Total Synthesis of (±)-Cylindricines A and B

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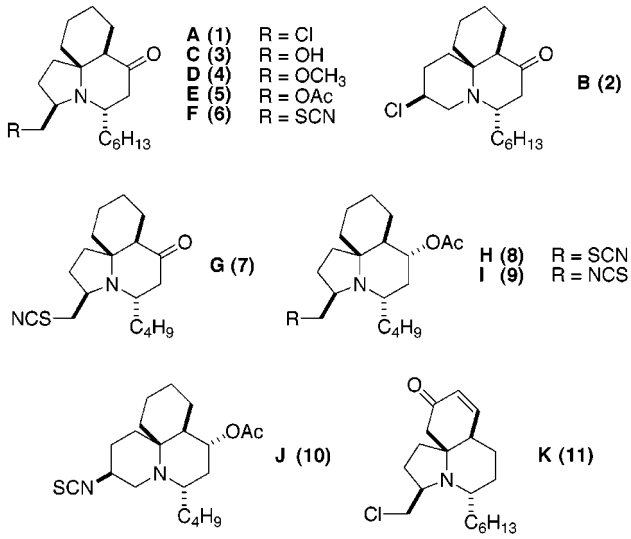
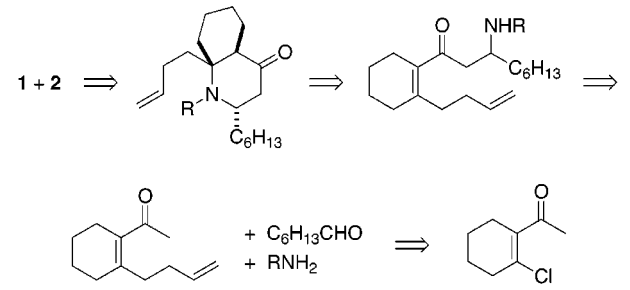
Cylindricine A (**1**) and cylindricine B (**2**) have been synthesized in 11 steps and 19% overall yield. The key reaction involves the addition of an organocopper species to a bicyclic vinylogous amide, which provides complete stereocontrol over the installation of the hexyl side chain.

Introduction

Marine ascidians, invertebrates of the phylum Chordata, subphylum Tunicata, have been investigated heavily in recent years as sources of interesting secondary metabolites. Many of the novel compounds isolated from these organisms are alkaloids belonging to families such as the quinolizidines,[1,2] indolizidines,[3] decahydroquinolines,[4−7] pyrroloiminoquinones,[8] and poly-heteroaromatics.[9,10] These molecules exhibit a broad range of biological activity including inhibition of topoisomerase II[8] and toxicity against murine leukemia,[1,9] human colon tumor cell lines,[8] bacteria such as *E. coli*, *S. aureus*, and *B. subtilis*,[3,8−10] *C. albicans*,[3] herpes simplex virus types I and II,[10] and a DNA-repair deficient yeast strain.[4] Blackman and co-workers examined several extracts of the Australian ascidian *Clavelina cylindrica* and reported in a series of papers the isolation of a new family of alkaloids. The tricyclic compounds are known as the cylindricines A−K.[11] Structurally related alkaloids are the clavepictines,[12a] fasicularin,[12b] and lepadiformine,[12c] which appears to be very similar, although the accuracy of the published structure has been called into question.[13]



Cylindricines A (**1**) and B (**2**), the major components of the initial extract, were the first members of the family to be identified. Additionally, their skeletal structures are the first known natural examples of the pyrrolo[2,1-*j*]-quinoline and the pyrido[2,1-*j*]quinoline ring systems, respectively.[11] Cylindricine A and cylindricine B are isomeric, and a pure solution of either alkaloid as the free base will isomerize to the 3:2 equilibrium mixture in 6 days at room temperature. The two molecules are believed to interconvert via an aziridinium ion.[11]



The novel skeletal structures of cylindricines A and B, as well as their interesting ability to interconvert, made these two natural products intriguing targets for total synthesis. At the outset of this project, no published syntheses for any of the cylindricine alkaloids existed. However, during the course of our work on cylindricines A and B a report was published by Snider et al. detailing the syntheses of (±)-cylindricines A, D, and E, which

