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Stereochemical Control in the Oxymercuration of 5-Alken-1-ols

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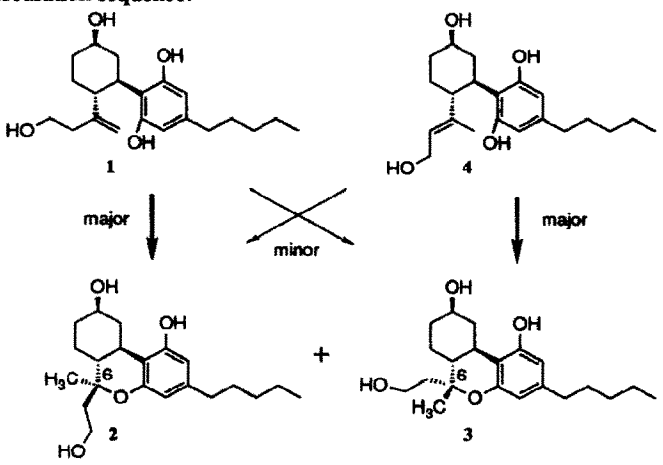
Abstract: The axial preference which had been observed during the intramolecular reaction of cannabinoid precursors **2** and **3** is not a heteroatom-mediated directing effect. Rather, it reflects a kinetic preference which may be related to the anomeric effect.

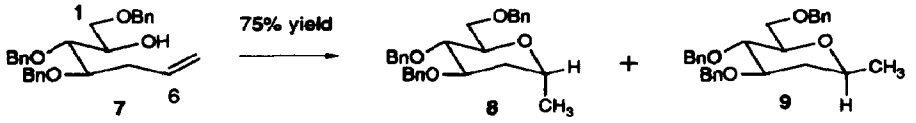
An interest in the synthesis of cannabinoids led us to design improved analogs with additional hydroxylic binding sites for the receptor. Analogs **2** and **3** were designed as conformationally restricted hybrids of the non-classical cannabinoid CP-55,940 and hexahydrocannabinol. The stereochemical problem which was presented by the stereogenic center at C6 was solved[1] by applying an intramolecular oxymercuration-demercuration sequence:



Exposure of ring-open compound **1** to one equiv of mercuric acetate in THF at 23 °C, followed by reductive demercuration with $NaBH_4$ in aq NaOH, provided the β-hydroxyethyl compound **2** selectively (86:14). Treatment of **4** under identical conditions produced the α-hydroxyethyl analog **3** with similar selectivity (85:15). Exposure of **1** to *p*-toluenesulfonic acid in refluxing toluene led to an equimolar mixture of **2** and **3**, reinforcing our notion that the selectivity which had been observed for the oxymercuration-demercurations had a kinetic origin. Since the major product in each case was derived from the axial organomercurial, the stereochemical preference could be the result of an anomeric effect of the developing mercurinium ion in the transition state. We were unable to find support for this hypothesis in the chemical literature on

oxymercuration, which sheds little light on the topic of stereochemistry.[2] However, a seminal paper by Sinaÿ had shown[3] that the intramolecular oxymercuration of **5** produces axial product **6** in high yield:

The stereochemical preference in this case was attributed to coordination of the incoming mercurio species by the adjacent benzyloxy oxygen.[3] Such a directing effect does not appear to be possible for **1** or **4**. In order to probe the origin(s) of the selectivity for the oxymercuration of **2** and **3**, a series of experiments was carried out.

