A General Approach to the Synthesis of Butanolides: Synthesis of the Sex Pheromone of the Japanese Beetle

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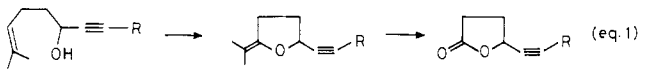
A variety of substituted γ-hydroxy olefins 1 have been converted to butanolides 4 in very high yield in a three-step sequence involving bromoetherification, elimination, and oxidative cleavage. The key step in the overall transformation is the highly selective oxidative cleavage of enol ethers 3 with PCC under very mild reaction conditions. Application of this methodology has been exemplified in the synthesis of the Japanese beetle pheromone.

Introduction

The chemistry of butanolides has attracted considerable attention mainly because many molecules that belong to this class have revealed diverse and significant biological activity. Synthetic methods continue to be developed for the construction of γ-lactone structural unit from readily available starting materials.[1] Earlier work from our laboratories has shown that the alcohol function in γ- and δ-unsaturated alcohols activates the double bond toward oxidative cleavage[2-4] and provides a useful route to γ- and δ-lactones. (Scheme I). When the alcohol is secondary, there are problems in selectivity. Chromium(VI) reagents will oxidize the alcohol faster than the double bond.[3,5] Cetyl trimethylammonium permanganate (CTAP)[4] will oxidize the double bond faster but not when the alcohol is allylic, propargylic, or benzylic. The observation that ketone-derived enol ethers are readily cleaved with pyridinium chlorochromate (PCC)[6] (Scheme II) suggests that prior formation of the enol ether followed by PCC oxidation will provide the desired selectivity (eq 1).

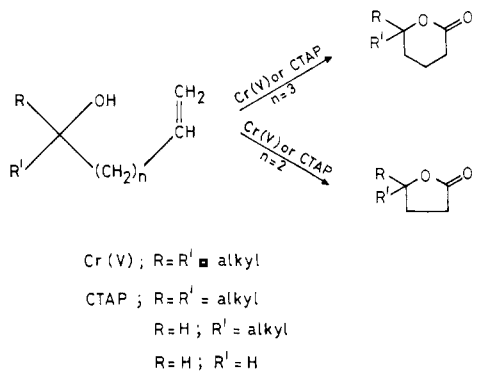


We report our results based on this strategy on the facile conversion of γ-hydroxy olefins 1 to butanolides 4[7] in a three-step sequence involving haloetherification,[8] base-induced elimination, and highly selective oxidative cleavage of the enol ether double bond. A successful application of this new general methodology has been illustrated with the synthesis of the sex pheromone of the Japanese beetle, *popilla japonica*.[9]

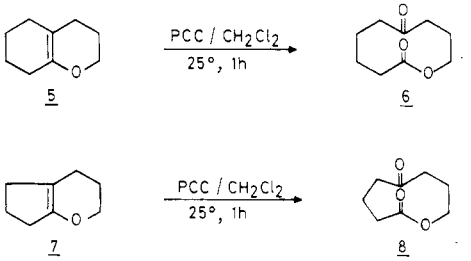
Results and Discussion

Synthesis of Enol Ethers 3a-j. A variety of enol ethers **3a-g** were synthesized by adapting a three-step strategy. The first step involved the synthesis of a number of substituted γ-hydroxy olefins **1a-g** from 6-methylhept-5-en-2-one (**10**)[10] by Grignard reaction. The γ-hydroxy olefins **1a-g** were then converted to the corresponding bromo ethers **2a-g** as a mixture of isomers on treatment with *N*-bromosuccinimide at 20 °C.[11] The dehydrobromination[12] was then carried out with potassium *tert*-butoxide in *tert*-butyl alcohol or THF, and the resulting crude enol ethers **3a-g** (Scheme III) were subjected to oxidative fragmentation with pyridinium chlorochromate. By a similar sequence of reactions, enol ethers **3h-i** were prepared from the corresponding carbonyl compounds. *trans*-2-Allylcyclohexan-1-ol[13] prepared from cyclohexene oxide and allylmagnesium bromide, followed by bromoetherification and elimination with potassium *tert*-butoxide, afforded the enol ether **3j**.

Scheme I



Scheme II



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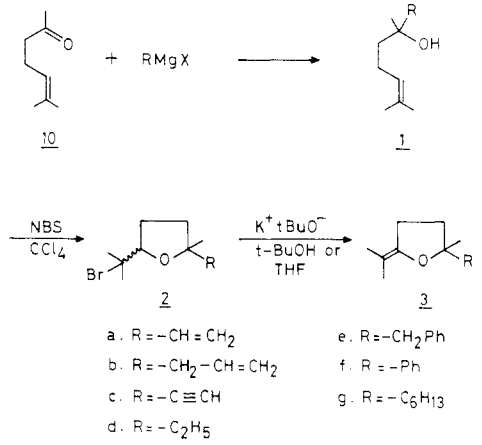
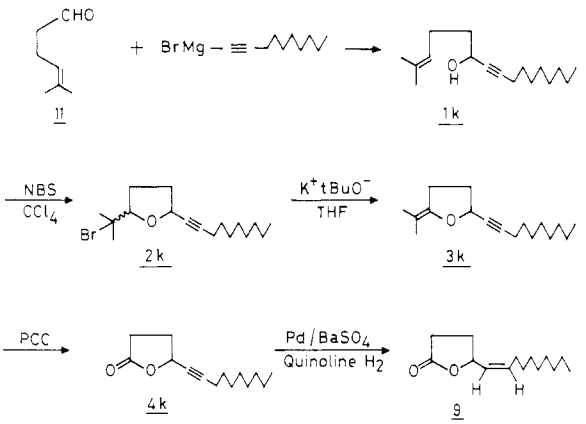
(7) This methodology is complementary to the direct conversion of 1 to 4 using CTAP (ref 4) and compares favorably in terms of ease of operation and overall yield.