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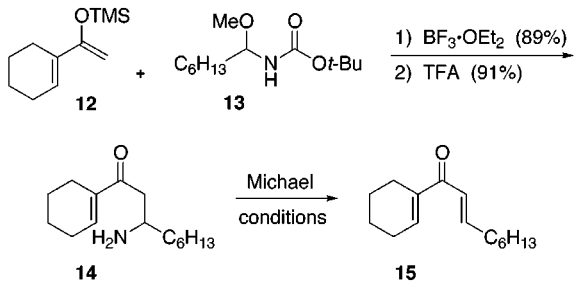
Scheme 1



utilizes a similar double-Michael reaction approach to the bicyclic core of the cylindricines.[14] In addition, a synthesis of (−)-cylindricine C by Molander et al., which also involves a double-Michael reaction, has recently appeared in print.[15]

Since cylindricines A and B interconvert, one could arrive at the natural mixture of the two compounds by the direct synthesis of either isomer, followed by equilibration to the 3:2 mixture. We envisioned that the third ring of the tricycle could be formed by attack of an amine moiety on an electrophilically activated terminal alkene or by radical cyclization. The bicyclic ketone could result from a Mannich−Michael reaction sequence beginning with an appropriately substituted enone. That enone in turn could potentially be synthesized by a conjugate addition−elimination reaction with a β-chloro enone.

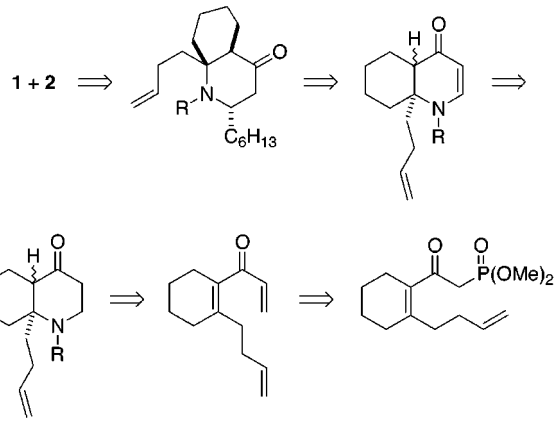
Results and Discussion

In an attempt to investigate this possible synthetic route, model silyl enol ether **12** and *N*-acylimmonium precursor **13** were prepared.[16] Upon treatment with BF_3·OEt_2 followed by deprotection of the nitrogen, Mannich product **14** was isolated in high yield (Scheme 1). However, efforts to synthesize the desired bicyclic product proved fruitless, as the β-amino moiety of ketone **14** displayed a marked tendency to eliminate from the molecule under a wide variety of Michael reaction conditions. This result led us to redesign the synthesis, using instead a double-Michael reaction to deliver the desired bicycle in one step from a dienone.

A conjugate addition−elimination reaction was successfully performed using known β-trifluoromethanesulfonyloxy ester **16**[17] and the Gilman cuprate formed from CuI and 2 equiv of 4-lithio-1-butene to provide desired β-substituted ester **17** (Scheme 2). In later larger-scale reactions, we switched to the lower-order mixed cuprate reagent derived from CuCN and 1 equiv of 4-lithio-1-butene in an effort to conserve the alkyllithium reagent, which must be synthesized from 3-buten-1-ol via the iodide. In both cases, the yield for the reaction was excellent. Addition of the lithium anion of dimethyl methylphosphonate provided the desired β-ketophosphonate **18** in 96% yield. A Horner−Emmons reaction with heptanal then afforded the dienone in 88% yield. The double-Michael addition of ammonia to the dienone was carried out in a thick-walled resealable Pyrex tube, using ammonia-saturated ethanol and concentrated ammonium hydroxide as cosolvents. After 16 h at 100 °C the bicyclic ketone was isolated in 78% yield as a separable mixture of three isomers. These isomers were identified by comparison to model compounds lacking the butenyl chain; the identities of the model compounds were proven using X-ray crystallography.[16] Compounds **20**−**22** have since been published by Snider and Liu, and their ^{1}H NMR data matches ours.[14]

