A Photochemical Route to the Formation of Threo Aldols

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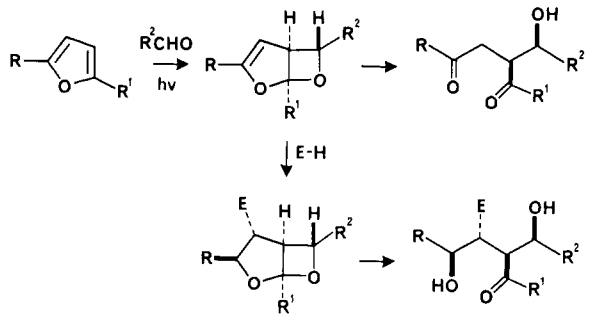
Over the last several years considerable progress has been made in the development of the stereoselective aldol condensation.[2] In addition, a number of processes have been developed that can act as operational equivalents to the aldol reaction.[2] We reasoned that the Paterno–Büchi photocycloaddition[3] of a furan with an aldehyde can serve as a photochemical version of the aldol reaction, since the photoadduct can be considered a type of protected aldol (eq 1).

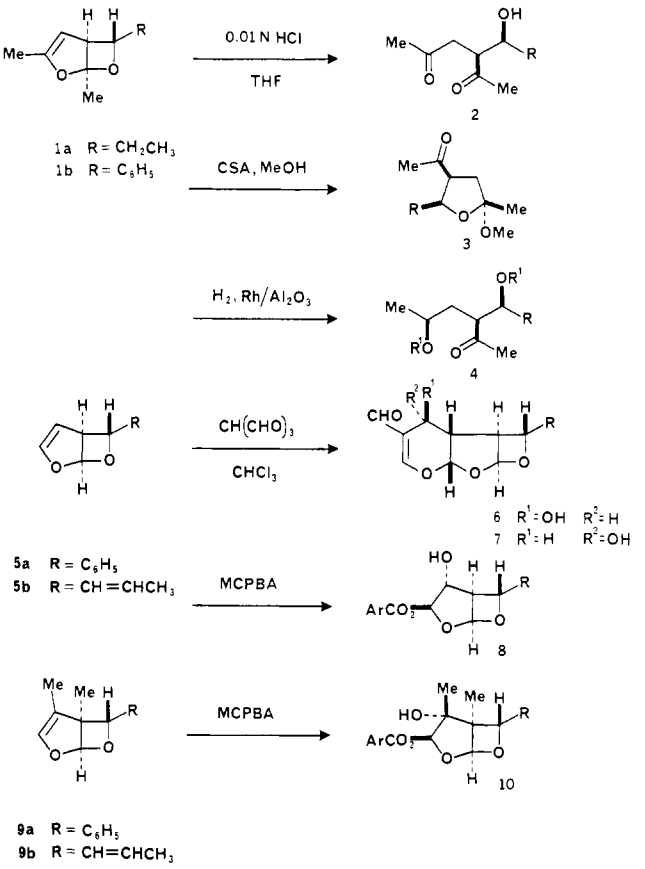


(1)

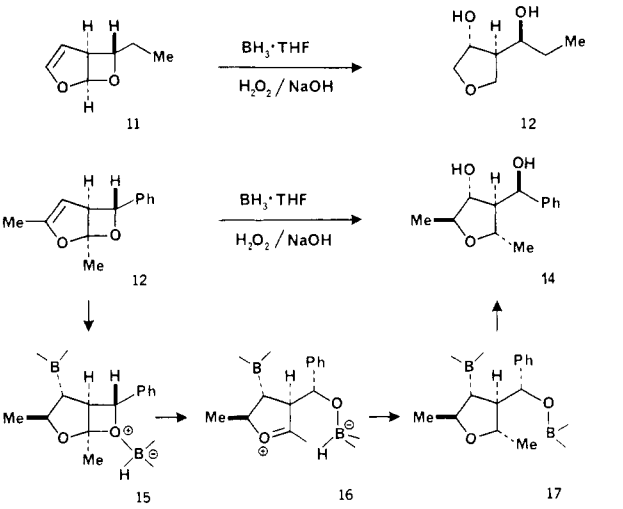
The photocycloaddition reaction[4] was initially investigated by Sakurai[5] in 1965 and demonstrated to regiospecifically afford the head-to-head photoadduct. The stereospecificity of the reaction was also apparent from this report, and an NMR study by Whipple and Evanega[6] later provided evidence for the preference of an exo cycloaddition. In all cases we have examined, an exo photoaldol[7] is afforded exclusively.[8] The photoaldol adducts can be hydrolytically unmasked to afford threo[9] aldols of 1,4-dicarbonyl compounds. The cis-fused dioxabicyclo[3.2.0]heptene skeleton of the photoaldol lends itself conveniently to a variety of functionalization schemes that can be carried out in a highly stereoselective fashion prior to hydrolytic unmasking. Acyclic chains containing chiral centers are afforded that could serve as valuable synthons for various target molecules.

