Synthesis of Bridged Bicyclic Ethers and Fused Oxetanes from Pyran-4-ones via Tandem Solvent Trapping and Norrish Type II Cyclization[1]

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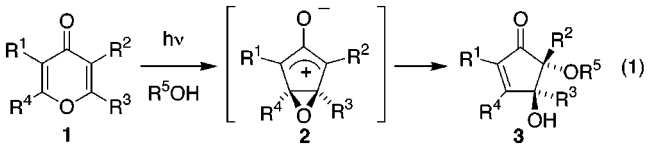
Polyalkyl pyran-4-ones **1a**−**c** were irradiated in methanol or ethanol. Although the expected solvent trapping products **3** could be observed, extended irradiation times allowed exclusive formation of secondary photoproducts **4** and **5** in combined yields of 37−64%. These bicyclic compounds are believed to arise from γ-hydrogen abstraction by the excited enone chromophore of **3**, followed by closure of the resulting biradical through one of two possible pathways. Moderate stereoselectivity was observed in the radical coupling to produce **4**, whereas the analogous closure to **5** was completely diastereoselective. Tautomerization of the enol precursors to **5** also occurred with complete selectivity for protonation from the exo face. Overall, this process converts simple, planar heterocycles and alkanols into complex products in a single transformation.

Introduction

Extensive studies of the photochemistry of pyran-4-ones in recent years[2] have elucidated a number of mechanistically complex and synthetically intriguing photorearrangements and trapping processes for these simple, heterocyclic reactants. Early observations identified dimerization[3] and unimolecular rearrangement[4] to pyran-2-ones or furfurals as common pathways. It was subsequently found that irradiation of pyran-4-ones **1** in polar, protic solvents led to solvent adducts (eq 1).[5] These



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novel photoproducts were shown to be 2-alkoxy-3-hydroxycyclopent-4-en-1-ones **3**, and their efficient formation implicated the bicyclic oxyallyl intermediate **2**, analogous to zwitterionic species formed during irradiation of carbocyclic cross-conjugated dienones.[6] Subsequent studies in our labs have shown that a variety of synthetically useful intramolecular trapping processes can be applied to intermediates such as **2** bearing pendant groups that can effectively intercept the reactive oxyallyl unit.[7]

Although various photocyclization and photocycloaddition reactions are possible using the intramolecular strategy, the intermolecular solvent trapping process is especially appealing because of the simplicity of the two reactants. Thus, a planar, achiral heterocycle and an inexpensive alcohol are combined photochemically to yield a functionalized carbocyclic product in diastereoselective fashion. This has been exploited for the facile, two-step construction of bicyclo[*n*.3.0]alkenones ($n = 4-6$) from cycloalkanone precursors.[8] Stereoselectivity derives from the apparent preference for attack of the nucleophilic solvent at the opposite face of the bicyclic oxyallyl intermediate from the epoxy group.[9] With unsymmetrically substituted pyran-4-ones, regiochemistry was also at issue. We[8,10] and others[11] had previously observed a marked preference for solvent trapping at the more substituted terminus of the oxyallyl system, presumably resulting from greater charge density at this position. To better understand the scope of this reaction, we examined the solvent trapping process with several polyalkyl pyran-4-ones and alcohols. The results of this study reveal a remarkably facile secondary photoprocess, in which the initially formed 2-alkoxycyclopentenones are further converted to complex, bicyclic ethers via 1,4-hydrogen abstraction/radical recombination.

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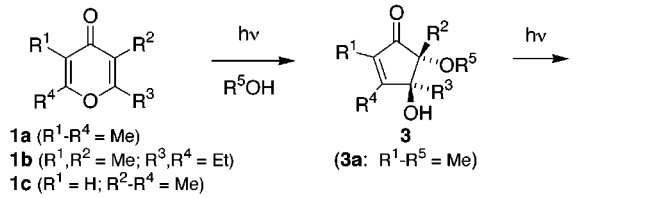
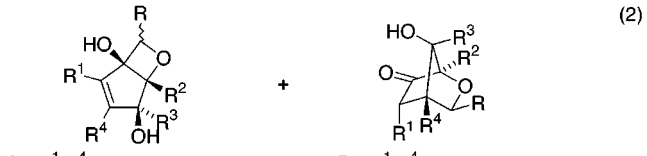
Results and Discussion

