Title

Enantioselective Total Syntheses of Akuammiline Alkaloids (+)-Strictamine, (−)-2(S)-Cathafoline, and (−)-Aspidophylline A

Journal

Journal of the American Chemical Society, 138(4)

ISSN

0002-7863

Authors

Moreno, Jesus
Picazo, Elias
Morrill, Lucas A
et al.

Publication Date

2016-02-03

DOI

10.1021/jacs.5b12880

Peer reviewed

HHS Public Access

Author manuscript

J Am Chem Soc. Author manuscript; available in PMC 2016 December 13.

Published in final edited form as:

J Am Chem Soc. 2016 February 03; 138(4): 1162–1165. doi:10.1021/jacs.5b12880.

Enantioselective Total Syntheses of Akuammiline Alkaloids (+)-Strictamine, (−)-2(*S*)-Cathafoline, and (−)-Aspidophylline A

Jesus Moreno[†], **Elias Picazo**[†], **Lucas A. Morrill**, **Joel M. Smith**, and **Neil K. Garg**[*]

Department of Chemistry and Biochemistry, University of California, Los Angeles, California 90095, United States

Abstract

The akuammiline alkaloids are a family of natural products that have been widely studied for decades. Although notable synthetic achievements have been made recently, akuammilines that possess a methanoquinolizidine core have evaded synthetic efforts. We report an asymmetric approach to these alkaloids, which has culminated in the first total syntheses of (−)-2(*S*)-cathafoline and the long-standing target (+)-strictamine. Moreover, the first enantioselective total synthesis of aspidophylline A is described.

The akuammiline alkaloids are a family of bioactive natural products that have been studied for over a century.[1] To date, over 30 akuammilines have been isolated, examples of which are shown in Figure 1 (**1**–**6**). These natural products can be divided into four structural subclasses, with completed total syntheses recently reported in three of these categories. Aspidophylline A (**3**), an example of the furoindoline-containing subclass, has been accessed synthetically by our group[2] and the laboratories of Zhu[3] and Ma.[4] In addition, our laboratory has completed the total synthesis of picrinine (**6**), a C5-oxidized akuammiline.[5] With regard to the skeletally rearranged akuammilines, breakthroughs include total syntheses of vincorine (**4**) by Qin,[6] Ma,[7] and MacMillan,[8] and total syntheses of scholarisine A (**5**) by Smith[9] and Snyder.[10]

Despite these synthetic triumphs, one structural subclass of the akuammilines has remained inaccessible. Namely, compounds that possess a methanoquinolizidine core have not yet succumbed to total synthesis. We have targeted the total synthesis of two such alkaloids: strictamine (**1**) and 2(*S*)-cathafoline (**2**), isolated in 1966[11] and 2014,[12] respectively. As a salient feature of their caged methanoquinolizidine cores, each of these natural products also contains a densely functionalized cyclohexane ring that is part of two conjoined [3.3.1]-azabicycles. Strictamine (**1**) possesses an indolenine motif and four stereocenters, whereas

[*]**Corresponding Author**. neilgarg@chem.ucla.edu.

[†]J.M. and E.P. contributed equally.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b12880.

Detailed experimental procedures and compound characterization data (PDF)

X-ray crystallographic data for **18** (CIF)

The authors declare no competing financial interest.

2(*S*)-cathafoline (**2**) bears an indoline unit and five contiguous stereocenters. The rich history, structural complexity, and bioactivity[13] of **1** have prompted many synthetic efforts beginning with seminal studies by Dolby and Bosch and Bennasar.[14a–d] More recent approaches by the laboratories of Sakai,[14e] Cook,[14f] Tokuyama,[14g] Matsuo,[14h] and Zhu[14i] have also been put forward. Herein, we describe an enantioselective approach to several akuammilines, including family members that contain the elusive methanoquinolizidine core. These efforts result in the first enantioselective total syntheses of aspidophylline A (**3**), strictamine (**1**), and 2(*S*)-cathafoline (**2**).

Our retrosynthetic analysis for the enantioselective total syntheses of strictamine (**1**) and 2(*S*)-cathafoline (**2**) is shown in Scheme 1. It was envisioned that both natural products could be derived from tetracyclic chloride **8**. In the forward sense, late-stage deprotection and cyclization would forge the methanoquinolizidine core (see transition structure **7**).[15] In turn, chloride **8** would arise from methanolysis and subsequent chlorination of lactone **9**. This key late-stage compound would be accessed from phenylhydrazine (**11**) and ketolactone **12** using an uncommon reductive variant of the interrupted Fischer indolization reaction.[16–18] The success of this step would lead to the introduction of two new rings and two stereogenic centers, including the C2 stereocenter seen in 2(*S*)-cathafoline (**2**) (via transition structure **10**) and the challenging C7 quaternary center common to all akuammilines. Ketolactone **12**, which would also be a viable intermediate toward aspidophylline A (**3**), would be prepared from enone **13**, the product of a gold-mediated cyclization[19] of enantioenriched silyl enol ether **14**.

