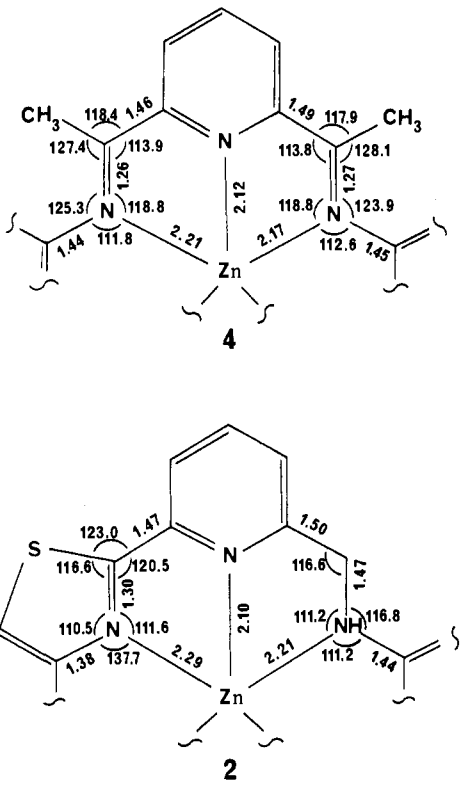
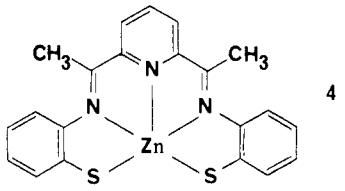


Figure 2. Bond lengths (Å) and angles (°) in the pyridino chelate rings of **4** and **2** (esd for lengths, <0.01 Å; for angles, <0.9°).

The formation of **2** was unexpected, since under identical reaction conditions the dimethyl derivative (**3**) of the 2,6-bis(2-benzothiazolinyl)pyridine gives[2] the complex **4** which

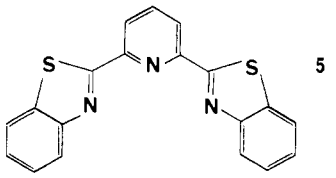


4

has been shown[3] to have an unusual "helical" five-coordinate structure. It has been proposed that this geometry results, at least in part, from the unfavorable steric interaction between the methyl substituent on the imine group and the anil ortho-hydrogen atom. We have studied reactions of **1** in order to investigate the importance of this interaction in determining the course of metal-ion assisted syntheses of related macrocyclic ligands.[4]

The most noteworthy feature of the formation of the product **1** is the change in hydrogenation levels of the two limbs of the ligand which accompanies the reaction (see bond lengths and angles in Figure 2). In addition to the ring opening of one of the thiazolinyl rings to give an imino thiolate chelate, a net "internal hydrogen transfer" reaction is required to account for the dehydrogenation of the other benzothiazolinyl ring and the hydrogenation of the imino linkage. Thus, the formation of **2** provides a rare example of a dehydrogenation/hydrogenation reaction which is promoted by a divalent metal ion which does not show facile oxidation state changes, and in this respect provides an analogy to the zinc-containing enzyme liver dehydrogenase. Also of interest is the formal resemblance of the N,S heterocycle to that in thiamine, which is a requisite cofactor for many enzymic reactions.

The reaction appears to be reversible since attempts to displace the ligands from the complex **2** by treating with solutions of cyanide or thiocyanate salts result in regeneration of the thiazolinyl ring, as demonstrated by the isolation of 2,6-bis(2-



5

benzothiazolyl)pyridine (55%) (**5**)[5] after extraction of organic materials into chloroform, followed by slow crystallization in air. Formation of **2** in relatively high yields may therefore be a result of a combination of (a) its low solubility and (b) the ability of zinc(II) to act as a "thermodynamic template ion".[6] Analogous results were obtained when zinc(II) nitrate was used instead of the acetate. Mechanistic studies of this and related reactions are planned.

Acknowledgment. We thank the Science Research Council (U.K.) for a grant for diffractometer equipment and for a studentship (to D.C.L), and Miss P. Haria for technical assistance.

