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CHIRAL QUATERNARY CARBON COMPOUNDS. II.

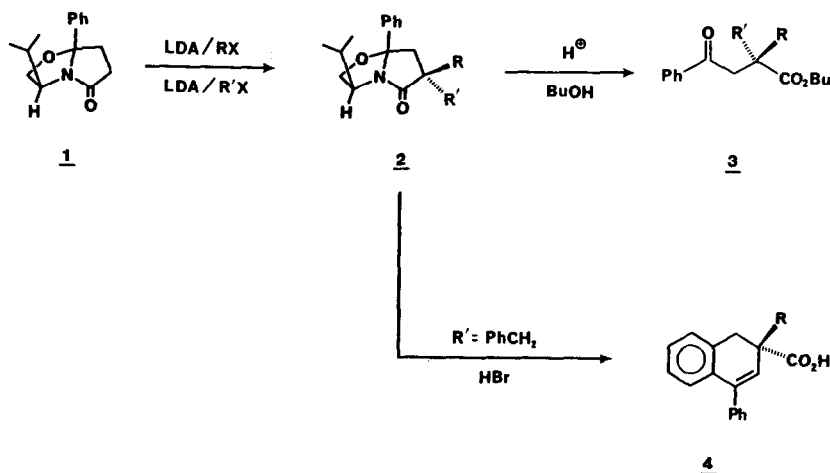
AN ASYMMETRIC SYNTHESIS OF (R) OR (S)-4,4-DIALKYL-2-CYCLOPENTENONES

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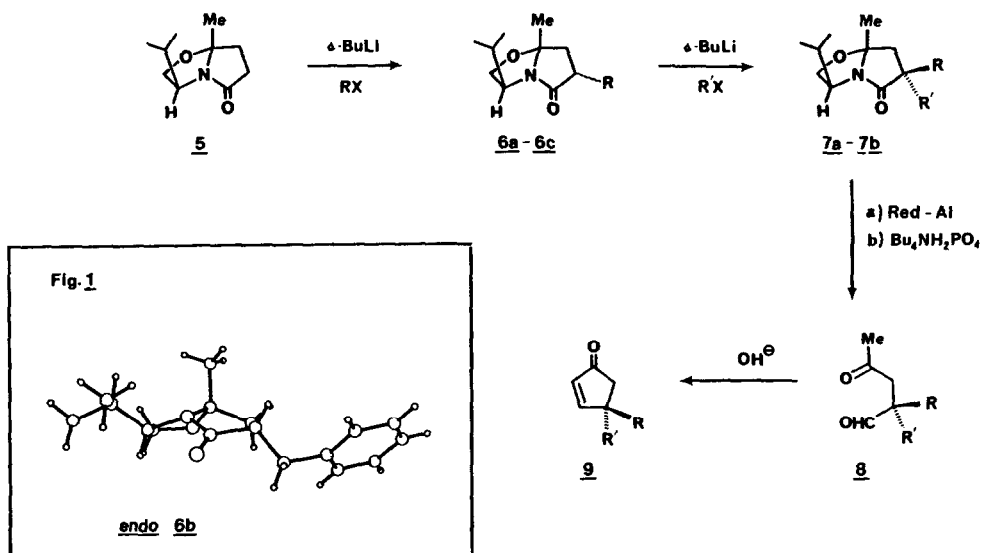
Summary: The chiral bicyclic lactam (5) derived from levulinic acid and (S)-valinol is sequentially alkylated and then cleaved to 2,2-dialkyl levulininaldehyde (8) which is cyclized to the title products (9) in > 99% ee.

We recently reported¹ a novel asymmetric synthesis of 2,2-dialkyl-4-keto carboxylic acids and 3,3-dialkyl-3,4-dihydronaphthalenes based on the bicyclic lactam, 1. The sequential alkylation, leading to 2 occurred with R'X entering from the endo face in



ratios between 10-40:1. Hydrolysis led to either the chiral keto esters 3 or the dihydronaphthalenes 4 in > 99% ee. It occurred to us that this novel method could be extended to cyclopentenones if the phenyl group at the ring junction in 2 was replaced

by methyl (5) and if the cleavage of 2 could be carried out to produce the keto aldehyde (8) rather than the keto acid, 3. The successful implementation of this plan would allow cyclization of the keto aldehyde to the cyclopentenones (8 → 9). This goal was indeed realized and is outlined in this Letter.



