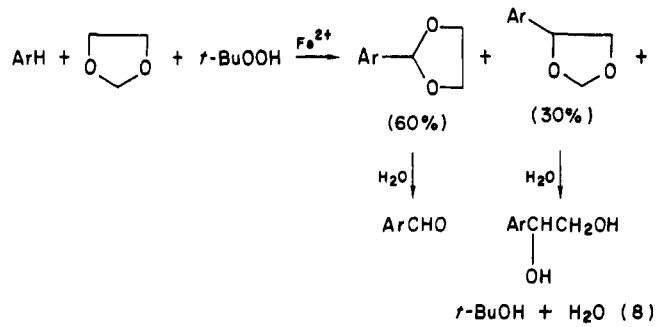

process is not selective (eq 8).

Experimental Section

Formylation Using *t*-BuOOH—General Procedure. A solution of the heteroaromatic base, CF_3COOH (equimolecular with the base), and *t*-BuOOH in the amounts reported in the table and 0.7% of ferrous sulfate (based on the hydroperoxide) were refluxed for 5 h with 120 g of trioxane and 200 mL of acetonitrile. The solution was concentrated by distilling the solvent, basified with 5% NaOH solution (50 mL, and extracted with ether (3 × 50). GLC and TLC analyses reveal only the presence of the starting base and of the trioxanyl derivative and small amounts (2–3%) of aldehyde. The solvent was distilled and the residue refluxed with 50 mL of 10% H_2SO_4, made basic with 5% NaOH, extracted with ether, and analyzed by GLC (with internal standard, 2- or 4-methylquinoline). The results are reported in the table. All the aldehydes were isolated as pure samples by silica gel chromatography (1:1 hexane–ethyl acetate under pressure) and identified by comparison with authentic compounds (mp, IR, NMR, MS).[1]

Formylation of 4-Methylquinoline Using H_2O_2. The procedure is identical with that used with *t*-BuOOH with the only difference being that 1 mol of 30% H_2O_2 per mol of lepidine is used. GLC and TLC show that the reaction product is a mixture of unreacted lepidine and 2-trioxanyl- and 2-formyllepidine. The hydrolysis by 10% H_2SO_4 leads to a mixture of lepidine and 2-formyllepidine. GLC analysis (2-methylquinoline as internal standard) indicates a conversion of 38% and a yield of 93% based on converted lepidine. The 2-formyllepidine (mp 76–77 °C) has been isolated by silica gel chromatography and identified by comparison (IR, NMR, MS) with an authentic sample.

Reaction of Lepidine with 1,3-Dioxolane. Lepidine (14 mmol), 16 mmol of CF_3COOH, 24 mmol of *t*-BuOOH, and 0.1 mmol of ferrous sulfate in 100 mL of 1,3-dioxolane were warmed under stirring for 5 h at 78 °C. The solution was then concentrated by distilling the dioxolane, made basic by 5% NaOH solution, extracted with ether, and analyzed by GLC (2-methylquinoline as internal standard). The conversion of lepidine was 93%; the yields of 2-dioxolan-2-yl-4-methylquinoline and 2-dioxolan-4-yl-4-methylquinoline were 61% and 30%, respectively. The products were isolated by silica gel chromatography.

2-Dioxolan-4-yl-4-methylquinoline: liquid; NMR ($CDCl_3$) δ 2.7 (s, 3 H, Me-4), 4–4.5 (m, 2 H, $OCHCH_2O$), 5.1–5.3 (m, 3 H, CHO, OCH_2O), 7.4–8.1 (m, 5 H, Ar); MS, *m/e* 215 ($M^{+\cdot}$), 201, 185, 184, 170, 157, 143, 115.

2-Dioxolan-2-yl-4-methylquinoline, liquid, was identified by comparison (IR, NMR, MS) with an authentic sample prepared by ethylene glycol ketalization of 2-formyl-4-methylquinoline. By hydrolysis with 10% H_2SO_4 it is transformed in 2-formyl-4-methylquinoline.

