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A general, enantioselective synthesis of *N*-alkyl terminal aziridines and C2-functionalized azetidines via organocatalysis

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ABSTRACT

A short, high-yielding protocol involving the enantioselective α-chlorination of aldehydes has been developed for the enantioselective synthesis of C2-functionalized aziridines and *N*-alkyl terminal azetidines from a common intermediate. This methodology allows for the rapid preparation of functionalized aziridines in 50–73% overall yields and 88–94% ee, and azetidines in 22–32% overall yields and 84–92% ee. Moreover, we developed a scalable and cost-effective route to the key organocatalyst (54% overall yield, >95% dr).

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Azetidines comprise an important class of nitrogen-containing heterocycles due to both their biological significance and increasing use in medicinal chemistry.[1] While recent approaches have made progress in the ability to access various types of azetidines in an enantioselective fashion, 2-alkyl substituted azetidines are notably scarce in the literature.[2,3]

Similarly, aziridines represent an important class of nitrogen-containing heterocycles that have garnered significant interest from the synthetic chemistry and chemical biology communities over the past two decades.[4] Aziridine's intrinsic ring strain positions them as synthetically valuable intermediates capable of undergoing highly regio- and stereoselective ring opening transformations.[5] Additionally, the aziridine moiety is found in compounds that possess interesting biological properties including antitumor or antibiotic activity. Together, these properties have shown aziridines to be useful synthetic intermediates and attractive targets in medicinal chemistry and the total synthesis of natural products.[6,7]

We recently reported a three step, one-pot protocol involving the enantioselective α-chlorination of aldehydes, subsequent reductive amination with a primary amine, followed by S_N2 displacement to afford chiral *N*-alkyl terminal aziridnes.[8] Under this protocol, yields and enantioselectivities in many cases were moderate and variable due to epimerization of the α-chlorinated aldehyde **3** during reductive amination. We sought to address these issues as well as provide a facile route to the synthesis of 2-substituted azetidines through a common, configurationally-stable intermediate.

According to the seminal work of Jorgensen and coworkers for the organocatalytic α-chlorination of aldehydes, in situ reduction of the α-chloro aldehydes with $NaBH_4$ to the corresponding β-chloro alcohols **5** would occur without loss of enantioselectivity.[9] We envisioned that these configurationally stable α-chloro alcohols **5** could function as bifunctional chiral building blocks.

Essentially, we reasoned that functionalization of this common intermediate with either an amine (**Route A**) or nitrile group (**Route B**) followed by an intramolecular cyclization strategy could provide access to both aziridines and azetidines (Fig. 1). As disclosed in our previous communication, catalyst **2** was optimal in terms of enantioselectivity and compatibility for the purposes of accessing the desired chloro alcohol.[8,10,11] This catalyst was difficult to obtain commercially. In our hands, we found that literature procedures to prepare **2** resulted in variable yields and an inseparable mixture of our desired catalyst with the *meso* isomer.[12,13] Recrystallization of the final product was achieved, successfully increasing the purity of the desired isomer to >92%. However, these conditions limited the scale and required careful temperature regulation during recrystallization. Therefore, we sought to improve the synthesis to both increase the yield and reliability of the protocol, with the goal of being able to rapidly obtain the pyrrolidine catalyst on multi-gram scale.

We successfully optimized the synthetic route as outlined in Scheme 1. Notably, we found that flash column chromatography of the penultimate intermediate **10** with a 7:3 hexanes/toluene