Our synthetic studies commenced with the asymmetric construction of the akuammiline [3.3.1]-azabicyclic core and the formation of enal **20** (Scheme 2). Beginning with dibenzoate **15**, a Trost desymmetrization[20] was performed. In the event, dibenzoate **15** was treated with sulfonamide **16** in the presence of a suitable Pd precatalyst and (*R, R*)-DACH-phenyl Trost ligand. Direct saponification of the product furnished alcohol **17** in 89% yield. Subsequent oxidation delivered enone **18**, a crystalline compound that was deemed suitable for X-ray analysis.[21] By virtue of the heavy atom, it was found that the desired C3 stereocenter had been introduced in the Trost desymmetrization step. To attempt the key gold-mediated cyclization, ketone **18** was advanced to silyl enol ether **14**, which in turn was subjected to a modification of Li's cyclization conditions.[19] This transformation smoothly delivered a 10:1 mixture of isomeric bicyclic adducts **13** (96% ee) and **19**, even when performed on multigram scale. Although the bicycles were inseparable, exposure of the mixture to a previously established two step epoxidation/Wittig olefination sequence[5] allowed enantioenriched enal **20** to be isolated in 49% yield from silyl enol ether **14**.

With enal **20** in hand, our next task was to install a C7 alkyl substituent and access ketolactone **12** (Scheme 3). Toward this endeavor, enal **20** was first oxidized by NIS in the presence of potassium carbonate in methanol[22] to provide enoate **21**. Next, treatment of enoate **21** with vinyl ether **22** and NIS furnished an intermediate mixed acetal bearing an iodide,[23] thus setting the stage for a Ueno–Stork cyclization.[24] Exposure of this compound to radical cyclization conditions efficiently delivered C7-alkylated product **23** with diastereocontrol about the two newly formed stereocenters. From **23**, the desired ketolactone

12 could be readily accessed via a sequence involving hydrolysis and reduction (**23** → **24**), followed by lactonization and alcohol oxidation (**24** → **12**).[2]

Having accessed ketolactone **12** in an enantioenriched form, we opted to pursue the asymmetric total synthesis of aspidophylline A (**3**) (Scheme 3). As suggested earlier, three prior total syntheses of **3** have been reported, all of which deliver racemic material.[2–4] Analogous to our earlier efforts,[2] albeit with a nosyl protecting group instead of a tosyl group, ketolactone **12** was exposed to phenylhydrazine (**11**) and TFA to provide Fischer indolization adduct **25**. In the same pot, treatment of **25** with K_2CO_3 in methanol furnished furoindoline **27**, presumably via transition structure **26**. This transformation serves to introduce two new rings, four new bond linkages, and the challenging C7 quaternary stereocenter, all with complete diastereoselectivity. For reasons that shall soon become apparent, it should be noted that no evidence of epimerization at C16 is seen in this complexity-generating transformation. To complete the synthesis of (−)-aspidophylline A (**3**), interrupted Fischer indolization[25] adduct **27** underwent nosyl cleavage using a solid-supported thiol resin, followed by *N*-formylation.

We next directed our attention to the methanoquinolizidine alkaloids, which have evaded prior synthetic efforts.[14] As shown in Scheme 4, Fischer indolization product **25** was accessed as demonstrated previously. However, this intermediate was directly intercepted by a hydride nucleophile. Interestingly, this process occurred in high yield and with complete control of stereochemistry to give the depicted 2*S* diastereomer of product **9**. The overall conversion of **12** to **9** represents an uncommon reductive variant[18] of the interrupted Fischer indolization reaction, and is also one of the most complex examples[26] of this venerable synthetic method. It proceeds by introducing two stereocenters (at C2 and C7) and establishes an intricate pentacyclic framework bearing five contiguous stereocenters.

From product **9**, we pursued the seemingly simple conversion to hydroxyester **29** (Scheme 4). Although intermediate **25** readily underwent smooth ring-opening (see Scheme 3), we were disappointed to find that exposure of its reduced counterpart (**9**) to methoxide or two-step hydrolysis/methylation protocols failed to furnish **29**. Instead, C16 epimer **28** was formed. Exhaustive efforts to overcome this roadblock were undertaken. For example, epimerization under a variety of acidic or basic conditions, attempted lactone opening via amidation,[27] Pd-catalyzed ring-opening,[28] or S_N2 displacements,[29] all proved fruitless. With our best efforts thwarted, we pursued a more stepwise approach. Reduction of **9**, followed by selective silylation of the less hindered primary alcohol, proceeded without stereochemical erosion at C16 and gave alcohol **30**. Lastly, an oxidation/esterification sequence (**30** → **31**), with in situ desilylation, provided a reliable means to synthesize the coveted late-stage intermediate **29**. Of note, the Dess–Martin oxidation was achieved in the presence of the indoline, a conversion that was not possible when other oxidants were tried.

Having accessed alcohol **29**, we set our sights on accessing the elusive methanoquinolizidine alkaloids (Scheme 5). Initial efforts to elaborate aminoalcohol **29** without using protecting groups were deemed challenging. However, a mesylation/chlorination sequence[30] was found to be viable and delivered aminochloride **8** in 77% yield. To our delight, chloride **8** could be elaborated to strictamine (**1**) and 2(*S*)-cathafoline (**2**). The former of the natural products

was accessed via oxidation of the indoline with PCC, followed by denosylation. To access 2(*S*)-cathafoline (**2**), an *N*-methylation/deprotection sequence was performed. In both cases, the denosylation step proceeded with the desired in situ chloride displacement by the liberated amine to establish the hexacyclic methanoquinolizidine framework. NMR spectra of synthetic (+)-**1** and (−)-**2** were found to be in accord with spectra for the natural samples.

