Solvent Effects on Diastereoselective Intramolecular [2 + 2] Photocycloadditions: Reversal of Selectivity through Intramolecular Hydrogen Bonding

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The intramolecular [2 + 2] enone–alkene photocycloaddition has been established as a powerful reaction in the rapid construction of advanced intermediates for the synthesis of complex natural products.[1,2] The diastereocontrol that is available through intramolecular processes is a result of geometric constraints imposed both by the intramolecular nature of the process and by the conformational bias on the transition states which can be invoked by substituents on the tether between the reactive functional groups. We and others have previously demonstrated the asymmetric induction imposed on the product by a single stereogenic center on the tether proximal to the enone function in an intramolecular [2 + 2] photocycloaddition.[1–3] The normal mode of cycloaddition[4] for **1** (Scheme 1) results in high diastereoselectivity for the product **2**, which has the proximal substituent (OSiEt$_3$ in **2**) *cis* to the substituent on the internal carbon of the alkene (Me in **2**). Conformation **A** (see Figure 1) for initial bond formation is the lowest energy conformation by approximately 1.8 kcal/mol (7.53 kJ/mol) and accurately predicts the stereochemistry of the product **2**. We report here additional examples which illustrate the ability to reverse the normal diastereoselectivity by taking advantage of hydrogen bonding between a hydroxyl group and a proximal carbonyl oxygen, as well as a dependence of the diastereoselectivity on the reaction solvent. Hydrogen bonding in a [4 + 4] photocycloaddition of pyridones has been postulated for an explanation of diastereoselectivity[5] and hydrogen bonding plays an important role in photocycloadditions of β-dicarbonyl compounds[6] (the de Mayo reaction). However, to our knowledge, these are the first examples which demonstrate the effects of hydrogen bonding, both intramolecular and intermolecular,
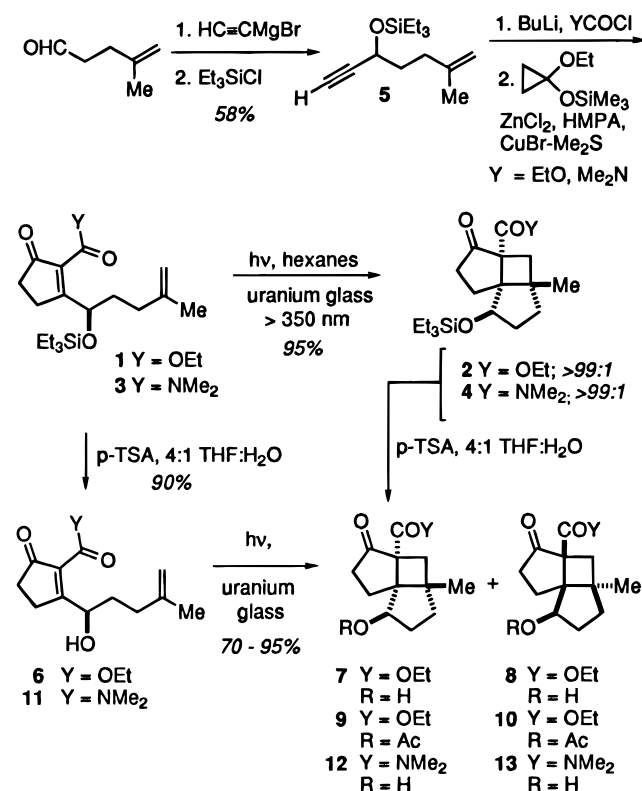
Scheme 1

Table 1

substrate	Y	R	solvent	ratio **7:8** (**12:13**)
1	OEt	SiEt$_3$	hexanes	>99:1
3	NMe$_2$	SiEt$_3$	hexanes	>99:1
6	OEt	H	hexanes	1.1:1
6	OEt	H	CH$_3$CN	3.3:1
6	OEt	H	MeOH	5:1
11	NMe$_2$	H	hexanes	1:4
11	NMe$_2$	H	CH$_2$Cl$_2$	1:3
11	NMe$_2$	H	MeOH	1.5:1

on the diastereoselectivity in intramolecular [2 + 2] enone–olefin photocycloadditions.[7]

The synthesis of photosubstrate **1** and the corresponding amide **3** is illustrated in Scheme 1. The addition of ethynyl magnesium bromide to 4-methyl-4-pentenal[8] in THF at 0 °C resulted in the formation of the acetylenic alcohol, which was then protected (Et$_3$SiCl, Et$_3$N, catalytic DMAP, CH$_2$Cl$_2$) to give silyl ether **5** in 58% yield (Scheme 1).[9] The protected acetylene **5** was then acylated with either ethyl chloroformate (*n*-BuLi, THF, −78 °C) to give the acetylenic ester or amide, which was converted to the cyclopentenone **1** with use of our zinc homoenolate procedure reported previously.[10]

Irradiation of a hexane solution of ester **1** produced a single detectable diastereomer **2** in 95% yield (Table 1).[9] These 2-carboalkoxycyclopentenone chromophores typically undergo

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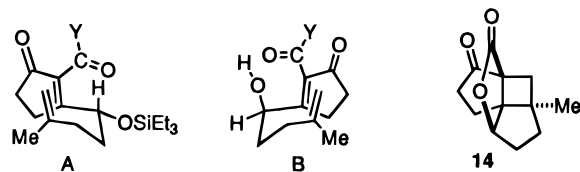(6) de Mayo, P. *Acc. Chem. Res.* **1971**, *4*, 41..

