α-Methoxylation of Unsaturated Carbonyl Compounds

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α-Methoxylation of enals or enones can be performed in high yield by a simple one-pot reaction sequence: Bromination of unsaturated hydrazones, HBr-elimination, and addition of methanol leads to the formation of β-bromo-α-methoxy hydrazones (**11**), which after hydrolysis and HBr-elimination yields the α-methoxy enals or α-methoxy enones (**13**), respectively.

Substitution reactions at the olefinic bond are greatly influenced by neighboring activating groups. Bromination of α,β-unsaturated carbonyl compounds and subsequent base-induced HBr elimination leads to the formation of α-substitution products of type **3**.

On the other hand, when unsaturated hydrazones are treated in the same way β-substitution products **7** are obtained.[1] The easy elimination of the α-bromine from the addition products **5** can be explained by the electron-donating properties of the final nitrogen atom when dialkylhydrazones are considered.

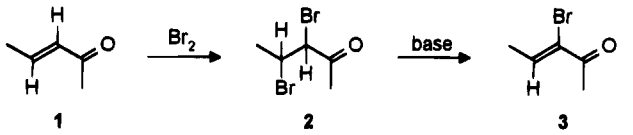
A slightly different reaction sequence with ene-azo compounds as unstable intermediates must be assumed when semicarbazones or (ethoxycarbonyl)hydrazones are employed.[2]

β-Bromo enones or -enals which can be obtained in high yield by the reaction sequence described above are versatile reagents in organic synthesis. Some other electrophiles like PhS^+ or NO_2^+ have been introduced into unsaturated carbonyl compounds by an analogous reaction sequence.[1]

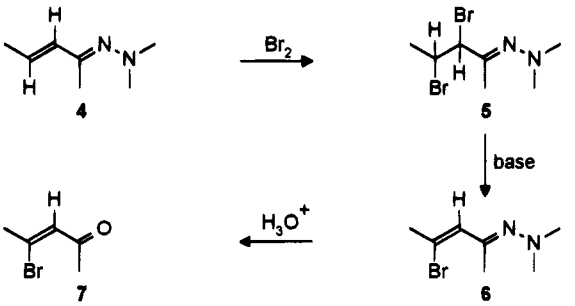
In a few cases it has been shown that dibromo hydrazones of type **5** react with methanol to give β-bromo α-methoxy derivatives, which after hydrolysis and HBr-elimination afford α-methoxy-substituted enones.[1] But the hydrazones investigated so far revealed some drawbacks. Dimethylhydrazones gave only moderate yields and methylbenzothiazolinone hydrazones require more drastic conditions for the hydrolytic cleavage. We report here that α-methoxylation of unsaturated carbonyl compounds can be performed in high yield when ethoxycarbonylhydrazones **8** are employed. This is a special case of introduction of a nucleophile into the α-position of α,β-unsaturated carbonyl compounds. The synthesis may be compared with the previously described addition of nucleophiles, especially metal organic compounds to α,β-epoxy hydrazones.[3]

Generally (ethoxycarbonyl)hydrazones **8** of enals or enones are easily obtained as crystalline compounds. In methylene chloride addition of bromine to the double bond is quantitative. Subsequent interaction with $NaHCO_3$ leads to the formation of the colored ene-azo compounds **10**, which add methanol in the presence of acid to give the bromo methoxy derivative **11**. Hydrolysis and elimination of HBr by a base leads finally to α-methoxy enals or α-methoxy enones **13**, respectively (see Table 1). Isolation of the intermediates is not necessary.

Scheme 1



Scheme 2



Combination of β-bromination and α-alkoxylation affords compounds which are suitable for the synthesis of aminoreductones. For instance **16** reacts with morpholine to give the substitution product **17a**. Aminoreductones are of great interest in carbohydrate chemistry. When glucose is heated with amines, aminoreductone products of different structures are formed. Compounds of type **17b** have been isolated from glucose/amine reaction mixtures.[4] Synthesis of other carbohydrate-derived aminoreductones is under investigation.

In some cases methylbenzothiazolinone hydrazones of enones (**18**) (not enals) are suitable for the α-methoxylation reaction. Bromination of the unsaturated hydrazones in methylene chloride and subsequent treating with methanol and $NaHCO_3$ affords the bromo methoxy derivatives **19** in high yield. Hydrolytic cleavage is performed by heating with aqueous hydrochloric acid. Some examples are shown in Table 1. The synthesis of **13k** and **13m** deserves special comment. In contrast to the other compounds the base-induced HBr elimination is successful only when $AgNO_3$ is added.

Preliminary experiments have shown that bromination products of ene hydrazones react with other nucleophiles as well. More detailed investigations in this area are under way.