In summary, we have completed the first total syntheses of two akuammiline natural products that possess a methanoquinolizidine core. Our asymmetric approach to **1** and **2** features a gold-mediated cyclization to assemble the [3.3.1]-azabicyclic core of the natural products, a reductive interrupted Fischer indolization reaction to introduce the key C7 quaternary stereocenter and access late-stage compounds, and a series of carefully executed late-stage transformations to complete the total syntheses. Moreover, we have also completed the first enantioselective total synthesis of aspidophylline A (**3**). These studies constitute new achievements in the popular area of akuammiline alkaloid synthesis, and provide many lessons that should impact future endeavors in the synthesis of complex molecules.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors are grateful to the National Science Foundation (CHE-0955864 and CHE-1464898), Bristol–Myers Squibb, the Dreyfus Foundation, the UCLA Gold Shield Alumnae, and the University of California, Los Angeles, for financial support. We are grateful to the NIH-NIGMS (F31-GM113642 to J.M. and F31-GM117945 to E.P.), the Foote Family (J.M. and L.A.M.), and the UCLA Cota-Robles Fellowship Program (E.P.). J.M.S. acknowledges the National Science Foundation for a GRFP (DGE-1144087) and the UCLA Graduate Division for a Dissertation Year Fellowship. We are grateful to Prof. T.-S. Kam (University of Malaya) for providing authentic samples of aspidophylline A, strictamine, and 2(*S*)-cathafoline. These studies were supported by shared instrumentation grants from the NSF (CHE-1048804) and the National Center for Research Resources (S10RR025631).

REFERENCES

1. For reviews on akuammiline alkaloids, see: Ramírez A, García-Rubio S. Curr. Med. Chem. 2003; 10:1891–1915. [PubMed: 12871110] Eckermann R, Gaich T. Synthesis. 2013; 45:2813–2823. Smith JM, Moreno J, Boal BW, Garg NK. Angew. Chem. Int. Ed. 2015; 54:400–412.
2. Zu L, Boal BW, Garg NK. J. Am. Chem. Soc. 2011; 133:8877–8879. [PubMed: 21553860]
3. Ren W, Wang Q, Zhu J. Angew. Chem. Int. Ed. 2014; 53:1818–1821.
4. Teng M, Zi W, Ma D. Angew. Chem. Int. Ed. 2014; 53:1814–1817.
5. (a) Smith JM, Moreno J, Boal BW, Garg NK. J. Am. Chem. Soc. 2014; 136:4504–4507. [PubMed: 24597784] (b) Smith JM, Moreno J, Boal BW, Garg NK. J. Org. Chem. 2015; 80:8954–8967. [PubMed: 26134260]
6. (a) Zhang M, Huang X, Shen L, Qin Y. J. Am. Chem. Soc. 2009; 131:6013–6020. [PubMed: 19326910] (b) Zhang D, Song H, Qin Y. Acc. Chem. Res. 2011; 44:447–457. [PubMed: 21491859]
7. Zi W, Xie W, Ma D. J. Am. Chem. Soc. 2012; 134:9126–9129. [PubMed: 22616754]
8. Horning BD, MacMillan DWC. J. Am. Chem. Soc. 2013; 135:6442–6445. [PubMed: 23586842]
9. (a) Adams GL, Carroll PJ, Smith AB III. J. Am. Chem. Soc. 2012; 134:4037–4040. [PubMed: 22280070] (b) Adams GL, Carroll PJ, Smith AB III. J. Am. Chem. Soc. 2013; 135:519–528. [PubMed: 23268611]
10. Smith MW, Snyder SA. J. Am. Chem. Soc. 2013; 135:12964–12967. [PubMed: 23964983]

