Complementary Selectivity in the Alkylation of Chiral Bicyclic Lactam Enolates

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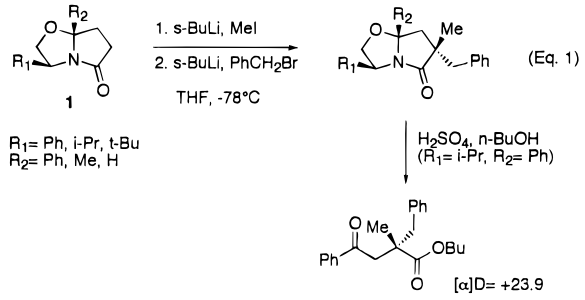
During the past decade Meyers and co-workers have provided the synthetic community with several powerful methods for the asymmetric construction of quaternary chiral centers. One particular vehicle has been the utilization of chiral [3.3.0] bicyclic lactams for the preparation of chiral α-disubstituted γ-keto acids,[1] 3,3-dialkyl-2-cyclopentenones,[2] and 4,4-diakyl-2-cyclohexenones.[3] The alkylation of [3.3.0] bicyclic lactams (**1**) derived from phenylglycinol, valinol, or *tert*-leucinol has been shown to proceed predominately by endo (α) facial attack of the electrophile (Figure 1), and limited mechanistic rationale, based on electronic effects such as the Cieplak effect, has been put forth in order to rationalize this selectivity.[4]



We wish to report a new polycyclic lactam system that offers complementary selectivity upon alkylation; that is, mono- and bis-alkylation is seen to occur with high exo (β) selectivity even at ice-bath and ambient reaction temperatures. Furthermore, the chiral auxilary is derived from readily available (*S*)-α-pinene. In addition, the alkylation selectivities observed are in some cases considerably higher than those obtained with the valinol template.

In conjunction with an on-going project, we have had access to kilogram quantities of the enantiomerically pure oxime derived from inexpensive (*R*)-2-hydroxypinan-3-one (**2**).[5] Reduction of the oxime with lithium aluminum hydride[6] furnished the desired amino alcohol **3** in good yield (eq 2). The corresponding lactams were prepared by heating the appropriate keto acids with **3**, in toluene, with a catalytic amount of *p*-toluenesulfonic acid. This gave the desired diastereomerically pure **4a**−**c** as highly crystalline solids in good to excellent yields after recrystallization from hexanes.

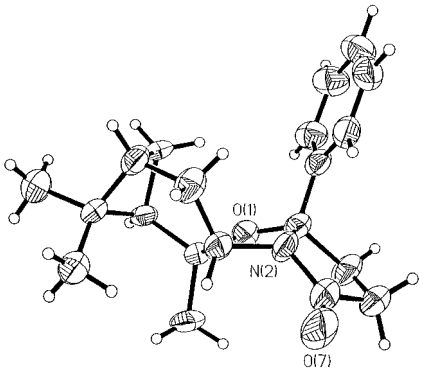
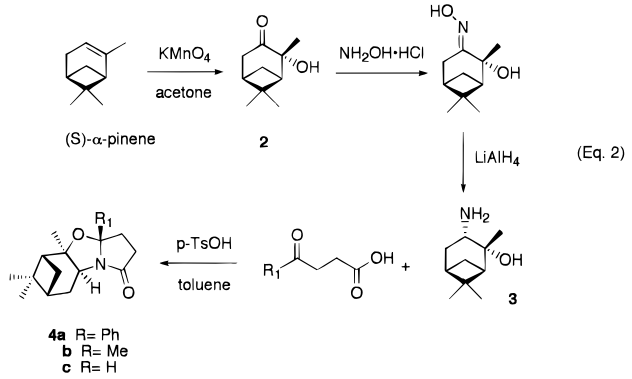
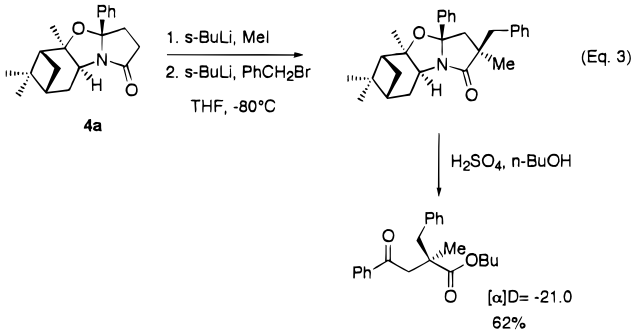


Figure 1. ORTEP diagram of **4a**.



In all three examples only a single diastereomer was formed, and the structures were verified by single-crystal X-ray analysis[7] (for example, **4a** is shown in Figure 1).