The desired isomer **20** was the major product, while the undesired isomers **21** and **22** were present in lesser amounts. However, the approximately 2:1 desired/undesired isomer ratio was not very impressive, so we attempted to recycle the minor isomers by resubjecting them to the double-Michael reaction conditions. Unfortunately, after extended heating only a trace amount of **20** was seen; apparently the retro-Michael reaction is not as facile as might be assumed. While we were able to perform the retro-Michael reaction using model compounds that lacked the butenyl chain by first generating the quaternary amine salt with excess iodomethane,[16] attempts to generate the quaternary amine salts of **21** and **22** were unsuccessful due to the steric bulk provided by the quaternary carbon substituents α to the nitrogen. This disappointing result encouraged us to explore more selective options for installation of the hexyl side chain.

Our final retrosynthesis involved preparing the required bicyclic ketone with a stereoselective organocopper addition to a vinylogous amide. The vinylogous amide could be prepared from a saturated ketone, which could arise from the double-Michael addition of an ammonia equivalent to a dienone. The dienone could be formed in turn via a Horner−Emmons reaction with a β-ketophosphonate and paraformaldehyde.



The desired Horner−Emmons reaction was successful, providing dienone **23** in 86% yield (Scheme 3). The double-Michael reaction was conducted as before, followed by the protection of the nitrogen to afford bicycles **25** as approximately 1:1 mixtures of ring-juncture isomers in excellent yield. The next step involved the conversion of the saturated ketone to the vinylogous amide substrate needed for the stereoselective organocopper addition. We investigated several methods for effecting this conversion, including the attempted elimination of various leaving groups α to the carbonyl such as bromo, phenylselenyl, and tosyloxy moieties. Unfortunately, these reactions largely resulted in the eventual decomposition of the starting materials rather than generation of the desired unsaturated compounds. Eventually, we determined the most effective method for the

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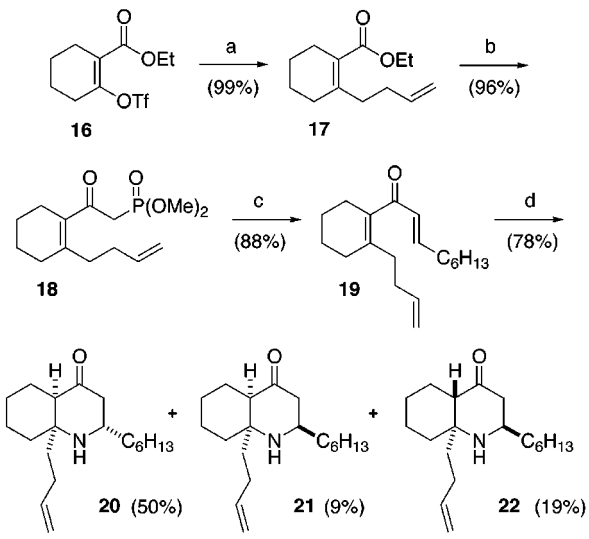
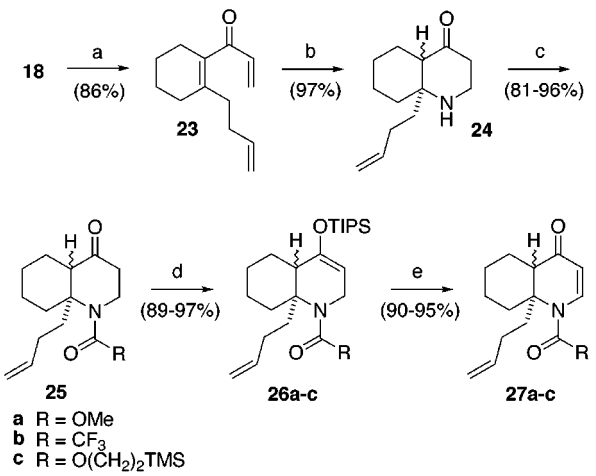
Scheme 2[a]



[a] Reagents: (a) $CH_2CHCH_2CH_2Cu(CN)Li$, Et_2O, −50 °C; (b) $LiCH_2P(O)(OMe)_2$, THF, −78 °C to rt; (c) $C_6H_{13}CHO$, LiCl, *i*-Pr_2NEt, CH_3CN; (d). NH_3−satd EtOH, concd NH_4OH, 100 °C.