11. For the initial isolation of strictamine, see: Schnoes HK, Biemann K, Mokrý J, Kompis I, Chatterjee A, Ganguli G. J. Org. Chem. 1966; 31:1641–1642. For the X-ray structure of strictamine, see Ahmad Y, Fatima K, Atta-ur-Rahman, Occolowitz JL, Solheim BA, Clardy J, Garnick RL, Le Quesne PW. J. Am. Chem. Soc. 1977; 99:1943–1946.
12. Lim S-H, Low Y-Y, Sinniah SK, Yong KT, Sim KS, Kam T-S. Phytochemistry. 2014; 98:204–215. [PubMed: 24342109]
13. (a) Bhattacharya SK, Bose R, Dutta SC, Ray AB, Guha SR. Indian J. Exp. Biol. 1979; 17:598–600. [PubMed: 500142] (b) Hou Y, Cao X, Wang L, Cheng B, Dong L, Luo X, Bai G, Gao W. J. Chromatogr. B. 2012; 908:98–104.(c) Zhang L, Zhang C-J, Zhang D-B, Wen J, Zhao X-W, Li Y, Gao K. Tetrahedron Lett. 2014; 55:1815–1817.(d) Liu L, Chen Y-Y, Qin X-J, Wang B, Jin Q, Liu Y-P, Luo X-D. Fitoterapia. 2015; 105:160–164. [PubMed: 26136061]
14. For previous synthetic studies on strictamine or related methanoquinolizidine akuammilines see: Dolby LJ, Esfandiari Z. J. Org. Chem. 1972; 37:43–46. [PubMed: 5007281] Dolby LJ, Nelson SJ. J. Org. Chem. 1973; 38:2882–2887. [PubMed: 4733444] Bennasar M-L, Zulaica E, López M, Bosch J. Tetrahedron Lett. 1988; 29:2361–2364. Bennasar M-L, Zulaica E, Ramírez A, Bosch J. J. Org. Chem. 1996; 61:1239–1251. Koike T, Takayama H, Sakai S-I. Chem. Pharm. Bull. 1991; 39:1677–1681. Edwankar RV, Edwankar CR, Namjoshi OA, Deschamps JR, Cook JM. J. Nat. Prod. 2012; 75:181–188. [PubMed: 22257244] Komatsu Y, Yoshida K, Ueda H, Tokuyama H. Tetrahedron Lett. 2013; 54:377–380. Kawano M, Kiuchi T, Negishi S, Tanaka H, Hoshikawa T, Matsuo J-I, Ishibashi H. Angew. Chem. Int. Ed. 2013; 52:906–910. Ren W, Tappin N, Wang Q, Zhu J. Synlett. 2013; 24:1941–1944.
15. It was envisioned that the deprotection/cyclization could be followed by either oxidation or *N*-methylation as suggested schematically. However, the order of operations could also be reversed.
16. For the classic Fischer indole synthesis, see: Fischer E, Jourdan F. Ber. Dtsch. Chem. Ges. 1883; 16:2241–2245. Fischer E, Hess O. Ber. Dtsch. Chem. Ges. 1884; 17:559–568.
17. For the use of the Fischer indolization reaction in akuammiline alkaloid synthesis, see refs 2 and 5.
18. For the reductive interrupted Fischer indolization reaction, see: Maligres PE, Houpis I, Rossen K, Molina A, Sager J, Upadhyay V, Wells KM, Reamer RA, Lynch JE, Askin D, Volante RP, Reider PJ, Houghton P. Tetrahedron. 1997; 53:10983–10992.
19. (a) Lu Z, Li Y, Deng J, Li A. Nat. Chem. 2013; 5:679–684. [PubMed: 23881499] (b) Xiong X, Li Y, Lu Z, Wan M, Deng J, Wu S, Shao H, Li A. Chem. Commun. 2014; 50:5294–5297.
20. For a review on catalytic asymmetric allylic alkylation employing heteroatom nucleophiles, see: Trost BM, Zhang T, Sieber JD. Chem. Sci. 2010; 1:427–440.
21. For the crystallographic data of **18**, refer to CCDC number 1440684, and the CIF Supporting Information.
22. McDonald C, Holcomb H, Kennedy K, Kirkpatrick E, Leathers T, Vanemon P. J. Org. Chem. 1989; 54:1213–1215.
23. Bian M, Wang Z, Xiong X, Sun Y, Matera C, Nicolaou KC, Li A. J. Am. Chem. Soc. 2012; 134:8078–8081. [PubMed: 22537293]
24. Salom-Roig XJ, Dénès F, Renaud P. Synthesis. 2004:1903– 1928.
25. For methodology studies, see: Boal BW, Schammel AW, Garg NK. Org. Lett. 2009; 11:3458–3461. [PubMed: 19601608] Schammel AW, Boal BW, Zu L, Mesganaw T, Garg NK. Tetrahedron. 2010; 66:4687–4695. [PubMed: 20798890]
26. For the Fischer indolization in late-stage total synthesis of complex alkaloids, see refs 2, 5, and 9, in addition to the following: Ueda H, Satoh H, Matsumoto K, Sugimoto K, Fukuyama T, Tokuyama H. Angew. Chem. Int. Ed. 2009; 48:7600–7603. Satoh H, Ueda H, Tokuyama H. Tetrahedron. 2013; 69:89–95.
27. (a) Basha A, Lipton M, Weinreb SM. Tetrahedron Lett. 1977; 18:4171–4172.(b) Shimizu T, Osako K, Nakata T. Tetrahedron Lett. 1997; 38:2685–2688.
28. Iwata A, Ohshita J, Tang H, Kunai A, Yamamoto Y, Matui C. J. Org. Chem. 2002; 67:3927–3929. [PubMed: 12027717]
29. (a) Liotta D, Sunay U, Santiesteban H, Markiewicz W. J. Org. Chem. 1981; 46:2605–2610.(b) McMurry JE. Org. React. 1977; 24:187–224.
30. Wang H, Reisman SE. Angew. Chem. Int. Ed. 2014; 53:6206–6210.

