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An asymmetric synthesis of the key precursor to (–)-indolizomycin

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Abstract

Using chiral bicyclic lactams, containing an α,β-unsaturation, the key precursor of (–)-indolizomycin was obtained in optically pure form. The sequence involved a >20:1 diastereoselective cyclopropanation of the unsaturated lactam **5** employing sulfoxonium methylide. $TiCl_4$ mediated addition of allyltrimethylsilane afforded pyrrolidone **7** in a diastereomeric ratio of >20:1. The appropriately substituted pyrrolidone **2** was prepared by debenzylation and subsequent alkylation with 3-bromoproponic ester. The six step sequence from commercially available starting materials was performed in 26% overall yield.

The chiral, nonracemic bicyclic lactam (e.g. **4**) has been utilized extensively in the total synthesis of optically pure alkaloids and carbocycles.[1] These applications have allowed us to demonstrate the variety of structures accessible via the bicyclic lactam template and provided insight into the reactivity and selectivity displayed by these systems. In our continuing efforts to expand the utility of the bicyclic lactam, we wish to report the formal synthesis of (–)-indolizomycin **1**. Indolizomycin is a bioengineered antibiotic obtained from the protoplast fusion of *Streptomyces tenjimariensis* and *Steptomyces grisline*.[2] Although the antibacterial properties are not exceptional, the structural complexity enticed Danishefsky to undertake its racemic synthesis.[3] Examination of Danishefsky's efforts revealed that the key racemic intermediate **2** would be an excellent target obtainable in optically pure form utilizing bicyclic lactam methodology (Scheme 1).

The construction of the requisite unsaturated bicyclic lactam **5** was accomplished by heating (*R*)-phenylglycinol with succinic anhydride affording the imide **3** in good yield (Scheme 2). The imide was selectively reduced with ethanolic sodium borohydride and subsequent acidification produced bicyclic lactam **4** in excellent yield. Introduction of the unsaturation required in **5** was accomplished via treatment of the potassium enolate of **4** with methylphenylsulfinate followed by heating in toluene as described previously.[4] Treatment of the bicyclic lactam **5** with sulfoxonium methylide[5] provided the cyclopropyl substituted bicyclic lactam **6** in 80% yield as a 20:1 mixture of diastereomers. The *exo* entry of the methylene group to **5** was in agreement with earlier reports which showed that the *exo* cycloaddition

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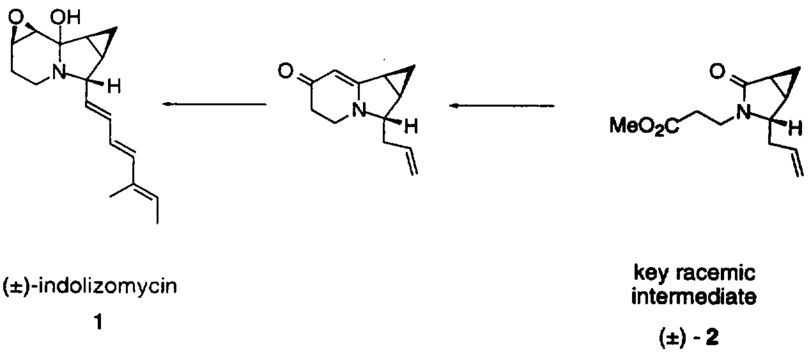
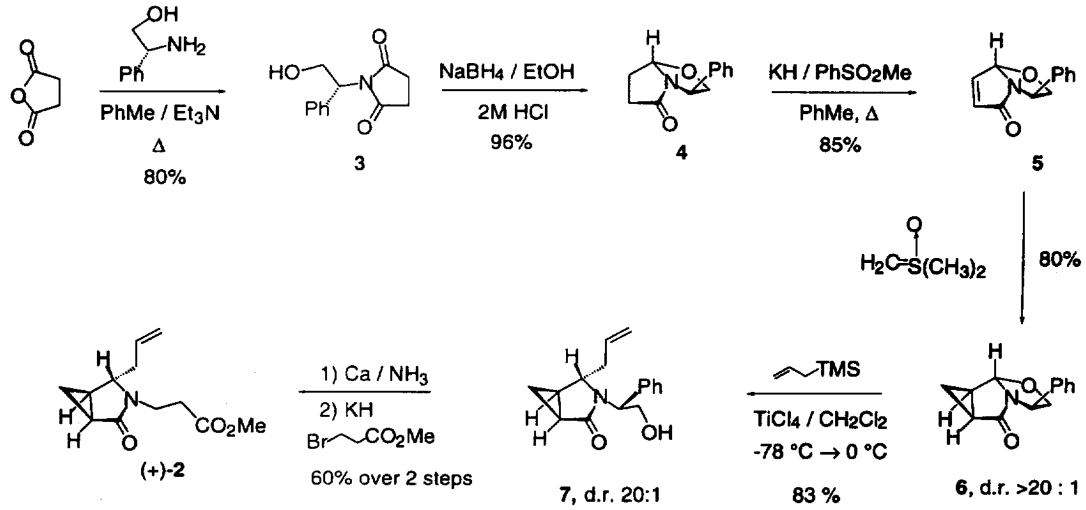