Acknowledgment. This work was supported by Progetto Finalizzato Chimica Fine e Secondaria, CNR.

Registry No. *t*-BuO_2H, 75-91-2; H_2O_2, 7722-84-1; quinoline, 91-22-5; 4-methylquinoline, 491-35-0; 2-methylquinoline, 91-63-4; isoquinoline, 119-65-3; quinoxaline, 91-19-0; benzothiazole, 95-16-9; 2-formylquinoline, 5470-96-2; 4-formylquinoline, 4363-93-3; 2-formyl-4-methylquinoline, 40105-30-4; 2-methyl-4-formylquinoline, 6760-22-1; 1-formylisoquinoline, 4494-18-2; 2-formylquinoxaline, 1593-08-4; 2-formylbenzothiazole, 6639-57-2; trioxane, 110-88-3; 2-(dioxolan-4-yl)-4-methylquinoline, 99687-43-1; 2-(dioxolan-2-yl)-4-methylquinoline, 99687-44-2; 1,3-dioxolane, 646-06-0; 2-trioxanyllepidine, 40105-26-8.

Methylcopper(I)-Catalyzed Selective Conjugate Reduction of α,β-Unsaturated Carbonyl Compounds by Diisobutylaluminum Hydride in the Presence of Hexamethylphosphoric Triamide

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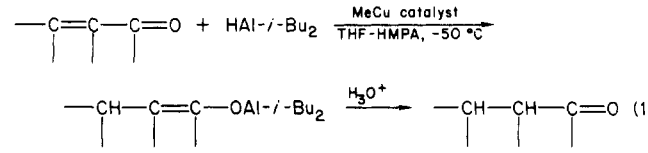
Received May 29, 1985

Selective conjugate reduction (1,4-reduction) of α,β-unsaturated carbonyl compounds is an important transformation in organic synthesis. Especially, the selective conjugate reduction on highly functionalized molecules is a recent subject of considerable interest. Several transition-metal hydride reagents including those produced in situ from transition-metal compounds and conventional reducing reagents have been developed.[1] Previously we reported that cuprous iodide catalyzes conjugate reduction of α,β-unsaturated carbonyl compounds by lithium aluminum hydride (LAH) in the presence of hexamethylphosphoric triamide (HMPA).[2] However, the efficiency and selectivity of the reduction were not very high. Diisobutylaluminum hydride (DIBAH) is a widely employed reducing reagent in organic synthesis, and it is interesting to exploit novel reducing reactivity of DIBAH modified by a transition-metal compound. Herein is reported methylcopper(I)-catalyzed highly efficient and selective conjugate reduction of α,β-unsaturated carbonyl compounds by DIBAH in the presence of HMPA (eq 1).



Reduction of α,β-unsaturated carbonyl compounds by DIBAH generally takes place at the carbonyl group (1,2-reduction) to produce allylic alcohols. It has been now found that a remarkable change of reducing reactivity of DIBAH is brought about by addition of HMPA. As is shown in Table I, conjugate reduction of *trans*-2-hexenal, 2-cyclohexen-1-one, and mesityl oxide by DIBAH was effectuated in a mixed solvent of HMPA–THF (v/v, 1:5) at 0 °C–room temperature in a good yield of ca. 90% without any 1,2-reduction. The DIBAH–HMPA system as a reagent of conjugate reduction, however, lacks generality, owing to limitation of applicable substrates. Conjugate reduction of 3-methyl-2-cyclopenten-1-one and α,β-unsaturated esters such as methyl crotonate and methyl cinnamate by DIBAH–HMPA did not proceed effectively.

