Total Synthesis of (±)-Epilupinine via an Organoyttrium-Catalyzed Sequential Cyclization/Silylation Reaction

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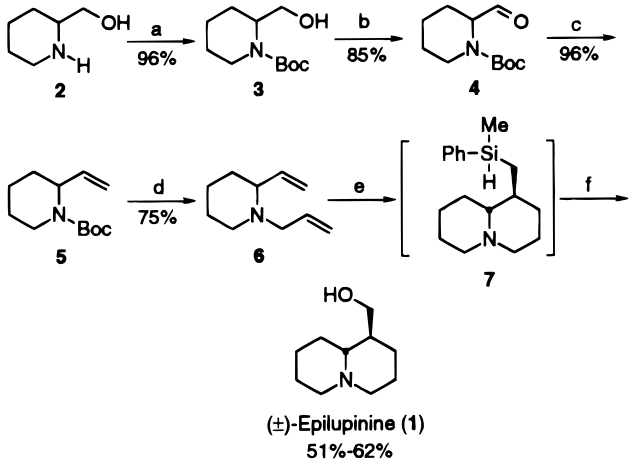
The use of group 3 organometallics and organolanthanides as catalysts to facilitate organic transformations is an area of considerable interest.[1] Some applications of these homogeneous catalysts include olefin polymerization,[2] hydrogenations,[3] hydrosilylations,[4] cyclooligomerizations,[5] hydroborations,[6] and hydroaminations.[7] Many of these reactions proceed with a high degree of stereoselectivity and/or regioselectivity. Recently, both organoyttrium[8] and organosamarium[4d] complexes have been shown to catalyze sequential cyclization/silylation reactions. Building upon previous organoyttrium reactions performed in our laboratories, we are currently extending the use of this protocol toward the synthesis of polycyclic ring systems. We envisaged that this method could be applied to the selective synthesis of ring systems present in a variety of natural products.

The quinolizidine ring structure is found in a number of naturally occurring alkaloids.[9] One of the simplest molecules known to contain this skeleton is (±)-epilupinine (**1**), a member of the lupin alkaloids.[9,10] (+)-Epilupinine has been reported to show in vitro inhibitory activity against P-388 ($LD_{50} = 28\ \mu g$) and L1210 ($LD_{50} = 28\ \mu g$) cell lines.[9] The structural features of this alkaloid make it an ideal candidate for synthesis via an organoyttrium-catalyzed cyclization reaction. Preparation of **1** would address key issues in selectivity and functional group compatibility while demonstrating the utility of the cyclooligomerization strategy. If successful, this protocol would utilize simple precursors to access a number of nitrogen bridgehead bicyclic structures that are widespread in natural alkaloids.[9a] Herein, we report an efficient total synthesis of **1** in which diastereoselectivity is achieved through an organoyttrium-catalyzed sequential cyclization/silylation reaction.

Scheme 1[a]



[a] Key: (a) $O(Boc)_2$, NEt_3, CH_2Cl_2; (b) pyridine·SO_3, NEt_3, CH_2Cl_2; (c) $KOC(CH_3)_3$, $Ph_3PMe^+Br^-$, Et_2O; (d) (1) CF_3COOH, CH_2Cl_2, (2) allyl bromide, K_2CO_3, THF, heat; (e) 5% $Cp^*_2YCH_3$·THF, $MePhSiH_2$, cyclohexane; (f) *t*-BuOOH, KH, DMF, CsF, 45 °C.

