent zirconium-catalyzed carboalumination/iodination procedure.[13] The palladium-catalyzed coupling[14,15] of **12** with (*E*)-5-benzyloxy-3-methyl-3-pentenylzinc bromide (**15**), which was derivable from 3-butyne-1-ol as indicated in Scheme 3, afforded the diterpenoid compound **4** in 68% yield. Although the synthetic path thus developed was efficient enough for the preparation of **4** (50% overall yield from **7**), we seeked further to settle the problem of the terpenic chain linkage aimed at the outset, extending the Negishi's method to the reaction with non-terminal alkenyl



Scheme 3 Reagents: HC-CLi/DMSO; ii, Cp_2ZrCl_2, $Me_3Al/ClCH_2CH_2Cl$; iii, I_2/THF; iv, *t*-$BuMe_2SiCl$, Et_3N; v, *t*-BuLi/Et_2O; vi, Me_3Al/n-C_6H_{14}; vii, $BnOCH_2Cl$/THF; viii, HF/MeCN; ix, MsCl, C_5H_5N; x, NaI/Me_2CO; xi, $ZnBr_2$/THF; xii, $PdCl_2$dppf/THF

halide. When the vinyl bromide **10** was treated with the zinc compound **16** derived from **7** in the presence of $PdCl_2dppf$, the coupling reaction did proceed smoothly to afford the product **4** in 66% yield. Thus the combination of a terpenic chain between C-3 and C-4 of the 3-methyl-2-butenyl unit now become feasible and this fact will enlarge the synthetic design of terpenic chains.



Scheme 4 Reagents: i, *t*-BuLi/Et_2O; ii, $ZnBr_2$/THF; iii, **10**, $PdCl_2dppf$ (3 mol%); iv, Li/NH_3; v, PBr_3, C_5H_5N/Et_2O; vi, N^6-methoxy-9-methyladenine/ $MeCONMe_2$; vii, Zn, H_2O/AcOH

To complete the synthesis of ageline A, **4** was transformed to the corresponding bromide **17**, with which the regioselective alkylation at the 7 position of 9-methyladenine ring was performed by the method previously established.[4] The spectral data (UV, IR, ^1H and ^{13}C NMR) of the synthetic product were indistinguishable with those of authentic ageline A.[2] In the ^1H NMR spectrun[16] we observed that the signals due to 2'-H and 8'-H, in addition to the resonance due to amino protons, showed concentration-dependent shifts: δ-values measured at the concentration of 80 mg, 4.8 mg, 2.4 mg, 1.2 mg/0.6 mL were 8.43, 8.48, 8.49, 8.50 (2'-H) and 10.40, 10.60, 10.69, 10.77 (8'-H) respectively.[17] The reason may be ascribed to the propensity of the molecules to associate through the polar moiety.

In conclusion we have achieved the total synthesis of (±)-ageline A by a method involving the construction of the carbocyclic ring through a stereocontrolled cyclization reaction and the linking of the terpenic chains at unprecedented position.

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16. 1H NMR(400 MHz, $CDCl_3$, 1.2 mg/mL): δ 0.84(3H, s), 0.85(3H, d, J = 7 Hz), 1.56(3H, s), 1.58(3H, s), 1.86 (3H, s), 4.10(3H, s), 5.02(1H, br s), 5.41 (1H, br s), 5.46(1H, br t, J = 7 Hz), 5.65(2H, br d, J = 7 Hz), 6.53(2H, br s), 8.50(1H, s), 10.77(1H, s).
17. At the extremely high concentration (80 mg/0.6 mL), the chemical shifts of even 14-H and 15-H showed some discrepancy from those measured in more dilute solution (14-H δ 5.50 *vs.* 5.46; 15-H δ 5.61 *vs.* 5.65). However we did not observed 'double' signals with respect to H-2' and H-8' resonances at any concentration as reported by Faukner.[5]

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