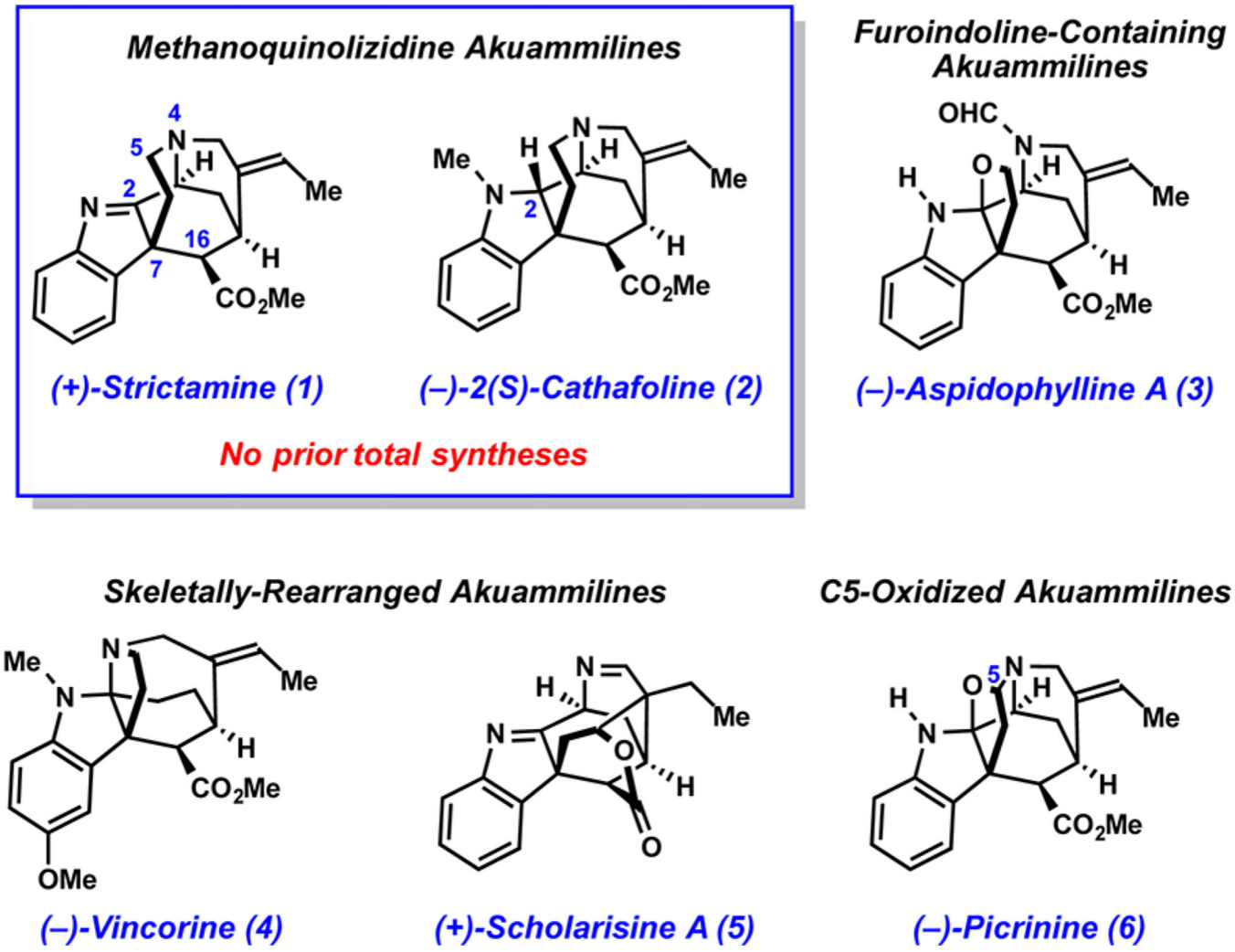
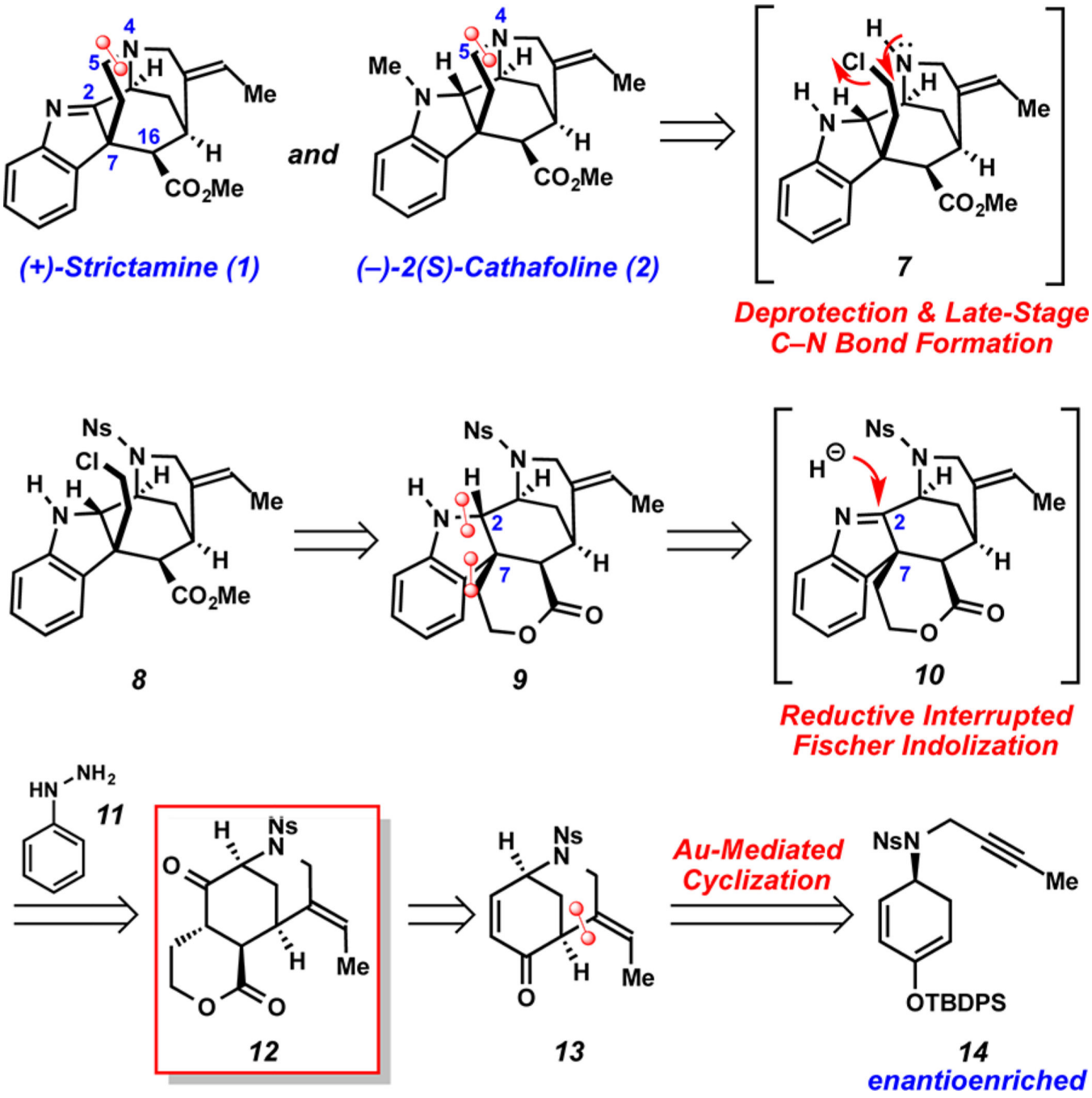
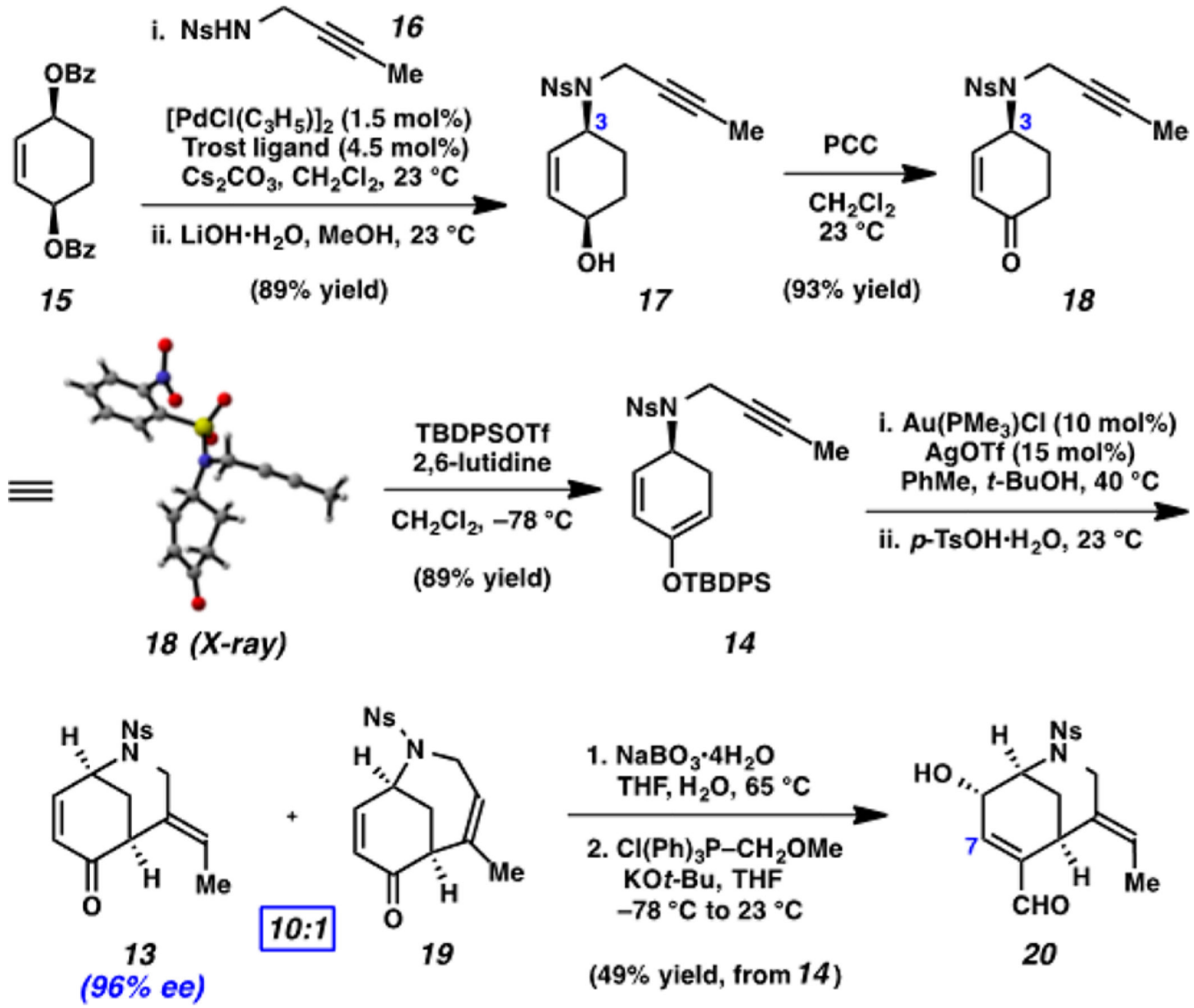