0022-3263/90/1955-0891$02.50/0

Scheme III



Scheme IV

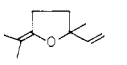
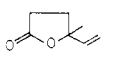
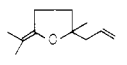
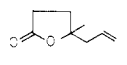
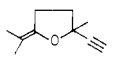
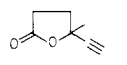
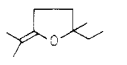
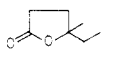
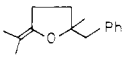
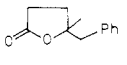
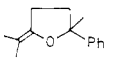
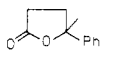
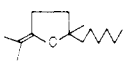
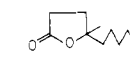
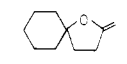
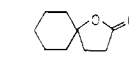
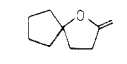
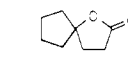
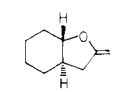
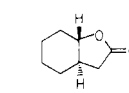
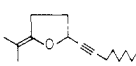
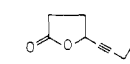


Selective Oxidative Cleavage of Enol Ethers 3a–j with PCC. The oxidative cleavage of enol ethers **3a–j** to the corresponding butanolides **4a–j** was effected by treatment with 4 equiv of PCC at room temperature (28 °C) for 1–3 h in dichloromethane and proceeded in high yield (Table I). As can be gauged from Table I the key feature of this methodology is that under the reaction conditions other isolated carbon–carbon double bonds and benzylic groups present in the molecule are not affected.

Synthesis of the Pheromone of the Japanese Beetle.[9] An application of this general methodology for the synthesis of butanolides has been exemplified in a synthesis of (±)-**9**, the pheromone component of the Japanese beetle (Scheme IV).[9] Enol ether **3k**, which is a precursor of **9**, was synthesised from aldehyde **11**[14] as shown in Scheme IV. Grignard reagent derived from 1-decyne was allowed to react with aldehyde **11**[14] to yield the alcohol **1k**[9c] (58%), which was treated with *N*-bromosuccinimide in CH_2Cl_2 at 20 °C to afford the bromo ether **2k** (68%) as a mixture of isomers. Dehydrobromination of **2k** was effected by reaction with potassium *tert*-butoxide in *tert*-butyl alcohol to yield the enol ether **3k**, which was quite unstable. The crude product was immediately treated with 4 equiv of PCC at room temperature, and the γ-lactone **4k** was obtained in 52% yield. Catalytic hydrogenation with Lindlar's catalyst afforded (±)-**9** (95%), which exhibited spectral data similar to those reported in the literature for the pheromone of the Japanese beetle.[9]

In this paper we have presented a simple but effective, general, four-step strategy for the synthesis of a variety of butanolides starting from readily available carbonyl compounds.[7] We hope that the highly selective oxidative cleavage of enol ether double bonds with the simple oxochromium reagent PCC would find further useful applications in organic synthesis.

Table I. Oxidative Cleavage of Enol Ethers with PCC at 28 °C

entry	enol ether		lactone		yield, %
1		3a		4a	90
2		3b		4b	89
3		3c		4c	70
4		3d		4d	85
5		3e		4e	82
6		3f		4f	75
7		3g		4g	79
8		3h		4h	66
9		3i		4i	56
10		3j		4j	51
11		3k		4k	52

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Experimental Section

Materials and Methods. NMR spectra were recorded on Varian EM-390, Bruker WP-80, and Bruker AM-250 spectrometers in $CDCl_3$ or CCl_4. Chemical shifts are reported in parts per million, and coupling constants are reported in hertz. IR spectra were obtained on a Perkin-Elmer 1320 spectrometer. Mass spectra were recorded on JEOL JMS-D 300 mass spectrometer. Chromatographic purification of bromo ethers **2a–g** was carried out by flash chromatography on silica gel and eluted with petroleum ether (60–80 °C). Carbon tetrachloride and dichloromethane were distilled over P_2O_5. Diethyl ether and tetrahydrofuran were dried over sodium. Thin-layer chromatography (TLC) was performed on 0.25 mm E. Merck precoated silica gel plates (60F-254). Silica gel (230–400 mesh) supplied by Merck was used for flash chromatography. The alcohols **1a** and **1c** were purchased from Aldrich Chemical Co.

General Procedure for the Preparation of the Alcohols 1. 4,8-Dimethyl-1,7-nonadien-4-ol (1b).[15] A solution of 6-methyl-5-hepten-2-one (**10**)[10] (2.52 g, 20 mmol) in 15 mL of dry ether was added under nitrogen atmosphere to a solution of allylmagnesium bromide [prepared from magnesium powder (0.528 g, 22 mg-atom) and allyl bromide (2.42 g, 20 mmol)] in 30 mL of dry ether over a period of 0.25 h, and the mixture was stirred at room temperature (28 °C) for additional 2 h. Saturated NH_4Cl solution (15 mL) was added to the reaction mixture, the organic layer was separated, and the aqueous phase was extracted with ether (2 × 50 mL). The combined organic extracts were washed with brine and dried ($MgSO_4$), and the solvent was removed to afford the alcohol **1b**[15] (2.35 g, 70%) as a colorless oil, after chromatographic purification on silica gel [1:9 ethyl acetate–petroleum ether (60–80 °C)]. IR (neat): 3450, 3080, 1635 cm^{-1}. NMR (CCl_4): δ 1.16 (s, 3 H), 1.3–1.70 (m, 3 H), 1.72 (s, 3 H), 1.76 (s, 3 H), 2.06–2.2 (m, 4 H), 4.86–5.15 (m, 3 H), and 5.6–6.2 (m, 1 H).

