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Total Synthesis of the *Akuammiline* Alkaloid (±)-Vincorine

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Abstract: The first total synthesis of the *akuammiline* alkaloid (±)-vincorine (**6**) has been accomplished in about 1% overall yield in 31 steps. A concise assembly of the core 1,2-disubstituted 1,2,3,4-tetrahydro-4a,9a-iminoethanocarbazole (**1**), a distinctive feature of *akuammiline* and *strychnos* alkaloids, was developed via a three-step one-pot cascade reaction consisting of copper-catalyzed intramolecular cyclopropanation, ring-opening, and ring closure. The construction of the last seven-membered E-ring in a rigid two-ring moiety (**31**, **45** to **47**) through Heck coupling, Michael addition, π-allyl/Heck or π-allyl/Stille coupling failed, leading us to seek an alternative method. After successful addition of an acetate side chain on C15 of the cyclohexenyl ring (D-ring) in Boc-protected **35b** by a Johnson−Claisen rearrangement and multistep modification of the functionality in the rearrangement product **33a**, the E-ring formation was then realized for providing pentacyclic lactam **32** through intramolecular condensation of the acid group on the D-ring and the amine group on the C-ring with Mukaiyama's reagent. An *E*-ethylidenyl group on the E-ring was stereoselectively added to afford lactam **56a** through a two-step reaction of **32** consisting of aldol addition with acetaldehyde and cis-elimination of the resulting hydroxyl group. Final elaboration of **56a**, including opening of the seven-membered E-ring, selective reduction of the α,β-unsaturated ester, and reclosure of the seven-membered E-ring completed the total synthesis of **6**.

Introduction

The tetracyclic core structure of 1,2-disubstituted 1,2,3,4-tetrahydro-4a,9a-iminoethanocarbazole (**1**) is found in a number of *akuammiline* alkaloids[1] such as echitamine (**2**),[2] corymine (**3**),[3] dihydropseudakuammine (**4**),[4] dihydroakuammine (**5**),[4] vincorine (**6**),[5] alstonamide (**7**),[6] demethoxyalstonamide (**8**),[6] vincophylline (**9**),[7] and *strychnos* alkaloid minfiensine (**10**)[8] (Figure 1). These indoline alkaloids have been historically used in traditional medicine in a formulation of multicomponent extracts from plants. For example, extracts from the leaves of *Winchia Callophylla A. DC.*, containing echitamine, have been used as a folk medicine to efficiently treat chronic tracheitis by the Thai minority and were introduced into the Chinese drug market (Dengtaiye Pian) in the 1970s.[9] Recent studies on these alkaloids have shown interesting biological activities including significant anticancer activity.[10]

Besides sharing the same **1** core, *akuammiline* alkaloids **2**−**9** are structurally characterized by a seven-membered E-ring, while the *strychnos* alkaloid minfiensine **10** has a six-membered E-ring. Methodologies for assembling **1** have been described by the Vollhardt group[11] using the oxidative cyclization reaction

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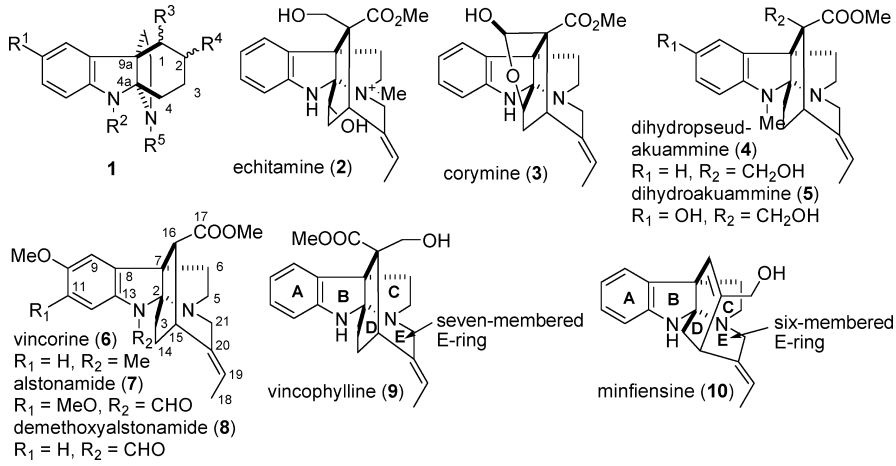
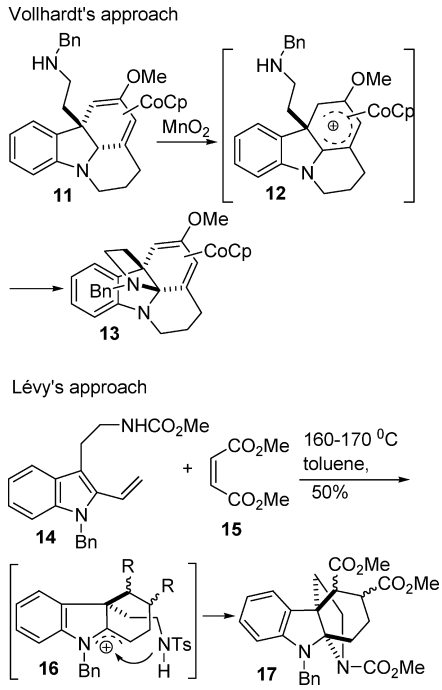
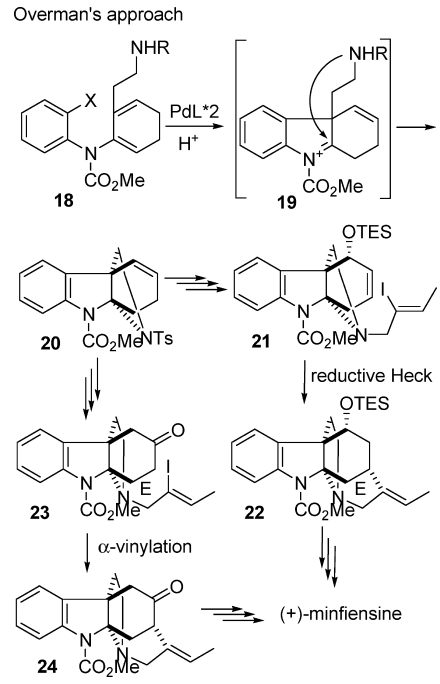