A broad range of furans and carbonyl compounds was surveyed; selected examples are given in Table I, which is available as supplementary material. Several features of the reaction deserve comment. Whereas photocycloaddition of symmetric furans give rise to a single[8] photoaldol, the unsymmetrically substituted furans that we have examined afford two exo photoadducts that result from addition to either olefin of the furan without selectivity. In the cases where we have examined the effect of a chiral substituent adjacent to the aldehyde, very little asymmetric induction has been observed (ca. 1:1 ratio of two exophotoadducts at −60 or 0 °C). A similar result has been reported by Zamojski on 1,4-asymmetric induction in the photocycloaddition of furan with several chiral alkyl glyoxylates.[10] α,β-Unsaturated enals undergo cycloaddition. The primary photochemical process is enal cis–trans isomerism resulting in the formation of equivalent amounts of stereoisomeric

Scheme I



Scheme II



(1) Searle Scholar, 1982–1985; Recipient of a Dreyfus Foundation Grant for Newly Appointed Faculty in Chemistry, 1981–1986.

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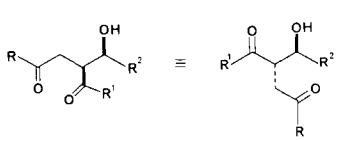
(7) We use the term photoaldol as a descriptor for a carbonyl–furan photoadduct; the term denotes a photochemically derived aldol equivalent.

(8) The degree of stereoselectivity is at least 20:1 as no other stereoisomer has been detected by ^{1}H NMR and ^{13}C NMR.

(9) Heathcock, C. H.; Pirrung, M. C.; Montgomery, S. H.; Lampe, J. *Tetrahedron* **1981**, *37*, 4087. We have adopted the Heathcock terminology so that if the carbonyl portion of the aldol product is drawn as part of the main chain, the compound is designated to be the threo diastereomer. For most synthetic applications, we consider the C-2 substituent part of the main chain.



(10) Jarosz, S.; Zamojski, A. *Tetrahedron* **1982**, *38*, 1447, 1453.

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olefin adducts when crotonaldehyde is employed. Ketones undergo efficient photocycloaddition in a nonstereoselective manner, but with enhanced chemoselectivity (7:1) favoring addition to the less substituted olefin of 2-methylfuran. In a single example, we have observed that thiophene undergoes photocycloaddition with benzaldehyde to afford a single exo photoadduct.[11]

Functionalization of the photoaldols can be carried out in a variety of manners as depicted in Schemes I and II. Hydrolysis (1:4 0.01 N HCl-THF, room temperature, 0.5 h) of **1a** and **1b** afforded the site-specific threo-aldolized 1,4-dicarbonyl compounds **2a** and **2b**, respectively, in 88-92% yield.[8,11] Methanolysis (CSA, MeOH, room temperature, 0.5 h) of **1a** and **1b** provided the rearranged tetrahydrofurans **3a** and **3b**, respectively, each as a single stereoisomer, in 94% yield.[8,11] Hydrogenation (1 atm of H_2, 5% Rh/Al_2O_3, Et_2O, 6 h) from the convex face of **1a** proceeded smoothly to afford a labile ketal oxetane (not isolated) which was hydrolyzed to the diol **4a** (R^1 = H) after filtration through wet Celite. The diol **4a** existed in equilibrium with its corresponding hemiketols and was most easily characterized as the bis-acetate (R^1 = Ac) after acetylation (Ac_2O, Et_3N, DMAP, CH_2Cl_2, O °C) in overall 78% yield from **1a**.[8,11]

To demonstrate the feasibility of forming carbon-carbon bonds to the β-carbon of the enol ether, inverse demand heterodiene Diels-Alder reaction was carried out with **5a** and Tietze's reagent ($HC(CHO)_3$).[12] Cycloaddition ($CHCl_3$, 67 °C, 4 h) occurred to produce two inseparable adducts, **6** and **7**,[8,11] with 7:1 stereoselectivity in 45% yield.[13] The corresponding acetates were readily separated and characterized individually.

