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Communication

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A Concise, Enantiospecific Total Synthesis of Chilocorine C Fueled by a Reductive Cyclization/Mannich Reaction Cascade

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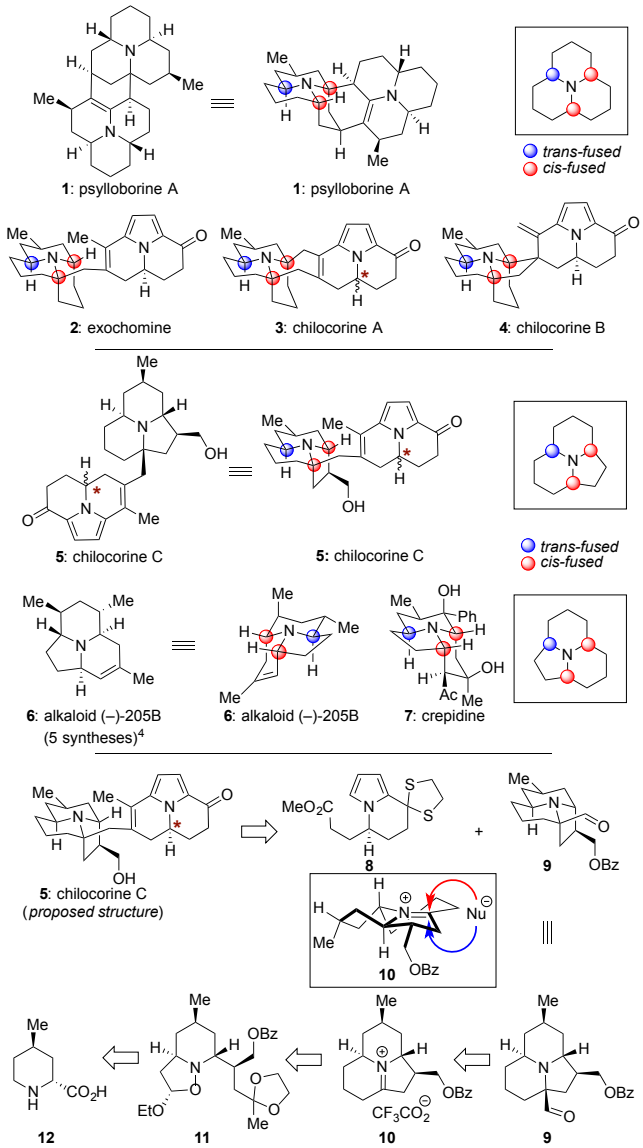
Supporting Information Placeholder

ABSTRACT: Among defensive alkaloids isolated from ladybugs, the heterodimeric member chilocorine C possesses an alluring monomeric unit that combines quinolizidine and indolizidine substructures. Indeed, the overall stereochemical disposition of its ring fusions is distinct from related natural products. Herein, we show that a carefully orchestrated sequence with several chemoselective transformations, including a designed cascade that accomplishes 9 distinct chemical reactions in one pot, can smoothly forge that domain and ultimately enable a 15-step, 11-pot enantiospecific synthesis of the natural product. Mechanistic studies, DFT calculations, and the delineation of several other unsuccessful approaches highlight its unique elements.

Over the past several decades, a number of alkaloids have been isolated and characterized from ladybugs of the *Coccinellidae* genus.[1] These structures include tricyclic alkaloids as well as more complex hexa- and heptacyclic members that have been termed as either homo- (as in **1**, Scheme 1) or heterodimeric (**2**–**4**) based on the structural homology between their two respective major domains.[2] All of these drawn compounds (**1**–**4**) have a conserved 6/6/6-tricycle with consistent *cis*- and *trans*-ring fusions as indicated within the inset boxed structure. Breaking this trend is chilocorine C (**5**), a compound obtained in minute quantities (0.6 mg from 460 beetles) and structurally characterized by Meinwald in 1998.[2d] Indeed, it possesses a saturated monomeric unit with a 6/6/5 fusion that formally combines one quinolizidine and two indolizidine subunits. While the overall patterning of its *cis*- and *trans*-ring fusions matches those of its 6/6/6 tricyclic counterparts, including the co-isolated and previously characterized natural products chilocorines A (**3**)[2b] and B (**4**),[2c] it possesses an overall stereochemical disposition that is, to the best of our knowledge, distinct among known natural products. For example, while there are a few alkaloids with 6/6/5 systems,[3] some of which are shown in Scheme 1 (**6**[3b,4] and **7**[3ac]), their 5-membered rings possess one *cis*- and one *trans*-fusion with their 6-membered neighbors; in **5**, however, both of these fusions are *cis*.[5] Herein, we show that forging this overall domain of chilocorine C is quite challenging and could only be achieved through a designed cascade conducted under carefully orchestrated conditions, terminating in a reversible Mannich reaction with a distinct nucleophile class. This operation, coupled with further unique and chemoselective steps, afforded a 15-step, 11-pot[6] enantiospecific synthesis of the title alkaloid from commercially available materials, reflecting the shortest pot effort for any related "dimeric" target.[7]

