

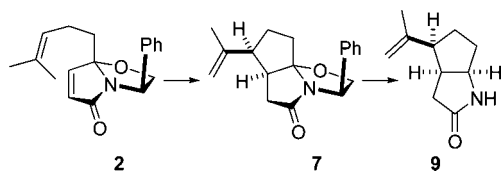
Intramolecular Ene Reaction of a Chiral Bicyclic Lactam¹

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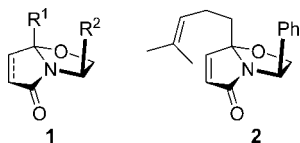
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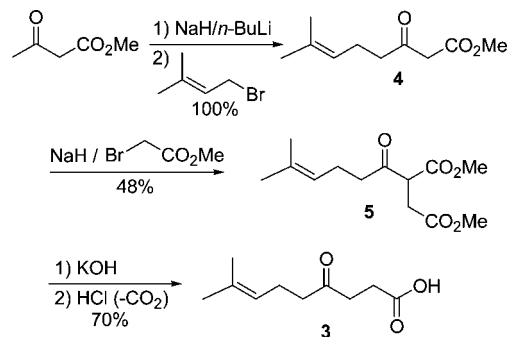
The preparation of bicyclic lactam **2** is described, employing an acetoacetate-based synthesis of 1,4-ketoacid **3**. The lactam **2** was shown to undergo a thermal ene reaction at 280–300 °C to afford tricycle **7**. Reduction of the ene product followed by removal of the chiral auxiliary fragment provided the unusual lactam system **9** in highly enantioenriched form.

Intramolecular pericyclic reactions are a powerful method for the construction of carbocycles and heterocycles. As part of the Meyers research program directed toward elucidation of the chemistry of chiral bicyclic lactams of type **1**,² the possibility of performing an intramolecular ene reaction³ on an appropriately substituted framework was investigated. In the envisioned system the C–C double bond of the unsaturated lactam **2** would act as the enophile, being activated by the carbonyl; and the ene component (CH₂C=CMe₂) would be appended onto the angular position, R¹. Herein the successful execution of such an ene process is described, thus serving to expand the portfolio of highly enantioenriched products available from the bicyclic lactam template.

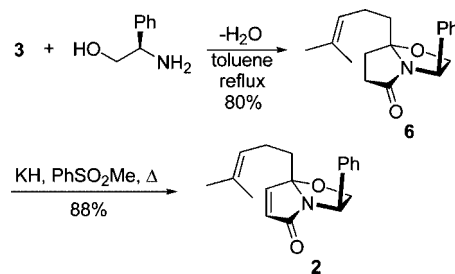


The most common method employed for the synthesis of saturated lactams of type **1** is a simple cyclodehydration reaction between a 1,4-ketoacid and the appropriate chiral nonracemic aminoalcohol.^{2a} When desired, unsaturated lactam rings can be prepared subsequently by common carbonyl dehydrogenation techniques. As such, synthesis of the target ene-substrate lactam **2** required the preparation of the ketoacid **3**, and the latter was

SCHEME 1



SCHEME 2



made as shown in Scheme 1.⁴ Thus, formation of the dianion derived from methyl acetoacetate by sequential treatment with NaH and *n*-BuLi⁵ followed by addition of 3-methyl-1-bromo-2-butene gave the elaborated ketoester **4** in 100% crude yield. Treatment of **4** with NaH and methyl bromoacetate provided **5** in 48% yield. Saponification followed by acidification resulted in decarboxylation to give the desired 1,4-ketoacid **3** in about 70% yield.⁶

The requisite saturated bicyclic lactam **6** was prepared in 80% yield by heating an equimolar mixture of ketoacid **3** and (*R*)-phenylglycinol in toluene with azeotropic removal of water (Scheme 2). Oxidation of this lactam to the corresponding α,β -unsaturated lactam *via* the selenoxide was somewhat capricious, providing yields of 29–65%. The yield and reproducibility of this transformation were significantly improved by treatment

(1) Dedicated to the memory of Professor Albert I. Meyers.

