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A Concise Approach to Paxilline Indole Diterpenes

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Abstract

A synthetic approach to paxilline indole diterpenes is described. The route to the pentacyclic core relies on a new regioselective alkenylation of ketones and a tandem radical addition−aldol reaction sequence to access vicinal quaternary stereocenters. Emindole SB, the simplest member of the family, is synthesized in 11 steps from commercially available material to demonstrate the application of this approach.

Paxilline indole diterpenes comprise a family of fungal metabolites with a diverse set of biological activities. Notable examples include inhibition of potassium channels by paspalinine, penitrem A, and aflatrem;[1] alteration of cellular lipid balance by terpendoles C and D;[2] insecticidal activity of nodulisporic acids;[3] and inhibition of mitosis by terpendole E and 11-ketopaspaline.[4] Other reports detail antimicrobial[5] and antiviral[6] activities of paxilline indole diterpenes, further broadening the scope of potentially useful biological effects exerted by these natural products. Over 80 congeners identified to date (e.g., **1**, **2**, and **3**, Figure 1) share a common polycyclic core that is believed to arise from an unusual polycyclization of a prenylated indole precursor.[7] The resulting structural complexity of paxilline indole diterpenes attracted considerable attention from synthetic organic chemists. In 1985, Smith and Mewshaw reported a pioneering synthesis of paspaline, with over a dozen more syntheses of this and other related natural products appearing in the following years.[8] A notable hallmark of many of those investigations has been the challenge associated with the direct assembly of an embedded *transhexahydroindene* fragment including vicinal quaternary stereocenters.[9] Here we demonstrate a solution to this problem that allows an 8-step stereocontrolled assembly of a functionalized pentacyclic core of paxilline indole diterpenes. As a proof of concept, we also report a synthesis of emindole SB (**3**),[6,10] a key biosynthetic precursor to more complex congeners, in 11 steps from commercially available material.

We believed that rapid access to a functionalized polycyclic terpenoid core (such as **4**, Figure 1) would allow the concise assembly of various paxilline indole terpenes. The aldol motif of **4** was expected to provide a convenient handle for diversification of the terpenoid scaffold, and a carbonyl or related functionality of the five-membered ring would serve for installation of the indole moiety. We sought to set the stereochemistry of the crucial *trans*-juncture of the hexahydroindene motif early in the synthesis and envisioned a direct assembly of the tricyclic core bearing vicinal quaternary stereocenters (at C3 and C4) via a radical–polar crossover polycyclization of a cyclopentanone derivative **5** initiated by chemoselective hydrogen atom transfer (HAT) to the 1,1-disubstitued alkene at C4.[11–13] In this process, the key carbon–carbon bond formations would result from intramolecular radical conjugate addition[12,14] (C4–C13 bond) and aldol (C12–C7 bond) reactions.[15]

We reasoned that the brevity of the proposed route would depend in part on effcient installation of the C3 quaternary stereocenter of **5** and we identified alkenylation of the corresponding cyclopentanone derivative as the most direct approach. A literature survey revealed that regioselective intermolecular alkenylation of unsymmetrical ketones bearing two unactivated enolizable positions finds little precedent,[16] with examples of formation of quaternary stereocenters being particularly scarce.[17] After extensive experimentation, we chose to employ terminal alkynes as electrophiles in the reaction with silyl enol ethers serving as enol surrogates.[18,19] The desired alkenylation was eventually achieved by treating enol ether **6** with *O*-TBS-protected 4-pentyn-1-ol in the presence of indium(III) bromide[19,20] (Scheme 1). Subsequent mild acidic workup afforded alcohol **7** in a highly regio- and stereoselective manner. This reaction likely proceeds via the intermediacy of corresponding vinylindium species and requires utilization of substoichiometric amounts of indium(III) bromide.[19] Subsequent chemoselective Sharpless allylic oxidation[21] of **7** followed by double oxidation of the resulting diol completed the assembly of dialdehyde **8**.

