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Unified Total Syntheses of Fawcettimine Class Alkaloids: Fawcettimine, Fawcettidine, Lycoflexine, and Lycoposerramine B

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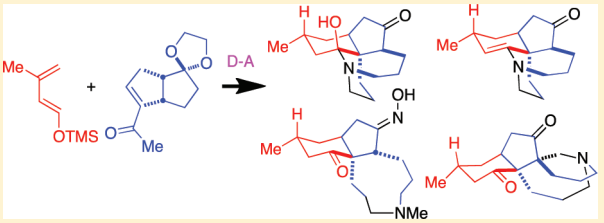
Supporting Information

ABSTRACT: The total syntheses of the lycopodium alkaloids fawcettimine, fawcettidine, lycoflexine, and lycoposerramine B have been accomplished through an efficient, unified, and stereocontrolled strategy that relies on a Diels–Alder reaction to construct the *cis*-fused 6,5-carbocycles with one all-carbon quaternary center. Access to the enantioselective syntheses of both antipodes of those alkaloids can be achieved by kinetic resolution of the earliest intermediate via a Sharpless asymmetric dihydroxylation (Sharpless AD). Compared to existing approaches to these alkaloids, our synthetic route possesses superior stereocontrol over the *C*-4 and *C*-15 stereogenic centers as well as allowing for more functional variation on the 6-membered ring.



INTRODUCTION

The *Lycopodium* alkaloids continue to attract attention within the chemical community due to their fascinating structures, biogenesis, and range of interesting biological activities, especially the demonstrated capacity of these substances to inhibit acetylcholinesterase.[1,2] The fawcettimine subclass, with more than 80 members isolated thus far, features a *cis*-fused 6,5-carbocyclic ring core connected to an azonine ring containing an all-carbon quaternary center (Figure 1). The first member of

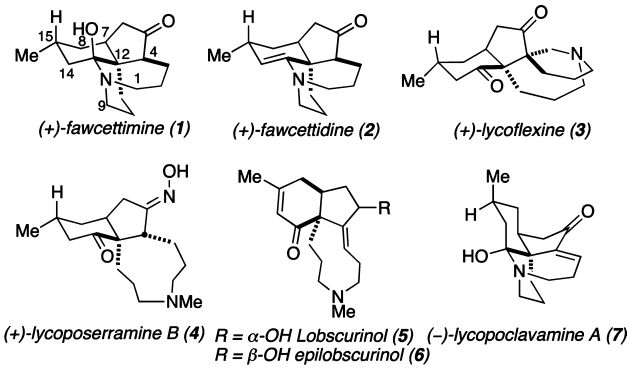


Figure 1. Structures of representative fawcettimine class alkaloids.

this class, fawcettimine (**1**), was isolated in 1959 by Burnell from *Lycopodium fawcetti*, collected in the Blue Mountain Range of Jamaica.[3a] This alkaloid has inspired significant interest from the synthetic community, resulting in five total syntheses (two racemic,[4,5] three enantioselective[6,7]) and two formal[8] syntheses. From the same plant, these workers also isolated fawcettidine (**2**).[3b] Plausibly, **2** is biosynthesized from **1** by dehydration.[9] The biogenetic dehydration of fawcettimine (**1**) to fawcettidine (**2**) seems to have been overlooked by the laboratories who have studied the total synthesis[10] of these alkaloids as interrogation of this transformation has not been heretofore reported. Lycoflexine (**3**) was isolated in 1973 by Ayer and co-workers from *Lycopodium clavatum* var. *inflexum*.[3c] This alkaloid contains two adjacent all-carbon quaternary centers. A biomimetic conversion of **1** to **3** via a Mannich reaction was also reported by Ayer, which serves as the key step in two recently reported total syntheses of (+)-**3**.[6b,11]

Lycoposerramine B (**4**), the first *lycopodium* alkaloid known to contain an oxime functionality, was isolated in 2005 by Takayama and co-workers from *Lycopodium serratum*.[12a] The biosynthesis of **4** from **1** was proposed, which requires the inversion of the *C*-4 stereogenic center. However, this inversion was found to be difficult,[12a] which is consistent with the observation made by Heathcock's group in their landmark fawcettimine synthesis that the *S*-configuration at *C*-4 was thermodynamically more stable than its epimer.[5] A 10:1 mixture in favor of the *S*-epimer was also observed by Toste's group in their (+)-fawcettimine synthesis.[6a] The difficulty in controlling the formation of the uncommon *R*-configuration at *C*-4 may, in part, account for the single reported total synthesis of (+)-**4**.[7]

Lobscurinol (**5**) and epilobscurinol (**6**) were isolated in 1989 by Ayer and Kasitu from *Lycopodium* obscurum.[3d] They are two isomeric alkaloids, and both contain an enone moiety. Lycopoclavamine A (**7**) was isolated in 2011 by Takayama and co-workers from *Lycopodium clavatum*. This alkaloid contains a β-oriented methyl group at *C*-15, which differs from other fawcettimine class members.[12b] To date, no total

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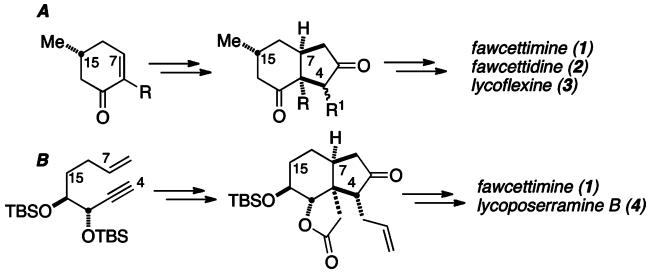
synthesis or synthetic approach to alkaloids **5**–**7** has been reported.

Inspired by the fascinating and challenging structural diversities demonstrated by the fawcettimine class alkaloids, we embarked on their total syntheses, with the aim that a general strategy could be developed to address many of the family members. Herein we report our syntheses of **1**–**4** via an efficient, unified, and stereocontrolled strategy.

RESULTS AND DISCUSSION

Retrosynthetic Analysis. From a strategic vantage, the critical challenge in contemplating the synthesis of this class alkaloids and many other members is the formation of the *cis*-fused 6,5-carbocyclic core with one all-carbon quaternary center. To date, the most frequently employed strategy has relied upon exploiting the existing methyl group of 5-methylcyclohex-2-enones to control the *trans*-addition of reagents (diene for Inubushi's synthesis[4] and nucleophiles for others[5,6,8,10a,11]) in setting the *C*-7 stereogenic center (Scheme 1, A).[13] Starting with enantiomerically pure 5-methylcyclohex-

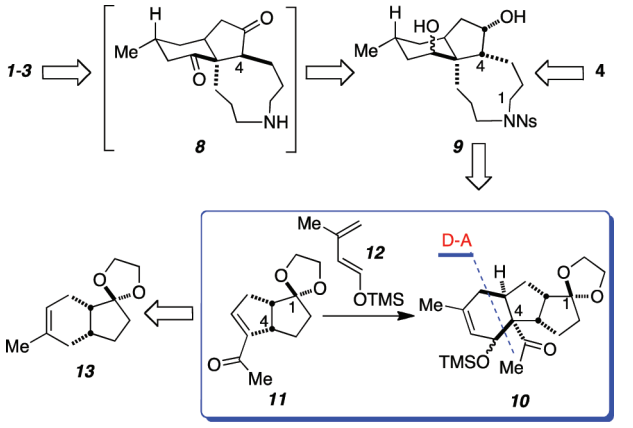
Scheme 1. (A) Strategies Employed by Inubushi, Heathcock, Toste, Liu and Chau, Jung, Yang, Dake, and Ramharter; (B) Strategy Employed by Mukai



2-enones, enantiospecific syntheses have been realized.[6,8,10a,11] Apparently, this strategy will not be suitable for the synthesis of (−)-lycopoclavamine A (**7**), which contains an unusual *β*-oriented methyl group at *C*-15. Very recently, the Mukai group reported an alternative strategy, which utilized a Pauson–Khand reaction to set the *C*-7 stereogenic center (Scheme 1, B). These workers also utilized the additional stereocontrol garnered at *C*-4 to construct lycoposerramine B, although their synthesis is quite lengthy, requiring more than 26 steps from commercially available materials.[7]

Given the fact that most of the fawcettimine class alkaloids are structurally related, a unified synthetic strategy[14] with inherent flexibility to access several members of this family constitutes the current state-of-art in natural products synthesis. In light of the common variations encountered on the 6-membered carbocycles (hexanone or hexenone, etc.), we envisioned that a highly stereoselective Diels–Alder reaction could be utilized to construct this ring. Scheme 2 summarizes our synthetic plan. Fawcettimine (**1**), fawcettidine (**2**), and lycoflexine (**3**) can be derived from the same intermediate diketo amine **8**,[15] which in turn can be obtained from nosylate **9** with the inversion of the *C*-4 stereogenic center. With the azonine *cis*-fused to the 5-membered ring, **9** was also envisioned to serve as the synthetic progenitor for lycoposerramine B (**4**). By disconnecting the azonine ring of **9** and reconnecting to form a 5-membered ring, **9** was envisioned to be derived from **10**, in which the ladder-like *cis*-fused 6,5,6 rings suggest a Diels–Alder reaction (D–A) between enone **11** and diene

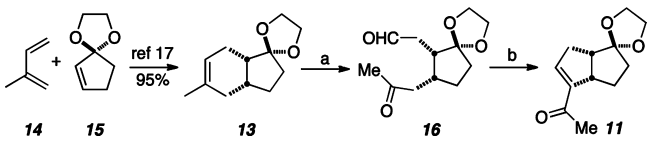
Scheme 2. Our Synthetic Plan for 1–4



12.[16] Enone **11** can be obtained from ketal **13**, which is a known compound.[17] It is worthy of note that by employing the enantiomerically pure form of **13**, the enantiospecific syntheses of **1**–**4** can also be achieved (vide infra).

Synthesis of 9. Our racemic syntheses of **1**–**4** commenced with the known ketal **13**, which could be synthesized in one step from commercially available isoprene (**14**) and cyclopentenone ethylene ketal (**15**) via an ionic Diels–Alder reaction (D–A) (Scheme 3).[17] Oxidative cleavage of the

Scheme 3. Synthesis of Enone 11[a]



[a]Reagents and conditions: (a) 1.0 mol % of $RuCl_3·H_2O$, $NaIO_4$, $ClCH_2CH_2Cl/H_2O$ (v/v 5:4), rt, 3 h, 75%; (b) KOH, H_2O, reflux, 15 h, 79%.

alkene moiety on **13** was effected under Yang's conditions[18] and afforded keto-aldehyde **16** in 75% yield. In comparison, the Lemieux–Johnson reagent (OsO_4 and $NaIO_4$)[19] or ozonolysis gave very low yield of the desired product. From **16**, the selective intramolecular aldol condensation/dehydration[20] process was achieved by treatment of **16** with KOH in refluxing H_2O for 15 h. Enone **11** was thus obtained in 79% yield, which set the stage for the key Diels–Alder reaction.

However, it is well-documented that enones like **11**, which lack a second activating group, are poor dienophiles for intermolecular Diels–Alder reactions.[21] In particular, this potential hurdle was exacerbated in our case by the fact that (1) enone **11** can be sensitive to Lewis or Brønsted acid catalyzed conditions because of the labile ketal moiety and (2) enone **11** is deactivated by *β*-alkyl substitution, both electronically and sterically.