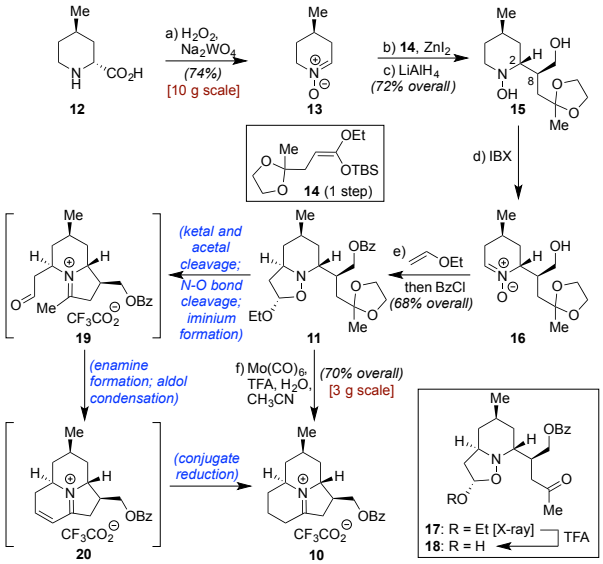
Our overall approach to chilocorine C (**5**) is shown retrosynthetically in Scheme 1. Assuming that its one unassigned chiral center, denoted with a star in the original depiction, matched that of exochomine (**2**), a molecule we previously synthesized in 16-steps,[7b] the two major domains could be connected through a similar terminating aldol/cyclization sequence. As such, with **8** in hand, we needed access to **9**, a compound whose electrophilic aldehyde could hopefully be installed from iminium **10** through a Strecker reaction. Unclear was the ease and stereoselectivity of that transformation that would be observed experimentally, given its stereochemical uniqueness discussed above, and the potential for addition from either face as indicated in the inset box. Assuming success, we hoped in turn that iminium ion **10** could arise in a single pot through a reductive cyclization cascade commencing from **11**, itself prepared expeditiously from commercially available **12** using the unique chemistry of nitrones.[8]

Scheme 1. Structures of selected coccinellid alkaloid dimers (**1**-**4**) all bearing consistent ring fusions, the structure of chilocorine C (**5**) that possesses a unique ring fusion relative to other tricyclic alkaloids containing one five-membered ring (such as **6** and **7**), and a retrosynthetic approach to access that unique stereochemical arrangement.



Synthetic efforts commenced by using the carboxylic acid domain of **12**[9] to effect a regiospecific formation of chiral nitrone **13** as shown in Scheme 2. This decarboxylative oxidation was ultimately achieved following extensive screening (see Supporting Information for more details) by adapting a literature protocol[10] utilizing H_2O_2 and Na_2WO_4 in 74% yield on decagram scale. Next, an *anti*-diastereoselective nitrone variant of the Mukaiyama–Mannich reaction,[11] using silylenol ether **14**, afforded the desired adduct and established two new chiral centers with 7:1:1 *dr* [(8*S*,2*R*):(8*R*,2*R*):(8*R*,2*S*)]. Subsequent treatment with $LiAlH_4$ achieved both reduction of the ester and TBS ether cleavage[12] to afford **15** in 72% overall yield. Next, in order to introduce a second sidechain using nitrone chemistry, **15** was oxidized with IBX[8a,13] to provide an 8:1 mixture of **16** and its ketonitrone isomer in near quantitative yield; no other condition screened was as regioselective. The remaining carbon chain was then introduced via an *exo*-selective (3+2)-cycloaddition[14] with ethyl vinyl ether that, when followed by *in situ* treatment with BzCl, afforded isoxazolidine **11** with high 2,6-*trans*-diastereoselectivity (*dr* >10:1). Pleasingly, an X-ray crystal structure of its ketal-deprotected variant (**17**) confirmed its relative configuration.

