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An Intramolecular *aza*-[3 + 3] Annulation Approach to Azaphenalene Alkaloids. Total Synthesis of Myrrhine†

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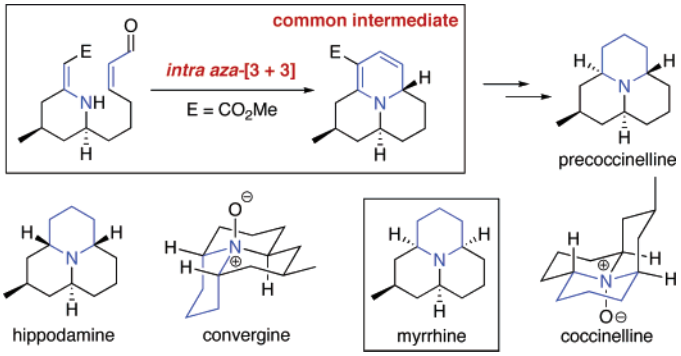

A detailed account on the stereoselective total syntheses of azaphenalene alkaloids via an intramolecular *aza*-[3 + 3] annulation strategy is described here. All five members of the *Coccinellidae* family of defensive alkaloids were prepared from the same common intermediate, which was derived from a stereoselective *aza*-[3 + 3] annulation reaction.

Introduction

We have been developing an intramolecular *aza*-[3 + 3] annulation reaction employing vinylogous amides tethered with α,β-unsaturated iminium salts **1** (Figure 1).[1−5] This annulation provides a powerful synthetic strategy to construct nitrogen heterocycles **2** that can lead to a range of prevalent structural motifs among alkaloids.[1] Two of the five carbons along with the nitrogen atom come from the vinylogous amide, with the remaining three carbons from the α,β-unsaturated iminium salt, thereby representing a formal *aza*-[3 + 3] cycloaddition reaction. The net result is the formation of two new σ-bonds with a new and significant stereocenter adjacent to the nitrogen atom. We have already applied this strategy to synthesize several alkaloids such as gephyrotoxin,[3a] tangutorine,[4b] deplancheine,[4c] and cylindricine C.[4d,e]

To advance our quest in demonstrating the utility of our intramolecular *aza*-[3 + 3] annulation methodology as a unified

† With deep respect and appreciation, this paper is dedicated to Professor Wayland E. Noland on the very special occasion of his 80th birthday.

(1) For reviews, see: (a) Harrity, J. P. A.; Provoost, O. *Org. Biomol. Chem.* **2005**, *3*, 1349. (b) Hsung, R. P.; Kurdyumov, A. V.; Sydorenko, N. *Eur. J. Org. Chem.* **2005**, 23. (c) Coverdale, H. A.; Hsung, R. P. *ChemTracts* **2003**, *16*, 238. For a review on vinylogous amide chemistry, see: (d) Kucklander, U. *Enaminones as Synthons*, in *The Chemistry of Functional Groups: The Chemistry of Enamines Part I*; Rappoport, Z., Ed.; John Wiley & Sons: New York, 1994; p 523.

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(4) For natural product syntheses, see: (a) McLaughlin, M. J.; Hsung, R. P.; Cole, K. C; Hahn, J. M.; Wang, J. *Org. Lett.* **2002**, *4*, 2017. (b) Luo, S.; Zificsak, C. Z.; Hsung, R. P. *Org. Lett.* **2003**, *5*, 4709. (c) Sydorenko, N.; Zificsak, C. A.; Gerasyuto, A. I.; Hsung, R. P. *Org. Biomol. Chem.* **2005**, *3*, 2140. (d) Swidorski, J. J.; Wang, J.; Hsung R. P. *Org. Lett.* **2006**, *8*, 777. (e) Wang, J.; Swidorski, J. J.; Sydorenko, N.; Hsung, R. P.; Coverdale, H. A.; Kuyava, J. M.; Liu, J. *Heterocycles* **2006**, *70*, 423−459.

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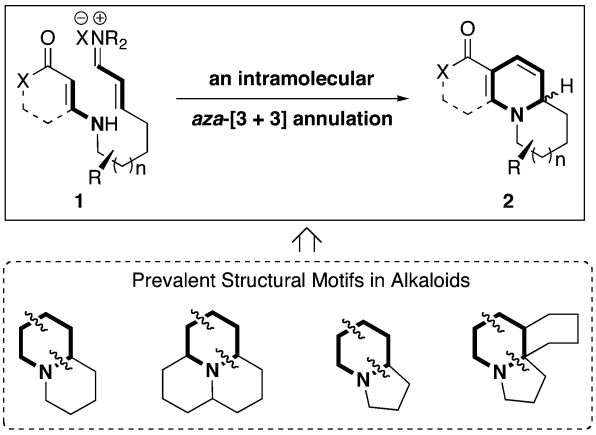

FIGURE 1. An intramolecular *aza*-[3 + 3] annulation.

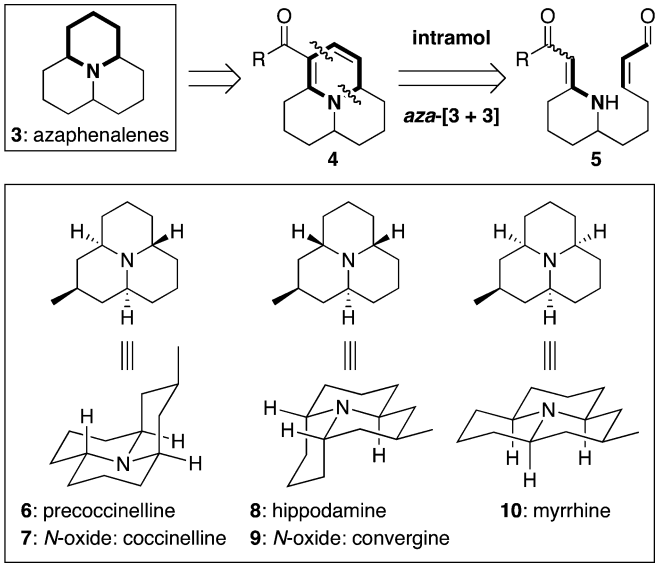

FIGURE 2. An *aza*-[3 + 3] annulation approach to azaphenalenes.

strategy to access different *N*-heterocyclic structure manifolds known in natural alkaloids, we became interested in the family of *Coccinellidae* defensive alkaloids **6**−**10** (Figure 2).[5] Ladybird beetles (*Coccinellidae*) play an important role in controlling populations of agricultural pests such as aphids, mealy bugs, and scale insects. To protect themselves from their natural predators such as ants and quails, they utilize a *reflex bleeding* mechanism[6a] in which, when being pressed into a defensive mode, they release from their joints an orange fluid that contains a mixture of alkaloids.[6]

In 1971, Tursch and co-workers reported their isolation of the crystalline substance coccinelline (**7**) along with its free base precoccinelline (**6**) from this fluid.[7a] The proposed structure of **7** was confirmed by a single-crystal X-ray analysis.[7b] Other stereoisomers of the 2-methyl-perhydro-9b-azaphenalene system with the methyl group occupying an equatorial position were later isolated and characterized as hippodamine (**8**),[7c,d] its *N*-oxide convergine (**9**),[7c,d] and the thermodynamically most stable all-*syn* myrrhine (**10**).[7e] Interestingly, *N*-oxide of myrrhine **10** is not known to occur in nature.