Figure 1. Indoline alkaloids with the 1,2-disubstituted 1,2,3,4-tetrahydro-4a,9a-iminoethanocarbazole skeleton.

Scheme 1



Scheme 2



of a cobalt complex **11** and by the Lévy group[12] using the Diels−Alder reaction of vinyltryptamine **14** and dimethyl maleate **15** at high temperature (Scheme 1). Later, the Overman group[13] used a cascade asymmetric Heck-iminium ion cyclization (Scheme 2) and our group[14] used a cascade reaction of cyclopropanation,[15] ring-opening, and ring closure (Scheme 3).

Although the methodology development has climaxed in the total synthesis of *strychnos* alkaloid minfiensine **10** by Overman's group[13] and our group,[14] and the first member of *akuammiline* alkaloids (echitamine) was characterized more than 80 years ago,[2] the synthesis of *akuammiline* alkaloids **2**−**9**, having a seven-membered E-ring, is unprecedented and remains as a great challenge to synthetic chemists[16] due to the difficulty of constructing the medium-size E-ring in a rigid cross-ring system. In Overman's first and second generation synthesis of (+)-minfiensine, a reductive Heck cyclization[13a] and a palladium-catalyzed α-vinylation of a ketone[13b] were employed to form the last six-membered E-ring (Scheme 2, **21** to **22**, **23**

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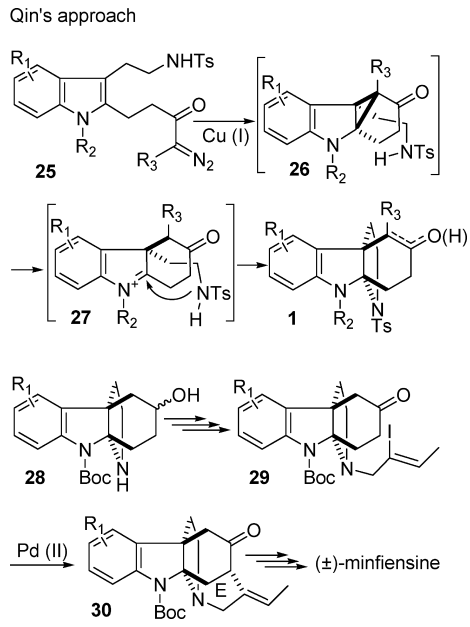
Scheme 3



to **24**). The palladium-catalyzed α-vinylation of a ketone was also employed to furnish the pentacyclic intermediate **30** from iodovinyl intermediate **29** in our synthesis of (±)-minfiensine (Scheme 3).[14] In our continuing synthetic study of *akuammiline* alkaloids, it has been questioned whether a similar strategy of Heck coupling or Michael addition can be adapted to form a seven-membered E-ring in a rigid cross-ring system like **1**. There is no doubt that the successful construction of the seven-membered E-ring from **1** would allow us to expand the application of our methodology and to complete the total synthesis of (±)-vincorine (**6**), a representative member of the *akuammiline* alkaloids. In this article, we report the efforts toward forming the seven-membered E-ring from **1**, which has led to the first total synthesis of **6**.

Results and Discussion

Retrosynthetic Analysis of the Total Synthesis and Construction of the Key E-ring. As shown in Scheme 4, we originally envisioned that the key seven-membered E-ring in vincorine might be assembled from heteroatomic substituted vinyl intermediate **31** (X = halogen, Me_3Sn) via a reductive Heck−Stille strategy, which was used for assembly of the six-membered E-ring in Overman's first generation synthesis of (+)-minfiensine.[13a] Although the Pd-catalyzed cross-coupling strategy was straightforward and attractive,[17] this approach could be problematic in this case, since it involves forming a seven-membered ring rather than a six-membered ring in a rigid two-ring system (C-ring and D-ring).[18] Alternatively, we also thought that E-ring formation could be realized through the condensation reaction of an ester group on the D-ring with a secondary amine group of the C-ring after removal of the Ts protecting group in **33**. Although there were multiple ways to add a methyl acetate side chain at C15 of the cyclohexenyl ring in allyl alcohol **35**, it seemed feasible that Johnson−Claisen rearrangement of **35** via intermediate **34** would generate **33**. Compound **35** could be easily obtained by multistep modification of tetracyclic intermediate **1**. Efficient assembly of **1** has been well established through a copper-catalyzed cascade reaction of cyclopropanation, ring-opening, and ring closure from the β-keto-α-diazoester **25**, which was prepared from readily available tetrahydrocarboline **36**.[19]

Improved Synthesis of Tetracycle 1 from Tetrahydrocarboline 36. In our previous preparation of **1** starting from tetrahydrocarboline **36** (Scheme 5),[14] a moderate yield (65−68%) for the two-step transformation of an ester group to a β-ketoester group (**37** to **38**) was acceptable, using Meldrum's acid and DCC as condensation reagents (conditions c and d), but the resulting β-ketoester **38** was always contaminated with an unidentified byproduct that required tedious purification. After rescreening some reagents, methyl potassium malonate, CDI and $MgCl_2$ were found to be the best choice for the condensation reaction to provide **38** in 85−88% yield over two steps (conditions c and e). After conversion of the β-ketoester group in **38a** and **38b** to a β-keto-α-diazoester group, the resulting α-diazoesters **25a** and **25b** were treated with 5 mol % of CuOTf in CH_2Cl_2 at room temperature to afford tetracyclic **1a** as a mixture of β-ketoester and enol ester (1:5 ratio) in 82% yield, and **1b** as a single enol isomer with 52% yield.