Alkyl pyranones **1a**−**c** are readily available via polyphosphoric acid mediated condensation of either 3-pentanone or 2-butanone with acetic or propionic anhydride.[12] 2,3,5,6-Tetramethylpyran-4-one **1a** was irradiated in methanol through quartz using a Hanovia 450W medium-pressure mercury vapor lamp (eq 2). To our



1a (R^1-R^4 = Me)
1b (R^1,R^2 = Me; R^3,R^4 = Et)
1c (R^1 = H; R^2-R^4 = Me)

3 (**3a**: R^1-R^5 = Me)



(2)

4a (R^1-R^4 = Me; R = H)
4b (R,R^1-R^4 = Me)
4d (R^1,R^2 = Me; R^3,R^4 = Et; R = H)
4e (R,R^1,R^2 = Me; R^3,R^4 = Et)
4f (R,R^1 = H; R^2-R^4 = Me)
4g (R^1 = H; R,R^2-R^4 = Me)

5a (R^1-R^4 = Me; R = H)
5b (R,R^1-R^4 = Me)
5d (R^1,R^2 = Me; R^3,R^4 = Et; R = H)
5e (R,R^1,R^2 = Me; R^3,R^4 = Et)
5f (R,R^1 = H; R^2-R^4 = Me)
5g (R^1 = H; R,R^2-R^4 = Me)

surprise, we found that the expected product **3a** was accompanied by substantial amounts of two additional products and that the relative ratios of the photoproducts was time-dependent. The latter observation suggested that the unexpected products might result from secondary photochemical processes, and the determination of their structures to be fused and bridged bicyclic ethers **4a** and **5a** strongly supported this (see mechanistic discussion below). With an additional ring and one or two additional stereocenters, the structures of **4a** and **5a** entailed a substantial increase in molecular complexity over that of the primary photoproduct **3a**. The value of the solvent trapping reaction as a synthetic method could be greatly enhanced if formation of the secondary products could be optimized. To that end, extended irradiation times were examined, and it was found that complete consumption of **1a** and **3a** to give only **4a** and **5a** in 59% combined yield could be realized by carrying out the irradiation for ≥2 h. When generalized to other alcohols and pyran-4-ones, we found that, with one exception, these conditions could be used to prepare **4a**−**g** and **5a**−**g** in moderate to good combined yield (Table 1).

Irradiation of **1a** in EtOH furnished oxetane **4b** as a 2:1 mixture of methyl epimers in 45% yield, along with 2-oxabicyclo[2.2.1]heptan-6-one **5b** as a single diastereomer in 19% yield (entry 2). In contrast, the analogous process in *i*-PrOH led to a complex mixture of products (entry 3). This may be attributed to the decreased efficiency of solvent trapping in the case of a secondary alcohol,[8] as well as the ratio of singlet and triplet biradicals in the subsequent Norrish type II hydrogen abstraction.[13] Regardless of the cause, this result prompted us to limit the trapping solvent to MeOH or EtOH in subsequent experiments using **1b** and **1c**. In the event, all of these examples furnished **4d**−**g** (with **4e** and **4g**

Table 1. Direct Formation of Bicyclic Ethers from Pyran-4-ones[a]

entry	substrate	solvent	irradiation time	products (% yield)[b]
1	**1a**	MeOH	2 h	**4a** (30), **5a** (29)
2	**1a**	EtOH	2 h	**4b** (45),[c] **5b** (19)
3	**1a**	*i*-PrOH	4.5 h	*d*
4	**1b**	MeOH	3 h	**4d** (23), **5d** (14)
5	**1b**	EtOH	3 h	**4e** (35),[c] **5e** (14)
6	**1c**	MeOH	8 h	**4f** (20), **5f** (17)
7	**1c**	EtOH	5.5 h	**4g** (33),[c] **5g** (14)

[a] See eq 2. Standard procedure: a deoxygenated solution of pyran-4-one substrate **1** in the appropriate alcohol (0.05−0.07 M) in a quartz test tube was irradiated until complete consumption of **1** and **3** was apparent by TLC. [b] Isolated yields after chromatography, averaged from at least two runs. [c] Methyl-substituted oxetanols **4b**,**e**,**g** were isolated as 2:1, 1.5:1, and 1.3:1 (β-methyl/α-methyl) mixtures of diastereomers, respectively. [d] All attempts to obtain **4c** and **5c** from **1a** and *i*-PrOH led to complex product mixtures.