The first total syntheses of **6**−**10** were reported by Ayer in 1976.[8a,9a] Subsequently, two syntheses of **6** and **7** were reported in 1979 by Mueller[9b,c] and Stevens[9d] along with a recent one by Royer.[9e] In addition, Takahata accomplished the formal synthesis of precoccinelline **6** in 2002.[9f] All of these syntheses intercept the same ketone intermediate that was first prepared by Ayer.[9a] Mueller also proceeded to finish syntheses of **8**, **9**, and **10** in 1984,[8b,9c] and recently, Adams[8c] and Stockman[8d] reported their approaches to hippodamine and *epi*-hippodamine. In all of these syntheses with the exception of one,[8a] the equatorial methyl group is being introduced in the latter steps of the synthetic sequence. We recently communicated our total syntheses of **6**−**9**,[5] and we report here details of our approach to the entire family of *Coccinellidae* alkaloids, featuring the construction of their azaphenalene core (see **3** in Figure 2) from a common *aza*-tricycle **4** attained via an intramolecular *aza*-[3 + 3] annulation.

Results and Discussions

Retrosynthetic Plan. Because of the symmetric nature of precoccinelline **6**, hippodamine **8**, and myrrhine **10**, retrosynthetically they could be derived via four distinct pathways depending upon the stereochemical outcome of intramolecular *aza*-[3 + 3] annulation and the location of the methyl substituent (Figure 3). If the *aza*-[3 + 3] annulation of vinylogous amide **11** proceeds selectively to favor the *anti* (defined by the angular hydrogen atoms in blue) annulation product **12** as shown in pathway **A**, we could then quickly access both precoccinelline **6** and hippodamine **8**, as **12** would match three of the four stereocenters in **6** and **8**. However, an appropriate epimerization (see the black arrow) of **12** would be required to access myrrhine **10**. A more direct synthesis of **10** would be to employ the *syn* (defined by the angular hydrogen atoms in red) *aza*-tricycle **13** via a *syn*-selective annulation of **11** (pathway **B**).

In pathway **C**, the methyl group required for these natural products is envisioned to be on the carbon tether of vinylogous amide **14**, and if **14** could be accessed in an optically enriched manner, it would constitute an enantioselective total synthesis of **8** (**6** and **10** are achiral or meso). Finally, these alkaloids could also be derived from **15** and/or **16** that can be attained through an intramolecular *aza*-[3 + 3] annulation reaction of vinylogous amide **17**, which would require an enone annulation (see pathway **D** in Figure 3). We focused on pathways **A** and **B** because it is not trivial to prepare **14** in an optically enriched

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(7) (a) Tursch, B.; Daloze, D.; Dupont, M.; Pasteels, J. M.; Tricot, M. C. *Experientia* **1971**, *27*, 1380. (b) Karlsson, R.; Losman, D. *J. Chem. Soc., Chem. Commun.* **1972**, 626. (c) Tursch, B.; Daloze, D.; Pasteels, J. M.; Cravador, A.; Braekman, J. C.; Hootele, C.; Zimmermann, D. *Bull. Soc. Chim. Belg.* **1972**, *81*, 649. (d) Tursch, B.; Daloze, D.; Braekman, J. C.; Hootele, C.; Cravador, A.; Losman, D.; Karlsson, R. *Tetrahedron Lett.* **1974**, 409. (e) Tursch, B.; Daloze, D.; Braekman, J. C.; Hootele, C.; Pasteels, J. M. *Tetrahedron* **1975**, *31*, 1541.

(8) For syntheses of hippodamine, convergine, and myrrhine, see: (a) Ayer, W. A.; Dawe, R.; Eisner, R. A.; Furuichi, K. *Can. J. Chem.* **1976**, *54*, 473. (b) Mueller R. H.; Thompson, M. E. *Tetrahedron Lett.* **1980**, 1093. (c) Adams, D. R.; Carruthers W.; Crowley, P. J. *J. Chem. Soc., Chem. Commun.* **1991**, 1261. (d) Rejzek, M.; Stockman, R. A.; Hughes, D. L. *Org. Biomol. Chem.* **2005**, *3*, 73.

(9) For syntheses of precoccineline and coccinelline, see: (a) Ayer, W. A.; Furuichi, K. *Can. J. Chem.* **1976**, *54*, 1494. (b) Mueller, R. H.; Thompson, M. E. *Tetrahedron Lett.* **1979**, 1991. (c) Mueller, R. H.; Thompson, M. E.; DiPardo, R. M. *J. Org. Chem.* **1984**, *49*, 2271. (d) Stevens, R. V.; Lee, A. W. M. *J. Am. Chem. Soc.* **1979**, *101*, 7032. (e) Yue, C.; Nicolay, J. F.; Royer, J.; Husson, H. P. *Tetrahedron* **1994**, *50*, 3139. (f) Takahata, H.; Ouchi, H.; Ichinose, M.; Nemoto, H. *Org. Lett.* **2002**, *4*, 3459.

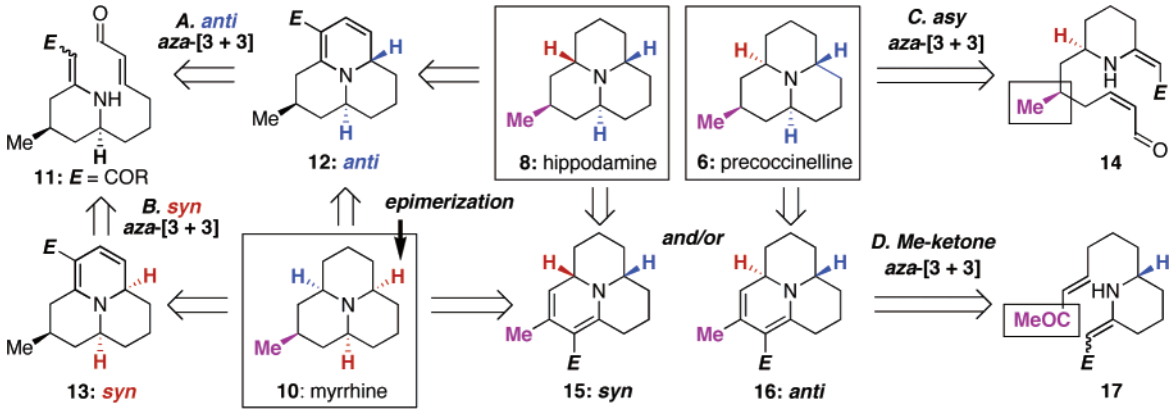


FIGURE 3. Retrosynthetic analysis.

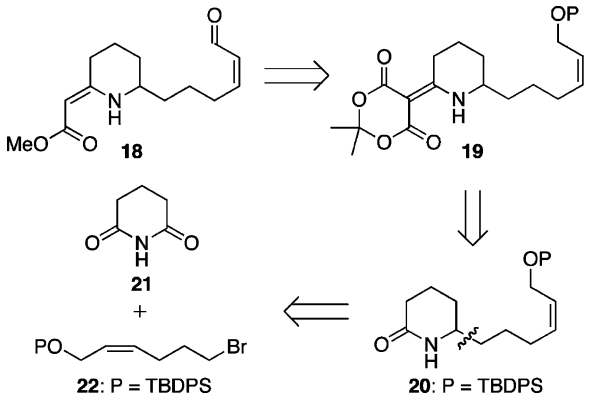


FIGURE 4. Retrosynthesis of the annulation precursor.