Our initial attempts to perform radical–polar crossover polycyclization of dialdehyde **8** resulted in successful formation of the desired C4–C13 and C12–C7 bonds, but favored the undesired diastereomer and exhibited overall low efficiency of the transformation. Extensive screening of catalysts and reductants revealed that application of iron(III) acetylacetonate[12] and (isopropoxy)phenylsilane[22] led to substantial increase in the yield of tricyclic products (Scheme 2). Thus, treatment of **8** with (isopropoxy)phenylsilane in a mixture of 1,2-dichloroethane and ethylene glycol at 0 °C in the presence of iron(III) acetylacetonate afforded a nearly equimolar mixture of **9** and **10** in ca. 58% yield (24% isolated yield of **9**).[23] This transformation likely involves HAT to the 1,1-disubstituted alkene, followed by the conjugate addition of the intermediate tert-alkyl radical **11**, reduction to the corresponding enolate **12** (or its diastereomer en route to **10**), and subsequent aldol reaction with the aliphatic aldehyde functionality. The structures of **9** and **10** (after conversion to dioxane **13**) were confirmed by X-ray crystallographic analysis. It should be noted that in both cases the *β*-hydroxyaldehyde motif was formed in a highly diastereoselective manner. Surprisingly, changing the nature of the solvent and performing the reaction at lower temperatures led only to the increase in content of the undesired diastereomer, with ratios as high as 2.5:1 favoring ketone **10** being obtained. Application of other iron(III), cobalt(III), and manganese(III)-based catalysts did not favorably affect the ratio of diastereomers **9** and **10**,

but instead led to increased formation of byproducts resulting from the conjugate reduction of α,β-unsaturated aldehyde **8**.

During our studies, we observed that aldehyde **8** existed predominantly in the form of the corresponding hemiacetals at C7 in the presence of alcoholic solvents such as deuterated methanol. We reasoned that introduction of a hydroxy group in place of the ketone functionality of **8** could allow for reversible formation of cyclic hemiacetal intermediates. Indeed, secondary alcohol **14** was found to exist as an approximately 1:2 mixture with the corresponding cyclic hemiacetal **15** in a solution of deuterated chloroform (Table 1). We speculated that this transient tether could allow for the desired stereocontrol over the initial radical cyclization. In accord with our predictions, subjection of **14** to the standard polycyclization conditions (see Scheme 2) afforded a 5:1 mixture of diols **16** and **17** (entry 1, Table 1),[24] effectively reversing the selectivity exhibited by the parent substrate **8**. The ratio of products was temperature dependent with lower temperatures favoring the desired scaffold **16** (entries 2 and 3), thereby reversing the trend observed for the parent substrate 8 (see discussion above). When the solvent was replaced with ethanol, the ratio of **16** to **17** deteriorated (entry 4).[25] Methylation of the secondary hydroxy group led to similar deterioration of diastereomeric ratios with ether **18** affording a 1.6:1 mixture of tricycles **19** and **20** (entry 5).[26] Effects of solvent and temperature on polycyclization of substrate **18** were similar to those for the parent compound **8** (entries 6 and 7).

Guided by the aforementioned logic, we proposed that an indole N–H in place of a hydroxy group could serve as an anchor to control the stereoselectivity of polycyclization in a similar fashion. Corresponding cyclic hemiaminal motifs have been previously identified in a number of indole-containing alkaloids,[27] suggesting viability of similar intermediates. To test our hypothesis, we began with the Fischer synthesis of indole **22** from ketone **21** (Scheme 3). Conversion of the N-phenylhydrazone of **21** into **22** was best achieved by heating with an excess of anhydrous zinc chloride in toluene.[28] Parikh– Doering conditions[29] proved optimal for oxidation of diol **22** and secured access to hemiaminal **23** after mild basic workup. Hemiaminal **23** was produced as a single diastereomer (stereochemistry of the hemiaminal was not determined) and underwent facile dehydration to the corresponding enamine upon prolonged exposure to acid. Subjection of **23** to the cyclization conditions ((isopropoxy)phenylsilane and iron(III) acetylacetonate in ethanol at 0 °C) triggered facile radical cyclization to pentacyclic intermediate **24**.[30] However, the stability of the hemiaminal fragment[31] required subsequent treatment with strong base in order to complete construction of the desired pentacyclic core, concluding the assembly of four new stereocenters with excellent selectivity. The radical cyclization required rigorous exclusion of oxygen from the reaction mixture due to facile oxidation of intermediates. Hemiaminal **24** proved unstable in the presence of acid, undergoing dehydration to the corresponding enamine. In the end, the key functionalized pentacycle **25** was prepared in a total of eight steps from commercially available 2-methyl-2- cyclopenten-1-one. To demonstrate the application of our strategy, we synthesized (±)-emindole SB (**3**) in three steps from hydroxyaldehyde **25**. Thus, treatment of **25** with a large excess of (Z)-2-ethoxyvinyllithium followed by acidic workup,[32] subsequent hydrogenation of the

corresponding unsaturated aldehyde, and Wittig olefination of the resulting mixture of lactols afforded emindole SB (**3**) in 11 steps from the commercially available precursor.

