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Expedient Pyrrolizidine Synthesis by Propargylsilane Addition to *N*-Acyliminium Ions followed by Gold-Catalyzed α-Allenyl Amide Cyclization

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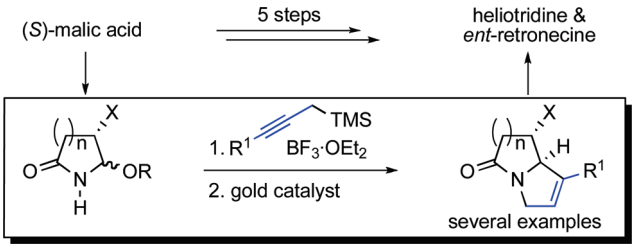
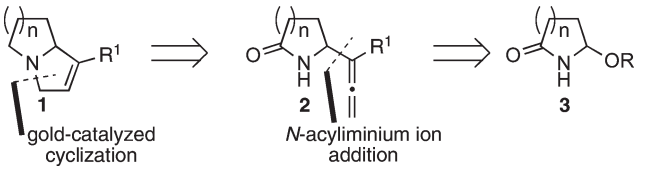


A reaction sequence, involving the addition of (substituted) propargylsilanes to lactam-derived *N*-acyliminium ions followed by gold-catalyzed cyclization of the resulting α-allenyl amide, is applied in expedient syntheses of pyrrolizidine alkaloids heliotridine and *ent*-retronecine in five steps from (*S*)-malic acid.

Pyrrolizidine and indolizidine alkaloids are well-studied synthetic targets.[1] Several members display interesting biological properties, and short synthetic approaches to these drug-like compounds are therefore desirable.[2] Many strategies start with one functionalized ring after which the bicyclic framework **1** (Scheme 1) is constructed using nucleophilic substitution by nitrogen,[1] through iminium ion cyclization,[3] ring-closing metathesis,[4] or other transition metal mediated cyclizations.[5,6] α-Allenyl lactams (**2**) would be interesting

SCHEME 1. Lactam Cyclization Strategy Using Gold Catalysis



substrates to cyclize in such an approach, leaving the remaining double bond in the product amenable for further functionalization.

Our group has ample experience in the formation of α-allenyl lactams like **2**, through *N*-acyliminium-type additions of propargylsilanes to alkoxylactams (**3**),[7,8] and we wished to explore a cyclization strategy of such lactams to arrive at bicyclic alkaloid building blocks in only a few steps. Especially the field of gold-catalyzed cyclizations caught our attention.[9] Lewis-acidic gold catalysts are capable of activating double and triple bonds toward nucleophilic acttack, even in the presence of other polar substituents. On the basis of the initial work of the groups of Krause and Lee,[10,11] gold catalysis seemed a suitable solution also for cycloamidations of α-allenyl lactams like **2**.[12] Krause showed that linear allenic amides like **4** could be cyclized using 2 mol % $AuCl_3$ in dichloromethane at room temperature to give dihydropyrrolidine **5** (Scheme 2).[10]

For allenyl azetidinones **6** (R = alkyl, aryl), the group of Lee reported successful gold-catalyzed cyclization to give bicycle **7** in good yields ranging from 65 to 85%.[11] Besides these gold-catalyzed examples, silver salts were shown to cyclize certain α-allenylazetidinones (**6**, R = H, Me) to give **7**, but in general requiring high catalyst loadings.[13] Alternatively, $PtCl_2$-catalyzed cyclizations of unsubstituted α-allenylazetidinones **6** were reported to be successful for R = H, alkyl, or aryl.[14] With oxygen-containing substituents present on the allene, yields dropped dramatically.

Our study toward the intended sequence of *N*-acyliminium ion additions of propargylsilanes, followed by the gold-catalyzed allenyl lactam cyclization, started with the synthesis of α-allenyl lactam substrates **19**−**31** (Scheme 3).