Attempts at E-ring Formation through Intramolecular Heck Coupling, Michael Addition, π-Allyl/Heck and π-Allyl/Stille Coupling. As outlined in Scheme 6, it was obvious that construction of the seven-membered E-ring from **31** by Heck coupling would be the most straightforward synthesis of vincorine **6**, so we tried this first. Toward this end, α-iodo-substituted allylamine **31** was prepared with an acceptable yield by a five-step procedure, consisting of the reduction of **1a** with $NaBH_4$, deprotection of the *N*-Ts group in **39** with Na/naphthalenide, allylation of the resulting secondary amine with (*Z*)-2-iodo-2-butenyl mesylate, mesylation of the hydroxyl group in **40** and removal of the mesylate group with DBU. To generate the desired vincorine **6**, the Pd-catalyzed Heck coupling of **31** employing a variety of reagents and conditions, such as $Pd(OAc)_2/HCO_2Na/Bu_4NCl/Ph_3P$,[13a,20] $Pd(PPh)_3/HCO_2H$/piperidine,[21] and $Pd(OAc)_2/Et_3N$[22] in different solvents exclusively provided amine **41** lacking the side chain as the major product. An intramolecular conjugate Michael addition of **31** for E-ring formation was also attempted, which yielded deiodinated **42** as a detectable byproduct after treatment of **31** with BuLi or ^{t}BuLi,[23] combined with CuCN/LiCl[24] or Me_3SiCl[25] in THF or HMPA at various temperatures. Application of a radical addition initiated with Bu_3SnH/AIBN and nickel-catalyzed addition, which have both been successfully used for forming a six-

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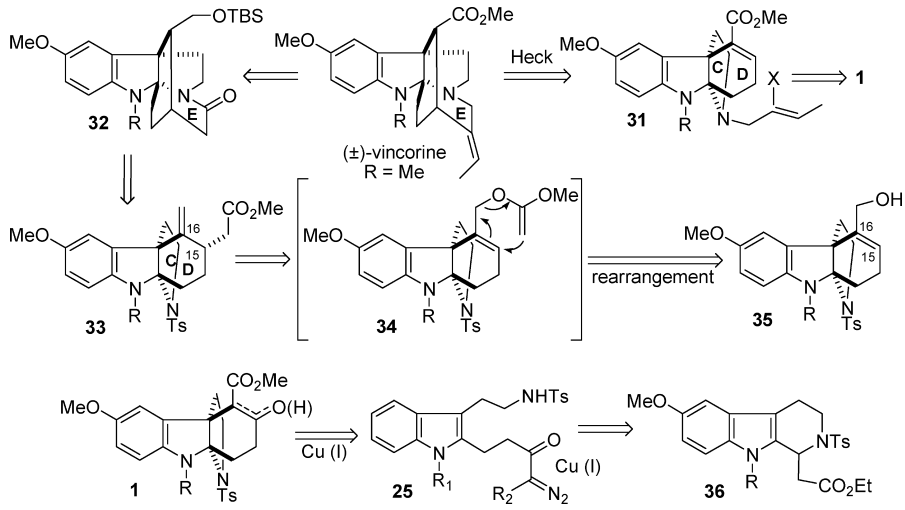
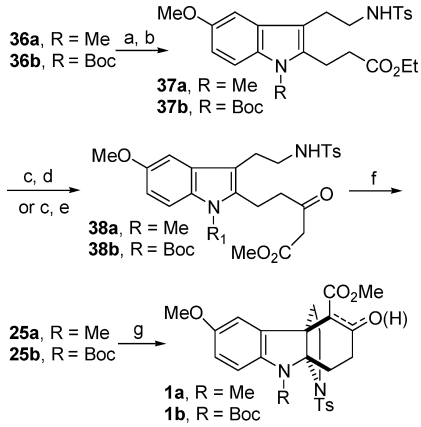
Scheme 4



Scheme 5[a]



[a] Reagents and conditions: (a) LiHMDS (1 M in THF, 1.5 equiv), THF, −40 °C, 10 h for **36a**; NaH (1.2 equiv), DMF, rt, 2 h for **36b**; (b) Pd/C (10 mol %), H_2 (1 atm), MeOH/THF 1:1, 24 h, **37a** (85% from **36a**), **37b** (87% from **36b**); (c) LiOH (3 equiv), MeOH/THF/H_2O 1:1:0.2, rt, 2 h; (d) DCC (1.1 equiv), DMAP (0.1 equiv), TEA (1.5 equiv), Meldrum's acid (1.5 equiv), CH_2Cl_2, 25 °C, 20 h, then reflux in MeOH for 10 h, 68% of **38a** from **37a**, 65% of **38b** from **37b**; (e) CDI, $MgCl_2$, methyl potassium malonate, 88% of **38a** from **37a**, 85% of **38b** from **37b**; (f) *p*-ABSA (1.1 equiv), TEA (3 equiv), CH_3CN, rt, 12 h, 82% of **25a**, 89% of **25b**; (g) 0.05 equiv of CuOTf, CH_2Cl_2, rt, 82% of **1a** from **25a** (1:5 ratio of ketone isomer/enol isomer), 52% of **1b** from **25b** (single enol isomer). *p*-ABSA=4-acetamidobenzenesulphonylazide.

membered ring in a multiring system by Cook,[26] resulted only in deiodinated product **42**.