Despite the fact that there was no literature precedent for a D–A reaction between a *β*-alkyl-substituted enone and a 1-siloxy-substituted diene, the reaction of enone **11** with diene **17** was chosen as a model to investigate the planned Diels–Alder reaction (Table 1). As anticipated, Lewis acids such as $ZnCl_2$ or $EtAlCl_2$ failed to yield any desired product. Both **11** and **17** were found to be unstable under these conditions (entries 1 and 2). We then focused our attention on thermal conditions. Although no reaction took place in toluene at 110 °C, a 15%

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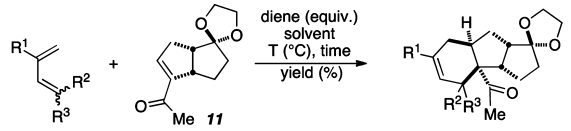
Table 1. Diels–Alder Reaction between Enone 11 and Dienes



17 R^1 = R^2 = H, R^3 = OTMS
12 R^1 = Me, R^2 = H, R^3 = OTMS
18 R^1 = R^2 = H, R^3 = OAc
19 R^1 = Me, R^2 = OMe, R^3 = OTMS
20 R^1 = Me, R^2 = R^3 = OTMS

21 R^1 = R^2 = H, R^3 = OTMS
10 R^1 = Me, R^2 = H, R^3 = OTMS
22 R^1 = R^2 = H, R^3 = OAc
23 R^1 = Me, R^2 = OMe, R^3 = OTMS
24 R^1 = Me, R^2, R^3 = O

entry	diene (equiv)	solvent	T (°C)	time	product	yield[a,b] (%)
1[c]	**17** (6.0)	CH_2Cl_2	0	3 h	**21**	0
2[d]	**17** (2.0)	CH_2Cl_2	−78	1 h	**21**	0
3	**17** (2.4)	PhMe	110	10 h	**21**	n.r.
4[e]	**17** (10.0)	xylene	170	4 d	**21**	15 (75)
5[e]	**17** (10.0)		190	3 d	**21**	30 (67)
6[e]	**17** (10.0)		240	10 h	**21**	9
7[e,f]	**17** (10.0)		190	9 h	**21**	48 (69)
8[e,f]	**17** (10.0)		200	16 h	**21**	37 (55)
9[e,f]	**12** (10.0)		195	6 h	**10**	35 (76)
10[e,f]	**12** (6.0)		185	9 h	**10**	56 (65)
11[e,f,g]	**12** (2.5)		180	9 h	**10**	74 (92)
12[e,f,g]	**12** (2.0)		180	10 h	**10**	58 (89)
13[e,f]	**18** (6.0)		190	4 h	**22**	0
14[e,f]	**19** (6.0)		190	4 h	**23**	0
15[e,f,h]	**20** (6.0)		190	4 h	**24**	22

[a]Yield of isolated product. [b]Yield in parentheses is based on recovered **11**. [c]25 mol % of $ZnCl_2$ was added. [d]2.5 equiv of $EtAlCl_2$ was added. [e]Reaction was performed in a sealed tube. [f]Reaction was performed in a microwave reactor. [g]Reaction was performed with >1.0 g of **11**. [h]Excess K_2CO_3 in MeOH was added to quench the reaction.

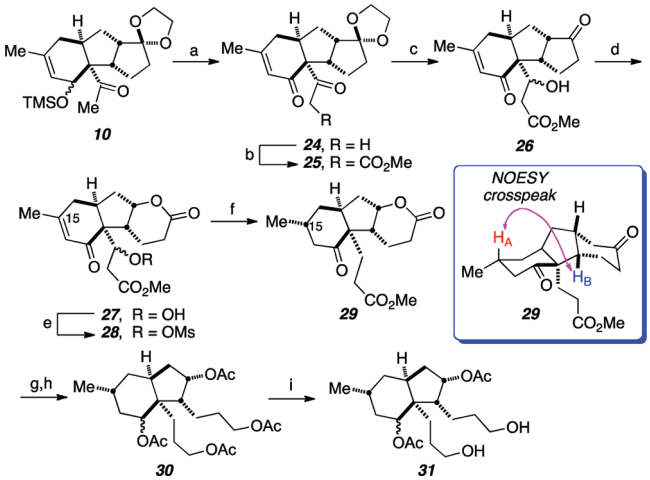
(75% brsm) yield of D–A adduct **21** was isolated by heating diene **17** and enone **11** in xylene at 170 °C for 4 days (entries 3 and 4). The yield could be improved to 30% (67% brsm) by heating **11** and **17** in the absence of solvent at 190 °C for 3 days (entry 5). To our delight, the reaction time could be dramatically shortened and the yield could be further improved by performing the reaction in a microwave reactor (entry 7).[22] However, higher temperature or longer reaction time resulted in lower yield of **21**, presumably due to the decomposition of starting materials or D–A adduct (entries 6 and 8).

Under these microwave-assisted conditions, diene **12** and enone **11** gave the desired adduct **10**, which held its key position in our synthetic route (entries 9–12). Further optimization showed that on gram-scale, the amount of **12** could be reduced to 2.5 equiv, which provided adduct **10** in 74% yield (92% brsm, dr = 1.0 (*endo*):0.4 (*exo*)) (entry 11).

Compared to 1-siloxybutadiene **17** and **12**, 1-acetoxybutadiene **18** gave no desired adduct **22** (entry 13). The polymerization of **18** was found to be a significant problem. 1,1-Disubstituted butadienes, such as **19**[23] and **20**,[23] were also tested under these microwave-assisted D–A conditions. Although no adduct **23** was formed when diene **20** was employed, it was interesting to find that diene **20** did furnish the desired enone **24** (with basic workup after D–A), albeit the yield was low (22%). To the best of our knowledge, this represents the first example of a Diels–Alder reaction between a 1,1-disiloxybutadiene and a β-alkyl-substituted enone.

The Diels–Alder adduct **10**, containing all but one carbon atom of the fawcettimine, fawcettidine, and lycoposerramine B skeletons, was converted to enone **24** in 95% yield by successive treatment of **10** with TBAF and Dess–Martin periodinane[24] (Scheme 4). This one-pot enone formation

Scheme 4. Synthesis of Diol 31[a]



[a]Reagents and conditions: (a) TBAF, CH_2Cl_2, rt, 12 h; then $NaHCO_3$, Dess–Martin periodinane, rt, 6 h, 95% for one pot; (b) LiHMDS, $NCCO_2Me$, Et_2O, −78 °C to rt, overnight, 60% (94% brsm); (c) $NaBH_4$, MeOH/CH_2Cl_2 (v/v 1:1), −42 °C, 5 h; then acetone, 1 M HCl, 5 h, 80% for one pot; (d) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, rt, 24 h, 92%; (e) MsCl, pyridine, rt, overnight, 97%; (f) 5 mol % of Pd/C, 5 mol % of Rh/Al_2O_3, H_2, 80 psi, 24 h; then DBU, H_2, 80 psi, 12 h, 93% for one pot; (g) $LiAlH_4$, THF, reflux, overnight; (h) Ac_2O, cat. DMAP, pyridine, rt, 24 h; (i) 5 mol % $[t\text{-}Bu_2Sn(OH)Cl]_2$, MeOH/THF (v/v 1:1), rt, 30 h, 85% for three steps (≥95% brsm).

together with the preceding highly selective Diels–Alder reaction should be very useful for the syntheses of lobscurinol (**5**), epilobscurinol (**6**) (Figure 1, vide supra), and other enone-containing alkaloids such as magellanine[25a] and magellaninone.[25b]

From enone **24**, homologation[26] and selective reduction of the newly formed β-keto ester **25** under Ward's conditions[27] gave, after acid workup, the β-hydroxy ester **26**. Although **26** is a keto enone, the Baeyer–Villiger oxidation[28] was found to be highly selective, and only the desired lactone **27** was isolated in 92% yield.

Installation of the correct relative stereochemistry at *C*-15 (fawcettimine numbering) was tackled next. We envisioned that by increasing the steric hindrance of the convex face of the *cis*-fused 6,5-carbocycles, hydrogenation could only take place from the more accessible concave face and set the required stereogenic center at *C*-15 for the syntheses of **1**–**4**. To this end, the hydroxyl group of **27** was mesylated to increase its steric bulk and facilitate its later removal. Pleasingly, the sequence of hydrogenation of the enone group on **28**, elimination of the mesylate and hydrogenation of the incipient α,β-unsaturated ester could be conducted in one-pot to afford the desired lactone **29** as a single diastereomer in 93% yield.[29] The correct stereochemistry at *C*-15 was confirmed by NOESY data.

It is worth noting that direct hydrogenation of β-keto ester **25** afforded the corresponding reduction product with a dr 1:1 at *C*-15. Apparently, devoid of the steric hindrance exerted by the mesylate on **28**, the facial selectivity of the enone reduction was significantly eroded. However, this nonselective reduction

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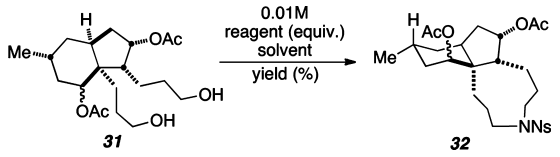
has an inherent advantage over existing fawcettimine class alkaloids syntheses in that the unusual β-oriented methyl group at C-15 can now be accessed and is potentially applicable to the synthesis of (−)-lycopoclavamine A (7) (Figure 1, vide supra). Efforts to control the facial selectivity of this reduction to give diastereomer are worthy of further pursuit.

Lactone **29** obtained above was fully reduced to the corresponding tetraol and then peracylated to give tetraacetate **30**. Selective removal of the two primary acetyl groups on **30** was accomplished by using Otera's catalyst,[30] with diol **31** isolated in 85% yield over this three-step sequence. The byproduct of this highly selective deacetylation could be readily recovered and recycled, which increased the yield of deacetylation product to ≥95% (brsm).

With diol **31** in hand, the hurdle remaining for the synthesis of fawcettimine (**1**) was the formation of the 9-membered azonine ring.[31] Guided by the elegant synthesis of (−)-strychnine by the Fukuyama group[32] as well as our own experience with the synthesis of FR900482,[33] we decided to employ a double (inter- then intramolecular) Fukuyama−Mitsunobu reaction to construct the medium-ring *N*-heterocycle. To this end, diol **31** was subjected to extensive screening of reaction parameters (Table 2). The effect of solvent was first examined,

Table 2. Double Fukuyama−Mitsunobu Reaction To Form Azonine 32



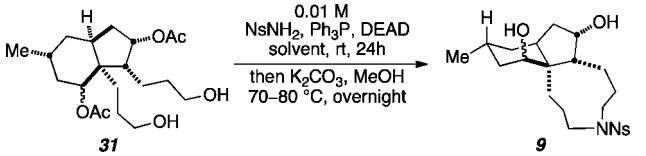
entry	reagent (equiv)	solvent	yield[a] (%)
1	$NsNH_2$ (4), Ph_3P (6), 40% DEAD (6)	THF	24
2	$NsNH_2$ (4), Ph_3P (6), 40% DEAD (6)	CH_2Cl_2	20
3	$NsNH_2$ (4), Ph_3P (6), 40% DEAD (6)	CH_3CN	36
4	$NsNH_2$ (4), Ph_3P (6), 40% DEAD (6)	DMF	33
5[b]	$NsNH_2$ (4), Ph_3P (6), 40% DEAD (6)	py	25
6	$NsNH_2$ (4), Ph_3P (6), 40% DEAD (6)	DMSO	38
7	$NsNH_2$ (4), Ph_3P (6), DEAD (6)	DMSO	16
8	$NsNH_2$ (4), Ph_3P (6), DIAD (6)	DMSO	28
9	$NsNH_2$ (4), Ph_3P (6), DIAD (6)	CH_3CN	19
10	$NsNH_2$ (4), $(n\text{-}Bu)_3P$ (6), 40% DEAD (6)	DMSO	nr
11	$NsNH_2$ (4), $(Me_2N)_3P$ (6), 40% DEAD (6)	DMSO	nr
12[c]	$NsNH_2$ (4), Diphos (6), 40% DEAD (6)	DMSO	nr
13[d]	$NsNH_2$ (4), $(n\text{-}Bu)_3P$ (6), ADDP (6)	DMSO	nr
14	$NsNH_2$ (4), Ph_3P (10), 40% DEAD (10)	DMSO	26
15	$NsNH_2$ (6), Ph_3P (6), 40% DEAD (6)	DMSO	23
16	$NsNH_2$ (4), Ph_3P (5), 40% DEAD (5)	DMSO	26
17	$NsNH_2$ (3), Ph_3P (6), 40% DEAD (6)	DMSO	20
18	$NsNH_2$ (2), Ph_3P (4), 40% DEAD (4)	DMSO	16

[a]Yield was determined by ^1H NMR. [b]Diol **31** was partially recovered. [c]Diphos = ethylenebis(diphenylphosphine). [d]ADDP = 1,1′-(azodicarbonyl)dipiperidine.

and it was found that the reaction performed best in a dipolar aprotic solvent, such as DMSO or acetonitrile (entries 1−6). Compared to 40% DEAD solution, pure DEAD or DIAD gave lower yields of **32** (entries 7−9). No reaction took place when other phosphines were used instead of the Ph_3P (entry 10−13). Finally, the relative ratio of each reagent to diol **31** was adjusted and it was found that the combination of 4 equiv of $NsNH_2$, 6 equiv of Ph_3P, and 6 equiv of 40% DEAD was optimal (entries 6 and 14−18).

