Synthesis C. N. Teijaro et al. Feature

Total Syntheses of (–)-Alstolucines A, B, and F, (–)-Echitamidine, and (–)-*N*-Demethylalstogucine

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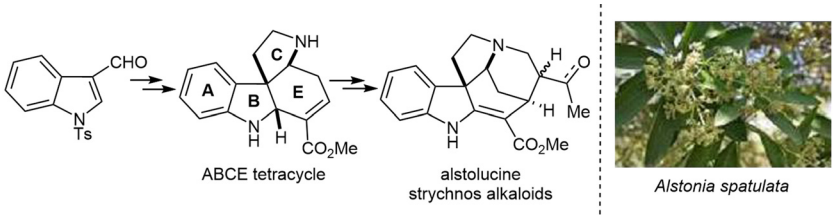

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Abstract The first enantioselective total syntheses of (–)-alstolucinces A, B, and F, (–)-echitamidine, and (–)-*N*-demethylalstogucine are reported. This article details the development of our first- and second-generation approaches toward the ABCE tetracyclic core of the strychnos alkaloids and the application thereof to the aforementioned targets. Key steps involve our sequential one-pot biscyclization method that constructs the C and E rings of the tetracyclic core and Rawal's application of the intramolecular Heck reaction to secure the pentacyclic framework common amongst all targets.

Key words total synthesis, natural products, strychnos alkaloids

Indole alkaloids represent a large class of biologically active natural products. The structural diversity of these small molecules has long been a source of inspiration for the development of novel synthetic methodology and a driver of progress in total synthesis.[1]

In 2010, Kam and co-workers isolated 25 strychnos alkaloids from *Alstonia spatulata* of which five (i.e., alstolucines A–E) were novel.[2] The known alkaloid *N*-demethylalstogucine (**5**),[3] along with alstolucines A (**6**), B (**3**), and F (**4**) were found to reverse multidrug resistance in vincristine-resistant KB cells (Figure 1). The structural complexity of these targets, coupled with their novelty and biological significance, motivated us to prepare these in asymmetric fashion, which we recently communicated.[4]

In 1994, Kuehne, reported the racemic syntheses of echitamidine (**24**) by the stereoselective hydride reduction of alstolucines B (**3**). Moreover, **3** was equilibrated to alstolucine F (**4**) in 2:1 ratio via treatment with sodium methoxide in methanol.[5]

Inspection of the targets reveals a pentacyclic framework with a pendant group at C20 that serves to differentiate each congener. Moreover, these features are reminiscent of the ABCE tetracycle **1** and the classic alkaloid (–)-akuammicine (**2**). The building blocks and inspiration for the

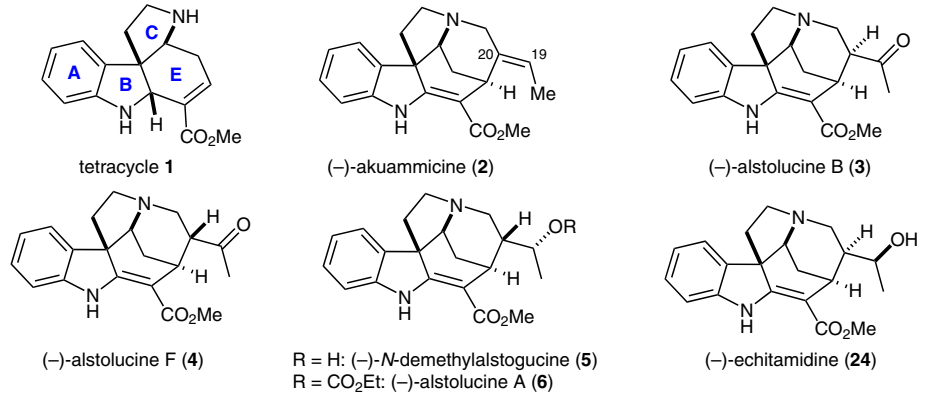


Figure 1 ABCE core **1**, known and novel pentacyclic strychnos alkaloids

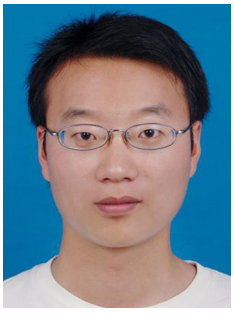
synthesis of (–)-alstolucines A (**6**), B (**3**), F (**4**), (–)-echitamidine (**24**), and (–)-*N*-demethylalstogucine (**5**) stemmed from our synthetic knowledge of **1** and **2**.

Akuammicine (**2**) is a common synthetic target among monoterpenoid indole alkaloids.[6] The isolation of akuammicine from *Picralima klaineana* (i.e., akumma) seeds was first described in 1932 by Henry.[7]

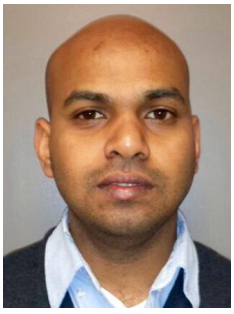
Akumma seeds are widely employed in traditional medicine throughout Africa, particularly for the treatment of malaria. More recently, akuammicine (**2**) was shown to possess additional biological activity relating to glucose uptake,[8] μ- and κ-opioid receptors,[9] as well as cytotoxicity in vincristine-resistant KB cells.[2]

Biographical Sketches

Christiana Teijaro obtained her B.A. in chemistry and psychology in 2012 from St. Mary's College, St. Mary's City, MD. She is a National Science Foundation Graduate Research Fellow currently pursuing her Ph.D. in organic chemistry under the supervision of Prof. Andrade at Temple University in Philadelphia, PA. Her research is centered on the total synthesis of indole alkaloids and understanding their function in biological systems. Her interests consist of methodology development applied to total synthesis, medicinal chemistry, and chemical biology.



Senzhi Zhao obtained his Bachelor of Engineering degree in Applied Chemistry from Xuzhou Normal University, Xuzhou, China. He earned his M.S. degree in organic chemistry from Nanjing University, Nanjing, China in 2007. He is currently pursuing his Ph.D. in organic chemistry under the direction of Prof. Andrade. His research interests include development of new synthetic methodology, total synthesis of natural products and medicinal chemistry.



Praveen Kokkonda obtained his B.S. in chemistry from Kakatiya University in 2003, Warangal, India, and M.S. in organic chemistry from Osmania University in 2006, Hyderabad, India. After completion of his M.S. degree, he worked as a Senior Chemist in GVK Bio sciences Pvt. Ltd, Hyderabad, India for three years. Praveen is currently a graduate student pursuing his Ph.D. under the supervision of Prof. Andrade. His research is focused on the total synthesis of indole alkaloids.