In summary, we disclose a concise approach to the functionalized pentacyclic core of paxilline indole diterpenes featuring a new and potentially useful alkenylation of ketones to construct quaternary stereocenters and a tandem radical addition–aldol reaction sequence to access challenging vicinal quaternary stereocenters in a highly stereoselective manner. We also demonstrate a short synthesis of (±)-emindole SB, which serves as a proof of concept for our approach. We anticipate that the strategy reported herein will be applicable to the asymmetric synthesis of a wide variety of paxilline indole diterpenes as well as their unnatural analogues,[33] the implementation of which is currently underway.

ACKNOWLEDGMENTS

REFERENCES

(1). Knaus H-G; McManus OB; Lee SH; Schmalhofer WA; Garcia-Calvo M; Helms LMH; Sanchez M; Giangiacomo K; Reuben JP; Smith AB III; Kaczorowski GJ; Garcia ML Biochemistry 1994, 33, 5819. [PubMed: 7514038]

(2). Huang X-H; Tomoda H; Nisnida H; Masuma R; mura SJ Antibiot 1995, 48, 1.

(3). Meinke PT; Smith MM; Shoop WL Curr. Top. Med. Chem 2002, 2, 655 and references therein. [PubMed: 12052184]

(4). Tarui Y; Chinen T; Nagumo Y; Motoyama T; Hayashi T; Hirota H; Muroi M; Ishii Y; Kondo H; Osada H; Usui T ChemBioChem 2014, 15, 934. [PubMed: 24648249]

(5). Ogata M; Ueda J; Hoshi M; Hashimoto J; Nakashima T; Anzai K; Takagi M; Shin-ya KJ Antibiot 2007, 60, 645.

(6). Fan Y; Wang Y; Liu P; Fu P; Zhu T; Wang W; Zhu WJ Nat. Prod 2013, 76, 1328.

(7). (a) de Jesus AE; Gorst-Allman CP; Steyn PS; van Heerden FR; Vleggaar R; Wessels PL; Hull WEJ Chem. Soc., Perkin Trans 1 1983, 1863.(b) Byrne KM; Smith KS; Ondeyka JG J. Am. Chem. Soc 2002, 124, 7055. [PubMed: 12059229] (c) Uchida R; Tomoda H; mura S J. Antibiot 2006, 59, 298.

(8). (a) Smith AB III; Mewshaw RJ Am. Chem. Soc 1985, 107, 1769.(b) Smith AB III; Leenay TL Tetrahedron Lett 1988, 29, 2791.(c) Mewshaw R; Taylor MD; Smith AB III. J Org. Chem 1989, 54, 3449.(d) Smith AB III; Leenay TL J. Am. Chem. Soc 1989, 111, 5761.(e) Smith AB III; Sunazuka T; Leenay TL; Kingery-Wood JJ Am. Chem. Soc 1990, 112, 8197.(f) Smith AB III; Kingery-Wood J; Leenay TL; Nolen EG; Sunazuka TJ Am. Chem. Soc 1992, 114, 1438.(g) Smith AB III; Kanoh N; Ishiyama H; Hartz RA J. Am. Chem. Soc 2000, 122, 11254.(h) Smith AB III; Cui H Org. Lett 2003, 5, 587. [PubMed: 12583776] (i) Smith AB III; Kanoh N; Ishiyama H; Minakawa N; Rainier JD; Hartz RA; Cho YS; Cui H; Moser WM J. Am. Chem. Soc 2003, 125, 8228. [PubMed: 12837093] (j) Smith AB III; Cui H Helv. Chim. Acta 2003, 86, 3908.(k) Smith AB III; Davulcu AH; Kürti L Org. Lett 2006, 8, 1665. [PubMed: 16597136] (l) Smith AB III; Kürti L; Davulcu AH; Cho Y-S; Ishiyama H; Ohmoto K J. Org. Chem 2007, 72, 4596. [PubMed: 17511507] (m) Enomoto M; Morita A; Kuwahara S Angew. Chem., Int. Ed 2012, 51, 12833.(n) Asanuma A; Enomoto M; Nagasawa T; Kuwahara S Tetrahedron Lett 2013, 54, 4561. (o) Teranishi T; Murokawa T; Enomoto M; Kuwahara S Biosci., Biotechnol., Biochem 2015, 79, 11. [PubMed: 25184606] (p) Sharpe RJ; Johnson JS J. Am. Chem. Soc 2015, 137, 4968.