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(3) (a) For a recent example, see: Meyers, E. L.; de Vries, J. G.; Aggarwal, V. K. *Angew. Chem., Int. Ed.* **2007**, *46*, 1893. (b) Remuson, R. *Beilstein J. Org. Chem.* **2007**, 3, no. 32 and references cited.
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(7) (a) Hiemstra, H.; Fortgens, H. P.; Speckamp, W. N. *Tetrahedron Lett.* **1984**, *25*, 3115. (b) Karstens, W. F. J.; Klomp, D.; Rutjes, F. P. J. T.; Hiemstra, H. *Tetrahedron* **2001**, *57*, 5123.
(8) (a) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817. (b) Yazici, A.; Pyne, S. G. *Synthesis* **2009**, 339.
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(11) Lee, P. H.; Kim, H.; Lee, K.; Kim, M.; Noh, K.; Kim, H.; Seomoon, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 1840.
(12) For other examples of gold- and silver-catalyzed hydroaminations of linear allenes, see: (a) Patil, N. T.; Lutete, L. M.; Nishina, N.; Yamamoto, Y. *Tetrahedron Lett.* **2006**, *47*, 4749. (b) Mitasev, B.; Brummond, K. M. *Synlett* **2006**, 3100. (c) Widenhoefer, R. A.; Han, X. *Eur. J. Org. Chem.* **2006**, 4555. (d) Lalonde, R. L.; Sherry, B. D.; Kang, E. J.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 2452. (e) Zhang, Z.; Bender, C. F.; Widenhoefer, R. A. *Org. Lett.* **2007**, *9*, 2887.
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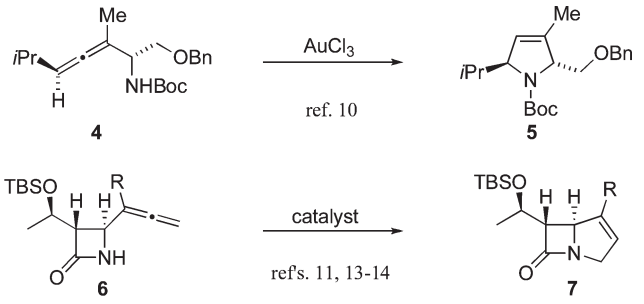
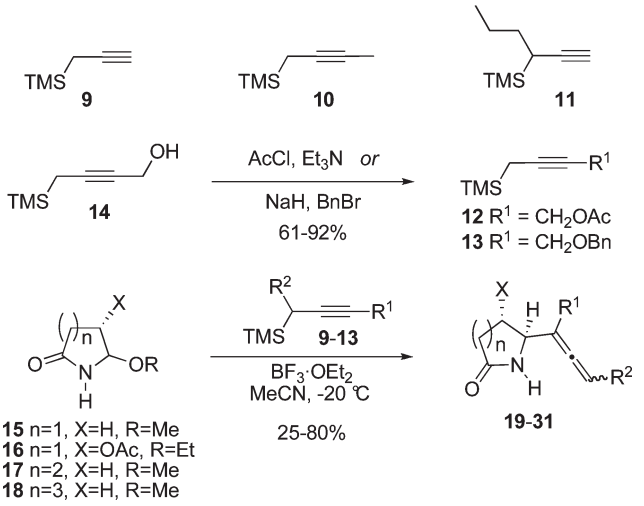
SCHEME 2. Known Linear and Cyclic α-Allenyl Amide Cyclizations



SCHEME 3. α-Allenyl Lactam Substrate Synthesis

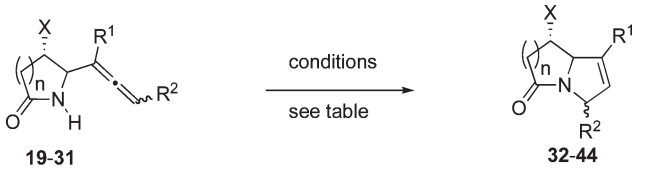


The required propargylsilanes **9**−**11** were synthesized according to known literature procedures.[15] The propargylsilanes **12** and **13** were easily obtained by acetylation or benzylation of known 4-trimethylsilyl-2-butynol **14**.[15a] Standard conditions ($BF_3 \cdot OEt_2$, MeCN, −20 °C) were used for the addition of the propargylsilanes to the five-, six-, and seven-membered lactam acetals **15**−**18**,[16] with yields ranging from 25 to 80%.

