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CARBONYL PARTICIPATION IN THE ADDITION OF p-CHLOROPHENYLSELENENYL BROMIDE TO (E)-4-HEXENAL: A NEW ROUTE TO 2,6-DIDEOXYLGYCOSIDES

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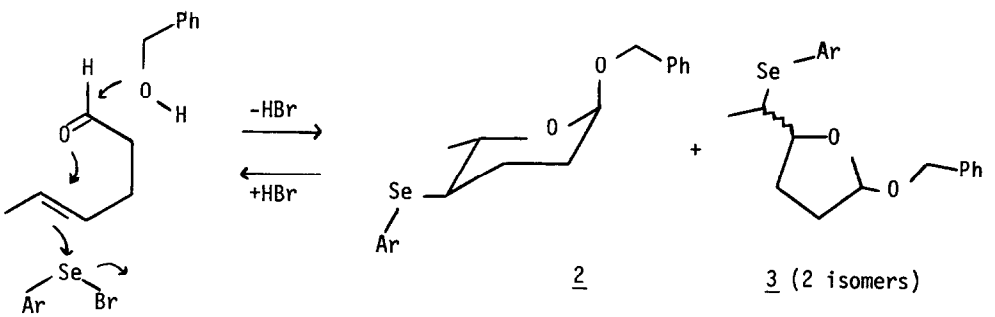
Several important natural products contain as an integral part of their molecular structure a 2,6-dideoxyglycoside.[1] For example the potent antileukemia drug adriamycin[2] consists of the aglycone adriamycinone coupled to the 3-amino-2,3,6-trideoxy sugar daunosamine. There are a number of good syntheses of specific 2,6-dideoxyglycosides[3], but there are no general routes to this important class of compounds. We wish to report the preparation of the olefinic sugar precursor trans-2-benzyloxy-3,6-dihydro-6-methyl-2H-pyran (4), a potentially useful precursor of a number of 2,6-dideoxyglycosides.

The key step in the synthesis relies on carbonyl participation[4] in the addition of p-chlorophenylselenenyl bromide (9.4 mmol in 20 ml carbon tetrachloride) to (E)-4-hexenal (1)[5] (8.0 mmol) in carbon tetrachloride (20 ml) containing benzyl alcohol (10 mmol) to yield 3 products as illustrated in Scheme I.[8] Under kinetic control (i.e. in the presence of solid potasium carbonate) 5-membered ring products 3 predominate (68%, mixture of two isomers),

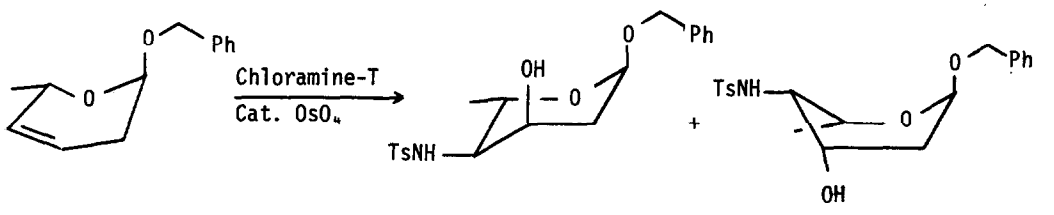
Scheme I



Ar = p-chlorophenyl

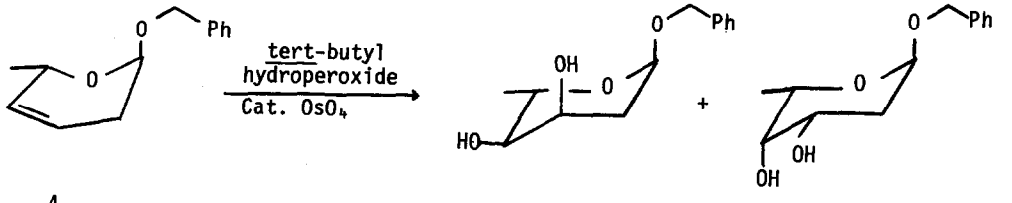
while under equilibrating conditions (i.e. 30 min. at reflux with no added base) the desired 6-membered ring isomer 2 is the major product (62%). When a reaction mixture which has been run under equilibrating conditions is washed with sodium carbonate solution and then filtered through Florisil [hexane (to remove diphenyl diselenide) then 5% ethyl acetate-hexane], isomer 2 crystallizes from hexane) from the crude product mixture. Furthermore, under the influence of acid (boron fluoride etherate) the mother liquor is re-equilibrated and a second crop of isomer 2 is obtained. After 3 equilibration/crystalization cycles and a final recrystalization a 67% yield of 2 (mp 80-81°)[9] from 1 is realized.