In order to further test the possibility of a coordinated palladium-catalyzed π-allyl/Heck coupling and π-allyl/Stille coupling[27] to form the E-ring via possible transition state **48**, a series of 2-heteroatomic substituted vinyl intermediates **45**−**47** were prepared (Scheme 7). After reduction of **1a** or **1b** with $NaBH_4$, the resulting isomer mixture was mesylated with MsCl, and then treated with DBU to afford **43a** or **43b** in high yield. Reduction of **43b** with DIBAL-H in CH_2Cl_2 at −78 °C afforded allyl alcohol **35b** in 94% yield. The reduction of **43a** surprisingly provided **35a** in low yield (25% yield), along with the C-ring opened product **44** as the major product (65% yield) under the same conditions. Considering the lower reduction yield, methyl-substituted **35a** was abandoned and Boc-substituted **35b** was chosen for the next sequence of reactions. Removal of the Ts group in **35b** with Na/naphthalenide, followed by allylation of the resulting secondary amine with (*Z*)-2-iodo-2-butenyl mesylate provided **45** in high yield. Palladium-catalyzed iodide/tin exchange with Me_6Sn_2 gave **46** in a moderate yield. Treatment of **46** with Cl_3CCN, Ph_3P, and 2,6-lutidine in CH_2Cl_2 afforded chloride **47** in high yield. After obtaining compounds **45**−**47**, two palladium catalysts, Pd_2dba_3 and $Pd(Ph_3)_4$, with or without additives[28] such as CsF, CuI, and NBS, were screened for the designed π-allyl/Heck coupling and π-allyl/Stille coupling. Unfortunately, none of the reactions gave the desired product **49**, and a complex mixture of byproduct was always observed.

E-ring Construction via Amide Bond Formation: Installation of a Side Chain on the D-ring through Johnson−Claisen Rearrangement.[29] Because the E-ring formation in a rigid cross-ring system in **31** and **45**−**47** failed to proceed via Heck coupling, radical coupling, Michael addition, π-allyl/Heck coupling, and π-allyl/Stille coupling, we turned our attention to a different approach. As shown in Scheme 8, we thought that E-ring construction through amide bond formation would be easier than previous approaches, provided we could stereoselectively prepare intermediate **33a** with an ester side chain on C15 of the D-ring.[30] It seemed feasible that **33a** could be generated from allyl alcohol **35b** via an acid promoted Johnson−Claisen rearrangement with trimethyl orthoacetate.[31]

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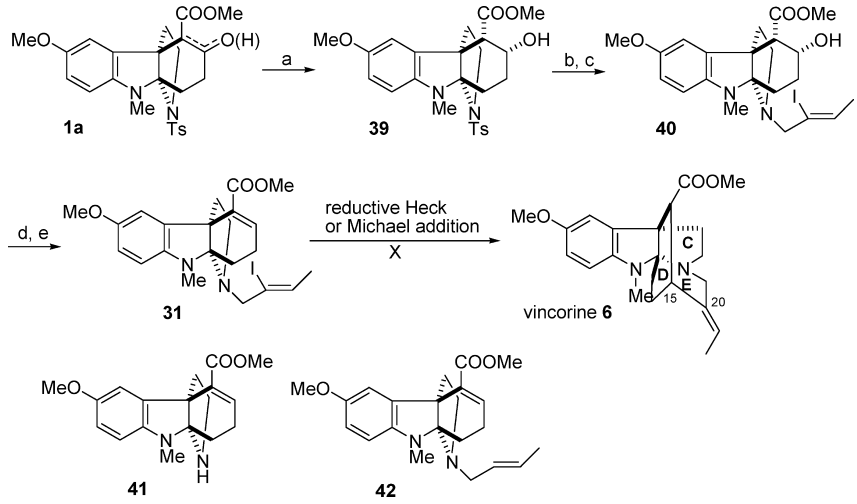
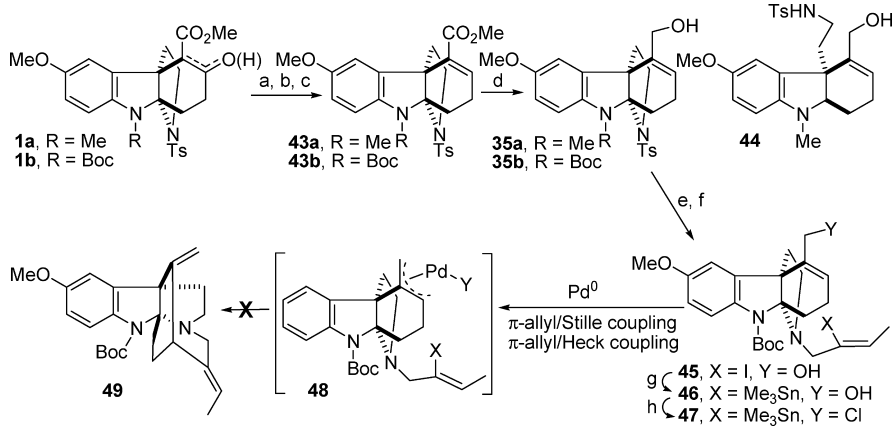
(30) Attempts to introducing an (*E*)-2-butenol group into compound **43a** to generate an intermediate with a side chain at C15 failed by an intermolecular Heck reaction with (*Z*)-2-iodo-2-butenol or by a Stille coupling with (*Z*)-2-trimethyltin-2-butenol, probably due to the hindrance of the pyrrolidine ring in **43a** preventing access of a nucleophile to the double bond.