Rodrigo Andrade obtained a B.A. degree in biophysics in 1996 from the Johns Hopkins University in Baltimore, MD. In 2001, he obtained his Ph.D. in organic chemistry from the Massachusetts Institute of Technology in Cambridge, MA under the supervision of Prof. Peter Seeberger. He was an NIH Postdoctoral Fellow in the laboratory of Prof. Stephen Martin at the University of Texas at Austin from 2003–2006. In August 2006, he began his independent research at Temple University in the Department of Chemistry and was promoted to Associate Professor in 2011. His research areas include chemical synthesis, chemical biology, and medicinal and bioorganic chemistry.

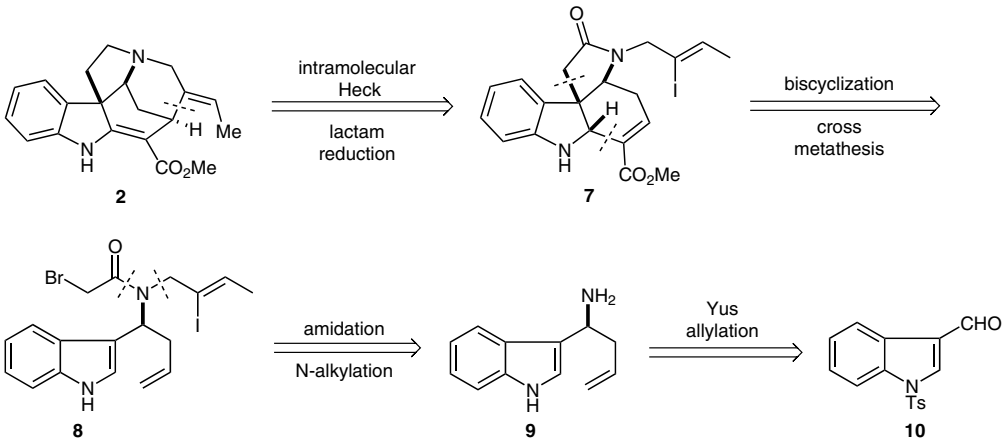
The synthesis of akuammicine (**2**) and other alkaloids, such as strychnine, have led to a wealth of chemistries. Our approach to the tetracyclic core of the alkaloids **1** and akuammicine (**2**) was inspired by the work of Heathcock[10] and Rawal.[11] In 1991, Rawal employed an elegant strategy to form the D ring of the pentacyclic core of the alkaloids via an intramolecular Heck reaction. In 2000, Heathcock reported the synthesis of (±)-aspidospermidine in which a 2-haloacetamide gramine derivative was employed to close the C ring. This inspiration was used for the formation of the C ring of the ABCE tetracycle **1** and the biscyclization in our approach to akuammicine (**2**).

Based on this inspiration a first generation asymmetric approach to akuammicine (Scheme 1) was devised. The most efficient manner to akuammicine is to employ Rawal's approach using the intramolecular Heck reaction as an endgame approach.

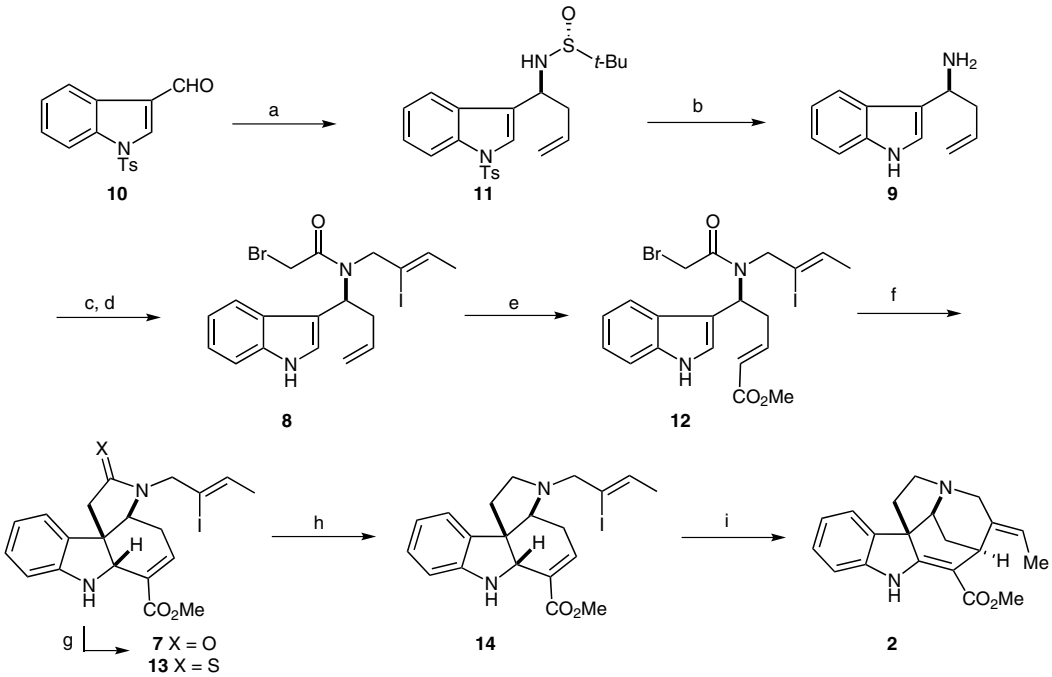
To gain entry to intermediate **7**, we envisioned using a biscyclization approach employing Heathcock's tactic in closing ring C followed by a novel intramolecular aza-Morita[12] or aza-Baylis–Hillman (IABH)[13] to close ring E to give the tetracyclic core; however, this would leave ring C at the amide oxidation state requiring subsequent deoxygenation. Arriving at intermediate **8** could be accomplished by N-alkylation of the primary amine **9** followed by amidation using the appropriate side chains. Chiral amine **9** could be accessed using Yus allylation chemistry[14] after removal of Ellman's *N*-*tert*-butyl sulfinamide[15] chiral auxiliary and deprotection of the indole nitrogen.