Scheme 2. Expeditious preparation of key iminium intermediate **10** fueled by a cascade sequence.[a]

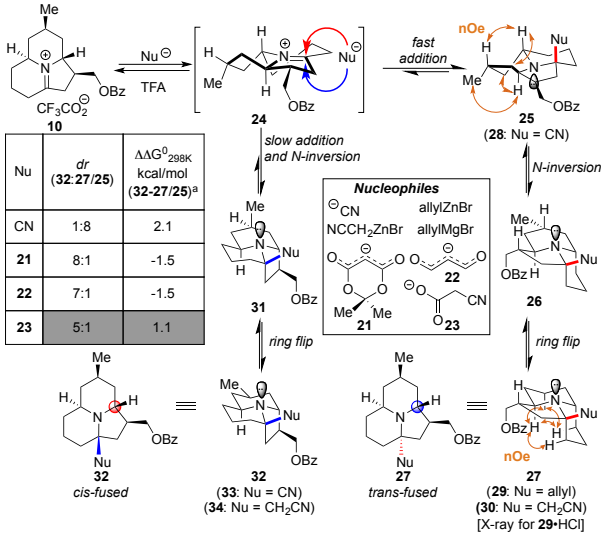


[a] Reagents and conditions: a) H_2O_2 (3.0 equiv), K_3PO_4 (1.2 equiv), Na_2WO_4•$2H_2O$ (0.1 equiv), Et_4NCl (0.1 equiv), CH_2Cl_2/H_2O, 5 °C to 23 °C, 1.5 h, 74%; (b) 14 (1.2 equiv), ZnI_2 (0.2 equiv), CH_2Cl_2, -78 °C to 23 °C, 9 h; (c) $LiAlH_4$ (4.0 equiv), THF, 66 °C, 3 h, 72% for 2 steps; (d) IBX (1.1 equiv), $MgSO_4$ (3.0 equiv), CH_2Cl_2, -20 °C to 23 °C, 1.5 h; (e) ethyl vinyl ether (10.0 equiv), toluene, 55 °C, 17 h; then concentrate; then BzCl (1.0 equiv), 4-DMAP (0.1 equiv), Et_3N (3.0 equiv), CH_2Cl_2, 0 °C to 23 °C, 2 h, 68%; (f) $Mo(CO)_6$ (1.5 equiv), TFA (2.0 equiv), CH_3CN/H_2O (4:1), 0 °C to 90 °C, 8 h; TFA (5.0 equiv), 90 °C, 0.5 h; benzene, Dean-Stark, 90 °C, 3 h, 70%. IBX = 2-iodoxybenzoic acid; 4-DMAP = 4-dimethylaminopyridine; TFA = trifluoroacetic acid.

We next sought to convert **11** into iminium **10**, a task requiring an initial N–O cleavage to introduce a β-aminoaldehyde moiety. However, given the sensitive nature and general instability of such functionality,[15] we expected that this event likely had to be coupled with an aldol condensation in a one-pot operation to prevent decomposition, thus requiring acidic conditions to enable the requisite events to proceed in a cascade fashion. Following extensive screening and optimization (see SI),[16] we found that $Mo(CO)_6$[17] alone proved capable of rising to the occasion, affording the means to achieve the full sequence. Thus, following dissolution of **11** in a 4:1 mixture of $MeCN/H_2O$ and sequential treatment with $Mo(CO)_6$ (1.5 equiv) and TFA (2.5 equiv) at 0 °C, the contents were heated to reflux for 8 h to effect conversion to **19** via 4 distinct chemical events: ketal cleavage, acetal hydrolysis, N–O bond cleavage, and iminium formation. In this process, **17**, **18**, and **19** were observed by NMR analysis, and **17** and **18** were also isolable. Further addition of TFA, dilution with benzene, and heating at reflux for 3 h under azeotropic conditions achieved both enamine formation and aldol condensation to forge **20**. A terminating conjugate reduction in the same pot then generated **10** in 70% yield, completing a 7-step, 6-pot synthesis from **12**.[18] Pleasingly, this final 7-operation cascade could be conducted with no decrease in yield on 3 g scale.