Results and Discussion

The generation of polycyclic ring systems through the selective formation of carbon−carbon bonds is of great importance in organic synthesis. One way to accomplish this transformation is to build upon a preexisting ring. We were interested in examining the selectivity of organoyttrium-catalyzed cyclization/silylation reactions of 1,2-disubstituted carbocyclic and heterocyclic dienes. An ideal substrate for this preliminary investigation was heterocyclic diene **6**. The straightforward preparation of this substrate is outlined in Scheme 1. The commercially available (±)-2-piperidinemethanol (**2**) in CH_2Cl_2 was converted to the BOC-protected amino alcohol **3** in 96% yield after addition of di-*tert*-butyl dicarbonate in the presence of NEt_3 and stirring for 14 h at rt.[11] Alcohol **3** could be easily oxidized over 2 h at 0 °C using a solution of sulfur trioxide−pyridine complex in DMSO in the presence of NEt_3 to provide aldehyde **4** in 85% yield.[12] A Wittig reaction was then performed on aldehyde **4** in Et_2O at rt, using 2 equiv each of potassium *tert*-butoxide and methyltriphenylphosphonium bromide to give the

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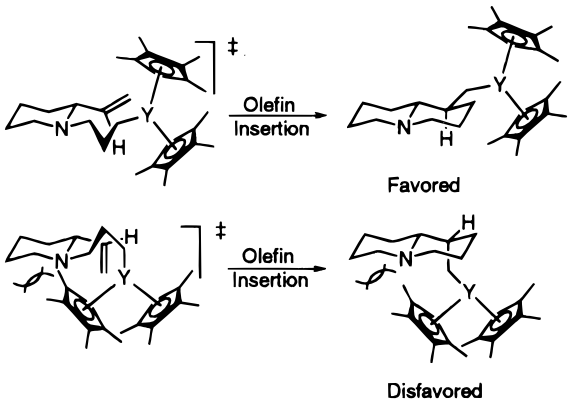

Figure 1.

2-vinyl-substituted, BOC-protected piperidine **5** in 96% yield.[13] The BOC group was then removed from **5** after exposure to trifluoroacetic acid in CH_2Cl_2.[14] The resulting crude trifluoroacetic acid amine salt was allylated using allyl bromide in the presence of excess potassium carbonate in THF, heated at reflux for 24 h.[15] The desired volatile diene **6** was isolated, after careful distillation, in 75% yield over two steps. It should be noted that diene **6** could also be prepared without BOC protection in three steps, albeit in significantly lower overall yield. In this approach, nitrogen allylation of (±)-2-piperidinemethanol (**2**), followed by a Swern oxidation and Wittig olefination, provided diene **6**.

The organometallic-catalyzed cyclization of substrate **6** was important to carry out for a variety of reasons. It had been previously shown that the active hydride catalyst "Cp^*_2YH", generated in situ from $Cp^*_2YCH_3$·THF, inserts the least hindered olefin preferentially in 1,5- and 1,6-dienes.[8] According to this precedent, the highly Lewis acidic active hydride was expected to react exclusively with the allyl unit of **6**, but the effect of the Lewis basic nitrogen was unknown. Second, after initial insertion of the most reactive olefin, a five-membered ring chelate could be formed between the nitrogen and the metal. It was unclear as to whether tight complexation with the amine would inhibit insertion of the remaining olefin and shut down the catalytic cycle, as has been observed previously in related systems.[5d] Finally, the inherent steric bulk of the cyclopentadienyl ligands was expected to provide high diastereoselectivity in the intramolecular insertion of the more hindered vinyl olefin while generating the quinolizidine ring structure according to the models depicted in Figure 1. In the event, when **6** was added to a mixture of 5 mol % of the precatalyst $Cp^*_2YCH_3$·THF[16] and $PhMeSiH_2$[17] in cyclohexane, the diene was converted to silane **7** within 1 h at rt. The desired product could be isolated in 84% yield. By GC analysis, it appeared that >95% of the desired isomer was generated. However, structural characterization proved to be difficult because of the three newly generated stereocenters within silane **7**. Thus, a final assessment of the diastereoselectivity of the reaction awaited conversion of the silanes to the corresponding alcohols, because both possible diastereomers were well-known natural products.

