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Communications

Efficient Total Synthesis of the Cytotoxic Halogenated Monoterpene Aplysiapyranoid D

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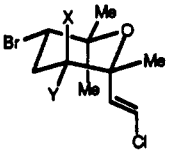
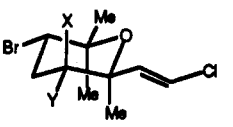
Summary: The first total synthesis of the antitumor marine natural product aplysiapyranoid D (**1d**) has been accomplished in seven steps from the dienol **2** using a key brominative cyclization that gives mainly the tetrahydropyran products rather than the expected tetrahydrofuran products.

Recently Kakisawa and co-workers reported the isolation and structure determination of four cytotoxic monoterpenes, the aplysiapyranoids A–D **1a–d**, from a marine mollusc, *Aplysia kurodai*.[1] In addition to their interesting polyhalogenated (dibromomonochloro or monobromodichloro) tetrahydropyran structures, these compounds also exhibit good cytotoxicity against various cell lines with aplysiapyranoid D, **1d**, being the most active and showing interesting activity against human tumor cells (Moser, IC_{50} = 14 μg/mL).[1] For this reason, the preparation of these compounds and others with related halogenated tetrahydropyran or hexahydrooxepine structures has become a synthetic goal.[2] We report here a very short, efficient synthesis of aplysiapyranoid D (**1d**) in optically pure form.

Although there are many reasonable disconnections possible, we chose the retrosynthetic route shown in Scheme I. The key steps of our approach were the preparation of the protected β-chloro alcohol **3** from (*E*)-2,6-dimethylhepta-2,5-dienol **2** by an application of



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



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

Sharpless epoxidation technology and then its brominative cyclization to produce specifically the required doubly anti dihalo ether **5a** which would then be easily converted into aplysiapyranoid D, **1d**. There was the serious question of whether one would obtain mainly the bromotetrahydropyrans or the bromotetrahydrofurans as the major products in this cyclization. Although the formation of the tetrahydropyrans is favored for mechanistic reasons (Markovnikov addition) and has been seen in some cases in the literature,[3] there are also several examples in the literature, especially the cyclization of analogous tertiary alcohols, in which the tetrahydrofurans are favored by a ratio of 2 or 3 to 1.[2b-d] We hoped that the presence of the electron-withdrawing chlorine atom on the chain connecting the alcohol and alkene might cause the desired tetrahydropyrans to be favored by destabilizing the partial positive charge at the secondary carbon center of the bromonium ion in compounds **4ab** because of its inductive effect. There was also the possibility that nonpolar solvents migh enhance this destabilizing β-inductive effect and thus favor the six-membered rings over the five. The key stereochemical question concerned the relative stereochemistry of the new carbon–bromine bond versus the established stereogenic carbons. Reaction of the olefin of **3** with the positive bromine source from either face of the double bond would generate reversibly the two bromonium

(1) Kusumi, T.; Uchida, H.; Inouye, Y.; Ishitsuka, M.; Yamamoto, H.; Kakisawa, H. *J. Org. Chem.* **1987**, *52*, 4597.

(2) 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.

(3) (a) Kato, T.; Ichinose, I.; Hosogai, T.; Kitahara, Y. *Chem. Lett.* **1976**, 1187. (b) Ting, P. C.; Bartlett, P. A. *J. Am. Chem. Soc.* **1984**, *106*, 2668. (c) Demole, E.; Enggist, P. *Helv. Chim. Acta* **1971**, *54*, 456.