Experimental Section

General. ^{1}H-NMR spectra were run in $CDCl_3$ on a 400 MHz instrument using TMS (δ_H 0.0) as internal standard. MS spectra were obtained with an electron beam operating at 70

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(1) (a) Severin, T.; Wanninger, G.; Lerche, H. *Chem. Ber.* **1984**, *117*, 2875. (b) Fischer, H.; Klippe, M.; Lerche, H.; Severin, T.; Wanninger, G. *Chem. Ber.* **1990**, *123*, 399.

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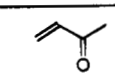
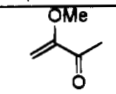
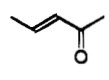
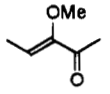
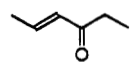
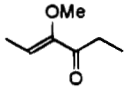
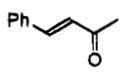
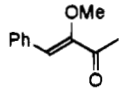
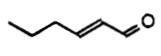
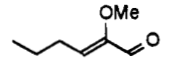
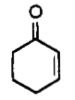
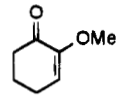
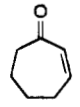
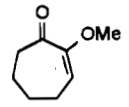
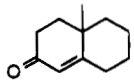
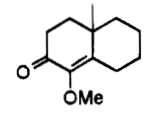
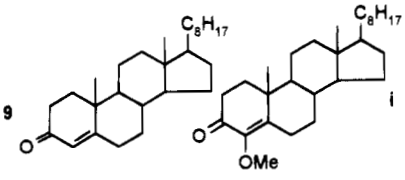
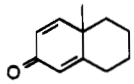
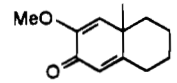
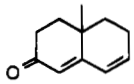
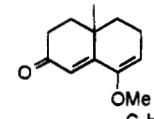
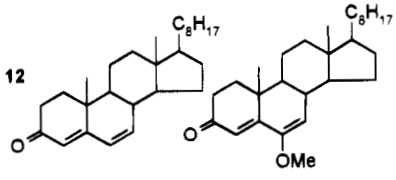
(3) (a) Stork, G.; Ponaras, A. *J. Org. Chem.* **1976**, *41*, 2937. (b) Corey, E. J.; Melvin, L.S.; Haslanger, M. F. *Tetrahedron Lett.* **1975**, 3117.

(4) (a) Mills, F. D.; Hodge, J. E. *Carbohydr. Res.* **1976**, *51*, 9. (b) Ledl, F.; Severin, T. *Z. Lebensm. Unters. Forsch.* **1979**, *169*, 173.

0022-3263/94/1959-6026$04.50/0

Table 1. Methoxylation of Unsaturated Carbonyl Compounds

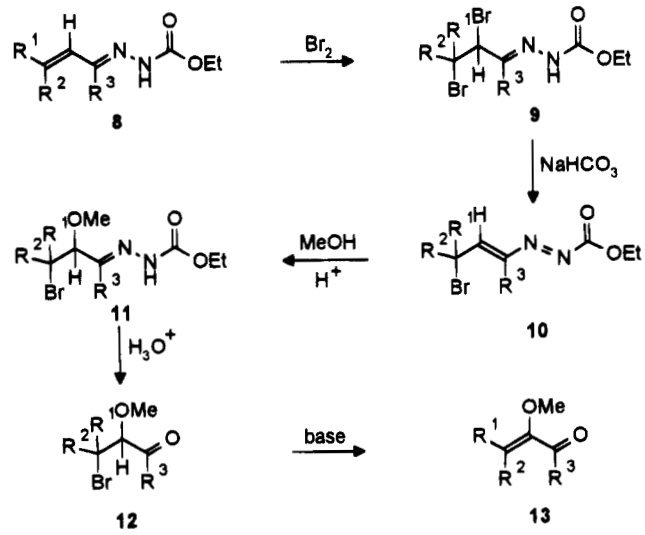
entry	substrate	product	13	method/yield(%)
1			a	A / 77
2			b	B / 68
3			c	A / 92
4			d	A, B / 84, 68
5			e	A / 85
6			f	A, B / 90, 68
7			g	A / 91
8			h	B / 62
9			i	B / 68
10			j	B / 69
11			k	A, B / 87, 82
12			m	B / 77

eV. Immediately prior to use tetrahydrofuran (THF) was distilled from $LiAlH_4$; methylene chloride (CH_2Cl_2) was distilled from calcium hydride.