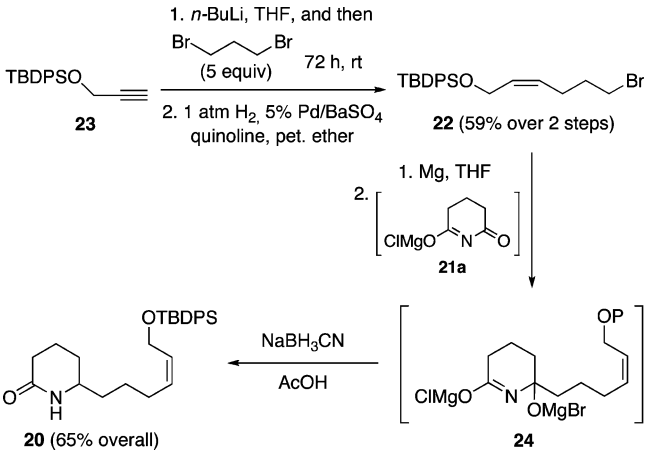
manner, and we have not yet developed a useful enone version of an *aza*-[3 + 3] annulation reaction.

Model Study. Based on our retrosynthetic analysis, a foremost critical question that needs to be addressed would be the stereochemical outcome of the strategic *aza*-[3 + 3] annulation reaction. To explore the feasibility and stereoselectivity of this key transformation, we commenced our efforts with a model system involving the annulation precursor **18** (Figure 4), which should be accessible from Meldrum's acid derivative **19** prepared from lactam **20** along with bromide **22** and glutarimide **21**. We note here that this effort involves only racemic materials because myrrhine **10** is meso.

To prepare vinylogous urethane **18**, alkylation of TBDPS-protected propargyl alcohol **23**[10,11] employing excess 1,3-dibomopropane followed by Lindlar hydrogenation led to bromide **22** in 59% overall yield (Scheme 1). Lactam **20** was prepared via reductive alkylation[12] of glutarimide **21**. The Grignard reagent generated from bromide **22** was added to the Mg-salt **21a** formed *in situ* from glutarimide **21** and 1.0 equiv of CH_3MgCl. Subsequent reduction of the hemi-aminal intermediate **24** with $NaBH_3CN$ and AcOH led to lactam **20** in 65% yield over three steps.

After an extensive screening of various methylating conditions, *O*-methyl imidate **25** was prepared in nearly quantitative

SCHEME 1. Synthesis of Lactam 20



yield via treatment of lactam **20** with freshly distilled MeOTf in CH_2Cl_2 (Scheme 2).[13] Without further purification, it was submitted for the condensation reaction with Meldrum's acid in the presence of $Ni(acac)_2$ catalyst.[14] The two-step sequence led to piperidine **19** in 30−45% overall yield. Alternatively, piperidine **19** was prepared in three steps with a higher yield from lactam **20**: (1) Lawesson's reagent, (2) methylation, and (3) $Ni(acac)_2$-catalyzed condensation with Meldrum's acid.

Treatment of piperidine **19** with an excess of MeONa in refluxing MeOH led to the formation of vinylogous urethane **28-*Z*** in 66% yield exclusively as a *Z*-isomer (Scheme 3),[14] and the TBDPS group was also cleaved under the reaction conditions. Mechanistically, the intriguing selectivity for the *Z*-isomer could be rationalized via a regioselective addition of methoxide anion to the carbonyl group (in red) in **19** that is activated by intramolecular hydrogen bonding to give sodium carboxylate **29**. Upon protonation of **29** during the workup, a neutral vinylogous carbamic acid **30** could be attained. However, this carbamic acid could also exist in equilibrium with the zwitterion **31** as shown through the arrow pushing (although proton could come from external sources). The zwitterion **31** would represent

(10) Toshima, K.; Ohta, K.; Ohashi, A.; Nakamura, T.; Nakata, M.; Tatsuta, K.; Matsumura, S. *J. Am. Chem. Soc.* **1995**, *117*, 4822.
(11) See Supporting Information.
(12) (a) Karstens, W. F. J.; Stol, M.; Rutjes, F. P. J. T.; Kooijman, H.; Spek, A. L.; Hiemstra, H. *J. Organomet. Chem.* **2002**, *624*, 244. (b) Esch, P. M.; Hiemstra, H.; Klaver, W. J.; Speckamp, W. N. *Heterocycles* **1987**, *26*, 75. (c) Evans, D. A.; Thomas, E. W.; Cherpeck, R. E. *J. Am. Chem. Soc.* **1982**, *104*, 3695.
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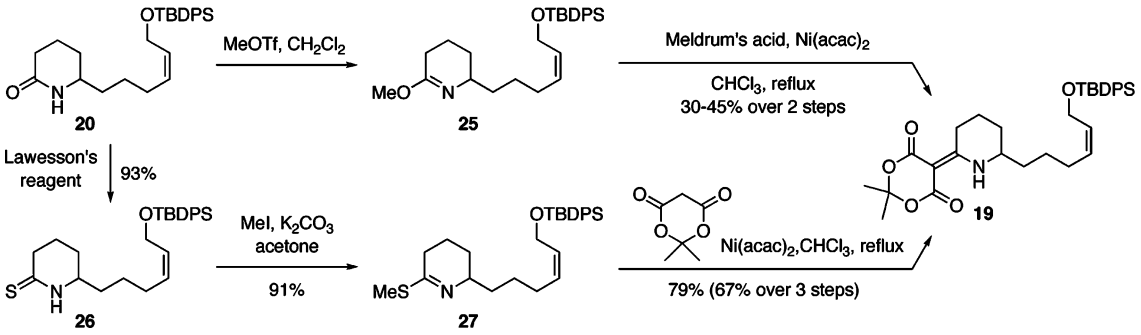
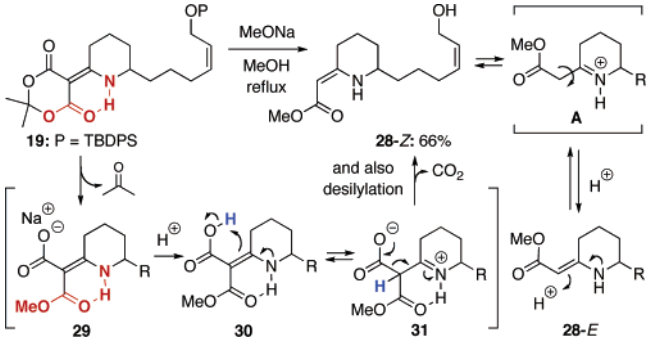
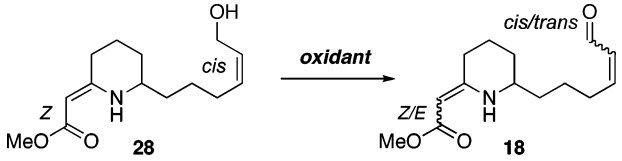
SCHEME 2. Synthesis of Meldrum's Acid Derivative 19



SCHEME 3. Synthesis of Allyl Alcohol 28



SCHEME 4. Oxidation of Allyl Alcohol 28



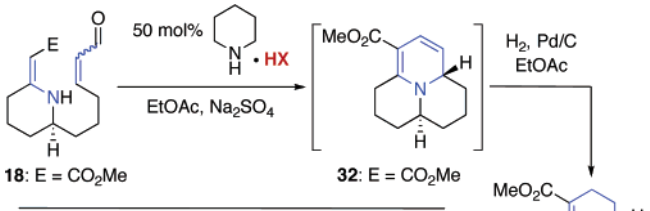
entry	*oxidants*	yield [%]	enal and amide ratios
1	MnO_2	49	*cis* : *trans* = 3 : 1 (enal)
2	$(COCl)_2$/DMSO	100	*Z* : *E* = 1 : 1 (amide)
3	Pyr-SO_3/DMSO	87	*cis* : *trans* = 7 : 1 (enal)

the most suitable intermediate to undergo a facile decarboxylation, leading to *Z*-urethane **28-*Z***. Alternatively, if decarboxylation of **31** would give enamine **28-*E***, it could still be converted to the *Z*-isomer via the iminium intermediate **A** upon protonation of **28-*E***. Rotation around C−C bond in intermediate **A** followed by deprotonation will lead to the thermodynamically more stable **28-*Z***.