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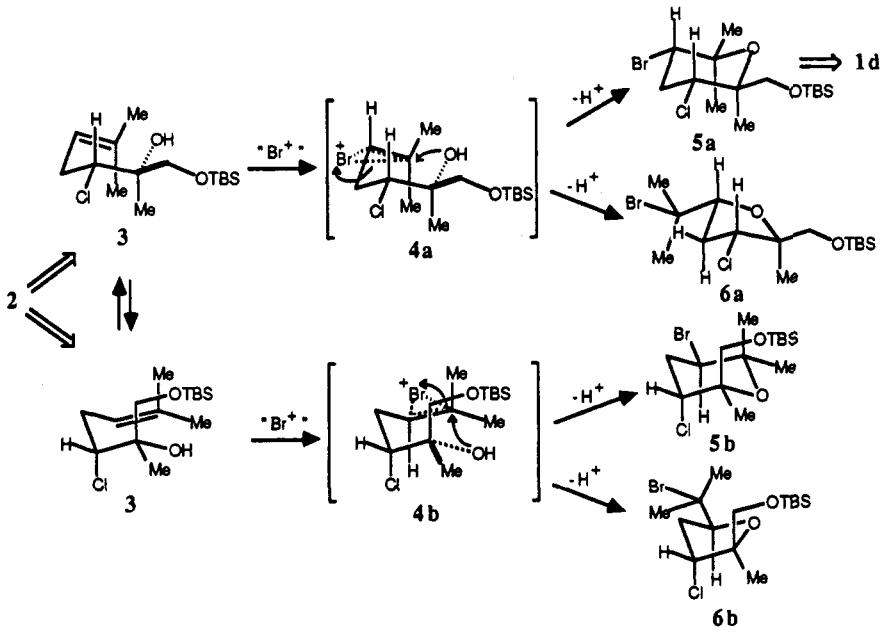
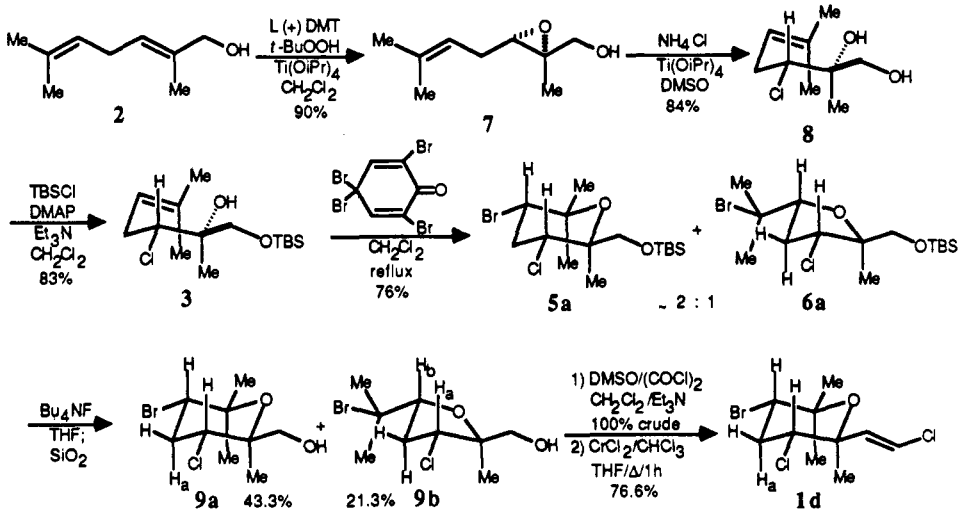
Scheme I



Scheme II



ions **4ab**. We expected that the transition states for cyclization leading to **5a** and/or **6a** from **4a** would be lower in energy than the corresponding ones giving **5b** and/or **6b** from **4b**, due to the small difference in 1,3-diaxial interactions (Me–Me vs Me–CH_2OR) and, more importantly, due to the preference for an equatorial vs an axial chlorine atom.[4] However, it was difficult to predict beforehand what regio- and stereoselectivity one would expect, namely what ratio of the four products, **5a**, **5b**, **6a**, and **6b** would be obtained. Therefore we carried out the synthetic sequence shown in Scheme II.