3,7-Dimethyl-6-octen-3-ol (1d).[16a,b] Ethylmagnesium bromide [prepared from ethyl bromide (2.18 g, 20 mmol) and magnesium powder (0.528 g, 22 mg atom)] was allowed to react with **10** (2.52 g, 20 mmol) in ether (30 mL) for 2 h, and **1d** (1.014 g, 65%) was obtained as a colorless oil. IR (neat): 3460 cm^{-1}. NMR ($CDCl_3$): δ 0.70–0.93 (t, 3 H), 1.16 (s, 3 H), 1.2–1.29 (m, 1 H), 1.44–1.54 (m, 4 H), 1.63 (s, 3 H), 1.69 (s, 3 H), 1.98–2.08 (q, 2 H), and 5.10–5.16 (t, 1 H).

1-Phenyl-2,6-dimethyl-5-hepten-2-ol (1e). Grignard reagent derived from benzyl bromide (1.71 g, 10 mmol) and magnesium powder (0.264 g, 11 mg-atom) in ether (30 mL) was allowed to react with **10** (1.26 g, 10 mmol) at room temperature for 2 h. Alcohol **1e** was obtained after chromatographic purification as an oil (1.286 g, 59%). IR (neat): 3460, 3080, 3050, 3020, 1590 cm^{-1}. NMR ($CDCl_3$): δ 1.12 (s, 3 H), 1.23–1.6 (m, 3 H), 1.62 (s, 3 H), 1.68 (s, 3 H), 2.0–2.26 (m, 2 H), 2.73 (s, 2 H), 5.12 (t, 1 H, J = 6 Hz), 7.2–7.5 (m, 5 H). Anal. Calcd for $C_{15}H_{22}O$: C, 82.56; H, 10.09. Found: C, 82.79; H, 10.41.

2-Phenyl-6-methyl-5-hepten-2-ol (1f).[17] Phenylmagnesium bromide prepared from magnesium powder (0.264 g, 11 mg-atom) and bromobenzene (1.57 g, 10 mmol) in ether (30 mL) was treated with **10** (1.26 g, 10 mmol) as above for 2.5 h. The alcohol **1f** was obtained as a colorless oil (1.49 g, 73%), bp 94 °C (1 mm) (lit.[17] bp 70 °C (0.1 mm)). IR (neat): 3380, 3080, 3050, 3020, 1590 cm^{-1}. NMR ($CDCl_3$): δ 1.48 (s, 3 H), 1.54 (s, 3 H), 1.65 (s, 3 H), 1.73–2.06 (m, 5 H), 5.06 (m, 1 H), 7.19–7.59 (m, 5 H).

2,6-Dimethyl-2-dodecen-6-ol (1g).[16b] Hexylmagnesium bromide obtained from hexyl bromide (1.65 g, 10 mmol) and magnesium powder (0.264 g, 11 mg-atom) in ether (30 mL) was reacted with **10** (1.26 g, 10 mmol) as above for 3 h. Alcohol **1g** was obtained as a colorless liquid (1.42 g, 67%) after distillation, bp 106–108 °C (0.3 mm) (lit.[16b] bp 106–110 °C (0.3 mm)). IR (neat): 3400 cm^{-1}. NMR ($CDCl_3$): δ 0.89 (t, 3 H), 1.17 (s, 3 H), 1.29 (br s, 10 H), 1.44–1.50 (m, 3 H), 1.63 (s, 3 H), 1.70 (s, 3 H), 2.01–2.05 (m, 2 H), and 5.13 (t, 1 H, J = 6 Hz).

1-(3-Butenyl)cyclohexan-1-ol (1h).[18] 3-Butenylmagnesium bromide, derived from magnesium powder (0.528 g, 22 mg-atom) and 3-butenyl bromide (2.7 g, 20 mmol), in 30 mL of dry ether was treated with cyclohexanone (1.96 g, 20 m mol) at room temperature for 2 h. Alcohol **1h**[18] was obtained after chromatographic purification as an oil (1.6 g, 52%). IR (neat): 3400, 3080, 1640 cm^{-1}. NMR ($CDCl_3$): δ 1.3–1.7 (m, 12 H), 2–2.3 (m, 3 H), 4.85–5.2 (m, 2 H), 5.5–6.15 (m, 1 H).

1-(3-Butenyl)cyclopentan-1-ol (1i).[18] 3-Butenylmagnesium bromide, prepared from magnesium powder (0.528 g, 22 mg-atom) and 3-butenyl bromide (2.7 g, 20 mmol), in 30 mL of dry ether was allowed to react with cyclopentanone (1.68 g, 20 mmol) as above for 2 h. Alcohol **1i**[18] was obtained as a colorless liquid (1.4 g, 50%) after distillation, bp 62–65 °C (3 mm) (lit.[18] bp 62–64 °C (3 mm)). IR (neat): 3400, 3080, 1640 cm^{-1}. NMR ($CDCl_3$): δ 1.4–1.8 (m, 10 H), 2.05–2.35 (m, 3 H), 4.85–5.2 (m, 2 H), 5.6–6.15 (m, 1 H).