The oxidation of phenylsilane **7** proved to be quite challenging, presumably because the presence of the amine created selectivity problems. Silanes that might have been more readily oxidized than arylsilanes (e.g., triethoxysilane or chlorodimethylsilane) have proven incompatible with the organometallic catalyst in other organoyttrium-catalyzed cyclization/silylation reactions. When a crude mixture of **7** was exposed to the acidic hydrogen peroxide conditions developed by Bosnich et al.[18] (a modified Tamao oxidation), the result was complete decomposition of the substrate. Additionally, oxidation using peracetic acid in the presence of bromine and acetic acid as developed by Fleming and Sanderson[19] also resulted in total decomposition. It became evident that a neutral or basic method was required to oxidize the acid-sensitive silane **7**. Fortunately, the development by Woerpel and Smitrovich of an oxidation method that utilizes excess potassium hydride and *tert*-butyl hydrogen peroxide in the presence of DMF provided the key to obtaining the desired alcohol.[20] Oxidation of a crude silane mixture using the Woerpel conditions at 45 °C for 12 h resulted in isolation of (±)-epilupinine (**1**) in yields ranging from 51% to 62% over the two steps (cyclization/silylation and oxidation). The product was >98% pure **1** by GC analysis, and none of the trans isomer, naturally occurring (±)-lupinine, could be observed by NMR. It is possible that any small amount of (±)-lupinine present after the formation of silane **7** might be selectively decomposed or epimerized to the more stable (±)-epilupinine under the basic conditions of the oxidation.[21] Approximately 1% of another, unidentified isomer could be seen by both GC analysis and NMR. This isomer may result from the opposite cyclization mode, in which the initial insertion occurs at the more hindered vinyl olefin.

In summary, we have shown that organoyttrium-catalyzed cyclization/silylation is a viable method for the selective preparation of interesting polycyclic ring systems. These results suggest that this strategy may be useful in generating a number of functionalized polycyclic molecules. The reaction appears to proceed with high regioselectivity and stereoselectivity while providing a phenylsilane that can be oxidized to the more versatile alcohol. The catalytic cyclooligomerization proceeds rapidly and is unaffected by the presence of the tertiary amine. The synthesis of the naturally occurring alkaloid (±)-epilupinine serves to illustrate the synthetic utility of this protocol.

Experimental Section

Reagents. Diethyl ether and THF were distilled from sodium benzophenone ketyl under argon immediately prior to use. CH_2Cl_2 was distilled from CaH_2 immediately prior to use. Trieth-

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ylamine, DMSO, and DMF were all distilled from CaH_2 and stored over 4 Å molecular sieves. Potassium hydride was purchased as a 35% dispersion in mineral oil from Aldrich. The white solid was isolated under argon after several washings with dry hexane using Schlenk techniques.[22] The catalytic cyclization/silylation reaction was performed in a nitrogen-filled Vacuum Atmospheres glovebox. The precatalyst $Cp^*_2YCH_3$·THF was prepared using standard Schlenk techniques and stored in a glovebox.[16] Cyclohexane was distilled from sodium benzophenone ketyl and freeze/pump/thaw-degassed prior to storage in a glovebox. Methylphenylsilane was purchased from United Chemical Technologies and freeze/pump/thaw-degassed prior to storage in a glovebox. All other materials were commercially available and were used without further purification.