Addition of a catalytic amount of MeCu which was prepared in situ from an equimolar reaction of methyllithium and CuI to the DIBAH–HMPA system produced a dramatic effect to cause at −50 °C selective and quantitative conjugate reduction of a variety of α,β-unsaturated carbonyl compounds including α,β-unsaturated esters and β,β-dialkyl-substituted α,β-enones without any 1,2-reduction. The results are summarized in Table I. A role of MeCu is crucial. Addition of an equimolar amount of

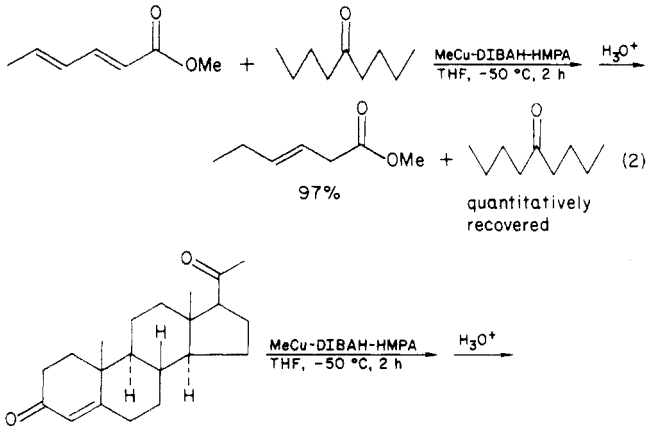
(1) (a) Keinan, E.; Gleize, P. A. *Tetrahedron Lett.* **1982**, *23*, 477 and references therein. (b) Four, P.; Guibe, F. *Tetrahedron Lett.* **1982**, *23*, 1825.

(2) Tsuda, T.; Fujii, T.; Kawasaki, K.; Saegusa, T. *J. Chem. Soc., Chem. Commun.* **1980**, 1013.

0022-3263/86/1951-0537$01.50/0

MeLi to DIBAH–HMPA without CuI resulted in nonselective reduction of 3-methyl-2-cyclohex-1-one. HMPA is also an indispensable component for efficient conjugate reduction. Even a nearly equimolar amount of HMPA to DIBAH is sufficient to manifest its effect. This finding suggests that HMPA functions not as a cosolvent but as a ligand. Use of pyridine, dimethylformamide, and dimethyl sulfoxide, instead of HMPA, produced no effect. CuI also catalyzed the conjugate reduction of α,β-unsaturated carbonyl compounds by DIBAH–HMPA at −50 °C but could not perform the quantitative conjugate reduction of less reactive substrates such as 3-methyl-2-cyclohexen-1-one, mesityl oxide, 2,4-heptadien-6-one, and methyl cinnamate.

Even in the coexistence of a saturated carbonyl group, the selective conjugate reduction of conjugated carbonyl compounds by MeCu–DIBAH–HMPA took place effectively (eq 2). Exclusive formation of 5α-pregnane-3,20-dione in the selective conjugate reduction of progesterone indicates trans stereochemistry of the conjugate reduction of steroidal 4-en-3-ones having a methyl group at C-10 (eq 3). Thus, the results obtained indicate that in feasibility,



efficiency, and/or selectivity of the conjugate reduction of α,β-unsaturated carbonyl functions, the presently developed MeCu–DIBAH–HMPA system offers several advantages over the conventional methods of catalytic hydrogenation[3] and dissolving metal reduction.[4] The conjugate reduction of α,β-unsaturated ketones and esters by the use of lithium and potassium tri-*sec*-butylborohydrides has been reported, where the scope of applicable α,β-unsaturated carbonyl compounds, however, is limited.[5] For example, β-substituted acyclic enones and β-substituted 2-cyclohexenones undergo the carbonyl (1,2) reduction instead of the conjugate (1,4) reduction, and 2-cyclopentenone and methyl cinnamate do not undergo the efficient conjugate reduction. Methyl sorbate is also highly resistant to conjugate reduction.