***trans*-2-(2-Propenyl)cyclohexanol (1j).**[13] Allylmagnesium bromide obtained from allyl bromide (9.1 g, 75 mmol) and magnesium powder (3.65 g, 150 mmol) in ether (60 mL) was treated with cyclohexene oxide (2.45 g, 25 mmol), and the resulting mixture was refluxed for 14 h. Alcohol **1j**[13] was obtained as a colorless liquid (3.325 g, 95%); bp 86–88 °C (23 mmHg) (lit.[13] bp 86–88 °C (23 mmHg)). IR (neat): 3450, 3100, 1650, 1000, 910 cm^{-1}. NMR ($CDCl_3$): δ 0.8–2.1 (m, 10 H), 2.3–2.7 (m, 1 H), 2.9–3.4 (m, 1 H), 3.5 (s, 1 H), 4.8–5.3 (m, 2 H), 5.4–6.2 (m, 1 H).

2-Methylhexadec-2-en-7-yn-6-ol (1k).[9c] To a stirred solution of ethylmagnesium bromide prepared from freshly distilled ethyl bromide (0.545 g, 5 mmol) and magnesium powder (0.122 g, 5 mg-atom) in 10 mL of dry ether under N_2 at 0 °C was added 1-decyne (0.690 g, 5 mmol) in THF (5 mL). After the addition was over the reaction mixture was heated under reflux for 2 h. It was cooled to 0 °C, and the aldehyde **11**[14] (0.560 g, 5 mmol) in THF 10 mL was added slowly. Then the reaction mixture was stirred at room temperature for 3 h. A saturated solution of NH_4Cl (15 mL) was added, and the reaction mixture was extracted thoroughly with ether. The combined ether extracts were washed with brine and dried ($MgSO_4$). The residue obtained after removal of solvent was purified by chromatography (1:20 ether/petroleum ether) to afford the alcohol **1k**[9c] (0.725 g, 58%) as an oil. IR (neat): 3340, 2940, 2860, 2220, 1470, 1460, 1380 cm^{-1}. NMR ($CDCl_3$): δ 0.88 (t, 3 H), 1.27 (br s, 12 H), 1.63 (s, 3 H), 1.69 (s, 3 H), 1.81–1.91 (m, 3 H), 2.12–2.19 (m, 4 H), 4.35 (t, 1 H), 5.13 (t, 1 H).

General Procedure for the Preparation of Bromo Ethers 2.[11] **Bromo Ether 2a.**[11a] To a solution of the alcohol **1a** (1.54 g, 10 mmol) in dry CCl_4 (15 mL) was added *N*-bromosuccinimide (1.958 g, 11 mmol) at 20 °C, and the mixture was stirred for 18 h. The reaction mixture was diluted with petroleum ether (40–60 °C) (30 mL) and filtered through a pad of Celite. Sodium acetate (0.025 g) was added to the filtrate, and the solvent was removed under reduced pressure. The crude product after a quick chromatographic purification yielded the bromo ether **2a**[11a] (1.980 g, 85%) as an oil. IR (neat): 1640 cm^{-1}. NMR (CCl_4): δ 1.2 (s, 3 H), 1.6 (s, 3 H), 1.68 (s, 3 H), 1.80–2.10 (m, 4 H), 3.8–4.0 (2 t, 1 H, J = 6 Hz), 4.83–5.26 (m, 2 H), 5.6–6.06 (m, 1 H). Anal. Calcd for $C_{10}H_{17}BrO$: C, 51.51; H, 7.36. Found: C, 51.72; H, 7.42.

Bromo Ether 2b. The alcohol **1b** (1.68 g, 10 mmol) in 15 mL of dry CCl_4 at 20 °C was treated as above with *N*-bromosuccinimide (1.958 g, 11 mmol) for 16 h to give the bromo ether **2b** (mixture of isomers) (1.86 g, 75%) as a pale yellow oil. IR (neat): 3070, 1640 cm^{-1}. NMR (CCl_4): δ 1.16 (s, 3 H), 1.26–1.60 (m, 2 H), 1.63, 1.67 (2 s, 6 H), 1.73–2.03 (m, 2 H), 2.16–2.23 (d, 2 H, J = 7.5 Hz), 3.82 and 4.21 (2t, 1 H, J = 6 Hz), 4.62–5.1 (m, 2 H), 5.5–6.0 (m, 1 H). MS (m/e): 246, 248 (M^+). Anal. Calcd for $C_{11}H_{19}BrO$: C, 53.44; H, 7.76. Found: C, 53.94; H, 7.84.

Bromo Ether 2c.[11b] Alcohol **1c** (1.30 g, 10 mmol) upon treatment with *N*-bromosuccinimide (1.958 g, 11 mmol) under similar conditions yielded bromo ether **2c**[11b] (1.547 g, 67%) after purification by flash chromatography as a colorless oil. IR (neat): 3300, 2100, 1460–1440, 1380, 1370, 1130–980 cm^{-1}. NMR (CCl_4): δ 1.47 (s, 3 H), 1.7 (s, 3 H), 1.76 (s, 3 H), 1.8–2.16 (m, 4 H), 2.23 (s, 1 H), 4.01–4.20 (m, 1 H). MS (m/e): 215, 217 ($M^+ - 15$). Anal. Calcd for $C_{10}H_{15}BrO$: C, 51.96; H, 6.55. Found: C, 52.23; H, 6.63.