Although pyridine (py) was not identified as a suitable solvent from the above solvent screening, it was noticed that fewer byproducts were formed in this solvent (entry 5). We were thus intrigued by the possible beneficial effect of pyridine as a cosolvent and conducted another survey for solvent combinations (Table 3). It is also worthy of note that because

Table 3. One-Pot Synthesis of 9 from 31



entry	solvent (v/v)	yield[a] (%)
1	DMSO	38
2	DMSO/py (1:1)	30
3	DMSO/py (3:1)	35
4	DMSO/py (6:1)	25
5	CH_3CN/py (1:1)	27
6	CH_3CN/py (3:1)	48
7	CH_3CN/py (5:1)	50
8	CH_3CN/py (6:1)	47

[a]Yield of isolated product.

azonine **32** coeluted with $NsNH_2$ upon column chromatography, an in situ deacylation procedure was conducted after the double Fukuyama−Mitsunobu reaction to obviate isolation and purification problems. Even though a favorable effect was not observed when pyridine was added to DMSO (entries 1−4), we were pleased to find that addition of pyridine to acetonitrile as the cosolvent improved the yield of azonine significantly (entries 5−8). The best result was achieved when a 5:1 (v/v) combination of acetonitrile and pyridine was used as the solvent, with azonine **9** isolated in 50% yield for this one-pot procedure (entry 7).

Synthesis of Fawcettimine, Fawcettidine, Lycoflexine, and Lycoposerramine B. Azonine **9** served as the common intermediate for our syntheses of **1**−**4** (Scheme 5). From **9**, the synthesis of fawcettimine (**1**) proved to be straightforward. Dess−Martin oxidation of **9** provided diketone **33**, which upon treatment with PhSH under basic conditions followed by acidic workup afforded (±)-fawcettimine (**1**) as its HBr salt. The inversion of the C-4 stereogenic center apparently occurs when the free amine resulting from nosyl group removal is treated with HBr rendering the HBr salt of the natural alkaloid. In this way, we were able to realize complete stereocontrol over the C-4 stereogenic center.

Next, the biomimetic dehydration of (±)-fawcettimine (**1**) to (±)-fawcettidine (**2**) was investigated. Although this transformation was reported to be realized through the agency of $POCl_3$−pyridine,[34] the yield and experimental details for this transformation were not reported, and we decided to investigate alternative conditions. To our delight, we found that this dehydration took place when (±)-**1** was treated with excess oxalic acid in AcOH at 160 °C for 12 h,[35] which afforded (±)-fawcettidine (**2**) in 80% yield. From diketone **33**, a one-pot nosyl group deprotection/Mannich reaction afforded (±)-lycoflexine (**3**) in 91% yield.

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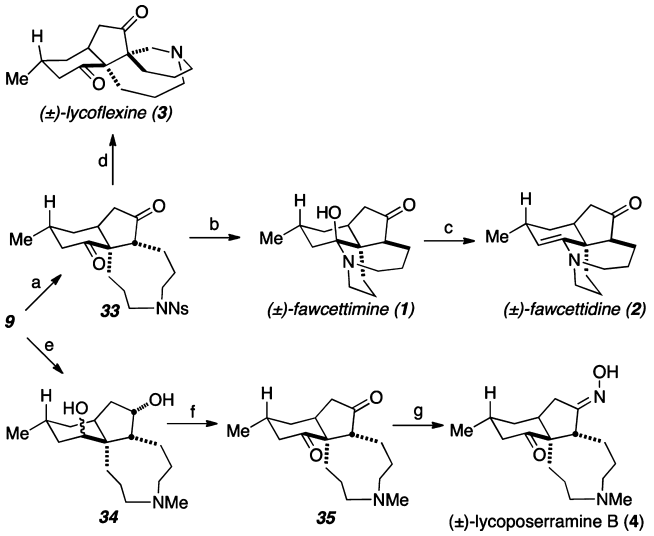
Scheme 5. Synthesis of (±)-1−4[a]



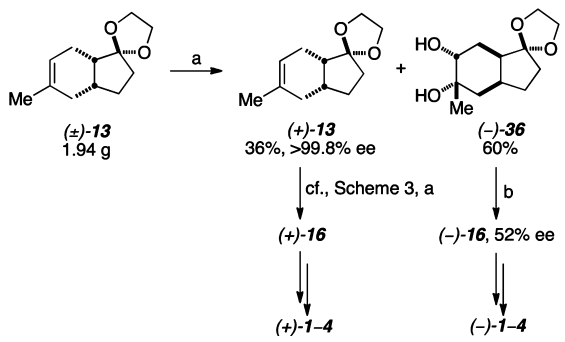
[a]Reagents and conditions: (a) Dess−Martin periodinane, $NaHCO_3$, CH_2Cl_2, rt, 6 h, 90%; (b) PhSH, 1 M KOH, CH_3CN, reflux, 8 h, 92%; (c) $(CO_2H)_2$, AcOH, 160 °C, 12 h, 80%; (d) PhSH, 1 M KOH, CH_3CN, reflux, 8 h; then HCO_2H, 37% HCHO (aq), reflux, overnight, 91% for one pot; (e) PhSH, 1 M KOH, CH_3CN, reflux, 8 h; then MeOH, 37% HCHO (aq), $NaBH_3CN$, rt, overnight, 90% for one pot; (f) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, 1 h; then Et_3N, −78 °C to rt, 2 h; (g) Et_2NH, NH_2OH·HCl, EtOH, rt, 24 h, 40% for two steps.

Azonine **9**, with the nine-membered *N*-heterocycle *cis*-fused to the 5-membered ring, was readily converted to (±)-lycoposerramine B (**4**). Removal of the nosyl group of **9** followed by in situ reductive amination generated tertiary amine **34** in 90% yield. Subsequent Swern oxidation[36] and selective oxime formation under Takayama's conditions[12a] afforded (±)-lycoposerramine B (**4**) in 40% overall yield from **34**. All of the spectral data obtained for the synthetic natural alkaloids were fully consistent with those reported.[5−7,10a,11,12a]

Enantiospecific Syntheses. While the protocols just detailed provided the racemic natural products, we recognized that the enantiospecific syntheses of these substances could be achieved by employing enantiomerically pure (+)-**13** (Scheme 6). Despite the fact that **13** is the intermediate for the synthesis of epijasmonate and some analogues, which possess pleasant olfactory properties and are widely used by the fragrance industry,[17] the asymmetric synthesis of enantiomerically pure **13** has not been reported. After a considerable amount of experimentation, we were pleased to find that (+)-**13** in high enantiomeric purity could be obtained through kinetic resolution of racemic **13**. Thus, when (±)-**13** was subjected to Sharpless asymmetric dihydroxylation (Sharpless AD) conditions,[37] a very effective kinetic resolution took place and provided (+)-**13** in 36% yield and greater than 99.8% ee, from which the naturally configured (+)-alkaloids can be synthesized.[38] On the other hand, the diol (−)-**36** obtained was cleaved to afford keto aldehyde (−)-**16** in 52% ee, which can be deployed for the synthesis of the corresponding (−)-antipodes.

With (+)-**13** of high enantiomeric purity in hand, the enantiospecific syntheses of epijasmonate and its analogues can also be realized.[17] Compared to AD-mix-β, kinetic resolution of (±)-**13** by AD-mix-α should provide the corresponding enantiomer, (−)-**13**. Thus, this kinetic resolution is readily adaptable to applications in the enantiospecific syntheses of the jasmonoid fragrances.[39]

Scheme 6. Kinetic Resolution of (±)-13[a]



[a]Reagents and conditions: (a) AD-mix-β, $MeSO_2NH_2$, K_2CO_3, *t*-BuOH/H_2O (v/v 1:1), 0−4 °C, 7 h; (b) $NaIO_4$, THF/H_2O (v/v 4:3), rt, 3 h, 90%.

CONCLUSIONS

The efficient total syntheses of fawcettimine, lycoflexine, fawcettidine, and lycoposerramine B have been accomplished through an efficient, unified, and stereocontrolled strategy that required 16, 16, 17, and 17 steps, respectively, from commercially available materials. The key transformations involve (1) a Diels−Alder reaction between enone **11** and 1-siloxy diene **12** to construct the *cis*-fused 6,5-carbocycles **10** with one all-carbon quaternary center and (2) a double Fukuyama−Mitsunobu reaction to form the azonine ring. Access to the enantiospecific syntheses of these alkaloids can be achieved by kinetic resolution of the earliest intermediate (**13**) via Sharpless asymmetric dihydroxylation technology which can be conducted on a multigram scale. We have further demonstrated that the putative biomimetic conversion of fawcettimine to fawcettidine can be realized and significantly, we have accomplished the most concise synthesis of lycoposerramine B thus far recorded. Compared to existing approaches to these alkaloids, our unified synthetic route possesses better stereocontrol over the *C*-4 and *C*-15 stereogenic centers as well as allowing for more variation in the 6-membered ring. The application of this strategic approach to the stereocontrolled synthesis of other *Lycopodium* alkaloid family members is currently under investigation.

EXPERIMENTAL SECTION

General Experimental Methods. All reactions were performed in single-neck round-bottom flasks fitted with rubber septa under positive pressure of argon with magnetic stirring, unless otherwise noted. Solvents were dried by passage through columns of activated alumina. $LiClO_4$ (ACS grade) was heated in oven (120 °C) for 3 days before use. All other reagents were prepared by known literature procedures or used as obtained from commercial sources without further purification, unless otherwise indicated. Reaction progress was monitored by thin-layer chromatography (TLC) carried out on 0.25 mm coated commercial silica gel plates impregnated with a fluorescent indicator (254 nm) visualized by UV light and/or submersion in standard TLC stains ($KMnO_4$, vanillin, anisaldehyde, etc.) followed by heating on a hot plate (~200 °C, 15 s). Flash column chromatography was performed on silica gel (230−400 mesh), unless otherwise indicated. ^1H and ^{13}C NMR spectra were obtained from 300 or 400 MHz spectrometers. The chemical shifts are given in parts per million (ppm) relative to TMS at δ 0.00 ppm or to residual $CDCl_3$ δ 7.27 ppm

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for proton spectra and relative to $CDCl_3$ at δ 77.23 ppm for carbon spectra, unless otherwise noted. IR spectra were recorded on a FT-IR spectrophotometer using NaCl plates. High-resolution mass spectra were obtained using a TOF spectrometer using simultaneous electrospray (ESI) and atmospheric pressure chemical ionization (APCI). Excess (ee) values were measured on a GC or HPLC device. Optical rotations were recorded on a polarimeter at a wavelength of 589 nm. Melting points were measured on a capillary melting point apparatus and are uncorrected. Unless otherwise noted, all compounds are racemates although they are drawn as a single enantiomers in the natural series.