[PubMed: 25856767] (q) Zou Y; Melvin JE; Gonzales SS; Spafford MJ; Smith AB III. J. Am. Chem. Soc 2015, 137, 7095. [PubMed: 26029849]

(9). For recent discussions, see refs 8m, 8p, and 8q.

(10). Nozawa K; Nakajima S; Kawai K.-i. J. Chem. Soc., Perkin Trans 1 1988, 2607.

(11). For pioneering work on relevant hydrofunctionalization, see: Mukaiyama T; Yamada T Bull. Chem. Soc. Jpn 1995, 68, 17and references therein. Shenvi and Herzon propose HAT as the initial step in their related hydrogenations: (a) Iwasaki K; Wan KK; Oppedisano A; Crossley SWM; Shenvi RA J. Am. Chem. Soc 2014, 136, 1300. [PubMed: 24428640] (b) King SM; Ma X; Herzon SB J. Am. Chem. Soc 2014, 136, 6884. [PubMed: 24824195] For similar mechanistic considerations, see: (c) Tang L; Papish ET; Abramo GP; Norton JR; Baik M-H; Friesner RA; Rappé AJ Am. Chem. Soc 2003, 125, 10093.(d) Ishikawa H; Colby DA; Seto S; Va P; Tam A; Kakei H; Rayl TJ; Hwang I; Boger DL J. Am. Chem. Soc 2009, 131, 4904. [PubMed: 19292450]

(12). HAT-initiated conjugate addition: (a) Lo JC; Yabe Y; Baran PS J. Am. Chem. Soc 2014, 136, 1304. [PubMed: 24428607] (b) Lo JC; Gui J; Yabe Y; Pan C-M; Baran PS Nature 2014, 516, 343. [PubMed: 25519131]

(13). For selected examples of chemoselective HAT to polyenes, see: (a) Magnus P; Payne AH; Waring MJ; Scott DA; Lynch V Tetrahedron Lett 2000, 41, 9725.(b) Waser J; González-Gómez JC; Nambu H; Huber P; Carreira EM Org. Lett 2005, 7, 4249. [PubMed: 16146399] (c) Smith DM; Pulling ME; Norton JR J. Am. Chem. Soc 2007, 129, 770. [PubMed: 17243807] (d) Taniguchi T; Goto N; Nishibata A; Ishibashi H Org. Lett 2010, 12, 112. [PubMed: 19954168] (e) Leggans EK; Barker TJ; Duncan KK; Boger DL Org. Lett 2012, 14, 1428. [PubMed: 22369097] (f) Crossley SWM; Barabé F; Shenvi RA J. Am. Chem. Soc 2014, 136, 16788. [PubMed: 25398144] (g) Ma X; Herzon SB Chem. Sci 2015, 6, 6250. [PubMed: 30090243]

(14). For selected examples of radical conjugate additions to form quaternary carbons, see: (a) Barton DHR; Crich D Tetrahedron Lett 1985, 26, 757.(b) Okada K; Okamoto K; Morita N; Okubo K; Oda MJ Am. Chem. Soc 1991, 113, 9401.(c) Schnermann MJ; Overman LE Angew. Chem., Int. Ed 2012, 51, 9576.(d) Sun Y; Li R; Zhang W; Li A Angew. Chem., Int. Ed 2013, 52, 9201.(e) Lackner GL; Quasdorf KW; Overman LE J. Am. Chem. Soc 2013, 135, 15342. [PubMed: 24074152] (f) Chu L; Ohta C; Zuo Z; MacMillan DW C. J. Am. Chem. Soc 2014, 136, 10886.(g) Zhou S; Zhang D; Sun Y; Li R; Zhang W; Li A Adv. Synth. Catal 2014, 356, 2867.(h) Müller DS; Untiedt NL; Dieskau AP; Lackner GL; Overman LE J. Am. Chem. Soc 2015, 137, 660. [PubMed: 25563555] (i) Chinzei T; Miyazawa K; Yasu Y; Koike T; Akita M RSC Adv 2015, 5, 21297.(j) Lackner GL; Quasdorf KW; Pratsch G; Overman LE J. Org. Chem 2015, 80, 6012. [PubMed: 26030387] (k) Pratsch G; Lackner GL; Overman LE J. Org. Chem 2015, 80, 6025. [PubMed: 26030520] (l) Nawrat CC; Jamison CR; Slutskyy Y; MacMillan DWC; Overman LE J. Am. Chem. Soc 2015, 137, 11270. [PubMed: 26322524]