Scheme 6[a]



[a] Reagents and conditions: (a) $NaBH_4$ (3 equiv), MeOH/THF, −5 °C, 24 h, 76%; (b) Na/naphthalenide (10 equiv), THF, −78 °C, 0.5 h; (c) (*Z*)-2-iodo-2-butenyl mesylate (2 equiv), K_2CO_3 (4 equiv), KI (0.2 equiv), CH_3CN, reflux, 24 h, 51% from **39**; (d) MsCl (3 equiv), Et_3N (5 equiv), DMAP (0.2 equiv), CH_2Cl_2, 0 °C, 10 min, then rt, 2 h; (e) DBU (5 equiv), benzene, reflux, 2 h, 84% from **40**.

Scheme 7[a]



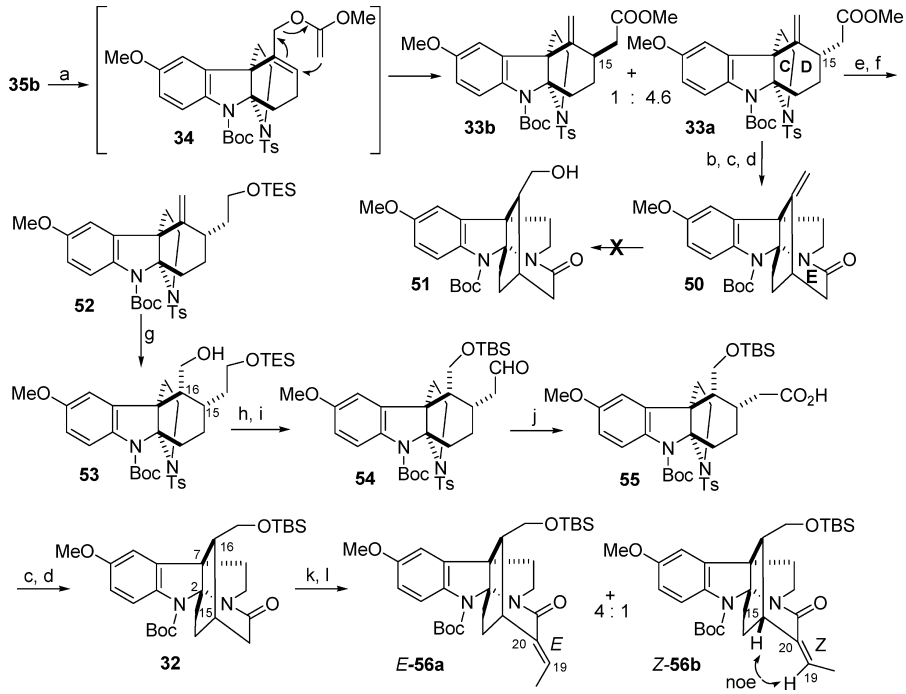
[a] Reagents and conditions: (a) $NaBH_4$ (3 equiv), THF/MeOH (50:1), −5 °C, 24 h; (b) MsCl (3 equiv), Et_3N (5 equiv), DMAP, 0 °C to rt, 5 h, CH_2Cl_2; (c) DBU (5 equiv), benzene, reflux, 10 h, 78% of **43a** from **1a**, 72% of **43b** from **1b**; (d) DIBAL-H (4 equiv), −78 °C, 0.5 h, CH_2Cl_2, 25% of **35a** and 65% of **44** from **43a**, 94% of **35b** from **43b**; (e) Na/naphthalenide, 0.5 h; (f) (*Z*)-2-iodo-2-butenyl mesylate (2 equiv), K_2CO_3 (4 equiv), KI (0.2 equiv), CH_3CN, reflux, 24 h, 93% of **45** from **35b**; (g) Me_6Sn_2 (5 equiv), $PdCl_2(PPh_3)_2$ (0.3 equiv), PhOK (2.5 equiv), dioxane, rt, 48 h, 63%; h) Cl_3CCN (2 equiv), PPh_3 (2 equiv), 2,6-lutidine (2 equiv), CH_2Cl_2, rt, 30 min, 92%.

Because methyl-substituted **35a** was obtained in low yield (Scheme 7) and was unstable when exposed to acid at higher temperatures, Boc-substituted **35b** was chosen for the Johnson−Claisen rearrangement. Treatment of **35b** with trimethyl orthoacetate in the presence of 0.3 equiv of pivalic acid in toluene at 110 °C gave two easily separated isomers, **33a** and **33b**, in 90% yield and a 4.6:1 ratio. The preferable formation of **33a** in the rearrangement probably resulted from the steric hindrance between the methoxy group on phenyl ring and the bulky methoxy ethylene substituent in the transition state **34** because the D-ring was close to the phenyl ring. An attempt at aldol addition of **33a** with acetaldehyde in the presence of LDA or LiHMDS failed, probably owing to the unexposed character of the α-methylene group located between the C-ring and D-ring. The relative stereochemistry at C15 in **33a** and **33b** was deduced from the pentacyclic intermediate **50**, which was generated in 55% yield from **33a**, via a three-step process consisting of hydrolysis, removal of the Ts protecting group, and condensation with Mukaiyama's reagent. The chemical structure of **50** was unambiguously identified by 2-D NMR spectra. The successful generation of **50** demonstrated a feasible strategy for assembling the E-ring of vincorine through amide bond formation.