(3a′*R*,7a′*S*)-5′-Methyl-2′,3′,3a′,4′,7′,7a′-hexahydrospiro-[[1,3]dioxolane-2,1′-indene] (13).[17] Following the procedure described by Hailes,[17] to an oven-dried 500 mL round-bottomed flask with reflux condenser were added $LiClO_4$ (136.18 g, 1.28 mol) and Et_2O (320 mL). After the mxiture was stirred at room temperature for 1.5 h, isoprene (**14**) (32 mL, 320 mmol, 4.0 equiv), 2-cyclopenten-1-one ethylene ketal (**15**) (9.46 mL, 80 mmol, 1.0 equiv), and camphorsulfonic acid solution (0.5 M in THF, 0.37 mL, 0.23 mol %) were added. The resulting solution was stirred for an additional 50 min before NEt_3 (0.40 mL) was added. Cold water (200 mL) was then added cautiously, and the organic layer was separated. The aqueous layer was extracted with Et_2O (2 × 200 mL). The combined organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated at reduced pressure (~15 mmHg, rotavap water bath temperature 0−5 °C). The crude obtained was purified by flash column chromatography (hexanes/EtOAc 50:1) to afford the title compound (14.76 g, 95%) as a colorless oil (R_f = 0.57, hexanes/EtOAc 10:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.36−5.40 (m, 1H), 3.80−3.96 (m, 4H), 2.26−2.37 (m, 1H), 1.66−2.18 (m, 8H), 1.64 (S, 3H), 1.39−1.52 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 132.2, 119.8, 119.2, 64.9, 64.0, 41.4, 35.0, 34.0, 31.9, 27.1, 24.1, 22.3.

2-((6*S*,7*R*)-7-(2-Oxopropyl)-1,4-dioxaspiro[4.4]nonan-6-yl)-acetaldehyde (16). In a 2000-mL three-neck round-bottomed flask equipped with mechanical stirrer were dissolved **13** (5.06 g, 26.05 mmol, 1.0 equiv), and $RuCl_3{\cdot}xH_2O$ (0.054 g, 0.26 mmol, 1.0 mol %) in $ClCH_2CH_2Cl$ (130 mL) and H_2O (104 mL). The resulting mixture was stirred vigorously at room temperature. $NaIO_4$ (11.142 g, 52.09 mmol, 2.0 equiv) was then added in portions over 5 min. After 3 h at room temperature, satd $Na_2S_2O_3$ (50 mL) was added. The organic layer was separated, and the aqueous layer was extracted with EtOAc (3 × 100 mL). The combined organic layer was dried over anhydrous $MgSO_4$. After filtration and concentration, the crude obtained was purified by flash column chromatography (hexanes/EtOAc, 2:1) to afford the title compound (4.42 g, 75%) as a colorless oil (R_f = 0.23, hexanes/EtOAc 2:1). IR (thin film): 3413, 2956, 2888, 1716, 1413, 1358, 1289, 1121 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.70 (dd, J = 2.7, 1.5 Hz, 1H), 3.73−3.91 (m, 4H), 2.60−2.74 (m, 2H), 2.30−2.48 (m, 3H), 2.16−2.24 (m, 1H), 2.10 (s, 3H), 1.71−2.02 (m, 3H), 1.23−1.36 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 208.1, 202.2, 117.7, 65.0, 64.5, 45.4, 43.7, 39.7, 34.6, 34.2, 30.4, 27.7. HRMS (ESI): calcd for $C_{12}H_{19}O_4$ $[M + H]^+$ 227.1278, found 227.1276.

Kinetic Resolution of (±)-13. In a 500-mL round-bottomed flask were dissolved (±)-**13** (1.94 g, 10 mmol, 1.0 equiv), methanesulfonamide (0.951 g, 10 mmol, 1.0 equiv), and K_2CO_3 (4.146 g, 30 mmol, 3 equiv) in *t*-BuOH/H_2O (v/v 1:1, 100 mL). The mixture was stirred at 0 °C, and then AD-mix-β (1.41 g/mmol, 14.1 g) was added in one portion. After the mxiture was stirred at 0−4 °C for 7 h, satd $Na_2S_2O_3$ (50 mL) was added. The mixture was extracted with hexanes (2 × 100 mL). The combined hexanes extract layer was washed successively with H_2O (4 × 50 mL) and brine (40 mL) and dried over anhydrous Na_2SO_4. After filtration and concentration at reduced pressure (~15 mmHg, rotavap water bath temperature 0−5 °C), the crude (+)-**13** was obtained, which also contains a small amount of (−)-**36**. All of the aqueous layers were combined, and NaCl was added until saturation. The aqueous layer was then extracted with $CHCl_3$ (3 × 50 mL). The combined $CHCl_3$ extract layer was dried over anhydrous Na_2SO_4. After filtration and concentration, the crude (−)-**36** was obtained. The crude (+)-**13** was purified by flash column chromatography (hexanes/EtOAc, 50:1) to afford (+)-**13** (0.67 g, 36%) as a colorless oil. $[\alpha]_D$ = +12.4 (c 16.23, $CHCl_3$), >99.8% ee. After eluting (+)-**13**, crude (−)-**36** was loaded to the same column and chromatographed (THF/hexanes/EtOAc 1:1:1) to yield (−)-**36** (1.104 g, 60%) as a colorless oil. Analytical data for (−)-**36**. IR (film): 3424, 2940, 1438, 1329, 1208, 1153, 1120, 1044, 1014 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.73−4.04 (m, 5H), 2.19−2.39 (m, 2H), 1.54−1.96 (m, 8H), 1.32−1.46 (m, 2H), 1.24 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 118.7, 72.3, 71.7, 65.2, 64.2, 46.0, 40.1, 35.7, 32.7, 28.0, 27.6, 27.3. HRMS (ESI): calcd for $C_{12}H_{20}NaO_4$ $[M + Na]^+$ 251.1254, found 251.1250.

The absolute stereochemistry of (+)-**13** was determined by converting (+)-**13** to **5-methyl-2,3,3a,4,7,7a-hexahydro-1*H*-inden-1-one** and comparing its optical rotation with the product obtained from Corey's CBS-catalyzed Diels−Alder reaction.

(3a*R*,7a*S*)-5-Methyl-2,3,3a,4,7,7a-hexahydro-1*H*-inden-1-one from (+)-13. Following the procedure described by Hailes,[1] in a 25-mL round-bottomed flask, (+)-**13** (95.0% ee, 0.157 g, 0.81 mmol, 1.0 equiv) was dissolved in MeOH (ACS grade, 4 mL) at 0 °C. Aqueous HCl solution (2.7 M, 0.25 mL) was added drop by drop. The resulting mixture was stirred at 0 °C for 2 h before satd $NaHCO_3$ (8 mL) was added. The mixture was extracted with hexanes (3 × 15 mL). The combined organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated at reduced pressure (~15 mmHg, rotavap water bath temperature 0−5 °C). The crude obtained was purified by flash column chromatography (hexanes/Et_2O, 15:1) to afford the title compound (0.092 g, 76%, 92.3% ee) as a colorless oil. $[\alpha]_D$ = +21.5 (c 3.57, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.31 (br s, 1H), 2.44−2.55 (m, 1H), 1.93−2.39 (m, 8H), 1.72−1.81 (m, 1H), 1.61 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 220.0, 132.5, 118.9, 46.8, 34.4, 33.0, 31.0, 26.7, 24.1, 21.9. $[\alpha]_D$ = +12.4 (c 16.23, $CHCl_3$), >99.8% ee. GC conditions: column: Chiraldex B-DM (cat. no. 77023), Adv. Separation Technologies, Inc., oven: 130 °c; carrier: helium, head pressure 15 psi; detection: FID 250 °C

(3a*R*,7a*S*)-5-Methyl-2,3,3a,4,7,7a-hexahydro-1*H*-inden-1-one from Corey's CBS-Catalyzed Diels−Alder Reaction. To a 25-mL flame-dried round-bottomed flask were added toluene (1.0 mL) and (*S*)-(−)-*O*-tolyl-CBS-oxazaborolidine solution (0.5 M in toluene, 0.80 mL, 0.4 mmol, 20 mol %), and the solution was stirred and cooled to −25 °C. $(CF_3SO_2)_2NH$ (0.20 M in CH_2Cl_2, freshly prepared, 1.80 mL, 0.36 mmol, 18 mol %) was then added dropwise. After 10 min at −25 °C, 2-cyclopenten-1-one (168 μL, 2 mmol, 1.0 equiv) and isoprene (1.0 mL, 10 mmol, 5 equiv) were added. The reaction mixture was stirred for 3 days at −25 °C before NEt_3 (56 μL) was added to quench. The mixture was then warmed to room temperature and concentrated at reduced pressure (~15 mmHg, rotavap water bath temperature 0−10 °C). The crude obtained was purified by flash column chromatography (hexanes/EtOAc, 10:1) to afford the title compound (0.157 g, 52%) as a colorless oil. The absolute stereochemistry of title compound was assigned as shown according to the model proposed by Corey's group.[2] $[\alpha]_D$ = +9.8 (c 8.32, $CHCl_3$), 73.5% ee. GC conditions: column: Chiraldex B-DM (cat. no. 77023), Adv. Separation Technologies, Inc., oven: 130 °c; carrier: helium, head pressure 15 psi; detection: FID 250 °C.

Compound (−)-16 from (−)-36. In a 25-mL round-bottomed flask was dissolved (−)-**36** (0.129 g, 0.70 mmol, 1.0 equiv) in THF (ACS grade, 4 mL) and H_2O (3 mL). The mixture was stirred vigorously at room temperature, and then $NaIO_4$ (0.225 g, 1.05 mmol, 1.5 equiv) was added in one portion. After 2 h, satd $Na_2S_2O_3$ (5 mL) was added to quench the reaction. The mixture was extracted with EtOAc (3 × 15 mL). The combined organic layer was washed with brine (5 mL) and dried over anhydrous $MgSO_4$. After filtration and concentration, the residue was purified by flash column chromatography (hexanes/EtOAc, 2:1) to afford the title compound (0.144 g, 90%) as a colorless oil. $[\alpha]_D$ = −11.3 (c 3.38, $CHCl_3$), 52% ee.

1-((3a′*S*,6a′*S*)-3′,3a′,6′,6a′-Tetrahydro-2′*H*-spiro[[1,3]-dioxolane-2,1′-pentalen]-4′-yl)ethanone (11). To a 1000-mL round-bottomed flask equipped with reflux condenser were added keto aldehyde **16** (3.30 g, 58.86 mmol, 1.0 equiv) and H_2O (740 mL). The mixture was stirred at room temperature, and oxygen was carefully removed under reduced pressure (~15 mmHg) for 20 min. The flask was refilled with Ar, and the *vacuo*-Ar cycle was repeated for three

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times. Solid KOH (3.30 g, 51.2 mmol, 3.5 equiv) was quickly added, and the *vacuo*-Ar cycle was repeated twice. The resulting pale yellow solution was gently refluxed for 15 h, cooled to room temperature, and extracted with EtOAc (3 × 100 mL). The combined organic layer was washed with brine (50 mL) and dried over anhydrous Na_2SO_4. After filtration and concentration, the crude obtained was purified by flash column chromatography (hexanes/EtOAc, 4:1) to afford the title compound (2.44 g, 79%) as a yellow oil (R_f = 0.17, hexanes/EtOAc 4:1). IR (thin film): 2960, 2883, 1708, 1666, 1619, 1435, 1373, 1107 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 6.61−6.62 (m, 1H), 3.77−4.00 (m, 4H), 3.45−3.55 (m, 1H), 2.48−2.78 (m, 3H), 2.28 (s, 3H), 1.90−2.11 (m, 1H), 1.51−1.70 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 196.6, 147.5, 144.1, 118.5, 65.1, 64.2, 47.2, 47.1, 35.2, 33.6, 28.4, 27.3. HRMS (ESI): calcd for $C_{12}H_{17}O_3$ $[M + H]^+$ 209.1172, found 209.1176.