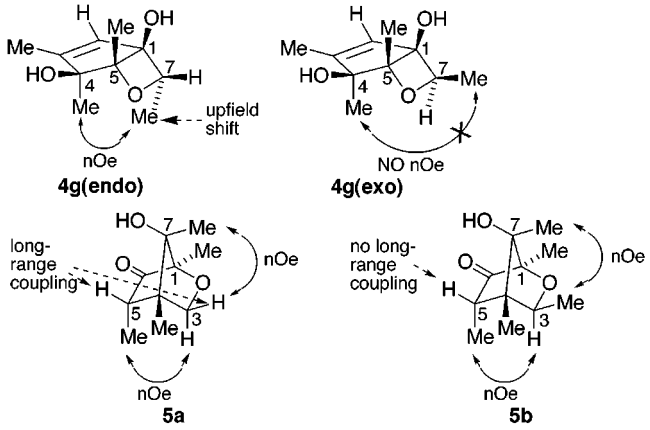


Figure 1.

appearing as mixtures of methyl epimers) along with lesser amounts of **5d**−**g** (entries 4−7). Further photochemistry was not observed upon extended irradiation of **4** and **5**, nor was any special lability of oxetanols **4** seen during chromatographic purification, as has been reported for related substrates.[14]

Assignment of the relative stereochemistry for several of the centers in **4** and **5** was straightforward and based on the known preference for a trans relationship between the C-2 alkoxy and C-3 hydroxy groups in primary photoproducts **3**,[8] along with the constraints of the bicyclic systems. However, the disposition of the methyl substituents at C-7 of **4b**,**e**,**g** and at C-3 and/or C-5 of **5a**,**b**,**d**,**e**,**g** could be determined only by two-dimensional NMR studies. 2D NOESY NMR spectra of both diastereomers of **4g** were obtained and clearly indicated an NOE interaction, between the indicated methyl groups in the endo isomer, which was absent in its exo counterpart (Figure 1). Moreover, the C-7 methyl of the endo diastereomer was shifted more than 0.3 ppm upfield relative to that of the exo diastereomer, presumably as a result of shielding by the cyclopentene π system. Support for an endo orientation of the C-5 methyl of **5a** could be found in the appearance of NOE interactions between this methyl and one of the C-3 methylene protons and between the C-7 methyl and the other C-3 methylene proton. Also, a long-range w-coupling was observed between the exo C-3 methylene proton and the C-5 methine. In the case of **5b**, NOE interactions as indicated

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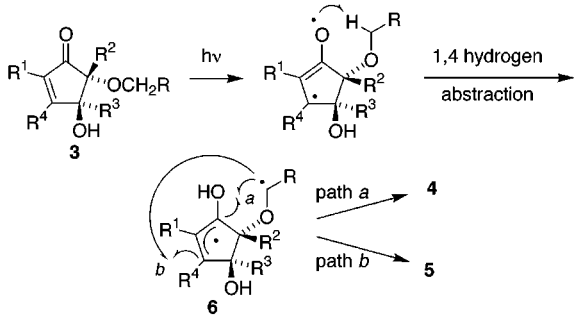
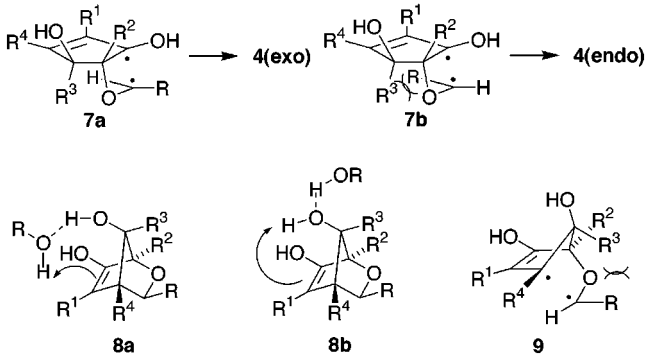
Scheme 1



Scheme 2



once again provided support for an endo methyl at C-5. The absence of any w-coupling and the observation of an NOE interaction between the C-3 and C-7 methyls were used to assign an exo methyl stereochemistry at C-3. Similar chemical shifts and coupling patterns allowed the stereochemical assignment of the other cases by analogy.