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Bromo Ether 2d. Bromo ether **2d** (mixture of isomers) (1.80 g, 76%) was obtained as a colorless oil on treatment of alcohol **1d** (1.56 g, 10 mmol) with *N*-bromosuccinimide (1.95 g, 11 mmol) for 18 h at 20 °C. IR (neat): 2980, 2960, 2940, 1465, 1455, 1370, 1130–1020 cm^{-1}. NMR (CCl_4): δ 0.87 (t, 3 H), 1.06, 1.11 (2 s, 3 H), 1.20–1.56 (m, 2 H), 1.63 (s, 3 H), 1.67 (s, 3 H), 1.73–2.31 (m, 4 H), 3.70–3.80 (2 t, 1 H). MS (*m/e*): 234, 236 (M^+). Anal. Calcd for $C_{10}H_{19}BrO$: C, 51.06; H, 8.16. Found: C, 51.23; H, 8.21.

Bromo Ether 2e. Alcohol **1e** (1.09 g, 5 mmol) under conditions described earlier was reacted with *N*-bromosuccinimide (0.89 g, 5 mmol) in CCl_4 and yielded **2e** (1.19 g, 80%) as a colorless oil. IR (neat): 3080, 3050, 3020, 1600, 1490, 1440, 1360, 1120–1020, 760, 700 cm^{-1}. NMR ($CDCl_3$): δ 1.26 (s, 3 H), 1.36–1.47 (m, 2 H), 1.73 (s, 6 H), 1.84–2.0 (m, 2 H), 2.96 (s, 2 H), 3.7–3.9 (m, 1 H), 7.3 (s, 5 H). MS (*m/e*): 297, 299 ($M^+ + 1$). Anal. Calcd for $C_{15}H_{21}BrO$: C, 60.60; H, 7.13. Found: C, 60.93; H, 7.20.

Bromo Ether 2f. Alcohol **1f** (1.02 g, 5 mmol) was treated with NBS (0.89 g, 5 mmol) in CCl_4 under similar conditions as described earlier and gave **2f** (mixture of isomers) (1.07 g, 76%) after chromatographic purification. IR (neat): 3070, 3060, 1600, 1495, 1445, 1380, 1320, 1130–1030, 760, 700 cm^{-1}. NMR (CCl_4): δ 1.28–1.4 (m, 2 H), 1.50 (br s, 3 H), 1.71 (s, 3 H), 1.80 (s, 3 H), 2.12–2.28 (m, 2 H), 3.86–4.20 (m, 1 H), 7.1–7.6 (m, 5 H). MS (*m/e*): 267, 269 ($M^+ - 15$). Anal. Calcd for $C_{14}H_{19}BrO$: C, 59.36; H, 6.77. Found: C, 59.72; H, 6.82.

Bromo Ether 2g. Alcohol **1g** (2.12 g, 10 mmol) and NBS (1.968 g, 11 mmol) in CCl_4 was stirred at 20 °C and gave the bromo ether (mixture of isomers) **2g** (2.33 g, 80%) as an oil after chromatographic purification. IR (neat): 2980, 2940, 2870, 1455, 1370, 1020, 860 cm^{-1}. NMR ($CDCl_3$): δ 0.89 (t, 3 H), 1.17 (s, 3 H), 1.29 (br s, 10 H). 1.64–1.70 (br s, 6 H), 1.82–2.13 (m, 4 H), 3.8–4.1 (m, 1 H). MS (*m/e*): 290, 292 (M^+). Anal. Calcd for $C_{14}H_{27}BrO$: C, 57.72; H, 9.36. Found: C, 58.04; H, 9.45.

Bromo Ether 2h.[19] Alcohol **1h** (1.54 g, 10 mmol) and NBS (1.96 g, 11 mmol) in CCl_4 under conditions described previously yielded the bromo ether **2h**[19] (1.84 g, 79%) as an oil after chromatographic purification. IR (neat): 2920, 2860, 1440, 1150, 890 cm^{-1}. NMR ($CDCl_3$): δ 1.56 (br s, 10 H), 1.74–1.80 (m, 4 H), 3.20–3.32 (dd, 1 H). 3.42–3.46 (dd, 1 H), 4.2 (m, 1 H). MS (*m/e*): 232, 234 (M^+). Anal. Calcd for $C_{10}H_{17}BrO$: C, 51.51; H, 7.36. Found: C, 51.72; H, 7.42.

Bromo Ether 2i.[19] Alcohol **1i** (1.4 g, 10 mmol) and NBS (1.96 g, 11 mmol) in CCl_4 as earlier described afforded bromo ether **2i**[19] (1.62 g, 74%) as an oil. IR (neat): 2980, 2860, 1445, 1130, 1020, 895 cm^{-1}. NMR ($CDCl_3$): δ 1.6 (br s, 8 H), 1.72–1.81 (m, 4 H), 3.19–3.32 (dd, 1 H), 3.43–3.47 (dd, 1 H), 4.22 (m, 1 H). MS (*m/e*): 218, 220 (M^+). Anal. Calcd for $C_9H_{15}BrO$: C, 49.32; H, 6.91. Found: C, 49.63; H, 6.98.

Bromo Ether (2j).[11c,19] A solution of the alcohol **1j** (1.4 g, 10 mmol) and NBS (1.96 g, 11 mmol) in CCl_4 as earlier gave bromo ether **2j**[11c,19] (1.49 g, 68%). IR (neat): 2920, 2880, 1440, 1350, 1140, 990, 650 cm^{-1}. NMR ($CDCl_3$): δ 1.26 (br s, 8 H), 1.76–2.23 (m, 3 H), 3.29–3.53 (dd, 2 H), 4.2–4.41 (m, 2 H). MS (*m/e*): 218, 220 (M^+). Anal. Calcd for $C_9H_{15}BrO$: C, 49.32; H, 6.91. Found: C, 49.58; H, 6.97.