***N*-[(*tert*-Butyloxy)carbonyl]-2-(hydroxymethyl)piperidine (3).** To a solution of (±)-2-piperidinemethanol (346 mg, 3.0 mmol) in CH_2Cl_2 (15 mL) were added triethylamine (1.11 g, 10.9 mmol) and di-*tert*-butyl dicarbonate (789 mg, 36.2 mmol). The clear yellow solution was stirred for 14 h and then transferred to a separatory funnel that contained water (25 mL). The organic phase was washed twice with water and dried over $MgSO_4$. Concentration in vacuo, followed by flash chromatography (1:1 hexanes/ethyl acetate), afforded *N*-[(*tert*-butyloxy)-carbonyl]-2-(hydroxymethyl)piperidine (**3**) as a white solid (617 mg, 96%) which was >99% pure by GC analysis: mp 76−77 °C; R_f 0.21 (1:1 hexanes/ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.32−4.23 (m, 1H), 3.98−3.86 (br d, J = 12.3 Hz, 1H), 3.85−3.77 (m, 1H), 3.62−3.55 (m, 1H), 2.91−2.80 (br t, J = 10.9 Hz, 1H), 1.68−1.52 (m, 4H), 1.47−1.37 (m, 3H), 1.44 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.0, 79.5, 61.0, 52.1, 39.8, 28.3, 25.1, 24.9, 19.3; IR (CCl_4) 3438, 2975, 2934, 2866, 1694 cm^{-1}; LRMS (EI) *m*/*z* (relative intensity) 216 (0.4), 184 (16.2), 142 (18.6), 128 (75.4), 84 (87.9), 57 (100.0), 41 (88.4). Anal. Calcd for $C_{11}H_{21}NO_3$: C, 61.36; H, 9.83. Found: C, 61.37; H, 9.75.

***N*-[(*tert*-Butyloxy)carbonyl]-2-piperidinecarboxaldehyde (4).** To a solution of **3** (1.08 g, 5.0 mmol) in CH_2Cl_2 (25 mL) was added triethylamine (1.31 g, 12.9 mmol). The reaction mixture was cooled to 0 °C prior to addition of a solution of sulfur trioxide−pyridine complex (1.54 g, 9.69 mmol) in DMSO (9.7 mL). The reaction mixture was stirred at 0 °C for 2 h and then partitioned between hexanes/Et_2O (2:1, 300 mL) and saturated aqueous $NaHCO_3$ (100 mL). The aqueous layer was extracted with hexanes/Et_2O (2:1, 2 × 75 mL), and the combined organic extracts were washed with 1 M NaH_2PO_4 solution (75 mL) and brine (75 mL) and then dried over Na_2SO_4. Concentration in vacuo, followed by flash chromatography (3:1 hexanes/ethyl acetate) and Kugelrohr distillation gave *N*-[(*tert*-butyloxy)-carbonyl]-2-piperidinecarboxaldehyde (**4**) as a colorless oil (904 mg, 85%) which was >99% pure by GC analysis: ot 79 °C/0.08 mmHg; R_f 0.22 (3:1 hexanes/ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.51 (s, 1H), 5.62−5.37 (br m, 1H), 5.04−4.71 (br m, 1H), 3.94−3.63 (br m, 1H), 3.12−3.01 (m, 1H), 2.69−2.32 (m, 4H), 2.39 (s, 9H), 2.27−2.09 (br m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.3, 100.6, 80.3, (61.5, 60.6), (43.1, 41.8), 28.2, 24.7, 23.5, 20.9; IR (neat) 2976, 2940, 2861, 1694, 1681 cm^{-1}; LRMS (EI) *m*/*z* (relative intensity) 214 (1.2), 184 (56.4), 158 (26.2), 128 (81.5), 100 (24.5), 84 (92.4), 57 (100.0), 41 (92.7). Anal. Calcd for $C_{11}H_{19}NO_3$: C, 61.94; H, 8.98. Found: C, 61.56; H, 9.01.