(15). For relevant aldol reactions, see: Isayama S; Mukaiyama T Chem. Lett 1989, 2005.

(16). (a) Kosugi M; Hagiwara I; Migita T Chem. Lett 1983, 12, 839.(b) Yamaguchi M; Tsukagoshi T; Arisawa MJ Am. Chem. Soc 1999, 121, 4074.(c) Ooi T; Goto R; Maruoka KJ Am. Chem. Soc 2003, 125, 10494.(d) Su W; Raders S; Verkade JG; Liao X; Hartwig JF Angew. Chem., Int. Ed 2006, 45, 5852.(e) Datta GK; Larhed M Org. Biomol. Chem 2008, 6, 674. [PubMed: 18264566] (f) Grigalunas M; Ankner T; Norrby P-O; Wiest O; Helquist PJ Am. Chem. Soc 2015, 137, 7019.

(17). See refs 16a, 16b, and 16e.

(18). (a) Staben ST; Kennedy-Smith JJ; Huang D; Corkey BK; LaLonde RL; Toste FD Angew. Chem., Int. Ed 2006, 45, 5991.(b) Schäfer C; Miesch M; Miesch L Chem. - Eur. J 2012, 18, 8028. [PubMed: 22674788]

(19). For pioneering work on indium(III)-mediated alkenylation of ketene silyl acetals, see: Nishimoto Y; Moritoh R; Yasuda M; Baba A Angew. Chem., Int. Ed 2009, 48, 4577.

(20). For relevant indium(III)-catalyzed alkenylation, see: Nakamura M; Endo K; Nakamura EJ Am. Chem. Soc 2003, 125, 13002.

(21). Umbreit MA; Sharpless KB J. Am. Chem. Soc 1977, 99, 5526.

(22). Shenvi, RA; personal communication.

(23). An elegant 19-step synthesis of hydroxyaldehyde (−)-9 from 2-methyl-1,3-cyclohexadione was recently reported. See ref 8q.

(24). Relative configuration of the decalin fragment of **16** was confirmed by reduction to the corresponding triol, which proved identical by ^{1}H and ^{13}C NMR analysis to the product of double reduction of compound **9**. Relative configuration of the cyclopentanol fragment of **16** was established by NOE experiments.

(25). Ethylene glycol and 1,2-dichloroethane are immiscible; therefore, the concentration of alcohols in the 1,2-dichloroethane phase is expected to be significantly lower than in ethanol, decreasing the extent of intermolecular hemiacetalization. The reagents appear to dissolve preferentially in the 1,2-dichloroethane phase.

(26). Relative configurations of compounds 19 and 20 were established by NOE experiments.

(27). Chbani M; Païs M; Delauneux J-M; Debitus C J. Nat. Prod 1993, 56, 99. [PubMed: 8450325]

(28). Vaswani RG; Day JJ; Wood JL Org. Lett 2009, 11, 4532. [PubMed: 19810762]

(29). Parikh JR; Doering W; von E J. Am. Chem. Soc 1967, 89, 5505.

(30). Aldehyde 24 is formed with high diastereoselectivity (dr > 10:1). Complete stereochemical assignment of 24 was not determined.

(31). (a) Arai E; Tokuyama H; Linsell MS; Fukuyama T Tetrahedron Lett 1998, 39, 71.(b) Evans DA; Borg G; Scheidt KA Angew. Chem., Int. Ed 2002, 41, 3188.

(32). Lau KSY; Schlosser MJ Org. Chem 1978, 43, 1595.