With iminium salt **10** in hand, we proceeded to install the atoms needed to forge the key *aza*-quaternary center and complete the unique tricyclic domain of chilocorine C. As denoted in Scheme 3, a Strecker reaction using KCN proceeded to afford a mixture of nitriles **28** and **33** with 8:1 *dr*, initially of unknown configuration. We became concerned, however, that the incorrect diastereomer had been formed preferentially when subsequent efforts to reduce this newly installed functionality with an array of aluminum-based hydrides [including $LiAlH_4$, Red-Al®, $(EtO)_2AlH$, and DIBAL-H] led to decyanation with the corresponding saturated amine being a major product. In addition, we found that unlike the parent exochomine-related analog, both **10** and **28** readily participated in the addition of organometallic reagents (preceeded by decyanation with **28**),[19] producing a single diastereomer in each case. Eventually, material suitable for X-ray crystallographic diffraction was obtained from the HCl salt of **29** (acquired by the addition of allylzinc to **10**) confirming that the kinetic product for these additions was the *trans*-fused diastereomer **27**,[20] thus reflecting the skeleton of alkaloid (–)-205B and crepidine (**6** and **7**, cf. Scheme 1).

Scheme 3. Studies in adding nucleophiles into key iminium intermediate **10** in service of delivering structures of type **32**. Free energy values (ΔG^0_{298K}) were calculated within ideal gas/1-D hindered rotor/harmonic oscillator model using DFT with PW6B95-D3/def2-TZVPPD//IEFPCM/B97-D/6-31+G(d,p) method (see SI for details).



Nu	*dr* (**32**:**27**/**25**)	$\Delta\Delta G^0_{298K}$ kcal/mol (**32**-**27**/**25**)[a]
CN	1:8	2.1
21	8:1	-1.5
22	7:1	-1.5
23	5:1	1.1

Given this information, we attempted to shift the equilibrium of the Strecker reaction through numerous variations in reaction conditions as well as additional substrate modifications (not shown); these efforts were unsuccessful. As a result, we wondered if Mannich-type additions, processes which are reversible, could offer a solution. Gratifyingly, we discovered that 1,3-dicarbonyl compounds such as **21** and **22**, can, in fact, favor formation of the desired diastereomer. For example, when **10** reacted with **21** (in the form of its potassium salt)[21] in MeOH, it readily formed the corresponding zwitterionic product with an initial *dr* of 1:1 that reached an equilibrium *dr* of 8:1 favoring the desired *cis*-fused isomer **32** upon standing.[22] Unfortunately, the synthetic utility of these addition products was found to be rather limited, as they were not readily able to be converted into the desired aldehyde. As such, other derivatives of malonic acid were considered,

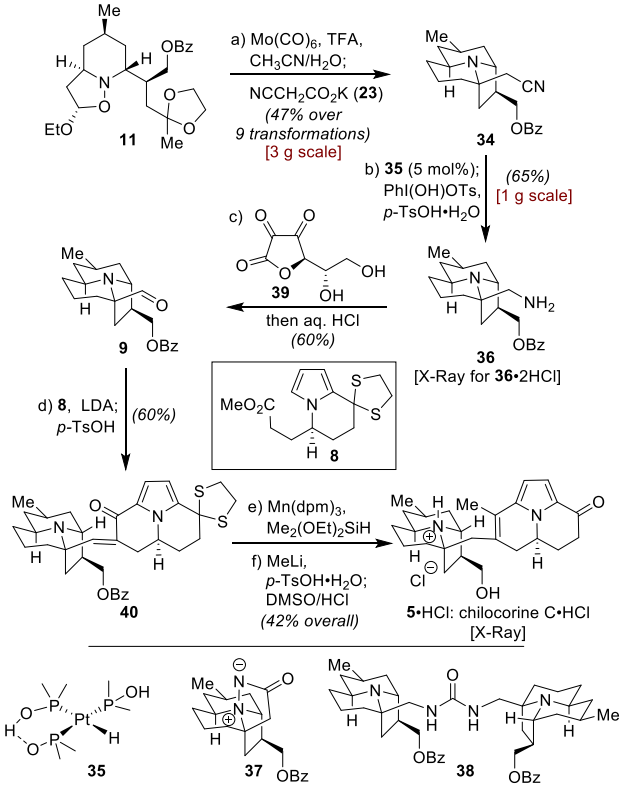
and eventually it was found that a decarboxylative Mannich reaction with the mono-salts of malonates[23] could promote the desired outcome. For example, potassium cyanoacetate **23** was able to provide a 1:1 ratio of **34** to **30** when the reaction was performed in refluxing 1,4-dioxane,[23c] while switching to a protic solvent such as *i*-PrOH boosted the *dr* to 5:1 favoring the desired **34**. In accordance with literature precedent,[23d] the addition precedes decarboxylation based on MS analysis of the crude reaction mixture.

