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The Enantioselective Total Synthesis of Exochomine

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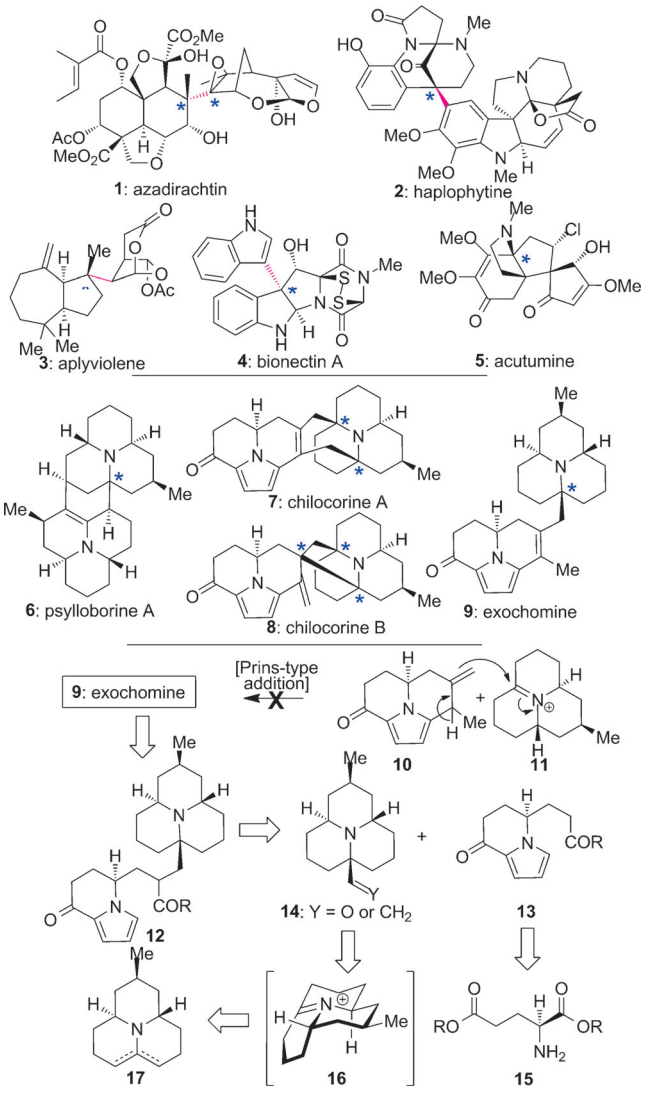
Dedicated to Professor K. C. Nicolaou on the occasion of his 70th birthday

Abstract: *Molecules that possess fully substituted chiral centers are often challenging to construct, particularly if those centers connect two seemingly different halves or include a nitrogen atom. Herein, we describe an efficient approach to a molecule that combines both challenges in a single center in the form of exochomine. Failures in direct coupling led to a design fueled by highly specific reaction conditions for several steps and the development of an improved protocol for 1,4-reduction in a hindered context where numerous side reactions were possible. These chemoselective solutions should have value to other problems. Challenges in obtaining matching spectral data for the synthesized natural product are also discussed.*

One of the key driving forces for new synthetic tactics and reactions are fully substituted chiral centers. Indeed, the efficient preparation of such centers often necessitates unique designs and novel reactivity considerations.[1] Those challenges, however, are arguably magnified in those molecules where nature has placed such fully substituted centers at the connection point of two seemingly different halves. Compounds such as azadirachtin (**1**, Scheme 1),[2] haplophytine (**2**),[3] aplyviolene (**3**),[4] and bionectin A (**4**)[5] are representative cases, where years of effort and creative solutions often based on novel methods were required to generate those centers marked with a blue asterisk, noting that direct coupling of the two halves has typically proven impossible to achieve. Similarly high challenge also exists with α-tertiary amine centers,[6] such as that found in acutumine (**5**).[7] We have recently embarked on a program exploring molecules that combine both of these challenges within single structures,[8] compounds that include the defensive alkaloids produced by ladybugs in the form of psylloborine A (**6**),[9] the chilicorines (**7** and **8**),[10] and exochomine (**9**).[11,12] As one reflection of that challenge, direct couplings of seemingly appropriate monomers,[8] such as the Prins-type addition[13] shown between **10** and **11**, have failed in our hands to deliver the needed products, necessitating the development of alternate solutions. Herein, we document a route which can enantioselectively deliver exochomine (**9**) in 16 steps, highlighting a series of substrate specific steps and unique reaction conditions whose success in such a hindered context should be relevant for other synthesis problems.