Several oxidative functionalization procedures wre investigated. For example, epoxidation (MCPBA, $NaHCO_3$, CH_2Cl_2, room temperature, 2 min)[14] of **5a** and **5b** afforded the corresponding β-hydroxytetrahydrofurans **8a** and **8b**, respectively, in 85-88% yield.[8,11] Acetylation of **8a** and **8b** was carried out to further characterize and demonstrate the stability of these substances. Similar oxidation of **9a** and **9b** afforded **10a** and **10b**, respectively, in 80-84% yield.[11] All five chiral centers present in **10** are suitably disposed for application to the synthesis of asteltoxin,[15] a project under investigation in our laboratories.

Hydroboration-oxidation (BH_3·THF (inverse addition), $H_2O_2/NaOH$) of the photoaldol **11** resulted in the anti-Markovnikov hydration of the enol ether[16] and hydrogenolysis of the acetal[17] to afford the 1,3-diol **12** in 40% yield. Subjection of **13** to similar conditions afforded the 1,3-diol **14** in 82% yield, *resulting in total stereocontrol over five contiguous chiral centers in a two-step procedure*. The stereochemistry of **14** (and the corresponding bis-acetate) was apparent from the 500-MHz ^1H NMR spectrum and was verified by single-crystal X-ray diffractometry[18] on the corresponding bis(*p*-bromobenzoate) derivative. Structure determination by this method establishes in an unambiguous manner the threo outcome[9] of the photocycloaddition reaction, syn-convex addition of the boron reagent, and hydrogenolysis with retention of configuration. The stereochemistry of the hydrogenolysis can be explained by the mechanism in Scheme II. Boron-mediated oxetane ring opening followed by internal delivery of hydride results in the replacement of the carbon-oxygen bond with a carbon-hydrogen bond with retention of configuration.

In summary, the methodology described represents a stereocontrolled route to highly functionalized systems that should find application in synthesis. In addition, the intramolecular furan-carbonyl photocycloaddition will be reported shortly and should enhance the overall utility of this methodology.

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Supplementary Material Available: Table I containing results for 23 furans and carbonyl compounds (2 pages). Ordering information is given on any current masthead page.

(11) All compounds reported gave ^{13}C NMR (22.6 MHz), ^1H NMR (500, 270, or 90 MHz), IR, and mass spectra (low resolution) in accord with the structure given. Exact mass calculations (CI) were performed on all functionalized photoaldol products.

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(13) The acidic Tietze reagent catalyzes a retro[2 + 2] pathway to afford furan and the aldehyde in 40% yield. In the other functionalization procedures, the retro[2 + 2] reaction occurs to an extent of 0-25%.

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(16) Zwiefel, G.; Plamondon, J. *J. Org. Chem.* **1970**, *35*, 898.

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(18) We gratefully acknowledge Professor J. M. McBride and Bruce Weber for carrying out the X-ray structure determination. Full details of the crystal data will be published separately.

Hindered Dialkylamino Nucleoside Phosphite Reagents in the Synthesis of Two DNA 51-Mers†

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Recent dramatic developments in recombinant DNA technology have been accompanied by equally impressive advances in the rapid chemical synthesis of DNA. In addition to utilizing the classical phosphate triester approach,[1-4] significant improvements have been realized by the application of phosphite triester chemistry[5-9] and, more recently, by the development of nucleoside phosphoramidite reagents **2**.[10] Additionally, the implementation of solid supports[7,8,11-14,20] has greatly simplified DNA synthesis by eliminating intermediate purification steps.

In this communication, we report the application of significantly improved nucleoside phosphoramidite reagents to DNA synthesis on a superior solid support.

Our experience with dimethyl phosphoramidites **2** dictated a need for improved solution stability. Consequently, a series of

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