Various oxidation protocols were evaluated to efficiently convert allyl alcohol **28** (the *Z*-isomer) to the corresponding enal **18** (Scheme 4). MnO_2 oxidation was relatively slow, giving only 49% yield of the desired enal **18** (entry 1), but under these conditions, we obtained a mixture of both *cis* and *trans* enals. The Swern oxidation conditions[15a] allowed us to access enal **18** in quantitative yield (entry 2) exclusively as *cis* isomer, but the *Z* geometry in the vinylogous urethane fragment was completely scrambled. Finally, the Doering−Parikh oxidation protocol[15b,c] provided **18** in excellent yield with retention of the *Z* geometry in the vinylogous urethane moiety (entry 3).

(15) (a) Omura, K.; Swern, D. *Tetrahedron* **1978**, *24*, 1651. (b) Chen, L.; Lee, S.; Renner, M.; Tian, Q.; Nayyar, N. *Org. Proc. Res. Dev.* **2006**, *10*, 163. (c) Parikh, J. R.; von Doering, W. E. *J. Am. Chem. Soc.* **1967**, *89*, 5505.

SCHEME 5. Intramolecular *aza*-[3 + 3] Annulation

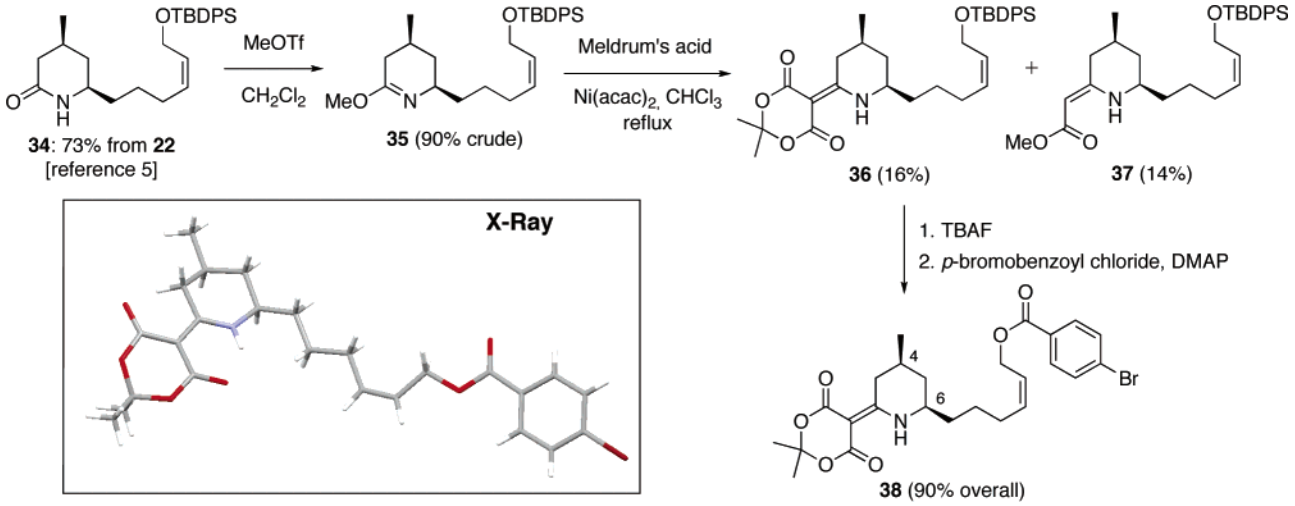


entry	HX	temp [°C]	time [h]	yield [%] of **32**
1	HOAc	25	24	trace
2	HOAc	85	3	decomp
3	HO_2CCF_3	25	3	35%

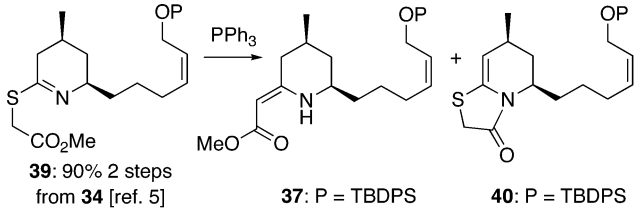
Enal **18** (*cis*:*trans* = 7:1) was subjected to the *aza*-[3 + 3] annulation conditions employing piperidinium acetate salts in EtOAc (Scheme 5).[3a,b] After 24 h at room temperature, only a trace amount of the desired *aza*-tricycle **32** was detected by ^{1}H NMR (entry 1). Subsequent heating of the reaction mixture to 85 °C for 3 h led to the decomposition of **18** (entry 2). Upon using the more reactive piperidinium trifluoroacetate salt[3b] (entry 3), complete consumption of **18** was observed at 25 °C after 3 h, and the desired *aza*-tricycle **32** was isolated in 35% yield as a single diastereomer. Its *anti* stereochemistry at the ring junction was established via NOE experiments (and also through an X-ray structure of a related intermediate[5]). Because of the unstable nature of **32**, we found it more convenient to hydrogenate the reaction mixture over Pd−C after the annulation.[3a] This one-pot protocol allowed us to access the more stable *aza*-tricyclic **33** in 38% overall yield.

An Approach to Precoccinelline and Hippodamine. Having succeeded in the model study, we turned our attention to the actual total syntheses of alkaloids **6**−**10** via the same route developed above for the des-methyl model. Toward this end, lactam **34** was prepared from bromide **22** and 4-methylglutarimide in 73% yield as described previously (Scheme 6).[5] After converting lactam **34** to methyl imidate **35** using fresh MeOTf in CH_2Cl_2, imidate **35** was again subjected to the condensation reaction with Meldrum's acid in the presence of $Ni(acac)_2$ catalyst (Scheme 6).[14] However, in this case, the desired piperidine **36** was isolated in only 16% yield over two steps along with 14% of vinylogous urethane **37**. The formation of **37** was likely a result of ring-opening of the 1,3-dioxanone ring in **36** with MeOH generated in situ during the condensation reaction followed by decarboxylation (see Scheme 3). Nevertheless, we were able to unambiguously assign the relative stereochemistry with respect to C4 and C6 on the piperidine ring as *syn* based on the single-crystal X-ray analysis of bromobenzoate derivative **38** prepared in two steps from **36**.