Scheme 1. The challenge of fully substituted chiral center formation, particularly in cases where two seemingly disparate halves are merged (**1**–**4**) and when those centers contain nitrogen (**5**), a problem combined in the coccinellid alkaloids (**6**–**9**).

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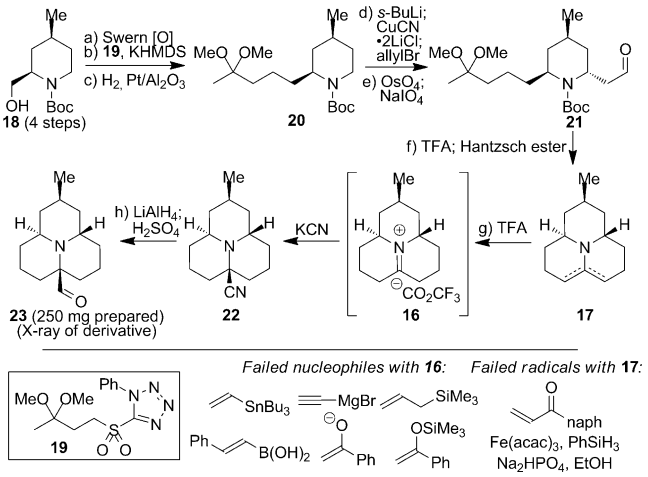
Our overall approach was predicated on attempting to achieve a late-stage coupling of pieces such as **13** and **14**, hoping that an appropriate merger, followed by a selective 1,4-reduction, could generate **12**; if successful, then only a final ring-closure and minor oxidation state changes would be left to complete the target. Of note, **13** was designed to afford maximal flexibility for that merger, both from an entropic perspective by leaving one ring unclosed as well as by affording several coupling reaction choices, with the challenging fully-substituted quaternary center of the target to be preinstalled as part of **14**. That center was hoped to arise through the facially-selective addition of an appropriate nucleophile onto the iminium ion (**16**) derived from enamine **17**. In practice, only a single form of **14** could be accessed, with one coupling reaction process and a hybrid of existing conditions for 1,4-reduction proving capable of delivering the exochomine skeleton.



Scheme 2. Preparation of key enamine building block **23** and challenges in effecting additions to iminium ion **16**: a) $(COCl)_2$ (1.5 equiv), DMSO (3.0 equiv), *i*-Pr_2NEt (6.3 equiv), CH_2Cl_2, −78 °C, 3 h; b) **19** (1.5 equiv), KHMDS (1.2 equiv), PhMe, −78 °C, 3 h, 67% over 2 steps); c) H_2 (1 atm), Pt/Al_2O_3 (5 mol%), EtOAc, 25 °C, 8 h, 98%; d) *s*-BuLi (2.0 equiv), TMEDA (2.0 equiv), −78→−45 °C, 1 h, CuCN·2LiCl (1.75 equiv), −78 °C, 1 h, allyl bromide (5.1 equiv), −78→25 °C, 3 h, 79%, 89:11 d.r.; e) OsO_4 (5 mol%), 2,6-lutidine (2.0 equiv), $NaIO_4$ (4.0 equiv), 1,4-dioxane/H_2O (3:1), 25 °C, 4 h, 95% (~50% ketal deprotection); f) TFA (5.0 equiv), $ClCH_2CH_2Cl$, 25 °C, 1 h then 80 °C, 13 h; evaporate solvent; Hantzsch ester (1.5 equiv), CH_2Cl_2, 25 °C, 4 h; g) TFA (3.3 equiv), KCN (6.6 equiv), THF, 25 °C, 66% over 2 steps, 89:11 ratio of **22** and epimer; h) $LiAlH_4$ (5.4 equiv), THF, −50 °C, 10 min, then 25 °C, 75 min; H_2SO_4 (41 equiv), 0→25 °C, 5 h, 91%, single diastereomer. HMDS = hexamethyldisilazane; TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine; TFA = trifluoroacetic acid.

