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TETRAHEDRON: *ASYMMETRY*

Highly diastereoselective radical cyclization of a glucose-derived enol ether radical cation/phosphate anion pair

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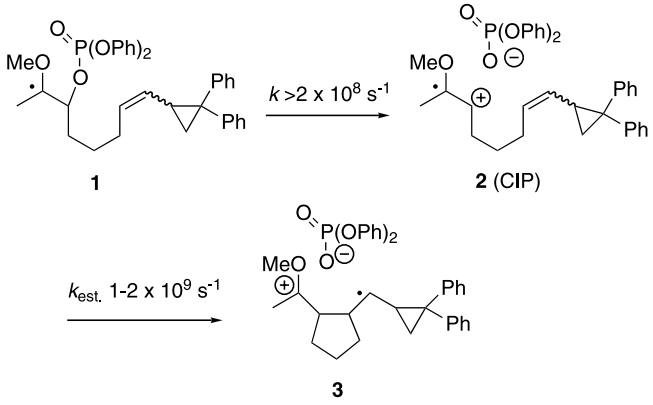
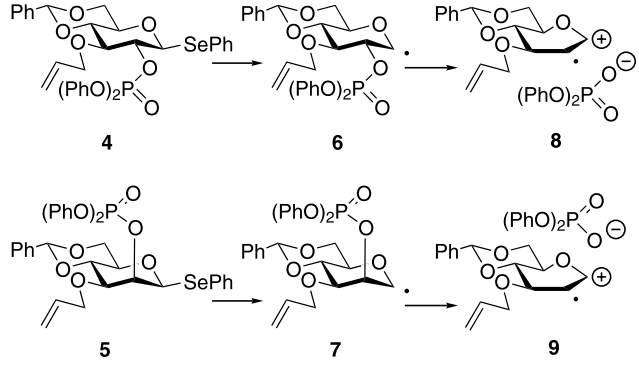
Abstract—Diastereomeric 3-*O*-allyl-4,6-*O*-benzylidene-2-*O*-(diphenylphosphatoxy) β-D-*gluco*- and β-D-*manno*-pyranosyl phenylselenides were prepared and subjected to treatment with tributyltin hydride and AIBN. The *gluco*-compound undergoes smooth radical cyclization to a single diastereomeric product in high yield whereas the *manno*-isomer reacts only reluctantly to give a complex mixture. This difference in behavior is interpreted as arising from the formation of two different contact radical ion pairs in which the phosphate group shields opposite faces of the enol ether (glycal) radical cation.

The advent of the fragmentative approach to the generation of alkene radical cations[1,2] has opened up whole new vistas[3] in the chemistry of these long-revered reactive intermediates.[4] Among the more exciting of the new avenues is the possibility of exploiting a stereochemical memory effect in the contact ion pair arising from fragmentation of a stereochemically defined β-(phosphatoxy)alkyl radical or related precursor. Previously, we have demonstrated how such an effect can be exploited in the nucleophilic trapping of formally planar alkene radical cations.[5] We now show that the ion-pair geometry has a profound influence on radical type cyclizations of fragmentatively generated alkene radical cations, as manifested by the dramatically different results obtained with a formally diastereomeric pair of contact radical ionic pairs.



Scheme 1. Estimated rate constants for fragmentation and cyclization in acetonitrile at ambient temperature.

By means of time-resolved laser flash photolyses and the probe **1**, Newcomb et al. have determined[6] that enol ether radical cations, of which **2** is an example, undergo 5-*exo*-radical cyclization within the initial contact ion pair, i.e. before equilibration with any solvent-separated ion pairs and/or free ions, even in polar solvents such as acetonitrile and acetonitrile/trifluoroethanol mixtures (Scheme 1). Moreover, the rate constant for cyclization of enol ether alkene radical cation **2**, as reported by the kinetically transparent opening of the cyclopropylcarbinyl radical **3**, was estimated to be $1–2\times10^9$ s^{-1} at ambient temperature, i.e. approximately four orders of



Scheme 2. Glycal radical cation generation.