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(2) L. F. Lindoy and D. H. Busch, *Inorg. Chem.*, **13**, 2494 (1974).
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David C. Liles, Mary McPartlin, Peter A. Tasker*
Department of Chemistry
The Polytechnic of North London, London N7 8DB, U.K.
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A New and Highly Effective Aldol Synthesis

Sir:

Reported here is a new method for the aldol synthesis which is regiospecific, simple, and efficient. It is expected that the process will find widespread use and that in many instances it will be found superior to currently important procedures.[1] The new process may be represented by Scheme I.

In principle, organoaluminum compounds have a vast potential as an agent of aldol reaction, although this concept has not been generally accepted for synthesis owing to the lack of an effective procedure for converting a carbonyl compound into a reactive aluminum enolate.[2] The critical part of the new process (Scheme I) consists of coupled attack on the α-halo ketone by dialkylaluminum chloride and zinc which generates

Scheme I

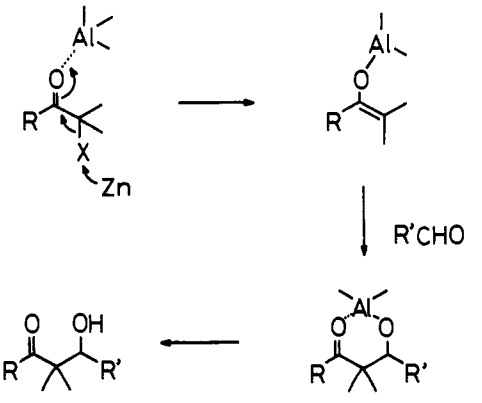
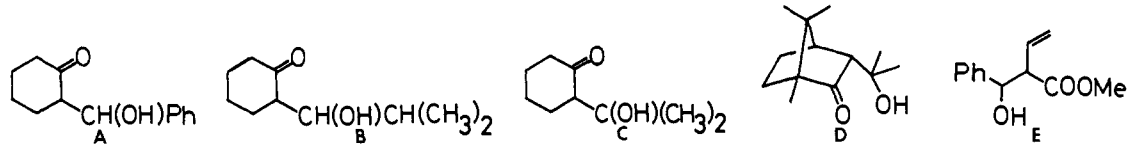


Table I. Synthesis of β-Hydroxy Carbonyl Compounds[a]

Bromo ketone or bromo ester	Aldehyde or ketone	Temp, °C	Product[b]	Isolated yield, %, (erythro/threo)
Bromoacetophenone	Benzaldehyde	−20	$PhCOCH_2CH(OH)Ph$	95
	Isobutyraldehyde	−20	$PhCOCH_2CH(OH)CH(CH_3)_2$	92
	Cinnamaldehyde	−20	$PhCOCH_2CH(OH)CH{=}CHPh$	92
	Cyclohexanone	−20	$PhCOCH_2C(OH)(CH_2)_5$	83
2-Bromocyclohexanone	Benzaldehyde	−20	A	97 (1/1)[c]
	Isobutyraldehyde	−20	B	93[d]
	Acetone[e]	−20	C	75
2-Bromo-2-methyl-cyclohexanone	Benzaldehyde	−20	1	100 (4/3)[f]
2-Bromocamphor	Acetone	r.t.	D	79
Ethyl bromoacetate	Benzaldehyde	0	$PhCH(OH)CH_2COOEt$	94
	Cyclohexanone	r.t.	$(CH_2)_5C(OH)CH_2COOEt$	93
$BrCH_2CH{=}CHCOOMe$	Benzaldehyde	−20	E[g]	100 (56/44)[h]

[a] Unless specified, the reactions were carried out on a 1-mmol scale exactly for the preparation of 1.[7] [b] Products A–E are shown below.

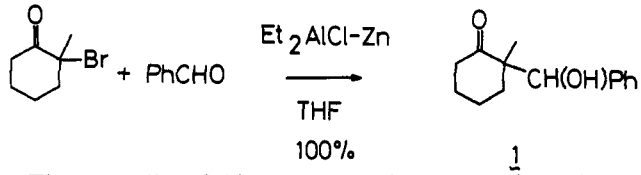


[c] Determined by an absorption due to the benzylic proton ($CDCl_3$): δ 5.30 (erythro), 4.73 (threo).[1a,b] [d] Erythro/threo ratio could not be determined by NMR analysis. [e] Excess acetone (~5 equiv) and Zn–Ag couple[13] were used for this reaction. [f] Note 7. [g] None of the γ-alkylation product ("normal Reformatsky ester") was detected in the reaction mixture. See M. W. Rathke, *Org. React.*, 22, 423 (1975). [h] Determined by the isolated yield: NMR (CCl_4) $J_{C(1)H-C(2)H}$ = 4.7 (erythro) and 8.0 Hz (threo).[1a,b]