The synthesis of akuammicine (**2**) was accomplished starting from known compound **10** (Scheme 2),[1,15] which was easily synthesized from commercially available indole-3-carbaldehyde in one step.[16] (*R*)-*N*-*tert*-Butanesulfinamide and **10** were condensed in the presence of titanium(IV) ethoxide and indium(0). Upon the formation of the chiral imine, allyl bromide was added to effect the Barbier formation. Stereoselective addition of the resulting allyl–indium species into the imine afforded compound **11** in 87% yield with dr 10:1.[14] Treatment of **11** with hydrochloric acid removed the chiral auxiliary to give the free, primary amine. Further treatment with magnesium(0) effectively removed the tosyl group from the indole nitrogen to afford gramine **9** in 75% over two steps.

Amine **9** was alkylated with (*Z*)-2-iodobut-2-enyl bromide[17] and cesium carbonate. The resulting secondary amine was reacted with bromoacetyl chloride and triethylamine to yield intermediate **8** in 83% over two steps. Cross metathesis of **8** with methyl acrylate in the presence of Hoveyda–Grubbs 2nd generation catalyst[18] furnished compound **12** in 80% yield, setting the stage for the biscyclization. The first attempts at the spirocyclization of ring C using Heathcock's original conditions, treatment of **12** with only silver(I) triflate, did not lead to product formation but instead decomposition due to triflic acid generated under the reaction conditions. To address this issue, a wide range of bases were screened [e.g., pyridine, Et_3N, *i*-Pr_2NEt, 2,6-lutidine, 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP), NaH, and *t*-BuOK] with the best result being the use of 2,6-di-*tert*-butyl-4-methylpyridine which gave the product in 95% yield and with dr 13:1. Next, we focused on the formation of the E ring; typical conditions to effect the intramolecular aza-Morita[12] or aza-Baylis–Hillman (IABH)[13] were employed (e.g., Bu_3P, DMAP, DABCO, Et_3N, *i*-Pr_2NEt) in various solvents with no product formation. It was only upon treatment of the tricycle with DBU that intermediate **7** was formed in 90% yield. Due to the fact that DBU was the only reagent capable of effecting this transformation, coupled with the fact that it is the most basic, led us to hypothesize an alternative mechanism, namely an intramolecular vinylogous Mannich reaction followed by an isomerization. In 2012, Kwon reported a similar intramolecular Morita reaction using trimethylphosphine. The use of DBU in their system, despite being more hindered, led to an unproductive, base-mediated elimination as opposed to cyclization.[19] Al-



Scheme 1 Retrosynthetic analyses for the synthesis of (–)-akuammicine (**2**)

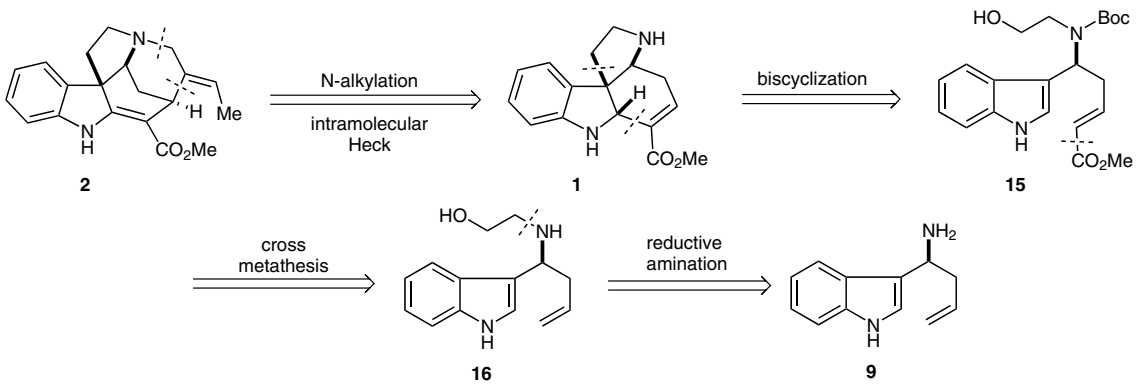


Scheme 2 *Reagents and conditions*: (a) (*R*)-*N*-*tert*-butanesulfinamide, In(0), $Ti(OEt)_4$ then allyl bromide, THF, 87%, dr 10:1; (b) 4 M HCl, dioxane then Mg(0), MeOH, 75% over 2 steps; (c) (*Z*)-2-iodobut-2-enyl bromide, Cs_2CO_3; (d) $BrCH_2COCl$, Et_3N, 83% over 2 steps; (e) methyl acrylate, Hoveyda–Grubbs 2nd generation catalyst (10 mol%), CH_2Cl_2, 80%; (f) AgOTf, DTEMP then DBU, toluene, r.t., 60%; (g) Lawesson's reagent, 87%; (h) Et_3OBF_4 then $NaBH_4$, MeOH, 92% over 2 steps; (i) $Pd(OAc)_2$, Ph_3P, Et_3N, 87%.

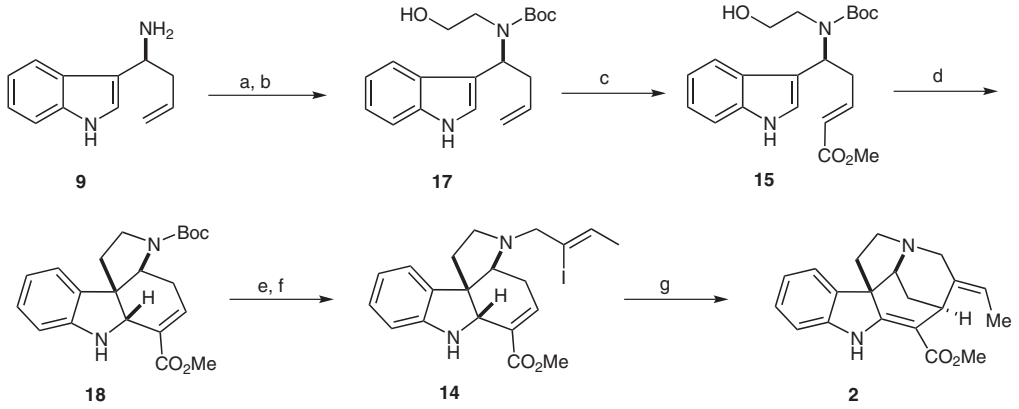
together, these data support the Mannich mechanism with DBU.