Bromo Ether (2k). Alcohol **1k** (0.5 g, 2 mmol) and NBS (0.392 g, 2.2 mmol) in CCl_4 under the same conditions as described earlier gave the bromo ether **2k** (0.45 g, 68%) as an oil after chromatographic purification. IR (neat): 2920, 2840, 2210, 1450, 1370, 1170, 1030 cm^{-1}. NMR ($CDCl_3$): δ 0.88 (t, 3 H), 1.26 (br s, 12 H), 1.40 (s, 3 H), 1.41 (s, 3 H), 1.45–1.81 (m, 4 H), 2.17–2.2 (m, 2 H), 3.92–4.18 (m, 1 H), 4.32–4.48 (m, 1 H). MS (*m/e*): 327, 329 ($M^+ - 1$). Anal. Calcd for $C_{17}H_{29}BrO$: C, 61.99; H, 8.89. Found: C, 62.23; H, 8.97.

General Procedure for the Preparation of Enol Ethers 3.[12] **Enol Ether 3a.**[12] Potassium metal (0.117 g, 3 mg-atom) in *tert*-butyl alcohol (5 mL) was refluxed until all the potassium metal dissolved (1.5 h). After the solution was cooled to 60 °C, bromo ether **2a** (0.699 g, 3 mmol) in THF (2 mL) was quickly added. A cream-colored precipitate (KBr) started forming immediately. The reaction mixture was stirred at 50–60 °C for 1 h. Then *tert*-butyl alcohol was removed under reduced pressure, petroleum ether (40–60 °C) (20 mL) was added, and it was filtered through a pad of Celite. Evaporation of solvent under reduced pressure yielded the enol ether **3a**[12] (0.437 g, 96%). The enol ether was used as such in the next step without purification. IR (neat): 3080, 1705, 1640, 1450, 1370, 1140, 1020, 920 cm^{-1}. NMR (CCl_4): δ 1.23 (s, 3 H), 1.44 (s, 3 H), 1.53 (s, 3 H), 1.6–1.9 (m, 2 H), 2.23–2.47 (m, 2 H), 4.83–5.18 (m, 2 H), 5.6–5.9 (m, 1 H).

Enol Ether 3b. IR (neat): 3070, 1708, 1635, 1455, 1375, 1150, 1000, 920 cm^{-1}. NMR (CCl_4): δ 1.20 (s, 3 H), 1.43 (s, 3 H), 1.6 (s, 3 H), 1.62–1.94 (m, 2 H), 2.1–2.43 (m, 4 H), 4.71–5.06 (m, 2 H), 5.32–5.98 (m, 1 H).

Enol Ether 3c. IR (neat): 3300, 2100, 1705, 1460, 1440, 1370, 1130, 1060, 980 cm^{-1}. NMR (CCl_4): δ 1.52 (s, 3 H), 1.58 (s, 3 H), 2.1–2.3 (m, 2 H), 2.23 (s, 1 H).

Enol Ether 3d. IR (neat) 1705, 1455, 1370, 1130, 1015 cm^{-1}. NMR (CCl_4): δ 1.6, 1.63 (2 s, 6 H), 2.16–2.23 (m, 2 H).

Enol Ether 3e. IR (neat): 3080, 3060, 3020, 1705, 1600, 1495, 1455, 1375, 1130, 1020, 750, 700 cm^{-1}. NMR (CCl_4): δ 1.68 (s, 6 H), 2.1–2.32 (m, 4 H), 2.92 (s, 2 H).

Enol Ether 3f. IR (neat): 3080, 3060, 3020, 1710, 1600, 1490, 1445, 1370, 1130, 970, 900, 765, 700 cm^{-1}. NMR (CCl_4): δ 1.46, 1.53 (2 s, 6 H), 2.0–2.23 (m, 2 H).

Enol Ether 3g. IR (neat): 2960, 2940, 2870, 1705, 1450, 1370, 1140, 860 cm^{-1}. NMR (CCl_4): δ 1.58, 1.62 (2 s, 6 H), 2.1–2.22 (m, 2 H).

Enol Ether 3h. IR (neat): 3090, 2960, 2860, 1685, 1450, 1160, 1070, 960 cm^{-1}. NMR ($CDCl_3$): δ 2.56–2.72 (t, 2 H), 3.75 (s, 1 H), 4.19 (s, 1 H).

Enol Ether 3i. IR (neat): 3080, 2960, 2860, 1680, 1450, 1160, 1070, 950 cm^{-1}. NMR ($CDCl_3$): δ 2.52–2.73 (t, 2 H), 3.81 (s, 1 H), 4.21 (s, 1 H).

Enol Ether 3j. IR (neat): 3080, 2960, 2860, 1680, 1450, 1160, 1060, 960 cm^{-1}. NMR ($CDCl_3$): δ 2.1–2.32 (m, 2 H), 4.13–4.38 (m, 1 H), 3.91 (s, 1 H), 4.16 (s, 1 H).

Enol Ether 3k. IR (neat): 2920, 2830, 2210, 1705, 1450, 1370, 1140, 1060 cm^{-1}. NMR ($CDCl_3$): δ 1.38 (s, 3 H), 1.40 (s, 3 H), 2.17–2.32 (m, 4 H), 4.32–4.48 (m, 1 H).