Experimental Section

IR spectra were determined on a Hitachi 260-50 grating spectrophotometer. ^{1}H NMR spectra were taken on a Hitachi R-20B spectrometer. ^{13}C NMR spectra were obtained on a Hitachi R-100 spectrometer. All chemical shifts are reported in parts per million (δ) downfield from internal tetramethylsilane. Mass spectra were obtained on a JEOL D-300 instrument. Gas chromatographic analyses (GLC) were made on a Shimadzu 4CPT instrument employing a 20% silicone DC 550 on Celite 545 column and a 20% polyethylene glycol (PEG) 20M on Celite 545 column.

All reactions were conducted under an atmosphere of nitrogen. Cuprous iodide was obtained from Nakarai Chemicals, Ltd., and used without further purification. Diisobutylaluminum hydride in hexane and methyllithium in ether were obtained from Aldrich Chemical Co. α,β-Unsaturated carbonyl compounds were commercial reagents and were distilled under nitrogen after drying over Drierite. Dry tetrahydrofuran (THF) was distilled from lithium aluminum hydride under nitrogen. Dry hexamethylphosphoric triamide (HMPA) was distilled from calcium hydride under nitrogen atmosphere.

The conjugate reduction products except hexanal, 3-methylcyclopentan-1-one, 3-methylcyclohexan-1-one, 4-phenylbutan-2-one, 4-hepten-2-one, methyl 3-hexenoate, and 5α-pregnane-3,20-dione were isolated by GLC and identified by the agreement of their GLC retention times and IR spectra with those of the commercially available authetic samples. The isolation and characterization of 4-phenylbutan-2-one, 4-hepten-2-one, methyl 3-hexenoate, and 5α-pregnane-3,20-dione are described in the following typical experimental procedures. Hexanal was isolated by column chromatography (silica gel, elution with pentane–ether (10:1 v/v)): IR (liquid film, cm^{-1}) 1740; ^{1}H NMR ($CDCl_3$) 0.90 (t, 3 H), 1.1–2.0 (m, 6 H), 2.43 (t, 2 H), 9.80 (s, 1 H); mass spectrum, M^+ at m/e 100. 3-Methylcyclopentan-1-one was isolated by column chromatography (silica gel, elution with pentane–ether (2:1 v/v)): IR (liquid film, cm^{-1}) 1740; ^{1}H NMR ($CDCl_3$) 1.14 (d, 3 H), 1.3–3.0 (m, 7 H); mass spectrum, M^+ at m/e 98. 3-Methylcyclohexan-1-one was isolated by Kugelrohr distillation at 110 °C (100 mmHg): IR (liquid film, cm^{-1}) 1710; ^{1}H NMR ($CDCl_3$) 1.03 (d, 3 H), 1.4–2.6 (m, 9 H); mass spectrum, M^+ at m/e 112.

Conjugate Reduction of 4-Phenyl-3-buten-2-one. To a stirred suspension of CuI (0.0570 g, 0.300 mmol) in 15 mL of THF cooled to −50 °C was added an ether solution of methyllithium (0.300 mmol). A yellow precipitate of MeCu was formed. HMPA (3 mL) and a hexane solution of DIBAH (3.30 mmol) were added successively. The reaction mixture was stirred for 30 min at −50 °C to produce a brown solution, and 4-phenyl-3-buten-2-one (0.435 mL, 3.00 mmol) was added. After being stirred at −50 °C for 1.5 h, the mixture was treated with 6 mL of 1 N HCl solution followed by 150 mL of ether. The separated ether solution was washed twice with 6 mL of 1 N HCl solution and then three times with 6 mL of water. The ether solution was dried over anhydrous magnesium sulfate, filtered, and concentrated. The residue was purified on a silica gel plate (20 × 20 × 0.2 cm) employing hexane–ether (1:1 v/v) as eluent to give 4-phenylbutan-2-one (0.365 g, 2.46 mmol, 82%): IR (liquid film, cm^{-1}) 1715; ^{1}H NMR ($CDCl_3$) 2.10 (s, 3 H), 2.80 (m, 4 H), 7.18 (s, 5 H); mass spectrum, M^+ at m/e 148. A small amount of unreacted 4-phenyl-3-buten-2-one (0.017 g, 0.12 mmol, 3.8%) was recovered.