SCHEME 6. Meldrum's Acid Approach



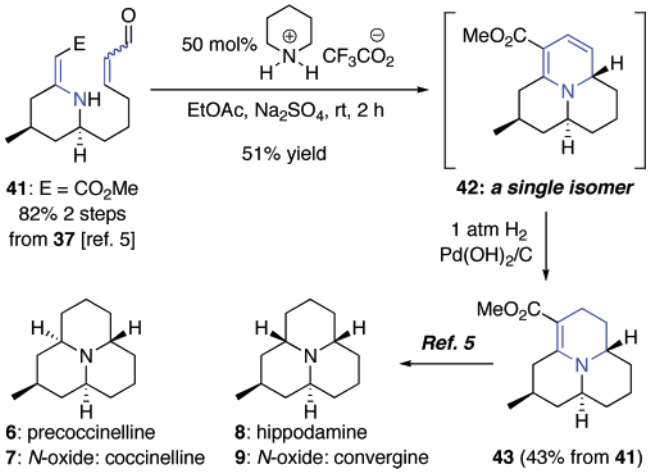
SCHEME 7. Eschenmoser Sulfide Contraction



entry	base	solvent	temp [°C]	time [h]	yield [%]: **37**	**40**
1	NEt_3	CH_3CN	25	72	no rxn	no rxn
2	NEt_3/DBU	CH_3CN	80	48	69%	5-10%
3	DIPEA	toluene	100	96	60%	trace
4	DIPEA	CH_3CN	100	48	82-90	trace

To access vinylogous urethane **37** more effectively, we investigated an alternative approach that would feature Eschenmoser sulfide contraction reaction.[16] As shown in Scheme 7, thiol imidate **39** was prepared in two steps from the lactam **34**[5] and was subsequently treated with PPh_3 in the presence of NEt_3 in CH_3CN. After 72 h at room temperature, no formation of the desired vinylogous urethane **37** was observed (entry 1). After addition of DBU and refluxing in CH_3CN for 48 h, vinylogous urethane **37** was isolated in 69% yield along with an interesting byproduct, thiazolidinone **40** (entry 2). There are literature precedents[17] for the formation of this byproduct in the Eschenmoser sulfide contraction reaction when using strong base such as DBU. After tuning both the base and the solvent for the reaction, an excellent yield of the desired vinylogous urethane **37** could be achieved (entry 4).

SCHEME 8. Key Intramolecular *aza*-[3 + 3] Annulation



The precursor for the *aza*-[3 + 3] annulation, **41**, was prepared in two steps from **37**[5] by cleavage of the TBDPS protecting group and Pyr·SO_3 oxidation of the resulting allyl alcohol (Scheme 8). Treatment of enal **41** with piperidinium trifluoroacetate salt in EtOAc at room temperature for 2 h afforded the desired *aza*-annulation product **42** in 51% yield as a single isomer with *anti* relative stereochemistry at the ring junction as assigned by NOE experiments.[11] A one-pot protocol involving *in situ* hydrogenation of the disubstituted double bond over $Pd(OH)_2/C$ after the annulation afforded *aza*-tricycle **43** in a reproducible 43% yield over two steps. We chose $Pd(OH)_2/C$ here because it is less prone to amine poisoning than Pd/C that was previously used for the hydrogenation of **32** (see Scheme 5), and we did not go back and repeat this work using $Pd(OH)_2/C$. It is noteworthy that *aza*-tricycle **43** contains three of the four stereocenters required for precoccinelline **6** and hippodamine **8**. Consequently, stereodivergent conversions of **43** to precoccinelline, hippodamine, coccinelline, and convergine were achieved, and details have been disclosed recently.[5]

Mechanistic and Computational Studies. Mechanistically, the intramolecular *aza*-[3 + 3] annulation is a stepwise process involving in situ formation of α,*β*-unsaturated iminium salt **44** (Figure 5) that undergoes an *N*-1,4-addition to give bicycle **45**.[3b,c] Subsequent *C*-1,2-addition followed by tautomerization leads to intermediate **47**. Formation of similar intermediates as **47** in *aza*-[3 + 3] annulation reactions was previously confirmed

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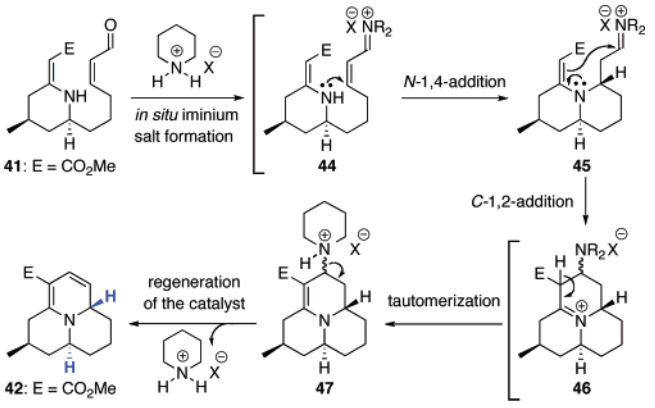


FIGURE 5. Mechanism of intramolecular *aza*-[3 + 3] annulation.

by ^{1}H NMR studies[3b] as well as by isolation of one of such intermediates from the reaction mixture.[3c] Elimination of the protonated piperidine in **47** affords the desired *aza*-tricycle **42** with regeneration of the amine salt catalyst. It is noteworthy that a new stereogenic center is formed during the *N*-1,4-addition step and that all of these mechanistic assessments have served as a fundamental basis for our recent work in designing an asymmetric *aza*-[3 + 3] annulation employing chiral amine salts as catalysts.[3b]

To rationalize the exclusive formation of *anti* stereochemistry at the ring junction (in blue) observed for the annulation product **42**, semiempirical calculations[19] on the simplified iminium salt derived from enal **41** and dimethyl amine were performed using the Spartan'02 program.[20] Corresponding transition state structures for the *N*-1,4-addition step of the reaction were located as confirmed by the presence of one negative eigenvalue and corresponding imaginary frequency, which reflects formation of the N−C bond. Models and their respective energies are shown in Figure 6. There are two possible *pro-syn* and *pro-anti* transition states **48**/**49** and **50**/**51**, which differ in the chair flip of the piperidine ring. In **48**/**49**, the lone pair on the nitrogen atom occupies the pseudo-equatorial position, whereas in **50**/**51** it is pseudo-axial, making it more nucleophilic. It turned out that both *pro-syn*-**TS-48** and *pro-anti*-**TS-49** (left side in Figure 6) are energetically disfavored in comparison with *pro-syn*-**TS-50** and *pro-anti*-**TS-51** (right side). Because of the *Z*-geometry of the vinylogous urethane, the methoxy carbonyl group in both **48** and **49** appear to be bumping into the iminium ion fragment during formation of N−C bond, thereby destabilizing both transition states.

On the other hand, this interaction is minimized in *pro-syn*-**TS-50** and *pro-anti*-**TS-51**, as shown in the models (right side in Figure 6). Within these two possible transitions states, *pro-anti*-**TS-51** was estimated to be 5.1 kcal/mol more stable than *pro-syn*-**TS-50**, which is likely due to the severe 1,3-diaxial interaction in **50**. According to computational results, the annulation reaction should be favored to proceed via *pro-anti*-**TS-51,** leading to the observed *anti*-isomer **42**.

Total Synthesis of Myrrhine. After successful conversions of *aza*-tricycle **42** to precoccinelline **6**, hippodamine **8**, and their corresponding *N*-oxides,[5] we were poised to achieve a total synthesis of myrrhine **10**, the final member of *Coccinellidae* family of defensive alkaloids, also from the same common intermediate **42**. However, the challenge in this endeavor is to achieve an appropriate epimerization at the stereocenter shown in red in *aza*-tricycle **42** (Figure 7). Toward this end, we envisioned two possible approaches for this transformation. The first one involves a 6π-electrocyclic ring opening of *anti*-tricycle **42** under thermal conditions *en route* to 1-azatriene **52**, which upon 6π-electrocyclic ring closure could lead to the thermodynamically more stable *syn aza*-tricycle **53**. The second approach consists of an aromatization of the dihydropyridine ring in **42** via hydride abstraction followed by *syn*-selective reduction of the pyridinium salt **54** to furnish all-*syn* stereochemistry at the ring junction required for myrrhine **10**.