General Procedure for the Oxidative Cleavage of Enol Ethers to Lactones with PCC. Oxidation of 3a with PCC. To a stirred mixture of pyridinium chlorochromate (PCC) (1.72 g, 8 mmol) and Celite (1.7 g) in dry dichloromethane (10 mL) was added a solution of crude enol ether **3a** (0.304 g, 2 mmol) in dry dichloromethane (2 mL) at room temperature (28 °C). The reaction mixture was stirred for 2 h and then was diluted with ether (50 mL). After the mixture was filtered through a pad of Celite and silica gel, the filtrate was evaporated and the residue was purified by flash chromatography on silica gel (elution with 1:4 ether–petroleum ether) to afford lactone **4a**[20a,b] (0.227 g, 90%) as a colorless oil. IR (neat): 3090, 1780, 1650 cm^{-1}. NMR ($CDCl_3$): δ 1.43 (s, 3 H), 1.89–2.20 (m, 2 H), 2.31–2.56 (m, 2 H), 5.03–5.33 (m, 2 H), 5.73–6.04 (m, 1 H). MS (*m/e*): 126 (M^+).

Lactone 4b.[21a,b] A mixture of enol ether **3b** (0.332 g, 2 mmol), PCC (1.72 g, 8 mmol), and Celite (1.7 g) in CH_2Cl_2 (10 mL) was treated as earlier for 2 h to give lactone **4b**[21a,b] (0.249 g, 89%). IR (neat): 3060, 1770, 1640 cm^{-1}. NMR ($CDCl_3$): δ 1.42 (s, 3 H), 1.8–2.8 (m, 6 H), 4.9–5.31 (m, 2 H), 5.52–6.2 (m, 1 H). MS (*m/e*): 140 (M^+).

Lactone 4c. Enol ether **3c** (0.3 g, 2 mmol) was treated with PCC (1.72 g, 8 mmol) and Celite (1.7 g) in CH_2Cl_2 (10 mL) for 2.5 h to yield lactone **4c** (0.174 g, 70%). IR (neat): 3300, 2100, 1780 cm^{-1}. NMR ($CDCl_3$): δ 1.72 (s, 3 H), 2.12–2.25 (m, 1 H), 2.48–2.68 (m, 3 H), 2.6 (s, 1 H). MS (*m/e*): 124 (M^+). Anal. Calcd for $C_7H_8O_2$: C, 67.72; H, 6.51. Found: C, 67.91; H, 6.62.

Lactone 4d.[16b,20a,21b,22] Enol ether **3d** (0.308 g, 2 mmol) was treated with PCC (1.72 g, 8 mmol) and Celite (1.7 g) in CH_2Cl_2 (10 mL) for 2 h as above to yield lactone **4d**[16b,20a,21b,22] (0.218 g, 85%). IR (neat): 1770 cm^{-1}. NMR ($CDCl_3$): δ 0.96–1.1 (t, 3 H), 1.38 (s, 3 H), 1.53–1.67 (m, 2 H), 1.76–1.97 (m, 2 H), 2.29–2.4 (m, 2 H). MS (*m/e*): 128 (M^+).

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Lactone 4e.[22] A mixture of enol ether **3e** (0.432 g, 2 mmol), PCC (1.72 g, 8 mmol), and Celite (1.7 g) in CH_2Cl_2 (10 mL) was treated as earlier for 2.5 h to afford the lactone **4e**[22] (0.312 g, 82%). IR (neat): 3080, 3060, 3020, 1770, 1600 cm^{-1}. NMR ($CDCl_3$): δ 1.44 (s, 3 H), 1.91-2.15 (m, 2 H), 2.16-2.27 (m, 1 H), 2.35-2.50 (m, 1 H), 2.94 (d, 2 H, J = 3.75 Hz), 7.21-7.35 (m, 5 H). MS (m/e): 190 (M^+).

Lactone 4f.[17,23a-d] Enol ether **3f** (0.404 g, 2 mmol) was treated with PCC (1.7 g, 8 mmol) and Celite (1.7 g) in CH_2Cl_2 (10 mL) for 1.5 h as described earlier to give lactone **4f**[17,23a-d] (0.264 g, 75%). IR (neat): 3080, 3060, 1775, 1600 cm^{-1}. NMR ($CDCl_3$): δ 1.72 (s, 3 H), 2.35-2.69 (m, 4 H), 7.3 (s, 5 H). MS (m/e): 176 (M^+).

Lactone 4g.[16b,24c] Enol ether **3g** (0.420 g, 2 mmol) was treated with PCC (1.72 g, 8 mmol) and Celite (1.7 g) in CH_2Cl_2 (10 mL) as described earlier to give the lactone **4g**[16b,24c] (0.290 g, 79%). IR (neat): 1780 cm^{-1}. NMR ($CDCl_3$): δ 0.90 (t, 3 H), 1.35 (s, 3 H), 1.2-1.6 (br s, 10 H), 1.71-2.13 (m, 2 H), 2.47-2.60 (m, 2 H). MS (m/e): 184 (M^+).

Lactone 4h.[23d,24a-d] A mixture of enol ether **3h** (0.304 g, 2 mmol), PCC (1.72 g, 8 mmol), and Celite (1.7 g) in CH_2Cl_2 (10 mL) was stirred for 1.5 h to give the lactone **4h**[23d,24a-d] (0.203 g, 66%) after flash chromatography. IR (neat): 1780 cm^{-1}. NMR ($CDCl_3$): δ 1.2-1.9 (m, 10 H), 2.04 (t, 2 H, J = 8 Hz), 2.62 (t, 2 H, J = 8 Hz). MS (m/e): 154 (M^+).

