STEREOSELECTIVE ALLYLATION FOR PREPARATION OF L-HEXOSE DERIVATIVES

D.R. Williams\* and Franz D. Klingler Department of Chemistry, Indiana University, Bloomington, IN 47405

Summary: The reaction of allyltrimethylsilane with  $\alpha$ ,  $\beta$ -dialkoxyaldehydes is catalyzed by magnesium bromide, and provides for a highly stereoselective allylation which is predicted by  $\alpha$ -chelation of the Lewis acid. The observed stereocontrol is opposite to that generally obtained from a variety of common allulation reagents.

Our recent synthetic investigations have required a versatile and convenient preparation of L-hexoses. Furthermore, these efforts required appropriate protecting units for hydroxyl differentiation. We wish to report a study of stereoselectivity in the allylation of the  $\alpha$ ,  $\beta$ -dialkoxyaldehydes 1 and 2, which affords access to a series of rare L-monosaccarides.<sup>1</sup> These experiments illustrate the utility of allyltrimethylsilane-magnesium bromide as a reagent of choice for predictable and highly stereocontrolled allylations.



I R <sub>1</sub> = OBn; R <sub>2</sub> =H	<u>3</u> R <sub>1</sub> =OBn; R <sub>2</sub> =H	<u>4</u> R <sub>1</sub> =OBn; R <sub>2</sub> =H
2 R, =H; R <sub>2</sub> =0Bn	<u>5</u> R <sub>1</sub> = H; R <sub>2</sub> = OBn	<u>6</u> R <sub>1</sub> = H; R <sub>2</sub> = OBn

Our starting aldehyde 1 was available in multigram guantities from 1,3-ethylidene-(L)erythritol 7 (prepared from D-glucose) as indicated by the sequence below.<sup>2</sup> The desired alcohol 8 was obtained in 50% overall yield. Swern oxidation conditions (ClCOCOC1; DMSO; CH<sub>2</sub>Cl<sub>2</sub> at -78°C; then Et<sub>3</sub>N at -50°C) gave aldehyde 1 in 92% yield. However, approximately 2% of the diastereomer resulting from C-2 epimerization was evident by high field



869

<sup>1</sup>H-NMR. Pyridinium chlorochromate oxidation (CH<sub>2</sub>Cl<sub>2</sub>; 22°C) gave <u>1</u> in 70-75% yields without detectable isomerization. Likewise, aldehyde <u>2</u> was prepared by oxidation (PCC on neutral alumina; NaOAc; CH<sub>2</sub>Cl<sub>2</sub>; 20°C) of its corresponding alcohol <u>9</u> which is readily available in three steps from L-tartrate.<sup>3,4,5</sup>

Allylation Reagent	Solvent	Temp (*C)	Aldehyde	Yield	3:4 or 5:6
Maci	THF or Et <sub>2</sub> 0	-78	<u> </u>	85%	45:55
1	THE	-78	2	86%	45:55
2. Cu·DMS/MgBr <sub>2</sub>	Et <sub>2</sub> O	-78	1	82%	40:60
-Ti (0	THF	-78	ı	90%	30:70
3. # • ( •/3			2	78%	50 50
z zn	THF	- 100	<u> </u>	91%	20:80
- · · · · · · · · · · · · · · · · · · ·			2	95%	65:35
5 B	CH2CI2	+20	L	84%	20:80
0 1			2	83%	40:60
6 SiMe <sub>3</sub> /MgBr <sub>2</sub>	CH_2CI_2	-20	<u> </u>	95%	> 98:2
			2	78%	2:98