***N*-[(*tert*-Butyloxy)carbonyl]-2-ethenylpiperidine (5).** To a suspension of potassium *tert*-butoxide (902 mg, 8.0 mmol) in Et_2O (30 mL) was added methyltriphenylphosphonium bromide (2.86 g, 8.0 mmol). The bright yellow mixture was heated at reflux for 1 h. A solution of **4** (853 mg, 4 mmol) in Et_2O (5 mL) was added slowly at rt to the reaction mixture. The yellow reaction mixture was stirred for 1 h, after which no starting material was detected by TLC. The reaction mixture was carefully quenched with water (15−20 mL), and the organic and aqueous phases were separated. The aqueous phase was extracted with Et_2O (30 mL) and hexanes (4 × 30 mL), and the combined organic layers were dried over $MgSO_4$. Cooling of the organic phase to −30 °C resulted in crystallization of the undesired triphenylphosphine oxide, which was easily separated by decantation. Concentration in vacuo, followed by flash chromatography (10:1 hexanes/ethyl acetate) and Kugelrohr distillation, gave *N*-[(*tert*-butyloxy)carbonyl]-2-ethenylpiperidine (**5**) as a colorless liquid (814 mg, 96%) which was >99% pure by GC analysis: ot 62 °C/0.09 mmHg; R_f 0.33 (10:1 hexanes/ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.72 (ddd, J = 17.4, 10.6, 4.1 Hz, 1H), 5.14 (ddd, J = 10.6, 2.0, 1.4 Hz, 1H), 5.01 (ddd, J = 17.4, 2.0, 1.4 Hz, 1H), 4.75 (br s, 1H), 3.91 (br d, J = 13.2 Hz, 1H), 2.79 (dt, J = 2.8, 12.8 Hz, 1H), 1.69−1.58 (m, 2H), 1.58−1.43 (m, 2H), 1.42−1.37 (m, 2H), 1.40 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.3, 136.8, 115.4, 79.2, 52.4, 39.6, 28.9, 28.4, 25.5, 19.4; IR (neat) 2976, 2937, 2861, 1694 cm^{-1}; LRMS (EI) *m*/*z* (relative intensity) 211 (0.3), 155 (48.4), 128 (14.4), 110 (31.5), 84 (17.3), 57 (100.0), 41 (42.0). Anal. Calcd for $C_{12}H_{21}NO_2$: C, 68.21; H, 10.02. Found: C, 68.07; H, 10.05.

***N*-(2-Propenyl)-2-ethenylpiperidine (6).** To a solution of **5** (627 mg, 2.97 mmol) in CH_2Cl_2 (15 mL) was added trifluoroacetic acid (3 mL). The reaction was stirred at rt for 1.5 h, after which no starting material was detected by TLC. The solvent was removed in vacuo, and the resulting oil was taken up in water (20 mL). The aqueous mixture was extracted with Et_2O (3 × 20 mL), and the aqueous phase was concentrated in vacuo to give the crude 2-ethenylpiperidine trifluoroacetic acid salt as a colorless oil. The salt was dissolved in THF (100 mL) prior to addition of allyl bromide (4.23 g, 35.0 mmol) and K_2CO_3 (4.98 g, 36.0 mmol). The reaction mixture was then heated at reflux for 24 h. Upon cooling to rt, the reaction mixture was quenched by the careful addition of 5% aqueous HCl (100 mL). The acidic aqueous layer was extracted with Et_2O (3 × 30 mL) and then brought to pH 9 by the addition of saturated Na_2CO_3 solution. The resulting basic aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL), and the combined extracts were dried over Na_2SO_4. Careful fractional distillation to remove the CH_2Cl_2, followed by Kugelrohr distillation, afforded the volatile *N*-(2-propenyl)-2-ethenylpiperidine (**6**) as a clear liquid (338 mg, 75%) which was >99% pure by GC analysis: ot 79 °C/30 mmHg; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.88−5.68 (m, 2H), 5.13−5.04 (m, 3H), 5.01 (dd, J = 10.2, 1.8 Hz, 1H), 3.40 (ddt, J = 13.8, 5.2, 1.6 Hz, 1H), 2.94−2.87 (m, 1H), 2.66 (dd, J = 13.8, 8.2 Hz, 1H), 2.58−2.51 (m, 1H), 1.90 (dt, J = 2.9, 11.6 Hz, 1H), 1.72−1.63 (m, 1H), 1.62−1.52 (m, 2H), 1.52−1.37 (m, 2H), 1.33−1.28 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.8, 135.4, 117.4, 115.7, 66.5, 58.7, 52.1, 33.5, 25.8, 23.9; IR (neat) 2934, 2784 cm^{-1}; HRMS calcd for $C_{10}H_{17}N^+$ 151.1361, found 151.1362; LRMS (EI) *m*/*z* (relative intensity) 151 (28.2), 150 (11.8), 125 (10.6), 124 (100.0), 110 (29.6), 82 (14.4), 68 (16.6), 54 (20.1), 41 (47.4). Anal. Calcd for $C_{10}H_{17}N$: C, 79.41; H, 11.33. Found: C, 78.90; H, 11.55.