To probe the feasibility of shuttling the *anti aza*-tricycle **42** to the more stable *syn*-**53** through 1-azatriene **52**, compound **42** was heated at 80 °C for 6 h in toluene-d_8. However, after no formation of desired isomer **53** was observed under these conditions, heating of **42** at higher temperatures for longer time (150 °C, 12 h; then 230 °C, 2 h) was pursued but led only to decomposition of the starting material. Ab initio calculations (B3LYP/6-31G*)[19] indicated that 1-azatriene **52** is relatively destabilized in comparison with *aza*-tricycle **42** (by ∼31 kcal/

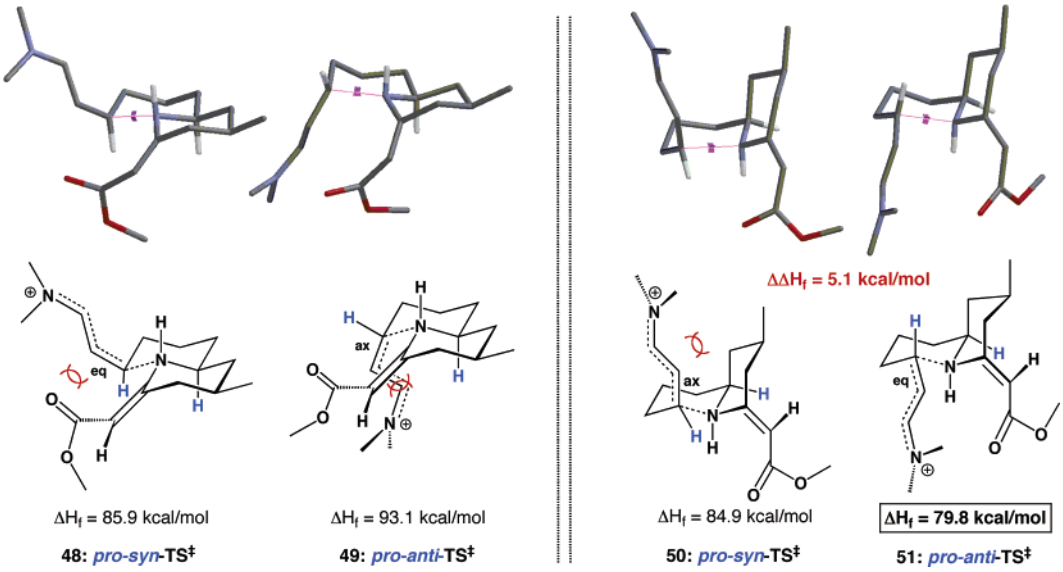


FIGURE 6. Transition states for the initial *N*-1,4-addition.

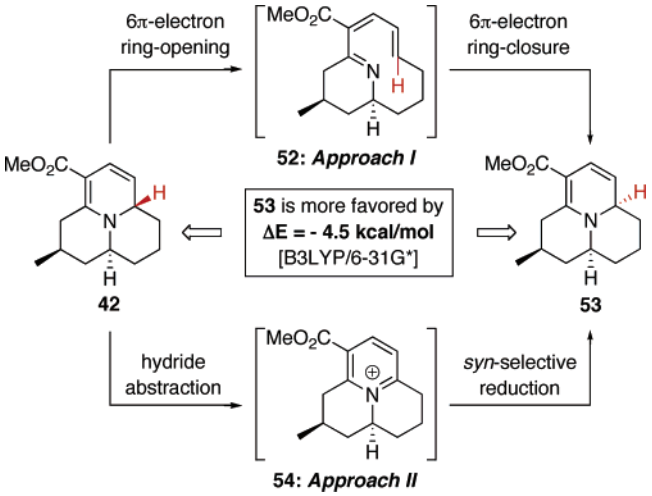
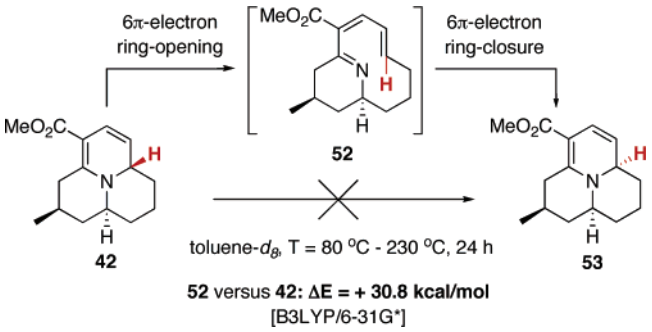
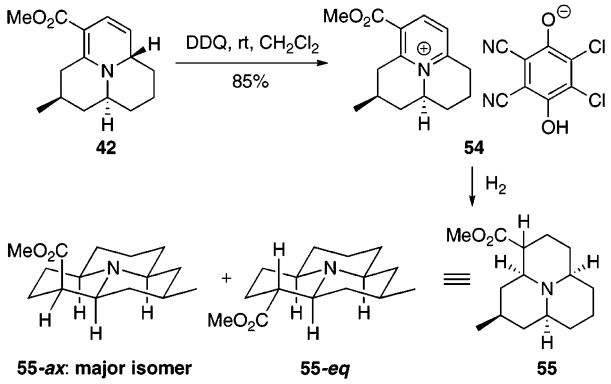


FIGURE 7. Possible epimerization approaches.

SCHEME 9. Failed Isomerization Attempts



SCHEME 10. Hydrogenation of a Pyridinium Salt

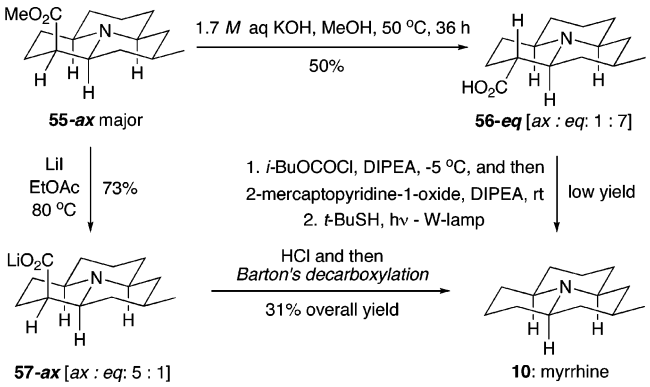


entry	catalyst	H_2 [psi]	solvent	yield [%]	*dr: ax : eq*
1	PtO_2	60	MeOH	61	2: 1
2	$Pd(OH)_2/C$	14	MeOH	44	5 : 1
3	PtO_2	60	AcOH	63	2 :1

mol) (Scheme 9). Since the activation barrier would be even higher, we believe that the 6π-electrocyclic ring-opening approach is not a thermally feasible option for our purpose. This experimental data is also in accord with our earlier findings.[3b,c]

We then pursued the aromatization-reduction approach by treatment of *aza*-tricycle **42** with DDQ in CH_2Cl_2 and isolated the pyridinium salt **54** in 85% yield (Scheme 10).[21] Subsequent hydrogenation of the salt **54** over PtO_2 (Adams' catalyst) in MeOH afforded 61% yield of the all-*syn aza*-tricycle **55** as a 2:1 mixture of diastereomers with respect to the ester group

SCHEME 11. Total Synthesis of Myrrhine: End-Game



(entry 1). This is likely a result of partial epimerization of the initially formed axial isomer **55-*ax*** to the thermodynamically more stable equatorial **55-*eq*** under the reaction conditions. Using $Pd(OH)_2/C$ as a catalyst for the hydrogenation led to the formation of **55** with some epimerization but also a lower yield (entry 2). The cleanest reaction with the highest isolated yield was obtained when the hydrogenation was carried out over Adams' catalyst in AcOH (entry 3).[22] The all-*syn* stereochemistry at the ring junctions was confirmed by the presence of strong Bohlmann bands[23] in IR spectra (2793, 2734, 2619 cm^{-1}) of the **55**.