(2) Reviews: (a) Romo, D.; Meyers, A. I. *Tetrahedron* **1991**, *47*, 9503. (b) Meyers, A. I. *Stereocontrolled Org. Synth.* **1994**, 145–175. More recent work: (c) Meyers, A. I.; Downing, S. V.; Weiser, M. J. *J. Org. Chem.* **2001**, *1413*–1419. (d) Meyers, A. I.; Andres, C. J.; Resek, J. E.; Woodall, C. C.; McLaughlin, M. A.; Lee, P. H.; Price, D. A. *Tetrahedron* **1999**, *55*, 8931–8952. (e) Lemieux, R. M.; Devine, P. N.; Mechelke, M. F.; Meyers, A. I. *J. Org. Chem.* **1999**, *64*, 3585–3591. (f) Groaning, M. D.; Brengel, G. P.; Meyers, A. I. *J. Org. Chem.* **1998**, *63*, 5517–5522. (g) Schwarz, J. B.; Meyers, A. I. *J. Org. Chem.* **1998**, *63*, 1619–1629. (h) Fray, A. H.; Meyers, A. I. *J. Org. Chem.* **1996**, *61*, 3362–3374. (i) Munchhof, M. J.; Meyers, A. I. *J. Org. Chem.* **1995**, *60*, 7084–7085.

(3) For a general ene reaction review, see: (a) Mikami, K.; Shimizu, M. *Chem. Rev.* **1992**, *92*, 1021–1050. Reviews focusing on intramolecular ene reactions: (b) Oppolzer, W.; Snieckus, V. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 476–486. (c) Conia, J. M.; Le Perche, P. *Synthesis* **1975**, 1–19. (d) Taber, D. F. *Intramolecular Diels-Alder and Alder Ene Reactions*; Springer Verlag: Berlin, 1984.

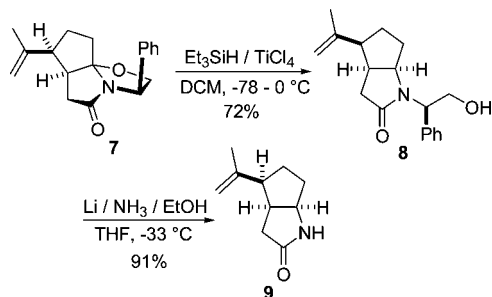
(4) Brown, E.; Guilmet, E.; Touet, J. *Tetrahedron* **1973**, *29*, 2589–2596.

(5) Hucklin, S. N.; Weiler, L. *J. Am. Chem. Soc.* **1974**, 1082–1087.

(6) The mass yield obtained was 84%, but the product clearly contained ethanol and diethyl ether impurities. The material was estimated to have ca. 85% weight purity by ¹H NMR. The presence of the solvents does not affect the subsequent reaction, and they were not rigorously removed.

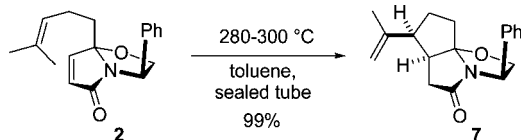
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SCHEME 3



of **6** with potassium hydride and methyl phenylsulfinate followed by thermal elimination of the resulting mixture of diastereomeric sulfoxide substituted lactams.⁷ This reaction provided the desired unsaturated lactam **2** in 88% yield. Analysis of both compounds **6** and **2** by ¹H and ¹³C NMR indicated the presence of a single diastereomeric form, which is the normal result when [3.3.0] fused bicyclic lactams of this type are prepared.^{2a}

The thermal ene reaction of **2** was executed in toluene solution in a sealed tube. The reaction proceeded smoothly at 280–300 °C (bath temperature) to provide the expected tricyclic product **7** in 99% yield. The reaction did in fact proceed at lower temperatures (190–250 °C), but the rate was impractically low. As might be expected in a reaction performed under such conditions, we observed a strong qualitative correlation between the purity of the starting material and the success of the reaction. Thus, in cases where pure and colorless **2** was employed, the product was analytically pure after simple concentration of the reaction solution. Starting material of lower purity and with more color tended to undergo higher levels of decomposition.