Scheme 2 presents the developed sequence for the preparation of generalized azaphenylene coupling partner **14** (cf. Scheme 1) in the form of aldehyde **23**. Starting from chiral alcohol **18**, prepared conveniently in just 4 steps from commercial materials [see Supporting Information (SI) for details], subsequent Swern oxidation, Julia–Kocienski olefination, and hydrogenation of the resultant alkene smoothly afforded homologated ketal **20** in 66% overall yield. From here, a Cu^I-promoted allylation[14] afforded the requisite side-chain with high diastereoselectivity (89:11 d.r.), with subsequent oxidative cleavage affording cyclization precursor **21** in 75% overall yield.

The stage was now set to generate the final tricyclic framework in a cascade operation. In the event, treatment of **21** with 5.0 equivalents of TFA in 1,2-dichloroethane at 25 °C for 1 h, followed by 13 h of heating at 80 °C, sequentially effected Boc deprotection, condensation of the resultant secondary amine onto the ketal and/or ketone to form an enamine, and finally enamine attack on the pendant aldehyde to generate the desired conjugated iminium ion tricycle as its TFA salt. After examining a number of reducing agents (such as DIBAL-H and L-selectride) both Stryker's reagent[15a,b] and the Hantzsch ester[15c,d] afforded full 1,4-selectivity in the final component of the cascade, providing enamine **17** after basic work-up. In practice, however, the Hantzsch ester reduction was used for scale-up as material from this process proved easier to purify, noting that the key element of this procedure relative to precedent is that the nitrogen atom of the intermediate iminium ion was retained in this cyclic setting rather than being hydrolyzed.

With this material in hand, we then tested its reactivity in its iminium ion form (**16**), generated by re-exposure to 3.3 equivalents of TFA in THF at 25 °C, with a range of nucleophiles to see what additions could be achieved and in what diastereoselectivity. To our surprise, virtually every nucleophile probed, such as tributylvinyl tin,[16] allyltrimethylsilane (under Sakurai conditions),[17] Grignard reagents,[18] vinyl boronic acids (under Petasis-type conditions),[19] or enolates (prepared both in situ[20a,b] and pre-formed),[20c,d] failed to deliver any coupling adduct; instead, recovered starting material or decomposition was observed. Similarly, radical-based additions, such as those recently developed by Baran,[21] were also unsucessful. Only a Strecker reaction[22] proved fruitful, affording nitrile **22** in 66% yield (including the previous cyclization cascade) and 89:11 d.r. when KCN was used as the quenching agent; that ratio of diastereomers derives from the stereoselectivity of the preceding allylation. The nitrile addition itself is likely fully stereoselective whether under kinetic or thermodynamic control. Indeed, the established kinetic preference for cyanide addition to cyclic iminium ions as governed by stereoelectronics should afford **22**,[23] while DFT calculations[24] using the B3LYP/6-31G** level of theory (Jaguar, version 8.8) reveals that the difference in the Gibbs free energies between **22** and its nitrile epimer favors **22** (9.31 kcal mol^{-1}).