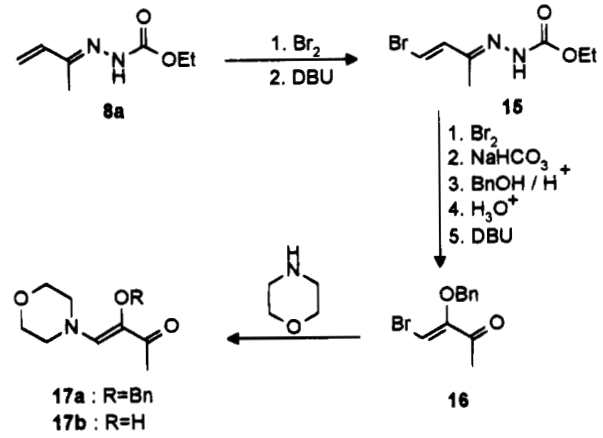
General Procedure for the Synthesis of (Ethoxycarbonyl)hydrazones 8. The appropriate carbonyl compound (20.0 mmol) was added to a solution of ethoxycarbonylhydrazine (20.0 mmol) and glacial acetic acid (10 drops) in EtOH (20 mL). The mixture was stirred at rt for 24 h. The volatile materials were removed in vacuo and the crude product recrystallized from a suitable solvent.

3-Buten-2-one (ethoxycarbonyl)hydrazone (8a): colorless crystals (from diethyl ether), mp 75–77 °C, yield 2.49 g (80%); ^{1}H-NMR 1.33 (t; 3H, J = 7 Hz), 1.92 (s; 3H), 4.29 (q; 2H, J = 7 Hz) 5.45 (d; 1H, J = 11 Hz), 5.54 (d; 1H, J = 18 Hz), 6.60 (dd; 1H, J = 18, 11 Hz), 7.72 (s, broad; 1H); MS *m/e* 156 (M^+). Anal. Calcd for $C_7H_{12}N_2O_2$: C, 53.83; H, 7.74; N, 17.93. Found: C, 53.73; H, 8.12; N, 17.73.

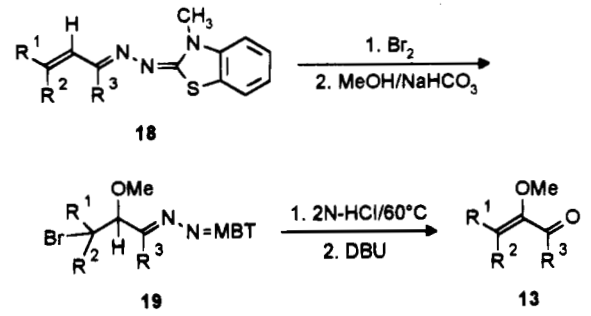
Scheme 3



Scheme 4



Scheme 5



4-Hexen-3-one (ethoxycarbonyl)hydrazone (8c): colorless crystals (from diethyl ether), mp 87–88 °C, yield 3.53 g (97%); ^{1}H-NMR 1.09 (t; 3H, J = 7 Hz), 1.33 (t; 3H, J = 7 Hz), 1.85 (dd; 3H, J = 6, 1 Hz), 3.35 (q; 2H, J = 7 Hz), 4.29 (q; 2H, J = 7 Hz), 6.03–6.12 (m; 1H), 6.23 (d; 1H, J = 16 Hz), 7.95 (s, broad; 1H); MS *m/e* 184 (M^+). Anal. Calcd for $C_9H_{16}N_2O_2$: C, 58.67; H, 8.75; N, 15.20. Found: C, 58.67; H, 9.06; N, 15.31.

Benzylideneacetone (ethoxycarbonyl)hydrazone (8d): colorless crystals (from 96% ethanol), mp 153–154 °C, yield 4.59 g (99%); ^{1}H-NMR 1.35 (t; 3H, J = 7 Hz), 2.04 (s; 3H), 4.32 (q; 2H, J = 7 Hz), 6.85 (d; 1H, J = 16 Hz), 7.06 (d; 1H, J = 16 Hz), 7.25–7.47 (m; 5H), 7.90 (s, broad; 1H); MS *m/e* 232 (M^+). Anal. Calcd for $C_{13}H_{16}N_2O_2$: C, 67.18; H, 6.94; N, 12.16. Found: C, 66.99; H, 6.94; N, 12.07.

2-Hexenal (ethoxycarbonyl)hydrazone (8e): colorless crystals (from diethyl ether), mp 85–86 °C, yield 3.42 g (93%); ^{1}H-NMR 0.91 (t; 3H, J = 7 Hz), 1.31 (t; 3H, J = 7 Hz), 1.49 (sext; 2H, J = 7 Hz), 2.16 (dq; 2H, J = 7, 1 Hz), 4.27 (q; 2H, J = 7 Hz), 6.04, 6.30 (m; 2H), 7.42 (d; 1H, J = 8 Hz), 7.71 (s,

broad; 1H); MS *m/e* 184 (M^+). Anal. Calcd for $C_9H_{16}N_2O_2$: C, 58.67; H, 8.75; N, 15.20. Found: C, 58.68; H, 8.77; N, 15.03.

