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STEREOSELECTIVE ALDOL CONDENSATIONS INDUCED BY A THERMOLABILE GROUP.

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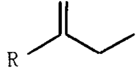
Abstract : Diastereoselective aldol condensations between exo, endo and 2-methyl endo bicyclo[2.2.1]-5-hepten-2-yl ethyl ketones and aldehydes are achieved via the ketones Z-lithium enolates prepared with lithium hexamethyldisilazide. The aldols thus obtained give rise by a retro Diels-Alder reaction to syn α-methyl-β-siloxy-α′-ethylenic ketones of potential value for polyhydroxylated natural product synthesis.

The aldol condensation constitutes a highly useful operation for carbon-carbon bond construction in organic synthesis. Over the past few years, much effort has been devoted to the stereochemical aspects of this reaction, leading to the development of highly diastereoselective condensation processes (1). It has been shown (2) that, under kinetic control, the Z and E lithium enolates of ethyl ketones such as 1 provide the 2,3-syn and the 2,3-anti aldol products respectively (3). However this simple relationship is stronger for Z than for E enolates and for enolates in which R is sterically demanding.



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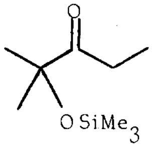

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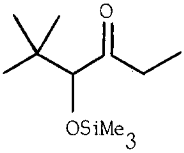

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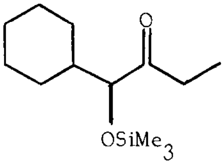

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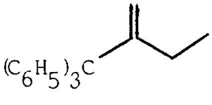

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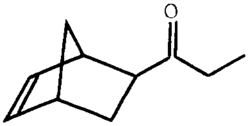
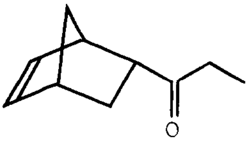
These considerations led several authors to develop the use of the ketones 2 to 5 (4) where R is a large group which can be transformed into OH, H, or alkyl groups. We wish to report in this communication the good to excellent syn diastereoselectivity shown for aldol condensation with various aldehydes by the three ketones 6a-c in which the necessary bulky R group is a thermolabile norbornene

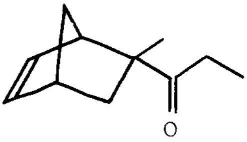
(5). A simple heating of the aldol formed will then provide, by a retro Diels-Alder reaction, an access to ethylenic hydroxy ketones which can be useful synthetic intermediates.



6a



6b



6c

First, the lithium enolates of the ketones 6a-c were prepared by addition of the ketones to a solution of lithium diisopropylamide (LDA) or lithium hexamethyldisilazide (LHMDS) in tetrahydrofuran at -78°C and quenched by the addition of trimethylsilyl chloride to provide mixtures of Z and E enolsilanes which were analyzed by gaz chromatography. The stereostructural assignment of the two isomers was based on the relative chemical shifts of the vinyl proton determined by ^{1}H NMR (7). If LDA gave rise, at least for 6a and 6b, to mixtures of enolate stereoisomers (6a → Z/E= 53/47 ; 6b → Z/E = 85/15 ; 6c → Z/E >98/2), only the Z enolates were formed by action of LHMDS.

Aldol reactions of these Z enolates were then carried out by litterature procedures (2b) and after addition of either aqueous NH$_4$Cl or trimethylsilylchloride led to the aldols 7 or the protected aldols 8 respectively. The compounds 8 could also be obtained by reaction of the aldols 7 with trimethylsilylchloride in the presence of triethylamine and a small amount (10%) of DMSO. As could be expected, the thermolysis of aldols 7 gave rise via a retro aldol and a retro Diels-Alder reaction to a mixture of cyclopentadiene, vinyl (or isopropenyl) ethyl ketone and the starting aldehyde. However when the protected aldols 8 were flash-thermolyzed at 500°C, the silyloxy ethylenic ketones 9 were obtained with excellent yields (8). The result of aldol condensations of the ketones 6a-c with various aldehydes are listed in the Table. All reactions proceeded with good to excellent syn stereoselectivity and, as can be seen from entries 1-4, the behaviours of exo and endo ketones 6a and 6b were quite equivalent and similar to that of isopropyl ethyl ketone (11). More interestingly, the ketone 6c gave rise in all cases to a single aldol stereoisomer, providing an easy access to stereochemically pure syn isopropenyl silyloxy ketones 9 (R = CH$_3$).

