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EFFICIENT TOTAL SYNTHESIS OF THE CYTOTOXIC HALOGENATED MONOTERPENE APLYSIAPYRANOID A

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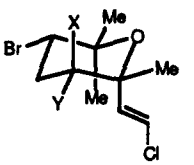
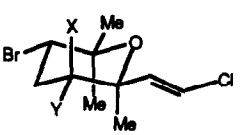
Abstract: Herein is described an efficient total synthesis of aplysiapyranoid A, **1a**, in which the key step is the diastereoselective bromoetherification of the hydroxy alkene **14** to give mainly the desired isomer **1a**.

The aplysiapyranoids A-D, **1a-d**, are four cytotoxic monoterpenes which were recently isolated by Kusumi, Kakisawa and coworkers from a marine mollusc, *Aplysia kurodai*.[2] They have interesting polyhalogenated tetrahydropyran structures and exhibit good cytotoxicity against several cell lines.[2] We recently reported the first total synthesis of the most active member of this series, namely aplysiapyranoid D, **1d**, which proceeded in 7 steps and 16% overall yield.[3] Other synthetic work aimed at these targets and others with related halogenated tetrahydropyran or hexahydrooxepine structures has also been described.[4] We report here the first total synthesis of aplysiapyranoid A **1a** in optically pure form by a short stereoselective route.