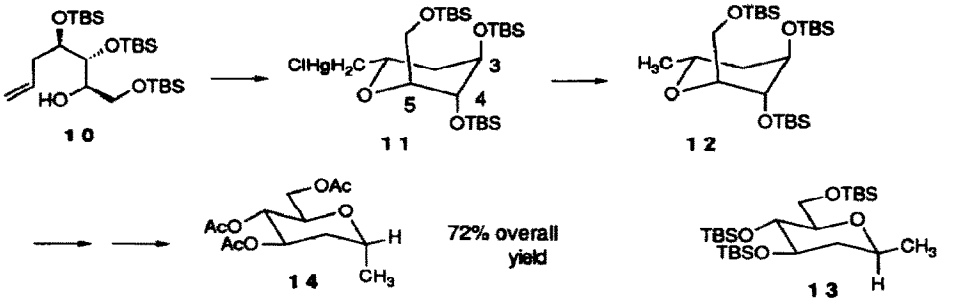


60:40

Tri-O-acetyl-D-glucal was converted to **7** by conventional means.[4,5] Since **7** differs from **5** only in lacking the C2 benzyloxy group (sugar numbering), a preference for the axial mercurio compound in the oxymercuration of **7** cannot be attributed to the directing effect of an adjacent heteroatom, and must have a different origin. Exposure of **7** to mercuric acetate in THF at 23 °C, followed by reductive demercuration with $NaBH_4$ in a two-phase system (aq NaOH, nBu$_4$NOH, CH_2Cl_2) led to a 60:40 mixture of **8**[6] and **9**[7] in 75% yield. This reflects the kinetic ratio of products. Molecular modeling on Biosym™ indicated that **9** was 2.6 kcal/mol lower in energy than **8**. Interrupting the oxymercuration at ca. 50% conversion led to the same 60:40 product mixture. Also, exposure of **7** to mercuric trifluoroacetate in nitromethane at 23 °C, followed by reductive demercuration, led to an equimolar mixture of **8** and **9** in 70% yield. Harding has reported that in a related system these conditions allow some equilibration of the organomercurial to take place.[8] The preference for the axial product **8** is smaller than the preferences for axial product seen for both **1** and **4**. In all likelihood this is because **7** lacks an alkyl substituent at C6. The presence of a C6 substituent larger than hydrogen would destabilize the transition state leading to the equatorial product (cf. **9**) through 1,3-diaxial interactions, whereas its presence in the transition state leading to the axial product (cf. **8**) would have a minimal effect. This leads to the interesting prediction that the best selectivity will be observed during the oxymercuration to form C1 *di*substituted saccharides. The ability to control quaternary C1 stereochemistry in the absence of a directing group at C2 is likely to be very useful.

The oxymercuration experiment was repeated with tri-*tert*-butyldimethylsilyloxy (TBS) compound **10**. Complexation of the benzyloxy groups in **7** with mercury appears to be precluded by geometric constraints; the reluctance of TBS ethers compared with benzyloxy groups to participate in chelation with Lewis acids makes such an interaction even more unlikely in the case of **10**.[9] Exposure of **10** to mercuric acetate followed by aqueous sodium chloride, produced chloromercurio sugar **11**. Demercuration, under the same conditions that were used for **7**, led to **12**[10] as the *sole* product. None of the isomeric product **13** was detected in the reaction mixture. The stereochemical assignment for **12** was confirmed by first cleaving the TBS groups with methylammonium fluoride (methanol, sealed tube, 80 °C, 3 d),[11] followed by acetylation of the free

hydroxyls with acetic anhydride/pyridine/DMAP, to produce the known triacetate **14** in 72% overall yield from **10**.[12]



This result is not a consequence of the suppression of a complexing interaction which favors equatorial product **13**. The ^{1}H NMR coupling constants for **11**, as well as for the reduced species **12** clearly indicate that neither ring is in the chair conformation in which the silyloxy and silyloxymethyl groups are equatorial. For example, for **11** $J_{3,4}$ = 3.2 Hz and $J_{4,5}$ = 1.3 Hz, whereas for **12** $J_{3,4}$ = 3.2 Hz and $J_{4,5}$ = 1.1 Hz. In **12** w-coupling is also observed: $J_{2\ eq,\ 4}$ = 1.1 Hz. Molecular modeling showed that the minimum energy conformation of **12** is the chair which places silyloxy and silyloxymethyl groups *axial*, and methyl equatorial. This conformation was predicted to be 4 kcal/mol lower in energy than the alternative chair, and 9 kcal/mol lower than the optimal twisted conformer. The results of molecular modeling are consistent with the measured coupling constants. The differences in calculated energy were largely due to the van der Waals interactions of the large TBS groups. Replacement of the TBS groups by acetates (**12** --> **14**) restores the six-membered ring to the chair conformation in which methyl is axial and all other substituents are equatorial. This was shown to be the case by observing a positive nOe in **14** between the methyl and each of the two transannular axial hydrogen atoms. Diastereomer **13** has been described, and exists as the all equatorial conformer.[13] The additional 1,3-diaxial repulsions in the all axial conformer due to the methyl are greater than the van der Waals repulsions of the silyloxy groups in the all equatorial conformer.