T	Δ	R	ı.	F	т
	· · ·	~		_	_

Patio

Reactions of aldehydes  $\underline{1}$  and  $\underline{2}$  with a variety of allylic organometallic reagents provided the diastereomeric pairs of homoallylic alcohols  $\underline{3}$  and  $\underline{4}$  or  $\underline{5}$  and  $\underline{6}$  in satisfactory yields as summarized in <u>Table I</u>. Initial attempts with allylmagnesium chloride or the organocopper complex<sup>6</sup> exhibited nearly indiscriminate nucleophilic attack. Diastereofacial selectivity was significantly increased with use of the allyl titanium reagent (entry 3)<sup>7</sup> or diallylzinc (entry 4).<sup>8</sup> These reagents displayed a preference for formation of the addition products  $\underline{4}$ and  $\underline{5}$ . Both alcohols  $\underline{4}$  and  $\underline{5}$  can be rationalized through a <u>non-chelated</u> Felkin-Anh<sup>9</sup> or Cornforth<sup>10</sup> arrangement to deliver the observed C<sub>4</sub>-C<sub>5</sub> anti-stereochemistry. Mixed results were obtained from the allylboronate reagent (entry 5).<sup>11</sup> The anti-arrangement corresponds to that which is generally obtained in nucleophilic additions to  $\alpha, \beta$ dialkoxyaldehydes.<sup>12</sup>

The most significant result is the magnesium bromide-catalyzed addition of allyltrimethylsilane to aldehydes <u>1</u> and <u>2</u> which afforded greater than 98% stereocontrol. In each case the products <u>3</u> and <u>6</u> are formed with nearly exclusive  $C_4-C_5$  syn-stereochemistry. While this result is opposite to that observed for the non-chelated models, it also establishes the controlling importance of the stereochemistry of the  $\alpha$ -benzyloxy substituent. These products support a strong  $\alpha$ -chelation effect <u>10</u> (as illustrated for <u>1</u>). We note that  $\beta$ -chelation may also play a role in our reactions.<sup>13</sup> However, chelation in the chair arrangements <u>11</u> and <u>12</u> would appear to predict formation of the *Syn* product <u>3</u> from <u>11</u>, and the *anti* alcohol <u>5</u> from <u>12</u>. Other Lewis acids, such as TiCl<sub>4</sub>, SnCl<sub>4</sub>, and ZnCl<sub>2</sub>, catalyzed the expected allylation of <u>1</u> or <u>2</u>, as well as a regioselective opening of the acetonide with allylation to yield diol <u>13</u> as the major reaction product.<sup>14</sup> Only by use of magnesium bromide could we preserve the acetonide protection.



The diastereomeric ratios of our products 3/4 and 5/6 could be determined from their <sup>1</sup>H-NMR (360 MHz) spectra, which displayed clearly separated doublets for the AB system of the benzylic methylenes. Full characterizations were made after benzoylation and prep tlc or flash chromatographic separation of the corresponding benzoates <u>14a-d</u>.<sup>15</sup> These compounds were readily transformed into the series of 2-desoxy-(L)-hexoses 15a-d as shown below.<sup>16,17</sup>



## overall yields 40-60%

140	R <sub>1</sub> = OBn; R <sub>2</sub> = H R <sub>3</sub> = H; R <sub>4</sub> = OBz	<u>14c</u> R <sub>1</sub> =H; R <sub>2</sub> =0Bn R <sub>3</sub> =08z: R <sub>4</sub> =H	<u>15c</u> r <sub>1</sub> = H; r <sub>2</sub> = OBn R <sub>3</sub> = OBz; r <sub>4</sub> = H	<u>15 a</u>	R <sub>1</sub> * OBn; R <sub>2</sub> = H R <sub>3</sub> = H; R <sub>4</sub> = OBz
<u>14b</u>	R <sub>1</sub> = OBn; R <sub>2</sub> = H R <sub>3</sub> = OBz; R <sub>4</sub> = H	<u>14d</u> R <sub>1</sub> =H; R <sub>2</sub> =0Bn R <sub>3</sub> =H; R <sub>4</sub> =0Bz	<u>15d</u> R <sub>1</sub> =H; R <sub>2</sub> =OBn R <sub>3</sub> =H; R <sub>4</sub> =OBz	<u>156</u>	R <sub>1</sub> =0Bn; R <sub>2</sub> =H R <sub>3</sub> =0Bz; R <sub>4</sub> =H

Acknowledgement: We thank the Alfred P. Sloan Foundation and the National Institutes of Health (AI17674) for generous support of our research and acknowledge assistance of the National Science Foundation for purchase of high field NMR (CHE81-05004) and high resolution mass spec instrumentation (CHE81-00957).