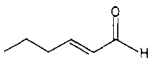
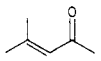
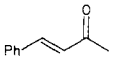
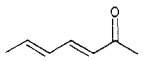
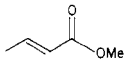
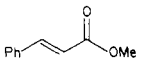
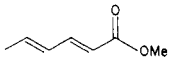
Conjugate (1,6) Reduction of 2,4-Heptadien-6-one. The reaction was carried out as described above, using 3 mmol of 2,4-heptadien-6-one. The conjugate (1,6) reduction product of 4-hepten-2-one (0.283 g, 2.52 mmol, 84%) was isolated by column chromatography (silica gel, pentane–ether (1:1 v/v) as eluent): IR (liquid film, cm^{-1}) 1717, 960; ^{1}H NMR 0.94 (t, 3 H), 2.06 (s, 3 H), 1.7–2.3 (m, 2 H), 2.94 (t, 2 H), 5.43 (m, 2 H); mass spectrum, M^+ at m/e 112. In the ^{13}C NMR of 4-hepten-2-one, seven major absorptions at 13.56, 25.66, 29.32, 47.70, 120.97, 136.92, and 207.65 ppm appeared together with minor absorptions at 17.88, 26.85, 29.94, 43.57, 125.98, and 129.81 ppm. This finding suggests that 4-hepten-2-one obtained is a mixture of *E* and *Z* isomers. The

(3) (a) House, H. O. "Modern Synthetic Reactions", 2nd ed.; Benjamin: Menlo Park, CA, 1972; p 26. (b) Augustine, R. L. "Advances in Catalysis"; Academic Press: New York, 1976; p 56.

(4) (a) House, H. O. "Modern Synthetic Reactions", 2nd ed.; Benjamin: Menlo Park, CA, 1972; p 173. (b) Caine, D. *Org. React. (N.Y.)* **1976**, *23*, 1.

(5) (a) Ganem, B. *J. Org. Chem.* **1975**, *40*, 146. See also: Chamberlin, A. R.; Reich, S. H. *J. Am. Chem. Soc.* **1985**, *107*, 1440. (b) Ganem, B.; Fortunato, J. M. *J. Org. Chem.* **1975**, *40*, 2846. (c) Fortunato, J. M.; Ganem, B. *J. Org. Chem.* **1976**, *41*, 2194.

Table I. MeCu-Catalyzed Conjugate Reduction of α,β-Unsaturated Carbonyl Compounds by DIBAH in the Presence of HMPA[a]

substrate (S)	Cu(I) compd	temp, °C	time, h	reduction products, %[b] 1,4 [or 1,6]	reduction products, %[b] 1,2	unreacted substrate, %
	none	0	1	92 (89)[d]	0	7
	none	room temp	3	49	0	21
	MeCu	−50	1	86 (71)[d]	0	trace
	none	0	1	100	0	0
	none	−50	0.5	11	0	83
	CuI	−50	0.5	100	0	0
	none	0	3	95	0	5
	CuI	−50	0.5	23	0	68
	MeCu	−50	0.5	100 (73)[c]	0	0
	MeCu (without HMPA)	−50	0.5	11	56	0
	MeLi	−50	0.5	43	16	23
	none	0	1	91	0	8
	CuI	−50	0.5	72	0	26
	MeCu	−50	0.5	100	0	0
	MeCu	−50	1.5	90 (82)[d]	0	trace
	CuI	−50	3	[78]	0	19
	MeCu	−50	1.5	[100 (84)][d]	0	0
	none	room temp	3	39	0	50
	MeCu	−50	0.5	100	0	0
	none	50	3	9	0	47
	CuI	−50	3	66	0	21
	MeCu	−50	1	94	0	0
	MeCu	−50	1.5	[93 (80)][c]	0	0

