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ASYMMETRIC SYNTHESIS OF 4-ALKOXY-4-ALKYLCYCLOHEXEN-2-ONES. APPLICATION TOWARD THE SYNTHESIS OF (+)-ABSCISIC ACID.

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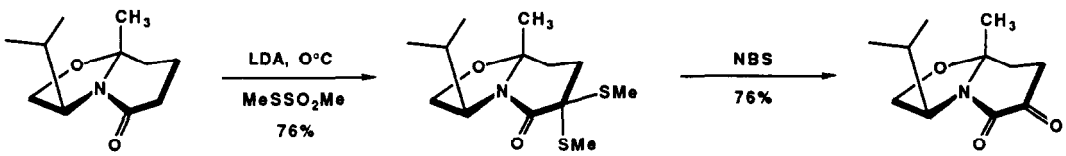
Summary - The chiral bicyclic lactam **3** serves as a useful starting material for the title compounds by steroselective additions with organometallics.

In earlier reports from this laboratory, we have demonstrated the powerful synthetic utility of chiral bicyclic lactams leading to chiral 4,4-substituted cyclopentenones, 4,4-substituted cyclohexenones, and a variety of natural products in high enantiomeric purity.[1] All of the chiral, non-racemic products of these studies had a single fact in common - quaternary carbons at the stereocenter. We now wish to describe further advances using these chiral bicyclic lactams

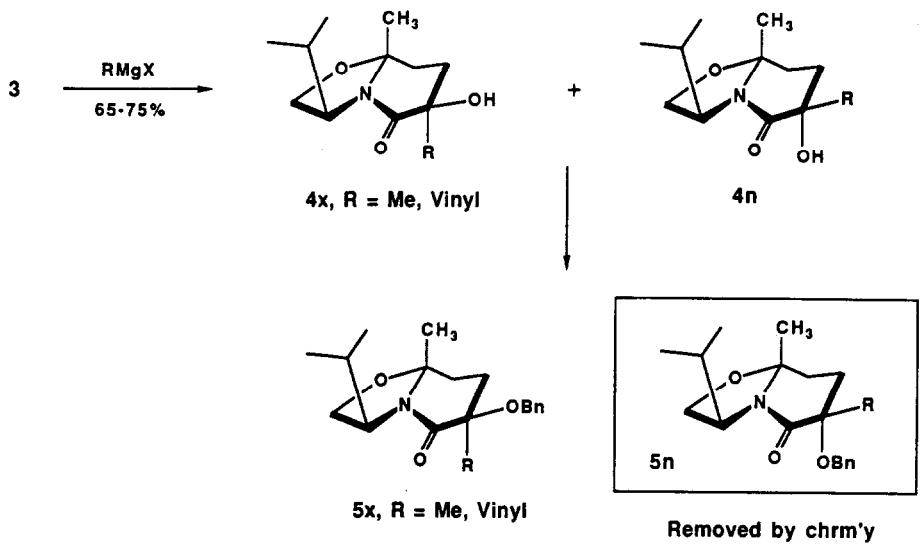


1 **2** **3**

wherein a 3°-alcohol or alkoxy group is placed at the stereocenter, thus demonstrating the potential of this methodology in reaching important natural products.

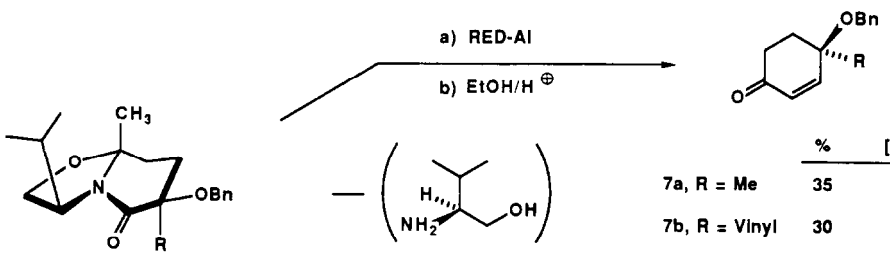
Starting from the bicyclic lactam **1**, readily obtained[2] by condensing S-valinol with 5-ketohexanoic acid, the α-dithiomethyl derivative **2** (mp 80° C, $[\alpha]_D$ = -1.3°, CH_2Cl_2) was obtained in good yield using 2.2 eq LDA and 2.5 eq methythiomethane sulfonate. Treatment of **2** with 8.0 equiv of N-bromosuccinimide (-5° C, acetone, 2.5 h), gave the requisite α-keto lactam **3** (76%, mp 84° C, $[\alpha]_D$ = -56.8°, CH_2Cl_2). Stereoselective addition of methyl magnesium bromide (THF, -100° to -78°, 20 min) to the keto lactam **3** gave the tertiary alcohols **4** (R = Me) as a 7:1 ratio (*via* NMR) of *endo* (**4x**) to *exo* (**4n**). Thus, the Grignard addition was

