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β-Oxy-α-Diazo Carbonyl Compounds. II. Conversion to Chiral α-Oxy-α'-Diazo Ketones and Photochemical Reaction.

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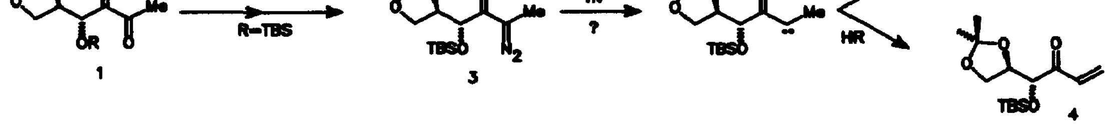
Abstract: Chiral β-oxy-α-diazo methyl ketone was successfully converted to α-oxy-α'-diazo ketone in three steps.The photochemical reaction of this new diazo compound provides an improved synthesis of the 3-hydroxy-2-methyl carboxylate derivative 2 in *threo* relative configurations via a Wolff rearrangement.The influence of the protective group on the stereochemical result of the photochemical reaction is discussed.

Stereoselective or especific syntheses of lineal structures containing syn or anti 1-methyl-2-hydroxy units are of interest in Organic Chemistry[1] on account of their frequent occurrence in chiral natural products such as macrolide and ionophore antibiotics[2] and some pheromones[3]. The challenge posed by the synthesis of such natural products prompted us to investigate new aldol condensations of simple monosaccharides as chiral auxiliar tools for asymmetric induction, with stabilized sulphur ylides[4a] and α-diazo carbonyl compounds[4b], which yield glycidic amides and β-hydroxy-α-diazo esters, respectively, with a high diastereoselectivity . In previous work[5] we developed a stereoselective synthesis for chiral β-hydroxy-α-diazo methyl ketones and studied their photochemical reaction, which affords 3-oxy-2-methyl esters with *threo* configuration via Wolff rearrangement (WR) in a completely stereoselective process. However, the yield of such significant products was only 41% after purification. As discussed elsewhere[5], the nature of the protecting group at free hydroxyl in β-hydroxy-α-diazo methyl ketones has a decisive influence on the result of the photochemical decomposition. Thus, electron-withdrawing groups, such as acetyl, favour the Wolff rearrangement (85%) over the 1,2-hydrogen shift process (15%) (HR); unfortunately, the reaction was accompanied by deacetylation. The t-butyldimethylsilyl ether derivative 1, provided a WR:HR ratio of 55:45, and the WR product, methyl ester 2, was isolated in a 41% proportion. In order to increase the yield of this product, we reasoned that the diazo compound 3, would lead to the Wolff rearrangement product (the same obtained from 1), preferentially over the 1,2 hydrogen shift product 4 because alpha protons relative to the diazo group would not be so highly activated as in the diazo compound 1 (Scheme I).

SCHEME I



We designed a synthesis for this new diazo compound starting from the diazo compound 1. First, 1 was treated with m-CPBA in dichloromethane to give the diketone 5 in quantitative yield. The same reaction in chloroform led to 5-10% epimerization at C-4. Isolation of 5 (yield 92%) was accomplished by successive washings with n-hexane, which precipitated m-chloro benzoic acid. The following step involved condensation of 5 with hydrazine in methanol. The two possible hydrazones **6a**:**6b** were formed in a ratio that was dependent on temperature (see table I); the desired hydrazone, **6b**, was obtained in virtually quantitative yield at -60°C. In order to confirm the structures of both hydrazones, **6a** was prepared in a 75% yield from 1 by treatment with triphenylphosphine and subsequent hydrolysis. Finally, oxidation of **6b** with activated manganese dioxide[6] gave the candidate diazo 3 in a very good yield (98%) (Scheme II).

SCHEME II

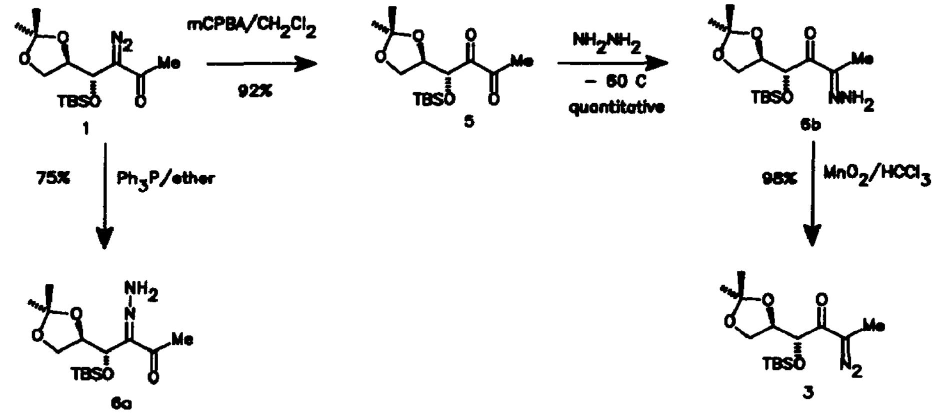
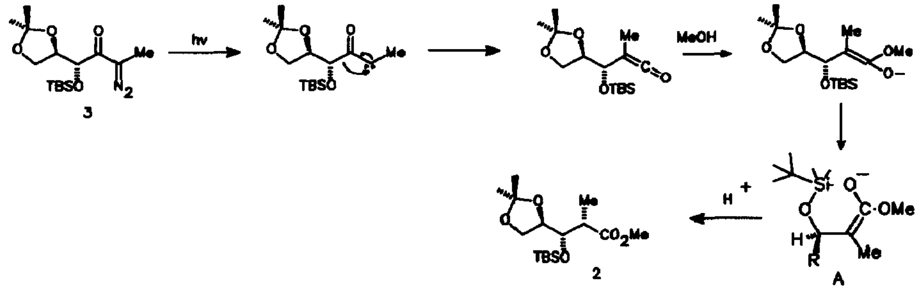