Attempts were made to promote this reaction with Lewis acids (TiCl₄, MeAlCl₂, Me₂AlCl), but in all cases decomposition of the lactam **2** was competitive with product formation and product mixtures were obtained.

Cleavage of the chiral auxiliary from lactam **7** was accomplished as shown in Scheme 3. The process began with the triethylsilane-TiCl₄ reduction reported by Burgess and Meyers.⁸ Treatment of lactam **7** with these reagents resulted in smooth reduction of the angular center to provide the expected bicyclic lactam **8** in 72% yield. Analysis of the crude mixture showed a single diastereomeric product. In previous work on this transformation, retention of configuration at the reduction center was the consistent result.⁸ To the extent the transition state is product-like, the present case favors retention of configuration to an even greater degree, as inversion would lead to a significantly more strained *trans*-fused [3.3.0] ring system.⁹ The stereochemical result of this reaction was confirmed after removal of the phenethanol fragment in the final step of the sequence. This was accomplished by treatment with lithium metal in liquid ammonia, which furnished the unusual bicyclic lactam **9** in 91% yield.¹⁰

The relative stereochemistry in the lactam **9** was determined by measurement of NOE enhancements between the protons on the stereogenic carbon atoms. This analysis indicated an all-*cis* relationship between the protons on the stereogenic carbon atoms, as shown. Given the rigidity of the bicyclic lactam system, this would be the expected stereochemical outcome if the ene reaction follows the thermal pericyclic pathway.^{3a}

The present work serves as yet another example of a potentially useful extension of the chiral bicyclic lactam methodology, that being exploitation of an intramolecular cycloaddition process on an angularly functionalized lactam template.

Experimental Section

6-Isopropenyl-3-phenylhexahydro-1-oxa-3a-azacyclo-penta[*c*]-pentalen-4-one (7). A solution of **2** (305 mg, 0.16 mmol) in toluene (20 mL) was sealed in a thick-walled glass tube and heated in a 280–300 °C oil bath for 12 h. The solution was cooled and analyzed by TLC (2/1 hexanes/EtOAc) to confirm completion of the reaction. The solution was concentrated by rotary evaporation to provide lactam **7** (302 mg, 99%) as a tan solid. mp 175–177 °C. [α]_D = –200.0° (*c* = 0.85 in CHCl₃). ¹H NMR (CDCl₃) δ 1.60–1.74 (m, 2H), 1.70 (s, 3H), 1.84 (m, 1H), 2.05 (m, 1H), 2.51 (m, 2H), 2.71 (m, 1H), 2.89 (m, 1H), 4.02 (dd, *J* = 8.6, 7.4 Hz, 1H), 4.59 (t, *J* = 8.2 Hz, 1H), 4.73 (s, 1H), 4.90 (q, *J* = 1.3 Hz, 1H), 5.16 (t, *J* = 7.6 Hz, 1H), 7.13–7.35 (m, 5H); ¹³C NMR (CDCl₃) δ 22.8, 26.5, 34.3, 43.6, 47.7, 57.5, 73.2, 109.6, 111.6, 125.6, 127.4, 128.7, 139.6, 144.3, 179.8. Anal. calcd for C₁₈H₂₁NO₂: C, 76.30; H, 7.47. Found: C, 76.15; H, 7.44.

