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Synthesis of Antitumor Marine Steroid Aragusterols

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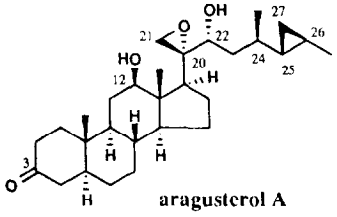
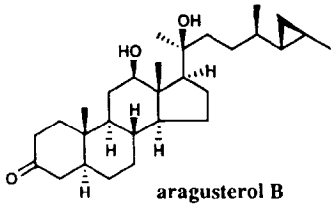
Abstract: The synthesis of antitumor marine steroid aragusterols A, B, C and D was successfully carried out. The synthesis involved stereoselective construction of side chain segment **8**, coupling of **8** with 20-keto steroid **11** giving aragusterol B and conversion of aragusterol B into aragusterols A, C and D.

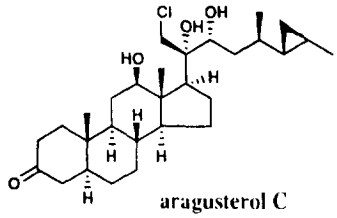
Aragusterols A, B, C and D [1] (xestokerol C [2]), isolated from the Okinawan marine sponge genus, *Xestospongia*, are structurally unique marine steroids each possessing a rare 26, 27-cyclo structure in the side chain. Aragusterols are also important for their biological activity. Aragusterols A and C very strongly inhibit the proliferation of KB cells at IC_{50} 0.042 and 0.041 μg/ml, respectively, and express potent *in vivo* antitumor activity against L1210 leukemia in mice (T/C 220 % and 257 %, at 1.6 mg/kg).[1a,c] For more detailed pharmacological research on aragusterols A and C, both compounds must be available in greater amounts. On this study it was decided to conduct this synthesis using hecogenin, a readily available material. The synthesis was conducted by initially obtaining from hecogenin aragusterol B, a natural resource more abundantly present in nature than either aragusterols A or C. This mode of synthesis is presented in detail in the following.



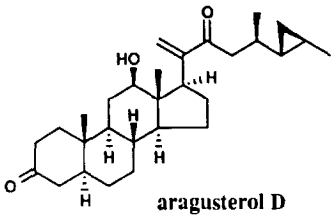
aragusterol A



aragusterol B



aragusterol C

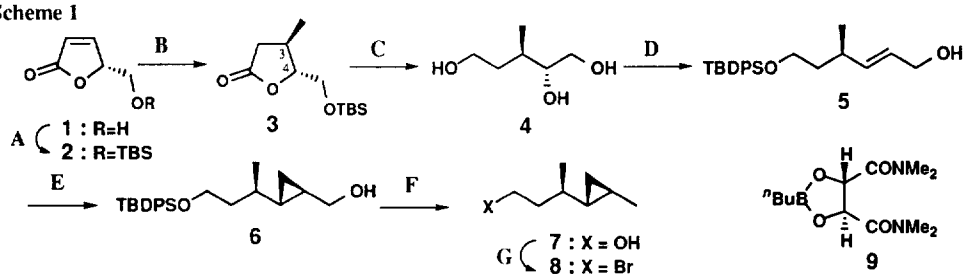


aragusterol D

The synthesis involves the stereoselective formation of side chain segment **8** present in all aragusterols, stereoselective coupling of **8** with 20-keto steroid **11** leading to aragusterol B and the conversion of aragusterol B to aragusterols A, C and D.

Side chain segment **8** was synthesized in the manner shown in Scheme 1. The hydroxy group of (*R*)-5-hydroxymethyl-2(5H)-furanone (**1**),[3] readily available from L-ascorbic acid, was protected as the TBS ether to give **2**[4] (92 % yield). Reaction of butenolide **2** with lithium dimethylcuprate in Et_2O at -78°C gave lactone **3** with high stereoselectivity in 90% yield.[5] Reduction of the lactone carbonyl in **3** with $LiAlH_4$, followed by deprotection of TBS ether with 80% AcOH gave triol **4** in 89% yield (two steps), which was then converted to allylic alcohol **5** in the following four steps: 1) $Pb(OAc)_4$ oxidation of 1,2-diol to give aldehyde, 2) Wittig reaction of the aldehyde to give α, β - unsaturated ester, 3) protection of the primary hydroxyl group as silyl ether and 4) diisobutylaluminum hydride (DIBAH) reduction of the ester. Diastereoselective cyclopropanation was successfully conducted according to the recent method of Charette.[6] Treatment of allylic alcohol **5** with CH_2I_2 in the presence of Et_2Zn and the *n*-butylboron complex of (*S*,*S*)-(-)-*N*,*N*,*N'*,*N'*-tetramethyltartaramide (**9**) gave the requisite cyclopropane derivative **6**[7] as the sole product in 99% yield. Compound **6** was converted to alcohol **7**[8] ($[\alpha]_D^{28}$ -36.6° (*c* 1.28, $CHCl_3$)) in three steps: 1) bromination of the hydroxy group, 2) reduction of the bromide with $LiAlH_4$ and 3) deprotection of the silyl group with $^nBu_4NF$. Finally bromide **8**, a segment of the side chain, was obtained by treating alcohol **7** with Ph_3P-NBS in 75% yield.