Our research on the cyclizations commenced by subjecting allenyl lactam **19**[7a] to several gold catalysts under different conditions (Table 1). For the unsubstituted system, the best conditions turned out to be $AuCl_3$ (5 mol %) in refluxing acetonitrile at 0.5 M concentration of substrate. Since there were no literature reports so far for the cyclization of such unsubstituted allenes, we were pleased with the isolated yield of 75% for pyrrolidine **32** (entry 1).[4a,5a] The major side product turned out to be dimeric **32**, formed by the gold-mediated coupling of two substrate molecules.[17]

Next, we turned our attention to other five-membered ring substrates bearing substituents on the allene moiety (**20**−**25**) and lactams with larger ring sizes (**27**−**29**, **31**). In general,

TABLE 1. Substrate Scope in the Gold-Catalyzed Lactam Cyclization



entry	substr., cond.	*n*	X	R^1, R^2	time (h)	prod.	yield (%)
1	**19**, A	1	H	H, H	22	**32**	75
2	**20**, B	1	H	CH_2OAc, H	0.5	**33**	74
3	**20**, C	1	H	CH_2OAc, H	4	**33**	92
4	**21**, C	1	H	CH_2OBn, H	4	**34**	80
5	**22**, C	1	H	Me, H	4	**35**	93
6	**23**, C	1	H	H, *n*-Pr	4	**36**	90
7	**24**, C	1	OAc	H, H	24	**37**	0
8	**25**, C	1	OAc	CH_2OBn, H	6	**38**	85
9	**26**, A	2	H	H, H	20	**39**	65
10	**27**, C	2	H	CH_2OAc, H	7	**40**	75
11	**28**, C	2	H	Me, H	6	**41**	82
12	**29**, C	2	H	H, *n*-Pr	7	**42**	71
13	**30**, A	3	H	H, H	22	**43**	52
14	**31**, C	3	H	Me, H	24	**44**	79

[a] A: $AuCl_3$ (10 mol %), MeCN (0.5 M), reflux. B: $AuCl_3$ (5 mol %), CH_2Cl_2 (0.1 M), rt. C: $ClAuPPh_3/AgBF_4$ (5 mol %), CH_2Cl_2, 0.1 M, rt. [b] Isolated yields after column chromatography.

substituents on alkenes and allenes enhance the reactivity of cationic cyclizations;[11,14] therefore, it was expected that the reactivity would show important differences. With an alkyl substituent on the allene, cyclizations already took place at room temperature in all cases. For example, substrate **20** cyclized using 5 mol % $AuCl_3$ in CH_2Cl_2 at ambient temperature in 74% isolated yield (entry 2). A cleaner cyclization was observed using 5 mol % of the cationic gold complex generated in situ from $ClAuPPh_3$ and $AgBF_4$ in CH_2Cl_2 at lower concentration (0.1 M, entry 3). This gave the product **33** in 92% yield after 4 h, without a trace of dimer. A benzyloxymethyl or simple methyl substituent on the allene showed similar conversions (entries 4 and 5), while also an *n*-propyl substituent at the R^2 position gave a quick conversion and 90% yield of a 1:1 mixture of diastereoisomers of **36** at room temperature (entry 6). The dramatic effect of a substituent on the allene in the cationic gold cyclizations was best demonstrated with substrate **24** (entry 7). No cyclization was observed at all, thus excluding a possible positive effect of the acetoxy moiety on the ring in the cyclizations. As expected, substrate **25** with an acetoxy substituent on the pyrrolidine ring and a substituted allene cyclized in a good yield of 85% (entry 8). This showed, in contrast to similar platinum-based cyclizations, the compatibility of the gold catalyst with oxygen substituents. The unsubstituted six-membered ring substrate **26** was best cyclized again using $AuCl_3$ (5 mol %) in refluxing acetonitrile to provide **39** in 65% yield (entry 9). The other substituted six-membered ring lactams **27**−**29** (entries 10−12) gave clean cyclization using $ClAuPPh_3/AgBF_4$ (5 mol %) in high yield without dimer formation. The parent seven-membered ring lactam **30** was cyclized with $AuCl_3$ and gave **43** in 52% yield (entry 13). Gratifyingly, also the seven-membered allenyl lactam **31** cyclized smoothly under the mild conditions used, providing the bicyclic lactam **44** in a yield of 79% (entry 14).

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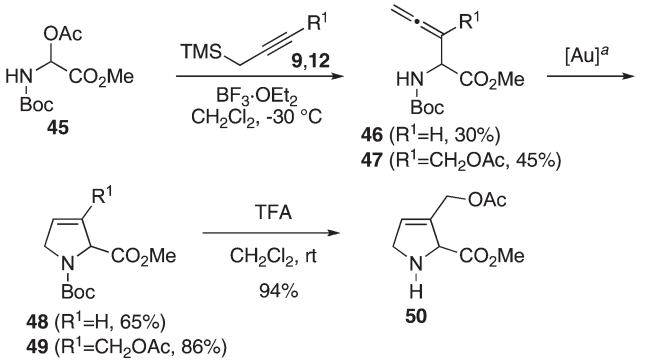
SCHEME 4. Linear Iminium Ion Addition/Gold Cyclization