[a] S, 0.50 mmol; DIBAH/S = 1.1; Cu(I) compound/S = 0.1; solvent, THF (5 mL)–HMPA (1 mL). [b] Yield was determined by GLC analysis and was based on a substrate. [c] Value in parentheses is an isolated yield by Kugelrohr distillation in the reaction using 10 mmol of substrate. [d] Value in parentheses is an isolated yield by column chromatography or preparative TLC in the reaction using 3.00 mmol of substrate.

strong IR absorption observed at 960 cm^{-1} with a weak absorption at 700 cm^{-1} shows the predominant formation of (*E*)-4-hepten-2-one.

Conjugate (1,6) Reduction of Methyl Sorbate. To a stirred suspension of CuI (0.190 g, 1.00 mmol) in 50 mL of THF cooled to −50 °C was added an ether solution of methyllithium (1.00 mmol). A yellow precipitate of MeCu was formed. HMPA (10 mL) and a hexane solution of DIBAH (15.0 mmol) were added successively. The reaction mixture was stirred for 30 min at −50 °C, and methyl sorbate (1.31 mL, 10.0 mmol) was added. After being stirred at −50 °C for 2 h, the mixture was treated with 30 mL of 0.5 N HCl solution followed by addition of 50 mL of ether. The aqueous solution was extracted twice with 50 mL of ether. The combined ether solution was washed with 1 N HCl solution, saturated aqueous $NaHCO_3$, and saturated brine. The ether solution was dried over anhydrous magnesium sulfate, filtered, and concentrated. The residue was purified by Kugelrohr distillation at 100 °C (120 mmHg) to give methyl 3-hexenoate (1.50 g, 8.03 mmol, 80% yield): IR (liquid film, cm^{-1}) 1740, 962; ^1H NMR ($CDCl_3$) 0.93 (t, 3 H), 1.8–2.3 (m, 2 H), 3.00 (d, 2 H), 3.66 (s, 3 H), 5.4–5.7 (m, 2 H); ^{13}C NMR ($CDCl_3$) 12.38, 25.47, 37.83, 51.63, 120.66, 136.35, 172.58; mass spectrum, M^+ at *m/e* 138. Methyl 3-hexenoate obtained showed an IR δ_{CH} absorption of the trans-disubstituted olefin at 962 cm^{-1} without that of the cis-disubstituted olefin at the region of 730–665 cm^{-1} and also showed only the two ^{13}C NMR signals of the carbon–carbon double bond at 120.66 and 136.35 ppm. These findings indicate that methyl 3-hexenoate produced has the *E* configuration.

Conjugate Reduction of Progesterone. To a stirred suspension of CuI (0.0570 g, 0.300 mmol) in 5 mL of THF cooled to 0 °C was added an ether solution of methyllithium (0.300 mmol). The mixture was cooled to −50 °C, and then 2 mL of HMPA and a hexane solution of DIBAH (4.00 mmol) were added successively. The reaction mixture was stirred for 30 min at −50 °C, and progesterone (0.314 g, 1.00 mmol) in 2 mL of THF was added. After being stirred at −50 °C for 2 h, the mixture was treated with 3 mL of 0.5 N HCl solution followed by addition of 5 mL of ether. The aqueous layer was extracted twice with 5 mL of ether. The combined ether solution was washed with 1 N HCl solution, saturated aqueous $NaHCO_3$, and saturated brine. The ether solution was dried over anhydrous magnesium sulfate, filtered, and evaporated. The residue dissolved in a small amount of $CHCl_3$ was placed on a silica gel plate and eluted with benzene–ethyl acetate (8:1 v/v) to give 5α-pregnane-3,20-dione (0.265 g, 0.837 mmol, 84%): IR (Nujol mull, cm^{-1}) 1710; ^1H NMR ($CDCl_3$) 0.62 (s, 3 H), 1.01 (s, 3 H), 2.12 (s, 3 H), 1.1–2.7 (m, 23 H); mass spectrum, M^+ at *m/e* 316. The IR and ^1H NMR spectra of 5α-pregnane-3,20-dione obtained here were identical with those of an authentic sample. In addition to 5α-pregnane-3,20-dione, a small amount of 20β-hydroxy-4-pregnen-3-one (0.018 g, 0.0597 mmol, 5.9%) was obtained: IR (KBr disk, cm^{-1}) 3500, 1670, 1610; ^1H NMR ($CDCl_3$) 0.82 (s, 3 H), 1.16 (d, 3 H), 1.21 (s, 3 H), 1.0–2.6 (m, 21 H), 3.57 (quint, 1 H), 5.77 (s, 1 H). These IR and ^1H NMR spectra were identical with those of an authentic sample of 20β-hydroxy-4-pregnen-3-one. Unreacted progesterone was not detected.