an aluminum enolate regiospecifically.[3] The enolate thus generated is sufficiently reactive to cause a facile addition to the carbonyl compounds present in the system producing the β-ketolates which then would yield the β-hydroxy carbonyl compounds after workup.

Although a comparable path can be followed by two molecules of an α-halo ketone condensing each other, this would be subject to experimental control using the simultaneous addition of α-halo ketones and carbonyl compounds at low temperature provided that the reduction is sufficiently faster under acceptable conditions.[4] The operability of this approach has now been demonstrated. For example, gradual addition (40 min) of a mixture of benzaldehyde (1.1 equiv) and α-bromoacetophenone (1.0 equiv) in dry tetrahydrofuran (THF) to 1.5 equiv of zinc, 0.05 equiv of cuprous bromide,[5] and 1.1 equiv of diethylaluminum chloride[6] in THF–hexane with stirring at −20 °C under argon resulted in clean generation of the ketolate. Addition of pyridine, removal of cooling bath, and aqueous workup afforded 1,3-diphenyl-3-hydroxy-1-propanone in 95% yield after chromatography.

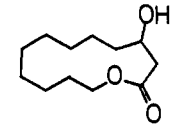
It was soon ascertained that the method is highly advantageous in the generation of aldols in regiospecific manner. Thus, treatment of 2-bromo-2-methylcyclohexanone and benzaldehyde with Et_2AlCl–Zn in THF at −20 °C produced the expected β-hydroxy ketone **1** in quantitative yield, uncontaminated by the regioisomer.[7]



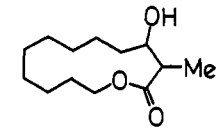
The generality of this new process is apparent from the results summarized in Table I which covers 12 examples. In addition to the β-hydroxy ketones, the β-hydroxy esters were produced from halo esters and carbonyl compounds in exceedingly high yields as are also indicated in Table I. It should be noted that the use of diethylaluminum chloride is crucial to the success of these reactions, since in its absence mere recovery of unchanged carbonyl compounds results under these mild conditions.[8]

To illustrate one of the unique synthetic application of this novel process, we have developed a new route to large ring lactones. Although the macrolide has been the objective of synthetic projects in a number of laboratories,[9] the number of basically different approaches is not large.

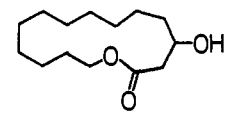
A series of α-bromocarboxylates of ω-hydroxyaldehydes, $BrCHRCOO(CH_2)_nCHO$ with n = 9, 11, or 12 and R = H or Me, was utilized in the intramolecular aldol cyclization studies. These substances were conveniently synthesized from 1,ω-diols in two steps: (1) partial esterification ($BrCH_2COBr$ or BrCHMeCOBr with *N,N*-dimethylaniline),[10] (2) Collins oxidation.[11] The bromoaldehydes (1 mmol), thus obtained,[12] in dry THF (10 mL) were added slowly from a mechanically driven syringe over 4 h to a stirred suspension of activated zinc (3.27 g)[13] and diethylaluminum chloride (1.5 mmol)[14] in THF (50 mL) at 35 °C under argon. Stirring was continued for an additional 20 min, and the reaction was terminated by the addition of pyridine (0.9 mL). After aqueous workup the crude product was subjected to column chromatography on silica gel (1:1 ether/hexane) to afford pure lactones.[12] The effectiveness of this method is apparent from the following list of lactones



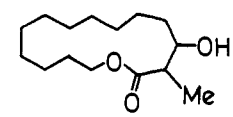
2 (35%)



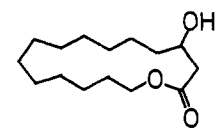
3 (48%)[15]



4 (48%)



5 (68%)[15]



6 (48%)[16]

(2–6) from the corresponding bromoaldehydes in the yields (after isolation by column chromatography) indicated.