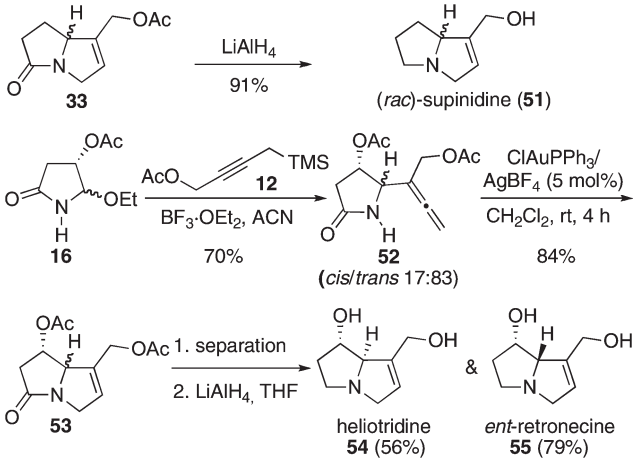


[a]Conditions for R[1] = H: $AuCl_3$ (5 mol %), MeCN, 60 °C; for $R^1 = CH_2OAc$: $ClAuPPh_3/AgBF_4$ (5 mol %), CH_2Cl_2, rt.

The *N*-acyliminium ion addition−gold cyclization sequence was further tested on two acyclic substrates prepared from *N*-Boc-α-acetoxyglycine methyl ester **45**[18] (Scheme 4). The allenylglycine derivatives **46** and **47** were synthesized in 30−45% yield using $BF_3 \cdot OEt_2$-induced addition of the indicated propargylsilanes. On using the standard cyclization conditions for the parent allene system ($AuCl_3$, MeCN, 60 °C), **48** was obtained in 65% yield. With dioxane as solvent at 80 °C, the yield could be increased slightly to 71%. Mild cationic gold-induced cyclization of **47** at room temperature provided **49** in 86% yield. The Boc protecting group could be selectively removed using TFA, leading to dihydropyrrole derivative **50** in high yield.

To illustrate the synthetic utility, we applied the sequence of *N*-acyliminium ion addition and gold-catalyzed cyclization to the synthesis of three pyrrolizidine alkaloids, supinidine **51**,[19] heliotridine **54**,[20] and retronecine **55**[21] (Scheme 5). Racemic supinidine was obtained by $LiAlH_4$ reduction of bicyclic **33** in a yield of 91%. Subjecting known ethoxylactam **16**[20a] (obtained from (*S*)-malic acid) to $BF_3 \cdot OEt_2$ in the presence of acetoxymethyl-substituted propargylsilane **12** afforded the allenyl lactam **52** in 70% yield with the *trans* product as the major diastereoisomer (Scheme 5). This diastereoisomeric mixture of allenyl lactam was successfully cyclized using 5 mol % cationic gold catalyst in CH_2Cl_2 at room temperature to afford the diastereoisomeric bicyclic lactams **53** in 84% isolated yield. The diastereoisomers were separated at this stage using column chromatography. Similar as for supinidine, one-pot reduction of the esters as well as the amide using $LiAlH_4$[20c] provided (+)-heliotridine **49** (56%, $[\alpha]^{20}_D$ +31.2, (*c* 0.75, MeOH); lit.[22] $[\alpha]^{20}_D$ +31 (10% in MeOH); lit.[20d] $[\alpha]^{30}_D$ +32.0 (*c* 0.22 MeOH)) and *ent*-(−)-retronecine **50** (79%, $[\alpha]^{20}_D$ −52.3, (*c* 0.4, EtOH); lit.[21a] $[\alpha]^{20}_D$ −52.9 (EtOH)).

SCHEME 5. Synthesis of (*rac*)-Supinidine, Heliotridine, and *ent*-Retronecine



In summary, a sequence of propargylsilane addition to *N*-acyliminium ions and gold-catalyzed cyclization of the resulting allenyl lactams was developed. For unsubstituted allenyl lactams and linear amides, elevated temperature $AuCl_3$ cyclization turned out to give the best yields. For substituted α-allenyl amide substrates, mild cationic gold cyclizations gave the cyclic products in good yields. The method is applicable to a wide range of substrates, including different ring-sized lactams. This method is a good alternative to Pd-, Pt-, and Ag-mediated cyclizations. This sequence was shown to be useful for short total syntheses of the alkaloids heliotridine and *ent*-retronecine from (*S*)-malic acid.