We were able to effect a sequential one-pot variant of the reaction (i.e., **12** to **7**) in 60% overall yield. Treatment of **7** with Lawesson's reagent afforded thioamide **13** in 87% yield. Chemoselective alkylation of sulfur with triethyloxonium tetrafluoroborate and subsequent sodium borohydride reduction effectively removed the sulfur to yield **14** in 92% over two steps.[20] Of mention is the fact the use of trimethyloxonium tetrafluoroborate resulted in partial N-methylation of the indoline nitrogen. Finally, the intramolecular Heck reaction of enoate **14** using a modification of Rawal's conditions, namely palladium(II) acetate, triphenylphosphine, and triethylamine as solvent, afforded akuammicine (**2**) in 87%.

The need for the reduction of lactam **7** to pyrrolidine **14** afforded an opportunity to avoid this redox step and streamline our approach. To this end, we devised a second-generation asymmetric synthesis of ABCE tetracycle **1**.[21] Inspiration for this new route (Scheme 3) came from Ellman's asymmetric synthesis of (–)-aurantioclavine.[22] Specifically, in a key step it was found that 3-(2-hydroxyethyl)indoles



Scheme 3 Retrosynthetic analyses for the synthesis of (–)-akuammicine (**2**)



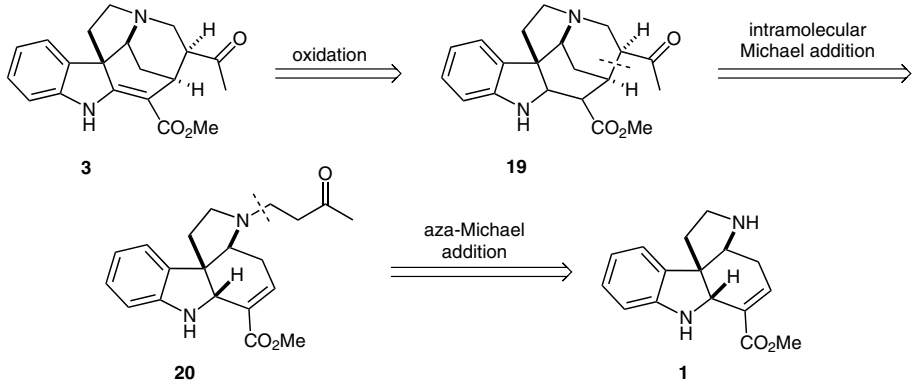
Scheme 4 *Reagents and conditions*: (a) 50% ethyl glyoxalate in toluene then $LiAlH_4$; (b) Boc_2O, *i*-Pr_2NEt, CH_2Cl_2, 57% over 2 steps; (c) methyl acrylate, Hoveyda–Grubbs 2nd generation catalyst (10 mol%), CH_2Cl_2, 80%; (d) Ph_3P, DEAD then DBU, 80 °C, 12 h, 56%; (e) TFA, CH_2Cl_2, quant.; (f) (*Z*)-2-iodobut-2-enyl bromide, K_2CO_3, MeCN, 71%; (g) $Pd(OAc)_4$, Ph_3P, Et_3N, 87%.

quickly undergo cyclization to form spiro[cyclopropyl]indolenines using Mitsunobu conditions.[21] We hypothesized that Mitsunobu activation of *N*-Boc-*N*-(2-hydroxyethyl)-substituted gramine **15** would access the desired spiroindolenine with the correct oxidation state on the C ring (Scheme 3).

Following the first-generation approach, the late stage intramolecular Heck reaction would be applied after alkylating ABCE tetracycle **1**. We envisioned arriving at **1** via a revised biscyclization of intermediate **15** where first ring C would form under Mitsunobu conditions followed by an intramolecular Mannich reaction to construct the E ring. Intermediate **15** could be readily made from **16** by *N*-Boc protection then cross metathesis. Intermediate **16** would in turn be accessed from **9**, which we had already synthesized in the first-generation approach using the Yus allylation strategy.[14]

Starting from gramine **9**, various alkylation reactions were attempted using substrates such as 2-bromoethanol and various other ethanol derivatives with little success. Recourse to reductive amination ultimately proved successful (Scheme 4).[1,4] Ethyl glyoxalate and **9** were condensed in the presence of 4-Å molecular sieves to form the imine, which was then reduced using lithium aluminum hydride to give amino alcohol **16**. Finally, *N*-Boc protection of **16** using di-*tert*-butyl carbonate and Hünig's base afforded **17** in 57% yield over two steps.

Alcohol **17** was then subjected to cross metathesis with methyl acrylate using Hoveyda–Grubbs 2nd generation catalyst[18] to provide **15** in 80% yield, setting the stage for the biscyclization. Under Mitsunobu conditions,[22] **15** cyclized forming ring C and the spirocenter with full stereocontrol. Upon further treatment with DBU in the same pot, the E ring cyclized to afford Boc-protected ABCE tetracycle **18** in 56% yield. Removal of the *N*-Boc group using trifluoroacetic acid furnished ABCE tetracycle **1**. Alkylation of **1** with (*Z*)-2-iodobut-2-enyl bromide generated compound **14** in 71% yield. Using Rawal's endgame strategy of the intramolecular Heck cyclization,[11] akuammicine (**2**) was obtained in 87% yield.

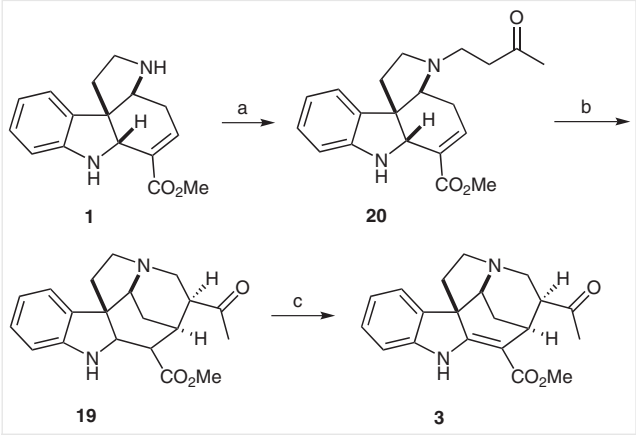


Scheme 5 Retrosynthetic approach to alstolucine B

With routes to the ABCE tetracycle **1** and akuammicine (**2**) in hand, we turned our focus to the alstolucines. Retrosynthetic analysis of alstolucine B (**3**) suggested it could be derived from **19** via oxidation (Scheme 5). Indoline **19** in turn would be prepared via an intramolecular Michael reaction of Mannich base **20**, which would be derived from tetracycle **1**. Finally, access to epimeric alstolucine F (**4**) from **3** would be possible using Kuehne's protocol for equilibration.[4]

The synthesis of **3** began with the site-selective intermolecular aza-Michael reaction[23] between **1** and methyl vinyl ketone (MVK) to afford Mannich base **20** in 58% yield (Scheme 6). Cyclization of the D ring was best accomplished by treating **20** with sodium hexamethyldisilazanide at –10 °C for two hours, which furnished pentacycle **19** in 25% yield. Finally, Swern oxidation of indoline **19** delivered alstolucine B (**3**) in 20% yield.