Saponification of a mixture of ester **55-*ax*** and **55-*eq*** (***ax*:*eq*** = 3:1) with aqueous KOH in MeOH at 50 °C for 36 h led to the predominant formation of equatorial acid **56-*eq*** (Scheme 11), thereby suggesting that significant epimerization of the axial isomer to the more stable equatorial one had occurred. However, subjecting this mixture to Barton's decarboxylation conditions[24] led to myrrhine **10** in a very low yield with almost complete recovery of the equatorial acid **56-*eq***. This result suggested that the axial acid **56-*ax*** is more reactive in the decarboxylation reaction than **56-*eq***.

To explore this hypothesis, ester **55** (5:1 isomer ratio in favor of **55-*ax***) was saponified by treatment with LiI in EtOAc at 80 °C. Under this condition, no epimerization was observed and the diastereomeric ratio of the isolated lithium carboxylate remained at ~5:1 in favor of **57-*ax***. Finally, acidification of this mixture and subjecting the resulting free acid **56-*ax*** to the Barton's decarboxylation conditions afforded myrrhine **10** in 31% yield over four operational steps. Our synthetic sample matched the literature spectroscopic data for the natural myrrhine **10**.[9c,25]

(19) Calculations were carried out in Spartan'02 software on a Dell Precision 650 Dual Xeon (2.00 GHz) workstation.

(20) *Spartan'02*, PC version; Wavefunction, Inc.: Irvine, CA, 2002.

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Conclusion

We have described here a detailed study on total syntheses of *Coccinellidae* defensive alkaloids featuring an intramolecular *aza*-[3 + 3] annulation approach. All five members of this family, precoccinelline, coccinelline, hippodamine, convergine, and myrrhine, have now been prepared from the same common intermediate derived from a stereoselective *aza*-annulation reaction. A mechanistic model for the observed *anti* stereoselectivity in the annulation step based on semiempirical calculations is also described here. This work provides a *de novo* stereoselective approach toward the 2-methyl-perhydro-9b-azaphenalene family of alkaloids.

Experimental Section

Preparation of Pyridinium Salt 54. To a solution of tricycle **42** (0.253 g, 1.02 mmol) in CH_2Cl_2 (7 mL) was added a warm solution of DDQ (0.270 g, 1.19 mmol) in CH_2Cl_2 (20 mL). An immediate color change from yellow to dark brown was observed. The reaction mixture was stirred vigorously for 1 h at room temperature, and the formation of dark brown oil on the bottom of the flask occurred, at which time the stirring was stopped. The reaction mixture was cooled to 0 °C, and CH_2Cl_2 was carefully decanted, leaving behind the precipitated brown oil that solidified upon placing the flask on the high vacuum. The brown solid was pulverized, washed with Et_2O (7 mL), and dried on high vacuum to give pyridinium salt **54** (0.414 g, 85%) as an orange solid: mp = 125−130 °C (decomp); ^{1}H NMR (400 MHz, CD_3OD) δ 1.14 (d, 3 H, J = 6.4 Hz), 1.55 (q, 1 H, J = 12.4 Hz), 1.70−1.90 (m, 2 H), 2.11−2.25 (m, 2 H), 2.38−2.44 (m, 2 H), 2.49−2.59 (m, 1 H), 3.18−3.36 (m, 2 H), 3.62 (ddd, 1 H, J = 18.8, 5.2, 2.4 Hz), 3.97 (s, 3 H), 4.54 (tt, 1 H, J = 11.2, 4.4 Hz), 7.84 (d, 1 H, J = 8.4 Hz), 8.66 (d, 1 H, J = 8.4 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ 17.3, 21.6, 25.17, 25.25, 30.0, 37.9, 54.1, 55.0, 64.0, 100.6, 116.4, 126.9, 129.9, 131.5, 145.5, 154.3, 159.1, 161.9, 165.1; IR (film) cm^{-1} 2956m, 2226s, 1734s; 1618s, 1564m, 1437s, 1278s, 1207s, 1135s, 1079s.

Hydrogenation of Pyridinium Salt 54. A solution of pyridinium salt **54** (40.0 mg, 90.0 μmol) in glacial AcOH (2 mL) was hydrogenated over prereduced Adams' catalyst PtO_2 (10.0 mg) in a Parr apparatus at 60 psi of H_2 overnight. After filtering off the catalyst, AcOH was evaporated under reduced pressure, and aqueous NaOH (1 M, 0.5 mL) and H_2O (1 mL) were added to the highly colored residue. The resulting mixture was extracted with Et_2O (5 × 4 mL), and the combined organic layers were washed with saturated aqueous NaCl (5 mL) and dried over $MgSO_4$. After removal of excess solvents under reduced pressure, the crude product was purified by flash column chromatography using NEt_3 deactivated (2% in EtOAc/hexanes = 9:1) silica gel (eluent 30% EtOAc in hexanes) to afford the all-*syn* tricycle **55** (13.3 mg, 63%) as an inseparable 2:1 mixture of axial and equatorial esters. **55-*ax***: R_f = 0.29 [10% EtOAc in hexanes, neutral Al_2O_3]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86 (d, 3 H, J = 6.4 Hz), 1.00 (q, 1 H, J = 11.6 Hz), 1.17 (q, 1 H, J = 11.6 Hz), 1.26−1.59 (m, 10 H), 1.61−1.66 (m, 1 H), 1.71−1.79 (m, 2 H), 1.87−1.95 (m, 2 H), 2.09 (ddd, 1 H, J = 11.6, 4.0, 2.4 Hz), 2.54 (ddt, 1 H, J = 6.8, 4.0, 1.6 Hz), 3.66 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.2, 24.5, 27.0, 29.9, 31.0, 34.0, 34.2, 40.5, 42.5, 45.2, 51.2, 62.9, 63.2, 63.4, 174.3. **55-*eq***: R_f = 0.29 [10% EtOAc in hexanes, neutral Al_2O_3]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85 (d, 3 H, J = 6.4 Hz), 0.89−1.06 (m, 2 H), 1.26−1.59 (m, 10 H), 1.61−1.66 (m, 1 H), 1.71−1.79 (m, 2 H), 1.87−1.95 (m, 2 H), 2.18 (td, 1 H, J = 10.8, 2.0 Hz), 2.37 (ddd, 1 H, J = 12.4, 10.8, 4.0 Hz), 3.67 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.1, 24.2, 28.4, 30.1, 32.8, 34.3, 34.4, 40.1, 42.6, 49.9, 51.7, 61.8, 62.2, 62.9, 175.9; IR (film) cm^{-1} 2925s, 2862s, 2793m, 2734m, 2619m, 1737s, 1445m, 1374m, 1152s; mass spectrum (APCI): *m*/*e* (% relative intensity) 252 (100) M^+ + H.