Sharpless epoxidation of the known alcohol **2** (prepared in four steps and 58% overall yield from 2-pyridinethiol and methallyl chloride by the method of Mori[5]) with L-(+)-dimethyl tartrate gave a 90% yield of the epoxy alcohol **7**. This compound was shown to be essentially optically pure (>95% ee) by examination of the ^1H NMR of its derived Mosher's ester using the ester of the racemic alcohol to guarantee nonoverlap of peaks. Nucleophilic opening of **7** with chloride using Ti(IV) catalysis[6] produced, as the only isolated product in 84% yield, the chlorodiol **8**, which was converted into the silyl ether **3** in 83% yield. The key brominative cyclization was carried out by treatment of **3** with 2,4,4,6-tetrabromocyclohexa-2,5-dienone (TBCD) in dichloromethane. At temperatures near or slightly above room temperature, only two products were observed, namely the desired compound **5a** and the isomer **6a**, in varying ratios always favoring **5a** (in refluxing dichloromethane we obtained a 76% yield of an approximately 2:1 mixture by ^1H NMR integration). Under these conditions, we obtained no more than traces of the diastereomeric products **5b** and **6b**, which would arise from the corresponding transition states derived from **4b**. The mixture of **5a** and **6a** could not be separated easily by chromatography so it was desilylated to give the alcohols **9a** and **9b**, isolated in yields of 43.3% and 21.3%, respectively, after simple flash chromatography. The stereochemistry of **9a** was determined primarily from its high-field ^1H NMR spectrum in benzene-d_6 which showed

(4) MM2 calculations of the two alcohols corresponding to **5ab**, namely **9a** and the des-silyl derivative of **5b**, indicate that **9a** is significantly more stable (>2.5 kcal/mol) than the des-silyl derivative of **5b**, and thus it is quite likely that the transition state leading to **5a** should reflect at least some of this energy difference and therefore be more stable than that leading to **5b**.

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

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

the characteristic apparent quartet (J = 12 Hz) for H_a that is also seen in the spectrum of **1d**.[1] Likewise the stereochemistry of **9b** was determined primarily from its high-field ^1H NMR spectrum which showed the expected coupling constants for the conformation drawn, namely: H_a dd, J = 11.8, 6.8 Hz; H_b dd, J = 10.7, 5.1 Hz.[7] Thus the cyclization does indeed proceed with good stereoselectivity to give only the isomers from the more stable transition states derived from **4a** in preference to those from **4b**. We have also carried out the cyclization of the des-chloro analogue of **3**, namely 1-((*tert*-butyldimethylsilyl)oxy)-2,6-dimethyl-5-hepten-2-ol, under similar conditions (TBCD, CH_2Cl_2, 25 °C, 40 min) and obtained an approximately 1:1 mixture of the analogous bromotetrahydrofurans and bromotetrahydropyrans in good yield.[8] Thus the chlorine atom does have an effect on the regioselectivity of the reaction, giving a higher proportion of the tetrahydropyran products. The synthesis was finished in short order by Swern oxidation of the alcohol **9a** to give in quantitative yield the crude aldehyde which was not purified but immediately subjected to chromium-promoted chlorovinylation using a slight modification of the conditions of Takai[9] to give aplysiapyranoid D (**1d**) in 76.6% isolated yield after chromatography.[10]

This ends a 7-step synthesis of **1d** from **2** with an overall yield of about 16% (Scheme II). This route should be a quite general one for the synthesis of the other aplysiapyranoids and related polyhalogenated ethers.

We have thus synthesized the cytotoxic marine natural product aplysiapyranoid D (**1d**) in excellent yield by a short route using a regio- and stereoselective bromoetherification as the key step. Further work in this area is in progress.

Acknowledgment. We thank the National Institutes of Health (GM-41592) and the University of California Cancer Research Coordinating Committee for generous financial support.

(7) MM2 calculations suggest that the tetrahydrofuran ring will exist mainly in the envelope conformation drawn with the CH_2 group as the flap and predicts very similar J's to those obtained. Compound **9b** was shown to be a tetrahydrofuran since reduction with tributylstannane afforded a product with an isopropyl group in the proton NMR.

(8) Determination of the structures of the des-chloro analogues were again made primarily by high field proton NMR of the bromoethers and their derived debrominated alcohols.

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

(10) The mixture of chromous chloride and chloroform in THF was refluxed for a few minutes until a purple color was observed, then it was cooled and the aldehyde added, followed by the usual procedure,[9] namely 1-h reflux, nonaqueous workup and chromatography.