Scheme 1.

products predominate when the angular substituent is hydrogen.[6] The reverse (*endo* entry) was found when the angular substituents were larger (e.g. methyl, phenyl). Cyclopropyl derivative **6** was treated with allyltrimethylsilane in the presence of stoichiometric $TiCl_4$ to effect addition at the angular position providing **7** in 83% yield as a 20:1 mixture of diastereomers.[7] The synthesis was completed by the removal of the auxiliary with Ca/NH_3 followed by *N*-alkylation (KH, methyl 3-bromopropionate) to afford (+)-**2** in 60% overall yield from **7**.



Scheme 2.

The optical purity of substituted lactam (+)-**2** was determined using chiral GLC (Chiraldex G-PN, 30 m, 170°C isotherm) and was found to be >99% e.e. by comparison to a racemic sample.[8] All physical and spectral data were identical to those reported earlier.[3]

Two key observations were made during this work: (1) the cyclopropyl moiety in **6** appears to be a very important steric determinant in the stereoselectivity of allylsilane addition to the angular position; and (2) the mildness of the calcium metal reductive debenzylation of lactam **7** in the presence of other reducible groups, which proved to be very efficient for accessing the *N*-unsubstituted pyrrolidinone. This reduction has previously been employed in our laboratories for the preparation of (–)-rolipram where it was observed that use of the sodium, lithium, or potassium–ammonia systems consistently provided lower yields.[9]

In summary, we have completed an asymmetric synthesis of the key precursor to (–)-indolizomycin, extending the utility of conformationally constrained bicyclic lactams.[10,11]

Acknowledgements

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References

1. (a) Romo, D.; Meyers, A. I. *Tetrahedron* **1991**, *47*, 9503. (b) Meyers, A. I.; Brengel, G. P. *Chem. Commun.* **1997**, 1.
2. (a) Yamashita, F.; Hotta, K.; Kurasawa, S.; Okami, Y.; Umezawa, H. *J. Antibiot.* **1985**, *38*, 58. (b) Gomi, S.; Ikeda, D.; Nakamura, H.; Naganawa, H.; Yamashita, F.; Hotta, K.; Kondo, S.; Okami, Y.; Umezawa, H.; Iitaka, Y. *J. Antibiot.* **1984**, *37*, 1491.
3. Kim, G.; Chu-Moyer, M. Y.; Danishefsky, S. J.; Schulte, G. K. *J. Am. Chem. Soc.* **1993**, *115*, 30.
4. Resek, J. G.; Meyers, A. I. *Tetrahedron Lett.* **1995**, *36*, 7051.
5. Corey, E. J.; Chaykovsky, M. J. *J. Am. Chem. Soc.* **1965**, *87*, 1353.
6. (a) Romo, D.; Romine, J. L.; Midura, W.; Meyers, A. I. *Tetrahedron* **1990**, *46*, 1936. (b) Meyers, A. I.; Romine, J. L.; Fleming, S. A. *J. Am. Chem. Soc.* **1989**, *110*, 7245.
7. Meyers, A. I.; Burgess, L. E. *J. Org. Chem.* **1991**, *56*, 2294.
8. A racemic sample of (1α,2α,5α)-(–)-2-(2-propenyl)-4-oxo-3-azabicyclo[3.1.0]hexane-3-propanoic acid methyl ester was provided by Professor Danishefsky.
9. Meyers, A. I.; Snyder, L. *J. Org. Chem.* **1993**, *58*, 36.
10. Combustion analyses were performed by Atlantic Microlabs Inc., Norcross, GA. High resolution mass spectra were obtained from U.C.-Riverside.
11. **Key experimental: (i) Allyl lactam (–)-7.** To a round bottomed flask was added 13 mL of $TiCl_4$ (1.0 M in CH_2Cl_2) under an argon atmosphere and the solution was cooled to –78°C. A CH_2Cl_2 solution of **6** (1.05 g, 4.8 mmol in 15 mL) was added via a syringe followed by a CH_2Cl_2 solution of allyltrimethylsilane (3.24 mL, 20.4 mmol in 10 mL). The reaction was slowly allowed to warm to rt over a period of 5 h at which time solid $NaHCO_3$ was carefully added. The mixture was partitioned between H_2O and CH_2Cl_2, the aqueous layer was extracted with CH_2Cl_2 (3×50 mL), the combined organic layers were dried over Na_2SO_4 and concentrated in vacuo to give an oil. ^1H NMR of crude product showed a 20:1 mixture of addition products by integration of the methine proton α to the lactam nitrogen (δ major: 3.38 ppm, minor: 3.63 ppm). Column chromatography (50% ether/hexane) of the residue provided 1.02 g of **7** (83%) as a colorless solid: mp 63–64°C; $[\alpha]_D=-85$ (c 0.9, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.64 (app dd, J=4, 8 Hz, 1H), 1.09 (ddd, J=5, 8, 13 Hz, 1H), 1.73 (ddd, J=4, 6, 7 Hz, 1H), 2.00 (dddd, J=2, 3, 5, 8 Hz, 1H), 2.12–2.23 (m, 1H), 2.30–2.40 (m, 1H), 3.38 (ddd, J=3, 5, 10 Hz, 1H), 4.04 (dd, J=4, 11 Hz, 1H), 4.29 (dd, J=9, 11 Hz, 1H), 4.67 (dd, J=4, 9 Hz, 1H), 5.04–5.15 (m, 2H), 5.67 (dddd, J=8, 10, 14, 16 Hz, 1H), 7.29–7.42 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 177.2, 137.6, 132.3, 128.7, 126.0, 118.9, 64.4, 61.9, 61.1, 39.6, 20.5, 16.2, 12.2; IR (film) 3380, 1664 cm^{-1}. Anal. calcd for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; N, 5.44. Found: C, 74.73; H, 7.42; N, 5.44. HRMS found 258.1506 (M+) requires 258.1494 (M+). **(ii) (1α,2α,5α)-(–)-2-(2-Propenyl)-4-oxo-3-azabicyclo[3.1.0]hexane-3-propanoic acid methyl ester (+)-2.** Into a round bottomed flask was condensed ca. 20 mL of NH_3 at –78°C. Calcium metal (2.0 g) was added and the mixture was vigorously stirred until a deep blue color formed (ca. 30 min). To this solution was slowly added **7** (1.02 g, 3.99 mmol in 5 mL of THF). The reaction was warmed to –40°C over a 2 h period and held at that temperature for 12 h at which time solid NH_4Cl was added and the mixture was allowed to warm to room temperature. After removal of NH_3, the solid residue was washed with Et_2O and the ethereal solution was concentrated in vacuo to provide a colorless oil. Column chromatography (ether) of the residue provided 507 mg of (1α,2α,5α)-(–)-2-(2-propenyl)-4-oxo-3-azabicyclo[3.1.0]hexane (93%) as a colorless oil: $[\alpha]_D=67$ (c 0.9, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.68 (app dd, J=4, 8 Hz, 1H), 1.10 (ddd, J=5, 8, 13 Hz, 1H), 1.76–1.84 (m, 2H), 2.30 (app t, J=8 Hz, 2H), 3.54 (app t, J=6 Hz, 1H), 5.11–5.19 (m, 2H), 5.79 (dddd, J=7, 10, 14, 16 Hz, 1H), 6.52 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 178.1, 132.9, 118.5, 55.1, 41.5, 19.7, 19.2, 12.6; IR (film) 3237, 1688 cm^{-1}. HRMS found 138.0924 (M+) ($C_8H_{11}NO$ (M^+) requires 138.0919). To a THF solution of the above azabicyclohexane (82 mg in 2 mL) was added