A solution of pyridinium salt **54** (0.131 g, 0.280 mmol) in MeOH (2 mL) was hydrogenated over $Pd(OH)_2$/C (10.0 mg) with H_2-balloon for 8 h. After filtering off the catalyst, MeOH was evaporated under reduced pressure, and aqueous NaOH (1 M, 0.5 mL) and H_2O (1 mL) were added to the highly colored residue. The resulting mixture was extracted with Et_2O (5 × 4 mL), and the combined organic layers were washed with saturated aqueous NaCl (5 mL) and dried over $MgSO_4$. After solvent removal under reduced pressure, the crude product was purified by flash column chromatography using NEt_3 deactivated (2% in EtOAc/hexanes = 9:1) silica gel (eluent 30% EtOAc in hexanes) to afford the all-*syn* tricycle **55** (30.0 mg, 44%) as an inseparable 5:1 mixture of axial and equatorial esters.

KOH Hydrolysis of Ester 55. To a solution of esters **55** (20.8 mg, 80.0 μmol) in MeOH (1.5 mL) was added KOH (1.7 M in H_2O, 500.0 μL, 8.50 mmol). The reaction mixture was heated at 50 °C for 36 h and monitored by TLC (Al_2O_3). After complete consumption of the starting material, the mixture was cooled to room temperature, after which MeOH was evaporated under reduced pressure and H_2O (2 mL) was added. The aqueous phase was extracted with CH_2Cl_2 (1 × 2 mL) to remove impurities and then acidified with 1 M HCl until pH = 3−4 before being saturated with solid NaCl. The crude product was extracted with $CHCl_3$ (6 × 5 mL), and the combined organic layers were dried over Na_2SO_4. Removal of $CHCl_3$ under reduced pressure afforded acid **56-*eq*** (9.80 mg, 50%) as colorless solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.96 (d, 3 H, J = 6.0 Hz), 1.54 (qt, 1 H, J = 13.5, 3.5 Hz), 1.63−1.91 (m, 9 H), 1.98 (brd, 1 H, J = 13.5 Hz), 2.13−2.23 (m, 3 H), 2.30 (q, 1 H, J = 13.0 Hz), 2.80 (t, 1 H, J = 12.0 Hz), 2.87 (t, 1 H, J = 12.0 Hz), 3.09 (t, 1 H, J = 11.5 Hz), 3.25 (td, 1 H, J = 11.5, 3.5 Hz), 11.15 (brs, 1 H).

LiI Hydrolysis of Ester 55. A solution of ester **55** (29.9 mg, 0.120 mmol) and LiI (65.0 mg, 0.490 mmol) in EtOAc (1.5 mL) was heated at 80 °C in a sealed tube overnight shielded from light with aluminum foil. The reaction mixture was cooled to room temperature, the precipitate was filtered off, and the filter cake was washed with EtOAc (1 mL) and Et_2O (1 mL) and dried on high vacuum to afford Li-carboxylate **57-*ax*** (21.0 mg, 73%) as slightly brown solid:[26] mp > 200 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 0.96 (d, 3 H, J = 6.0 Hz), 1.25 (q, 1 H, J = 12.0 Hz), 1.55−1.70 (m, 4 H), 1.77−2.02 (m, 10 H), 2.59 (brs, 1 H), 3.07 (tt, 1 H, J = 12.0, 2.4 Hz), 3.10−3.18 (m, 1 H), 3.21 (dd, 1 H, J = 11.6, 2.4 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ 21.6, 23.3, 24.3, 26.9, 29.3, 29.7, 33.1, 33.6, 38.9, 40.7, 64.8, 65.5, 65.8, 180.4; IR (film) cm^{-1} 2931s, 2871s, 2730m, 2652m, 1573s, 1425s, 1415s, 1187m, 1047m.

Synthesis of Myrrhine 10. Li-carboxylate **57-*ax*** (11.8 mg, 50.0 μmol) was dissolved in H_2O and acidified with 1% aqueous HCl until pH = 3−4 before being saturated with solid NaCl. The mixture was extracted with $CHCl_3$ (5 × 5 mL), and the combined organic layers were dried over Na_2SO_4. Removal of $CHCl_3$ under reduced pressure afforded acid **56-*ax*** (3.80 mg) as colorless solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.91 (d, 3 H, J = 6.5 Hz), 1.17 (q, 1 H, J = 11.5 Hz), 1.40−1.50 (m, 3 H), 1.53−1.60 (m, 1 H), 1.64 (brd, 1 H, J = 14.0 Hz), 1.68−1.79 (m, 8 H), 2.06−2.09 (m, 1 H), 2.24 (t, 1 H, J = 11.5, 2.4 Hz), 2.32 (t, 1 H, J = 10.5 Hz), 2.44 (d, 1 H, J = 11.0 Hz), 2.61 (brs, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.6, 23.6, 27.0, 29.4, 29.7, 33.3, 33.7, 39.2, 40.8, 46.9, 62.7, 62.9, 63.2, 176.5; mass spectrum (APCI): *m*/*e* (% relative intensity) 238 (100) M^+ + H.

To a suspension of above acid **56-*ax*** (3.80 mg, 16.0 μmol) in THF (0.5 mL) was added diisopropylethylamine (8.00 μL, 48.0 μmol), and the resulting mixture was cooled to −10 °C. *i*-BuOCOCl (4.00 μL, 31.0 μmol) was then added, and the mixture was stirred at −10 °C for 15 min before being allowed to warm to room

(26) Hydrogens α to nitrogen atom in Li-carboxylate **57-*ax*** are deshielded compared to these hydrogens in **55-*ax*** likely due to the fact that **57-*ax*** is a lithum salt and its ^{1}H NMR was taken in a different solvent.

temperature. After 2 h at room temperature, the mixture was cooled to −10 °C, and a solution of 2-mercaptopyridine-*N*-oxide (40.0 mg, 31.0 μmol) and diisopropylethylamine (6.00 μL, 36.0 μmol) in THF (0.5 mL) was added. The reaction mixture was stirred at this temperature for 2 h while being shielded from light. Next, *t*-BuSH (30.0 μL, 0.270 mmol) was added, and the mixture was irradiated with a tungsten lamp (200 W) while being cooled in a water bath. Excess of solvent and *t*-BuSH were removed under reduced pressure, and 5% aqueous $NaHCO_3$ (2 mL) was added. The aqueous phase was extracted with Et_2O (5 × 3 mL), and the combined organic layers were washed with saturated aqueous NaCl (2 mL) and dried over $MgSO_4$. After concentration under reduced pressure, the crude residue was filtered through a short plug of deactivated silica gel (2% NEt_3 in 10% EtOAc in hexanes) with 20% EtOAc in hexanes. Solvent removal under reduced pressure afforded myrrhine **10** (ca. 2.90 mg, 75%) as colorless oil: $R_f = 0.60$ [10% EtOAc in hexanes, neutral Al_2O_3]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86 (d, 3 H, $J = 6.4$ Hz), 1.04 (q, 2 H, $J = 12.0$ Hz), 1.30−1.38 (m, 6 H), 1.44−1.50 (m, 1 H), 1.52−1.57 (m, 6 H), 1.64−1.67 (m, 2 H), 1.79−1.84 (m, 1 H), 1.86 (brt, 2 H, $J = 10.0$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.1, 24.3, 30.4, 34.0, 34.1, 42.6, 62.3, 62.5; IR (film) cm^{-1} 2924s, 2852s, 2730m, 1464s, 1426m, 1377m, 1315m; mass spectrum (APCI): *m*/*e* (% relative intensity) 194 (100) $M^+ + H$; *m*/*e* calcd for $C_{13}H_{24}N$ ($M^+ + H$) 194.1909, found 194.1915.

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Supporting Information Available: Experimental procedures, characterization data for all new compounds, ^{1}H NMR spectra, NOEs and X-ray structural data in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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