2-Cyclohexen-1-one (ethoxycarbonyl)hydrazone (8f): colorless crystals (from petroleum ether/ethyl acetate 7:4), mp 82–84 °C, yield 3.56 g (98%); ^{1}H-NMR 1.32 (d; 3H, J = 7 Hz), 1.84 (quint; 2H, J = 7 Hz), 2.18–2.22 (m; 2H), 2.35 (t; 2H, J = 7 Hz), 4.29 (q; 2H, J = 7 Hz), 6.24–6.32 (m; 2H), 7.82 (s, broad; 1H); MS *m/e* 182 (M^+). Anal. Calcd for $C_9H_{14}N_2O_2$: C, 59.32; H, 7.74; N, 15.37. Found: C, 59.04; H, 7.82; N, 15.45.

2-Cyclohepten-1-one (ethoxycarbonyl)hydrazone (8g): colorless oil, yield 3.72 g (95%); ^{1}H-NMR 1.24–1.28 (m; 3H), 1.66–1.82 (m; 4H), 2.29–2.36 (m; 2H), 2.47–2.68 (m; 2H), 4.09–4.29 (m; 2H), 5.93–6.34 (m; 2H), 7.95 (s, broad; 1H); MS *m/e* 196 (M^+). Anal. Calcd for $C_{10}H_{16}N_2O_2$: C, 61.20; H, 8.21; N, 14.27. Found: C, 61.13; H, 8.34; N, 14.21.

2,3,4,4a,5,6-Hexahydro-4a-methylnaphthalen-2-one (ethoxycarbonyl)hydrazone (8k): yellow crystals (from ethyl acetate/ethanol 2:1), mp 130–131 °C , yield 4.56 g (92%); ^{1}H-NMR 1.02 (s; 3H), 1.33 (t; 3H, J = 7 Hz), 1.42–1.73 (m; 4H), 2.17–2.53 (m; 4H), 4.30 (q; 2H, J = 7 Hz), 5.94 (ddd; 1H, J = 10, 6, 3 Hz), 6.03 (s; 1H), 6.13 (dd; 1H, J = 10, 2 Hz); MS *m/e* 248 (M^+). Anal. Calcd for $C_{14}H_{20}N_2O_2$: C, 67.72; H, 8.12; N, 11.33. Found: C, 67.70; H, 8.14; N, 11.33.

4,6-Cholestadien-3-one (ethoxycarbonyl)hydrazone (8m): colorless crystals (from methanol), mp 82–84 °C, yield 9.08 g (97%); ^{1}H-NMR 0.73 (s; 3H), 0.85–1.58 (m; 29H), 1.33 (t; 3H, J = 7 Hz), 1.74–1.80 (m; 1H), 1.84–1.96 (m; 2H), 2.02–2.14 (m; 2H), 2.21–2.30 (m; 1H), 2.50 (dd; 1H, J = 4 Hz), 4.30 (q; 2H, J = 7 Hz), 5.83 (dd; 1H, J = 9.5, 2.9 Hz), 6.06 (s; 1H), 6.13 (dd; 1H, J = 9.5, 2.2 Hz), 7.67 (s, broad; 1H); MS *m/e* 468 (M^+). Anal. Calcd for $C_{30}H_{48}N_2O_2$: C, 76.87; H, 10.32; N, 5.98. Found: C, 76.62; H, 10.61; N, 5.93.

General Procedure for the Synthesis of Methylbenzothiazolinone Hydrazone (18). This hydrazones were prepared according to a literature method.[1]

2-(3-Penten-2-ylidenehydrazono)-3-methylbenzothiazoline (18b): colorless crystals (from ethanol/ethyl acetate 2:1), mp 127–128 °C, yield 4.5 g (92%); ^{1}H-NMR 1.88 (dd; 3H, J = 7, 2 Hz), 2.19 (s; 3H), 3.55 (s; 3H), 6.18 (dq; 1H, J = 11, 7 Hz) 6.36 (dq; 1H, J = 11, 2 Hz), 6.95, 7.00, 7.21, 7.37 (d,t,t,d; 4H, J = 8 Hz); MS *m/e* 245 (M^+). Anal. Calcd for $C_{13}H_{15}N_3S$: C, 63.64; H, 6.16; N, 17.12. Found: C, 63.71; H, 6.01; N, 17.13.

2-(4-Phenyl-3-buten-2-ylidenehydrazono)-3-methylbenzothiazoline (18d): yellow crystals (from ethanol), mp 136–139 °C, yield 6.1 g (100%); *syn/anti*-isomers (2/1), ^{1}H-NMR (*syn*-isomer) 2.34 (s; 3H), 3.60 (s; 3H), 6.92–7.97 (m; 11H); (*anti*-isomer) δ 2.31 (s; 3H), 3.62 (s; 3H), 6.92–7.97 (m; 11H); MS *m/e* 307 (M^+). Anal. Calcd for $C_{18}H_{17}N_3S$: C, 70.33; H, 5.57; N, 13.67. Found: C, 70.33; H, 5.58; N, 13.64.

