Tetrahedron Letters, Vol.31, No.30, pp 4257-4260, 1990
Printed in Great Britain

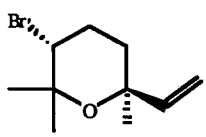
0040-4039/90 $3.00 + .00
Pergamon Press plc

SYNTHESIS OF 3-BROMO-6-ETHENYLTETRAHYDRO-2,2,6-TRIMETHYL-2H-PYRAN

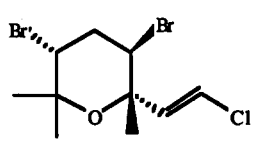
Granville Wrensford, Lawrence A. Grab, Joseph M. Salvino and Paul G. Williard*
Department of Chemistry, Brown University
Providence, RI 02912

Abstract: N-Phenylselenophthalimide cyclization of bromohydrins gives exclusively pyran derivatives. These derivatives are then elaborated into the title compound (**1**), a possible analog of the Aplysia pyranoids.

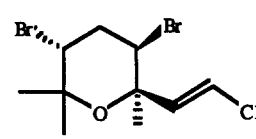
Aplysia pyranoids A and B (**2** and **3** respectively, Fig 1) were isolated from *Aplysia kurodai* .[1] They both exhibit cytotoxicities against Vero, MDCK and B_{16} cells.[1] We have been working on the total syntheses of both **2** and **3**. During these studies we developed a short and efficient route to the bromo-pyran ring system.



1



2

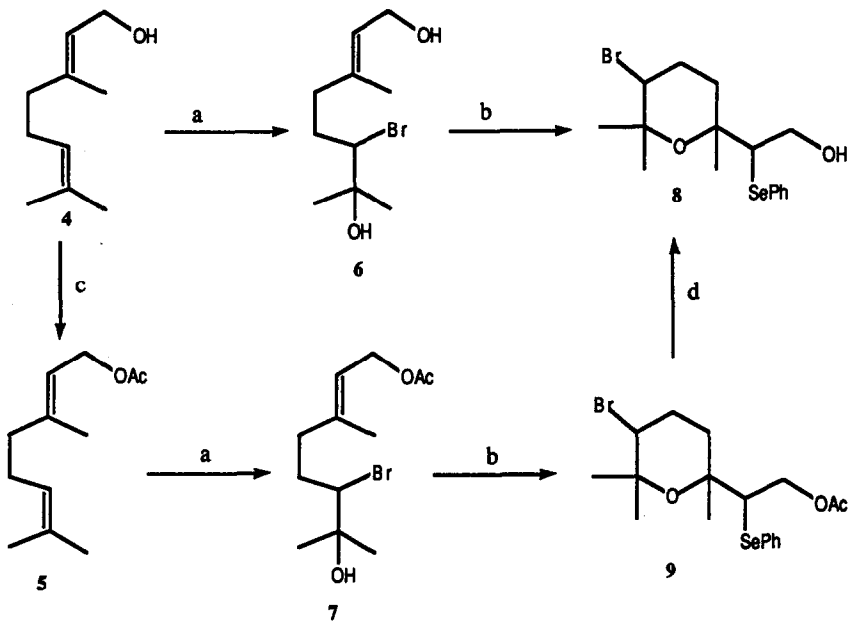


3

Although there are reports of methods for constructing bromo-pyrans, the yields are moderate or the method almost always effects concomitant formation of the furan ring.[2] We wish to report a short and efficient method for constructing a bromo-pyran ring without formation of the furan ring, and subsequent elaboration to the title compound (**1**) (a possible analog of the Aplysia pyranoids) in fairly good yields.