The starting lactam 5 was readily prepared by heating levulinic acid (50 mmol) (S)-valinol (50 mmols), and toluene (180 ml) with 10-30 mg p-TsOH and azeotropic removal of water (30-35 h). The lactam was formed in 86% yield; oil, bp 76-80° (0.5 torr) $[\alpha]_D^{25} + 95.48^\circ$ (c 2.8, EtOH) as a single diastereomer whose configuration was verified by X-ray crystallography (Fig. 1). Metalation, using *s*-butyl lithium (1 equiv, THF, -78° C) was followed by addition of the alkyl halide (allyl bromide, benzyl bromide, or ethyl bromide) to give 6 in 85-90% yield, but with poor selectivity (*endo* : *exo* alkyl ratio = 1-1.5:1). The pure *endo*- or *exo* products could be separated and in the case of the 2-benzyl lactams (6, R = PhCH₂), both were crystalline (*endo*-6 mp

70°; exo-6 mp 49-50°). The X-ray (Fig. 1) shows the endo-benzyl group in 6 as well as the syn-relationship of the angular methyl and isopropyl groups. Since the carbon bearing the isopropyl group is known to be *S* all other stereocenters become known with regard to their absolute configurations. This will also allow us to make the stereochemical assignment to the newly created stereocenter generated by the second alkylation step (vide infra). When 6, as a mixture of diastereomers, was metalated (1.05 equiv *s*-BuLi, -78°, THF) and cooled to -100° prior to addition of alkyl halides (Table 1), there was obtained, in 80-90%, the dialkyl lactams 7. The stereoselectivity

Table 1. Dialkylated Lactams 7 and Cyclopentenones 9

<u>6</u> , R	R'X ^a	Dialkyl Lactams <u>7</u>			Cyclopentenones <u>9</u> ^e		
		endo-exo ^b	% yield ^c	% <u>g</u> ^d	%	[α] _D	conf'n
a) Allyl	PhCH ₂ Br	96.7:3.3	77	70	92	-64.1°	<i>S</i>
b) PhCH ₂	Allyl Br	95.1:4.9	63	73	95	+60.9°	<i>R</i>
c) Et	PhCH ₂ Br	94.9:5.1	74	61	91	-78.3°	<i>S</i>

a) 2-3 equiv added to lithiated 6 at -100° C. b) Determined by HPLC on a μ-Porasil column eluted with 5-20% hexane in ethyl acetate. c) Yield of pure diastereomer, 7, from flash chromatography. d) Yield of pure keto aldehyde, after radial chromatography. e) Pure products obtained by radial chromatography (Ethyl acetate-hexane: 1:4). All gave correct combustion analysis and expected 270 MHz ¹H-NMR spectra; specific rotations are 0.4-0.9 in EtOH

of this step was greatly enhanced and the pure diastereomer (if desired) was easily obtained by chromatography. Assignment of the quaternary carbon of the major product was based on the chemical shift of the angular methyl group when the benzyl group is exo or endo. The shielding is very strong and the methyl appears at 0.58-0.61 ppm when the benzyl group is exo (7b) whereas the methyl group shifts to 1.35-1.40 ppm when the benzyl group is endo (7a, c).² In all cases, the alkylation of 6 occurred by endo entry.

The dialkyl lactams 7, purified to a single diastereomer were reduced with Red-Al (0.67 equiv, 0°-25°, THF, 30 min) and cleaved to the keto aldehydes 8, using a 1 M solution of $\text{Bu}_4\text{NH}_2\text{PO}_4$ in aqueous ethanol (1:1) and stirring overnight. The pure keto aldehydes (radial chromatography, silica, ethyl acetate-hexane, 1:4) were treated in THF with 0.25 equiv of ethanolic KOH. After 1 hour the cyclopentenones were isolated in high yield by extraction (hexane) and purified as described in Table 1 (Footnote e).

It is clear that this method will give good yields of 4,4-dialkyl cyclopentenones of high enantiomeric excess (> 99%) and either antipode is accessible by the sequence of alkylation. Further studies on scope and mechanism are in progress.

Acknowledgment

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References and Notes

1. A. I. Meyers, M. Harre, and R. Garland, J. Am. Chem. Soc., **106**, 1146 (1984).
2. From the X-ray structure (Fig. 1), the benzyl group is endo and the pmr spectrum showed the angular methyl singlet at 1.36 ppm. The other diastereomer (exo-benzyl) showed the methyl at 0.58 ppm. This same pattern was seen for all the dialkylated examples 7a-7c.

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