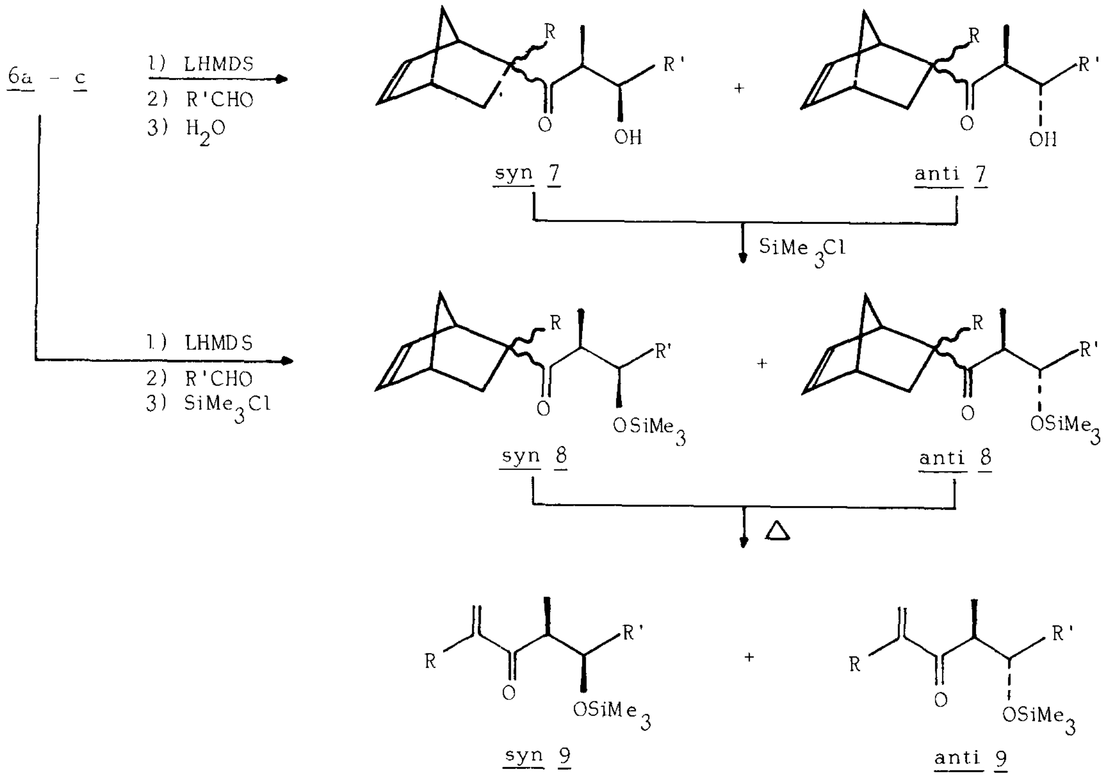
The use of these valuable synthons 9 in natural product synthesis is currently under investigation.

Table : Syn-selective aldolisation of norbornenyl ethyl ketone

Entry	Ketone	Aldehyde	Reaction time	Protected Aldol Yield [(a)]	Syn/anti [(b)]	Thermolysis Yield [(a)]
1	6a	PhCHO	5 s	77	82/18	81
2	6a	C_4H_9CHO	5 min	61	87/13	67
3	6b	PhCHO	5s	70	83/17	80
4	6b	C_4H_9CHO	5 min	60	89/11	71
5	6c	PhCHO	5 s	56	$>$ 98/2	80
6	6c	PhCHO	5 min	82	$>$ 98/2	80
7	6c	C_4H_9CHO	20 min	63	$>$ 98/2	75
8	6c	Furfural	10 min	67	$>$ 98/2	80

a) Yields are given for pure isolated compounds.

b) For simplicity the ratios syn/anti have been determined from ^{1}H NMR spectra (9) of the crude vinyl ketones 9 obtained by thermolysis. However since the reactions $7 \rightarrow 8 \rightarrow 9$ do not affect the stereochemistry of the aldols 7, these ratios are well representative of the diastereoselectivity of the aldol condensation (10).



References and Notes

1) Several excellent reviews relative to this topic have been published : a) D.A. Evans, J.V. Nelson and T.R. Taber in "Topics in stereochemistry", ed. by N.L. Allinger, E.L. Eliel and S.H. Wilen, John Wiley and sons, New York, 1982, vol. 13, p. 1 ; b) S. Masamune and W. Choy, Aldrichimica Acta, 1982, 15, 47 ; c) C.H. Heathcock, in "Current Trends in Organic Synthesis", ed. by H. Nozaki, Pergamon Press, Oxford, 1983, p. 27 ; d) C.H. Heathcock in "Asymmetric Synthesis", ed. by J.D. Morrison, Academic Press, Orlando, 1984, Vol. 3, p. 111.

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3) For reason of simplicity we used here the description "syn" and "anti" in the sense proposed by Masamune and coworkers : S. Masamune, S.A. Ali, D.L. Snitman and D.S. Garvey, Angew. Chem. Int. Ed., 1980, 19, 557.

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5) The ketones 6a and 6b were prepared by reaction of ethyl magnesium bromide with commercial bicyclo [2.2.1]-5-hepten-2-nitrile followed by liquid column chromatography. The ketone 6c was obtained by action of ethyl magnesium bromide on the corresponding acid chloride (endo/exo = 60/40) in the presence of Fe(acac)$_3$ (6) and purified by liquid chromatography.

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8) All new compounds were fully characterised by spectroscopy (^{1}H NMR, IR, MS).

9) We used the well established fact that for the α-methyl-β-hydroxy ketones the two protons beared by the two asymetric carbon schow J anti > J syn. This result can be extended to the protected aldol. We found in all cases $J_{syn} \sim 7$ Hz and $J_{anti} \sim 10$ Hz (10).

10) This result has been confirmed from ^{1}H NMR (250 MHz) spectra analysis of the aldol obtained from ketone 6a and benzaldehyde. The same stereoselectivity was found and coupling constants were determined : $J_{syn} = 5{,}75$ Hz ; $J_{anti} = 8{,}50$ Hz.

11) Since the syn and anti aldols 7 (R = H) are easily separated by flash column chromatography, the syn vinylketones 9 (R = H) were also obtained stereochemically pure.

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