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Intramolecular Ene Reaction of a Chiral Bicyclic Lactam[1]

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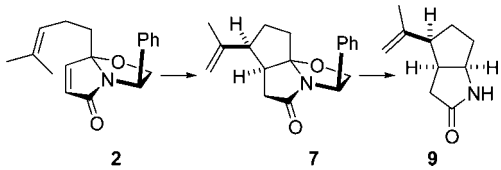
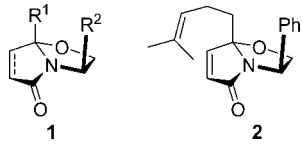
Received August 12, 2008



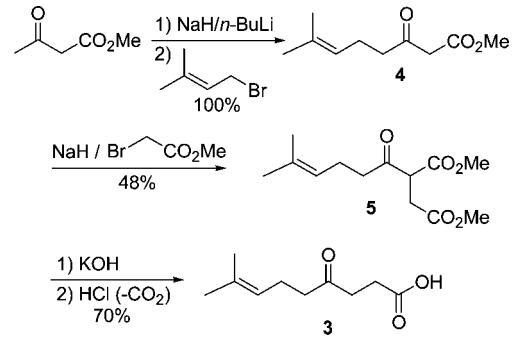
The preparation of bicylic lactam **2** is described, employing an acetoacetate-based synthesis of 1,4-ketoacid **3**. The lactam **2** was shown to undergo a thermal ene reaction at 280−300 °C to afford tricycle **7**. Reduction of the ene product followed by removal of the chiral auxiliary fragment 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 reaction[3] 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 eneophile, being activated by the carbonyl; and the ene component ($CH_2C{=}CMe_2$) would be appended onto the angular position, R^1. 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.

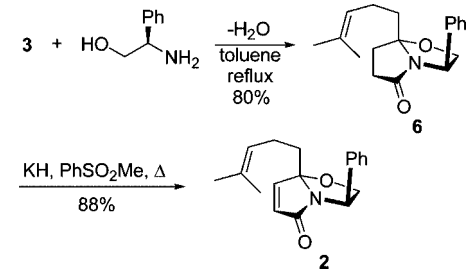


The most common method employed for the synthesis of saturated lactams of type **1** is a simple cyclodehydration reaction between a 1,4-ketoacid and the appropriate chiral nonracemic aminoalcohol.[2a] When desired, unsaturated lactam rings can be prepared subsequently by common carbonyl dehydrogenation techniques. As such, synthesis of the target ene-substrate lactam **2** required the preparation of the ketoacid **3**, and the latter was made as shown in Scheme 1.[4] Thus, formation of the dianion derived from methyl acetoacetate by sequential treatment with NaH and *n*-BuLi[5] 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 bromoaceate 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]

SCHEME 1



SCHEME 2



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

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(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 Perchec, P. *Synthesis* **1975**, 1–19. (d) Taber, D. F. *Intramolecular Diels-Alder and Alder Ene Reactions*; Springer Verlag: Berlin, 1984.

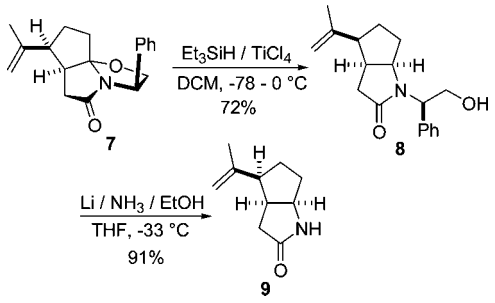
(4) Brown, E.; Guilmet, E.; Touet, J. *Tetrahedron* **1973**, *29*, 2589–2596.

(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 ^{1}H NMR. The presence of the solvents does not affect the subsequent reaction, and they were not rigorously removed.

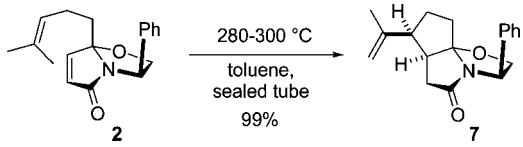
10.1021/jo801696r CCC: $40.75
Published on Web 11/01/2008

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 ^{1}H and ^{13}C 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 ($TiCl_4$, $MeAlCl_2$, Me_2AlCl), 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-$TiCl_4$ 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]

(7) Resek, J. E.; Meyers, A. I. *Tetrahedron Lett.* **1995**, 7051–7054.
(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.

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. $[\alpha]_D$ = −200.0° (c = 0.85 in $CHCl_3$). ^{1}H NMR ($CDCl_3$) 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); ^{13}C NMR ($CDCl_3$) 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 $C_{18}H_{21}NO_2$: 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 CH_2Cl_2 (2 mL) solution of the tricyclic lactam **7** (51 mg, 0.18 mmol) and triethylsilane (67 mg, 92 μL, 0.58 mmol, 3.2 equiv) at −78 °C was added $TiCl_4$ (75 mg, 43 μL, 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 NH_4Cl (20 mL) and diluted with CH_2Cl_2 (10 mL). The mixture was stirred for 10 min and the layers were separated. The aqueous portion was extracted with CH_2Cl_2 (3 × 20 mL), and the combined organic solutions were washed with saturated NaCl (20 mL), dried (Na_2SO_4), and concentrated. The crude product was purified by flash chromatography (1/1 hexane/EtOAc) to give **8** (37 mg, 72%). ^{1}H NMR ($CDCl_3$) 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); ^{13}C NMR ($CDCl_3$) 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 CH_2Cl_2 (4 × 15 mL), and the combined organic solutions were washed with saturated NaCl (20 mL), dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography (EtOAc) to give **9** (36 mg, 91%) as a colorless solid. $[\alpha]_D$ = −34.2° (c = 0.65 in $CHCl_3$). ^{1}H NMR

($CDCl_3$) 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); ^{13}C NMR ($CDCl_3$) 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 $C_{10}H_{15}NO$: C, 72.69; H, 9.15. Found: C, 72.50; H, 9.11.

Acknowledgment. This work was supported by the National Institutes of Health.

Supporting Information Available: Experimental procedures for compounds **2**−**6**, and ^{1}H and ^{13}C 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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(10) For related compounds: Bartmann, W.; Rupp, H.; Beck, G.; Knolle, J. German Patent DE2947493, 1981.