Scheme 1

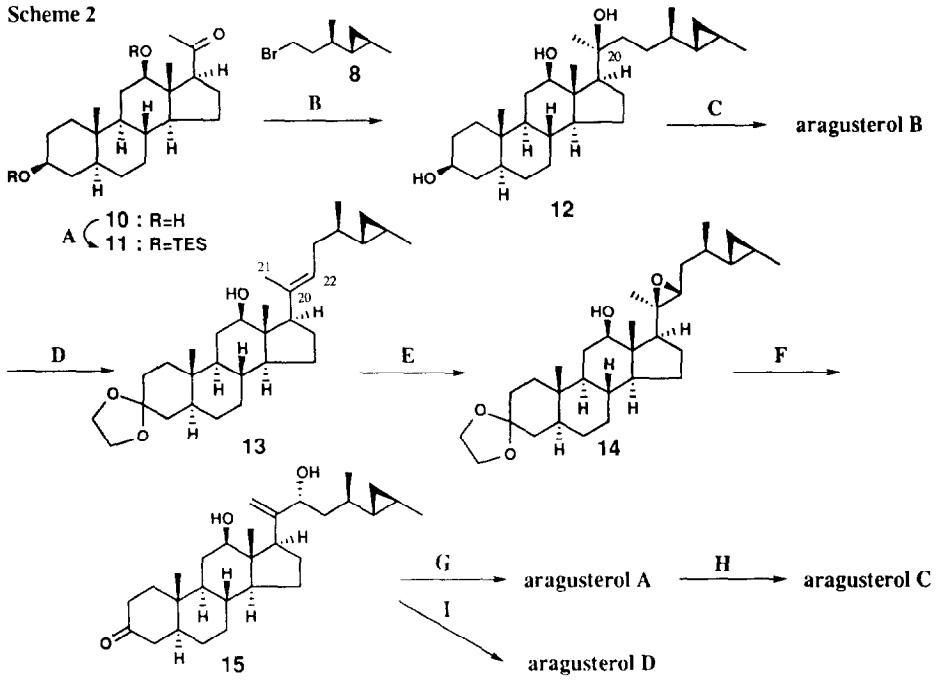


Reagents: A. TBSCl, imidazole, DMF, r.t., 92%; B. Me_2CuLi, Et_2O, -78°C, 90%; C. i) $LiAlH_4$, THF, 0°C, ii) 80% AcOH, r.t., 89% (2 steps); D. i) $Pb(OAc)_4$, K_2CO_3, benzene, r.t., ii) $Ph_3P{=}CHCO_2Me$, benzene, r.t., 67% (2 steps), iii) TBDPSCl, imidazole, DMF, r.t., iv) DIBAH, CH_2Cl_2, -78°C, 91% (2 steps); E. CH_2I_2, Et_2Zn, **9**, CH_2Cl_2, r.t., 99%; F. i) Ph_3P, CBr_4, CH_2Cl_2, r.t., ii) $LiAlH_4$, THF-Et_2O, r.t., iii) $^nBu_4NF$, THF, r.t., 88% (3 steps); G. Ph_3P, NBS, CH_2Cl_2, r.t., 75%.

Aragusterol B was synthesized *via* stereoselective coupling of side chain segment **8** with 20-keto steroid **11** (Scheme 2). The hydroxy groups of steroid **10**, prepared from (+)-hecogenin acetate in five steps,[9] were protected as triethylsilyl (TES) ether to give 20-keto steroid **11**. Reaction of 20-keto steroid **11** with alkyllithium, prepared from bromide **8** with lithium naphthalenide in THF at 0°C, followed by deprotection of TES ether with $^nBu_4NF$ at room temperature gave alcohol **12** with high stereoselectivity (20*S*:20*R* = 26:1).[10,11] The regioselective Oppenauer oxidation of C-3 hydroxyl group of **12** afforded aragusterol B (mp 194-195°C, $[\alpha]_D^{24}$ +4.7° (*c* 0.22, $CHCl_3$)).