Experimental Section

Representative Procedure for the *N*-Acyliminium Ion Additions, *cis* and *trans*-(*3S*)-Lactam 52. To a cooled solution of ethoxylactam **16** (200 mg, 1.06 mmol) and acetoxy-4-trimethylsilyl-2-butyne **12** (0.628 g, 3.2 mmol) in dry acetonitrile (2 mL) at −20 °C was slowly added $BF_3 \cdot OEt_2$ (0.41 mL, 3.2 mmol, 3 equiv). The resultant mixture was allowed to warm to room temperature and stirred until all starting material had disappeared according to TLC. The reaction mixture was then diluted with CH_2Cl_2 (20 mL) and quenched with brine (20 mL). After layer separation, the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated to afford the crude product as a *cis*/*trans* 17:83 mixture. The diastereoisomers were separated using column chromatography. Combined yield: 201 mg (0.74 mmol, 70%).

trans: $[\alpha]^{20}_D$ +25.1 (*c* 1.0, MeOH); R_f 0.18 (EtOAc); IR (neat) ν 3242, 2940, 1959, 1707, 1435, 1377, 1236, 1033, 865 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.47 (s, 1H), 5.21 (d, J = 6.4 Hz, 1H), (t, J = 2.7 Hz, 2H), 4.59−4.53 (m, 2H), 4.04 (s, 1H), 2.68 (dd, J = 17.9, 6.6 Hz, 1H), 2.21 (dd, J = 17.9, 1.5 Hz, 1H), 2.00 (s, 3H), 1.99 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.7, 175.0, 170.0, 169.7, 99.1, 80.0, 72.8, 61.9, 59.1, 35.4, 20.4, 20.2.

cis: $[\alpha]^{20}_D$ −48.6 (*c* 1.0, MeOH); R_f 0.28 (EtOAc); IR (neat) ν 3241, 2940, 1960, 1709, 1433, 1378, 1236, 1035, 866 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.42 (s, 1H), 5.51 (m, 1H), 5.04 (m, 2H), 4.57 (t, J = 2.0 Hz, 2H), 4.44 (t, J = 2.7 Hz, 1H), 2.72

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(21) For previous syntheses of *ent*-(−)-retronecine, see: (a) Nishimura, Y.; Kondo, S.; Umezawa, H. *J. Org. Chem.* **1985**, *50*, 5210. (b) Huang, J.-M.; Hong, S.-C.; Wu, K.-L.; Tsai, Y.-M. *Tetrahedron Lett.* **2004**, *45*, 3047.

(22) Menshikov, G. *Chem. Ber.* **1932**, *65B*, 974.

(dd, J = 17.4, 6.7 Hz, 1H), 2.42 (dd, J = 17.5, 3.3 Hz, 1H), 2.06 (s, 3H), 2.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.4, 174.4, 170.5, 169.9, 97.1, 80.1, 62.5, 57.3, 37.2, 20.8, 20.8; HRMS (EI) calcd. for $C_{12}H_{16}O_5N$ 254.1028 (MH^+), found 254.1025.

Representative Procedure for the $AuCl_3$-Catalyzed Cycloisomerization of Unsubstituted Allenes, 5,7a-Dihydro-1*H*-pyrrolizin-3(2*H*)-one (32). To a solution of allenyl lactam **19** (61.5 mg, 0.5 mmol) in acetonitrile (1 mL) was added $AuCl_3$ (7.5 mg, 0.025 mmol). The mixture was heated at 82 °C, until all the starting material cyclized according to ^{1}H NMR (22 h). The mixture was then concentrated and the crude product purified by silica gel column chromatography (EtOAc). Yield: 46 mg (0.37 mmol, 75%). R_f 0.13 (EtOAc); IR (neat) ν 3471, 2865, 1681, 1396, 1281, 1191 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.92−5.87 (m, 2H), 4.69−4.64 (m, 1H), 4.43−4.37 (m, 1H), 3.70−3.65 (m, 1H), 2.78−2.68 (m, 1H), 2.46−2.31 (m, 2H), 1.90−1.80 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.0, 130.6, 128.2, 67.4, 49.7, 34.0, 29.6; HRMS (FAB^+) calcd. for $C_7H_{10}NO$ 124.0762 (MH^+), found 124.0764.