Asymmetric Carbon–Carbon Bond Formation via Sulfoxide-Directed S_N2' Displacements of Acyclic Allylic Mesylates

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Summary: The addition of organocyanocuprates to acylic allylic mesylates bearing a chiral sulfoxide in the 2-position occurs with complete S_N2' regioselectivity, high E/Z stereoselectivity (15:1) and high asymmetric induction to produce enantiometrically pure trisubstituted vinyl sulfoxides.

Despite the development of new synthetic methods for alkene synthesis and asymmetric carbon centers in recent years,[1] acyclic stereocontrol remains a challenging problem in organic chemistry. In connection with our interest in using chiral vinyl sulfoxides in asymmetric synthesis[2a,b] and in organocopper chemistry,[2c] we sought new strategies for constructing systems containing chiral centers allylic to the vinyl sulfoxide unit. To this end we have found that the conjugate addition[3] of organocuprates to acyclic allylic mesylates activated with a chiral sulfoxide group in the β-position (**4** and **5**) occurs with complete S_N2' regioselectivity, high E/Z stereoselectivity and high asymmetric induction[4] to produce enantiomerically pure trisubstituted vinyl sulfoxides (**6**–**9**) in very good yields.

At the initial stage of this investigation, styryl sulfoxides **4a** and **5a** were studied; these substrates were prepared by lithiation of vinyl sulfoxide **1a**[5,6] and condensation with propionaldehyde to produce a 45:55 mixture[7] of readily separable diastereomeric alcohols **2a** and **3a**,[8] which were converted to their respective mesylates under standard conditions (MsCl, Et_3N, THF, 0 °C).[9] Unfortunately, most attempts to isolate styryl mesylates **4a** and **5a** were

(1) For some leading reviews, see: (a) Oare, D. A.; Heathcock, C. H. In *Topics in Stereochemistry*; Eliel, E. L., Wilen, S. H., Eds.; Wiley: New York, 1989; Vol. 19, pp 227–407. (b) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Ibid.* Allinger, N. L., Eliel, E. L., Wilen, S. H., Eds.; Wiley: New YOrk, 1982; Vol. 13, pp 1–115.

(2) (a) Marino, J. P.; Kim, M.-W.; Lawrence, R. *J. Org. Chem.* **1989**, *54*, 1782–1784. (b) Marino, J. P.; Fernández de la Pradilla, R.; Laborde, E. *Synthesis 1987*, 1088. (c) Marino, J. P.; Fernández de la Pradilla, R.; Laborde, E. *J. Org. Chem.* **1987**, *52*, 4898.

(3) A related process was studied by Posner et al. See: Posner, G. H. *Acc. Chem. Res.* **1987**, *20*, 72–78 and references cited therein.

(4) For asymmetric induction during conjugate addition to acyclic ethylenic sulfoxides, see: Takaki, K.; Maeda, T.; Ishikawa, M. *J. Org. Chem.* **1989**, *54*, 58–62. See also: Pyne, S. G. *J. Org. Chem.* **1986**, *51*, 81–87.

(5) Posner, G. H.; Tang, P. W.; Mallamo, J. P. *Tetrahedron Lett.* **1978**, 3995–3998.

(6) Prepared by the Andersen method from β-bromostyrene. Andersen, K. K. *Tetrahedron Lett.* **1962**, 93–95.

(7) Low stereoselectivities have been reported for these processes. Posner, G. H.; Mallamo, P.; Miura, K.; Hulce, M. *Pure Appl. Chem.* **1981**, *54*, 2307–2314. It should be pointed out that all isomermic alcohols **2** and **3** were separated readily by column chromatography with CH_2Cl_2–ethyl acetate mixtures as eluents.

(8) All new compounds were fully characterized spectrally and analytically.

(9) For recent reports on chiraly transfer by S_N2' displacements on allylic mesylates, see: Ibuka, T.; Habashita, H.; Funakoshi, S.; Fujii, N.; Oguchi, Y.; Uyehara, T.; Yamamoto, Y. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 801–803 and references cited therein.

0022-3263/91/1956-1349$02.50/0