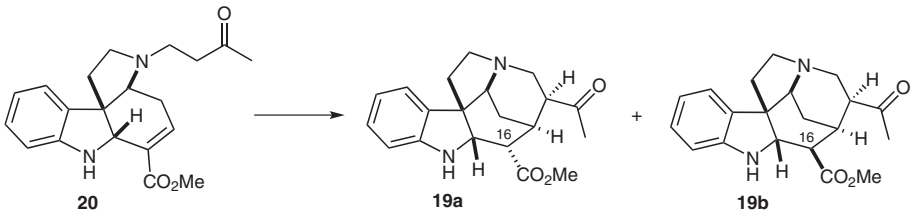
Numerous conditions were screened to optimize the intramolecular Michael addition of **20**[24] (Table 1). Upon determining the effects of substrate concentration, addition rate, addition sequence, solvents, equivalents of base, and counterions, the best conditions found were the addition of 1 M sodium hexamethyldisilazanide in tetrahydrofuran (0.95 equiv) to the substrate (0.01 M in THF) over 10 minutes at –2 °C to 0 °C. Upon stirring for two hours at this temperature, compounds **19a** and **19b** were formed as a mixture of two inseparable diastereomers in 25% yield with a ratio of 1.4:1 to 1.7:1. Furthermore, if a protecting group such as the benzyloxycarbonyl (Z) group was used on the indoline nitrogen prior to the Michael addition, the resulting diastereomers at C16 were separable. The diastereomers differed in the stereochemical configuration at C16 as determined through NOE based on the known stereocenters (Figure 2). Ultimately this is of no consequence as the stereocenter is destroyed following oxidation.



Scheme 6 *Reagents and conditions*: (a) MVK (1.0 equiv), MeOH, –78 °C, 3 h, 58%; (b) 1 M NaHMDS in THF (0.95 equiv), THF, –10 °C, 2 h, 25%; (c) oxalyl chloride (2.4 equiv), DMSO (4.2 equiv), Et_3N (5.0 equiv), –60 °C to r.t., 2 h, 20%.

In an attempt to optimize the D ring cyclization, we studied the effects of protecting the indole nitrogen. It was determined that addition of either a methyl, ethyl, or benzyl carbamate on the indole nitrogen (not shown) did slightly increase the yield of the intramolecular Michael addition to 29%, 39%, and 60% respectively. At this stage, we turned our attention to indoline **19** oxidation (Table 2).

Table 1 Intramolecular Michael Addition Conditions



Entry	Base	Solvent	Temp (°C)	Time (h)	Yield (%)
1	DBU	THF	r.t.	48	–[a]
2	NaOMe	MeOH	0 to r.t.	5	–[a]
3	Triton B (*t*-Bu_4NOH)	DME	reflux	16	–[a]
4	BEMP[b]	THF	r.t.	24	–[a]
5	pyrrolidine	MeCN	r.t.	48	–[a]
6	NaH	THF	70	5	20
7	NaHMDS	THF	–78 to r.t.	15	–[a]
8	NaHMDS	THF	–10 to 0	2	5–25

[a] Not observed.
[b] 2-(*tert*-Butylimino)-2-(diethylamino)-1,3-dimethylperhydro-1,3,2-diazaphosphorine.

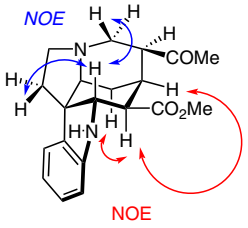
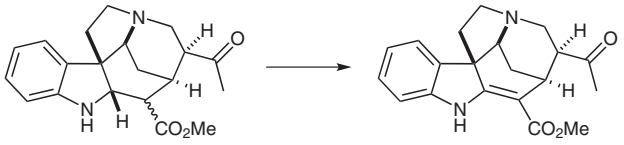


Figure 2 NOE data for compound **19b**

Table 2 Indoline Oxidation



19 **3**

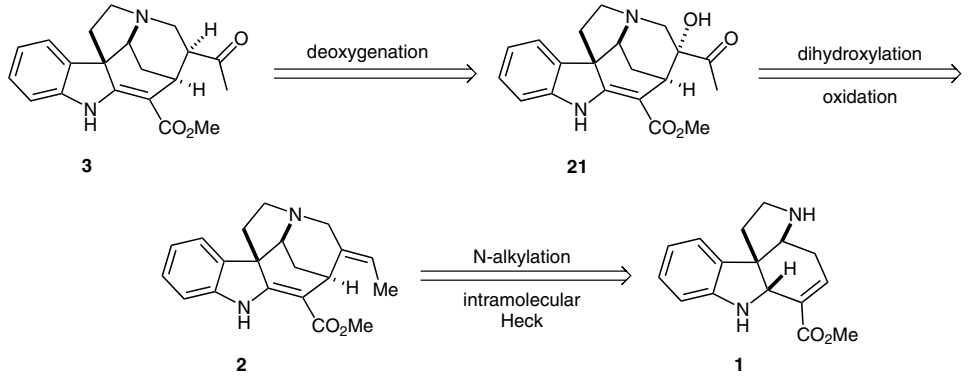
Entry	Oxidant	Solvent	Temp (°C)	Time (h)	Yield (%)
1	$Pb(OAc)_4$	CH_2Cl_2	–10	1	–[a]
2	DDQ	dioxane	r.t., reflux	18	–[a]
3	$PdCl_2$, Et_3N	MeOH	r.t.	96	trace[b]
4	DMS, NCS, Et_3N	CH_2Cl_2	–78	4	trace[b]
5	$(COCl)_2$, DMSO, Et_3N	CH_2Cl_2	–78 to r.t.	1.5	trace[b]
6	$(COCl)_2$, DMSO, Et_3N	CH_2Cl_2	–60 to 0	2	20

[a] Not observed.
[b] Observed by LC-MS.