Table 1

Temperature (°C)	25	0	-15	-30	-60
Ratio 6a	40	25	18	10	0
Ratio 6b	60	75	82	90	100

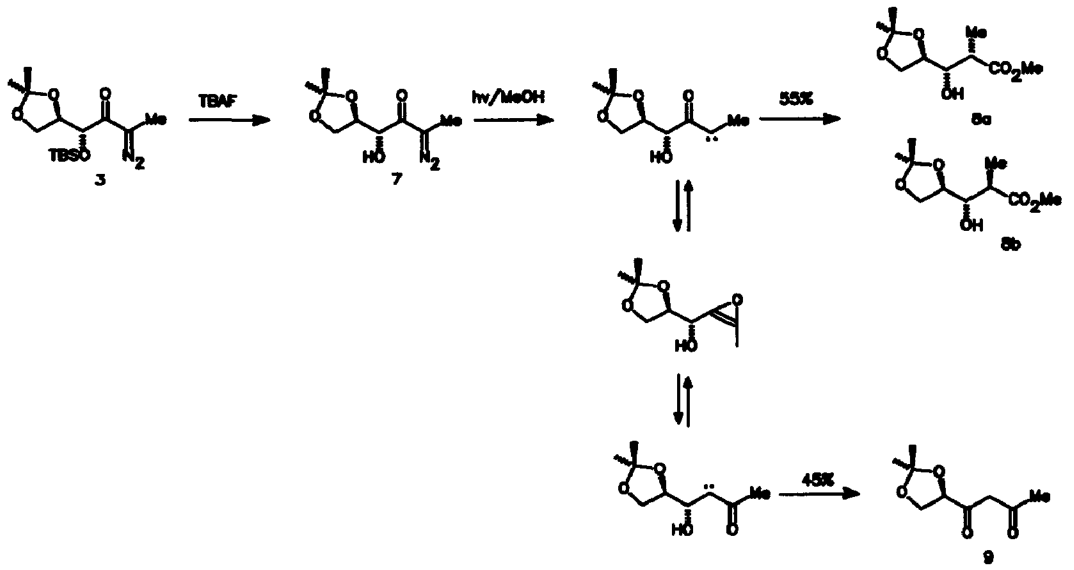
Irradiation of this compound 3 in methanol at 253.7 nm and -4°C gave the ester 2 in a yield over 90%. No 1,2 hydrogen shift product was detected by GC-MS analysis, product 2 was purified by column cromatography on silica-gel (83%) and was found to posess the same physical and spectroscopic properties as that obtained from the diazo compound 1. Stereochemically, it is worthy emphisizing preservation of asymmetric sites during photolysis, previously observed in other diazo compounds including a chiral centre in the migrating fragment[7]. On the other hand, the fact that the formation of the new chiral site (C-2) was fully stereoselective is consitent with the results obtained by using the diazo compound 1 to arrive at the same ketene (Scheme III).

SCHEME III



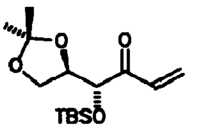
This stereochemical result can be ascribed to the potential formation of an intermediate cyclic complex A that might be retained by a transient silicon-oxygen bond. In order to confirm such a prominent role of the TBS group in the stereochemical control, we prepared the unprotected diazo compound 7 from 3 by removal of the TBS group with tetrabutylammonium fluoride. Photolysis of 7 afforded a 1:1 C-2 epimer mixture of 3-hydroxy-2-methyl esters 8a:8b' in a 55% yield and the β-diketone 9 in a 45% yield. Formation of this last product can be assigned to a ketocarbene-oxirene-ketocarbene equilibrium (Scheme IV), evidence for which has been reported in some instances of Wolff rearrangement[9]. Why this equillibrium works with 7 but not with 3 is unclear. In any case, we suspect that the bulky t-Butyldimethylsilane group might prevent the formation of the strained oxirene ring and are currently conducting theoretical studies in order to check this assertion.

SCHEME IV



Finally, the decomposition products of the new diazo compound 3 were analysed by treatment with other usual reagents: silver oxide and rhodium (II) acetate. The former reagent gave the unsaturated ketone 4 (Figure 1) in a 80%yield, and the W.R. product (the ester 2) in a 20% yield as determinated from their H-NMR spectra. The second latter in chloroform and in presence of air afforded an equimolar ratio of two products: the diketone 5 and an unknown product that seemingly decomposed when tried to separate by chromatography on silica gel, so it could not be isolated for further structural analysis. Formation of the diketone 5 takes place via oxygen insertion as previously shown for other hydroxy diazo derivatives[10]. Its formation was avoided by working under inert atmosphere; a complex mixture was thus obtained whose main product was also that of unknown structure, which was probably formed by intramolecular insertion of one of the dioxolane ring oxygens.Two-dimensional NMR experiments are being conducted in order to elucidate the structure of this product.

FIGURE 1



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