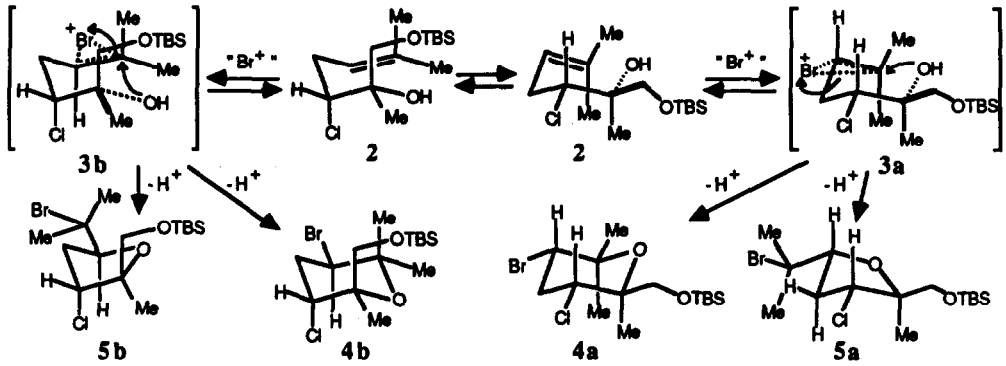


1a X = Br Y = H
1c X = H Y = Cl

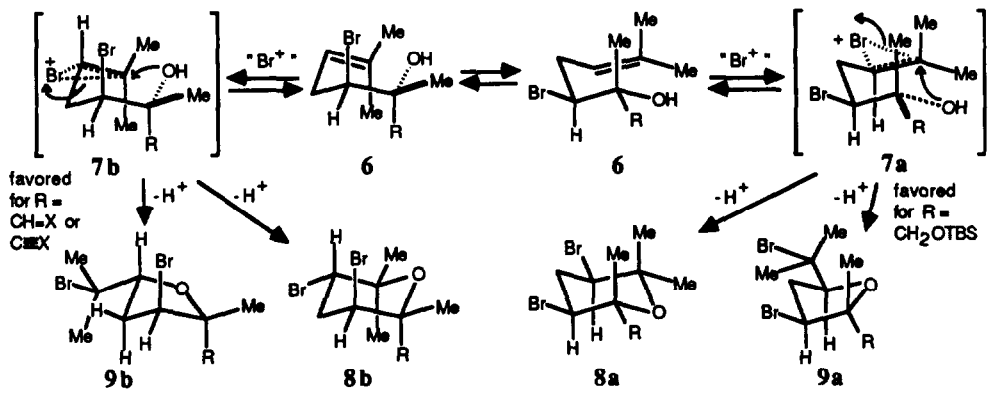


1b X = Br Y = H
1d X = H Y = Cl

In our synthesis of aplysiapyranoid D,[3] the stereochemical problems of our key cyclization were solved as follows. Cyclization of the optically pure chloroolefinic alcohol **2** proceeded preferentially via bromonium ion **3a** rather than **3b** because of additional non-bonded interactions in **3b** and the transition states leading from it to products, namely those due to the axial chlorine and the silyloxymethyl-methyl interaction, which are probably slightly larger than the methyl-methyl interaction in **3a** and the transition states leading from it to products. Therefore only the products with an equatorial chlorine are formed, namely **4a** and **5a**, in an approximately 2-3:1 ratio. The desired tetrahydropyran **4a** is preferred over the tetrahydrofuran **5a** due to the inductive effect of the chlorine on the transition states for opening of the bromonium ion, namely the partial positive charge on the carbon bearing chlorine disfavors

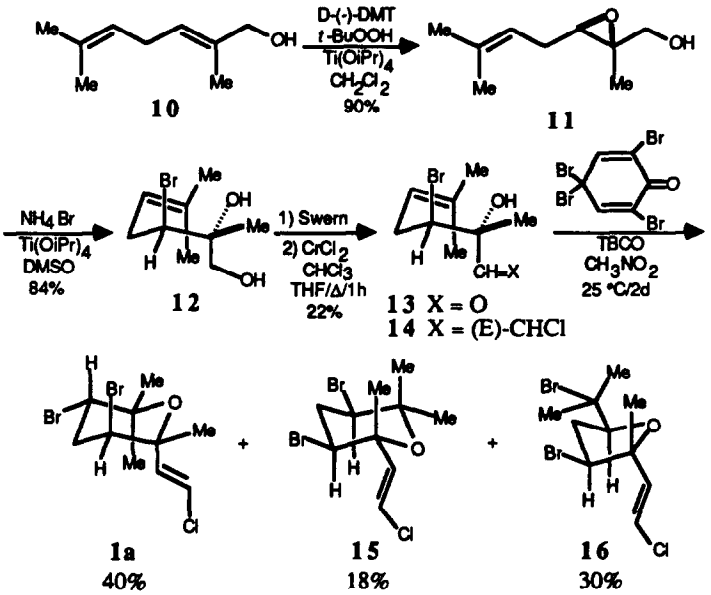


opening of the bromonium ion at the proximal carbon (leading to **5a**) more than opening at the distal carbon (leading to **4a**).[5] Thus the combination of stereochemical and inductive effects cause the desired product **4a** to be the major isomer formed.[3] However for the synthesis of aplysiapyranoid A, **1a**, the stereochemical situation must be reversed and the product with an axial bromine must be favored over that with an equatorial bromine. Examination of the substrates and intermediates for the key cyclization shows how this might be accomplished. Treatment of the optically pure diol **6** with a positive bromine source would give reversibly the two bromonium ions **7ab**. When R is a substituted methyl group, e.g., CH_2OTBS, cyclization via **7a** would be favored since the nonbonded interactions in **7b** and the transition states leading from it (axial bromine, silyloxymethyl-methyl) are larger than those in **7a** (methyl-methyl). This situation is exactly analogous to **3a** being favored over **3b**. In fact, when we treated **6** (R = CH_2OTBS) (prepared by silylation of diol **12** which is described below) with tetrabromocyclohexadienone (TBCO), we obtained a 3:1 mixture of **8a** and **9a** (R = CH_2OTBS), exactly in accord with this prediction. However, since the largest interactions in the system are the 1,3-diaxial methyl-methyl interactions, when R is a sterically small group, then the stabilities of **7a** and **7b** should be inverted. For example, if R = CH=X (X = O, NR, CHCl) or R = C≡X (X = N, CH), one would expect the interactions in **7b** (axial bromine, but now methyl-sp^2 carbon or methyl-sp carbon) to



be less than those in **7a** (methyl-methyl). MM2 calculations bear this out: when R = CH_2OH, the product **8a** is 2.3 kcal/mol more stable than **8b**, but when R = CH=CHCl, **8b** is 1.7 kcal more stable than **8a** (although these calculations were done on the products of the reactions and not on the transition states, we expect similar energy differences in the transition states leading to the products).