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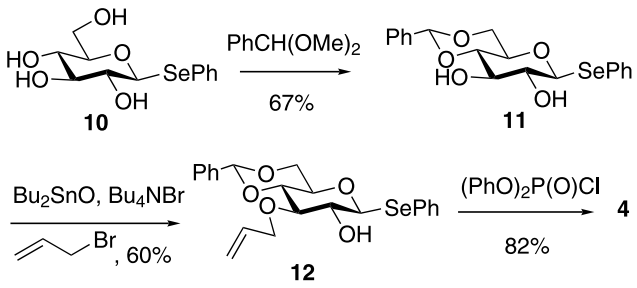
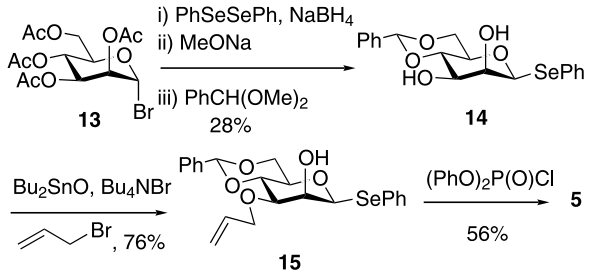


Scheme 3. Preparation of *gluco*-radical precursor **4**.



Scheme 4. Preparation of *manno*-radical precursor **5**.

magnitude faster than that of an analogous uncharged alkyl radical.[7]

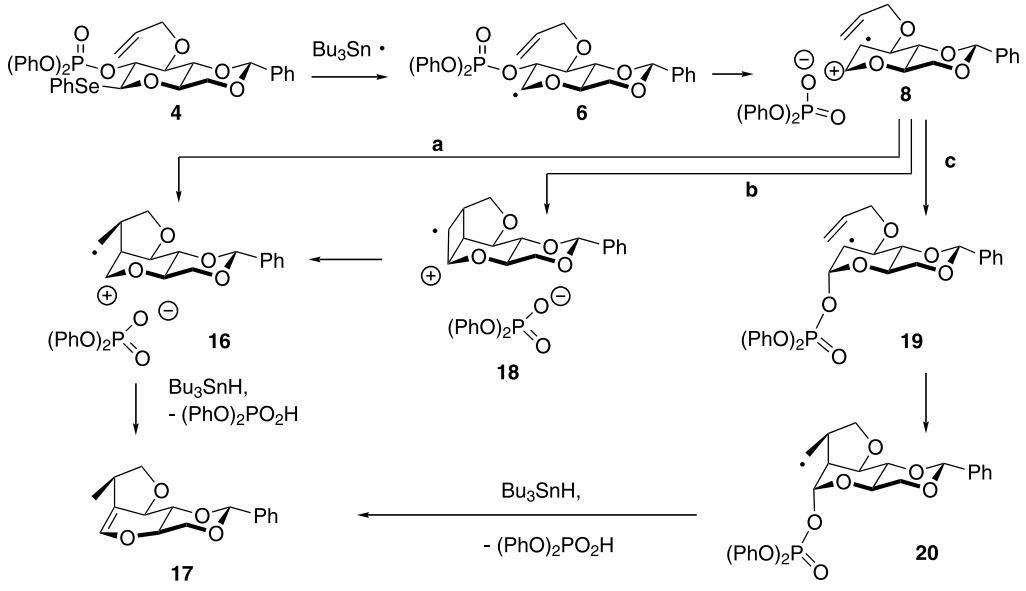
In the light of the above we reasoned that radical precursors **4** and **5** would lead, via the anomeric radicals **6** and **7**, to diastereomeric contact ion pairs **8** and **9** (Scheme 2) and that these latter would exhibit fundamentally distinct behavior owing to the differential shielding of the alkene radical cation by the phosphate counter ion.