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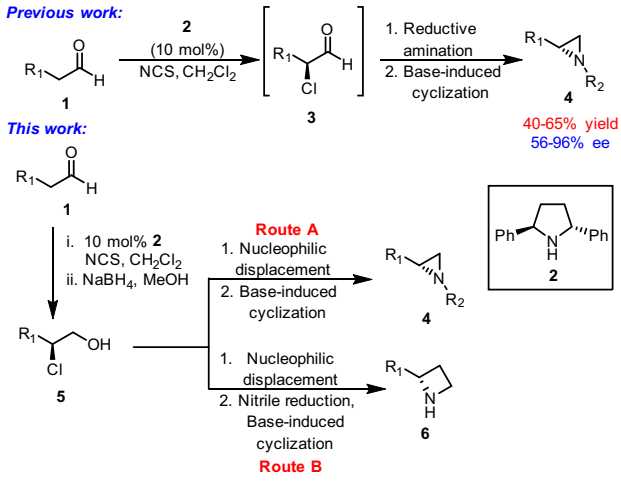
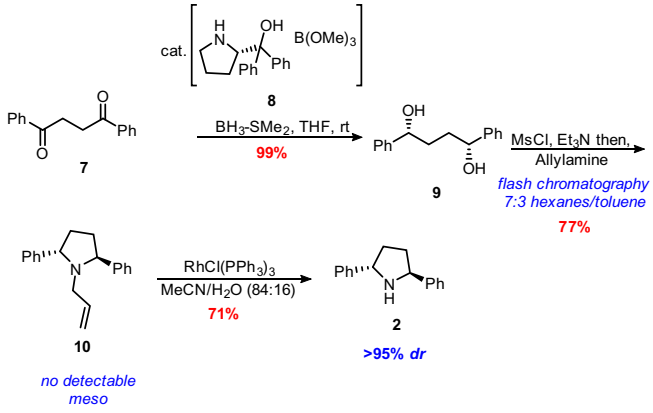


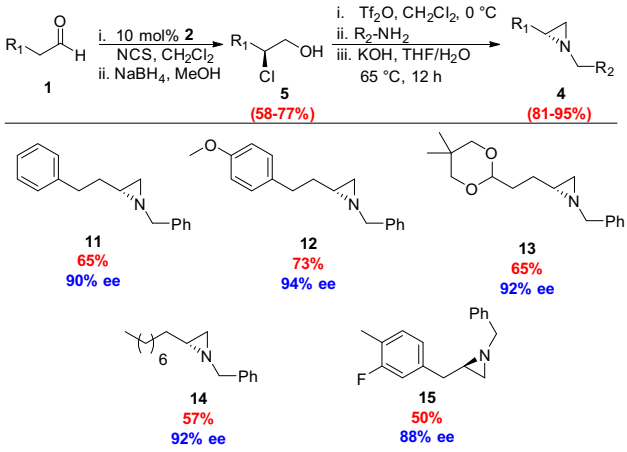
Figure 1. Top: first-generation organocatalytic approach for the enantioselective synthesis of *N*-alkyl aziridines. Bottom: envisioned second generation organocatalytic approach for the enantioselective synthesis of C2-functionalized aziridines and azetidines.



Scheme 1. Scalable, cost-effective synthesis of organocatalyst **2**.

solvent system provided excellent separation of the desired isomer. Additionally, increasing the amount of Wilkinson's catalyst in the allyl deprotection to 10 mol % increased the yield of the deprotection to 71%. These improvements allowed for the gram-scale production of catalyst **2** in >54% overall yield and <95% dr.

With sufficient organocatalyst for α-chlorination in hand, our attention was turned towards the synthesis of the aziridines. Preparation of β-chloro alcohols **5** proceeded via facile asymmetric organocatalytic chlorination and in situ sodium borohydride reduction of achiral aldehydes **1**. To transform primary alcohols into bifunctional electrophiles, the β-chloro alcohols **5** were treated with triflic anhydride and lutidine in CH_2Cl_2 at 0 °C. These conditions smoothly generated the desired triflates, which were then immediately treated with benzylamine to generate β-chloro amines in good yields for this one-pot procedure. The resulting amines were of sufficient purity to subject directly to intramolecular cyclization. Potassium hydroxide in THF/H_2O at 65 °C promoted clean cyclization to afford the desired chiral *N*-alkyl terminal aziridines **11**–**15** in 50–73% overall yield and 88–94% ee from the readily available aldehyde starting materials. This mild, two-pot protocol from the common configurationally stable 2-chloro alcohol intermediate represents a robust approach to access aziridines, and this optimized approach avoids epimerization of the α-chloro aldehyde and extremely low temperature reaction conditions necessary in previous methodologies (Scheme 2).[8]

