

## $\beta$ -Oxy- $\alpha$ -Diazo Carbonyl Compounds. I. Photochemistry of Chiral $\beta$ -Oxy- $\alpha$ -Diazo Methyl Ketones. Stereoselective Synthesis of Chiral Macrolide Synthons.

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**Abstract:** In this work we studied the reaction of 2,3-O-isopropylidene-D-glyceraldehyde **1** with diazoacetone **2**, the photochemical behaviour of the condensation product, and analysed the protector group effect that modifies the photochemically induced intramolecular processes of the condensation product and its derivatives. We report the successful stereoselective synthesis of 3-hydroxy-2-methyl carboxylate derivatives with *threo* relative configurations.

Further study on the stereoselective synthesis of 1-methyl-2-hydroxy units in lineal structures is needed to discover more efficient methods of preparing valuable natural chiral products such as macrolide antibiotics<sup>1</sup>. Conventionally, this type of synthesis is carried out by aldolic condensation of (chiral?) propionates with (chiral?) enolates<sup>2</sup> in single or double diastereoselective processes. The interesting stereochemical results of previous work in this laboratory in which aldolic condensations of chiral aldehydes with methyl diazoacetate gave  $\beta$ -hydroxy- $\alpha$ -diazo esters<sup>3</sup>, suggested a more detailed study of new condensations of 2,3-O-isopropylidene-D-glyceraldehyde **1** with other diazo compounds and the reactivities of their reaction products. Formerly, we carried out stereoselective synthesis of epoxyamides by reacting aldehydes or chiral aldehydes with sulphur ylides<sup>4</sup>. This type of reaction could be used to synthesise new glycidic derivatives and would have much potential usefulness for the preparation of macrolide antibiotics and other interesting chiral products.

Consequently, we decided to explore new methods based on the diazoacetone reaction that might lead to new and efficient asymmetric syntheses of these products. In this present work we successfully carried out the enantioselective synthesis of the methyl 3-hydroxy-2-methyl pentanoate derivative **14** by photochemical transformation of chiral  $\beta$ -oxy- $\alpha$ -diazo carbonyl compounds previously prepared by condensing **1** with diazoacetone.

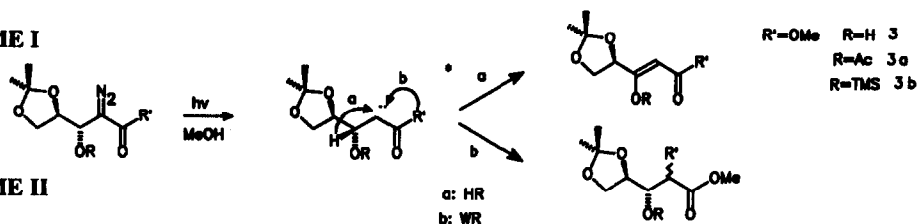
As a continuation of our previous studies on the synthesis of glycidic esters or amides as intermediate products for the preparation of structures related with polypropionates<sup>4</sup>, we decided to explore a different approach, the Wolf rearrangement (W.R.) of  $\beta$ -hydroxy- $\alpha$ -diazomethylketones, that were prepared by the aldol-like condensation of chiral aldehydes with diazoketones.

Two unknowns must be resolved, (1) the reactivity and stereoselectivity of the addition step of the diazoketones, and (2) the predominance of the W.R. over the 1,2-hydride shift of H-4 that gives the undesirable  $\beta$ -diketone. As reported previously for  $\beta$ -hydroxy- $\alpha$ -diazo esters derivatives of sugars<sup>5</sup>, photochemical reactions give the corresponding enols as the result of a 1,2-hydride shift. We observed the same hydride rearrangement (HR) after photochemical reactions of **3**<sup>3</sup> and their derivatives **3a** and **3b**<sup>6</sup>. This is generally ascribed to the fact that the hydrogen has a larger migrational capacity than that of the methoxy group (Scheme I). Consequently, we decided to study the reaction of **1** with diazoacetone<sup>7</sup> in 10% of KOH/methanol. After 2 hours at room temperature the reaction finished and we isolated a quantitative yield of a 72:28 mixture (by <sup>1</sup>H-NMR) of (4S,5R) and (4R,5R)-5,6-O-isopropylidene-3-diazo-4,5,6-trihydroxy-2-hexanone **4**. This poor stereoselectivity led us to study the reaction under neutral conditions and without solvent at 4°C. After four weeks, the reaction was complete and the