Acknowledgment. This investigation was supported by Grant-in-Aid for Developmental Scientific Research (Grant 59850143) from the Ministry of Education, Science, and Culture of Japan.

Registry No. DIBAH, 1191-15-7; HMPA, 680-31-9; MeCu, 1184-53-8; (*E*)-$Me(CH_2)_2CH$=CHCHO, 6728-26-3; Me_2C=CHCOMe, 141-79-7; PhCH=CHCOMe, 122-57-6; MeCH=CHCH=CHCOMe, 3916-64-1; MeCH=$CHCO_2Me$, 623-43-8; PhCH=$CHCO_2Me$, 1754-62-7; (*E,E*)-MeCH=CHCH=$CHCO_2Me$, 689-89-4; $Me(CH_2)_4CHO$, 66-25-1; Me_2CHCH_2COMe, 108-10-1; $Ph(CH_2)_2COMe$, 2550-26-7; (*E*)-$MeCH_2CH$=$CHCH_2COMe$, 24332-22-7; (*Z*)-$MeCH_2CH$=$CHCH_2COMe$,

90605-45-1; $Me(CH_2)_2CO_2Me$, 623-42-7; $Ph(CH_2)_2CO_2Me$, 103-25-3; (*E*)-$MeCH_2CH{=}CHCH_2CO_2Me$, 13894-61-6; 3-methyl-2-cyclohexen-1-ol, 21378-21-2; progesterone, 57-83-0; 5α-pregnane-3,20-dione, 566-65-4; 20β-hydroxy-4-pregnen-3-one, 145-15-3; 3-methyl-2-cyclopenten-1-one, 2758-18-1; 2-cyclohexen-1-one, 930-68-7; 3-methyl-2-cyclohexen-1-one, 1193-18-6; 3-methylcyclopentanone, 1757-42-2; cyclohexanone, 108-94-1; 3-methylcyclohexanone, 591-24-2.

Conversion Reactions of Cepham into Penam Systems. A Route To Determine the Relative Configurations of Two Diastereoisomeric 3-Bromo-4-methoxycepham Derivatives

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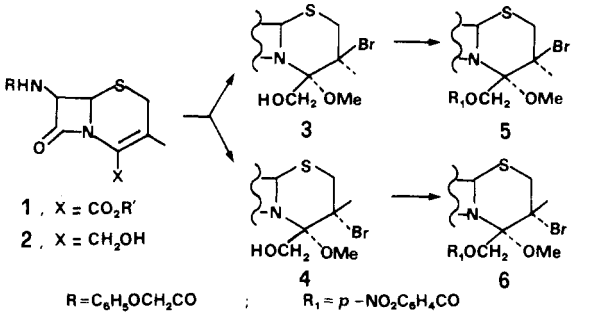
Received July 8, 1985