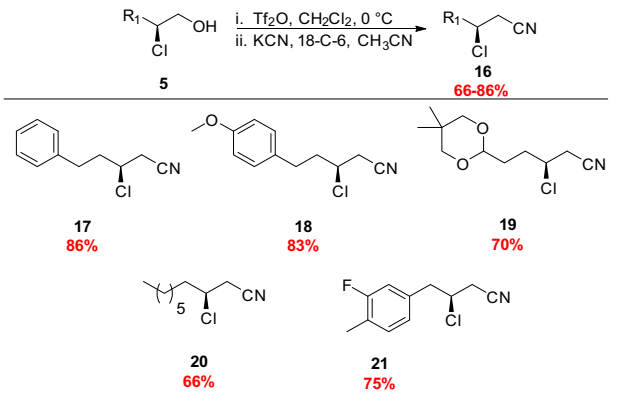


Scheme 2. Protocol for enantioselective synthesis of *N*-alkyl terminal aziridines.[14]

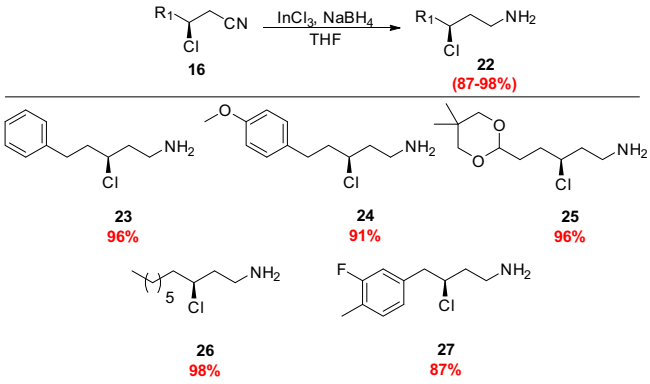
We next focused on the synthesis of the azetidines (Fig. 1, **route B**), as there are very few approaches for their preparation. Starting from the common 2-chloro alcohol intermediate, we planned to access the β-chloro nitrile intermediates **17**–**21** through analogous activation of the primary alcohol as the triflate, followed by displacement with potassium cyanide. Initial conditions using potassium cyanide in CH_2Cl_2, THF, or acetonitrile led to poor conversion at room temperature and elimination at elevated temperature. However, we found that potassium cyanide in acetonitrile, with 18-crown-6 as an additive, was effective in conversion to the desired nitrile after 24 h at room temperature. Under these optimized conditions, displacement of the in situ prepared triflate with potassium cyanide facilitated formation to the desired β-chloro nitrile **17**–**21** in 66–86% yield. While these products were relatively stable at room temperature in CH_2Cl_2 solution, elevated temperatures resulted in the formation of an elimination byproduct. Similarly, the concentrated products were prone to elimination, and decomposed within hours at room temperature (Scheme 3).

Related to the instability of the β-chloro nitriles, we found that conventional methods to reduce the nitrile such as lithium aluminum hydride and hydrogenation led to either elimination or dehalogenation of the starting material. After screening various mild nitrile reduction conditions we found that using an indium(III) chloride–sodium borohydride system to be generally applicable across substrates in excellent yield and sufficient purity to carry forward without purification towards cyclization (Scheme 4).

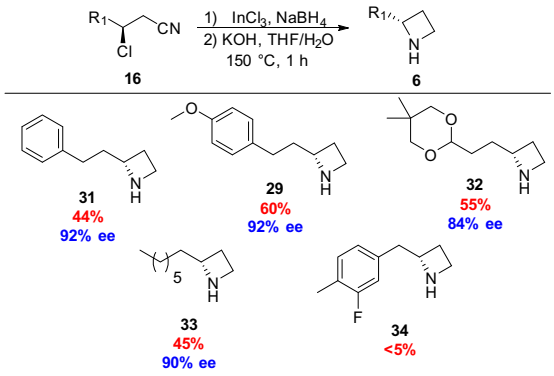
With the γ-chloro amine **22** in hand, we focused on the cyclization conditions to afford the desired azetidine **6**. We initially



Scheme 3. Protocol for the synthesis chiral β-chloro nitriles **17**–**21**.