1-((3a*S*,3b*R*,7a*S*,8a*S*)-4-((Trimethylsilyl)oxy)-3,3a,3b,4,7,7a,8,8a-octahydro-2*H*-spiro[cyclopenta[*a*]indene-1,2′-[1,3]dioxolane]-3b-yl)ethanone (21). To a 10-mL CEM Discover reaction vessel with magnetic stirring bar were added enone **11** (0.208 g, 1.0 mmol, 1.0 equiv) and diene **17** (1.423 g, 10.0 mmol, 10.0 equiv). The vessel was flushed with Ar, capped, and put in the microwave reactor. The mixture was heated to 190 °C and kept at this temperature with high-speed stirring for 9 h. After being cooled to room temperature, the pale yellow solution was transferred to a 25-mL round-bottomed flask by pipet. A short-path distillation head was attached and the volatiles (contain diene **17** and crotonaldehyde) were removed (∼100 °C/4 mmHg for 0.5 h). The residue was purified by flash column chromatography (hexanes/EtOAc, 7:1 to 2:1) to afford recovered **11** (0.062 g, 30%) and title compound (0.168 g, 48%, 69% brsm) as a pale yellow oil (inseparable diastereomers, dr 1:0.6; R_f = 0.21, hexanes/EtOAc 6:1). IR (thin film): 3029, 2957, 2883, 1697, 1426, 1350, 1251, 1222, 1093 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.70−5.77 (m, 0.67H), 5.58−5.68 (m, 1.5H), 5.39−5.45 (m, 0.94H), 4.34 (app d, J = 5.1 Hz, 0.57H), 4.13−4.19 (m, 1H), 3.84−3.98 (m, 6H), 3.01 (dt, J = 8.7, 6.9 Hz, 0.97H), 2.82 (q, J = 8.7 Hz, 0.6H), 2.35−2.61 (m, 4.7H), 2.14 (s, 2.6H), 2.11 (s, 1.6H), 1.98−2.08 (m, 0.74H), 1.59−1.96 (m, 8H), 1.41 (td, J = 13.2, 10.8 Hz, 1.2H), 1.01−1.19 (m, 1.7H), 0.18 (s, 7.5H), 0.16 (s, 4.8H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 211.3, 210.0, 129.6, 128.6, 127.9, 125.9, 118.4, 118.2, 70.2, 66.5, 65.2, 65.1, 64.9, 64.40, 64.35, 49.2, 48.5, 46.84, 46.78, 36.4, 36.0, 35.5, 33.9, 32.4, 31.85, 31.81, 28.2, 27.1, 26.2, 26.0, 0.6, 0.4. HRMS (ESI): calcd for $C_{19}H_{30}NaO_4Si$ $[M + Na]^+$ 373.1806, found 373.1803.

(*E*)-Trimethyl((3-methylbuta-1,3-dien-1-yl)oxy)silane (12).[16] Following the procedure described by Duhamel,[16] to a 500-mL 2 necked round-bottomed flask equipped with reflux condenser and glass stopper was added $ZnCl_2$ (0.30 g, 2.2 mmol, 0.8 mol %). The condenser was connected to vacuum, and the flask was heated by flame until all the solid $ZnCl_2$ melted. After being cooled to room temperature, the flask was charged with Ar. Et_2O (60 mL), 3-methylcrotonaldehyde (24 mL, 250 mmol, 1.0 equiv), NEt_3 (40 mL, 287.5 mmol, 1.15 equiv), and TMSCl (34.9 mL, 275 mmol, 1.10 equiv) were added. The suspension was stirred at gentle reflux for 25 h. After the solution was cooled to room temperature, hexanes (200 mL) were added, and the triethylamine hydrochloride precipitate was removed by filtering over sintered glass funnel under reduced pressure and washed with hexanes (50 mL). The filtrate was concentrated by rotavap and the residue was distilled under reduced pressure (55−65 °C/20 mmHg) to give title compound (30.96 g, 79%, *E*:*Z* = 1.0:0.11) as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$, *E* isomer): δ 6.53 (dt, J = 12.3, 0.6 Hz, 1H), 5.79 (dd, J = 12.3, 0.6 Hz, 1H), 4.66−4.76 (m, 2H), 1.81 (dd, J = 1.2, 0.6 Hz, 3H), 0.22 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$, *E* isomer): δ 142.0, 140.2, 116.3, 111.7, 18.2, 0.6.

1-((3a*S*,3b*R*,7a*R*,8a*S*)-6-Methyl-4-((trimethylsilyl)oxy)-3,3a,3b,4,7,7a,8,8a-octahydro-2*H*-spiro[cyclopenta[*a*]indene-1,2′-[1,3]dioxolan]-3b-yl)ethanone (10). To a 10-mL CEM Discover reaction vessel with magnetic stirring bar were added diene **12** (2.08 g, 13.28 mmol, 2.5 equiv) and enone **11** (1.11 g, 5.31 mmol, 1.0 equiv). The vessel was flushed with Ar, sealed, and put in microwave reactor. The mixture was heated to 180 °C and kept at this temperature with high speed stirring for 9 h. After cooling to room temperature, the pale yellow solution was transferred to a 25-mL round-bottomed flask by pipet. A short-path distillation head was attached, and the volatiles were removed (∼100 °C/4 mmHg for 0.5 h). The residue was purified by flash column chromatography (hexanes/EtOAc, 7:1 to 2:1) to afford recovered **11** (0.21 g, 19%) and title compound (1.44 g, dr 1:0.4, 74%, 92% brsm) as inseparable diastereomers. IR (thin film): 2957, 1696, 1350, 1251, 1096, 1065 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, major diastereomer): δ 5.07 (s, 1H), 4.09 (t, J = 1.8 Hz, 1H), 3.75−3.91(m, 4H), 2.92 (td, J = 8.4, 8.0 Hz, 1H), 2.23−2.52 (m, 3H), 2.06(s, 3H), 1.72−1.88 (m, 2H), 1.60−1.70 (m, 3H), 1.56 (app d, J = 1.8 Hz, 3H), 1.26−1.38 (m, 1H), 0.96−1.10 (m, 1H), 0.12(s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$, major diastereomer): δ 211.3, 135.6, 123.1, 118.3, 70.9, 67.5, 65.1, 64.8, 64.3, 46.77, 46.75, 36.8, 35.4, 32.4, 31.8, 26.1, 23.2, 0.4. HRMS (ESI): calcd for $C_{20}H_{32}NaO_4Si$ $[M + Na]^+$ 387.1962, found 387.1963.

(3a*S*,3b*S*,7a*R*,8a*S*)-3b-Acetyl-6-methyl-3,3a,7,7a,8,8a-hexahydro-2*H*-spiro[cyclopenta[*a*]indene-1,2′-[1,3]dioxolan]-4-(3b*H*)-one 24. To a solution of **10** (1.556 g, 4.27 mmol, 1.0 equiv) in CH_2Cl_2 (ACS grade, 43 mL) was added TBAF (1.228 g, 4.70 mmol, 1.1 equiv). The reaction was stirred at room temperature for 12 h, and $NaHCO_3$ (1.434 g, 17.07 mmol, 4.0 equiv) was added. Dess−Martin periodinane (2.534 g, 5.98 mmol, 1.4 equiv) was then added in portions over 5 min. The suspension was stirred for 6 h then quenched with satd $Na_2S_2O_3$ (10 mL) and satd $NaHCO_3$ (20 mL). After being stirred for another 6 h, the organic layer was separated and the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic layer was washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography (hexanes/EtOAc, 4:1) to afford the title compound (1.18 g, 95%, R_f = 0.28, hexanes/EtOAc 4:1) as a white solid. Mp = 111−113 °C. IR (thin film): 2959, 2888, 1702, 1658, 1355, 1197, 1094 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.81−5.83 (m, 1H), 3.80−3.91 (m, 4H), 3.64 (q, J = 8.7 Hz, 1H), 2.73−2.92 (m, 2H), 2.39 (t, J = 9.9 Hz, 1H), 2.15 (d, J = 19.2 Hz, 1H), 2.03 (s, 3H), 1.87 (s, 3H), 1.81 (td, J = 6.0, 1.5 Hz, 1H), 1.67−1.76 (m, 2H), 1.53−1.65 (m, 1H), 1.38 (td, J = 13.2, 10.5 Hz, 1H), 0.99−1.11 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 204.4, 196.1, 161.5, 124.7, 118.0, 73.9, 65.2, 64.5, 46.7, 46.6, 37.2, 35.7, 32.0, 30.2, 27.7, 25.2, 24.7. HRMS (ESI): calcd for $C_{17}H_{23}O_4$ $[M + H]^+$ 291.1591, found 291.1595.

Compound 24 from Diels−Alder Reaction between 20 and 11. To a 10-mL CEM Discover reaction vessel with magnetic stirring bar were added diene **20**[23] (0.733 g, 3.0 mmol, 6.0 equiv) and enone **11** (0.104 g, 0.5 mmol, 1.0 equiv). The vessel was flushed with Ar, sealed, and put in a microwave reactor. The mixture was heated to 190 °C and kept at this temperature with high speed stirring for 4 h. After cooling to room temperature, the brown solution was transferred to round-bottomed flask by pipet with the aid of MeOH (10 mL). K_2CO_3 (0.70 g) was added, and the mixture was stirred at room temperature overnight. EtOAc (20 mL) was added, and the mixture was washed with brine (2 × 10 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography (hexanes/EtOAc, 4:1) to afford the title compound (0.032 g, 22%).

Methyl 3-((3a*S*,3b*S*,7a*R*,8a*S*)-6-Methyl-4-oxo-3,3a,3b,4,7,7a,8,8a-octahydro-2*H*-spiro[cyclopenta[*a*]indene-1,2′-[1,3]dioxolan]-3b-yl)-3-oxopropanoate (25). To a stirred solution of **24** (0.6663 g, 2.295 mmol, 1.0 equiv) in Et_2O (23 mL) at −78 °C (dry ice/acetone bath) was added solid LiHMDS (0.4608 g, 2.754 mmol, 1.2 equiv). The solution was stirred at −78 °C for 40 min before the cooling bath was removed. The flask was allowed to warm to room temperature over 20 min and then cooled to −78 °C. Methyl cyanoformate (0.22 mL, 2.754 mmol, 1.2 equiv) was added, and the solution was allowed to warm to room temperature on its own overnight. Saturated $NaHCO_3$ (12 mL) was then added to quench the reaction. The organic layer was separated, and the aqueous layer was extracted with EtOAc (2 × 15 mL). The combined organic layer was washed with brine (15 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography (hexanes/EtOAc, 7:1 to give **24** then 1:1 to give **25**) to afford recovered **24** (0.2392 g, 36%) and title compound

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(0.4814 g, 60%, 94% brsm) as a colorless oil (contains ~8% enol ester forms, R_f = 0.14, hexanes/EtOAc 4:1). IR (thin film): 2955, 2888, 1746, 1703, 1658, 1437, 1321, 1236, 1152, 1017 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 12.37 (s, 0.08H), 5.84 (s, 1H), 5.05 (s, 0.08H), 3.79−3.90 (m, 6.3H), 3.77 (s, 0.76H), 3.50−3.70 (m, 4.9), 3.44 (d, J = 2.4 Hz, 2H), 2.64−3.02 (m, 3.1H), 2.06−2.55 (m, 3.5H), 2.04 (s, 0.84H), 1.98 (s, 0.49H), 1.34−1.88 (m, 13H), 0.96−1.12 (m, 1.8H). ^{13}C NMR (75 MHz, $CDCl_3$, β-keto ester form): δ 198.9, 195.4, 167.7, 162.1, 124.8, 117.7, 73.7, 65.1, 64.5, 52.4, 47.3, 46.8, 46.3, 37.1, 35.8, 31.8, 30.1, 25.1, 24.8. HRMS (ESI): calcd for $C_{19}H_{25}O_6$ $[M + H]^+$ 349.1646, found 349.1644.