N-Bromosuccinimide bromination of geraniol (**4**) or geraniol acetate (**5**) gives the corresponding bromohydrins **6** and **7** (Scheme 1). Cyclization of the bromohydrins is achieved with N-phenylselenophthalimide (N-PSP).[3] Other electrophilic Se reagents such as phenylselenenyl chloride or phenylselenenyl bromide do not give any reaction under the conditions specified in Scheme 1. The mild conditions for the cyclization are important due to the very sensitive nature of **6** and **7** and the relative instability of N-PSP. Thus in the cyclization step, if one adds 1 eq of N-PSP all at once, the reaction stops after 8 hours and some starting bromohydrin is recovered. This factor can be eliminated by using 1.4 eq of N-PSP under strictly anhydrous conditions. A typical procedure is as follows: a catalytic amount of pyridinium *p*-toluenesulfonate was added at -78^0 C to a solution of

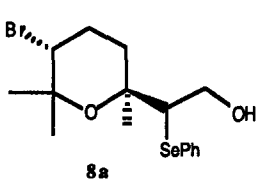
the bromohydrin in methylene chloride under a stream of dry nitrogen. Subsequently 1.4 eq of N-PSP was added and the mixture stirred at the same temperature for 2 hours. The cold bath was removed and replaced with an ice bath and the reaction mixture stirred for a further 6 hours with the ice bath temperature gradually rising to room temperature. The solid was filtered away and the filtrate purified by flash chromatography to give a diastereomeric mixture of the bromo-pyrans (**8** or **9**).



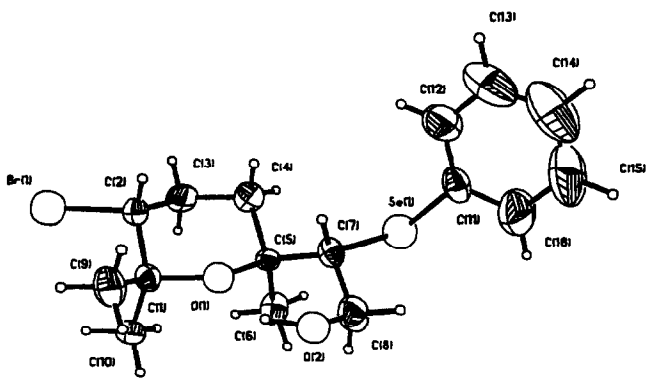
Scheme 1

Reagents and conditions: a) NBS / DME /H_2O, 0^0C, 2 hrs; b) N-PSP, PPTS (cat. amt), CH_2Cl_2, -78°C to rt 8 hrs; c) Ac_2O / Pyr, DMAP, 0°C to rt 2 hrs; d) aq NaOH, MeOH, rt 1 hr.

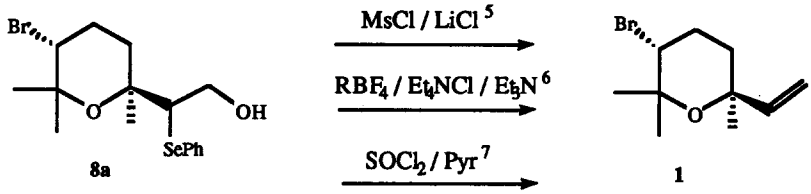
The bromo-selenyl alcohol **8a** separated from a mixture of diastereomeric alcohols **8** by fractional crystallization in a 1 : 5 ethyl acetate/hexane solution. X-ray diffraction analysis proved that the crystalline isomer **8a**, has the stereochemistry shown below.[4] This product has the same relative stereochemistry as the natural product **3**.



8a



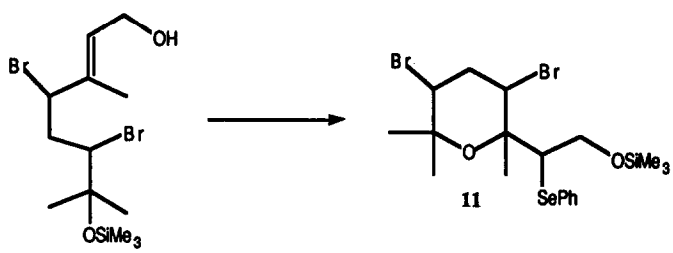
Having obtained the bromo-pyran it is necessary to transform the alcohol functionality into a chloride. Several methods (Scheme 2) were tried but none gave us the desired chloride. In all cases the bromo-pyran **1** bearing a terminal olefin was isolated as the major product. One possible explanation may be that the alcohol is transformed to the chloride, then an elimination whose net result is a reverse addition of phenylselenenyl chloride to a double bond occurs. This sequence yields the terminal olefin.[8]



8a **1**

Scheme 2

The exclusive formation of the bromo-pyran ring during the mild cyclization step is noteworthy. We feel that this cyclization procedure is generally applicable to derivatives of the bromohydrins **6** and **7** to give exclusively the bromo-pyran ring. Preliminary results in our laboratory indicate that the dibromo pyran derivative **11** has been isolated utilizing this procedure on the dibromo alcohol **10**. With this dibromo pyran we can now elaborate the side chain to complete our total synthesis of Aplysia pyranoid A and B.