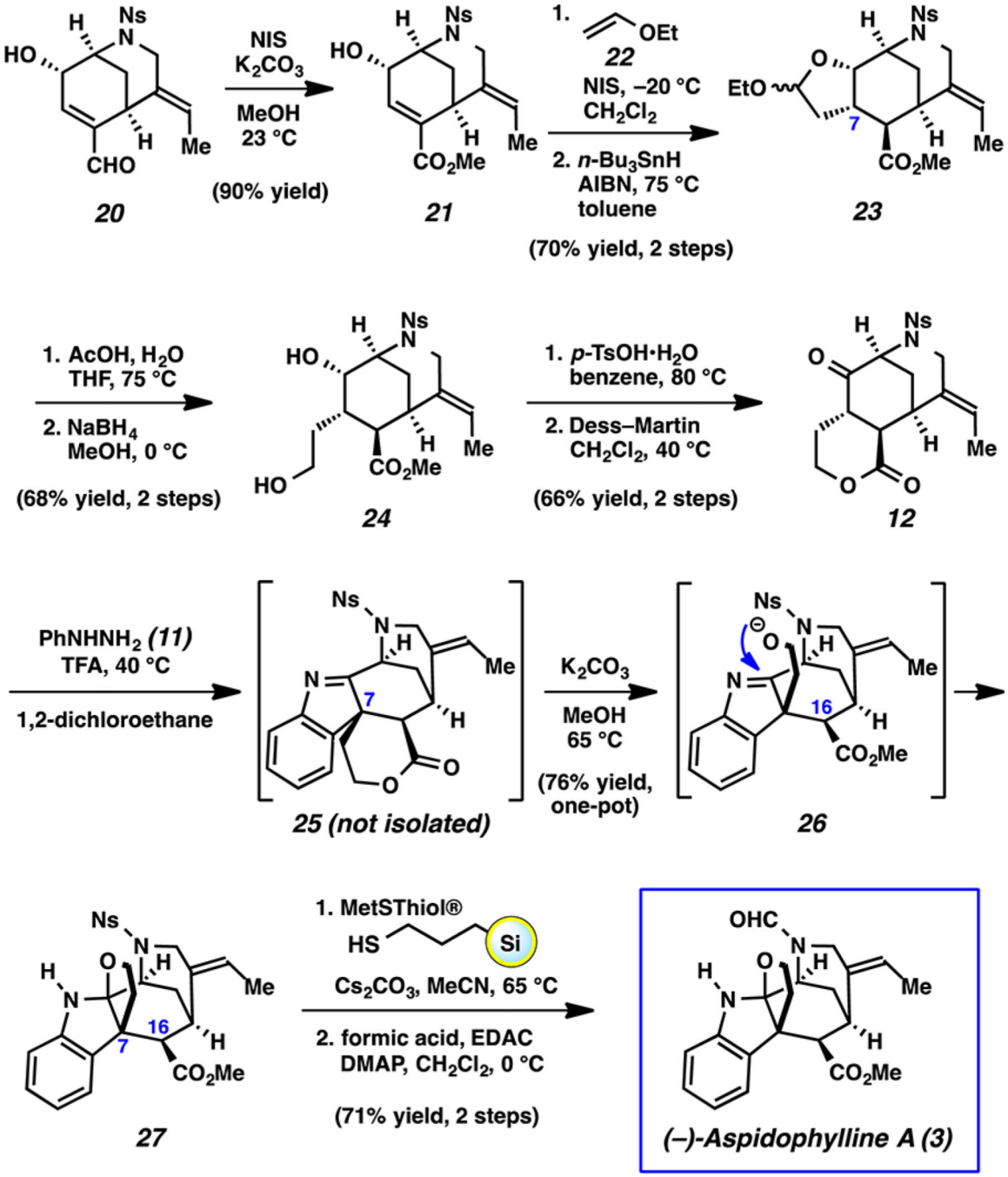
Figure 1.
Representative akuammiline alkaloids **1**–**6**.