Previous work on the oxidation on indolines with similar core ABCE structures had shown modest to good yields when using lead tetraacetate or 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) as the oxidants.[25] Upon trying these conditions on substrate **19**, varying the equivalents of oxidant, temperature, and reaction time, no product formation was observed. At this time we turned to oxidation conditions shown to oxidize simple indoline systems employing palladium(II) chloride, Corey–Kim, and Swern conditions, all showing trace amounts of product formation.[17b,26] Upon optimizing the Swern oxidation conditions, particularly temperature, alstolucine B (**3**) was prepared in 20% yield.

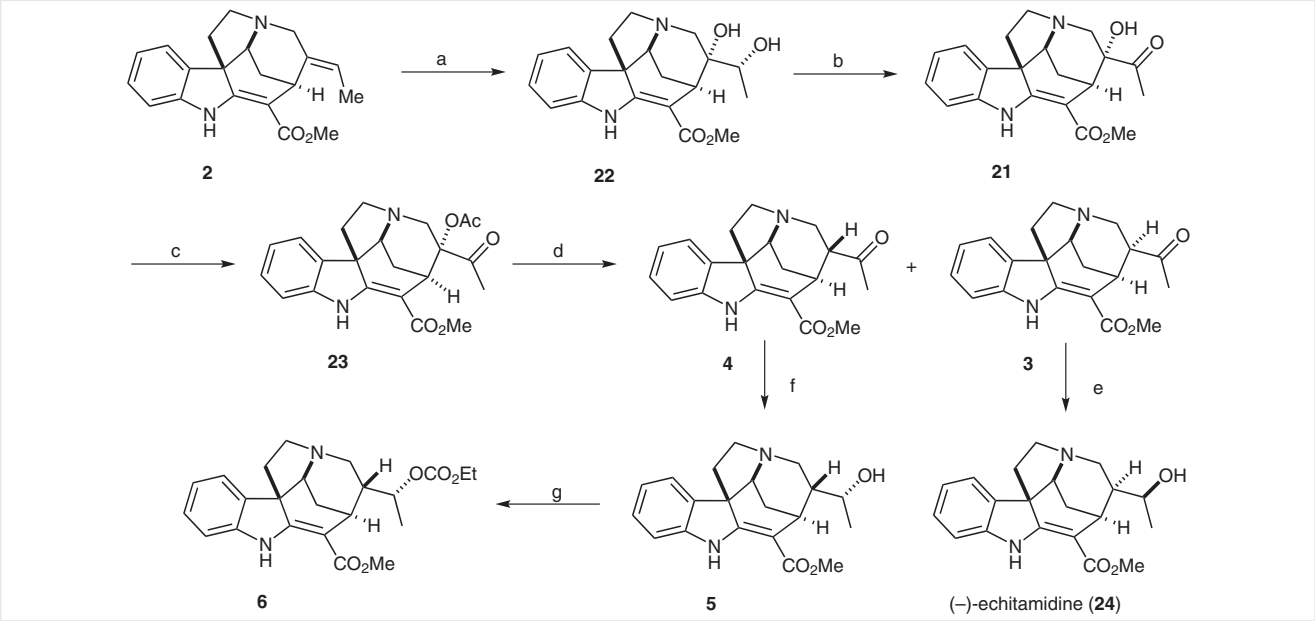
The low yields plaguing our synthetic route to the alstolucines justified a newer, more efficient approach. As we had an efficient route to structurally similar akuammicine (**2**) in place, we reasoned that manipulations of the ethylidene in **2** would be the most straightforward route to accessing the alstolucines. A concise route would certainly feature anti-Markovnikov hydroboration followed by a subsequent oxidation; however, Levy and co-workers had shown that akuammicine (**2**) under standard hydroboration conditions underwent Markovnikov addition.[27] Numerous attempts to alter the hydroboration conditions using bulkier boranes, such as thexylborane,[28] were unsuccessful with no product formation. In addition, one might envision using ozonolysis on the pendent alkene followed by a Wittig or Horner–Wadsworth–Emmons reaction[29] to install the pendant ketone; however, these attempts were ineffective with only the ozonolysis followed by the Horner–Wadsworth–Emmons forming a trace amount of alstolucine B (**3**) or F (**4**). With this in mind, we envisioned a more conservative, second-generation route (Scheme 7) consisting of dihydroxylation, oxidation of the resulting secondary alcohol followed by selective deoxygenation of the tertiary alcohol to afford alstolucine B (**3**).

To realize our new approach (Scheme 8),[4] akuammicine (**2**) was subjected to Upjohn dihydroxylation conditions to afford 19,20-dihydroxyakuammicine (**22**) in 86% yield.[30] The resulting secondary alcohol was oxidized using Corey–Kim conditions to give 19-hydroxyalstolucine B (**21**) in 66% yield.[31] Employing elegant work by Molander on the acyloin reduction,[32] we set out to deoxygenate the α-hydroxy group using samarium diiodide chemistry. After initial attempts to reduce the free hydroxy were unsuccessful (i.e., the more step-efficient option), recourse was made to the α-acetoxy variant by acylating the acyloin using acetic anhydride, triethylamine, and catalytic 4-(dimethylamino)pyridine to access 19-acetoxyalstolucine B (**23**) in 95% yield. Subjecting



3 **21** **2** **1**

Scheme 7 Second-generation retrosynthesis of alstolucine B



Scheme 8 *Reagents and conditions*: (a) NMO (5 equiv), OsO_4 (10 mol%), *t*-BuOH–THF–MeOH (3:2:1), 18–36 h, 86%; (b) NCS (1.5 equiv), DMS (1.65 equiv), Et_3N (2.0 equiv), CH_2Cl_2, 0 °C, 3 h, 66%; (c) Ac_2O (1.1 equiv), Et_3N (1.2 equiv), DMAP (0.1 equiv), 0 °C to r.t., 18 h, 95%; (d) 1.0 M SmI_2 in THF (5.0 equiv), MeOH–THF (1:2), –78 °C to r.t., 71%; (e) $NaBH_4$, MeOH, 85%; (f) $NaBH_4$, $CeCl_3·7H_2O$, MeOH, 83%; (g) $EtCO_2Cl$, Et_3N, CH_2Cl_2, 73%.

23 to samarium diiodide furnished a readily separable mixture of alstolucines B (**3**) and F (**4**) in 1.6:1 ratio with an overall yield of 71%.

Subsequent reduction of alstolucine B (**3**) with sodium borohydride resulted in the formation of (–)-echitamidine (**24**) as a single diastereomer in 85% yield. The Luche reduction of alstolucine F (**4**) led to (–)-*N*-demethylalstogucine (**5**) in 83% as a single diastereomer.[33] Upon reaction of **5** with ethyl chloroformate in the presence of triethylamine, alstolucine A (**6**) was formed in 73% yield.