(±)-Epilupinine (1). In a typical experiment, 5 mol % of the precatalyst $Cp^*_2YCH_3$·THF (0.024 g, 0.05 mmol) was dissolved in cyclohexane (2 mL) in a nitrogen-filled glovebox. To this were added methylphenylsilane (134 mg, 1.1 mmol) and finally diene **6** (151 mg, 1.0 mmol), which was freeze/pump/thaw-degassed prior to use. The faint yellow reaction mixture was stirred at rt for 1 h, after which the mixture was dark yellow and contained no starting material by GC analysis. The reaction mixture was then removed from the glovebox and filtered through a small plug of Florisil with excess EtOAc. Concentration by rotary evaporation, followed by exposure to reduced pressure, provided the crude silane **7**, which was then submitted to oxidation conditions. In a typical oxidation procedure, a 90% solution of *tert*-butyl hydroperoxide (1.01g, 10 mmol) was diluted with DMF (5 mL), and the solution was cooled to 0 °C. Solid potassium hydride (401 mg, 10 mmol) was then slowly added under argon to provide a white foam slurry. The crude silane was diluted with DMF (5 mL) and added slowly to the mixture at 0 °C. Finally, cesium fluoride (760 mg, 5 mmol) was added, and the mixture was warmed to room temperature. The reaction vessel was then fitted with a condenser, and the reaction was warmed to 45 °C for 12 h, after which time no starting material could be detected by TLC. The oxidation was quenched by adding solid sodium thiosulfate (2.0 g) and stirring for 0.5 h at rt. The reaction mixture was then exposed to reduced pressure until only a white solid residue remained. The residue was extracted with MeOH (100 mL) and filtered through a plug of Florisil. The extracts were concentrated via rotary evaporation to provide a large amount of white solid. This mixture was filtered through a large column of neutral alumina. This removed the solid and provided an oil, which could be purified by flash chromatography on neutral silica gel (3:1 CH_2Cl_2/MeOH). If the alumina filtration was not performed prior to

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flash chromatography, decomposition of the desired product resulted in all cases. After concentration in vacuo, (±)-epilupine (**1**) was isolated as a clear oil (86.3−104.9 mg, 51%−62%) which was >98% pure by GC analysis. Recrystallization was performed in petroleum ether to provide a white crystalline solid, which was only used for a melting point comparison. The characterization data are consistent with literature values reported for (±)-epilupinine:[10] mp 81−82 °C; R_f 0.10 (3:1 CH_2Cl_2/MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.65 (dd, J = 10.8, 3.6 Hz, 1H), 3.55 (dd, J = 10.8, 5.8 Hz, 1H), 2.88−2.77 (m, 2H), 2.07−1.98 (m, 2H), 1.92−1.54 (m, 9H), 1.48−1.37 (m, 1H), 1.28−1.14 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 64.3, 63.9, 56.6, 56.4, 43.6, 29.3, 28.0, 25.2, 24.7, 24.3; IR (neat) 3625, 2928, 2857, 2807, 2759, 2676, 1445, 1295, 1112, 1093, 1014 cm^{-1}; HRMS calcd for $C_{10}H_{19}NO^+$ 169.1467, found 169.1463; LRMS (EI) m/z (relative intensity) 169 (18.3), 168 (18.3), 152 (28.2), 138 (49.3), 110 (69.0), 96 (88.7), 83 (100.0). Anal. Calcd for $C_{10}H_{19}NO$: C, 70.95; H, 11.32. Found: C, 70.50; H, 11.41.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of **6** and **1** (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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