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Synthesis of Non-Racemic 5,5-Disubstituted 2-Cyclopentenones

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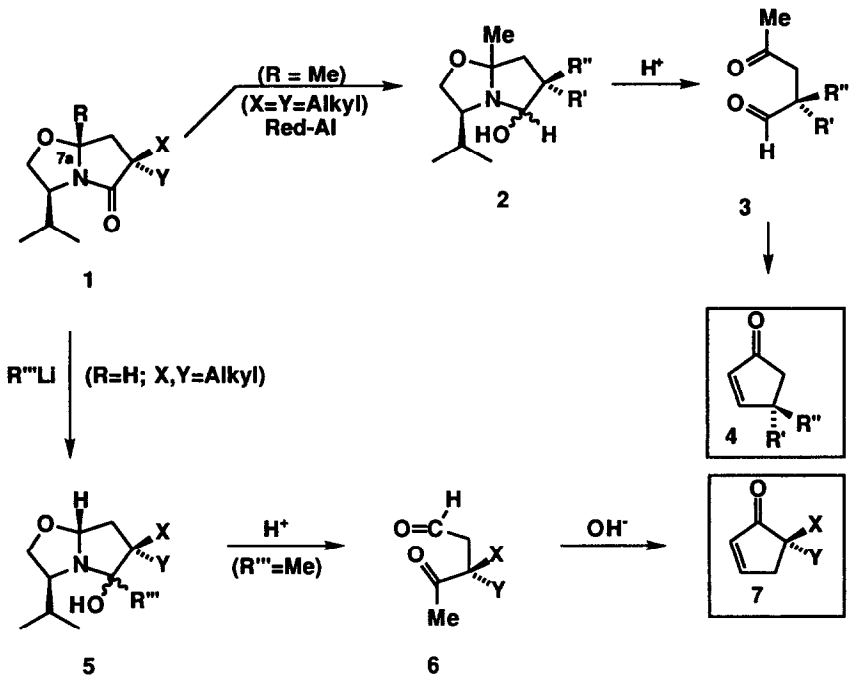
Summary: *Chiral, non-racemic, bicyclic lactam* ***1*** *(X=Y=H) bearing an angular hydrogen at C-7a (****1****, R=H), underwent efficient diastereoselective dialkylation producing the quaternary substituted lactams* ***1*** *(X=Y=alkyl). The latter were transformed into carbinol amines* ***5*** *and then hydrolyzed to the appropriate 1,4-dicarbonyl compound which was cyclized to the title compounds.*

The prevalence of chiral, non-racemic cyclopentanoids in natural products continues to stimulate the development of new methods for the assembly of substituted cyclopentane rings.[1] Chiral, substituted cyclopentenones have also been described and appear to be useful synthetic intermediates.[2,3]

We have reported extensively[3] on the rich chemistry of the chiral bicyclic lactams, **1** (X,Y=H, R=H, Alkyl) and showed that they can be dialkylated efficiently (X,Y = Alkyl) to provide precursors to substituted cyclopentenones, **4** (*via* **2** and **3**). The aminal carbon at 7a was usually methyl-substituted, **1** (R = Me), which makes it a latent methyl ketone whereas if **1** would contain an angular H at C-7a (R = H), it now becomes a latent formyl group (e.g. **6**). Thus, addition of an organometallic, R'''Li, to the carbonyl of **1** (R = H) would give rise to **5** which, upon hydrolysis forms the keto aldehyde, **6** and after basic treatment should lead to the isomeric chiral cyclopentenone, **7**. We now report the successful implementation of the synthetic route to **7** utilizing the readily accessible angular-H lactam **1** (R,X,Y=H).[4] Sequential deprotonation-alkylation of **1** using lithium diisopropylamide (THF, -78° C) gave generally excellent yields of the dialkylated lactams **8** with diastereoselectivity ranging from 76:24 to 94:6 in favor of the endo



alkylation product (Table 1). Thus, the endo-alkyl derivative **8a** was consistently favored after the enolate was generated from the mono-alkyl derivative of **1**. The reason for endo-selective alkylation has been discussed and still remains a clouded issue.[3] It is interesting to note that the selectivity to reach **8** varied by the nature of the electrophile as seen from entries b and e in Table 1. The use of methyl iodide in the second alkylation gave a 94:6 ratio of endo-exo products whereas use of benzyl bromide in the second alkylation gave an 84:16 product ratio. Perhaps the reactivity of the electrophile, if too high, leads to poorer levels of selectivity.[5] The product ratios in the table were readily assessed by following the 7a-proton at the angular position which was very sensitive to the exo-endo ratios. The major diastereomer **8a** was separated *via* flash chromatography (sg, ethyl acetate-hexane) in all cases except entries b and c, which defied separation. These were carried forward as 94:6 and 91:9 mixture respectively to the cyclopentenones.