Scheme 3[a]



[a] Reagents: (a) NaH, $(CH_2O)_n$, benzene; (b) NH_3−satd EtOH, concd NH_4OH, 105 °C; (c) $ClCO_2Me$, K_2CO_3, CH_3CN (or) TFAA, Et_3N, CH_2Cl_2 (or) TEOC−OSu, K_2CO_3, CH_3CN; (d) LDA, TIPSOTf, THF, −78 °C to rt; (e) CAN, DMF, 0 °C.

formation of the vinylogous amides to be the ceric ammonium nitrate oxidation of triisopropylsilyl enol ethers **26**,[18,19] which were easily formed from ketones **25**. This mild procedure provided excellent yields of the cis and trans vinylogous amide products, which were separated via HPLC.

The next challenge was the stereoselective addition of an organocopper species to the vinylogous amide substrates. Comins and co-workers have developed an excellent method for achieving this type of addition to *N*-acyl vinylogous amides that involves the use of a Grignard reagent in the presence of $BF_3{\cdot}OEt_2$ and $CuBr{\cdot}Me_2S$.[20,21] The method has been demonstrated to provide excellent stereoselectivity for the axial installation of the incoming

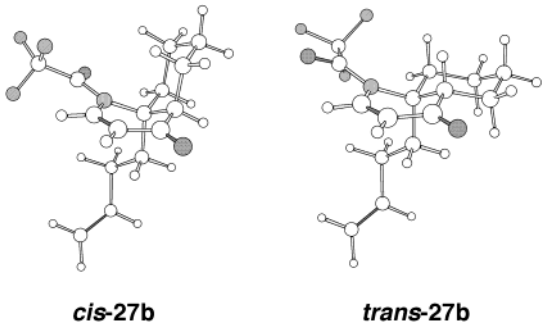
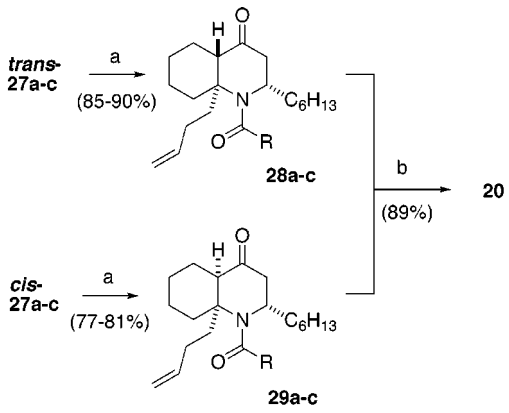


Figure 1. Global minimization structures of cis and trans vinylogous amide 27b.

Scheme 4[a]



[a] Reagent: (a) $C_6H_{13}MgBr$, $CuBr{\cdot}Me_2S$, $BF_3{\cdot}OEt_2$, THF, −78 °C; (b) TBAF, THF (for **28c** and **29c** only).

alkyl or aryl group. The question, therefore, was whether vinylogous amides **27** would occupy conformations in which axial attack by the incoming organocopper species would furnish the desired stereoisomers.

Molecular modeling[22] supported our expectation that both of the vinylogous amide isomers would indeed occupy appropriate conformations (Figure 1) with the butenyl chains in the axial orientation. However, should the selectivity of the addition prove acceptable in only one isomer, we could simply epimerize bicyclic ketone **24** iteratively to a single isomer earlier in the synthesis.