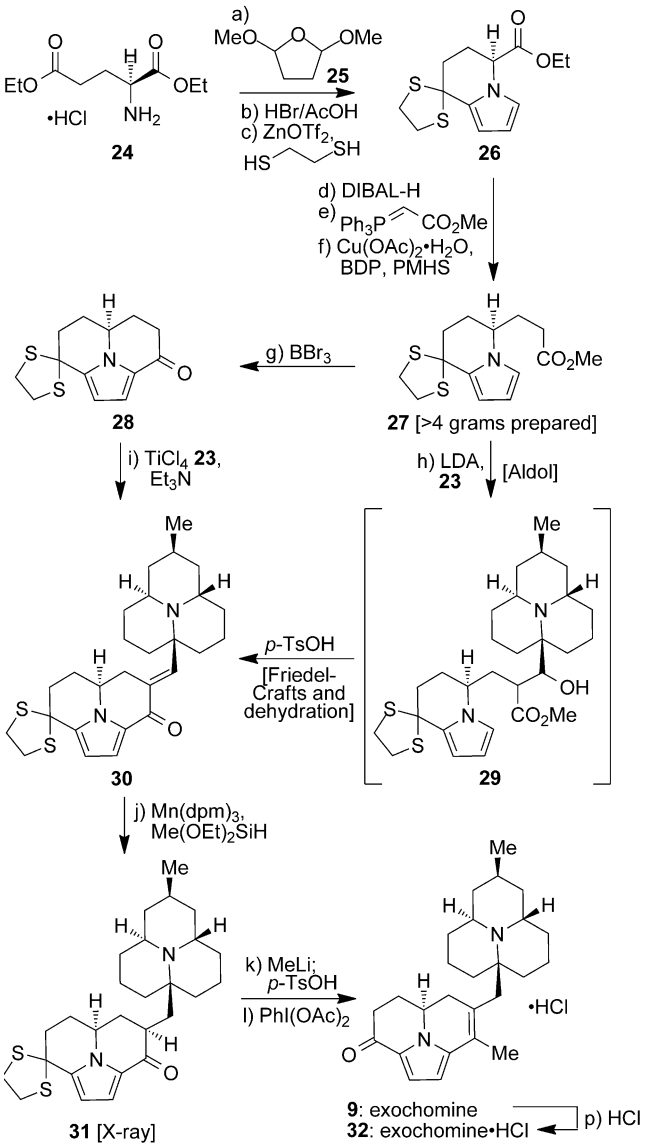
Nevertheless, the new functional group within this compound proved challenging to reduce, with conventional reagents such as DIBAL-H and Red-Al giving modest and variable yields of aldehyde **23**. An optimal procedure proved to be using $LiAlH_4$ in THF at −50 °C for 10 min, followed by stirring at 25 °C for ~75 min, conditions which allowed for in situ hydrolysis using a final H_2SO_4 treatment. This one-pot process proceeded in 91% yield. To date we have prepared nearly 1 gram of **23** (~250 mg through this route and ~700 mg via a slightly longer route, not shown) and obtained it as a single diastereomer; the overall scalability is of note relative

to most efforts towards similarly complex tricyclic amines.[25] The relative stereochemistry of **23** was verified by X-ray diffraction of a benzoate derivative of its corresponding alcohol (see SI).

The synthesis of the pyrrole-based coupling partner commenced with heterocycle formation using inexpensive, commercially available L-glutamic acid ethyl ester **24** (Scheme 3) and 2,5-dimethoxytetrahydrofuran **25**. A subsequent HBr/AcOH-promoted Friedel–Crafts cyclization smoothly gave the desired acyl pyrrole,[26] and was followed by dithiolane protection with 1,2-ethanedithiol as promoted by $Zn(OTf)_2$[27] to give **26** in 37% yield overall for these 3 steps. Homologation to ester **27** was achieved in a further 3-step sequence involving DIBAL-H reduction of the ester to an aldehyde, Wittig olefination, and reduction using the copper hydride formed by premixing $Cu(OAc)_2{\cdot}H_2O$, BDP, and poly(methylhydrosiloxane).[28] The use of standard heterogeneous hydrogenation was precluded in the final step as it also impacted the dithiolane group, noting that this protecting group proved critical as other alternatives, such as ketals or protected alcohols, were too fragile. Of note, although the sequence proceeded through a potentially epimerizable aldehyde, the enantiopurity was largely retained, being determined to be 97% *ee* by chiral HPLC, and **27** could readily be prepared (> 4 g synthesized). Finally, **27** could also be converted into cyclized product **28** in 51% yield through exposure to BBr_3 in CH_2Cl_2 at 0 °C for 20 min. This latter material had been previously prepared racemically by Meinwald in 5 steps;[12] our overall route, though 2 steps longer, was asymmetric.

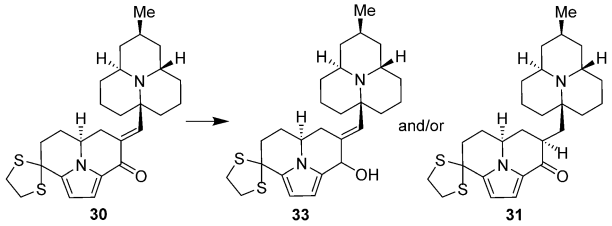
With azaphenylene aldehyde **23** in hand, as well as two potential coupling partners (**27** and **28**), studies were undertaken to bring the two halves together. Using these pieces and a range of other compounds (not shown), that process initially proved challenging, with approaches based on metathesis, Horner–Wadsworth–Emmons olefinations,[29] and Nozaki–Hiyama–Kishi couplings[30] all failing.