(33). For asymmetric cuprate additions to 2-methyl-2-cyclopenten-1-one, see: Calvo BC; Madduri AVR; Harutyunyan SR; Minnaard AJ Adv. Synth. Catal 2014, 356, 2061.
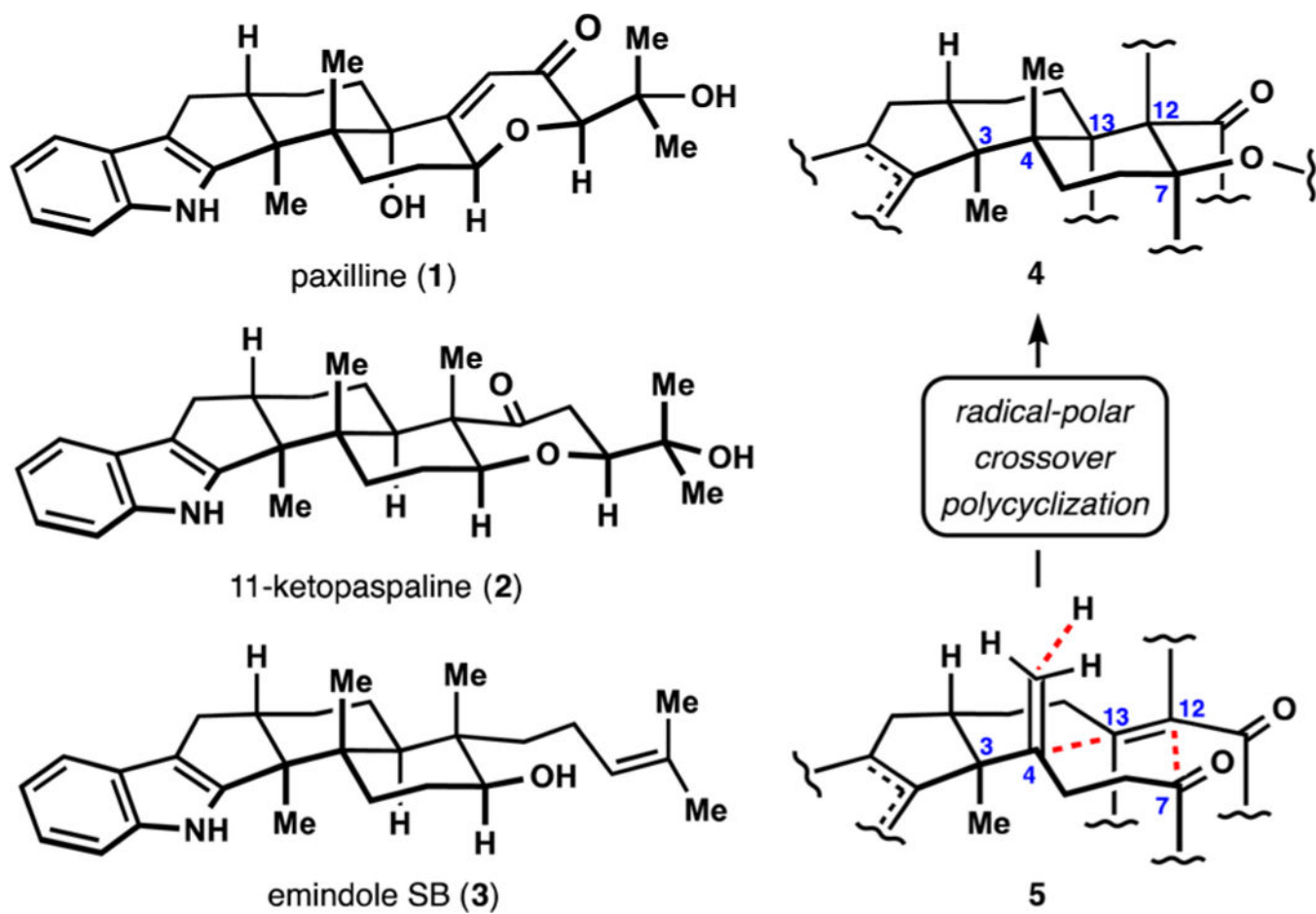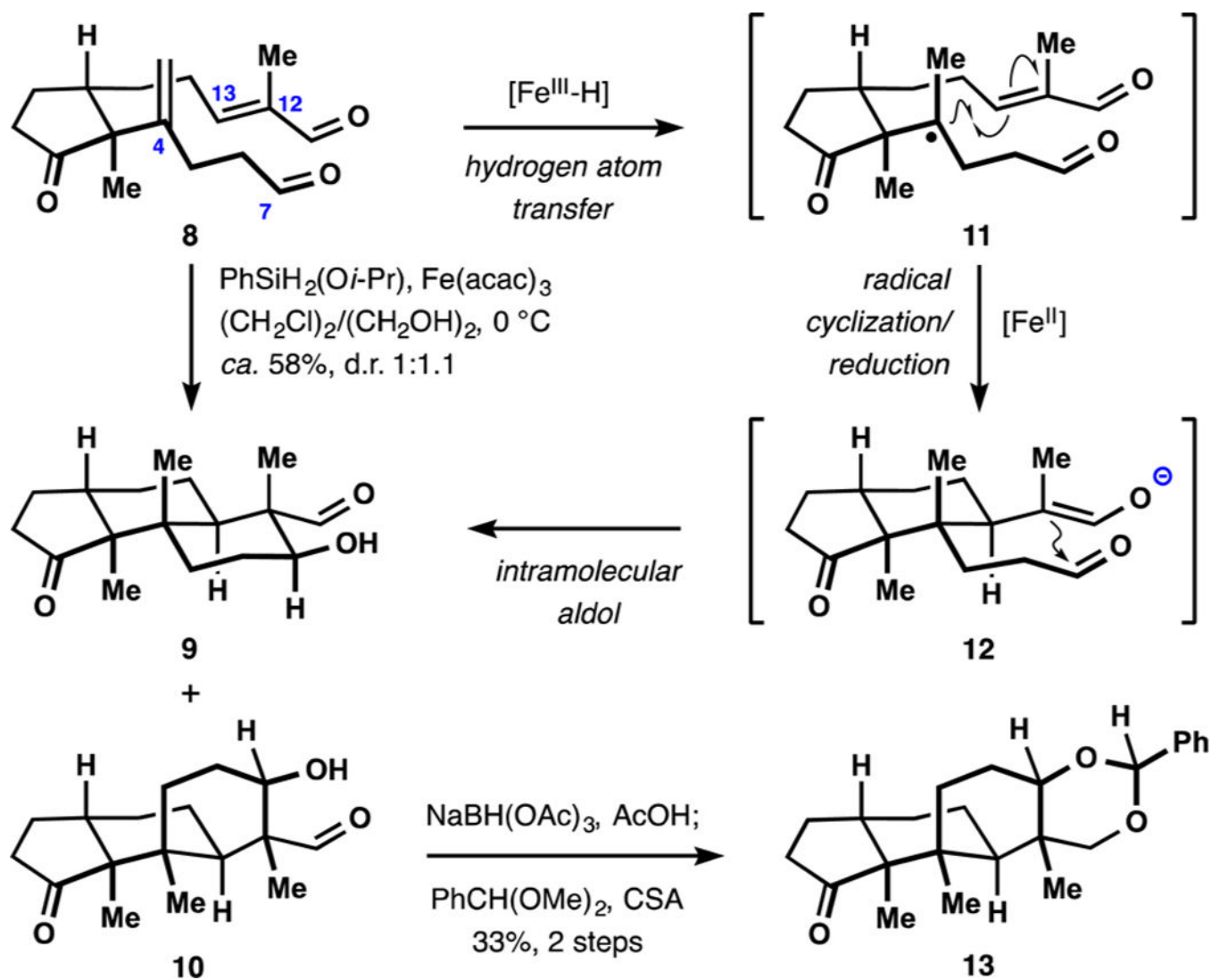
Figure 1.