In order to quantify these results and to potentially explain the observed reactivity, we computed free energy differences between each pair of isomers using DFT (for the full details, see SI). As can be seen from the inset table in Scheme 3, the trends for the preference in the major diastereomer for the addition of the cyanide anion and **21**–**22** correlate well with the estimated ΔG^0_{298K} values. Furthermore, the most stable conformation for the major aminonitrile isomer **28** was found to have an antiperiplanar arrangement between the lone pair and CN group (drawn here as conformation **25** and confirmed by nOe experiments). This finding helps to explain the reactivity of **28** towards aluminum-based hydrides, since decyanation is a common pathway for strained antiperiplanar aminonitriles.[24] However, the difference in free energies computed for the two possible addition products of **23** to **10** (prior to decarboxylation), favor the *trans* isomer [$\Delta\Delta G^0_{298K}$(*cis*-*trans*) = 1.1 kcal/mol], suggesting kinetic control. The investigation of the potential energy surface for the two possible pathways with DFT revealed several key features that may provide an explanation for the observed selectivity. First, the barriers for the Mannich reaction differ significantly ($\Delta H^{\ddagger}_{0K}$ = 4.7 kcal/mol), with the pathway leading to *trans*-fused isomer **26** having the lower barrier.[20] Most important was the finding that the rate-limiting transition state is decarboxylation, rather than the Mannich reaction. Thus, the kinetics of the reaction are most likely controlled by the Curtin–Hammett principle.[25] With the energy of the decarboxylation transition state for the *cis*-pathway being lower than that of the *trans*-pathway ($\Delta H^{\ddagger}_{0K}$ = 1.4 kcal/mol), the *cis*-fused isomer **34** is predicted to be the major product, in accordance with experimental results.[26]

Having established access to the desired diastereomer, we found that we could successfully integrate the addition/decarboxylation step (i.e. **10** to **34**) into the full cascade without any compromise in stereoselectivity. Therefore, **34** could be obtained from **11** in a single-pot, 2-step operation that combined 9 distinct reactions in 47% yield (Scheme 4).[27] Seeking now to couple the two halves of chilocorine C, we sought to convert the nitrile of **34** into the aldehyde of **9**. To this end, hydration of **34** with **35**[28] quantitatively afforded the corresponding carboxamide; however, the following Hofmann rearrangement turned out to be quite capricious. For example, under neutral conditions with any I^{III} source,[29] the major and/or exclusive isolated product was aminimide **37**,[30] hence, an acid additive was needed to suppress the nucleophilicity of the tertiary nitrogen. Additionally, we found that conducting the reaction under anhydrous conditions produced substantial amounts of urea **38**.[29c] After extensive optimization, the use of Koser's reagent[29bc] in aqueous MeCN with *p*-TsOH•H_2O as an additive provided reproducible and scalable results, producing **36** in 65% yield on gram scale. Finally, while several efforts[31] were made to oxidize the primary amine, we found that a modified protocol[31b] with dehydroascorbic acid (**39**) could afford **9** in good yield (60%).

With a route to **9** now secured, we proceeded to couple the two fragments (**8** and **9**) following our reported sequence;[7b] these processes worked well, with minor modifications effected in some cases to achieve improved yields. Most critical among those was the final elements of the route: MeLi addition, dehydration, and thioacetal deprotection. Pleasingly, initial screens showed that the conditions used for the first two operations could also accomplish removal of the Bz protecting group at the same time. However, the final thioacetal deprotection with $PhI(OAc)_2$[32] proceeded with a disappointingly low yield (20% here; 31% for exochomine). Eventually, we found a DMSO/HCl protocol[33] could promote a very clean and chemoselective thioacetal removal in high yield (86%). In order to reduce the isolation of highly sensitive intermediates, the MeLi addition/dehydration reaction was ultimately combined with the DMSO-promoted thioacetal removal protocol, which, after purification, provided chilocorine C•HCl (**5**•HCl) in a 42% isolated yield. The spectral data for **5**•HCl matched that of the natural sample,[2d] noting that both its ^1H and ^{13}C chemical shifts displayed a dependence on concentration,[34] with only relatively concentrated solutions matching the reported chemical shifts (see SI).[35,36] An X-ray structure of **5**•HCl was also obtained.

