Chiral Bicyclic Lactams. A New Study on Facial Alkylation

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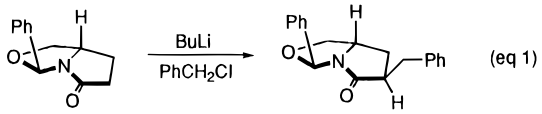
The chiral bicyclic lactams **1** have been shown to be highly useful templates for the asymmetric construction of compounds containing quaternary carbon centers.[2] The major stereochemical event surrounding this methodology was the *endo*-alkylation of the enolate, **2** (Scheme 1). In a large number of cases, the preferred *endo* approach was 10−50:1, yet the reasons for this were vague at best.[2,3] In contrast to other instances[4] where isomeric chiral lactams produced mainly *exo*-alkylated products (eq 1) from their lithium enolate, lactam enolate

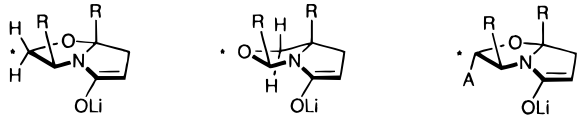


(eq 1)

2 invariably furnished *endo* alkylated products, **3**. The synthetic utility of chiral lactams **3** was amply demonstrated as they were transformed into a host of chiral compounds, including 4,4-dialkylcyclopentenones **4** in high enantiomeric purity.[2,5]

We now report that a slight remote modification in the substitution of lactams **1** has a dramatic effect on the *exo*/*endo* selectivity.[6] First, it is important to note the subtle difference between lactams **1** and that shown in eq 1 (Figure 1). The former (A) contains an oxygen atom at the bridgehead and a methylene group at the starred position. The latter (B) has its oxygen at the starred position and methylene group connected to the bridgehead carbon. When models were constructed[7] of both enolates A and B, they suggested that the *endo* alkylation pathway in B was somewhat inhibited by the psuedoaxial hydrogen projecting down into the concave region. On the other hand, enolate A has an oxygen in place of the methylene and therefore only projects lone pairs. This may not be sufficient to inhibit the *endo* entry in **A**, which is indeed the major pathway.

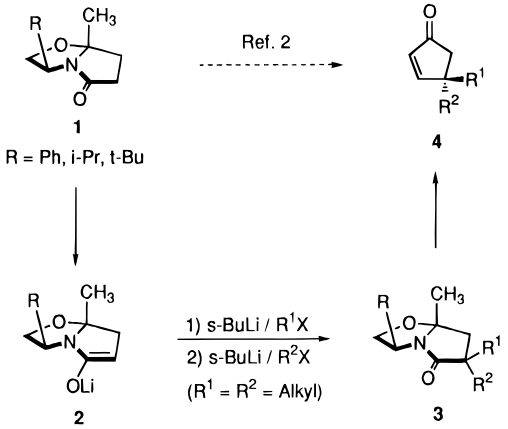
Due to our continued efforts to expand the synthetic scope of the chiral lactams, we were most interested in reversing the order of enolate facial alkylation and felt that addition of a bulky substituent to **A** in the concave region might impede alkylation (enolate C). Since hydrogen in **B** was sufficient to inhibit *endo* alkylation, the trajectory of the alkyl halide toward the enolate must be from a direction between the methylene group and the starred position. Thus, it appeared reasonable that a



(R = Alkyl, H, Aryl, etc.)

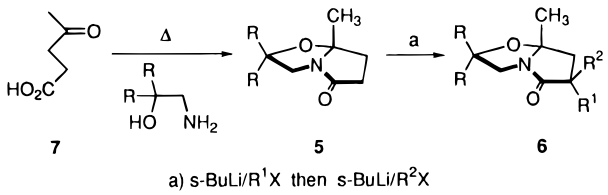
Figure 1.

Scheme 1



group larger than hydrogen in **A** might have the same effect, and this led to consideration of enolate C. If this could be successfully implemented then it would not only expand the synthetic potential for generating the enantiomeric chiral quaternary compounds of **4** but would also go far in explaining the subtlety of the *endo*-alkylation in A and the *exo*-alklylations in B.