Treatment of substrate **4a** with *sec*-butyllithium followed by quenching with iodomethane furnished a single diastereomer as determined by proton NMR. Subsequent enolization of this intermediate with a second equivalent of *sec*-butyllithium and trapping with benzyl bromide again afforded a single diastereomer (**5a**) in 82% yield after recrystallization from hexanes. The dialkylated lactam was then subjected to acidic hydrolysis (eq 3) to



give the desired butyl ester. This ester was found to have an optical rotation opposite of that reported by the Meyers group,[1] indicating that the absolute stereochemistry was opposite (*R* configuration) and that alkylation must have occurred from exo electrophilic attack.

(1) Meyers, A. I.; Harre, M.; Garland, R. *J. Am. Chem. Soc.* **1984**, *106*, 1146−1148. For the most recent comprehensive review see: Romo, D.; Meyers, A. I. *Tetrahedron* **1991**, *47*, 9503−9569.

(2) Meyers, A. I.; Wanner, K. Th. *Tetrahedron Lett.* **1985**, *26*, 2047−2050.

(3) Meyers, A. I.; Lefker, B. A.; Wanner, K. Th.; Aitken, R. A. *J. Org. Chem.* **1986**, *51*, 1936−1938.

(4) Durkin, K. A.; Liotta, D. *J. Am. Chem. Soc.* **1990**, *112*, 8162−8163. Meyers, A. I.; Wallace, R. H. *J. Org. Chem.* **1989**, *54*, 2509−2510.

(5) Carlson, R. G.; Pierce, J. K. *J. Org. Chem.* **1971**, *36*, 2319−2324.

(6) Masui, M.; Shioiri, T. *Tetrahedron* **1995**, *51*, 8363−8370.

(7) Colorless crystals of **4a** belong to the orthorhombic crystal system, space group $P2_12_12_1$, with $a = 7.479(1)$ Å, $b = 14.214(2)$ Å, $c = 16.137(2)$ Å. There are four molecules in the unit cell. The final *R* factor is 4.2%, and the final goodness-of-fit value is 0.78. The author has deposited atomic coordinates for **4a** and **5d** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

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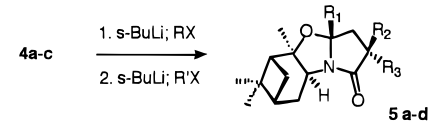
Table 1. Mono- and Bis-Alkylation of Lactams 4a−c



entry (compd)	R^1	R^2	R^3	base[a]	T (°C)	exo:endo[b]
1 (**5a**)	Ph	Bn	Me	*s*-BuLi	−80	>99:1[c]
2	Ph	Me	H	*s*-BuLi	−80	96:4
3	Ph	Me	H	LDA	25	92:8
4	Ph	Bn	H	*s*-BuLi	−80	90:10
5	Ph	Me	Bn	*s*-BuLi	−80	98:2
6	Ph	allyl	Me	*s*-BuLi	−80	>99:1[c]
7 (**5b**)	Me	Me	H	*s*-BuLi	−80	>99:1
8	Me	Me	H	*s*-BuLi	0	97:2
9	Me	Me	H	*s*-BuLi/TMEDA[d]	−80	>98:2
10	Me	Me	H	*s*-BuLi/DMPU[d]	−80	>98:2
11	Me	Me	H	$NaN(TMS)_2$	−80	>98:2
12 (**5c**)	Me	Bn	Me	*s*-BuLi	−80	>99:1
13	H	Me	H	*s*-BuLi	−80	2:1
14	H	Me	H	*s*-BuLi	0	1:1
15 (**5d**)	H	Bn	Me	*s*-BuLi	−80	>99:1[c]

[a] All reactions were conducted at 0.1 M in THF. [b] Diastereomeric ratio determined by ^{1}H NMR at 270 MHz [c] Crude product was recrystallized from hexanes; the minor diastereomer could not be detected in the NMR of the crude product. [d] An excess of 4 equiv of the additive was used.

With this result, a series of experiments were conducted in order to probe the preliminary scope of this alkylation methodology. A summary of the results is provided in Table 1. To our surprise, it was found that substrate **4a** will undergo exo alkylation with good diastereoselectivity even when the reaction is conducted at ambient temperature (Table 1, entry 3). Bis-alkylation of substrates **4b** and **4c** with iodomethane and then benzyl bromide also proceeded in an identical manner (Table 1, entries 12 and 15). The exo selectivity was verified via two methods, ^{1}H NMR spectroscopy[8] and X-ray crystallography. Two-dimensional nuclear Overhauser spectroscopy[9] (NOESY) spectra for **5b** and **c** (Table 1, entries 7 and 12) yield cross peaks from the methyl hydrogens of R^1 to the corresponding methyl hydrogens of R^2 for **5a** and to the aromatic ring hydrogens (2,6) for **5c** (Table 1, entry 12). In addition, NOE cross peaks from hydrogens of R^1, R^2, and or R^3 to regiospecific hydrogens on neighboring and proximal carbon atoms confirm the unambiguous exo substitution. Similar arguments stand true for compound **5d**.