(7) Photoisomerizations which rely on the effects of hyrdogen bonds have also been reported. Lewis, F. D.; Yoon, B. A.; Arai, T.; Iwasaki, T.; Tokumaru, K. *J. Am. Chem. Soc.* **1995**, *117*, 3029–3036. Lewis, F. D.; Yoon, B. A. *J. Org. Chem.* **1994**, *59*, 2537–2545.

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(9) All new compounds gave consistent ^{1}H, ^{13}C, and IR spectra as well as satisfactory C, H combustion analyses or HRMS. All yields are for homogeneous, chromatographically pure products unless otherwise indicated.

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Figure 1.

intramolecular photocycloadditions in excellent yield.[3] Use of other solvents such as dichloromethane, THF, acetonitrile, or methanol did not alter the diastereoselectivity of the reaction. However, a pronounced solvent effect on the diastereoselectivity was observed when the free alcohol **6**, obtained in 90% yield[9] by treatment of the silyl ether with either *p*-toluenesulfonic acid or 5% HF in a 4:1 THF:H_2O solution, was irradiated in different solvents. In methanol, a 5:1 preference for **7** over **8** was obtained, while in acetonitrile, only a 3.3:1 preference was observed. Finally, nearly equal amounts of **7** and **8** were observed when the reaction was carried out in dichloromethane or hexanes. The alcohol photoadducts were converted to the corresponding acetates **9**, **10** (Ac_2O, Et_3N, CH_2Cl_2) for convenience of analysis. The stereochemistry of the secondary alcohol **8** was confirmed by treatment with *p*-toluenesulfonic acid in benzene to produce the bridged lactone **14**. The other diastereomer **7** failed to lactonize under the same conditions. The stereochemistry of **2** and **7** was correlated by hydrolysis of the silyl ether **2** to the alcohol **7**.

The hydrogen bonding ability of the solvent and the diastereoselectivity of the photoadditions appeared to correlate well. An intramolecular hydrogen bond between the hydroxyl and the ester group, which might stabilize an alternate transition state such as **B**, was also possible. In **B** an axially oriented hydroxyl is properly positioned for hydrogen bonding to the carbonyl oxygen of the ester. More highly hydrogen bonding solvents would tend to break up this intramolecular hydrogen bond, while less polar solvents would not. If intramolecular hydrogen bonding were indeed occurring, an amide would be a better electron donor for the hydrogen bonding and might improve the selectivity for the abnormal diastereomer **8**.

The amide was prepared by the same sequence as ester **1** by simply changing the acylating agent for the acetylide (Scheme

1). Once again, irradiation of the protected silyl ether **3** gave very high diastereoselectivity (>99:1) for the normal diastereomer **4**, respectively, and no solvent effect was observed. When the alcohol **11** was irradiated in nonpolar, non-hydrogen bonding solvents such as dichloromethane or hexanes, a reversal of the normal diastereoselectivity was achieved. The dimethyl amide **11** provided a 3:1 selectivity for the reversed product **13**.

Arnett has measured intermolecular hydrogen bonds between *p*-fluorophenol and a large number of hydrogen bond acceptors including ethyl acetate [−4.7 kcal/mol (−19.7 kJ/mol)], *N*,*N*-dimethylacetamide [−7.4 kcal/mol (−31.0 kJ/mol)], and *N*,*N*-dimethylformamide [−7.0 kcal/mol (−29.3 kJ/mol)].[11] Thus a hydroxyl−amide hydrogen bond is approximately 2.3−2.7 kcal/mol (9.6−11.3 kJ/mol) stronger than a hydroxyl−ester hydrogen bond. A more selective reaction might have been expected for the amide than that observed. However, the increased steric bulk of the *N*,*N*-dimethyl amide may somewhat destabilize the hydrogen-bonded form for the amide resulting in lower selectivity than predicted by the difference in hydrogen bond strengths. The intramolecular nature of the hydrogen bond may also preclude ideal geometry for the hydrogen bonds.

In conclusion, hydrogen bonding and solvent effects can be important factors in controlling the diastereoselectivity in intramolecular [2 + 2] photocycloadditions. Other similar examples which are consistent with the above interpretation have also been studied. Application of these observations in a stereocontrolled synthesis of ginkgolide B and other polycyclic systems is in progress.

Supporting Information Available: Experimental procedures and spectral data (^{1}H, ^{13}C NMR, IR, and elemental analyses) for compounds **1**−**6** and **9**−**14** (^{1}H NMR only for compunds **9**, **10**, and **14**) (6 pages). See any current masthead page for ordering and Internet access instructions.

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