As noted above, time-dependent product ratios suggested that **4** and **5** arise from secondary photoreactions of the initially formed solvent adducts **3**. A likely mechanism involves excitation of the cyclopentenone chromophore, followed by γ-hydrogen abstraction to provide the 1,4-biradical **6** (Scheme 1).[15] Oxetanols **4** are analogous to photoproducts arising from irradiation of 2-alkyl[16] or 2-alkoxycycloalkanones.[14,17] This process, involving closure of the initially formed biradical, has enjoyed recent attention as an efficient route to bicyclo[*n*.2.0]-alkanols. Unlike the saturated ketones employed in those cases, primary photoproducts **3** possess additional unsaturation. As a result, one of the radical centers in intermediate **6** is allylic, which permits an alternative closure of the biradical via the former β-carbon of the enone system, leading to oxabicyclo[2.2.1]heptanones **5**. Excellent precedent for this pathway can be found in the prior observation by Smith and Agosta of both fused and bridged bicyclic products from irradiation of several simple α'-substituted cyclopentenones.[18]

Examples employing ethanol trapping showed a modest diastereoselectivity in favor of the β-methyl isomer for oxetanols **4** (entries 2, 5, and 7). This is presumed to arise from a preference for an exo-disposed methyl of conformer **7a** over the more sterically encumbered endo methyl conformer **7b** in the transition state for oxetane closure (Scheme 2). The isolation of a single diastereomer of the bridged bicyclic products **5** in each case is more striking and requires additional comment. Peralkylated pyran-4-ones **1a**,**b** must necessarily furnish photoadducts **5** possessing a stereocenter at C-5 (entries 1−5), derived from tautomerization of the enol initially formed after radical coupling. In all cases, the methyl group at this position was determined to be in the endo position, an outcome that may result from preferred kinetic protonation from the exo face. Selective exo approach of electrophiles is well precedented, even in relatively hindered camphor derivatives;[19] moreover, the C-7 hydroxyl group is well positioned to participate in enol protonation through either hydrogen bonding to a solvent molecule (**8a**) or direct delivery (**8b**). Surprisingly, with ethanol trapping (entries 2, 5, and 7), complete stereoselectivity was observed in favor of an exo-disposed methyl at C-3. Although this high selectivity is welcome, its origins are not well understood. Smith and Agosta also noted the exclusive formation of exo isomers;[18] however, their examples lacked substituents at C-7. Unfavorable nonbonded interactions between the C-3 and C-7 methyls in the exo transition state (**9**) would be expected to cause a degradation in the stereoselectivity.

Conclusions

We have described a novel method for the direct formation of complex, bicyclic products from simple precursors. Irradiation of alcohol solutions of polyalkyl pyran-4-ones leads to 2-alkoxycyclopentenones **3** via nucleophilic trapping by solvent of the photochemically generated oxyallyl zwitterion. These photoadducts then undergo efficient secondary photochemistry, in which hydrogen abstraction by the excited enone chromophore furnishes 1,4-biradicals **6**. These intermediates can undergo subsequent radical coupling in two ring-closure modes to give 6-oxabicyclo[3.2.0]hept-2-ene-1,4-diols **4** and 2-oxabicyclo-[2.2.1]heptan-6-ones **5**. Oxetanols **4** possess three or four newly generated stereocenters, and in cases employing ethanol as the solvent trap, a moderate selectivity in favor of the β-isomer was seen. Bridged bicyclic isomers **5** contain up to five contiguous stereocenters, all of which were set with complete selectivity. Further applications of this interesting tandem process will be reported in due course.

Experimental Section

General. All spectrograde solvents (MeOH, EtOH, *i*-PrOH) were used as purchased without further purification. Thin-layer chromatography (TLC) was performed on glass plates precoated with Kieselgel 60 F_{254}. Melting points are uncorrected. NMR spectra were recorded on a 500 MHz instrument using $CDCl_3$ or d_6-acetone as solvent. All elemental analyses were carried out by Atlantic Microlabs, Norcross, GA. Photoreactions were conducted using an Ace-Hanovia medium-pressure 450 W Hg lamp.

Representative Procedure. Preparation of 4a and 5a. Pyran-4-one **1a** (100 mg, 0.67 mmol) was dissolved in MeOH (100 mL) in a polished quartz tube, and the solution was deoxygenated for 15 min with a slow stream of dry N_2. The tube was placed ca. 10 cm from the outside of the lamp's water jacket and irradiated until consumption of **1a** (as judged by TLC). Solvent was removed under reduced pressure, and the residue was purified via flash column chromatography (2:1:1

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CH_2Cl_2/Et_2O/Hex) to give 36 mg (29%) of compound **5a** as a colorless oil. The eluting solvent was then changed to 1:19 Hex/EtOAc to furnish compound **4a** (37 mg, 30%) as a white waxy solid.