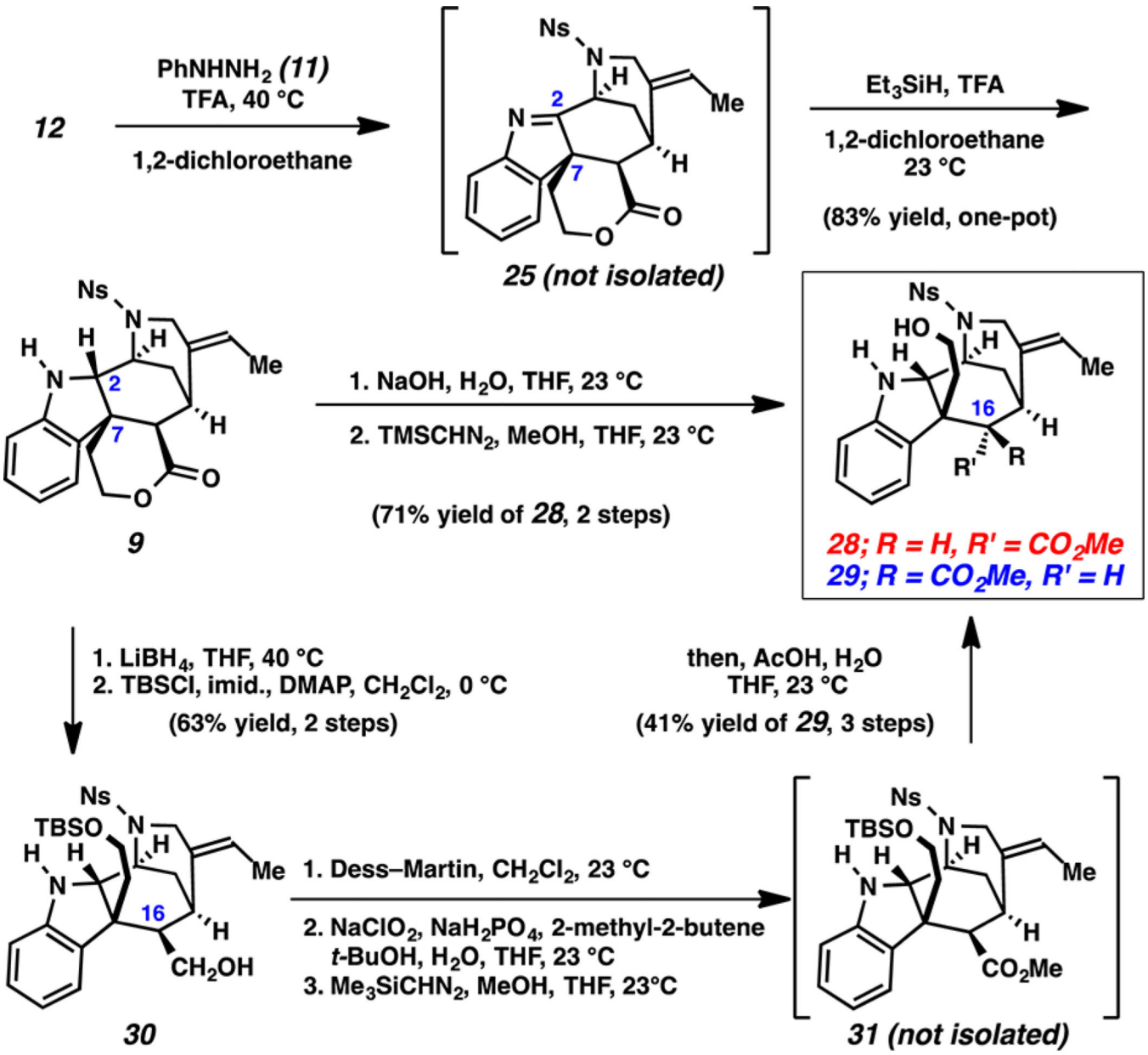
Scheme 1.