Lactone 4i.[23d,24b] Enol ether **3i** (0.276 g, 2 mmol) was treated with PCC (1.72 g, 8 mmol) and Celite (1.7 g) in CH_2Cl_2 (10 mL) for 1 h as described earlier to afford lactone **4i**[23d,24b] (0.157 g, 56%). IR (neat): 1770 cm^{-1}. NMR ($CDCl_3$): δ 1.5-2.0 (m, 8 H), 2.12-2.53 (t, 2 H), 2.51-2.75 (t, 2 H). MS (m/e): 140 (M^+).

Lactone 4j.[23c,26] Enol ether **3j** (0.276 g, 2 mmol), PCC (1.72 g, 8 mmol), and Celite (1.7 g) in CH_2Cl_2 (10 mL) were allowed to react for 1.5 h as described earlier to give the lactone **4j**[23c,26] (0.143 g, 51%). IR (neat): 1780 cm^{-1}. NMR ($CDCl_3$): δ 1.1-2.12 (m, 8 H), 2.13-2.7 (m, 3 H), 3.82-4.06 (m, 1 H). MS (m/e): 140 (M^+).

Lactone 4k.[9] Enol ether **3k** (0.248 g, 1 mmol) was treated with PCC (0.86 g, 4 mmol) and Celite (0.86 g) in CH_2Cl_2 (7 mL) for 1.5 h as described earlier to afford the lactone **4k**[9] (0.115 g, 52%) after chromatographic purification. IR (neat): 2200, 1780 cm^{-1}. NMR ($CDCl_3$): δ 0.87 (t, 3 H), 1.26 (m, 12 H), 2.21-2.63 (m, 6 H), 5.06-5.35 (m, 1 H). MS (m/e): 222 (M^+).

(±)-(Z)-5-Tetradecen-4-olide 9.[9c] Palladium on barium sulfate (50 mg, 5%) and quinoline (1 drop) were added to a solution of (±)-**4k** (0.111 g, 0.5 mmol) in 25 mL of ether. The mixture was stirred under a hydrogen atmosphere at room temperature for 12 h. The concentrated filtrate was subjected to column chromatography on silica gel to afford (±)-**9**[9c] (0.106 g, 95%) as a colorless oil. IR (neat): 3020, 2940, 2860, 1785, 1660, 1460, 1220, 1180, 1015, 980, 720 cm^{-1}. NMR ($CDCl_3$): δ 0.89 (t, 3 H), 1.0-1.48 (br s, 12 H), 1.5-2.5 (m, 6 H), 5.08 (m, 1 H), 5.20-5.66 (m, 2 H). MS (m/e): 224 (M^+).

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Registry No. **1b**, 124099-62-3; **1d**, 2270-57-7; **1e**, 124099-61-2; **1f**, 124099-68-9; **1g**, 121402-96-8; **1h**, 1773-40-6; **1i**, 53544-43-7; **1j**, 111268-65-6; **1k**, 72130-70-2; **2a** (stereoisomer 1), 124152-05-2; **2a** (stereoisomer 2), 124152-06-3; **2b** (stereoisomer 1), 124099-63-4; **2b** (stereoisomer 2), 124099-64-5; **2c** (stereoisomer 1), 124099-89-4; **2c** (stereoisomer 2), 124099-93-0; **2d** (stereoisomer 1), 124099-65-6; **2d** (stereoisomer 2), 124099-66-7; **2e** (stereoisomer 1), 124099-67-8; **2e** (stereoisomer 2), 124099-87-2; **2f** (stereoisomer 1), 124099-69-0; **2f** (stereoisomer 2), 124099-70-3; **2g** (stereoisomer 1), 124099-71-4; **2g** (stereoisomer 2), 124099-72-5; **2h**, 124099-90-7; **2i**, 124099-91-8; **2j** (stereoisomer 1), 124099-92-9; **2j** (stereoisomer 2), 124099-94-1; **2k** (stereoisomer 1), 124099-73-6; **2k** (stereoisomer 2), 124099-88-3; **3a**, 124099-83-8; **3b**, 124099-74-7; **3c**, 124099-75-8; **3d**, 124099-76-9; **3e**, 124099-77-0; **3f**, 124099-78-1; **3g**, 124099-79-2; **3h**, 124099-80-5; **3i**, 124099-81-6; **3j**, 124099-82-7; **3k**, 124125-59-3; **4a**, 40478-72-6; **4b**, 124099-84-9; **4c**, 124099-85-0; **4d**, 1193-36-8; **4e**, 61520-92-1; **4f**, 69854-29-1; **4g**, 124099-86-1; **4h**, 699-61-6; **4i**, 33448-80-5; **4j**, 61248-46-2; **4k**, 72130-77-9; (±)-**9**, 72151-71-4; **10**, 110-93-0.

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Azapsoralens. Synthesis of 8-Azapsoralens

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The synthesis of some *N*-methyl-8-azapsoralen salts **1** is described for use as water-soluble analogues of psoralens. A key intermediate is the furopyridine carboxaldehyde **16** prepared in four steps from simple acyclic precursors. The pyrone ring is fused on by first extending the carbon chain via a Reformatsky or Doebner condensation followed by deprotection and ring closure. Since stability of this ring system in water is crucial to its potential use as a nucleic acid cross-linking reagent, rates of pyrone hydrolysis for the *N*-methylazapsoralens were measured. Sufficient stability in the necessary pH range was found for several analogues.

Linear furocoumarins, commonly named psoralens, have proved useful as drugs for the treatment of skin diseases and also as reagents for the biophysical study of nucleic acids.[1] They have been shown to intercalate nucleic acids and undergo photochemically induced [2 + 2] cycloadditions to adjacent pyrimidine bases.[2] Work toward increasing the yields of photoadducts has led to a number of analogues having hydrophilic side chains that confer

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