Aragusterols A, C and D were synthesized from aragusterol B by chemical modification of the side chain. Ketalization and dehydration of aragusterol B by treatment with ethylene glycol and *p*-toluenesulfonic acid in

Scheme 2



Reagents : **A**. TESCl, imidazole, DMF, r.t., 85%; **B**. i) **8**, lithium naphthalenide, THF, 0°C, ii) $^{n}Bu_4NF$, THF, r.t., 93% (2 steps); **C**. $Al(O^{t}Bu)_3$, cyclohexanone, toluene, reflux, 66%; **D**. ethylene glycol, TsOH, benzene, reflux, 79%; **E**. $^{t}BuOOH$, $VO(acac)_2$, CH_2Cl_2, r.t., 78%; **F**. i) $^{i}Pr_2NMgBr$, THF, r.t., 93%, ii) 80%AcOH, r.t., 98%; **G**. mCPBA, Na_2HPO_4, CH_2Cl_2, 0°C, 54%; **H**. Li_2CuCl_4, THF, r.t., 90%; **I**. PDC, 4ÅMS, CH_2Cl_2, r.t., quant.

benzene gave 20(22)*E* olefin **13** and the 20(22)*Z* isomer in a 10:1 ratio with the concomitant formation of a trace amount of the 20(21) isomer. Epoxidation of *E* olefin **13** with $^{t}BuOOH$ in the presence of vanadium (III) acetylacetonate[12] gave (20*R*, 22*R*) epoxide **14** along with a trace amount of (20*S*, 22*S*) isomer in 26:1 ratio[10] in 81% yield.[13] Epoxide **14** was converted to allylic alcohol **15** by treatment with $^{i}Pr_2NMgBr$,[14] prepared from diisopropylamine and methylmagnesium bromide, followed by acid hydrolysis of the ketal with 80% AcOH at room temperature. The stereoselective epoxidation of allylic alcohol **15** with mCPBA at 0°C provided aragusterol A (mp 158-161°C, $[\alpha]_D^{26}$ +38.0° (*c* 0.11, $CHCl_3$)).[15] Reaction of aragusterol A with dilithium tetrachlorocuprate[16] at room temperature afforded exclusively aragusterol C (mp 203-205°C, $[\alpha]_D^{28}$ +19.4° (*c* 0.27, $CHCl_3$)) in 90% yield. The selective oxidation of the hydroxy group at C-22 of allylic alcohol **15** with pyridinium dichromate (PDC) at room temperature gave aragusterol D (mp 151-152°C, $[\alpha]_D^{26}$ -59.2° (*c* 0.15, $CHCl_3$)) in quantitative yield. Physical data for the synthetic aragusterols obtained above showed agreement with those of the corresponding natural aragusterols.[17]

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References and Notes

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4. Structural assignments for all stable synthetic intermediates were made based on ^{1}H-NMR (400 or 300 MHz), IR, high resolution mass spectroscopy and/or combustion analysis.
5. The *trans* stereochemistry of substituents at C-3 and C-4 positions on lactone **3** was strongly suggested by preferential attack of the reagent from less hinder side. Similar stereoselective reactions have been reported. For example: Hannessian, S.; Murray, P. J.; Sahoo, S. P. *Tetrahedron Lett.*, **1985**, *26*, 5627: Nagaoka, H.; Iwashima, M.; Abe, H.; Iguchi, K.; Yamada, Y. *Chem. Pharm. Bull.*, **1992**, *40*, 1742.
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7. Cyclopropanation of **5** in the absence of dioxaborolane chiral ligand **9** resulted in the formation of diastereomeric mixtures at a ratio of 3 : 2.
8. Alcohol **7** was converted to *p*-nitrobenzoate ($[\alpha]_D^{26}$ -24.3° (*c* 0.29, $CHCl_3$) which was subsequently shown identical with *p*-nitrobenzoate ($[\alpha]_D^{28}$ -25.1° (*c* 0.39, $CHCl_3$) derived from the natural aragusterol by chemical degradation.[1a]
9. Tschesche, R.; Schwinum, E. *Chem. Ber.*, **1967**, *100*, 464.
10. The ratio of the diastereomers was determined by ^{1}H-NMR analysis.
11. Similar stereoselective reactions for 20-keto steroids have been reported. For example: Chaudhuri, N. K.; Williams, J. G.; Nickolson, R.; Gut, M. *J. Org. Chem.*, **1969**, *34*, 3759: Kametani, T.; Katoh, T.; Tsubuki, M.; Honda, T. *J. Am. Chem. Soc.*, **1986**, *108*, 7055.
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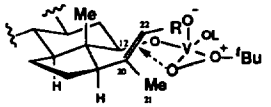
13. Diastereoselectivity in the epoxidation of **1** **3** can be explained based on the transition state in which vanadium metal is coordinated with hydroxy group at C-12.



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15. The stereoselectivity of epoxidation with mCPBA is explained by preferential attack of the reagent from the less hindered side.
16. Ciaccio, J. A.; Addess, K. J.; Bell, T.W. *Tetrahedron Lett.*, **1986**, *27*, 3697.
17. aragusterol A[1a] mp 157-158°C, $[\alpha]_D$ +37.6° (*c* 1.06, $CHCl_3$); aragusterol B[1b] mp 194-195°C, $[\alpha]_D$ +4.0° (*c* 1.56, $CHCl_3$); aragusterol C[1c] mp 204-205°C, $[\alpha]_D$ +20.1° (*c* 0.35, $CHCl_3$); aragusterol D[1b] mp 152.5-153.5°C, $[\alpha]_D$ -61.3° (*c* 0.30, $CHCl_3$).

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