potassium hydride (24 mg) under an argon atmosphere at 0°C. After 15 min methyl 3-bromopropionate was added and the mixture was allowed to warm to rt over 2 h. To this solution was carefully added H_2O and the reaction mixture was partitioned between CH_2Cl_2 and H_2O. The aqueous layer was washed with CH_2Cl_2 (3×10 mL), the organic layers were combined, dried over Na_2SO_4 and concentrated in vacuo to provide a colorless oil. Column chromatography (ether) of the residue provided 78 mg of (+)-**2** (65%) as a colorless oil: $[\alpha]_D=24$ (c 0.9, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.48 (ddd, J=3.3, 4.4, 4.5 Hz, 1H), 1.03 (ddd, J=5, 7, 8 Hz, 1H), 1.69 (ddd, J=4, 6, 8 Hz, 1H), 1.85–1.93 (m, 1H), 2.29 (dt, J=8, 14 Hz, 1H), 2.46–2.66, (m, 3H), 3.18 (dt, J=7, 14 Hz, 1H), 3.61 (dddd, J=2, 3, 5, 7 Hz, 1H), 3.71 (s, 3H), 3.81 (dt, J=6, 12 Hz, 1H), 5.16–5.25 (m, 2H), 5.72–5.88 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.1, 132.3, 119.0, 60.3, 59.2, 37.9, 36.0, 32.4, 20.9, 16.2, 14.2, 12.0; IR (film) 1735, 1682 cm^{-1}. HRMS found 224.1287, ($C_{12}H_{17}NO_3$ (M^+) requires 224.1293). Chiral GLC analysis (Chiraldex G-PN, 30 m, isothermal (170°C) with a head pressure of 10 psi) proved the sample of (+)-**2** to be >99% enantiomerically pure when compared to a sample of racemic **2** exhibiting the following retention times: 35.38 min and 36.19 min. The sample from the present study appeared at 35.35 min with no visible trace of the other enantiomer. Further mixing of the two samples gave only the peaks at 35.36 (enhanced) and 36.21 min.