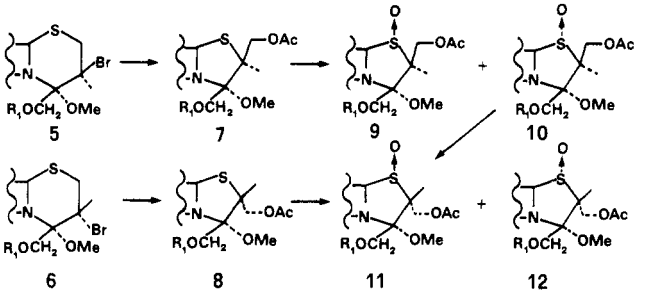
The 3-cephem double bond of cephalosporins of type **1** (R′ = H or alkyl) could appear to be a useful moiety in order to functionalize the dihydrothiazine ring of this class of β-lactam antibiotics. This double bond, however, is practically unreactive toward the classical electrophilic reagents.[1] This low reactivity could be due to the unfavorable electronic effects of the substituents on the C(3)–C(4) double bond of the cephalosporanic acid derivatives **1**. It was therefore conjectured that the electrophilic reactivity that is lacking in this unsaturated system might be restored by replacing the CO_2R' function present at C(4) of **1** with a less electron-withdrawing group such as the hydroxymethyl one. In accordance with this hypothesis, we found that the double bond of the 4-(hydroxymethyl)-3-cephem derivative **2** easily reacts with bromine in methanol, yielding a mixture of two bromomethoxy adducts **3** and **4** in a ratio of about 6:1.[2] The structure and configuration of the major product **3** was unequivocally determined by single-crystal X-ray analysis.[2] The very similar ^{13}C chemical shifts of the tetrasubstituted C(3) and C(4) carbons of both the adducts **3** and **4** led us to suggest the same regiochemistry for these compounds.[2] Unfortunately no information could be obtained about the configuration of **4**, and this did not allow us to make a complete rationalization of the formation of **3** and **4**.

It is known that 3-halosubstituted cepham derivatives can be converted by ring contraction into structurally related penam derivatives.[3,4] Bearing in mind that the



structure and configuration of compound **3** had been firmly established,[2] this kind of transformation carried out on **3** and **4** should have been able both to confirm the regiochemistry of **4** and to demonstrate its configuration. Furthermore the above-mentioned cepham–penam conversion reactions could have given β-lactam derivatives more complex than those of natural origin.

The reaction of the bromomethoxy adducts **3** and **4**, obtained by bromination of **2** in methanol,[2] with *p*-nitrobenzoyl chloride, afforded the corresponding esters **5** and **6**. The treatment of **5** and **6** with silver acetate in glacial acetic acid for a few minutes at 100 °C gave in good yields the two diastereoisomeric penam derivatives **7** and **8**, respectively. When the reaction with silver acetate was



carried out on the hydroxymethyl derivatives **3** and **4**, only complex mixtures of decomposition products were obtained. Oxidation of the penam derivatives **7** and **8** with *m*-chloroperoxybenzoic acid afforded mixtures of the corresponding *S* and *R* sulfoxides **9** and **10** and **11** and **12**, respectively, in which the *R* epimers predominated. Heating the *R* sulfoxide **10** in refluxing benzene resulted in its conversion to the penicillin *S* sulfoxide **11**. Treatment of **12** in refluxing benzene for a few hours led only to the recovery of the starting material together with small amounts of decomposition products. The *S* sulfoxides **9** and **11** were stable under these reaction conditions.

The penam nature of **7** and **8** was established on the basis both of the values of the geminal coupling constants (12.6 and 11.2 Hz, respectively) of the methylene protons of the CH_2OAc moiety, and of the high values of the stretching frequency of the β-lactam C=O (1786 and 1784 cm^{-1}, respectively).[5,6] The configurations of the sulfoxide group of **9–12** were deduced from intermolecular hydrogen-bonding studies of the amide proton using Me_2SO-d_6 (see Table I).[4,7-9] The small changes in the shift for the amide proton of the penam derivatives **9** and **11** observed on passing from $CDCl_3$ to Me_2SO-d_6 suggested the *S* con-

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