Representative Procedure for the Cationic Gold-Catalyzed Cycloisomerization of Substituted Allenes, *cis*- and *trans*-(1*S*)-Lactam 53. To $ClAuPPh_3$ (24.7 mg, 0.05 mmol) in dry dichloromethane (10 mL) was added $AgBF_4$ (9.7 mg, 0.05 mmol). After stirring for 10 min, a *cis*/*trans* mixture of allenyl lactam **52** (270 mg, 1.06 mmol) was added, and the mixture was stirred until all starting material had disappeared according to ^{1}H NMR. The crude mixture was concentrated and the product purified using column chromatography. Combined yield: 226 mg (0.89 mmol, 84%).

trans: yellowish oil, $[\alpha]^{20}_D$ +26.8 (*c* 1.0, MeOH); R_f 0.27 (EtOAc); IR (neat) ν 2938, 2871, 1744, 1713, 1381, 1246, 1045 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.82 (s, 1H), 5.23−5.19 (m, 1H), 4.66 (dd, J = 21.9, 13.6 Hz, 2H), 4.53 (d, J = 4.8 Hz, 1H), 4.37 (dd, J = 17.8, 1.8 Hz, 1H), 3.64 (d, J = 14.1 Hz, 1H), 2.78 (dd, J = 16.4, 8.4 Hz, 1H), 2.65 (dd, J = 16.4, 9.2 Hz, 1H), 1.98 (s, 3H), 2.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8, 170.0, 169.8, 136.4, 127.6, 72.9, 71.6, 59.5, 49.8, 39.5, 20.6, 20.4; HRMS (EI) calcd. for $C_{12}H_{16}O_5N$ 254.1028 (MH^+), found 254.1028.

cis: yellowish oil, R_f 0.22 (EtOAc); IR (neat) ν 2938, 2871, 1744, 1713, 1381, 1246, 1045 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.82 (s, 1H), 5.23−5.19 (m, 1H), 4.66 (dd, J = 21.9, 13.6 Hz, 2H), 4.53 (d, J = 4.8 Hz, 1H), 4.37 (dd, J = 17.8, 1.8 Hz, 1H), 3.64 (d, J = 14.1 Hz, 1H), 2.78 (dd, J = 16.4, 8.4 Hz, 1H), 2.65 (dd, J = 16.4, 9.2 Hz, 1H), 1.98 (s, 3H), 2.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8, 170.0, 169.8, 136.4, 127.6, 72.9, 71.6, 59.5, 49.8, 39.5, 20.6, 20.4.

Heliotridine (54).[20] Following the literature procedure,[20c] *trans*-**53** (158 mg, 0.59 mmol) was reduced with $LiAlH_4$ (152 mg, 3.95 mmol) to give (+)-heliotridine after column chromatography. Yield: 51 mg (0.33 mmol, 56%). R_f 0.23 ($CHCl_3$/MeOH/NH_4OH 10:4:1); $[\alpha]^{20}_D$ +31.2 (*c* 0.75, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.50 (s, 1H), 5.06 (br s, 2H), 4.24 (d, J = 5.6 Hz, 2H), 4.10 (q, J = 4.8 Hz, 1H), 4.02 (s, 1H), 3.86 (d, J = 15.2 Hz, 1H), 3.27 (m, 1H), 2.68 (m, 1H), 1.88 (m, 1H), 1.79 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.3, 122.6, 80.0, 74.4, 61.9, 59.1, 54.0, 33.3. All other analytical data were in accordance to those reported in the literature.

(*ent*)**-Retronecine (55).**[21] Yield: 16 mg (0.1 mmol, 79%). R_f 0.20 ($CHCl_3$/MeOH/NH_4OH 10:4:1); $[\alpha]^{20}_D$ −52.3 (*c* 0.4, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.73 (s, 1H), 4.33 (t, J = 4.9 Hz, 2H), 4.22 (br s, 1H), 4.15 (d, J = 11.7 Hz, 1H), 3.86 (d, J = 11.3 Hz, 1H), 4.30 (dd, J = 15.6, 5.2 Hz, 1H), 3.29 (t, J = 7.9 Hz, 1H), 2.78−2.71 (m, 1H), 2.60−2.10 (br, 2OH), 2.03−1.92 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.4, 127.9, 79.5, 71.2, 62.1, 59.2, 54.1, 35.5. All other analytical data were in accordance to those reported in the literature.

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Supporting Information Available: Detailed experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.