Scheme 4. Mild reduction of β-chloro nitriles to γ-chloro amines **23**–**27**.



Scheme 5. Protocol for intramolecular cyclization to C2-functionalized azetidines **31**–**34**.[15]

attempted the same conditions that were successful in facilitating the 3-*exo*-tet cyclization of the β-chloro amine to aziridines. However, treatment with KOH in THF/H_2O at 65 °C led to minimal consumption of the starting material. Additionally, a variety of modifications to the base and solvent system promoted elimination to an undesired byproduct **30**. To find conditions that might promote 4-*exo*-tet cyclization, we performed a screen of a broad selection of organic and inorganic bases, solvents, and temperatures (Table 1).

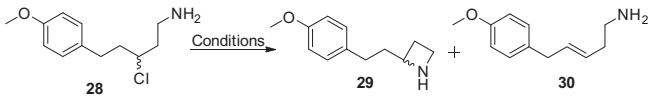
This screen revealed that many conditions which promoted cyclization also facilitated elimination to the olefin **30**. We identified optimal conditions which provided the desired azetidine in a 3:1 ratio with the competing elimination pathway. Specifically, potassium hydroxide in THF/H_2O (1:1), under high thermal conditions (170 °C) was effective in conversion to the desired azetidine **29**. Microwave irradiation for 1 h at this temperature resulted in full consumption of the γ-chloro amine starting material.

Of note, the major by-product was identified as the olefin resulting from chloride elimination. γ-Chloro amines with branched alkyl groups or aryl groups β to the secondary chloride were especially susceptible to elimination, as reflected in the decreased yields for **34**. This can be rationalized by the high energetic requirements necessary to enable ring closure to the highly strained 4-member azetidine ring, which rapidly promoted elimination to the conjugated olefin. Gratifyingly, the azetidine and olefin products were readily separated by flash column chromatography.

In order to determine the scope of this methodology, we prepared several 2-alkyl azetidines from readily available aldehydes. Nitrile reduction and azetidine cyclization were performed sequentially without purification of the γ-chloroamine in all cases. This provided the desired azetidines in 44–55% yield. Attempts to induce cyclization to **34** resulted in nearly complete elimination to the conjugated byproduct, with less than 5% recovered product. Importantly, this approach provides the azetidines without N-functionalization, allowing for rapid derivatization using robust synthetic methods such as reductive amination and N-alkylation (Scheme 5).

In summary, we have developed an optimized three-step procedure for the enantioselective synthesis of *N*-alkyl terminal aziridines and azetidines with alkyl substituents at the C2 position of each heterocycle. This methodology allows for the rapid preparation of the functionalized aziridines in 50–73% overall yields and 88–94% ee, and functionalized azetidines in 22–32% overall yields and 84–92% ee. This new method addresses deficiencies in our first

Table 1
Conditions for the base-induced cyclization of γ-chloro amines to azetidines **29** and elimination product **30**



Entry	Base	Solvent	Temperature (°C)	Additive	Conversion (%) (**29**:**30**)
1	K_2CO_3	NMP	25	—	0
2	K_2CO_3	NMP	120	—	40 (2:1)
3	K_2CO_3	NMP	180	—	80 (2:1)
4	—	THF/H_2O (1:1)	150	—	75 (1.5:1)
5	NaH	DMF	25	—	0
6	NaH	DMF	65	—	0
7	NaH	DMF	25	15-C-5	Trace (1:2)
8	NaH	DMF	65	15-C-5	<5 (0:1)
9	LHMDS	DMF	25	—	60 (0:1)
10	LHMDS	DMF	25	—	100 (0:1)
11	K_2CO_3	DMF	25	—	0
12	K_2CO_3	DMF	120	—	10 (2:1)
13	K_2CO_3	DMF	25	$AgNO_3$	0
14	K_2CO_3	DMF	65	$AgNO_3$	0
15	KOH	THF/H_2O (1:1)	65	—	<5 (3:1)
16	KOH	THF/H_2O (1:1)	120	—	20 (3:1)
17	KOH	THF/H_2O (1:1)	170	—	100 (3:1)