2-(2-Cyclohexen-1-ylidenehydrazono)-3-methylbenzothiazoline (18f): yellow crystals (from ethanol/ethyl acetate 1:1), mp 108–109 °C, yield 4.67 g (92%); *syn/anti*-isomers, ^{1}H-NMR 1.82, 1.90 (2 quint; 2H, J = 7 Hz), 2.24, 2.28 (2dq; 2H, J = 7, 2 Hz), 2.58, 2.82 (2t; 2H, J = 7 Hz), 3.55, 3.56 (2s; 3H), 6.25–6.36 (m; 2H), 6.94–7.39 (m; 4H, J = 8 Hz); MS *m/e* 257 (M^+). Anal. Calcd for $C_{14}H_{15}N_3S$: C, 65.34; H, 5.88; N, 16.33. Found: C, 65.41; H, 5.85; N, 16.54.

2-(2,3,4,4a,5,6,7,8-Octahydro-4a-methylnaphth-2-ylidenehydrazono)-3-methylbenzothiazoline (18h): yellow crystals (from 2-propanol/ethyl acetate 2:1); mp 110–112 °C , yield 5.85 g (90%), *syn/anti*-isomers; ^{1}H-NMR 1.14, 1.18 (2s; 3H), 1.20–1.42 (m; 2H), 1.59–1.72 (m; 5H), 1.80–1.88 (m; 1H), 2.04–2.41 (m; 3H), 3.25–3.31 (m; 1H), 3.55, 3.56 (2s; 3H), 6.02, 6.80 (2s; 1H), 6.94, 7.00, 7.23, 7.37 (d,t,t,d; 4H); MS *m/e* 325 (M^+). Anal. Calcd for $C_{19}H_{23}N_3S$: C, 70.12; H, 7.12; N, 12.91. Found: C, 70.19; H, 7.38; N, 12.78.

2-(4-Cholesten-3-ylidenehydrazono)-3-methylbenzothiazoline (18i): yellow crystals (from ethyl acetate), mp 195–196 °C , yield 21.1 g (98%), *syn/anti*-isomers; ^{1}H-NMR 0.70 (s; 3H), 0.82–1.68 (m; 32H), 1.75–2.04 (m; 4H), 2.22–2.41 (m; 3H), 2.51–2.59, 3.26–3.37 (2m; 1H), 3.54, 3.56 (2s; 3H), 6.01, 6.77 (2s, 1H), 6.94, 7.00, 7.23, 7.37 (d,t,t,d; 4H, J = 8 Hz); MS *m/e* 545 (M^+). Anal. Calcd for $C_{35}H_{51}N_3S$: C, 77.01; H, 9.42; N, 7.70. Found: C, 76.84; H, 9.65; N, 7.68.

2-(2,4a,5,6,7,8-Hexahydro-4a-methylnaphth-2-ylidenehydrazono)-3-methylbenzothiazoline (18j): yellow crystals (from ethanol), mp 152–154 °C, yield 6.13 g (95%) *syn/anti*-isomers; ^{1}H-NMR 1.22 (s; 3H), 1.34–1.45 (m; 2H), 1.66–1.73 (m; 3H), 1.92–1.95 (m; 1H), 2.31–2.50 (m; 2H) 3.57, 3.59 (2s; 3H), 6.02, 6.04 (2d; 1H, J = 10 Hz), 6.19, 6.34 (2dd; 1H, J = 10, 1 Hz), 7.01 (t; 1H, J = 10, 1 Hz), 6.94–7.39 (m; 4H); MS *m/e* 323 (M^+). Anal. Calcd for $C_{19}H_{21}N_3S$: C, 70.55; H, 6.54; N, 12.99. Found: C, 70,41; H, 6.39; N, 12.83.

2-(2,3,4,4a,5,6-Hexahydro-4a-methylnaphth-2-ylidenehydrazono)-3-methylbenzothiazoline (18k): yellow crystals (from ethanol/ethyl acetate 1:1), mp 109–111 °C , yield 6.00 g (93%), *syn/anti*-isomers; ^{1}H-NMR 1.07, 1.11 (2s, 3H), 1.43–1.70 (m; 4H), 2.19–2.36 (m; 2H), 2.49–2.66 (m; 1H), 2.77–2.86, 3.26–3.39 (2m; 1H), 3.57, 3.58 (2s; 3H), 5.92, 6.01 (2ddd, 1H, J = 10, 6, 3 Hz), 6.08, 6.83 (2s, 1H), 6.15, 6.18 (2dd, 1H, J = 10, 2 Hz), 6.94–7.40 (m; 4H); MS *m/e* 323 (M^+). Anal. Calcd for $C_{19}H_{21}N_3S$: C, 70.55; H, 6.54; N, 12.99. Found: C, 70.57; H, 6.72; N, 12.79.