Given the conformational preference of **11**, the oxymercuration of **10** appears to be anomalous, since it does not reflect the kinetic preference for axial product which is manifested in the reactions of **1**, **4** and **7**. If the transition state for the oxymercuration resembles the conformation of **11**, then the preference in this system is for the equatorial mercuriomethyl group (axial silyloxy and silyloxymethyl groups). This is not surprising, since axial placement of the mercuriomethyl group would introduce large unfavorable 1,3-diaxial interactions with the substituents at C3 and C5, which would overwhelm the modest preference for the axial product. The observation that the conformational preferences of 2-deoxy sugars are so easily manipulated by appropriate choice of protecting groups should be a consideration when planning a synthesis.

In conclusion, the preference for the axial chloromercurio sugar **6** which has been observed by Sinaÿ[3] is not solely due to complexation of mercury by the adjacent ether oxygen. The effect of the adjacent heteroatom is superimposed upon a kinetic preference for the axial product which is independent of any directing effect. Such a kinetic preference, perhaps an anomeric effect, can rationalize the preference for the axial product which has been observed for the oxymercuration reactions of **1**, **4** and **7**. Some of the apparent inconsistencies in the relevant chemical literature can probably be traced to equilibration of the kinetically

formed products. By conducting the oxymercuration under conditions favoring kinetic control, the axial isomer can be made to predominate.

The results discussed above provide a plausible rationalization of an unexpected stereochemical effect, and suggest an effective strategy for, inter alia, C-glycosyl and cyclic polyether synthesis.