As compared with the current processes for the preparation of the large ring lactones, this route provides a convenient and versatile method for the introduction of *α-methyl-β-hydroxy lactones* as they appear in many naturally occurring macrolides[17] starting with simple 1,ω-diols.[18]

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(3) This procedure has its origins in the classical Reformatsky reaction (see R. L. Shriner, *Org. React.*, **1,** 1 (1942); M. W. Rathke, *ibid.*, **22,** 423 (1975)) and, at the present time, we have no reason to believe the zinc enolate would not be involved in the above reaction. However, the milder reaction conditions and the higher selectivities (see, for example, footnote c of Table I) of this reaction would support the existence of the intermediary aluminum enolate in our process. For a related reaction of α-halo ketone to form silyl enol ether, see G. G. Joshi and L. M. Pande, *Synthesis*, 450 (1975); S. Hashimoto, A. Itoh, Y. Kitagawa, H. Yamamoto, and H. Nozaki, *J. Am. Chem. Soc.*, in press.

(4) In the absence of carbonyl compounds, the dimeric condensation product of the α-halo ketone was isolated as the major product: $RC(=O)CH_2Br \rightarrow RC(=O)CH_2C(OH)(CH_2Br)R$. See also T. A. Spencer, R. W. Britton, and D. S. Watt, *J. Am. Chem. Soc.*, **89,** 5727 (1967).

(5) Although commercial zinc dust could be used without any activation, the addition of cuprous bromide is recommended for the reproducible results.

(6) 1.1 mL of a 1 M hexane solution was used. All operations involving organoaluminum reagents were conducted in an atmosphere of dry argon or nitrogen.

(7) The simplicity and the key details of the new aldol synthesis are illustrated by the following procedure for the preparation of 1. Diethylaluminum chloride (1.1 mmol, 1.1 mL of a 1 M solution) was added to a slurry of zinc dust (98 mg, 1.5 mmol) and a catalytic amount of cuprous bromide (7 mg, 0.05 mmol) in dry THF (3 mL) with stirring under argon at 20 °C. The resulting mixture was cooled to −20 °C and a solution of 2-bromo-2-methylcyclohexanone (191 mg, 1 mmol) and benzaldehyde (117 mg, 1.1 mmol) in dry THF (5 mL) was added slowly over 40 min at −20 °C. After 15 min at −20 °C the reaction mixture was quenched by the addition of pyridine (0.3 mL) and then poured into 2 N hydrochloric acid and the product was extracted with ether three times. The ether extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo to afford erythro and threo mixtures of 2-(1′-hydroxybenzyl)-2-methylcyclohexanone (1) in quantitative yield after preparative layer chromatography on silica gel (1:1 ether/hexane). The ratio of the erythro and threo isomer was determined by the relative intensities of the benzylic proton absorptions (NMR ($CDCl_3$) δ 4.92 (erythro) and 5.00 (threo)) to be nearly 4:3.

(8) The extraordinary mild reaction conditions and high efficiencies of this new process are in sharp contrast to the classical Reformatsky reaction.

(9) (a) Internal esterification: E. J. Corey and K. C. Nicolaou, *J. Am. Chem. Soc.*, **96,** 5614 (1974), and references cited therein; S. Masamune, S. Kamata, and W. Schilling, *ibid.*, **97,** 3515 (1975). (b) Formation of C–C bonds in a cyclization reaction: B. M. Trost and T. R. Verhoeven, *ibid.*, **99,** 3867 (1977); E. J. Corey and H. A. Kirst, *ibid.*, **94,** 667 (1972); R. N. Hurd and D. H. Shah, *J. Org. Chem.*, **38,** 390 (1973). For a recent review, see K. C. Nicolaou, *Tetrahedron*, **33,** 683 (1977).

(10) B. Abramovitch, J. C. Shivers, B. E. Hudson, and C. R. Hauser, *J. Am. Chem. Soc.*, **65,** 986 (1943).

(11) J. C. Collins, W. W. Hess, and F. J. Frank, *Tetrahedron Lett.*, 3363 (1968).