Oxidation of 2 (4.7 mmol in 50 ml carbon tetrachloride and 10 ml pyridine[10a] with 10 ml 30% hydrogen peroxide, 100 h room temperature) followed by in situ selenoxide elimination[10b] results in the formation of 4 (80% yield after chromatography on alumina eluting with 4% ether in hexane).[11] A number of ways to further functionalize 4 can be envisioned. For example, hydroxyamination of 4 (Chloramine-T, silver nitrate, catalytic osmium tetroxide)[12] results in the formation of 2 isomeric products, isolated in 28% (5) and 41% (6) yield.[13] The structures of 5 (mp. 149°)[9] and 6 (oil, acetate, mp. 118-119°)[9] have been tentatively assigned as shown



4 5 6

on the basis of their ^1H NMR spectra.[13] Olefin 4 can also be converted to the isomeric diols 7 (25%) and 8 (13%) (tert-butyl hydroperoxide, tetraethylammonium acetate, catalytic osmium tetroxide).[15]



4 7 8

In the cyclization step (Scheme 1) benzyl alcohol was used for convenience in the ^1H NMR identification of the products. Good yields of cyclized products were also obtained with cyclohexanol, menthol, borneol, and cholesterol; although, the isomeric composition of these mixtures was not determined. The use of a chiral alcohol in this step has the potential of an asymmetric synthesis but this has not been pursued.

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Notes and References.

1. See for example: W.D. Ollis, C. Smith and D.E. Wright, J.C.S. Chem. Comm., 882 (1974); F. Arcamone, W. Barbier, G. Franceschi, S. Penco, and A. Vigevani, J. Amer. Chem. Soc., 95, 2008 (1973); Y.A. Berlin, M.N. Kolosov, I.V. Yartseva, Khim. Prir. Soedin, 9, 539 (1974); W.W. Lee, H.Y. Wu, J.J. Marsh, C.W. Mosher, E.M. Acton, L. Goodman, and D.W. Henry, J. Medicinal Chem., 18, 767 (1975).

2. A. DiMarco and F. Arcamone, Arzneim-Forsh, 25, 368 (1975).

3. See for example: C.M. Wong, T.-L. Ho, and W.P. Niemezura, Can. J. Chem., 53, 3144 (1975); D. Horton and W. Weckerle, Carbohydrate Research,44, 227 (1975); D. Horton and W. Weckerle, ibid., 46, 227 (1976); F. Arcamone, A. Bargiotti, G. Cassinelli, S. Penco, and S. Hanessian; ibid., 46, C3 (1976).

4. For other examples of ArSeX additions to olefins involving cyclizations through captures by internal nucleophiles see: R.F. Lauer, Ph.D. Thesis, Massachusetts Institute of Technology, Cambridge, Mass., 1974; K.C. Nicolaou and Z. Lysenko, Tetrahedron Letters, 1259, (1977); K.C. Nicolaou and Z. Lysenko, J. Amer. Chem. Soc., 99, 3186 (1977); D.L.J. Clive, G. Chittattu, and C.K. Wong, Can. J. Chem., 55, 3894 (1977); D.L.J. Clive, G. Chittattu, N.J. Curtis, W.A. Kiel, and C.K. Wong, J.C.S. Chem. Comm., 725, (1977); D.L.J. Clive, C.K. Wong, W.A. Kiel, and S.M. Menchen, ibid., 379 (1978); D.L.J. Clive, G. Chittatta, and C.K. Wong, ibid., 441, (1978).