4a: R_f 0.33 (EtOAc); mp 153−156 °C dec; IR (KBr) 3351, 1435 cm^{-1}; ^1H NMR (500 MHz, d_6-acetone) δ 4.33 (d, J = 6.0 Hz, 1H), 4.12 (br s, 1H), 3.89 (d, J = 6.0 Hz, 1H), 3.11 (br s, 1H), 1.66 (s, 3H), 1.64 (s, 3H), 1.34 (s, 3H), 1.15 (s, 3H); ^{13}C NMR (125 MHz, d_6-acetone) δ 140.4, 134.5, 98.1, 84.0, 83.2, 76.9, 18.2, 13.7, 9.7, 9.1. Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 64.98; H, 8.69.

5a: R_f 0.30 (2:1:1 CH_2Cl_2/Et_2O/Hex); IR (neat) 3431, 1749, 1453 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.76 (d, J = 8.0 Hz, 1H), 3.56 (dd, J = 8.0, 1.0 Hz, 1H), 2.60 (qd, J = 7.5, 1.0 Hz, 1H), 1.74 (br s, 1H), 1.30 (s, 3H), 1.17 (s, 3H), 1.12 (d, J = 7.5 Hz, 3H), 1.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.0, 84.7, 80.2, 69.8, 49.9, 46.2, 15.4, 9.6, 8.1, 7.9. Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.05; H, 8.77.

Preparation of 4b and 5b. Pyran-4-one **1a** (100 mg, 0.67 mmol) was dissolved in EtOH and irradiated via the procedure described above. Purification via flash column chromatography (2:1:1 CH_2Cl_2/Et_2O/Hex) gave 26 mg (19%) of compound **5b** as a colorless oil. The eluting solvent was then changed to 1:19 Hex/EtOAc to furnish the exo (40 mg, 30%) and endo (20 mg, 15%) isomers of compound **4b** as white waxy solids.

4b(exo): R_f 0.35 (EtOAc); mp 123−125 °C; IR (KBr) 3397, 1440 cm^{-1}; ^1H NMR (500 MHz, d_6-acetone) δ 4.06 (q, J = 7.0 Hz, 1H), 3.96 (br s, 1H), 3.11 (br s, 1H), 1.65 (s, 3H), 1.61 (s, 3H), 1.35 (s, 3H), 1.34 (d, J = 6.5 Hz, 3H), 1.15 (s, 3H); ^{13}C NMR (125 MHz, d_6-acetone) δ 139.5, 135.7, 95.9, 84.3, 83.6, 83.0, 18.7, 18.4, 16.9, 9.6, 9.0.

4b(endo): R_f 0.23 (EtOAc); mp 136−138 °C; IR (KBr) 3338, 1439 cm^{-1}; ^1H NMR (500 MHz, d_6-acetone) δ 4.53 (q, J = 6.0 Hz, 1H), 4.11 (br s, 1H), 3.10 (br s, 1H), 1.69 (s, 3H), 1.62 (s, 3H), 1.29 (s, 3H), 1.16 (s, 3H), 0.96 (d, J = 6.0 Hz, 3H); ^{13}C NMR (125 MHz, d_6-acetone) δ 142.2, 132.1, 93.9, 86.1, 84.2, 83.2, 18.4, 17.5, 14.0, 10.9, 9.6. Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.57; H, 9.25.

5b: R_f 0.35 (2:1:1 CH_2Cl_2/Et_2O/Hex); IR (neat) 3484, 1756, 1448 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.98 (q, J = 7.0 Hz, 1H), 2.75 (q, J = 7.5 Hz, 1H), 1.60 (br s, 1H), 1.40 (s, 3H), 1.23 (d, J = 7.0 Hz, 3H), 1.15 (s, 3H), 1.07 (d, J = 7.5 Hz, 3H), 1.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.4, 84.5, 80.3, 73.9, 51.7, 48.2, 18.2, 18.1, 9.5, 8.3, 6.8. Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.53; H, 9.23.

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Supporting Information Available: Purification and physical data for **4d**−**g** and **5d**−**g**; ^{13}C NMR spectra for compounds **4b(exo)**, **4e(endo)**, **4f**, and **5e**−**g**; and 2D-NOESY spectra for compounds **4g(endo)**, **5a**, and **5b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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