All reactions run at 0.1 mmol, 0.125 M in solvent. Conversion determined by LCMS and ^{1}H NMR.

generation approach for the synthesis of aziridines while facilitating the synthesis of azetidines through a common bifunctional intermediate. Alternative methods to access azetidines that do not rely on the chiral pool is a demonstrated need in natural products synthesis and medicinal chemistry applications, and the ability to employ simple aldehydes and organocatalysts towards their synthesis allows for straightforward access to either enantiomer. Additional refinements and applications of this methodology to the synthesis of biologically relevant small molecules are under development and will be reported in due course.

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References and notes

1. Bott, T. M.; West, F. G. *Heterocycles* **2012**, *84*, 223.
2. Brandi, A.; Cicchi, S.; Cordero, F. M. *Chem. Rev.* **2008**, *108*, 3988.
3. Wells, J. N.; Tarwater, O. R. *J. Pharm. Sci.* **1971**, *60*, 156.
4. Yudin, A. K. *Aziridines and Epoxides in Organic Synthesis*; Wiley-VCH Verlag GmbH & Co. KGaA, 2006.
5. Müller, P.; Fruit, C. *Chem. Rev.* **2003**, *103*, 2905.
6. Degennaro, L.; Trinchera, P.; Luisi, R. *Chem. Rev.* **2014**. ASAP.
7. Majumdar, K. C.; Chattopadhyay, S. K. *Heterocycles in Natural Product Synthesis*; Wiley-VCH: Weinheim, Germany, 2011.
8. Fadeyi, O. O.; Schulte, M. L.; Lindsley, C. W. *Org. Lett.* **2010**, *12*, 3276.
9. Halland, N.; Braunton, A.; Bachmann, S.; Marigo, M.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 4790.
10. O'Reilly, M. C.; Lindsley, C. W. *Org. Lett.* **2012**, *14*, 2910.
11. O'Reilly, M. C.; Lindsley, C. W. *Tetrahedron Lett.* **2012**, *53*, 1539.
12. Aldous, D. J.; Dutton, W. M.; Steel, P. G. *Tetrahedron: Asymmetry* **2000**, *11*, 2455.
13. Kemppainen, E. K.; Sahoo, G.; Valkonen, A.; Pihko, P. M. *Org. Lett.* **2012**, *14*, 1086.
14. *Representative experimental for the synthesis of N-alkyl terminal aziridine*: (*R*)-1-Benzyl-2-octylaziridine (**13**). To a round bottom flask equipped with a stir bar, 4-(5,5-dimethyl-1,3-dioxan-2-yl)butanal (0.25 g, 1.34 mmol) was dissolved in CH_2Cl_2 (3.84 mL) at 0 °C and to the stirring solution was added (2*R*,5*R*)-2,5-diphenylpyrrolidine (0.03 g, 0.13 mmol) and then *N*-chlorosuccinimide (0.233 g, 1.75 mmol). Solution was maintained at 0 °C, and stirring was continued for 12 h, at which point starting material was consumed by ^{1}HNMR. The reaction was diluted with MeOH (3.84 mL) and cooled to 0 °C, then $NaBH_4$ (0.254 g, 6.72 mmol) was slowly added while stirring. The reaction was stirred for additional 30 min at the same temperature, then quenched with H_2O and extracted three times with EtOAc. The organic fractions were combined, washed with brine, and dried over Na_2SO_4. The organic layer was concentrated in vacuo and a crude oil was purified by column chromatography (4:1 Hexane/EtOAc) to yield desired product as a clear oil in 0.23 g (76%). ^{1}H NMR (400.2 MHz, $CDCl_3$) δ (ppm): 4.49 (t, J = 4.4 Hz, 1H), 4.08 (m, 1H), 3.81 (dd, J = 12.2, 4.0 Hz, 1H), 3.69 (dd, J = 11.7, 7.0 Hz, 1H), 3.62 (d, J = 10.8 Hz, 2H), 3.44 (d, J = 10.8 Hz, 2H), 2.05 (s, 1H), 2.00–1.74 (m, 4H), 1.20 (s, 3H), 0.74 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 101.2, 76.6, 66.8, 64.7, 31.2, 30.1, 28.3, 22.9, 21.7; HRMS (TOF, ES+) $C_{10}H_{19}ClO_3$ $[M+H]^+$ calcd 223.1021, found 223.1020; specific rotation $[\alpha]_D^{23}$ −3.0° (*c* 1.0, CH_3Cl). To a round bottom flask equipped with a stir bar, alcohol (0.10 g, 0.45 mmol) and 2,6-lutidine (0.241 g, 2.25 mmol) were dissolved in CH_2Cl_2 (2.25 mL) and cooled to 0 °C. Tf_2O (0.54 mL, 1 M in CH_2Cl_2, 0.54 mmol) was then added dropwise, and the solution was left to stir at 0 °C for 30 min. At this time, the triflate solution was taken up by syringe and added dropwise to a stirring solution of benzylamine (0.48 g, 4.50 mmol) in CH_2Cl_2 (1.00 mL) at 0 °C. The flask containing the triflate solution was washed 2 times with CH_2Cl_2 (1.00 mL) and added to reaction. The solution was then slowly warmed to ambient temperature and stirred overnight. The reaction was quenched with $NaHCO_3$, diluted with CH_2Cl_2, and extracted 3 times with CH_2Cl_2. The organic layers were combined and washed with brine. The organic layer was dried over Na_2SO_4 and concentrated in vacuo to yield the crude product. The crude product was isolated as a pale yellow oil quantitatively and carried forward directly to the next step. In an open microwave vial equipped with a stir bar, crude amine (0.14 g, 0.45 mmol) was dissolved in 1:1 THF/H_2O (2.99 mL), followed by the addition of KOH (0.16 g, 2.92 mmol). The microwave vial was sealed and stirred overnight at 65 °C. The reaction mixture was allowed to cool to ambient temperature, then extracted 3 times with EtOAc. The organic layers were combined and dried over Na_2SO_4, then concentrated in vacuo to give the crude product a pale yellow oil. Purification by flash column chromatography (1:1 Hexane/EtOAc) afforded the desired product as pale yellow oil in 0.11 g, (85%). ^{1}H NMR (400.2 MHz, $CDCl_3$) δ (ppm): 7.23 (m, 5H), 4.28 (t, J = 5.0 Hz, 1H), 3.50 (d, J = 10.8 Hz, 2H), 3.43 (d, J = 13.6 Hz, 1H), 3.27 (m, 3H), 1.61 (m, 2H), 1.55 (d, J = 3.4 Hz, 1H), 1.47 (m, 3H), 1.32 (d, J = 6.0 Hz, 1H), 1.10 (s, 3H), 0.63 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 139.5, 128.4, 128.3, 127.0, 101.7, 77.3, 65.1, 39.5, 34.0, 32.6, 30.2, 27.6, 23.1, 21.9; HRMS (TOF, ES+) $C_{17}H_{25}NO_2$ $[M+H]^+$ calcd 276.1886, found 276.1886; specific rotation $[\alpha]_D^{23}$ +4.0° (*c* 1.0, CH_3Cl).
15. *Representative experimental for the synthesis of C2-functionalized azetidine*: (*S*)-2-(3-Fluoro-4-methylbenzyl)azetidine (**32**). To a round bottom flask equipped with a stir bar, alcohol **39** (0.19 g, 0.89 mmol) and 2,6-lutidine (0.48 g, 4.44 mmol) were dissolved in CH_2Cl_2 (4.4 mL) and cooled to 0 °C. Tf_2O (0.30 g, 1.07 mmol) was then added dropwise, and solution left to stir at 0 °C for 30 min. Reaction was diluted with CH_2Cl_2 and washed with H_2O. The organic fraction was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The