Unfortunately, efforts to hydroborate the double bond in **50** with 9-BBN failed under various conditions. In most cases, compound **50** remained unchanged. Under harsh conditions, such as microwave irradiation, a complex mixture was obtained. The failure of hydroboration of **50** led us to modify the double bond before E-ring formation. After transformation of the ester group in **33a** to a TES protected hydroxyl group by a two-step sequence of reduction with DIBAL-H and protection of the resulting hydroxyl group with TESCl, compound **52** was

(31) For recent application of Johnson−Claisen rearrangement in natural product synthesis, see: (a) Schlama, T.; Baati, R.; Gouverneur, V.; Valleix, A.; Falck, J. R.; Mioskowski, C. *Angew. Chem., Int. Ed.* **1998**, *49*, 369. (b) Ng, F. W.; Lin, H.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2002**, *124*, 9812. (c) Birman, V. B.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2002**, *124*, 2080. (d) Kim, D.; Lee, J.; Shim, P. J.; Lim, J. I.; Jo, H.; Kim, S. *J. Org. Chem.* **2002**, *67*, 764. (e) Shigeyama, T.; Katakawa, K.; Kogure, N.; Kitajima, M.; Takayama, H. *Org. Lett.* **2007**, *9*, 4069.

Scheme 8[a]



[a] Reagents and conditions: (a) pivalic acid (0.3 equiv), $CH_3C(OMe)_3$/toluene 1:4, 110 °C, 72 h, 90%; (b) LiOH (3 equiv), THF/MeOH/H_2O 2:2:1, rt, 5 h; (c) Na/naphthalenide (10 equiv), THF, −78 °C, 2 h; (d) Mukaiyama's reagent (2-chloro-1-methylpyridinium iodide, 2 equiv), Et_3N (4 equiv), CH_2Cl_2, rt, 12 h, 55% from **33a**; (e) DIABL-H (1.2 M in toluene, 4 equiv), CH_2Cl_2, −78 °C, 0.5 h; (f) TESCl (2 equiv), Et_3N (3 equiv), DMAP (0.2 equiv), CH_2Cl_2, rt, 10 min, 90% of **52** from **33a**; (g) 9-BBN (6 equiv), toluene, microwave 550 W, 2 h, then H_2O_2, NaOH, 12 h, 90%; (h) TBSOTf (2 equiv), 2,6-lutidine (3 equiv), CH_2Cl_2, −78 °C, 30 min, 87%; (i) IBX (6 equiv), H_2O (20 equiv), DMSO/CH_2Cl_2 1:1, 48 h, 85%; (j) $NaClO_2$ (6 equiv), NaH_2PO_4 (3 equiv), *t*-BuOH/CH_3CN/H_2O 2:2:1, rt, 30 min, then step c) and step d), 65% of **32** from **54**; (k) LDA (3 equiv), $TiCl(O^iPr)_3$ (6 equiv), CH_3CHO (10 equiv), THF, −78 °C, 12 h; (l) DCC (5 equiv), CuCl (10 equiv), benzene, reflux, 12 h, 65% of *E*-**56a** and *Z*-**56b** in a 4:1 ratio from **32**.

subjected to a stereoselective hydroboration with 9-BBN under microwave conditions to furnish the desired alcohol **53** as the sole detectable product in 90% yield (the cis relationship between the hydroxymethyl group at C16 and the TES-protected hydroxyethyl group at C15 in **53** was confirmed by X-ray analysis of a pentacyclic intermediate **32** (see next paragraph). The excellent diastereoselectivity in the hydroboration reaction of **52** most likely resulted from the bottom face of the double bond being completely shielded by the pyrrolidine ring and the TES-protected ethanol group at C15.

After protection of the hydroxyl group in **53**, selective deprotection of the TES group and coincident oxidation of the resulting hydroxyl group to the aldehyde with a large excess of IBX[32] were realized in a one-pot reaction to afford aldehyde **54** in 85% yield. Further oxidation of aldehyde **54** to an acid group with $NaClO_2$ and NaH_2PO_4, removal of the Ts protecting group in **55** and then condensation of the resulting amine with the acid group using Mukaiyama's reagent provided pentacyclic lactam **32** in 65% yield from **54** over three steps. Easy formation of a single crystal of **32** from ethanol allowed us to confirm the relative configurations at C2, C7, C15, and C16 by X-ray analysis (Figure 2).[33] Compared with ester **33a**, possessing a flexible and shielded α-methylene group, lactam **32** has a fixed and more exposed α-methylene group, which was accessible to an electrophile. Installation of an ethylidenyl group at C20 of **32** was realized stereoselectively via a

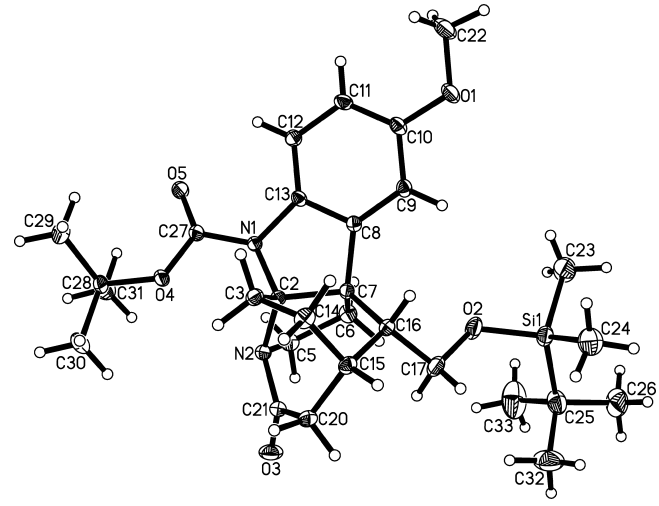


Figure 2. ORTEP diagram of **32**.