(*R*)-Methyl 3-Hydroxy-3-((3a*S*,3b*S*,7a*R*,8a*S*)-6-methyl-1,4-dioxo-1,2,3,3a,3b,4,7,7a,8,8a-decahydrocyclopenta[*a*]inden-3b-yl)propanoate (26). To a stirred solution of β-keto ester **25** (0.214 g, 0.613 mmol, 1.0 equiv) in CH_2Cl_2 (4 mL) and MeOH (4 mL) at −42 °C (dry ice/CH_3CN bath) was added $NaBH_4$ (0.214 g, 5.66 mmol, 9.2 equiv). The solution was stirred at −42 °C for 4.5 h. TLC showed complete consumption of **25**. Acetone (4 mL) was added to quench the additional $NaBH_4$. The reaction was allowed to warm to room temperature over 3 h, and 1 M HCl (6 mL) was added to adjust the pH to 1.0 (pH paper). The mixture was stirred at room temperature overnight and then extracted with EtOAc (3 × 15 mL). The combined organic layer was washed with satd $NaHCO_3$ (10 mL) and brine (10 mL) and dried over anhydrous Na_2SO_4. After filtration and concentration, the residue obtained was purified by flash column chromatography (hexanes/EtOAc, 2:1) to afford the title compound (0.150 g, 80%) as a colorless oil (inseparable diastereomers, dr 1:0.14; R_f = 0.28, hexanes/EtOAc 1:1). IR (thin film): 3470, 2953, 1735, 1653, 1437, 1173, 1116 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, major diastereomer): δ 5.79 (s, 1H), 4.12 (br d, J = 10.8 Hz, 1H), 3.62 (s, 3H), 3.37−3.46 (m, 2H), 2.71−2.79 (m, 1H), 2.51−2.62 (m, 2H), 2.33−2.46 (m, 2H), 2.15−2.24 (m, 3H), 2.03−2.14 (m, 1H), 1.87−1.99 (m, 5H), 1.63−1.77 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, major diastereomer): δ 221.5, 201.1, 173.4, 159.9, 125.2, 68.3, 61.4, 52.1, 47.9, 45.1, 40.0, 38.2, 36.4, 32.9, 31.5, 24.7, 23.4. HRMS (ESI): calcd for $C_{17}H_{23}O_5$ $[M + H]^+$ 307.1540, found 307.1542.

(*R*)-Methyl 3-Hydroxy-3-((4a*R*,4b*S*,8a*S*,9a*S*)-7-methyl-2,5-dioxo-2,3,4,4a,4b,5,8,8a,9,9a-decahydroindeno[2,1-*b*]pyran-4b-yl)propanoate (27). (Note: open flask reaction.) In a 100-mL round-bottomed flask equipped with reflux condenser was dissolved β-hydroxy ester **26** (0.595 g, 1.94 mmol, 1.0 equiv) in CH_2Cl_2 (ACS grade, 20 mL). $NaHCO_3$ (0.978 g, 11.64 mmol, 6 equiv) was added, and the reaction was cooled to 0 °C (ice−water bath). *m*-CPBA (77%, 0.739 g, 3.30 mmol, 1.7 equiv) was then added in portions over 5 min, and the reaction was allowed to warm to room temperature on its own. After 24 h, satd $Na_2S_2O_3$ (6 mL) was added to quench the reaction. Saturated Na_2CO_3 (14 mL) was added, and the mixture was extracted EtOAc (3 × 20 mL). The combined organic layer was washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography (hexanes/EtOAc, 1:1 to 1:2) to afford the title compound (0.575 g, 92%) as a colorless oil (inseparable diastereomers, dr 1:0.14; R_f = 0.12, hexanes/EtOAc 1:1). IR (thin film): 3383, 1736, 1648, 1437, 1071 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, major diastereomer): δ 5.82 (s, 1H), 4.78−4.51 (m, 1H), 4.11 (br d, J = 10.8 Hz, 1H), 3.58 (s, 3H), 2.99−3.08 (m, 1H), 2.92 (td, J = 9.6, 5.4 Hz, 1H), 2.01−2.60 (m, 9H), 1.89 (s, 3H), 1.78−1.87 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$, major diastereomer): δ 201.0, 172.8, 172.4, 160.9, 125.7, 80.0, 68.5, 59.8, 52.1, 42.5, 38.0, 34.9, 31.8, 30.4, 24.8, 20.0. HRMS (ESI): calcd for $C_{17}H_{23}O_6$ $[M + H]^+$ 323.1489, found 323.1488.

(*R*)-Methyl 3-((4a*R*,4b*S*,8a*S*,9a*S*)-7-Methyl-2,5-dioxo-2,3,4,4a,4b,5,8,8a,9,9a-decahydroindeno[2,1-*b*]pyran-4b-yl)-3-((methylsulfonyl)oxy)propanoate (28). To a stirred solution of **27** (0.410 g, 1.27 mmol, 1.0 equiv) in pyridine (13 mL) at 0 °C (ice−water bath) was added MsCl (0.40 mL, 5.09 mmol, 4 equiv). The solution was allowed to warm to room temperature on its own overnight. Saturated $NaHCO_3$ (15 mL) was then added carefully, and the mixture was extracted with EtOAc (3 × 15 mL). The combined organic layer was washed with brine (15 mL) and dried over anhydrous Na_2SO_4. After filtration and concentration, the residue obtained was purified by flash column chromatography (hexanes/EtOAc, 2:1) to afford the title compound (0.494 g, 97%) as a colorless oil (inseparable diastereomers, dr 1:0.18; R_f = 0.19, hexanes/EtOAc 2:1). IR (thin film): 2954, 1738, 1654, 1437, 1339, 1249, 1172, 1131, 1021 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, major diastereomer): δ 5.81 (s, 1H), 5.27 (dd, J = 8.4, 3.0 Hz, 1H), 4.54 (td, J = 8.4, 3.3 Hz, 1H), 3.61 (s, 3H), 3.19 (dt, J = 13.2, 6.6 Hz, 1H), 3.01 (s, 3H), 2.94−2.96 (m, 1H), 2.80−2.88 (m, 1H), 2.63−2.72 (m, 1H), 2.55 (dt, J = 16.8, 3 Hz, 1H), 1.97−2.29 (m, 4H), 1.93 (s, 3H), 1.67−1.88 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, major diastereomer): δ 197.8, 171.8, 170.8, 161.8, 124.2, 79.0, 76.6, 60.5, 52.5, 41.2, 39.3, 37.0, 36.8, 35.3, 30.5, 30.4, 24.8, 20.5. HRMS (ESI): calcd for $C_{18}H_{24}NaO_8S$ $[M + Na]^+$ 423.1084, found 423.1076.

Methyl 3-((4a*R*,4b*S*,7*R*,8a*S*,9a*S*)-7-Methyl-2,5-dioxododecahydroindeno[2,1-*b*]pyran-4b-yl)propanoate (29). In a 100-mL hydrogenation vessel was dissolved **28** (0.494 g, 1.23 mmol, 1.0 equiv) in EtOAc (ACS grade, 13 mL). Five wt % Pd/C (0.494 g) and 5 wt % Rh/Al_2O_3 (0.494 g) were added, and the vessel was sealed. H_2 (80 psi) was filled and then released. This process was repeated twice, and the vessel was refilled with H_2 (80 psi). After the mixture was stirred at room temperature for 1 day, H_2 was released and TLC showed complete consumption of **28**. DBU (0.28 mL, 1.85 mmol, 1.5 equiv) was then added, and the vessel was resealed and refilled with H_2 (80 psi). The reaction was stirred at room temperature for another 12 h and then filtered over a Büchner funnel at reduced pressure and washed with EtOAc. The filtrate was concentrated and the residue obtained was purified by flash column chromatography (hexanes/EtOAc, 2:1) to afford the title compound (0.353 g, 93%) as a white solid (R_f = 0.16, hexanes/EtOAc 2:1). Mp = 78−80 °C. IR (thin film): 2955, 1737, 1699, 1437, 1248, 1191, 1132, 1033 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 4.65 (td, J = 7.8, 3.0 Hz, 1H), 3.63 (s, 3H), 3.20 (dt, J = 13.2, 6.9 Hz, 1H), 2.60 (dt, J = 16.5, 3.0 Hz, 1H), 2.43−2.53 (m, 1H), 2.24−2.35 (m, 4H), 1.99−2.19 (m, 2H), 1.67−1.96 (m, 7H), 1.49 (qd, J = 13.3, 3.3 Hz, 1H), 1.02 (d, J = 6.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 213.6, 173.1, 172.6, 80.0, 60.2, 52.1, 47.0, 43.6, 38.9, 36.5, 31.9, 30.4, 30.1, 29.9, 27.5, 22.4, 19.6. HRMS (ESI): calcd for $C_{17}H_{25}O_5$ $[M + H]^+$ 309.1697, found 309.1698.

(2*S*,3*R*,3a*S*,6*R*,7a*S*)-3,3a-Bis(3-acetoxypropyl)-6-methyloctahydro-1*H*-indene-2,4-diyl Diacetate (30). In a 50-mL oven-dried round-bottomed flask equipped with reflux condenser was dissolved **29** (0.204 g, 0.66 mmol, 1.0 equiv) in THF (14 mL) and the mixture stirred at room temperature. $LiAlH_4$ (0.075 g, 1.98 mmol, 3 equiv) was added in one portion, and the mixture was heated at reflux overnight. After being cooled to room temperature, the reaction was quenched by successive addition of H_2O (75 μL), 15% NaOH (75 μL), and H_2O (225 μL). The resulting slurry was stirred for another 4 h and then filtered over a Büchner funnel at reduced pressure and washed with EtOAc. After concentration, the crude tetraol obtained was used in the next step without further purification.

To a stirred solution of the tetraol obtained from above (0.66 mmol, theoretical, 1.0 equiv) in pyridine (7 mL) were added one crystal of DMAP and Ac_2O (0.50 mL, 5.30 mmol, 8 equiv). The reaction was stirred at room temperature for 1 day and then quenched with satd $NaHCO_3$ (10 mL). The mixture was extracted with EtOAc (3 × 10 mL), washed with brine (10 mL), and dried over anhydrous Na_2SO_4. After filtration and concentration, the crude obtained was used in the next step directly without further purification. An analytic sample was purified by flash column chromatography (hexanes/EtOAc, 2:1) to afford the title compound as a colorless oil (inseparable diastereomers, dr 9:1; R_f = 0.14, hexanes/EtOAc 4:1). IR (thin film): 2956, 1737, 1458, 1370, 1239, 1024 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, major diastereomer): δ 5.17 (app t, J = 4.2 Hz, 1H), 4.63 (dd, J = 11.4, 3.9 Hz, 1H), 3.86−4.05 (m, 4H), 2.24−2.32 (m, 1H), 1.982 (s, 3H), 1.961 (s, 3H), 1.957 (s, 3H), 1.948 (s, 3H), 1.79−1.87 (m, 1H), 1.22−1.76 (m, 13H), 1.04−1.16 (m, 2H), 0.84 (d, J = 6.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, major diastereomer): δ 171.2, 171.1, 170.9, 170.4, 81.5, 75.7, 65.3, 64.6, 53.3, 46.5, 39.9, 36.4, 36.3, 33.2, 28.1, 27.0, 24.8, 24.2, 22.7, 22.0, 21.40, 21.36, 21.2, 21.1. HRMS (ESI): calcd for $C_{24}H_{42}NO_8$ $[M + NH_4]^+$ 472.2905, found 472.2900.