2-(4,6-Cholestadien-3-ylidenehydrazono)-3-methylbenzothiazoline (18m): yellow crystals (from methanol), mp 201–202 °C , yield 10.3 g (96%); ^{1}H-NMR 0.76 (s; 3H), 0.86 (d; 3H, J = 7 Hz), 0.87 (d; 3H, J = 7 Hz), 0.92 (d; 3H, J = 7 Hz), 1.00 (s; 3H), 0.95–1.55 (m; 17H), 1.74–1.80 (m; 1H), 1.84–1.91 (m; 2H), 2.03 (dd; 1H, J = 9, 3 Hz), 2.13 (t; 1H, J = 10 Hz), 2.41–2.50 (m; 1H), 3.29 (dd, 1H, J = 18, 3 Hz), 3.56 (s; 3H), 5.82 (dd; 1H, J = 10, 1 Hz), 6.07 (s; 1H), 6.10 (dd; 1H, J = 10, 3 Hz), 6.96, 7.01, 7.24, 7.39 (d,t,t,d; 4H); MS *m/e* 543 (M+). Anal. Calcd for $C_{35}H_{49}N_3S$: C, 77.30; H, 9.08; N, 7.73. Found: C, 77.34; H, 9.26; N, 7.62.

General Procedure for the α- or γ-Methoxylation of Unsaturated Carbonyl Compounds. Method A: A stirred solution of ethoxycarbonylhydrazone **8** (1.0 mmol) in CH_2Cl_2 (10 mL) was cooled to −50 °C and Br_2 (0.16 g, 1.0 mmol in 0.5 mL CH_2Cl_2) was added dropwise under N_2. After warming to 0 °C the reaction mixture was treated with 1 N $NaHCO_3$ (10 mL) and was stirred vigorously for 1 h at rt. The red organic layer was separated, washed with brine, dried ($MgSO_4$), and concentrated (~2 mL). After cooling to 0 °C and diluting with CH_3OH (5 mL), the mixture was treated dropwise with 1 mL of methanolic H_2SO_4 (2 drops concd H_2SO_4 in 1 mL CH_3OH). The reaction mixture was stirred at rt until the red color disappeared. To the concentrated solution were added 1 N HCl (10 mL) and CH_2O solution (1 mL, 38%) and the resulting mixture was allowed to stirred at rt for 1 h.

Method B: A stirred solution of the methylbenzothiazolinone hydrazone **18** (1.0 mmol) in CH_2Cl_2 (10 mL) was cooled to −30 °C and Br_2 (0.16 g, 1.0 mmol in 0.5 mL CH_2Cl_2) was added dropwise under N_2. After warming to 0 °C the reaction mixture was diluted with CH_3OH (3 mL) and then treated with solid $NaHCO_3$ (0.2 g, 3.0 mmol). The suspension was stirred vigorously at rt for 3 h. After filtration the solution was concentrated and treated with 2 N HCl (10 mL), CH_2O solution (1 mL, 38%), and THF (5 mL). The reaction mixture was kept at 60 °C for 2 h.

Both procedures continue as follows: The reaction mixture was extracted with ether (3 × 10 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and treated with DBU (0.3 g, 2.0 mmol). The reaction was monitored by TLC. After complete conversion the mixture was washed with 1N HCl and brine and dried ($MgSO_4$). Removal of the solvent affords a crude product.

3-Methoxy-3-buten-2-one (13a):[5] colorless oil, yield 0.07 g (77%), method A; ^{1}H-NMR 2.25 (s; 3H), 3.57 (s; 3H), 4.45 (d; 1H, J = 3 Hz), 5.14 (d; 1H, J = 3 Hz).

3-Methoxy-3-penten-2-one (13b): colorless oil, bp 50 °C/4.5 Torr, yield 0.07 g (66%), method B; ^{1}H-NMR 1.83 (d; 3H, J = 7 Hz), 2.27 (s; 3H), 3.65 (s; 3H), 4.12 (q; 1H, J = 7 Hz); MS: *m/e* 114 (M^+). Anal. Calcd for $C_6H_{10}O_2$: C, 63.14; H, 8.83. Found: C, 63.45; H, 8.51.

4-Methoxy-4-hexen-3-one (13c): colorless oil, bp 70–71 °C/6.8 Torr; yield 0.12 g (82%), method A; *E/Z*-isomers (1/3); ^{1}H-NMR, *E*-isomer: 1.03 (t; 3H, J = 7 Hz), 1.75 (d; 3H, J = 7 Hz), 2.54 (q; 2H, J = 7 Hz), 3.57 (s; 3H), 6.16 (q; 1H, J = 7 Hz); *Z*-isomer: =0.98 (t; 3H, J = 7 Hz), 1.88 (d; 3H, J = 7

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Hz), 2.54 (q; 2H, J = 7 Hz), 3.48 (s; 3H), 4.99 (q; 1H, J = 7 Hz); MS *m/e* 128 (M^+). Anal. Calcd for $C_7H_{12}O_2$: C, 65.60; H, 9.44. Found: C, 65.63; H, 9.32.