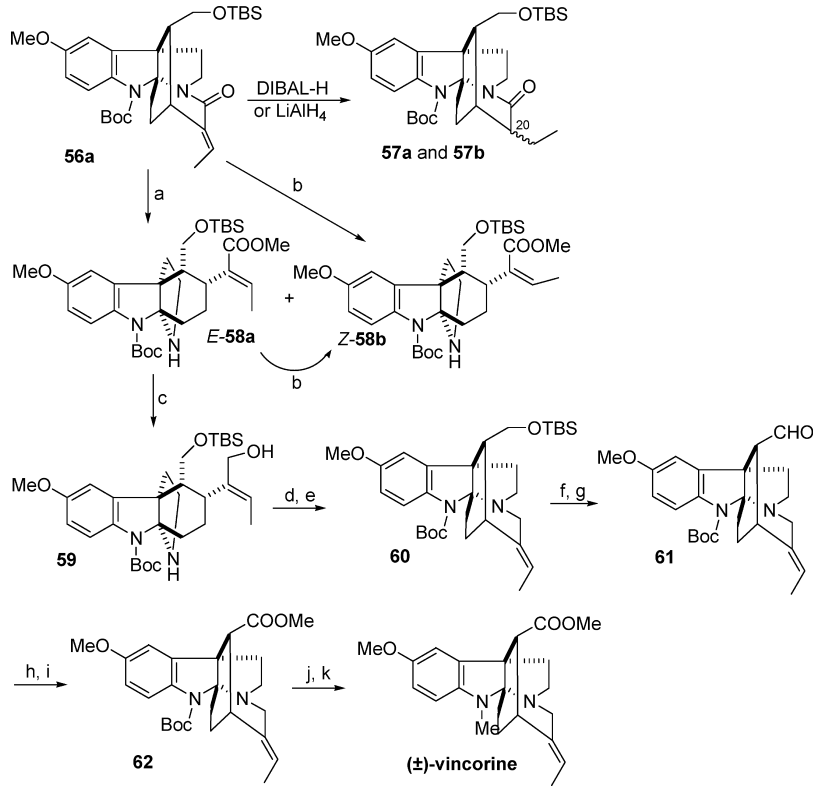
two-step sequence consisting of aldol addition with acetaldehyde in THF at −78 °C in the presence of LDA, followed by cis-elimination of the resulting hydroxyl group with DCC and CuCl in benzene[34] to provide separable *E*-**56a** and *Z*-**56b** in 62% yield in a 4:1 ratio. The minor isomer *Z*-**56b** was determined to have the *Z*-configuration at the C19−20 double bond by NOE experiments. A NOE correlation was observed between the C15 proton

(32) Wu, Y. K.; Huang, J.-H.; Shen, X.; Hu, Q.; Tang, Ch.-J.; Li, L. *Org. Lett.* **2002**, *4*, 2141.

(33) A colorless crystal of **32** ($C_{29}H_{44}N_2O_5Si$, mp 173−175 °C) for the X-ray analysis was obtained by recrystallization from EtOH. The crystallographic data have been deposited with the Cambridge Crystallographic Data Centre, CCDC 717828.

(34) (a) Alexandre, C.; Rouessac, F. *Bull. Soc. Chim. Fr.* **1971**, 1837. (b) Knight, S. D.; Overman, L. E.; Pairaudeau, G. *J. Am. Chem. Soc.* **1993**, *115*, 9293. (c) Knight, S. D.; Overman, L. E.; Pairaudeau, G. *J. Am. Chem. Soc.* **1995**, *117*, 5776.

Scheme 9[a]



[a] Reagents and conditions: (a) NaOMe, MeOH/CH_2Cl_2 1:1, 0 °C, 48 h, 83% of *E*-**58** and trace amount of *Z*-**58**; (b) NaOMe, MeOH/THF 1:1, 65 °C, 5 h, 75% of *Z*-**58** and trace amount of *E*-**58**; (c) DIBAL-H (4 equiv), −78 °C, CH_2Cl_2, 30 min, 95%; (d) Cl_3CCN (3 equiv), PPh_3 (3 equiv), rt, 30 min, CH_2Cl_2; (e) KI (0.3 equiv), K_2CO_3 (4 equiv), CH_3CN, 60 °C, 12 h, 93% yield from **59**; (f) 40% HF, CH_3CN/CH_2Cl_2 (1:1), rt, 8 h, 91%; (g) Dess−Martin reagent (2 equiv), CH_2Cl_2, rt, 30 min, 89% yield from **60**; (h) $NaClO_2$ (6 equiv), NaH_2PO_4 (3 equiv), *t*-BuOH/CH_3CN/H_2O 2:2:1, rt, 30 min; (i) CH_2N_2, Et_2O, rt, 30 min, 82% yield from **61**; (j) TMSOTf (2 equiv), CH_2Cl_2, 0 °C, 30 min; (k) HCHO, $NaBH_3CN$, CH_3CN/AcOH (10:1), rt, 30 min, 75% yield from **62**.

and the olefinic proton in *Z*-**56b**, and no NOE was observed between the C15 proton and the olefinic proton in the major isomer *E*-**56a**, which has the same *E*-configuration of the C19−20 double bond as the natural product vincorine. Typically, the olefinic protons in the *E*-**56a** and *Z*-**56b** were distinguishable by ^{1}H NMR. The olefinic proton of *E*-**56a** appeared at 5.92 ppm, while the olefinic proton of *Z*-**56b** was shifted downfield to 6.83 ppm.