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(2*S*,3*R*,3a*S*,6*R*,7a*S*)-3,3a-Bis(3-hydroxypropyl)-6-methyloctahydro-1*H*-indene-2,4-diyl Diacetate (31). To a stirred solution of **30** (0.66 mmol, theoretical, 1.0 equiv) obtained above in MeOH (ACS grade, 3.3 mL) and THF (ACS grade, 3.3 mL) was added Otera's catalyst[30] ($[t\text{-}Bu_2Sn(OH)Cl]_2$) (0.019 g, 33 μmol, 5 mol %). The reaction was stirred at room temperature for 30 h, and NEt_3 (50 μL) was added to quench the reaction. After concentration, the residue was purified by flash column chromatography (hexanes/EtOAc/THF, 1:2:0.5) to afford recovered materials (0.052 g, contains mono- or triacetate, which could be recycled by reacetylation to **30**) and **31** (0.208 g, 85% for three steps, ≥95% brsm) as a colorless oil (inseparable diasteromers, dr 9:1; R_f = 0.07, hexanes/EtOAc 1:2). IR (thin film): 3386, 2951, 2871, 1734, 1457, 1375, 1242, 1052, 1023 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, major diastereomer): δ 5.24 (t, *J* = 4.5 Hz, 1H), 4.70 (app dd, *J* = 12.0, 4.2 Hz, 1H), 3.47−3.74 (m, 4H), 2.71 (br s, 2H), 2.31−2.40 (m, 1H), 2.007 (s, 3H), 2.004 (s, 3H), 1.76−1.94 (m, 2H), 1.32−1.74 (m, 12H), 1.08−1.25 (m, 2H), 0.87 (d, *J* = 6.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, major diastereomer): δ 171.4, 170.9, 81.7, 76.2, 63.6, 62.6, 53.3, 46.7, 40.1, 36.6, 36.2, 33.2, 32.2, 28.8, 27.1, 24.1, 22.5, 22.1, 21.55, 21.52. HRMS (ESI): calcd for $C_{20}H_{38}NO_6$ $[M + NH_4]^+$ 388.2694 found 388.2696.

(7a*R*,8*S*,9a*S*,11*R*,13a*S*)-11-Methyl-4-((2-nitrophenyl)sulfonyl)tetradecahydro-1*H*-indeno[1,7a-*e*]azonine-8,13-diyl Diacetate (32). To a stirred solution of **31** (0.0039 g, 10.5 μmol, 1.0 equiv), 2-nitrobenzenesulfonamide (0.0085 g, 42 μmol, 4.0 equiv), and Ph_3P (0.0165 g, 63 μmol, 6.0 equiv) in DMSO (1.0 mL) at room temperature was added DEAD (40 wt % in toluene, 29 μL, 63 μmol, 6.0 equiv). The reaction was stirred at room temperature for 1 day, and then H_2O (8 mL) was added. The mixture was extracted with EtOAc (3 × 3 mL). The combined organic layer was washed with H_2O (3 mL) and brine (3 mL) and then dried over anhydrous Na_2SO_4. After filtration and concentration, to the residue obtained was added Et_2O (2 mL). The white precipitate was removed by filtering through a filter funnel with a cotton plug and washed with Et_2O (3 mL). The filtrate was concentrated, and the crude obtained was purified by preparative TLC (hexanes/EtOAc 1:1) to give the title compound (0.0021 g, 38%; R_f = 0.24, hexanes/EtOAc 1:1) as a white solid. IR (thin film): 2925, 2854, 1730, 1546, 1458, 1374, 1248, 1166, 1028 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.90−7.94 (m, 1H), 7.65−7.72 (m, 2H), 7.56−7.59 (m, 1H), 5.30−5.39 (m, 1H), 4.86−4.93 (m, 1H), 3.42−3.62 (m, 2H), 2.85−3.04 (m, 2H), 1.07−2.24 (m, 23H), 0.90 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.0, 170.6, 133.6, 131.8, 131.5, 130.8, 124.1, 75.9, 75.8, 50.7, 50.4, 46.04, 45.96, 42.5, 36.2, 33.6, 32.2, 30.0, 28.9, 26.9, 24.8, 24.1, 22.1, 21.7, 21.4, 17.0. HRMS (ESI): calcd for $C_{26}H_{36}N_2NaO_8S$ $[M + Na]^+$ 559.2085, found 559.2093.

(7a*R*,8*S*,9a*S*,11*R*,13a*S*)-11-Methyl-4-((2-nitrophenyl)sulfonyl)tetradecahydro-1*H*-indeno[1,7a-*e*]azonine-8,13-diol (9). To a stirred solution of **31** (0.0876 g, 236 μmol, 1.0 equiv), 2-nitrobenzenesulfonamide (0.191 g, 0.94 mmol, 4.0 equiv), and Ph_3P (0.372 g, 1.42 mmol, 6.0 equiv) in CH_3CN (20 mL) and pyridine (4 mL) at room temperature was added DEAD (40 wt % in toluene, 0.65 mL, 1.42 mmol, 6.0 equiv) over 10 min. After 24 h at room temperature, MeOH (24 mL) and K_2CO_3 (0.326 g, 10.0 equiv) were added. A reflux condenser was connected, and the suspension was stirred with gentle reflux overnight. After cooling to room temperature, the stirring bar was removed, and the solution was concentrated. The residue was partitioned between EtOAc (15 mL) and brine (15 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (2 × 15 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated. To the residue was added EtOH (3 mL), and the resulting $NsNH_2$ precipitate was removed by filtering over a filter funnel with a cotton plug and washed with EtOH (3 × 3 mL). The filtrate was concentrated and the residue obtained was purified by flash column chromatography (hexanes/EtOAc, 1:1 to 1:2) to afford the title compound (0.054 g, 50%; R_f = 0.07, hexanes/EtOAc 1:2) as a white solid contaminated with trace amount of Ph_3PO. An analytical sample was further purified by preparative TLC (hexanes/EtOAc 1:2). IR (thin film): 3385, 2925, 1545, 1373, 1343, 1164 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.91−7.96 (m, 1H), 7.64−7.72 (m, 2H), 7.56−7.62 (m, 1H), 4.62 (dt, *J* = 8.4, 6.0 Hz, 1H), 3.67−3.78 (m, 1H), 3.47−3.55 (m, 2H), 3.13 (ddd, *J* = 14.8, 9.6, 4.8 Hz, 1H), 2.95 (dt, *J* = 13.2, 4.0 Hz, 1H), 1.51−2.31 (m, 16H), 1.22−1.31 (m, 2H), 1.06−1.14 (m, 1H), 0.92 (d, *J* = 6.4, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 133.5, 132.1, 131.4, 130.9, 124.1, 74.1, 73.0, 51.8, 50.8, 48.0, 46.4, 42.5, 40.4, 36.9, 32.8, 29.5, 27.4, 24.6, 24.5, 22.3, 16.5. HRMS (ESI): calcd for $C_{22}H_{33}N_2O_5S$ $[M + H]^+$ 453.2059, found 453.2061.

(7a*R*,9a*S*,11*R*,13a*S*)-11-Methyl-4-((2-nitrophenyl)sulfonyl)-decahydro-1*H*-indeno[1,7a-*e*]azonine-8,13(2*H*,9*H*)-dione (33). To a stirred solution of **9** (0.022 g, 49 μmol, 1.0 equiv) in CH_2Cl_2 (ACS grade, 2 mL) were added $NaHCO_3$ (0.033 g, 0.39 mmol, 8.0 equiv) and Dess−Martin periodinane (0.084 g, 0.20 mmol, 4.0 equiv). The suspension was stirred at room temperature for 6 h, and then satd $Na_2S_2O_3$ (3 mL) and satd $NaHCO_3$ (3 mL) were added. After being stirred for an additional 1 h, the mixture was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layer was washed with brine (5 mL) and dried over anhydrous Na_2SO_4. After filtration and concentration, the residue obtained was purified by flash column chromatography (hexanes/EtOAc, 1:1) to afford the title compound (0.0195 g, 90%) as a white solid. Mp = 232−235 °C dec. IR (thin film): 2924, 1737, 1700, 1544, 1439, 1373, 1347, 1168, 1128 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.92 (dd, *J* = 5.7, 2.0 Hz, 1H), 7.66−7.74 (m, 2H), 7.59 (dd, *J* = 5.4, 2.0 Hz, 1H), 3.63 (td, *J* = 12.8, 4.8 Hz, 1H), 3.52 (ddd, *J* = 15.2, 6.0, 4.0 Hz, 1H), 2.91−2.99 (m, 2H), 2.82 (dt, *J* = 13.6, 4.0 Hz, 1H), 2.60−2.66 (m, 1H), 1.60−2.41 (m, 13H), 1.48−1.54 (m, 1H), 1.23−1.34 (m, 1H), 1.09 (d, *J* = 6.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 218.7, 214.0, 148.9, 134.0, 131.6, 131.1, 130.9, 124.2, 60.3, 50.1, 49.4, 46.8, 45.5, 42.4, 39.6, 31.2, 30.2, 29.7, 25.0, 22.5, 22.1, 20.9. HRMS (ESI): calcd for $C_{22}H_{29}N_2O_6S$ $[M + H]^+$ 449.1741, found 449.1735.

(±)-Fawcettimine (1). In a 10-mL round-bottomed flask equipped with reflux condenser was dissolved **33** (0.0127 g, 30 μmol, 1.0 equiv) in CH_3CN (3 mL). KOH (1.0 M, 300 μmol, 0.30 mL, 10 equiv) and PhSH (15 μL, 150 μmol, 5 equiv) were added. The reaction was stirred at gentle reflux for 6 h and then cooled to room temperature. EtOAc (8 mL) was added, and the mixture was extracted with 1 M HCl (3 × 4 mL). Solid Na_2CO_3 was added to the combined aqueous layer until saturation. The resulting mixture was extracted with 3% MeOH in $CHCl_3$ (3 × 5 mL). The combined organic layer was dried over anhydrous Na_2SO_4. After filtration and concentration, the residue obtained was dissolved in CH_2Cl_2 and HBr (0.1 M in H_2O, 0.30 mL, 30 μmol) added. After the solution was allowed to stand at room temperature overnight, all of the volatiles were removed under vacuum. To the solid obtained was added a minimum amount of Et_2O, rinsed, and removed by pipet. The (±)-fawcettimine hydrobromide salt remained was dissolved in CH_2Cl_2 and dried over anhydrous K_2CO_3 overnight. After filtration and concentration, (±)-fawcettimine (0.0073 g, 92%) was obtained as a pale yellow foam (R_f = 0.35, *n*-BuOH/AcOH/H_2O 7:2:2). IR (thin film): 3287, 2923, 2856, 1735, 1637, 1458, 1340, 1264, 1144, 1100, 1056 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 3.76−3.85 (m, 1H), 3.58−3.70 (br, 1H), 3.40 (td, *J* = 14.2, 4.0 Hz, 1H), 3.03 (dd, *J* = 14.4, 4.8 Hz, 1H), 2.81−2.86 (m, 1H), 2.60 (dd, *J* = 18.0, 13.6 Hz, 1H), 1.82−2.35 (m, 11H), 1.37−1.76 (m, 5H), 1.00 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 218.2, 59.9, 54.7, 50.6, 48.1, 43.4, 42.5, 41.6, 34.8, 31.8, 29.9, 27.6, 26.6, 23.9, 21.8, 20.9. HRMS (ESI) calcd. for $C_{16}H_{26}NO_2$ $[M + H]^+$ 264.1958, found 264.1962. Analytical Data for (±)-Fawcettimine Hydrobromide. ^1H NMR (400 MHz, $CDCl_3$): δ 10.01 (br s, 1H), 5.80 (s, 1H), 4.18 (br s, 1H), 3.51−3.64 (m, 1H), 3.21 (br d, *J* = 11.2 Hz, 1H), 3.02 (br s, 1H), 2.81 (d, *J* = 12.4 Hz, 1H), 2.60 (dd, *J* = 16.8, 12.4 Hz, 1H), 1.82−2.46 (m, 12H), 1.75 (br d, *J* = 14.0 Hz, 1H), 1.64 (d, *J* = 12.8 Hz, 1H), 1.48 (td, *J* = 13.4, 4.8 Hz, 1H), 1.05 (d, *J* = 6.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 216.2, 96.3, 59.2, 56.0, 51.6, 47.7, 43.3, 41.2, 40.3, 33.5, 31.4, 26.8, 24.2, 24.0, 21.6, 19.2.