Toward this end, we have constructed a series of racemic bicyclic lactams **5** from simple 1,2-amino alcohols[8] and levulinic acid, **7**. It was not necessary at this



juncture to prepare optically active lactams since the only question we were concerned with was the diastereofacial selectivity of **5**. If the notion that properly placed substitutents in **5** was a valid one, then chiral, nonracemic lactams fulfilling this requirement would eventually be evaluated.

As seen from Table 1, lactams containing *gem*-dimethyl (entries 1 and 2), *gem*-diisopropyl (entries 3−5), and *gem*-diphenyl (entries 6−8) all gave, after sequential metalation−alkylation, 94−99% *exo* alkyl products. In the first alkylation step (Table 1, entries 3 and 6) a 94:6 ratio of *exo*/*endo* product **6** ($R_2 = CH_2Ph$, $R_1 = H$) was obtained. It was noted, however, that some epimerization occurred due to difficulty in controlling the amount of excess base present. This effect, as expected, was of no consequence since in the second metalation−alkylation step, epimerization of the doubly alkylated products **6** was not a concern and the diastereoselectivity was >99% exofacial. Furthermore, and of great significance, there was little

(1) Present address: Pfizer Central Research, Groton, CT.

(2) For a review on this subject, see: Romo, D.; Meyers, A. I. *Tetrahedron* **1991**, *47*, 9503. A discussion on the *endo*/*exo* selectivity is presented in this review (pp 9557−9564).

(3) Liotta, D.; Durkin, K. A. *J. Am. Chem. Soc.* **1990**, *112*, 8162.

(4) Thottathill, J. K.; Maniot, J. L.; Mueller, R. H.; Wong, M. K. Y.; Kissick, T. P. *J. Org. Chem.* **1986**, *51*, 3140.

(5) Meyers, A. I.; Wanner, K. Th. *Tetrahedron Lett.* **1985**, *26*, 2047.

(6) For a similar dramatic effect in changing from *endo* to *exo* alkylation see Roth, G. P.; Leonard, S. F.; Tong, L. *J. Org. Chem.* **1996**, *61*, XXXX. We thank Dr. Roth for sharing this information with us prior to publication.

(7) In addition to models, some preliminary molecular modeling studies were also performed that further indicated the steric interference of an alkyl or aryl substituent to alkylation of the enolate carbon.

(8) Evans, D. A.; Carroll, G. L.; Truesdale, L. K. *J. Org. Chem.* **1974**, *39*, 914.

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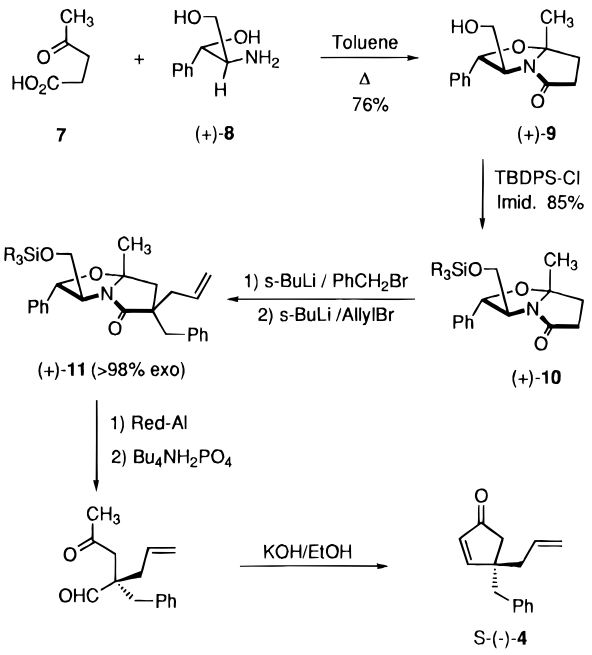
Table 1. Alkylation of Racemic Bicyclic Lactams 5

entry	R	R^1	R^2	*T*/°C	% yield[a]	exo:endo[b,e]
1	Me	Bn	allyl	−78	89	99:1[c]
2	Me	Bn	allyl	0	88	99:1[c]
3	i-Pr	H	Bn	−78	91	96:4[d]
4	i-Pr	Bn	allyl	−78	93	99:1[c]
5	i-Pr	Bn	allyl	0	90	99:1[c]
6	Ph	H	Bn	−78	94	94:6[d]
7	Ph	Bn	allyl	−78	95	99:1[c]
8	Ph	Bn	allyl	0	90	99:1[c]