substantially in favor of *endo* entry by the nucleophile affording **4x**. Similarly, vinyl magnesium bromide gave **4** (R = vinyl) as an 8:1 ratio of diastereomers (**4x**:**4n**). It was not convenient to separate the diastereomers **4x**, **4n** by usual chromatographic means and consequently they were converted into the benzyl ethers (NaH, $PhCH_2Br$, Bu_4NI)[3] whereupon separation was more facile (silica, Hex-EtOAc, 7:1). The assignment of stereochemistry at the tertiary benzyloxy stereocenter was made by proton NOE experiments. Irradiation of the angular methyl group signal produced a small (0.6%) but positive response at the benzylic ether protons. Thus, the major diastereomer **5x** was assigned. The minor isomer **5n** showed no NOE under similar irradiation.



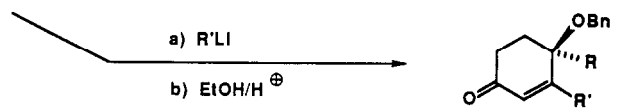
The pure diastereomers **5x** were each subjected to hydride reduction with Red-Al (-42° C, toluene, 48 h). The resulting carbinol amines, derived from reduction of the carbonyl group, were directly hydrolyzed with $Bu_4NH_2PO_4$ in aqueous ethanol[4] affording the cyclohexenones **7a** and **7b**. The enantiomeric purity of **7a** and **7b** is assumed to be > 98% due to the diastereomeric purity of **5x**. Alternatively, the lactams **5x** were treated with methyl or phenyl lithium (0° C, THF, 2.5 h) and the resulting carbonyl adducts were directly hydrolyzed in

aqueous ethanol (reflux, 7.0 equiv $Bu_4NH_2PO_4$). In this fashion, the chiral cyclohexenones **9a-9c** were obtained in 34-57% overall yields (from **5**) and with enantiomeric purity greater than 98%.



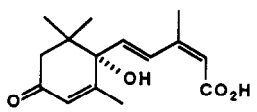
5x (R = Me, Vinyl)

	%	$[\alpha]_D$ (ref. 8)
7a, R = Me	35	+80.4°
7b, R = Vinyl	30	+22.0°

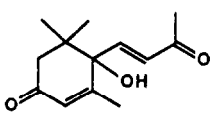


	%	$[\alpha]_D$ (ref. 8)
9a, R = R' = Me	34	+6.2°
9b, R = Vinyl, R' = Ph	40	+76.3°
9c, R = Vinyl, R' = Me	57	-76.6°

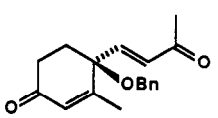
To assess the value of this asymmetric method, we have chosen to target abscisic acid **10**, a sesquiterpene known to be an important substance in regulation of plant dormancy.[5] With the results in hand, we proceeded to synthesize an analog of **11**, an intermediate in a previous total synthesis of racemic abscisic acid.[6] Due to the utilization of S-valinol to prepare **1**, our scheme would lead to the optical antipode, **12**. Furthermore, the latter in this



(+)-10



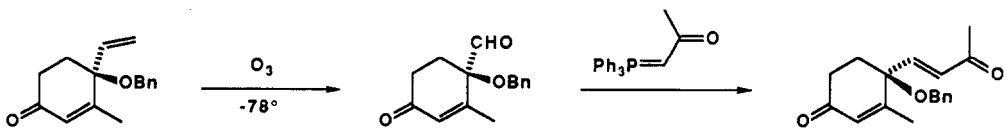
(±)-11



(-)-12

model study would also be devoid of the gem-methyl groups required for the synthesis of **11** and ultimately **10**. Toward this end, the vinyl cyclohexenone **9c** was ozonized (1.0 equiv

pyridine, CH_2Cl_2) to the formyl derivative **13** in 65% yield and then homologated to the target **12** by olefination with acetonylmethylenetriphenyl phosphine[7] [yield, 99%, silica-EtOAc-Hexane 3:1, $[\alpha]_D$ -77.2° (c 0.3, CH_2Cl_2)]. This model study provides considerable



9c **13** **(-)-12**

encouragement to prepare the natural and unnatural abscisic acids by asymmetric synthesis. This work is currently in progress.

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8. It should be noted that all the $[\alpha]_D$'s for **7** and **9** were also obtained in CH_2Cl_2, conc. = 0.1-0.5.

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