The organocopper addition was successfully performed using hexylmagnesium bromide in the presence of $BF_3{\cdot}OEt_2$ and $CuBr{\cdot}Me_2S$. We were pleased to find that the reaction provided complete stereoselectivity in the case of trans isomers **27** and excellent stereoselectivity in the case of the cis isomers, as only a trace of the undesired product isomer was seen (Scheme 4). This positive result eliminated any need for the epimerization of bicyclic ketone **24**. The next step proved rather difficult, as the exceedingly hindered nitrogen atom was surprisingly challenging to deprotect. We initially examined the use of a methyl carbamate protecting group. Carbamates **28a** and **29a** were treated exhaustively with basic hydrolysis conditions, acidic removal conditions, and nucleophilic cleavage conditions such as the use of LiI/collidine or mercaptan anion/HMPA. All attempts to remove the protecting group failed, resulting in recovery of the starting material. We switched to the TFA amide pro-

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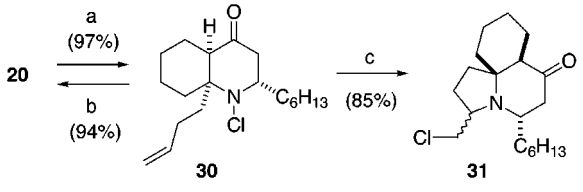
(22) Molecular modeling was performed using Macromodel with the MM3 force field. Global minimizations were performed using the Monte Carlo method.

Scheme 5[a]



[a] Reagents: (a) NCS, CH_2Cl_2; (b) $AgNO_3$, MeOH;(c) CuCl, $CuCl_2$, THF, H_2O, AcOH, 0 °C.

tecting group on the theory that it would be easier to remove, but this acyl group proved equally difficult to hydrolyze. In the case of amides **28b** and **29b**, after extended reaction times all conditions resulted in the complete elimination of the TFA amide moiety from the molecule, thus providing dienone **19**. Presumably, this occurs with the TFA amide and not with the methyl carbamate due to the former protecting group's increased electron-withdrawing ability. We ultimately moved to the use of the TEOC protecting group in the hope that its TMS cleavage site would extend well outside the hindered amine pocket, leaving the TMS moiety readily susceptible to fluoride ion attack. Carbamates **28c** and **29c** were duly prepared, and we were pleased to find that upon treatment with TBAF the desired free amine was liberated cleanly in 89% yield.

With the desired amine in hand, we examined a number of methods for closing the third ring. Treating amine **20** with electrophilic reagents such as NBS, NCS, or I_2 failed to produce any of the desired tricyclic products. However, the NCS reaction resulted in the isolation of a surprisingly stable *N*-chloramine in 97% yield (Scheme 5), and we decided to investigate the possibility of converting this compound to the tricyclic cylindricine ring system via nitrenium ion closure onto the terminal olefin. Unfortunately upon treatment of **30** with a series of silver(I) salts in MeOH the nitrenium ion appears to undergo spin-inversion,[23] abstracting hydrogen from the solvent to provide simple amine **20**. We eventually found success with the metal-coordinated radical procedures of Stella.[24,25] Use of $TiCl_3$ in aqueous acetic acid returned a mixture of the simple amine and the starting *N*-chloramine, but use of copper(I) and copper(II) salts in aqueous acetic acid/THF provided the desired tricyclic product **31** in 85% yield as a 1.14:1.00 mixture of cylindricine A and *epi*-cylindricine A. These compounds were separated, and cylindricine A was allowed to convert to the natural mixture of cylindricines A and B as a solution in C_6D_6.[26]

Conclusion

In conclusion, tricyclic alkaloids cylindricine A and cylindricine B have been synthesized in 11 steps and in 19% overall yield from known β-trifluoromethanesulfonyloxy ester **16**. The key reaction involved the addition of an organocopper species to a bicyclic vinylogous amide, which provided complete stereocontrol over the installation of the hexyl side chain.

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Supporting Information Available: Full experimental procedures and characterization data for all compounds prepared, as well as selected ^{1}H NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(26) The ^{1}H NMR spectra of synthetic cylindricine A and of the mixture of synthetic cylindricines A and B were compared to ^{1}H NMR spectra kindly provided by Professor Adrian J. Blackman of the University of Tasmania, Hobart. The spectra of the natural compounds were plotted with reference to the solvent peak of C_6D_6 at 7.40 ppm; the spectra of the synthetic compounds were plotted with reference to the solvent peak of C_6D_6 at 7.16 ppm. With allowance made for this difference, the data were identical.