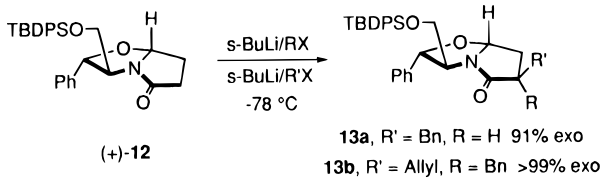
[a] Isolated yield of both diastereomers. [b] Diastereomeric ratio was determined by ^{1}H NMR at 300 MHz. [c] No minor diastereomer could be detected in the ^{1}H NMR spectrum. [d] Epimerization noted. [e] Stereochemistry was determined by the strong shielding effect on angular methyl with the *exo*-benzyl group.

Scheme 2



effect of temperature on the *exo*/*endo* ratio as seen from entries 1, 2, 4, 5, 7, and 8 (Table 1). Thus, comparable ratios of facial selectivity were obtained at −78 or 0 °C, and this was also observed in the β-pinene-derived lactams reported by Roth.[6]

These remarkable results, using simple substituents in the α-face of lactams **5** (from enolate C, Figure 1), were consistent with our preliminary model, and we next proceeded to examine nonracemic lactams. For this task we chose the readily available (+)-amino diol **8** (Aldrich) and transformed it to the bicyclic lactam (+)-**9** in 76% yield by simple reflux in toluene (Scheme 2). The hydroxyl group in the latter was blocked as its *tert*-butyldiphenyl silyl ether, (+)-**10**, and the two-step procedure was performed without the need for chromatographic purification. Sequential metalation−alkylation with benzyl bromide and allyl bromide gave **11** with greater than 98% *exo*-facial selectivity. The allyl group in the second step entered almost exclusively from the *exo* side of **10** due to the presence of the phenyl substituent occupying the concave region. Similar behavior was noted for the chiral lactam containing angular H ((+)-**12**).[9] Thus, metalation and alkylation gave the monoalkyl benzyl product **13a** in a 91:9 *exo*/*endo* ratio, whereas the second metalation−alkylation gave >99% *exo* quaternary substituted material **13b**. These results indicate that the angular substituents (Me *vs* H) appear to have little effect on the approach to the lithium enolate. Again, the stereochemical assignments were made by shielding of the angular substituents by the *exo*-benzyl (aromatic anisotropic shielding). It is noteworthy that once again



the alkylation temperature had little effect on the extent of diastereoselectivity, producing comparable results at either −78 or 0 °C. To further confirm the stereochemical assignments in the chiral lactams, **11** was reduced with Red-Al and hydrolyzed with dihydrogen phosphate to the ketoaldehyde as performed in earlier studies.[2] Aldol cyclization gave (*S*)-(−)-4-allyl-4-benzylcyclopentenone, **4**, the optical antipode to that obtained from **3** (R^1 = CH_2-Ph, R^2 = allyl). This was expected in view of the change in facial alkylation when performing these diastereoselective reactions on **3** or **10**.

In summary, we have determined the basis of *exo* alkylation for particular bicyclic lactams to be steric control. We have also introduced two easily prepared chiral, nonracemic lactams that display excellent *exo* alkylation selectivity and should be of complementary use in the asymmetric construction of quaternary compounds. Further investigation into the understanding of alkylation selectivity in bicyclic lactams is in progress.

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Supporting Information Available: Experimental details, physical data, and ^{1}H and ^{13}C NMR spectra for all new compounds (46 pages).

JO960952G

(9) Meyers, A. I.; Lefker, B. A.; Sowin, T. J.; Westrum, L. J. *J. Org. Chem.* **1989**, *54*, 4243.