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References and Notes

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4. Tri-O-acetyl-D-glucal was exposed to K_2CO_3/CH_3OH, followed by $PhCH_2Cl/NaOH/K_2CO_3/Et_4NClO_4$ in PhH/DMSO to produce tri-O-benzyl-D-glucal in 60% overall yield. Hydration of the enol ether was accomplished by exposure to $Hg(OAc)_2$ in aq THF, followed by sequential treatment with KI and $NaBH_4$, in 72% overall yield. Treatment with methylenetriphenylphosphorane produced 7 in 82% yield. See: Corey, E. J.; Goto, G. *Tetrahedron Lett.* **1980**, *21*, 3463-3466, and Ref. 3 above.
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6. **8**: ^{1}H NMR (500 MHz, benzene-d_6) δ 7.34-7.08 (m, 15 H), 4.74 (d, J = 11.5 Hz, 1 H), 4.59 (d, J = 11.5 Hz, 1 H), 4.47 (d, J = 12.0 Hz, 1 H), 4.42 (d, J = 12.0 Hz, 1 H), 4.37 (d, J = 12.0 Hz, 1 H), 4.36 (d, J = 12.0 Hz, 1 H), 4.07 (tdd, J = 6.5, 5.0, 4.5 Hz, 1 H), 4.03 (dt, J = 6.5, 4.5 Hz, 1 H), 3.85 (dd, J = 10.0, 4.5 Hz, 1 H), 3.80 (dd, J = 10.0, 4.5 Hz, 1 H), 3.74 (ddd, J = 8.0, 6.5, 4.5 Hz, 1 H), 3.68 (t, J = 6.5 Hz, 1 H), 1.74 (ddd, J = 13.0, 5.0, 4.5 Hz, 1 H), 1.65 (ddd, J = 13.0, 8.0, 4.5 Hz, 1 H), 1.05 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (125 MHz, benzene-d_6) δ 140 (3C), 129-127 (15C), 76.7, 76.6, 73.6, 73.4, 73.3, 71.2, 69.9, 66.0, 34.8, 19.2; ir (neat) 3090, 3060, 3030, 2970, 2920, 2860, 1495, 1450, 1365, 1100, 1030, 805, 740, 700 cm^{-1}; EI-ms 341 (M^+-91, 1%), 235(3), 181(7), 127(8), 91(100); HRMS calcd for $C_{21}H_{25}O_4$ 341.1752, found 341.1755.
7. **9**: ^{1}H NMR (500 MHz, benzene-d_6) δ 7.35-7.05 (m, 15 H), 5.02 (d, J = 11.0 Hz, 1 H), 4.66 (d, J = 11.0 Hz, 1 H), 4.50 (d, J = 12.0 Hz, 1 H), 4.49 (d, J = 12.0 Hz, 1 H), 4.42 (d, J = 12.0 Hz, 2 H), 3.77 (dd, J = 11.0, 4.5 Hz, 1 H), 3.76 (dd, J = 11.0, 2.5 Hz, 1 H), 3.64 (dd, J = 9.5, 9.0 Hz, 1 H), 3.47 (ddd, J = 12.0, 9.0, 5.0 Hz, 1 H), 3.40 (ddd, J = 9.5, 4.0, 2.5 Hz, 1 H), 3.13 (dtd, J = 12.0, 6.5, 1.5 Hz, 1 H), 1.73 (ddd, J = 12.5, 5.0, 1.5 Hz, 1 H), 1.30 (dt, J = 12.5, 12.0 Hz, 1 H), 1.07 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (125 MHz, benzene-d_6) δ 140 (3C), 129-127 (15C), 81.4, 79.6, 79.0, 75.0, 73.6, 71.5, 71.1, 70.3, 39.0, 21.5; ir (neat) 3090, 3060, 3030, 2970, 2920, 2860, 1495, 1450, 1365, 1100, 1025, 805, 735, 700 cm^{-1}; EI-ms 341 (M^+-91, 4%), 181(4), 127(23), 91(100); HRMS calcd for $C_{21}H_{25}O_4$ 341.1752, found 341.1741.
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10. **12**: ^{1}H NMR (500 MHz, acetone-d_6) δ 3.95 (dtd, J = 9.8, 6.2, 1.1 Hz, 1 H), 3.94 (d, J = 6.6 Hz, 2 H), 3.88 (ddd, J = 3.2, 2.6, 2.5 Hz, 1 H), 3.68 (td, J = 6.6, 1.1 Hz, 1 H), 3.64 (dt, J = 3.2, 1.1 Hz, 1 H), 1.79 (ddd, J = 13.2, 9.8, 2.4 Hz, 1 H), 1.41 (ddt, J = 13.2, 3.3, 1.1 Hz, 1 H), 1.08 (d, J = 6.2 Hz, 1 H), 0.92 (s, 9 H), 0.91 (s, 9 H), 0.90 (s, 9 H), 0.11 (s, 3 H), 0.10 (br s, 9 H), 0.07 (s, 3 H), 0.06 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 80.2, 69.7, 67.8, 61.7, 61.2, 35.9, 26.0, 25.9, 25.8, 21.8, 18.3, 18.0(2C), -4.7, -4.8, -5.0, -5.2, -5.3; ir (neat) 2960, 2930, 2860, 1465, 1360, 1260, 1100, 835, 780 cm^{-1}; EI-ms 447 (M^+-57, 4%), 245 (13), 171(86), 147(28), 117(21), 73(100); HRMS calcd for $C_{21}H_{47}O_4Si_3$ 447.2782, found 447.2792.
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