10 **11**

Acknowledgment. We acknowledge the National Institutes of Health for partial support of this work through grants GM-35982 and CA-01330. The X-ray equipment was purchased with an instrument grant from the NSF (CHE-8206423).

References

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

2. For example: a) T. Kato, I. Ichinose, and T. Hosogai, *Chem. Lett.*, 1187, (1976); b) E. Demole and P. Enggist, *Helv. Chim. Acta*, **54**, 456, (1971).

3. K. C. Nicolau, D. A. Claremon, W. E. Barnette, and S. P. Seitz, *J. Am. Chem. Soc.*,**101**, 3704, (1979).

4. Compound **6a** crystallized in the centrosymmetric, monoclinic space group P $2_1/a$. The unit cell parameters were determined to be a = 13.497(3) Å, b = 7.611(2) Å, c = 17.258(6) Å, and ß = 106.14(5)° based upon least squares fitting of 25 independent reflections in the range $24° < 2\theta < 26°$. There are four asymmetric units of molecular formula $C_{18}H_{23}BrO_2Se$ in a volume of 1703.0 $Å^3$, which produces a calculated density of 1.58 g/cm^3. A total of 2893 reflections were recorded in the range $3.5° < 2\theta < 46°$ on a Nicolet $R3_m/E$ crystallographic system using the $\theta:2\theta$ scan routine and graphite monochromated MoKα radiation ($\lambda = 0.71069$ Å) at approximately - 100° C. After Lorentz and polarization corrections, the structure was solved by the SHELXTL 5.1 programs. All non -hydrogen atoms were refined anisotropically. The approximate location of all hydrogen atoms was determined by Fourier difference synthesis. In the final stages of refinement the hydrogen atoms were placed in calculated positions and allowed to ride with the atom to which they are attached. The final agreement factors are R = 0.058 and $R_w = 0.047$ for 1825 unique, observed reflections [$F_0 > 3\sigma(F_0)$] and 181 independent variables. The atomic coordinates and anisotropic thermal parameters for this structure have been submitted and are available on request from the Director of the Cambridge Crystallographic Data Center, University Chemical Laboratory, Lensfield Rd., Cambridge CB2 1EW, UK. Any request should be accompanied by the full literature citation for this communication.

5. E. W. Collington and A. I. Meyers, *J. Org. Chem.*,**36**, 3044, (1971).

6. T. Mukaiyama, S. Shoda, and Y. Watanabe, *Chem. Lett.*, 383, (1977).

7. J. Cason and J. S. Correia, *J. Org. Chem.*, **26**, 3645, (1961).

8. All non-aqueous reactions were done under a positive pressure of dry nitrogen utilizing solvents that were previously dried and distilled. All products were purified by column chromatography and were fully characterized by IR, ^{1}H-NMR, ^{13}C-NMR and appropriate parent ion identification by high resolution mass spectrometry (electron impact at an ionizing voltage of 70eV). Selected spectral data for **1** include the following: ^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.90 (q, 1H), 5.00 (m, 2H), 4.08 (dd, 1H), 2.15 (m, 2H), 1.82 (m, 2H), 1.40 (s, 3H), 1.37 (s, 3H), 1.29 (s, 3H). ^{13}C-NMR (400 MHz, $CDCl_3$): δ 147.10, 112.0, 75.40, 59.90, 38.80, 31.90, 29.50, 28.00, 22.50. EIMS: m/z 234 (M^+).

(Received in USA 22 November 1989; accepted 4 June 1990)