Scheme 4. Completion of the total synthesis of chilocorine C (**5**).[a]



[a] Reagents and conditions: (a) $Mo(CO)_6$ (1.5 equiv), TFA (2.5 equiv), CH_3CN/H_2O (4:1), 0 °C to 90 °C, 8 h; TFA (2.5 equiv), 90 °C, 0.5 h; benzene, Dean-Stark, 90 °C, 3 h; then concentrate; then **23** (1.6 equiv), *i*-PrOH, 100 °C, 15 h; **23** (2.4 equiv), 120 °C, 8 h, 9% **30**, 47% **34**; (b) **35** (0.05 equiv), EtOH/H_2O (4:1), 79 °C, 10 h; then concentrate; then PhI(OH)(OTs) (1.2 equiv), *p*-TsOH•H_2O (1.0 equiv), CH_3CN/H_2O (4:1), 85 °C, 2.5 h; PhI(OH)(OTs) (0.8 equiv), 85 °C, 2.5 h, 65%; (c) **39** (3.0 equiv), DMF, 60 °C, 11 h; then HCl (1 M), 23 °C, 2.5 h, 60%; (d) **8** (1.2 equiv), LDA (1.5 equiv), THF, -78 °C, 4.5 h; then *p*-TsOH (7.0 equiv), -78 °C to 23 °C; then concentrate; then benzene, 50 °C, 13 h, 60%; (e) $Mn(dpm)_3$ (2.2 equiv), $MeSi(OEt)_2H$ (5.0 equiv), *i*-PrOH/CH_2Cl_2 (8:1), 30 °C, 16 h; (f) MeLi (4.0 equiv), THF, -78 °C to -30 °C, 2 h; then *p*-TsOH•H_2O (10.0 equiv), -30 °C to 23 °C, 8 h; then concentrate; then DMSO (10.0 equiv), HCl (6 M)/1,4-dioxane (3:7), 0 °C to 23 °C, 4 h, 42% for 2 steps. *p*-TsOH = *p*-toluenesulfonic acid; LDA = lithium diisopropylamide.

In conclusion, we have completed the first total synthesis of chilocorine C via a highly convergent strategy. Our approach featured a series of chemo- and stereoselective reactions using the power of nitrones to attach key carbon sidechains and stereocenters in advance of the critical 9 chemical event reaction cascade that enabled construction of the unique 6/6/5-saturated tricycle of

the target. The final reaction of that cascade included the formation of the key *aza*-quaternary stereocenter via a Mannich reaction/decarboxylation sequence with **23**, with computational analysis affording mechanistic insights on the reactivity of iminium **10**. Finally, a series of carefully orchestrated reactions converted **34** into **9**, and was followed by a further optimized sequence to complete the synthesis of chilocorine C in just 15-steps (11-pots) from commercially available starting materials, while also assigning a previously unknown chiral center. That brevity and general scalability, with more than half of the steps performed on gram-scale, should provide efficient access to other indolizidine, quinolizidine, and pyrrole alkaloids as well as reaction parameters suitable for other problems of significance.

ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures, copies of all spectral data, cif files, and full characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

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Notes: the authors declare no competing financial interest.

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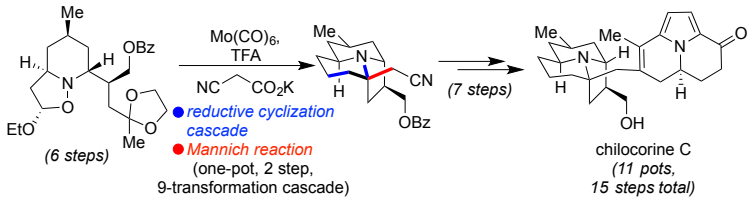
(36) As noted by a referee, we have not explicitly prepared the enantiomer of **8** for coupling with **9** to afford a diastereomer of **5**•HCl to ensure that it does not, also, have similar spectra. We believe such additional structural proof is unnecessary given the level of NMR match between synthetic and natural material and that the consistency observed for the pyrrole subunit within other dimeric members of the family that is supported either by X-ray crystallographic analysis [exochomine (**2**) and chilocorine B (**4**)] or nOe studies (chilocorine D). Moreover, since chilocorine B (**4**) has been co-isolated with chilocorine C (**5**), as reported by Meinwald (Ref. 2d), it would seem to be a fair assumption that **5** would have the same configuration. Additionally, if such a preparation were undertaken and the spectra were similar, optical rotation data could not distinguish the diastereomers since no value has been reported for natural **5**•HCl that we can identify.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15 steps total)