Our first success was registered with a titanium-mediated aldol condensation[31] between ketone **28** and aldehyde **23** which delivered **30**, albeit in low and variable yields due principally to the instability of ketone **28** under the reaction conditions. Pleasingly, after much optimization, we found that a milder coupling could be achieved by using the more conformationally flexible ester **27**. In the event, LDA-mediated enolization and aldol addition with **23** (0.9 equiv) in THF at −78 °C for 2 h provided **29** (any warming led to retro-aldol reactions); this intermediate was then treated with *p*-TsOH in situ, with subsequent solvent evaporation, resuspension in benzene, and heating at 60 °C for 4 h effecting dehydration and Friedel–Crafts cyclization in one pot, delivering **30** in 32% yield. No intermediates were characterizable, so the exact order of steps is unknown, and though this outcome is not numerically high, 3 steps were achieved overall, with the likely culprit for throughput being the Friedel–Crafts reaction given the observed yield (51%) in the conversion of **27** into **28**. Also worth noting is that the same conditions (as well as other protocols) did not lead to coupling products when **28** was the enolate partner, likely because retro-aldol pathways might be favored due to its more rigid framework.



Scheme 3. Completion of the total synthesis of exochomine: a) **25** (1.05 equiv), $ClCH_2CH_2Cl$, 65 °C, 4 h, 80%; b) HBr (2 equiv), AcOH, 25 °C, 3 h, 60%; c) 1,2-ethanedithiol (1.3 equiv), $Zn(OTf)_2$ (1.3 equiv), CH_2Cl_2, 25 °C, 12 h, 78%; d) DIBAL-H (1.05 equiv), CH_2Cl_2, −78 °C, 30 min; e) PPh_3CHCO_2Me (1.1 equiv), CH_2Cl_2, 0→25 °C, 12 h, 81% over 2 steps; f) $Cu(OAc)_2{\cdot}H_2O$ (5 mol%), BDP (0.5 mol%), PMHS (2.0 equiv), *t*-BuOH (2.0 equiv), toluene, 25 °C, 8 h, 90%; g) BBr_3 (2.5 equiv), CH_2Cl_2, 0 °C, 20 min, 51%; h) LDA (1.5 equiv), **23** (0.9 equiv), THF, −78 °C, 2 h; *p*TsOH·H_2O (5.0 equiv), −78→25 °C; evaporate; benzene, 60 °C, 4 h, 32%; i) $TiCl_4$ (2.0 equiv), Et_3N (2.1 equiv), CH_2Cl_2, −78 °C, 2 h, 19%; j) $Mn(dpm)_3$ (2.2 equiv), $MeSi(OEt)_2H$ (5.0 equiv), *i*-PrOH/CH_2Cl_2 (8:1), 25 °C, 16 h, 48%, 10:1 d.r.; k) MeLi (2.0 equiv), THF, −78→−30 °C, 30 min, *p*TsOH·H_2O (5 equiv), −30→25 °C, 4% **9** and 65% protected **9**; l) $PhI(OAc)_2$ (1.3 equiv), $CH_3CN/CH_2Cl_2/H_2O$ (5:1:1), −10 °C, 10 min, 31%, 23% from **31**; p) HCl (1.0 M in Et_2O, 1.5 equiv), EtOAc, 25 °C, 30 min, 70%. Ts = tosyl; BDP = 1,2-bis(diphenylphosphino)benzene; PMHS = poly(methylhydrosiloxane).

Table 1: Key optimization studies for the selective 1,4-reduction of enone **30**.