In summary, we have achieved the first enantioselective total syntheses of (–)-alstolucines A (**6**), (–)-B (**3**), and (–)-F (**4**), (–)-echitamidine (**24**), and (–)-*N*-demethylalstogucine (**5**) using our second-generation biscyclization method for the synthesis of ABCE tetracycle **1** and a dihydroxylation/acyloin reduction sequence to modify the ethylidene side chain of akuammicine (**2**). The newly synthesized alkaloids, **3**–**6**, were shown to resensitize vincristine-resistant KB cells to vincristine[2] and further investigation into the biological activity of **3**–**6** is currently being pursued. Those results will be reported in due course.

All reactions containing air or water sensitive reagents were performed in flame-dried or oven-dried glassware under an argon or N_2 atmosphere. CH_2Cl_2 and THF were passed through two columns of neutral alumina and toluene was passed through one column of neutral alumina and one column of Q5 reactant. Prior to use, methyl acrylate was distilled, Et_3N was distilled from CaH_2 and 4-Å molecular sieves were activated by flame-drying under vacuum. For cross-metathesis and SmI_2 reactions, all solvents were deaerated by bubbling argon through for at least 1 min/mL. (*Z*)-2-Iodobut-2-enyl bromide was prepared according to the procedure of Cook.[17b] All other reagents and solvents for workup procedures were purchased from commercial sources and used without further purification. TLC was performed on Analtech $60F_{254}$ silica gel plates. Detection was performed using UV light, $KMnO_4$ stain, PMA stain, and subsequent heating. Flash column chromatography was performed according to the procedure of Still[34] using ICN Silitech 32-63 D 60Å silica gel with the indicated solvents. ^1H and ^{13}C NMR spectra were recorded at the indicated field strength in $CDCl_3$ at r.t. and internally referenced to residual solvent signals.

Methyl 3-(3-Oxobutyl)-2,3,3a,4,6,7-hexahydro-1*H*-pyrrolo[2,3-*d*]carbazole-6-carboxylate (20)

To a stirred solution of **1** (670 mg, 2.48 mmol) in anhydrous MeOH (20 mL) at –78 °C was added a solution of methyl vinyl ketone (0.209 mL, 2.48 mmol) in anhydrous MeOH (20 mL) over 15 min. The mixture was stirred at –78 °C for a further 3 h. The reaction was quenched with H_2O (10 mL) at –78 °C. The resulting mixture was concentrated in vacuo to remove MeOH, followed by extraction with CH_2Cl_2 (2 × 10 mL). The combined organic phases were dried (Na_2SO_4) and concentrated under vacuum. The residue was purified by flash column chromatography (MeOH–CH_2Cl_2, 1:100 to 3:100) to give **20** (490 mg, 58%) as a pale yellow gum.

IR (neat): 3392, 2952, 2362, 1704, 1250, 1098, 743 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.05–7.01 (m, 3 H), 6.69 (td, *J* = 7.5, 1.0 Hz, 1 H), 6.56 (dd, *J* = 8.0, 1.0 Hz, 1 H), 4.53 (s, 1 H), 4.26 (s, 1 H), 3.76 (s, 3 H), 3.18–3.04 (m, 2 H), 2.95 (dd, *J* = 4.5, 2.9 Hz, 1 H), 2.66–2.51 (m, 4 H), 2.44–2.37 (m, 1 H), 2.29–2.22 (m, 1 H), 2.21–2.14 (m, 1 H), 2.13 (s, 3 H), 1.98–1.90 (m, 1 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 208.23, 167.28, 150.06, 139.25, 132.55, 129.98, 128.06, 122.79, 118.46, 109.05, 63.64, 61.27, 53.29, 51.68, 50.69, 48.32, 42.55, 37.68, 30.08, 24.89.

HRMS (FAB): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{25}N_2O_3$: 341.1865; found: 341.1860.

(±)-2,16-Dihydroalstolucine B (19)

To a stirred solution of **20** (120 mg, 0.352 mmol) in THF (30 mL) at –10 °C was added 1 M NaHMDS in THF (0.33 mL, 0.33 mmol) in THF (2 mL) over 10 min. The resulting mixture was stirred at –10 °C for a further 2 h. The reaction was quenched with sat. aq NH_4Cl (10 mL) and diluted with H_2O (5 mL). The resulting mixture was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic phases were dried (Na_2SO_4) and concentrated under vacuum. The residue was purified by flash column chromatography (MeOH–CH_2Cl_2, 5:100) to give an inseparable mixture of two diastereomers (30 mg, 25%) as a pale yellow solid.

IR (neat): 3381, 2949, 1723, 1706, 1482, 1170, 742 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.07 (td, *J* = 7.6, 1.2 Hz, 1 H), 6.99 (d, *J* = 7.4 Hz, 1 H), 6.75 (td, *J* = 7.4, 0.9 Hz, 1 H), 6.64 (d, *J* = 7.6 Hz, 1 H), 4.37 (s, 1 H), 3.75 (s, 1 H), 3.73–3.72 (m, *J* = 8.4 Hz, 4 H), 3.35–3.30 (m, 1 H), 3.10–2.91 (m, 3 H), 2.79 (s, 1 H), 2.73 (dd, *J* = 13.7, 5.0 Hz, 1 H), 2.34 (dd, *J* = 10.1, 3.3 Hz, 1 H), 2.22–2.18 (dd, *J* = 12.8, 6.0 Hz, 1 H), 2.16–2.08 (m, 4 H), 1.69 (ddd, *J* = 12.8, 11.3, 8.0 Hz, 1 H), 1.41 (dt, *J* = 14.4, 2.3 Hz, 1 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 208.30, 174.53, 149.34, 129.76, 128.35, 122.17, 118.96, 109.68, 62.14, 57.69, 53.52, 52.05, 51.35, 51.27, 47.55, 45.42, 38.88, 28.91, 26.74, 23.46.

HRMS (FAB): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{25}N_2O_3$: 341.1865; found: 341.1862.