(±)-Fawcettidine (2). In a 10-mL round-bottomed flask equipped with reflux condenser were dissolved fawcettimine (0.0054 g, 20 μmol, 1.0 equiv) and oxalic acid (0.0540 g, 0.6 mmol, 29.0 equiv) in AcOH (2 mL). Oxygen was carefully removed through a freeze−pump−thaw cycle 3 times. The flask was refilled with Ar, and the reaction was

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stirred at 160 °C for 12 h. After the mixture was cooled to room temperature, *n*-heptane was added, and all the volatiles were removed under vacuum. To the residue was added aq 5% $NH_3·H_2O$ solution (5 mL), and the resulting mixture was extracted with 3% MeOH in $CHCl_3$ (4 × 4 mL). The combined organic layer was dried over anhydrous Na_2SO_4. After filtration and concentration, the crude obtained was purified by flash column chromatography (basic alumina, hexanes/EtOAc, 2:1 then 3% MeOH in $CHCl_3$) to afford the title compound (0.0040 g, 80%) as a white foam (R_f = 0.24, MeOH/$CHCl_3$ 5:95). IR (thin film): 2924, 2848, 1737, 1662, 1549, 1447, 1328, 1302, 1253, 1216, 1193, 1169, 1149, 1105, 1030 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 5.69 (d, J = 4.8 Hz, 1H), 2.97−3.15 (m, 4H), 2.74 (ddd, J = 16.8, 7.6, 1.6 Hz, 1H), 2.22−2.36 (m, 2H), 2.05−2.20 (m, 3H), 1.82−2.00 (m, 2H), 1.54−1.79 (m, 3H), 1.21−1.41 (m, 4H), 1.06 (d, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 219.1, 146.2, 127.4, 60.6, 56.5, 52.2, 46.4, 44.3, 39.4, 37.5, 34.4, 31.6, 29.4, 28.0, 24.1, 21.1. HRMS (ESI): calcd for $C_{16}H_{24}NO$ $[M + H]^+$ 246.1852, found 246.1855.

(±)-Lycoflexine (3). In a 10-mL round-bottomed flask equipped with reflux condenser was dissolved **33** (0.0024 g, 5.3 μmol, 1.0 equiv) in CH_3CN (2 mL). KOH (1.0 M, 42 μmol, 42 μL, 8.0 equiv) and PhSH (2.7 μL, 26 μmol, 5.0 equiv) were added. The reaction was stirred at gentle reflux for 8 h and then cooled to room temperature. H_2O (1 mL), HCO_2H (16 μL, 424 μmol, 80 equiv), and 37% HCHO (aq, 34 μL, 424 μmol, 80 equiv) were added. The resulting mixture was stirred at gentle reflux overnight before all of the volatiles were removed at vacuum. The residue was dissolved in EtOAc (10 mL) and extracted with 1 M HCl (3 × 4 mL). Solid Na_2CO_3 was added to the combined aqueous layer until saturation. The mixture was then extracted with 3% MeOH in $CHCl_3$ (3 × 4 mL), and the combined organic layer was dried over anhydrous Na_2SO_4. After filtration and concentration, the residue was purified by flash column chromatography (basic alumina, hexanes/EtOAc, 1:2 then 3% MeOH in $CHCl_3$) to afford the title compound (0.0013 g, 91%) as a white solid (R_f = 0.23, *n*-BuOH/AcOH/H_2O 7:2:2). IR (thin film): 2924, 2853, 1727, 1699, 1456, 1352, 1208, 1174, 1127, 1063 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 3.19 (ddd, J = 14.4, 2.8, 1.2 Hz, 1H), 3.13 (ddd, J = 13.6, 8.0, 4.0 Hz, 1H), 2.94−3.02 (m, 1H), 2.78−2.91 (m, 2H), 2.61−2.72 (m, 2H), 2.19−2.42 (m, 6H), 2.06−2.17 (m, 2H), 1.91−2.01 (m, 2H), 1.71−1.89 (m, 3H), 1.56−1.64 (m, 1H), 1.31−1.36 (m, 1H), 1.04 (d, J = 6.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 218.6, 214.1, 60.8, 58.7, 56.9, 53.8, 53.5, 46.9, 40.5, 40.3, 36.4, 31.5, 29.5, 28.2, 26.3, 22.6, 19.6. HRMS (ESI): calcd for $C_{17}H_{26}NO_2$ $[M + H]^+$ 276.1958, found 276.1962.

(7a*R*,8*S*,9a*S*,11*R*,13a*S*)-4,11-Dimethyltetradecahydro-1*H*-indeno[1,7a-*e*]azonine-8,13-diol (34). In a 25-mL round-bottomed flask equipped with reflux condenser was dissolved **9** (0.0310 g, 69 μmol, 1.0 equiv) in CH_3CN (ACS grade, 4 mL). KOH (1.0 M, 0.55 mmol, 0.55 mL, 8 equiv) and PhSH (35 μL, 0.35 mmol, 5 equiv) were added. The reaction was stirred at gentle reflux for 8 h and then cooled to room temperature. MeOH (ACS grade, 4 mL), aq HCHO (37%, 154 μL, 2.07 mmol, 30 equiv), and $NaBH_3CN$ (0.013 g, 0.21 mmol, 3 equiv) were added. After the solutionw as stirred at room temperature overnight, aq HCl (1.0 M, 2.0 mL) was added, and the mixture was extracted with 1 M HCl (3 × 3 mL). Solid Na_2CO_3 was added to the combined aqueous layer until saturation. The resulting mixture was extracted with 5% MeOH in $CHCl_3$ (4 × 4 mL), and the combined organic layer was dried over anhydrous Na_2SO_4. After filtration and concentration, the residue was purified by flash column chromatography (basic alumina, 3% MeOH in $CHCl_3$) to afford the title compound (0.0175 g, 90%) as a white solid. IR (thin film): 3356, 2925, 2869, 1721, 1660, 1455, 1376, 1273, 1107, 1066 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 4.58−4.66 (m, 1H), 3.59−3.66 (m, 1H), 2.51−2.76 (m, 3H), 2.17−2.47 (m, 6H), 1.81−2.14 (m, 5H), 1.11−1.74 (m, 12H), 0.93 (d, J = 6.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 74.4, 73.8, 55.8, 51.9, 48.0, 46.8, 43.3, 39.4, 37.6, 33.0, 28.4, 27.5, 26.7, 25.8, 22.4, 19.6. HRMS (ESI): calcd for $C_{17}H_{32}NO_2$ $[M + H]^+$ 282.2428, found 282.2434.

(7a*R*,9a*S*,11*R*,13a*S*)-4,11-Dimethyldecahydro-1*H*-indeno-[1,7a-*e*]azonine-8,13(2*H*,9*H*)-dione (35). To a 15-mL flame-dried round-bottomed flask was added CH_2Cl_2 (1.0 mL), and the flask was cooled to −78 °C (dry ice/acetone bath). $(COCl)_2$ (13 μL, 152 μmol, 10.0 equiv) and DMSO (21.6 μL, 304 μmol, 20.0 equiv) were added. The mixture was stirred at −78 °C for 30 min before **34** (4.3 mg, 15.2 μmol, 1.0 equiv) in 1.0 mL of CH_2Cl_2 was added via syringe. The resulting mixture was stirred at −78 °C for 1 h, and then NEt_3 (85 μL, 608 μmol, 40.0 equiv) was added. After another 20 min, the reaction was allowed to warm to room temperature and stirred at room temperature for 2 h. Brine (4 mL) was added, and the resulting mixture was extracted with 3% MeOH in $CHCl_3$ (3 × 4 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated to afford crude **35**, which was used immediately in next step without further purification. An analytical sample was purified by flash column chromatography (3% MeOH in CH_2Cl_2) to give title compound as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ 2.90 (d, J = 5.2 Hz, 1H), 2.49−2.62 (m, 2H), 2.04−2.45 (m, 12H), 1.72−1.99 (m, 5H), 1.31−1.52 (m, 3H), 1.12−1.20 (m, 1H), 1.07 (d, J = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 220.4, 214.4, 60.9, 55.0, 50.4, 49.0, 46.9, 44.5, 42.8, 39.6, 31.3, 30.4, 28.3, 25.5, 22.7, 22.6, 21.9. HRMS (ESI): calcd for $C_{17}H_{28}NO_2$ $[M + H]^+$ 278.2115, found 278.2110.

(±)-Lycoposerramine B (4). Following the procedure described by Harayama and Takayama,[12a] to a solution of crude **35** (15.2 μmol, theoretical) obtained above in EtOH (1.5 mL) was added Et_2NH (7.9 μL, 76 μmol, 5.0 equiv). The mixture was stirred at room temperature for 3 h, and then $NH_2OH·HCl$ (0.2 M in EtOH, 83.5 μL, 1.1 equiv) was added dropwise via syringe. After the mixture was stirred at room temperature for an additional 24 h, the reaction was quenched with chilled satd $NaHCO_3$ (3 mL) and extracted with 5% MeOH in $CHCl_3$ (4 × 5 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was chromatographed (10% MeOH in $CHCl_3$) to afford crude titled compound. The crude was rechromatographed ($NH_3·H_2O$/MeOH/$CHCl_3$ 0.05/5/95) to afford the title compound (1.8 mg, 40%) as a colorless oil. IR (thin film): 2918, 2849, 1702, 1451, 1369, 1268, 1210, 1139, 1076 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 3.18 (d, J = 3.2 Hz, 1H), 2.66 (app td, J = 13.6, 3.6 Hz, 1H), 2.55 (ddd, J = 18.8, 9.2, 0.8 Hz, 1H), 2.38−2.45 (m, 1H), 2.18−2.36 (m, 8H), 1.96−2.16 (m, 4H), 1.55−1.80 (m, 5H), 1.43−1.50 (m, 1H), 1.15−1.40 (m, 3H), 1.04 (d, J = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 214.0, 169.8, 61.9, 55.2, 48.7, 47.0, 44.5, 43.1, 31.8, 30.1, 29.9, 28.9, 27.7, 25.7, 25.6, 22.6, 21.6. HRMS (ESI): calcd for $C_{17}H_{29}N_2O_2$ $[M + H]^+$ 293.2224, found 293.2226.

■ ASSOCIATED CONTENT

Supporting Information

^1H and ^{13}C NMR spectra for all compounds. Determination of absolute configuration and GC chromatogram of (+)-**13**. HPLC chromatogram of (−)-**16** This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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