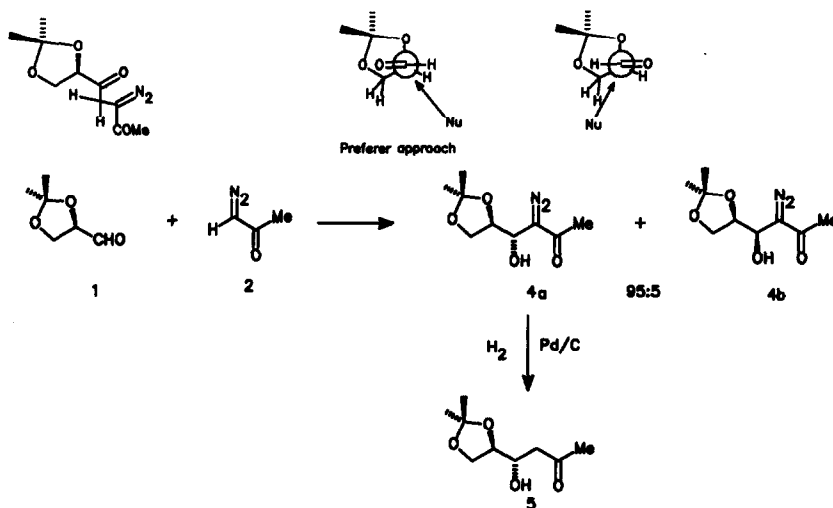
condensation product **4** (61% after purification) was isolated by column chromatography on silicagel. The reaction was found to be highly stereoselective at C-4 (95:5)<sup>8</sup> by integrating the H-4 proton signals in the <sup>1</sup>H-N.M.R. spectra. This high stereoselectivity is justified by the Felkin-Ahn models<sup>9</sup> and is shown in **Scheme II**.

Moreover, we observed epimerization at C-2 of product **1** under basic conditions and was confirmed by comparing the specific rotations of **4a** synthesized under basic and neutral conditions. The most abundant pure isomer, **4a**, formed under neutral conditions was transformed into the corresponding β-hydroxy ketone **5** by catalytic hydrogenation. Its specific rotation ( $[\alpha]_{20}^{D} = -20^{\circ}$  in CHCl<sub>3</sub>) was compared with data in the literature<sup>10</sup>, and this permitted us to establish the S configuration at C-4 that is predicted by the Felkin-Ahn model.

SCHEME I

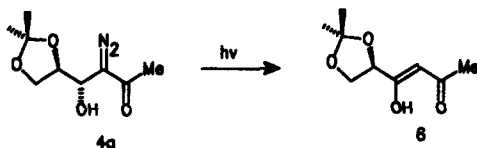


SCHEME II



Compound **4a** was irradiated at 253.7 nm in methanol, however, the only product was the β-diketone **6**, the result of 1,2-hydride shift of the proton H-4 from C-4 to C-3 (**Scheme III**), as occurred in the photochemical reactions of β-oxy-α-diazo esters **3**, **3a** and **3b**.

SCHEME III



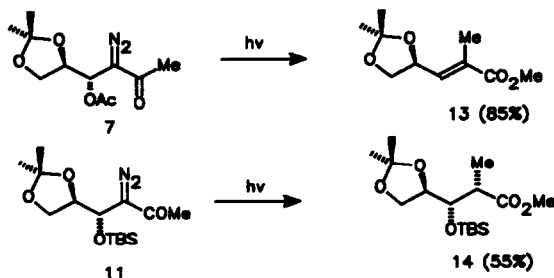
We reasoned that the nature of the protecting group at the 4-OH of **4a** would modify the course of the reaction and it was expected that the use of withdrawing electron protecting groups would decrease the usual 1,2-hydride shift to favour the transfer of the methyl group. To test this hypothesis, we prepared a series of different derivatives (**7**, **8**, **9**, **10**, **11** and **12**) and analyzed the result of the photolysis (Table I). Our predictions were confirmed because the protector effect increased the WR, but as we also expected, the yield produced in each case by WR depended on the electronic characteristic of the protector group: the electron-withdrawing groups (**7** and