(±)-Alstolucine B (3)

A solution of DMSO (23.8 mg, 0.304 mmol) in CH_2Cl_2 (0.5 mL) was added under argon to a solution of oxalyl chloride (14.6 mg, 0.115 mmol) in CH_2Cl_2 (2 mL) at –78 °C. The resulting mixture was stirred at –78 °C for 20 min, followed by addition of a solution of **19** (26 mg, 0.1 mmol) in CH_2Cl_2 (0.5 mL). The stirring was continued at –78 °C for a further 20 min, and then a solution of Et_3N (38 mg, 0.4 mmol) in CH_2Cl_2 (0.5 mL) was added. The mixture was allowed to warm to r.t. over 2 h. Then the reaction was quenched with water (3 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic phases were dried (Na_2SO_4) and concentrated under vacuum. The residue was purified by flash column chromatography (MeOH–CH_2Cl_2, 1:100 to 5:100) to give an intermediate that was dissolved in CH_2Cl_2 (5 mL) and subsequently washed with 1 M aq HCl (2 mL) and 10% aq NaOH (2 mL) to give of **3** (5 mg, 20%) as a white foam. ^{1}H and ^{13}C NMR spectra were identical with reported literature values.[2,4]

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Supporting Information

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References

(1) Sirasani, G.; Andrade, R. B. In *Strategies and Tactics in Organic Synthesis*; Harmata, M., Ed.; Academic Press: Oxford, **2013**.
(2) Tan, S.-J.; Low, Y.-Y.; Choo, Y.-M.; Abdullah, Z.; Etoh, T.; Hayashi, M.; Komiyama, K.; Kam, T.-S. *J. Nat. Prod.* **2010**, *73*, 1891.
(3) Hesse, M.; Zhu, J.-P.; Hu, W. *Planta Med.* **1989**, *55*, 463.
(4) Teijaro, C. N.; Munagala, S.; Zhao, S.; Sirasani, G.; Kokkonda, P.; Malofeeva, E. V.; Hopper-Borge, E.; Andrade, R. B. *J. Med. Chem.* **2014**, *57*, 10383.
(5) Kuehne, M. E.; Brook, C. S.; Frasier, D. A.; Xu, F. *J. Org. Chem.* **1994**, *59*, 5977.
(6) Millson, M. F.; Robinson, R.; Thomas, A. F. *Experientia* **1953**, *9*, 89.
(7) Henry, T. A. *J. Chem. Soc.* **1932**, 2759.
(8) Shittu, H.; Gray, A.; Furman, B.; Young, L. *Phytochem. Lett.* **2010**, *3*, 53.
(9) Menzies, J. R. W.; Paterson, S. J.; Duwiejua, M.; Corbett, A. D. *Eur. J. Pharmacol.* **1998**, *350*, 101.
(10) Toczko, M. A.; Heathcock, C. H. *J. Org. Chem.* **2000**, *65*, 2642.
(11) Rawal, V. H.; Michoud, C. *Tetrahedron Lett.* **1991**, *32*, 1695.
(12) Matsui, K.; Takizawa, S.; Sasai, H. *J. Am. Chem. Soc.* **2005**, *127*, 3680; and references cited therein.
(13) For a comprehensive review, see: Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811.
(14) Gonzalez-Gomez, J. C.; Medjahdi, M.; Foubelo, F.; Yus, M. *J. Org. Chem.* **2010**, *75*, 6308.
(15) (a) Sirasani, G.; Andrade, R. B. *Org. Lett.* **2009**, *11*, 2085. (b) Sirasani, G.; Paul, T.; Dougherty, W. Jr.; Kassel, S.; Andrade, R. B. *J. Org. Chem.* **2010**, *75*, 3529. (c) Sirasani, G.; Andrade, R. B. *Org. Lett.* **2011**, *13*, 4736.
(16) Robak, M. T.; Herbage, M. A.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 3600.
(17) (a) Rawal, V. H.; Michoud, C.; Monestel, R. F. *J. Am. Chem. Soc.* **1993**, *115*, 3030. (b) Yin, W.; Kabir, S.; Wang, Z.; Rallapalli, S. K.; Ma, J.; Cook, J. M. *J. Org. Chem.* **2010**, *75*, 3339.
(18) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168.
(19) Andrews, I. P.; Kwon, O. *Chem. Sci.* **2012**, *3*, 2510.
(20) Raucher, S.; Klein, P. *Tetrahedron Lett.* **1984**, *21*, 4061.
(21) Zhao, S.; Sirasani, G.; Vaddypally, S.; Zdilla, M. J.; Andrade, R. B. *Angew. Chem. Int. Ed.* **2013**, *52*, 8309.
(22) Brak, K.; Ellman, J. A. *Org. Lett.* **2010**, *12*, 2004.
(23) Martin, S. F.; Clark, C. W.; Corbett, J. W. *J. Org. Chem.* **1995**, *60*, 3236.
(24) (a) Yang, R.; Huang, P. *Chem. Eur. J.* **2010**, *16*, 10319. (b) Deiters, A.; Chen, K.; Eary, C. T.; Martin, S. F. *J. Am. Chem. Soc.* **2003**, *125*, 4541.
(25) (a) Wenkert, E.; Pestchanker, M. J. *J. Org. Chem.* **1988**, *53*, 4875. (b) Wenkert, E.; Orito, K.; Simmons, D. P. *J. Org. Chem.* **1983**, *48*, 5006.

(26) (a) Kuehne, M.; Hall, T. C. *J. Org. Chem.* **1976**, *41*, 2742. (b) Dufour, M.; Gramain, J. C.; Husson, H. P.; Sinibaldi, M. E.; Troin, Y. J. *J. Org. Chem.* **1990**, *55*, 5483. (c) Jones, S. B.; Simmons, B.; Mastracchio, A.; MacMillan, D. W. *Nature (London)* **2011**, *475*, 183.
(27) Mirand, C.; Massiot, G.; Le Men-Oliver, L.; Levy, J. *Tetrahedron Lett.* **1982**, *23*, 1257.
(28) Nakano, A.; Ushiyama, M.; Iwabuchi, Y.; Hatakeyama, S. *Adv. Synth. Catal.* **2005**, *347*, 1790.
(29) Hon, Y.-S.; Lu, L.; Li, S.-Y. *Chem. Commun.* **1990**, 1627.
(30) Vanrheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, *17*, 1973.
(31) Corey, E. J.; Kim, C. U. *J. Am. Chem. Soc.* **1972**, *94*, 7586.
(32) Molander, G. A.; Hahn, G. *J. Org. Chem.* **1986**, *51*, 1135.
(33) Luche, J. L.; Rodriguez-Hahn, L.; Crabbe, P. *Chem. Commun.* **1978**, 601.
(34) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.