Se-Phenyl 2,3,4,6-tetra-*O*-acetyl-β-D-selenoglucoside[8] was converted to the tetraol **10** by Zemplen deacetylation. This was elaborated to the benzylidene acetal **11**, and then to the 3-*O*-allyl derivative **12** by standard means and, finally, phosphorylated with diphenyl chlorophosphate to give the *gluco* radical precursor **4**[9] (Scheme 3).

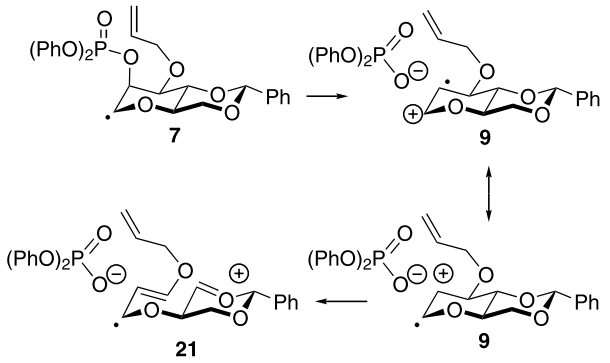
The *manno*-isomer **5**[10,11] was similarly obtained (Scheme 4).

Photolysis of **4** with tributyltin hydride and AIBN in benzene resulted in the formation of a single major compound, identified as the glycal **17**,[12] in 95% yield and whose stereochemistry was confirmed by single-crystal X-ray diffraction. We envisage formation of this compound as proceeding via radical cyclization on the initial contact ion pair **8** leading to the formation of **16**, followed finally by chain transfer and deprotonation (Scheme 5, path a). In ring closures of 2-(3-butenyl)cyclohexyl radicals and their substituted and heterocyclic variants, cyclization typically affords the *cis*-fused bicyclic system, hence our assignment of the *manno*-stereo chemistry to intermediate radical **16**. The *endo*-position of the methyl radical in **16** can be seen as arising from a Beckwith–Houk[13] chair-like transition state for cyclization in which both substituents (C1 and C4 of the pyranose ring) are *pseudo*-equatorial. Alternative possibilities that cannot be entirely ruled out include the transient formation of a fused cyclobutane radical cation **18**[14] followed by opening to **16** (Scheme 5, path b) and the collapse of the initial contact ion pair to the anomeric phosphate **19**[15] followed by cyclization and eventual elimination of phosphoric acid (Scheme 5, path c).

A dramatically different result was observed with the *manno*-precursor **5**. First, prolonged heating of **5** over a period of more than a day with tributyltin hydride with repeated additions of AIBN was required in order to drive the reaction to completion. Such behavior is usually indicative of the breakdown of the chain reac-



Scheme 5. Cyclization of the *gluco*-precursor **4**.



Scheme 6. Retarded cyclization and decomposition in the *manno*-series.

tion due to the failure of one or more of the propagation steps. A complex reaction mixture was obtained from which only minor amounts (<10%) of **17** could be isolated. Instead, a number of unidentified products were formed, all in minor amounts strongly suggesting that decomposition of one or more intermediates had taken place.

We suggest that the difference in reactivity between precursors **4** and **5** is due to the different placement of the phosphate counter ion in the respective contact ion pairs **8** and **9**. In effect, in **8** (Scheme 5) the phosphate is located on the opposite face of the radical cation to that from which the alkene must approach resulting in a clean cyclization, smooth propagation and a high yield of product. In the case of **9**, on the other hand, if the cyclization is to lead to a *cis*-fused product the alkene of essence has to approach the same face of the radical cation as is shielded by the counter ion. This obvious steric impedance to such a trajectory retards cyclization and permits competing decomposition of the alkene radical cation, one possibility for which is shown in Scheme 6.