## References

- For recent reviews of chelation and non-chelation stereoselection: McGarvey, G.J.; Kimura, M.; Oh, T.; Williams, J.M. J. Carbohydrate Chem. <u>1984</u>, 3, 125. Reetz, M.T. Angew. Chem. Int. Ed. Engl. 1984, 23, 556.
- 2. Barker, R.; MacDonald, D.L. J. Am. Chem. Soc. 1960, 82, 2301.
- 3. Fumita, K.; Nakai, H.; Kobayashi, S.; Inoue, K.; Nojima, S.; Ohno, M. Tetrahedron Lett. 1982, 23,3507.
- 4. Swern oxidation of 9 leads to v15% epimerization at C-2.
- 5. We have also prepared the diastereometric alcohol *ii* from ester *i* which is readily available from isoascorbic acid. For related efforts: Jung, M.E.; Shaw, T.J. J. Am. Chem. Soc. <u>1980</u>, 102, 6304.
  OOC-COOMe



- 6. Our organocopper reagent was prepared by addition of allylmagnesium chloride (1 equiv) to  $Cu_2Br_2 \cdot DMS$  complex in ether with cooling to -78 °C.
- 7. Mulzer, J.; Angermann, A. Tetrahedron Lett. <u>1983</u>, 24, 2843. Widler, L.; Seebach, D. Helv. Chim. Acta <u>1982</u>, 65, 1085.
- Diallylzinc was prepared by the Kishi procedure: Nagaoka, H.; Kishi, Y. Tetrahedron 1981, 37, 3873. Fuganti, C.; Serri, S.; Zirotti, C. Tetrahedron Lett. 1983, 24, 5285.
- Cherest, M.; Felkin, H.; Prudent, N. Tetrahedron Lett. <u>1968</u>, <u>2199</u>. Ahn, N.T.; Eisenstein,
   O. Nouv. J. Chim. <u>1977</u>, 1, 61. Ahn, N.T. Top. Curr. Chem. <u>1980</u>, 88, 145.
- 10. Cornforth, J.W.; Cornforth, R.H.; Mathew, K.K. J. Chem. Soc. 1959, 112.
- 11. Hoffman, R.W.; Endesfelder, A.; Zeiss, H.J. Carbohydr. Res. 1983, 123, 320.
- For recent developments: Roush, W.R.; Adam, M.A.; Walts, A.E.; Harris, D.J. J. Am. Chem. Soc. <u>1986</u>, 108, 3422. Mead, K.; MacDonald, T.L. J. Org. Chem. <u>1985</u>, 50, 422. See also ref. 1a.
- 13. Keck, G.E.; Castellino, S. J. Am. Chem. Soc. 1986, 108, 3847.
- We have observed similar results using allyltri-n-butylstannane with various Lewis Acids. For tin-mediated allylations: Keck, G.E.; Abbott, D.E. Tetrahedron Lett. <u>1984</u>, 25, 1883. Keck, G.E.; Boden, E.P. Ibid. <u>1984</u>, 25, 1879. Mukaiyana, T.; Yamada, T.; Suzuki, K. Chem. Lett. 1983, 5.