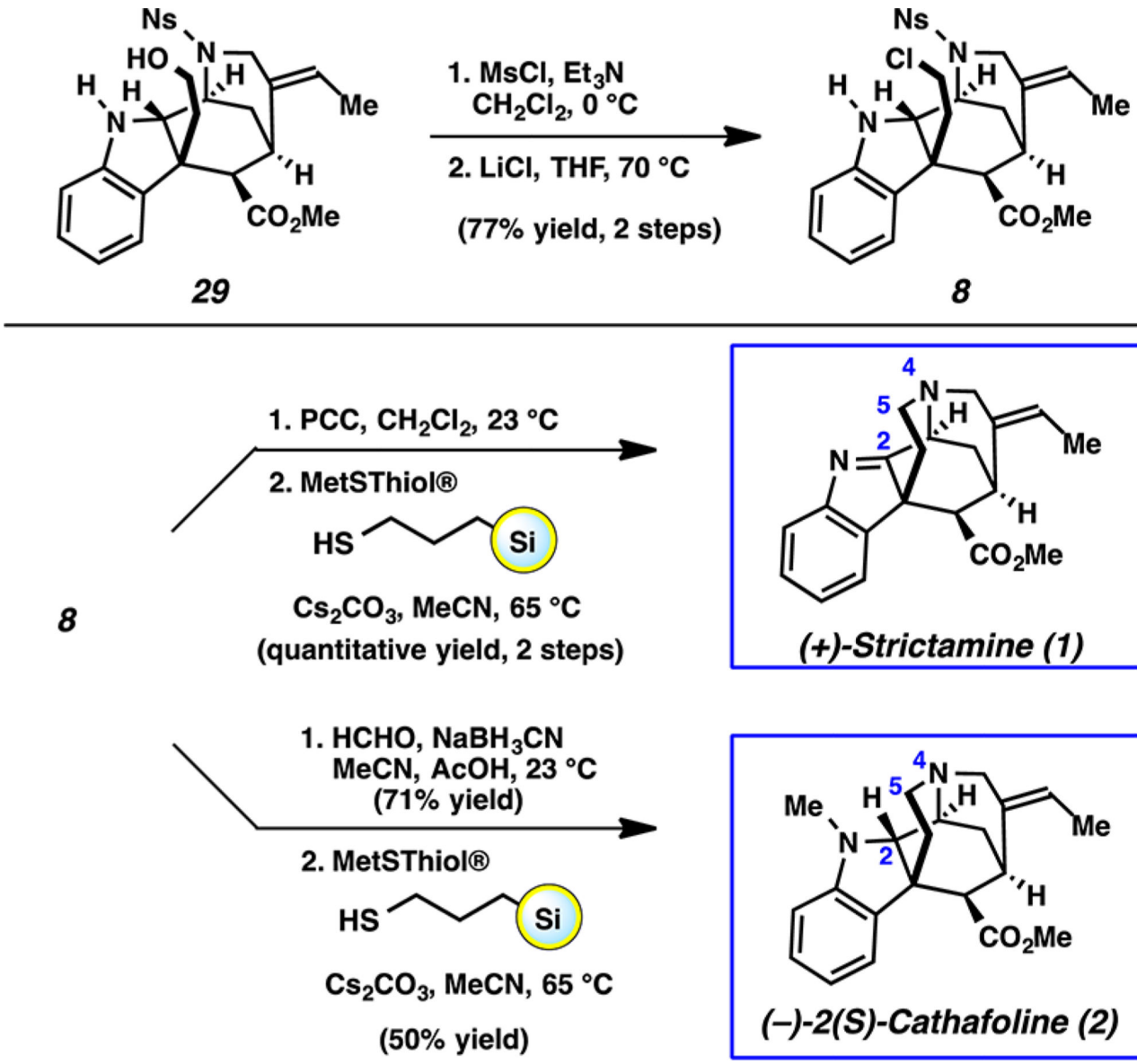
Scheme 2.



Scheme 3.



Scheme 4.



Scheme 5.