8) favoured the WR and yields ranged from 65%-85%. However, this reaction eliminated the acyloxy group when the methanol attacked the ketene and consequently the chiral centre generated initially was lost. The resulting photolysis product 13 from 7 was the only isomer obtained and this is already described in the bibliography<sup>11</sup> (Scheme IV). In the case of donor-electron groups (R=Me,9) HR was favoured (70%) and WR only 30%. Finally, the silyloxy groups (11 and 12) favoured Wolff rearrangements (55%), perhaps due to the weak electron-withdrawing effect of silicon. In these cases, the silyloxy groups were retained and, consequently, the initial chiral centre remained intact in 14. In addition, and most importantly, a second chiral centre was created at C-2, in a completely stereoselective form, when the intermediate ketene was attacked by the methanol (Scheme IV). Thus, <sup>1</sup>H-NMR and GC-MS only showed the existence of one of the two possible isomers, compound 14.

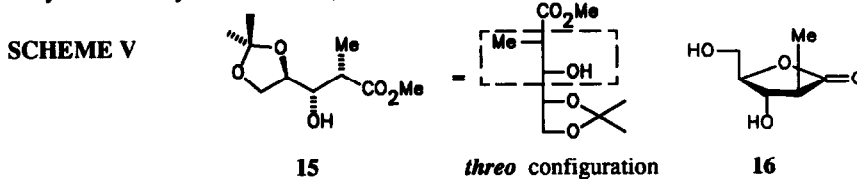
**Table I**

Group R	Ac (7)	CONHPh (8)	Me (9)	TMS (10)	TBDMS (11)	TBDPS (12)
Yield H.R. (%)	15	35	70	95	45	45
Yield W.R. (%)	85	65	30	5	55	55

SCHEME IV

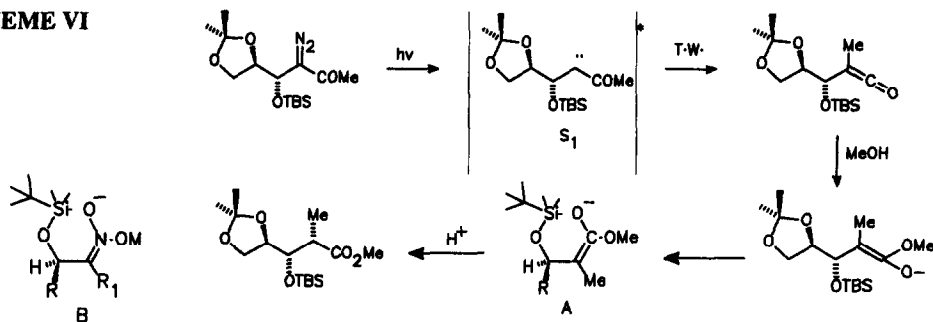


Thus, product 14 was formed from 11. Its structure was established from its <sup>1</sup>H-N.M.R., <sup>13</sup>C-N.M.R., 2D-COSY and C-H spectra data, and also by elemental analysis<sup>12</sup>. The presence of only one epimer at C-2 and its stereochemical configuration were confirmed by subsequent hydrolysis of the silyloxy group of 14, either with tetrabutylammonium fluoride to give the corresponding alcohol 15 (methyl 4,5-O-isopropylidene-2-deoxy-2-methyl-D-arabinonate), or by hydrolysis with boron trifluoride to give the corresponding lactone 16, both products are already described by Heathcock<sup>13</sup> (Scheme V).



The complete stereoselectivity found in this last photochemical reaction and the absolute configuration of the C-2 chiral carbon may be explained by a mechanism that postulates the formation of the intermediate cyclic complex A, retained by a transitory silicon-oxygen bridge, after the methanol attack on the ketene. Subsequent kinetic protonation of this cyclic intermediate would probably occur only on one face of the alkene because the other face would be hindered by the ring itself and by the presence in the ring of the bulky TBS group (Scheme VI). Seebach advanced a similar hypothesis in his reports about protonation reactions of chiral nitroaldols protected by TBS or TMS groups<sup>14</sup> in which he proposes cyclic intermediates (Type B in Scheme VI) to explain the high stereoselectivity found that ranges from 84 to 95% for products with *threo* configurations reacted at -90°C under kinetic conditions.