- 15. Characterization of purified diastereoisomers by <sup>1</sup>H-NMR (360 MHz, CDCl<sub>3</sub>, Hertz) data: <u>benzoate 14a</u>:  $[\alpha]_{D}^{29}$  -14.0° (c.84, CHCl<sub>3</sub>);  $\delta$  1.38 (s,3H), 1.46 (s, 3H), 2.62 (m 2H), <u>3.81</u> (dd, 1, C<sub>5H</sub>, D=3.4, J=6.4), 3.95 (dd, 1, C<sub>7H</sub>, J=5.8, J=8.4), 4.08 (dd, 1, C<sub>7H</sub>, J=6.4, J=8.4), 4.22 (m, 1, C<sub>6H</sub>), 4.64 (d, 1H, O-CH<sub>2</sub>-Ph, J=11.2), 4.83 (d, 1H, O-CH<sub>2</sub>-Ph, J=11.2), 5.06 (ddd, 1, C<sub>1H</sub>, J=10.3, J=2.8, J-0.8), 5.14 (ddd, 1, C<sub>1H</sub>, J=17.3, J=2.8, J=1.0), 5.51 (ddd, 1, C<sub>4H</sub>, J=8.4, J=5.3, J=3.4), 5.84 (dddd, 1, C<sub>2H</sub>, J=17.3, J=10.3, J=6.6, J=6.6), 7.3-8.05 (m, 10H, aromatic); <u>benzoate 14b</u>:  $[\alpha]_{D}^{29}$  -16.7° (c.80, CHCl<sub>3</sub>);  $\delta$  1.33 (s, 3H), 1.42 (s, 3H), 2.58 (m, 2H), 3.92 (m, 1, C<sub>5H</sub>), 4.05 (dd, 1, C<sub>7H</sub>, J=7, J=14), 4.12 (dd, 1, C<sub>7H</sub>, J=7, J=14), 4.25 (ddd, 1, C<sub>6H</sub>, J=4, J=7, J=7), 4.73 (d, 1, O-CH<sub>2</sub>-Ph, J=11), 4.86 (d, 1, O-CH<sub>2</sub>-Ph, J=11), 5.08 (m, 2, C<sub>1H<sub>2</sub></sub>), 5.78 (dddd, 1, C<sub>2H</sub>, J=17, J=14, J=7, J=7), 7.3-8.1 (m, 10H, aromatic); <u>benzoate 14c</u>:  $[\alpha]_{2}^{22}$  -14.3° (c.80, CHCl<sub>3</sub>);  $\delta$  1.37 (s, 3H), 1.43 (s, 3H), 2.65 (m, 2H), <u>3.72</u> (dd, 1, C<sub>5H</sub>, J=4, J=7), 3.85 (dd, 1, C<sub>7H</sub>, J=6, J=8), 3.99 (dd, 1, C<sub>7H</sub>, J=8, J=7), 4.26 (ddd, 1, C<sub>6H</sub>, J=7, J=7), 4.77 (d, 1, O-CH<sub>2</sub>-Ph, J=11.5), 4.83 (d, 1, O-CH<sub>2</sub>-Ph, J=11.5), 5.02-5.16 (m, 3, C<sub>1H<sub>2</sub></sub> and C<sub>4H</sub>), 5.81 (dddd, 1, C<sub>2H</sub>, J=16.5, J=10, J=7, J=7), 7.2-8.0 (m, 10H, aromatic); <u>benzoate 14d</u>:  $[\alpha]_{1}^{19}$  +9.6° (c.30, CHCl<sub>3</sub>);  $\delta$  1.37 (s, 3H), 1.43 (s, 3H), 2.58 (m, 2H), 3.62 (dd, 1, C<sub>5H</sub>, J=7, J=7), 3.74 (dd, 1, C<sub>7H</sub>, J=7, J=7), 4.03 (dd, 1, C<sub>7H</sub>, J=7, J=7), 4.32 (ddd, 1, C<sub>6H</sub>, J=7, J=7), 4.75 (d, 1, O-CH<sub>2</sub>-Ph, J=11.5), 4.92 (d, 1, O-CH<sub>2</sub>-Ph, J=11.5), 5.0-5.3 (m, 3, C<sub>1H<sub>2</sub></sub> and C<sub>4H</sub>), 5.72 (dddd, 1, C<sub>2H</sub>, J=17.5, J=9.9, J=7.5, J=7.2), 7.2-8.1 (m, 10H, aromatic).
- 16. Excess ozone can provide further oxidation of the intermediate lactols to afford useful yields ( $\sqrt{75}$ ) of the corresponding lactones.
- Recent related studies include: Mukaiyana, T.; Suzuki, K.; Yamada, T. Chem. Lett. <u>1982</u>, 929. Mukaiyama, T.; Yamaguchi, M. Ibid. <u>1981</u>, 1005. Danishefsky, S.; DeNinno, M. Tetrahedron Lett. <u>1985</u>, , 823. Hatakeyama, S.; Sakurai, K.; Takano, S. Tetrahedron Lett. 1986, 27, 4485.

(Received in USA 28 October 1986)