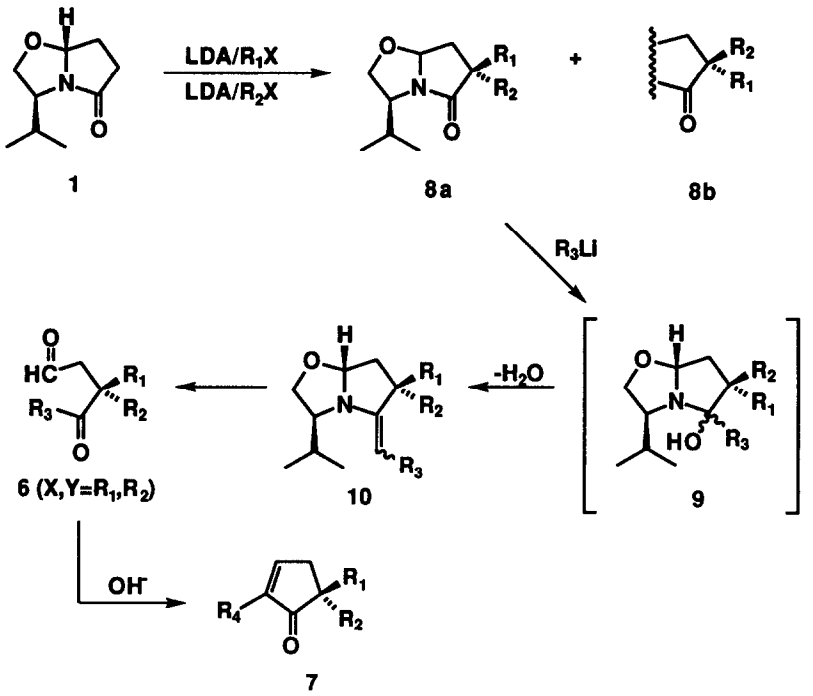
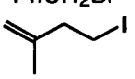
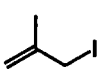


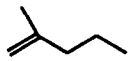
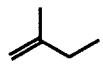
Table 1. Dialkylation of Bicyclic Lactam, 1.

				Product Ratios (NMR)[a]	
Entry	R^1X	R^2X	Yield, (% **8a**·**8b**)	**8a** (endo)	**8b** (exo)
a	MeI	AllylBr	88	76	24
b	$PhCH_2Br$	MeI	99	94	6
c		MeI	93	91	9
d		MeI	95	84	16
e	MeI	$PhCH_2Br$	90	84	16

a) Angular proton at 7a appears at 5.10-4.70 ppm as doublet of doublets and integrated to arrive at ratios.

Addition of 4 equiv of alkyl lithium reagent to **8a** (-78° C to -30° C, THF) gave the presumed carbinol amines **9**, which rapidly underwent dehydration to the enamines, **10**. The instability of the latter dictated that it be subjected to immediate hydrolysis (1M $Bu_4NH_2PO_4$, 20 equiv, EtOH-H_2O, 60° C, 6 h) and afforded the keto aldehydes **6** in satisfactory yields (Table 2).

Table 2. Chiral Non-Racemic Cyclopentenones, 7.

Lactam 8a							
R_1	R_2	R_3Li	%6	R_4	%7	%ee	$[\alpha]_D$[a]
Me	Allyl	MeLi	76	H	75	99	+53.1°
$PhCH_2$	Me	MeLi	65	H	73	89	-82.3[b]
	Me	MeLi	64	H	82	82	-30.2°
	Me	MeLi	48	H	82	99	-61.1°[c]
Me	$PhCH_2$	BuLi	75	n-Pr	73	99	+112°

a) c, 1.2-1.5 in CH_2Cl_2. b) c, 0.42, THF. c) c, 1.42, THF.

Cyclization of the keto aldehydes **6** was accomplished at moderate dilution (0.01 M) in diethyl ether using 5 equiv of 2 M ethanolic NaOH at room temperature for 1.5 h. Catalytic quantities of base gave repeatedly poor yields of **7**. Under these conditions, good yields of the cyclopentenones were obtained and the enantiomeric excesses and $[\alpha]_D$ values are given in the table. The ee's reflect the diastereomeric excesses of the bicyclic lactams **8a**, including the two cases in Table 1 which could not be rendered free from the diastereomers **8b**. These, therefore, are presented as 89 and 82% ee respectively.

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REFERENCES and NOTES.

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3. Romo, D.; Meyers, A. I. *Tetrahedron* **1991**, *47*, 9503 and references therein.
4. Meyers, A. I.; Lefker, B. A.; Sowin, T. J.; Westrum, L. J. *J. Org. Chem.* **1989**, *54*, 4243. At the time this work appeared we were not aware that the synthesis of **1** (X,Y,R=H), although efficient as described, would not be amenable to scale up from (~1 g to 10 g). The yields of the lactam were significantly lower (30-40%) on larger scale. We have now successfully scaled the procedure (~10 g) using Red-Al (toluene) at 0° followed by 2N HCl/EtOH and then 3 equiv formic acid in CH_2Cl_2. Thus, the Red-Al replaced the $NaBH_4$ and the formic acid replaced the trifluoracetic acid in the original procedure described above.
5. For discussion on the reactivity-selectivity principle see March, J. *Advanced Org. Chem.*, Third Edition; J. Wiley & Sons: New York, pp 174-175.

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