1-(2-Hydroxy-1-phenylethyl)-4-isopropenylhexahydro-cyclo-penta[*b*]pyrrol-2-one (8). To a CH₂Cl₂ (2 mL) solution of the tricyclic lactam **7** (51 mg, 0.18 mmol) and triethylsilane (67 mg, 92 μ L, 0.58 mmol, 3.2 equiv) at –78 °C was added TiCl₄ (75 mg, 43 μ L, 0.40 mmol, 2.2 equiv). The resulting yellow solution was stirred at –78 °C for 1 h and allowed to warm to 0 °C over 2 h (Note: extended stirring or higher temperatures resulted in apparent migration of the double bond). The reaction was quenched by addition of saturated NH₄Cl (20 mL) and diluted with CH₂Cl₂ (10 mL). The mixture was stirred for 10 min and the layers were separated. The aqueous portion was extracted with CH₂Cl₂ (3 \times 20 mL), and the combined organic solutions were washed with saturated NaCl (20 mL), dried (Na₂SO₄), and concentrated. The crude product was purified by flash chromatography (1/1 hexane/EtOAc) to give **8** (37 mg, 72%). ¹H NMR (CDCl₃) δ 1.4–1.8 (m, 4H), 1.67 (s, 3H), 2.28 (dd, *J* = 18.3, 6.7 Hz, 1H), 2.40 (m, 1H), 2.41 (dd, *J* = 10.7, 18.3 Hz, 1H), 2.90 (m, 1H), 3.96 (m, 2H), 4.27 (m, 1H), 4.42 (dd, *J* = 7.8, 3.5 Hz), 4.60 (br, 1H), 4.71 (s, 1H), 4.88 (s, 1H), 7.20–7.36 (m, 5H); ¹³C NMR (CDCl₃) δ 22.9, 25.7, 30.6, 32.8, 36.5, 49.9, 62.9, 64.1, 64.4, 111.7, 127.4, 127.9, 128.7, 137.3, 144.0, 176.6. GC/MS: 285(1, M⁺), 254(100), 212(13), 166(24), 91(48).

4-Isopropenylhexahydrocyclopenta[*b*]pyrrol-2-one (9). To a flask containing a glass-covered magnetic stirbar was charged a THF (3 mL) solution of lactam **8** (68 mg, 0.238 mmol). The flask was fitted with a dry ice-acetone cooled coldfinger condenser and liquid ammonia (ca. 20 mL) was condensed into the flask. To the solution was added ethanol (0.1 mL) followed by a freshly cut piece of lithium metal (20 mg). After a few minutes the solution became dark blue in color, and stirring was continued under ammonia reflux (–33 °C) for 4 min. The reaction was quenched by addition of solid ammonium chloride (vigorous bubbling/foaming was observed). The ammonia was allowed to evaporate and water (10 mL) was added. The mixture was extracted with CH₂Cl₂ (4 \times 15 mL), and the combined organic solutions were washed with saturated NaCl (20 mL), dried (Na₂SO₄), and concentrated. The residue was purified by flash chromatography (EtOAc) to give **9** (36 mg, 91%) as a colorless solid. [α]_D = –34.2° (*c* = 0.65 in CHCl₃). ¹H NMR

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(8) Burgess, L. E.; Meyers, A. I. *J. Org. Chem.* **1992**, 57, 1656.

(9) See, for example: Lautens, M.; Ren, Y. *J. Am. Chem. Soc.* **1996**, 118, 10668–10669, and references cited therein.

(CDCl₃) δ 1.55–1.70 (m, 4H), 1.66 (s, 3H), 2.06 (dd, $J = 18.2$, 5.6 Hz, 1H), 2.20 (dd, $J = 18.2$, 10.6 Hz, 1H), 2.41 (br m, 1H), 2.97 (m, 1H), 4.13 (m, 1H), 4.69 (s, 1H), 4.86 (s, 1H), 6.70 (br, 1H); ¹³C NMR (CDCl₃) δ 22.9, 25.5, 31.2, 33.8, 38.5, 50.4, 58.6, 111.7, 144.4, 178.6. IR (film) cm⁻¹ 3395, 3181, 1661, 1329, 1290, 897. GC/MS 165(97, M⁺), 150(12), 136 (27), 122 (38), 108 (59), 96 (100), 83 (66), 55 (76). Anal. calcd for C₁₀H₁₅NO: C, 72.69; H, 9.15. Found: C, 72.50; H, 9.11.

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Supporting Information Available: Experimental procedures for compounds **2–6**, and ¹H and ¹³C NMR spectra for compounds **2–9**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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