3-Methoxy-4-phenyl-3-buten-2-one (13d): yellow oil, bp 110–113 °C/1.5 Torr, yield 0.13 g (84%), method A; 0.1 g (68%), method B; ^{1}H-NMR, *E*/*Z*-isomers (1/1), *E*-isomer: 2.34 (s; 3H), 3.66 (s; 3H), 6.77 (s; 1H), 7.34–7.77 (m; 5H); *Z*-isomer: 2.11 (s; 3H), 3.66 (s; 3H), 5.95 (s; 1H), 7.34–7.77 (m; 5H); MS *m/e* 160 (M^+). Anal. Calcd for $C_{11}H_{12}O_2$: C, 74.97; H, 6.86. Found: C, 74.73; H, 7.10.

2-Methoxy-2-hexenal (13e): colorless oil, bp 60–62 °C/7.6 Torr, yield 0.11 g (85%), method A; ^{1}H-NMR 0.97 (t; 3H, J = 7 Hz), 1.42–1.57 (m; 2H), 2.34 (q; 2H, J = 7 Hz), 3.77 (s; 3H), 5.96 (t; 1H, J = 7 Hz), 9.22 (s; 1H); MS *m/e* 128 (M^+). Anal. Calcd for $C_7H_{12}O_2$: C, 65.60; H, 9.44. Found: C, 65.81; H, 9.22.

2-Methoxy-2-cyclohexen-1-one (13f):[6] colorless oil, yield 0.11 g (90%), method A; 0.09 g (68%), method B.

2-Methoxy-2-cyclohepten-1-one (13g): colorless oil, bp 85–86 °C/1.5 Torr; yield 0.13 g (96%), method A; ^{1}H-NMR 1.63–1.75 (m; 4H), 2.31 (t; 2H, J = 7 Hz), 2.55 (q; 2H, J = 7 Hz), 3.51 (s; 3H), 5.68 (t; 1H, J = 7 Hz); MS *m/e* 140 (M^+). Anal. Calcd for $C_8H_{12}O_2$: C, 68.55; H, 8.63. Found: C, 68.35; H, 8.83.

4,4a,5,6,7,8-Hexahydro-1-methoxy-4a-methyl-2(3*H*)-naphthalinone (13h):[7] colorless oil, bp 50 °C/0.1 Torr, yield 0.12 g (62%), method B; ^{1}H-NMR 1.22 (s; 3H), 1.21–1.40 (m; 3H), 1.59–1.95 (m; 6H), 2.37–2.43 (m; 1H), 2.50–2.59 (m; 1H), 2.97–3.03 (m; 1H), 3.57 (s; 3H).

4-Methoxy-4-cholesten-3-one (13i):[8] colorless crystals (from petroleum ether), mp 136–138 °C, yield 0.27 g (67%), method B; ^{1}H-NMR 0.70 (s; 3H), 0.85 (d; 3H, J = 7 Hz), 0.87 (d; 3H, J = 7 Hz), 0.91 (d; 3H, J = 7 Hz), 1.18 (s; 3H), 0.98–1.75 (m; 10H), 1.81–2.04 (m; 10H), 2.27–2.47 (m; 7H), 3.02–3.07 (m; 1H), 3.58 (s; 3H).

5,6,7,8-Tetrahydro-3-methoxy-4a-methyl-2(4a*H*)-naphthalinone (13j):[9] colorless crystals (from petroleum ether), mp 105–107 °C, yield 0.13 g (69%), method A; ^{1}H-NMR 1.28 (s; 3H), 1.25–1.40 (m; 1H), 1.66–1.69 (m; 2H), 1.85–1.89 (m; 1H), 2.00–2.03 (m; 1H), 2.38–2.45 (m; 2H), 3.45–3.62 (m; 1H), 3.66 (s; 3H), 5.69 (s; 1H), 6.12 (s; 1H).