Therefore we have prepared aplysiapyranoid A **1a** as follows. Sharpless epoxidation of the readily available[3,6] dienol **10** with D-(-)-DMT gave the epoxide **11** in 90% yield and >95% ee. Opening with bromide[7] afforded in 84% yield the bromo diol **12** which was oxidized under Swern conditions to the very unstable hydroxyaldehyde **13**.[8] Takai chloroolefination[9] gave the desired cyclization substrate **14** in only fair yield (22% purified) along with ene reaction products, a problem that Takai mentions in his paper.[9] The key brominative cyclization of **14** with TBCO in nitromethane at 25 °C for 2d afforded a mixture of compounds in which the desired product, aplysiapyranoid A **1a**, was the major product (40% yield) along with the diequatorial dibromide **15** (18%) and the tetrahydropyran **16** (30%). The structure of **1a** was established by comparison of its ^1H NMR spectrum with that supplied by Dr. Kusumi. Thus we have completed a short (5 steps, 7% overall yield from the dienol **10**) stereoselective synthesis of aplysiapyranoid A, **1a**, which shows that the relative steric size of the substituents allows for diastereomeric control in the key step.



In summary, we have prepared aplysiapyranoid A **1a** by a short route in which the key bromoetherification reaction proceeds stereoselectively in a predictable fashion. Further work in this area is currently underway.

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References and Notes

(1) UCLA McCoy Award recipient, 1991-92; UCLA Hanson-Dow Teaching Award recipient, 1992.

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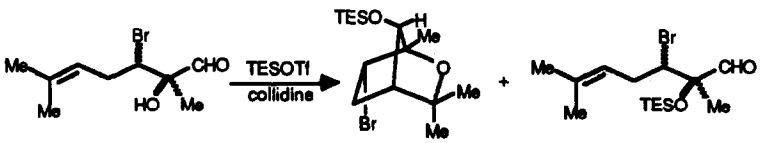
(4) See for example: (a) Wrensford, G.; Grab, L. A.; Salvino, J. M.; Williard, P. G. *Tetrahedron Lett.* **1990**, *31*, 4257. (b) Broka, C. A.; Lin, Y.-T. *J. Org. Chem.* **1988**, *53*, 5876. (c) Corey, E. J.; Ha, D.-C. *Tetrahedron Lett.* **1988**, *29*, 3171. (d) Hashimoto, M.; Kan, T.; Nozaki, K.; Yanagiya, M.; Shirahama, H.; Matsumoto, T. *Tetrahedron Lett.* **1988**, *29*, 1143. (e) González, A. G.; Martín, J. D.; Pérez, C.; Ramírez, M. A.; Ravelo, F. *Tetrahedron Lett.* **1981**, *22*, 5071. (f) Hoye, T. R.; Caruso, A. J.; Dellaria, J. F., Jr.; Kurth, M. J. *J. Am. Chem. Soc.* **1982**, *104*, 6704. (g) Hoye, T. R.; Kurth, M. J. *J. Am. Chem. Soc.* **1979**, *101*, 5065. (h) White, J. D.; Nishiguchi, T.; Skeean, R. W. *J. Am. Chem. Soc.* **1982**, *104*, 3923. (i) Shieh, H.-M.; Prestwich, G. D. *Tetrahedron Lett.* **1982**, *23*, 4643.

(5) The deschloro analogue of **2** gave a 1:1 mixture of the 6- and 5-membered rings corresponding to **4a** and **5a**, thereby indicating the importance of the inductive effect of the chlorine atom on the formation of the two isomeric products.

(6) Mori, K.; Ueda, H. *Tetrahedron* **1981**, *37*, 2581.

(7) Caron, M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 1557.

(8) Attempts to protect the alcohol of this hydroxyaldehyde as the TES ether led to Prins reaction and trapping, giving the 2-oxabicyclo[2.2.1]hept-7-yl silyl ether **A** as the major product with some of the desired TES ether **B**



13 **A** 60% : 30% **B**

also being formed. Therefore we chose to carry out the Takai reaction directly on **13**.

(9) Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408.

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