These observations closely parallel the results of our study on intramolecular nucleophilic attack by amines on alkene radical cations derived by a related fragmentation approach wherein attack on the opposite face of the radical cation to the one shielded by the departing phosphate is strongly favored.[5a]

Acknowledgements

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7. In the particular example illustrated the slow step, with a lower limit of $>2\times10^8$ s^{-1}, was the fragmentation.[6]
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9. **4**: mp = 95–97°C; $[\alpha]_D^{20} = -26.7$ (*c*, 3.0, $CHCl_3$); ^1H NMR ($CDCl_3$), δ: 3.45–3.54 (m, 1H), 3.62 (t, $J = 9.8$ Hz, 1H), 3.70–3.85 (m, 2H), 4.12–4.20 (m, 1H), 4.28–4.41 (m, 2H), 4.49–4.60 (m, 1H), 4.98 (d, $J = 9.8$ Hz, 1H), 5.00–5.18 (m, 2H), 5.53 (s, 1H), 5.71–5.85 (m, 1H), 7.15–7.60 (m, 20 H); ^{13}C NMR ($CDCl_3$), δ: 68.6, 71.7, 73.7, 78.8 (d), 80.0, 81.1, 81.9 (d), 101.1, 117.5, 120.1 120.2, 120.3, 120.4, 125.1, 125.8, 126.6, 128.2, 128.4, 128.9, 129.0, 129.0, 129.5, 129.6, 134.4, 135.5, 136.9, 150.7 (q); ^{31}P NMR ($CDCl_3$), δ: −12.8. Anal. calcd for $C_{34}H_{33}O_8PSe$: C, 60.09; H, 4.89; Found: C, 60.56; H, 5.56.
10. Acetobromomannose was prepared according to the literature method: Talley, E. A.; Reynolds, D. D.; Evans, W. L. *J. Am. Chem. Soc.* **1943**, *65*, 575–582.
11. **5**: mp = 154–155°C; $[\alpha]_D^{24} = -29.6$ (*c*, 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$), δ: 3.36–3.46 (m, 1H), 3.65–3.69 (m, 1H), 3.75–3.84 (m, 2H), 4.11–4.18 (m, 1H), 4.24–4.33 (m, 2H), 5.09 (d, $J = 3.9$ Hz, 1H), 5.15 (d, $J = 10.8$ Hz, 1H), 5.32–5.39 (m, 2H), 5.43 (s, 1H), 5.81–5.93 (m, 1H), 7.16–7.59 (m, 20H); ^{13}C NMR ($CDCl_3$), δ: 68.8, 71.9, 73.3, 77.0, 77.7, 80.3 (d), 83.4 (d), 102.0, 118.0, 120.5, 120.98, 121.02, 121.11, 121.14, 125.5, 125.7, 126.4, 128.6, 129.4, 129.6, 129.7, 129.9, 130.1, 134.3, 134.8, 137.7, 151.3 (q); ^{31}P NMR ($CDCl_3$), δ: −11.6. Anal. calcd for $C_{34}H_{33}O_8PSe$: C, 60.09; H, 4.89; Found: C, 60.28; H, 5.01.
12. **17**: mp = 73–75°C; $[\alpha]_D^{20} = +0.6$ (*c*, 1.1, $CHCl_3$); ^1H NMR ($CDCl_3$), δ: 1.10 (d, $J = 6.5$ Hz, 3H), 2.81–2.95 (m, 1H), 3.37 (t, $J = 8.0$ Hz, 1H), 3.74–3.91 (m, 3H), 4.12 (t, $J = 8.0$ Hz, 1H), 4.40–4.46 (m, 1H), 4.51–4.56 (m, 1H), 5.61 (s,

1H), 6.15 (t, $J=1.9$ Hz, 1H), 7.30–7.40 (m, 3H), 7.49–7.56 (m, 2H); ^{13}C NMR ($CDCl_3$), δ: 14.5, 33.9, 66.7, 68.6, 75.5, 76.1, 78.9, 101.3, 117.6, 126.1, 128.9, 135.5, 137.0. Anal. calcd for $C_{16}H_{18}O_4$: C, 70.06; H, 6.61; Found: C, 69.71; H, 6.62.

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