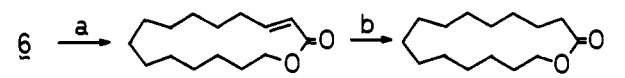
(12) All new compounds reported in this communication have been characterized spectrometrically and analytically.

(13) Zn–Ag couple was used for this reaction: J. M. Denis, C. Girard, and J. M. Conia, *Synthesis*, 549 (1972).

(14) 1.5 mL of a 1 M hexane solution.

(15) Although **3** and **5** were found to be mixtures of erythro and threo isomers (~1:1 by TLC assay (1:2 hexane–ether, two developments) after trimethylsilylation; attempted separation of these isomers by GLC or column chromatography was unsuccessful), the better selectivities would be expected in the naturally occurring macrolide synthesis by this methodology since such compounds were known to be conformationally rather rigid molecules.[9] A study on the synthesis of macrolides along this possibility is under way.

(16) 6 (colorless liquid): IR (liquid film) 3425, 1726 cm^{-1}; NMR ($CDCl_3$) δ 2.50 (d, 2 H); mass *m/e* (%) 41 (100), 238 (4, $M^+ - 18$); TLC (silica gel, 1:1 ether-hexane) R_f 0.27. The structure of **6** was further confirmed by its conversion into exaltolide (identical by spectroscopic (NMR, IR, and mass spectra) and chromatographic (GLC and TLC) comparison with an authentic sample).[9b]



a: CH_3SO_2Cl, Et_3N, CH_2Cl_2, r.t. 11 h. b: H_2, Pd/C, EtOH–EtOAc.

(17) The α-methyl-β-hydroxy unit is a common functionality in a variety of macrolide antibiotics including erythromycin and methymycin; see, for a general review, K. Nakanishi, T. Goto, S. Itoh, S. Natori, and S. Nozoe, "Natural Products Chemistry", Vol. 2, Kodansha Ltd., Tokyo, 1975.

(18) This work was supported financially by the Grant-in-aid administered by the Ministry of Education, Japanese Government (247077).

Keiji Maruoka, Shinsuke Hashimoto, Yoshizo Kitagawa Hisashi Yamamoto,* Hitosi Nozaki

Department of Industrial Chemistry, Kyoto University Yoshida, Kyoto 606, Japan

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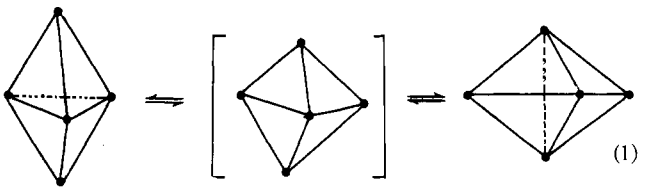
Gas Phase Hydrolysis of Phosphorus Esters

Sir:

There has been considerable interest for some time in the hydrolysis of phosphorus esters.[1] This is due in part to the importance of phosphate esters in biological systems as well as similarities and differences compared with carboxylates. The remarkable differences in hydrolysis rates of cyclic phosphorus esters have provided important insights into the effects of strain and energetics on trigonal-bipyramidal intermediates in these reactions.[1-5] In this communication we report gas phase hydrolysis studies which show that the effects observed in solution persist in the gas phase and thus are mechanistically intrinsic and not an artifact of solvation.

In solution, alkaline hydrolysis of five-membered cyclic phosphate esters without ring opening is considerably faster than cleavage in acyclic analogues.[3] However, exocyclic hydrolysis of five-membered cyclic phosphonate and phosphinate esters shows virtually no acceleration relative to acyclic analogues.[3,4] While rapid hydrolysis with ring opening can be readily explained by the release of ring strain in the transition state, exocyclic cleavage requires that the pentacoordinate intermediate must undergo positional isomerization (pseudorotation) (eq 1) to place the leaving group in the apical po-



(1)

sition necessary for cleavage.[5] Such intervening intermediates have been shown to be energetically favorable for the cyclic phosphate esters but not for the cyclic phosphonate and phosphinate esters.

Using the trapped ion, pulsed ICR technique,[6] we have measured the rates of reaction of trimethyl phosphate (**1**), methyl ethylenephosphate (**2**), methyl propylphostonate (**3**), ethyl tetramethylenephosphinate (**4**), and ethyl propylphos-