Total Synthesis of 6. With *E*-**56a** in hand, the total synthesis of **6** had reached a stage where all of the rings and relative configurations, including the *E*-double bond, were correctly assembled. Aiming at the target vincorine, the amide group in *E*-**56a** had to be selectively reduced without touching the double bond (Scheme 9). Attempts at reducting the amide group rather than the double bond in *E*-**56a** with DIBAL-H, $LiAlH_4$ and *N*-selectride under a variety of conditions always afforded the double bond saturated epimers **57a** and **57b** as the major products. Treatment of *E*-**56a** with $Et_3OBF_4/NaBH_4$/2,6-di-*tert*-butylpyridine,[35] a special reducing reagent used for the reduction of α,β-unsaturated lactams, gave a complex mixture.

Failure to selectively reduce the amide bond in *E*-**56a** forced us to open the lactam ring with NaOMe in a solution of MeOH/CH_2Cl_2 to provide two separable α,β-unsaturated esters, *E*-**58a** and *Z*-**58b**, in 83% yield in more than a 20:1 ratio (condition a). The ring-opening reaction with NaOMe had to be conducted at a lower temperature (0 °C) to yield *E*-**58a** as the major product. At a higher temperature (65 °C), the double-bond-isomerized product *Z*-**58b** was exclusively obtained in a 75% yield (condition b). The *E*-configuration of the double bond in *E*-**58a** was completely converted to the *Z*-configuration of *Z*-**58b** (88% yield) when heating *E*-**58a** in a mixture of MeOH/THF (1:1) with MeONa at 65 °C. As anticipated, reduction of *E*-**58a** at −78 °C with DIBAL-H generated allyl alcohol **59** in 95% yield. After conversion of the hydroxyl group in **59** to a chloride with Cl_3CCN/Ph_3P, the seven-membered E-ring was reformed to give pentacyclic **60** in 93% yield by treatment of the resulting chloride intermediate with K_2CO_3 and KI in acetonitrile. Transformation of the TBS-protected hydroxyl group in **60** to an aldehyde group was completed to generate **61** in 81% yield through a two-step procedure consisting of deprotection with 40% HF and Dess−Martin oxidation. Further oxidation of the aldehyde group in **61** to an acid group with $NaClO_2/NaH_2PO_4$, followed by esterification of the acid with CH_2N_2, afforded ester **62** in 82% yield. Final removal of the Boc group in **62** and methylation of the indoline nitrogen with formaldehyde and $NaBCNH_3$ produced **6** in 75% yield. The synthetic **6** showed ^{1}H and ^{13}C NMR spectra that were identical to those of natural vincorine.[36]

Conclusion

In summary, the first total synthesis of the *akuammiline* alkaloid **6** has been accomplished from the readily available

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(36) (a) Kam, T.-S.; Choo, Y. M. *J. Nat. Prod.* **2004**, *67*, 547. (b) Kam, T.-S.; Choo, Y. M. *Phytochemistry* **2004**, *65*, 603.

tetrahydrocarboline **36** in about 1% overall yield in 31 steps. The synthesis of **6** greatly benefitted from our newly developed methodology of concisely assembling the key tetracyclic core structure of **1** from the diazoketoester **25** through a three-step one-pot cascade reaction consisting of intermolecular cyclopropanation, ring-opening, and ring closure. The inability to construct the seven-membered E-ring in a rigid two-ring system in **31**, **45**, **46**, and **47** through Heck coupling, Michael addition, radical Michael addition, π-allyl/Heck addition, and π-allyl/Stille addition guided us to seek an alternative method to construct the last E-ring of vincorine.

After successful installation of an acetate side chain at C15 of the cyclohexenyl ring in Boc-protected **35b** by a Johnson−Claisen rearrangement and multistep modification of the functionality present in the rearrangement product **33a**, E-ring formation was readily realized through intramolecular condensation of an acid functional group with an amine group to give pentacyclic **32**. The *E*-configured ethylidenyl group in lactam **56a** was selectively installed through a sequence of reactions from **32**, consisting of aldol addition to acetaldehyde and cis-elimination of the resulting hydroxyl group. Failure to selectively reduce the amide bond over the double bond in **56a** led us to open the seven-membered lactam ring to give ester *E*-**58a**. Selective reduction of the α,β-unsaturated ester in *E*-**58a**, followed by reclosure of the E-ring by intramolecular allylation generated pentacyclic **62**. Final elaboration of **62** including esterification of C20 and replacement of the Boc group with a methyl group resulted in the total synthesis of **6**. The current synthesis provides a feasible route to other members of the *akuammiline* family.

Acknowledgment. This work was supported by NSFC (Grants No. 20632030, 20772083, and 20825207), Ministry of Education, and the State Key Laboratory of Bio-organic and Natural Products Chemistry, CAS. We are grateful to Prof. T.-S. Kam (University of Malaya, Malaysia) for kindly providing the NMR spectra of natural vincorine. We thank the Analytic and Testing Center of Sichuan University for recording spectroscopic data.

Supporting Information Available: Experimental procedures, spectroscopic analytical data for all new compounds, and CIF files of crystallographic information for compound **32**. This material is available free of charge via the Internet at http://pubs.acs.org.

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