5. Prepared in our hands by 2 routes: (a) Mercuric acetate catalyzed exchange between 1-butene-3-ol and butyl vinyl ether at 100° (23%).[6] (b) Conversion of cyclopropylmethylcarbinol to (E)-1-bromopentene-3 followed by Grignard addition to dimethylformamide (35%).[7]

6. J.K. Crandall and C.F. Meyer, J. Org. Chem., 35, 3049 (1970).

7. M. Julia, S. Julia, and T.S. Yu, Bull. Soc. Chim. France, 1849 (1961); S.F. Brady, M.A. Ilton, and W.S. Johnson, J. Amer. Chem. Soc., 90, 2882 (1968).

8. The products were identified by their ^1H NMR spectra. Compound 2 exhibits a methyl doublet (δ1.35) coupled to an OCH proton at δ3.95 (J = 6Hz) while the mixture 3 exhibits 2 methyl doublets (δ1.41 and 1.50) coupled to a SeCH proton at δ3.28. Furthermore in 2 the OCH and SeCH protons show axial-axial coupling and the anomeric proton (δ4.91) is equatorial (J < 3Hz).

9. Correct combustion analysis was obtained for this compound.

10. (a) The use of a two phase system containing pyridine for the oxidation/elimination of selenide was developed by Reich: H.J. Reich, J.M. Renga and I.L. Reich, J. Org. Chem., 39, 2133 (1974); (b) The use of the p-chlorophenylselenide is important here since the rate of elimination was very slow, and the yield of olefin 4 was poor, when the unsubstituted phenylselenide derivative analogous to 2 was oxidized under the same conditions. The beneficial effect of electron-withdrawing groups on the elimination has been previously established: K.B. Sharpless and M.W. Young, J. Org. Chem., 40, 947 (1975).

11. ^{1}H NMR (90 MHz)($CDCl_3$) δ 1.25 (d, J = 6; 3H), 2.05 (d, J = 16; 1H), 2.42 (d of t, J =16, 4; 1H), 4.34 (m; 1H), 4.68 (AB, J = 12; 2H), 5.02 (d, J = 4; 1H), 5.65 (s, 2H) and 7.30 (s, 5H).

12. (a) K.B. Sharpless, A.O. Chong, and K. Oshima, J. Org. Chem., 41, 177 (1976); (b) I. Dyong, Q. Lam-Chi, G. Schulte, B. Fraser-Reid, and J. Primeau, Angew. Chem. Int. Ed., 16, 553 (1977); (c) For recent improvements in the osmium-catalyzed oxyamination reaction see: E. Herranz, S.A. Biller, and K.B. Sharpless, J. Am. Chem. Soc., 100, 3596 (1978); and E. Herranz and K.B. Sharpless, J. Org. Chem., 43, 2544 (1978).

13. In the ^{1}H NMR spectrum of 5 both the OCH(Me)(δ3.76) and the NCH (δ2.95) protons show axial-axial coupling (J = 10Hz) while the HOCH (δ3.35) proton shows only equatorial coupling (J = 3Hz). In the ^{1}H NMR spectrum of 6, again both the OCH(Me)(δ3.74) and NCH protons show axial-axial coupling (J = 9Hz) while the HOCH proton shows only equatorial coupling. This can be rationalized by assigning a boat conformation to 6 with the bulky tosylamide group in the equatorial position.[14]

14. See for comparison: M.M. Janot, Q. Khuong-Huu, C. Monueret, I. Kabore, J. Hiblesheim, S.D. Gero, and R. Goutarel, Tetrahedron, 26, 1695 (1970) and Q. Kluong-Huu, C. Monueret, I. Kabore, P. Choay, J.-M. Tekam, and R. Goutarel, Bull. Soc. Chim. France, 864, (1971).

15. K. Akashi, R.E. Palermo, and K.B. Sharpless, J. Org. Chem., 43, 2063, (1978).

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