4,4a,5,6-Tetrahydro-8-methoxy-4a-methyl-2(3*H*)-naphthalinone (13k). This compound was prepared according to the general methods with the exception of the HBr elimination by DBU. The ethereal layer was evaporated and the residue dissolved in xylene (10 mL). The solution was treated with DBU (0.3 g, 2.0 mmol) and $AgNO_3$ (0.25 g, 1.5 mmol) and allowed to reflux for 2 h. After concentration the residue was dissolved in ether (10 mL), filtered, washed with 1 N HCl and brine and dried ($MgSO_4$). Removal of the solvent affords the crude product: colorless crystals (from petroleum ether), mp 86–88 °C, yield 0.17 g (87%), method A; 0.15 g (77%), method B; ^{1}H-NMR 1.18 (s; 3H), 1.49–1.58 (m; 2H), 1.77–1.83 (m; 1H), 1.86–1.94 (m; 1H), 2.26–2.34 (m; 1H), 2.39–2.49 (m; 2H), 2.58–2.67 (m; 1H), 3.60 (s; 3H), 5.25 (dd; 1H, J = 3, 2 Hz), 6.23 (s; 1H); MS *m/e* 192 (M^+). Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.92; H, 8.30. Found: C, 74.88; H, 8.47.

6-Methoxy-4,6-cholestadien-3-one (13m): colorless crystals (from methanol), mp 158–160 °C, yield 0.32 g (77%), method B; ^{1}H-NMR 0.75 (s; 3H), 0.85 (d; 3H, J = 7 Hz), 0.86 (d; 3H, J = 7 Hz), 0.91 (d; 3H, J = 7 Hz), 1.10 (s; 3H), 0.96–1.41 (m; 14H), 1.48–1.54 (m; 2H), 1.66–1.81 (m; 2H), 1.85–2.07 (m; 3H), 2.21 (dt; 1H, J = 11, 2 Hz), 2.37–2.57 (m; 2H), 3.56 (s; 3H), 5.16 (d; 1H, J = 2 Hz), 6.23 (s; 1H); MS *m/e* 412 (M^+). Anal. Calcd for $C_{28}H_{44}O_2$: C, 81.50; H, 10.75. Found: C, 81.26; H, 10.49.

4-Bromo-3-buten-2-one (Ethoxycarbonyl)hydrazone (15). To a solution of **8a** (1.56 g, 10.0 mmol) in CH_2Cl_2 (50 mL) cooled to −50 °C was added dropwise Br_2 (1.6 g, 10.0 mmol in 5 mL CH_2Cl_2) under N_2. After being warmed to 0 °C the reaction mixture was treated with DBU (3 g, 20.0 mmol) and allowed to stir at rt for 1 h. The solution was extracted with 1 N HCl (3 × 10 mL), washed with brine, and dried ($MgSO_4$). After removing the solvent the residue was purified by column chromatography on silica gel using petroleum ether/ethyl acetate (1/1) as eluent: colorless crystals (from petroleum ether/ethyl acetate 1/1), mp 115–117 °C, yield 2.2 g (95%); ^{1}H-NMR 1.32 (t; 3H, J = 7 Hz), 2.26 (s; 3H), 4.29 (q; 2H, J = 7 Hz), 6.79 (d; 1H, J = 15 Hz), 7.54 (d; 1H, J = 15 Hz), 8.42 (s, broad; 1H); MS *m/e* 155 (−Br), 154 (−HBr) (M^+). Anal. Calcd for $C_7H_{11}BrN_2O_2$: C, 35.76; H, 4.71; N,11.92. Found: C, 35.77; H, 4.55; N, 11.96.

3-(Benzyloxy)-4-bromo-3-buten-2-one (16). This compound was prepared according to the method A starting from **15**. Instead of 5 mL of CH_3OH/2 drops of concd H_2SO_4 in CH_3OH we used 3 mL of benzyl alcohol/2 drops of concd H_2SO_4 in THF. The crude product was purified by flash chromatography on silica gel using petroleum ether/ethyl acetate (6/1) as eluent to give 0.22 g (87%) of **16**. This compound was used for the next step without further purification. *E*/*Z*-isomers (10/1); ^{1}H-NMR, *E*-isomer: 2.24 (s; 3H), 5.05 (s; 2H), 6.96 (s; 1H), 7.31–7.45 (m; 5H); *Z*-isomer: 2.23 (s; 3H), 5.07 (s; 2H), 6.82 (s; 1H), 7.31–7.45 (m; 5H).

3-(Benzyloxy)-4-morpholino-3-buten-2-one (17a). To a solution of **16** (0.25 g, 1.0 mmol) in THF (10 mL) was added morpholine (0.95 g, 1.1 mmol). The reaction mixture was stirred for 24 h, cooled to 5 °C, and filtered. The volatile materials were removed in vacuo and the crude product recrystallized: colorless crystals (from hexane/ethyl acetate (5/2)), mp 70–72 °C, yield 0.255 g (98%); ^{1}H-NMR 2.19 (s; 3H), 3.49 (t; 4H, J = 5 Hz), 3.62 (t; 4H, J = 5 Hz), 4.71 (s; 2H), 6.82 (s; 1H), 7.31–7.39 (m; 5H); MS *m/e* 261 (M^+). Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.93; H, 7.33; N, 5.38. Found: C, 68.64; H, 7.45; N, 5.54.

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