crude oil was carried on directly to the next step. The crude triflate was dissolved in MeCN (4.4 mL), then 18-C-6 (0.05 g, 0.18 mmol) was added to the mixture and allowed to dissolve. KCN (0.578 g, 8.88 mmol) was then added, and the reaction was allowed to stir for 12 h at ambient temperature. The reaction was then quenched with $NaHCO_3$ and extracted three times with CH_2Cl_2. The organic fractions were combined and dried over Na_2SO_4. The organic layer was concentrated in vacuo, and purification by flash chromatography (4:1 Hexane/EtOAc) afforded the desired product as a clear/rose colored oil in 0.11 g (70%). ^{1}H NMR (400.2 MHz, $CDCl_3$) δ (ppm): 4.45 (dd, J = 10.4, 1.6 Hz, 1H, (tt, J = 10.2, 3.5 Hz, 1H), 3.60 (m, 2H), 3.38 (d, J = 8.9 Hz, 1H), 3.20 (m, 3H), 2.54 (m, 1H), 2.07 (m, 2H), 1.71 (dt, J = 15.4, 5.0 Hz, 1H), 0.85 (s, 3H), 0.82 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 117.9, 75.9, 75.7, 72.7, 68.5, 53.86, 36.7, 35.4, 28.2, 23.2, 23.1; HRMS (TOF, ES+) $C_{11}H_{18}ClNO_2$ $[M+H]^+$ calcd 232.1025, found 232.1025; specific rotation $[\alpha]_D^{23}$ +6.4° (*c* 1.1, CH_3Cl). To a microwave vial with magnetic stir bar was added $InCl_3$ (0.10 g, 0.43 mmol) and $NaBH_4$ (0.05 g, 1.30 mmol). Anhydrous THF (1.0 mL) was added and the heterogeneous mixture was stirred under argon for 1 h. **25** (0.10 g, 0.43 mmol) was then slowly added as a solution in THF (1.0 mL). Reaction mixture was allowed to stir at ambient temperature for 4 h. The reaction was quenched by dropwise addition (CAUTION: results in rapid generation of gas) of H_2O (1.0 mL) and the solution was heated to 75 °C for 30 min MeOH (2.0 mL) was then slowly added, and stirring continued at 75 °C for 30 min. The reaction mixture was allowed to cool to room temperature, then filtered through a celite pad to remove solid indium byproducts. The resulting colorless solution was concentrated in vacuo to provide **32** in 96% yield. The crude residue was carried forward directly to the next step. To an open microwave vial equipped with a stir bar, the crude residue from the previous step was dissolved in a solution of 1:1 THF/H_2O (3.40) and KOH (0.16 g, 2.76 mmol) was then added. The vial was sealed and submitted to microwave irradiation at 170 °C. for 1 h. The biphasic solution was extracted three times with EtOAc and washed with brine. The organic fractions combined, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash column chromatography (9:0.9:0.1 CH_2Cl_2/MeOH/NH_4OH) afforded desired product as a light yellow oil in 45 mg (55%). ^{1}H NMR (400.2 MHz, MeOD) δ (ppm): 3.89 (dd, J = 12.5, 3.6 Hz, 1H), 3.63 (m, 1H), 3.62 (d, J = 12.0 Hz, 1H), 3.57 (d, J = 12.0 Hz, 1H), 3.35 (m, 3H), 1.97 (m, 1H), 1.79 (d, J = 7.0 Hz, 1H), 1.50 (m, 4H), 1.35 (d, J = 3.4 Hz, 1H), 0.94 (s, 3H), 0.88 (s, 3H); ^{13}C NMR (100.6 MHz, MeOD) δ (ppm): 81.8, 81.0, 79.3, 77.2, 38.1, 29.6, 29.3, 29.1, 24.1, 23.0, 22.6; specific rotation $[\alpha]_D^{20}$ +1.7 (*c* 1.0, $CHCl_3$); HRMS (TOF, ES+) $C_{11}H_{22}NO_3S$ $[M+H]^+$ calcd 200.1574, found 200.1575.