## SCHEME VI



## ACKNOWLEDGEMENT

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- Analytical and spectroscopic data not included in the work corresponding to these and others products cited, are in agreement with the proposed structures.
- Diazoacetone **2** was made by the procedure of J. B. Hendrickson and W. A. Wolf; *J. Org. Chem.*, **33**, 3610 (1968).
- <sup>1</sup>H-NMR signals of **4a** were the following:  $\delta$  ppm (CDCl<sub>3</sub>), -4.48 (t, 1H,  $J_{4,5} = 6.5$  Hz,  $J_{4,OH} = 6.5$  Hz, H-4); 4.23 (ddd, 1H,  $J_{4,5} = 6.5$  Hz,  $J_{5,6} = 6.3$  Hz,  $J_{5,6} = 4.8$  Hz, H-5); 4.08 (dd, 1H,  $J_{5,6} = 6.3$  Hz,  $J_{6,6} = 8.8$  Hz, H-6); 3.93 (dd, 1H,  $J_{5,6} = 4.8$  Hz,  $J_{6,6} = 8.8$  Hz, H-6'); 3.61 (d, 1H,  $J_{4,OH} = 6.5$  Hz, -OH); 2.25 (s, 3H, -Me); 1.38 and 1.31 (2s, 6H, CMe<sub>2</sub>). The <sup>1</sup>H-NMR data of **4b** were: (CDCl<sub>3</sub>)  $\delta$  ppm, -4.70 (m, 1H, H-4); 4.30 (m, 1H, H-5); 4.17 (dd, 1H, H-6); 3.95 (dd, 1H, H-6'); 3.05 (d w., 1H, -OH); 2.29 (s, 3H, -Me); 1.50 and 1.35 (2s, 6H, CMe<sub>2</sub>). I.R. spectra of **4** presented a strong absorption at 2100 cm<sup>-1</sup> due to the diazo functional group. The pure epimer **4a** was a solid of m.p.=47.2°C.
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- The <sup>1</sup>H-NMR data of **14** were: (CDCl<sub>3</sub>)  $\delta$  ppm : 4.16 (dd, 1H,  $J_{2,3} = 2.9$  Hz,  $J_{3,4} = 5.6$  Hz, H-3); 4.02 (dd, 1H,  $J_{3,5} = 7.1$  Hz,  $J_{4,5} = 4$  Hz, H-4); 3.94 (ddd, 1H,  $J_{4,5} = 4$  Hz,  $J_{4,5} = 5$  Hz,  $J_{3,4} = 5.6$  Hz, H-4); 3.79 (dd, 1H,  $J_{3,5} = 7.1$  Hz,  $J_{4,5} = 5$  Hz, H-5); 3.65 (s, 3H, -CO<sub>2</sub>Me); 2.70 (dq, 1H,  $J_{2,3} = 2.9$  Hz,  $J_{2,Me} = 7.1$  Hz, H-2); 1.37 and 1.30 (2s, 6H, CMe<sub>2</sub>); 1.13 (d, 3H,  $J = 7.1$  Hz, Me-2); .85 (s, 9H, -SiCMe<sub>3</sub>); 0.1 and -0.05 (2s, 6H, -SiMe<sub>2</sub>). The <sup>13</sup>C-NMR data were: (CDCl<sub>3</sub>)  $\delta$  ppm : 175.15 (C-1); 109.01 (CMe<sub>2</sub>); 76.55 (C-4); 73.88 (C-3); 67.32 (C-5); 51.64 (-CO<sub>2</sub>CH<sub>3</sub>); 42.42 (C-2); 26.69 and 25.26 (CMe<sub>2</sub>); 25.75 (-SiCMe<sub>3</sub>); 18.11 (-SiCMe<sub>2</sub>); 9.55 (Me-2); -0.61 and -0.60 (-SiMe<sub>2</sub>).  $[\alpha]_D^{20}(\text{CHCl}_3) = +0.13$   
Elemental Analysis of **14** C<sub>16</sub>H<sub>32</sub>O<sub>5</sub>Si. - Calculated: 57.83 %C; 9.60 %H. Found : 57.79 %C.; 9.53 %H. M.S. m/z : 317 (M<sup>+</sup>-15).
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