The addition of lithium-aggregate disrupting reagents or use of the sodium enolate did not alter the course of the reaction (Table 1, entries 9−11).

As reported for the [3.3.0] bicyclic lactams,[10] the hydrogen-substituted substrate **4c** did not exhibit the high diastereoselectivity on monoalkylation with iodomethane (Table 1, entry 13). Subsequent re-enolization and quenching with benzyl bromide furnished the quaternary asymmetric center with high selectivity (Table 1, entry 15, **5d**). It is worth noting that the corresponding valinol-derived lactam described by Meyers afforded only a 54% diastereomeric excess (endo attack favored) for the same alkylation sequence.[10] The

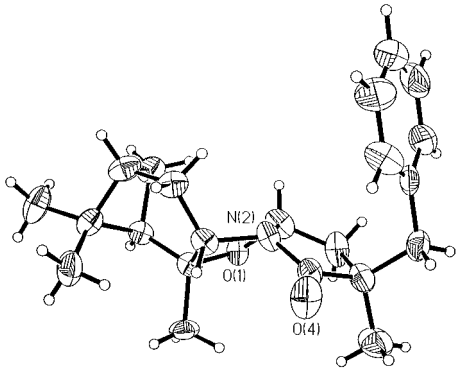


Figure 2. ORTEP diagram of **5d**.

single-crystal X-ray structure of the product (Figure 2)[11] serves as confirmation of the NMR assignment for exo alkylation.

From a mechanistic standpoint, it is not immediately obvious as to the nature of the high exo selectivity of the alkylation reaction. Intuition would suggest a strong steric effect, with the α-face of the enolate fully blocked by either the bridging *gem*-dimethyl groups of the pinene ring system or the axial methyl adjacent to the ring oxygen, thus accounting for the high exo-selectivity even at ambient temperatures. However, the poor monoalkylation selectivity of the hydrogen-substituted lactam **4c** does not fit this rationale, suggesting that there may indeed be an electronic influence on the trajectory of electrophilic attack.

In summary, we have described a "Meyers-type" enolate−lactam system, derived from γ-keto acids, that undergoes asymmetric alkylation in high enantiomeric excess with unprecedented exo selectivity and where the stereochemical induction can occur at unusually warm temperatures. We believe that these observations extend the synthetic utility of the "bicyclic lactam" approach to enantiomerically pure compounds by providing access to complementary enantiomers with a cost-effective template and mild reaction conditions. Also, these observations are of theoretical interest generated by the opposite sense of the selectivity.[12] Work is currently in progress to understand the mechanistic aspects for this selectivity and to extend this methodology to the preparation of more complex systems.

Supporting Information Available: Experimental Procedures and copies of spectra are included (22 pages).

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(8) NMR spectral assignments were performed using 1D and 2D phase-sensitive DQ filtered COSY and NOESY experiments (mixing time of 500 ms at 27 °C in $CDCl_3$ at 500 or 600 MHz (approximately 3−5 mg/mL)).

(9) Jeener, J.; Meier, B. H.; Bachmann, P.; Ernst R. R. *J. Chem. Phys.* **1979**, *71*, 4546−4553.

(10) Lefker, B. A. Ph.D. Dissertation, Colorado State University, Fort Collins CO, 1988.

(11) Colorless crystals of the product **5d** belong to the orthorhombic crystal system, space group $P2_12_12_1$, with a = 7.764(1) Å, b = 10.568(3) Å, c = 23.395(7) Å. There are four molecules in the unit cell. The final R factor is 6.8% and the final goodness-of-fit value is 2.02.

(12) A single related example has been reported in the literature to give specific exo alkylation but was shown to readily epimerize to a 1:1 exo/endo mixture under thermodynamic conditions. Thottathil, J. K.; Moniot, J. L.; Mueller, R. H.; Wong, M. K. Y.; Kissik, T. P. *J. Org. Chem.* **1986**, *51*, 3140−3147. With our lactam system this is not the case. Treatment of the methylated lactam **5b** at ambient temperature with sodium methoxide in methanol for 18 h only epimerized the newly formed chiral center to a small extent, furnishing **5b** with a 10:1 exo/endo ratio. This is essentially identical to entry 3 in Table 1.