30 **33** **31**

Entry	Conditions	Product	Yield of **31** [%][a]
1	$Cu(OAc)_2{\cdot}H_2O$, BDP, PMHS	n.r.	0
2	$[CuH(PPh_3)]_6$	n.r.	0
3	$Cu(OAc)_2{\cdot}H_2O$, $P(Oi\text{-}Pr)_3$, $MeSi(OEt)_2H$	**31** + 1,6-reduction	<20[b]
4	SmI_2, *t*-BuOH, THF	**33** + **31** + 1,6-reduction	<20[b]
5	$Pd(PPh_3)_4$, $ZnCl_2$, *n*-Bu_3SnH	n.r.	0
6	catecholborane	**33**	0
7	DIBAL-H	**33**	0
8	RedAl, CuBr, $BF_3{\cdot}OEt_2$	n.r.	0
9	$CuBr{\cdot}Me_2S$, *t*-BuLi, DIBAL-H, THF/HMPA	n.r.	0
10	NBSH, Et_3N	n.r.	0
11	$TsNHNH_2$, NaOAc, THF/H_2O	n.r.	0
12	$Mn(dpm)_3$, $PhSiH_3$, TBHP	**31** + deprotection	25
13	$Mn(dpm)_3$, $PhSiH_3$	**31**	40
14	$Mn(dpm)_3$, $MeSi(OEt)_2H$	**31**	52

[a] A very small amount of isomer at the newly formed chiral center was also observed in these reductions, but was separated and is not part of these yield calculations; [b] Isolated yield, but includes some minor inseparable contaminants.

From here, only a few operations remained to complete the target, with the next, selective conjugate enone reduction of **30** to give **31**, proving highly challenging to effect as the dithiolane group, benzylic ketone, and acyl pyrrole all proved prone to reduction (leading to products such as **33**). As shown in Table 1, copper hydride-based approaches gave sluggish reactions and, when products were observed, typically the major adduct was 1,6-reduction across the pyrrole ring (entries 1–3). Radical-based methods such as SmI_2 also afforded predominantly 1,6-reduction (entry 4), while a variety of other standard protocols for conjugate enone reduction did not provide promising results (entries 5–11). Only Mn^{III}-mediated conditions as reported by Shenvi[32] (entry 12) and Magnus[33] (entry 13) provided encouraging selectivity and yield, with the use of the same hydride source from entry 3, that is, $MeSi(OEt)_2H$, providing the best overall outcome for this transformation in 52% isolated yield (entry 14). The identity and absolute configuration of **31** was confirmed by X-ray analysis.

Finally, a one-pot methyl addition, elimination, and ketone deprotection from **31** afforded a small amount of exochomine (**9**) alongside its protected form in 4% and 65% yield, respectively. The use of $PhI(OAc)_2$ in a 5:1:1 mixture of $CH_3CN/CH_2Cl_2/H_2O$ converted any remaining protected intermediate into the final compound (i.e. **9**).[34] As NMR data for the free base form of the target was not available, synthetic exochomine was converted into its corresponding HCl salt (i.e. **32**) and purified by preparative TLC. However, upon comparison of both its ^1H and ^{13}C NMR data to that reported by the isolation team, including experiments which sought to alter the acid content by titration with HCl as well as eliminate water content in the sample,[35] there were always subtle discrepancies from the isolation data without specific patterning. Pleasingly, however, X-ray diffraction of a suitably grown crystal of synthetic **32** obtained from slow evaporation in CH_2Cl_2/EtOAc was able to confirm its structure. We are not completely sure of the source of the variances in the respective NMR spectra between the synthetic and natural material, but believe that water content is the likely culprit and should be considered as an additional point of concern for such compounds;[36] counterion impurities could also be at play as the exact procedure by which the isolation team obtained their HCl salt from the crude extract is not defined.[37]

In conclusion, we have completed the first enantioselective total synthesis of the coccinellid alkaloid exochomine (**9**) in 16 linear steps. The key α-tertiary amine center linking the two disparate halves was constructed using a highly diastereoselective Strecker reaction from an iminium precursor, with the key linking C–C bond formed convergently using an aldol reaction from two advanced intermediates in a cascade where a Friedel–Crafts cyclization proceeded in the same pot. Flexibility in coupling partners was key to its success. In addition, selective 1,4-reduction conditions based on the combination of Mn^{III} and a unique hydride source succeeded on a reactive and sterically encumbered system where other tools failed, and should be of use for other challenging systems. Current efforts seek to deploy the strategies and methodological advances from this synthesis to other challenging targets.

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