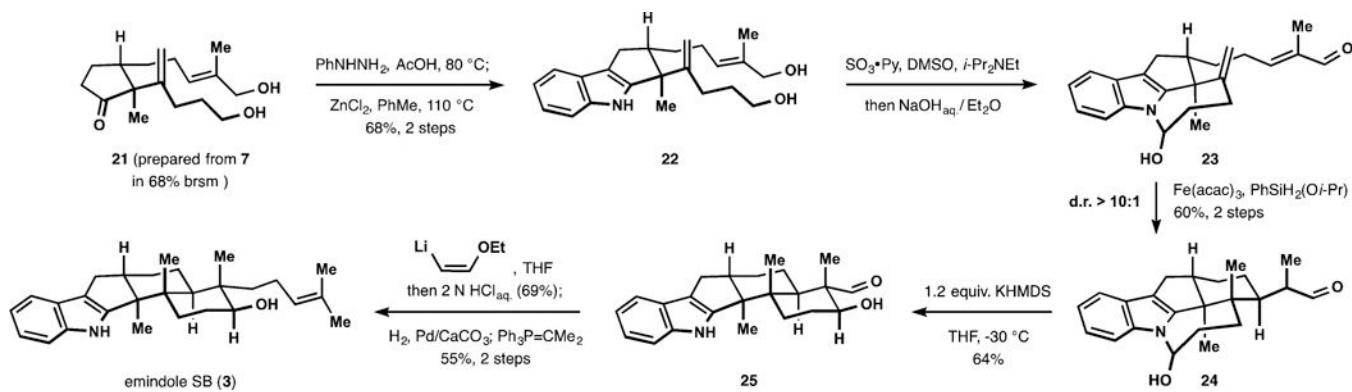Representative paxilline indole diterpenes.
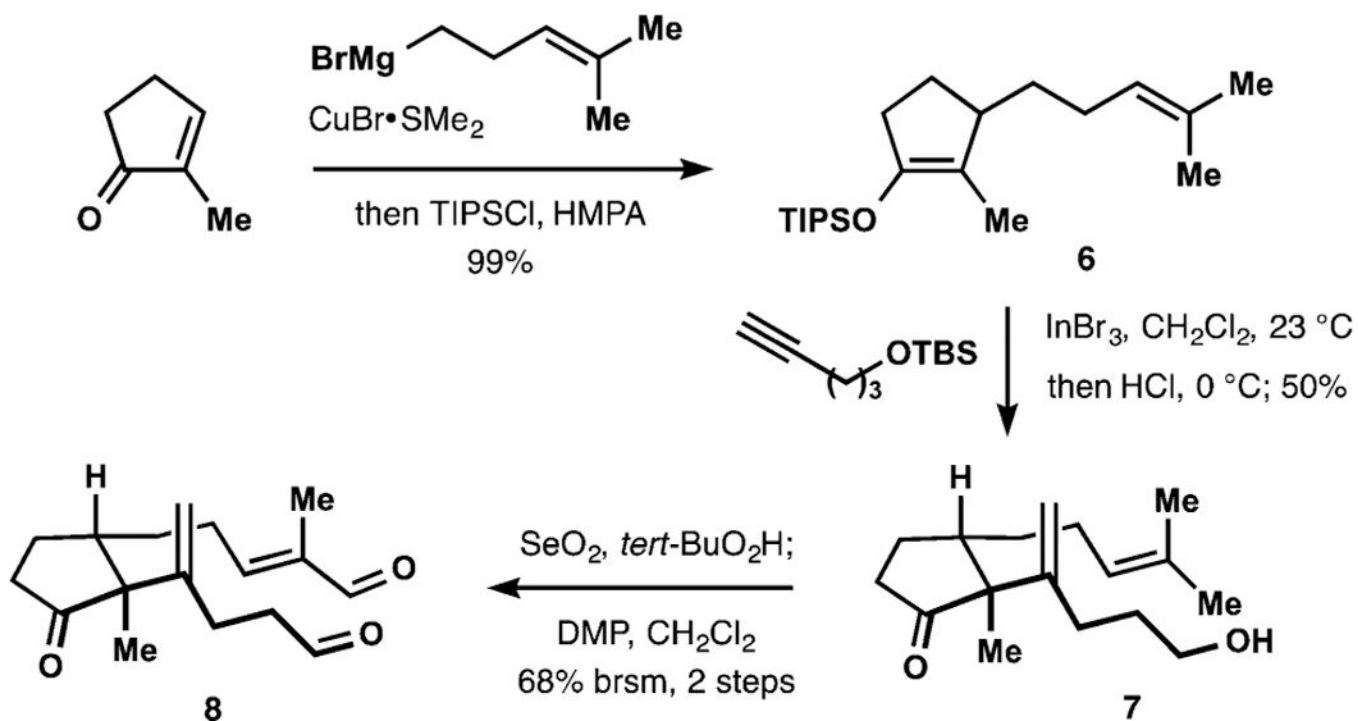
Scheme 1.
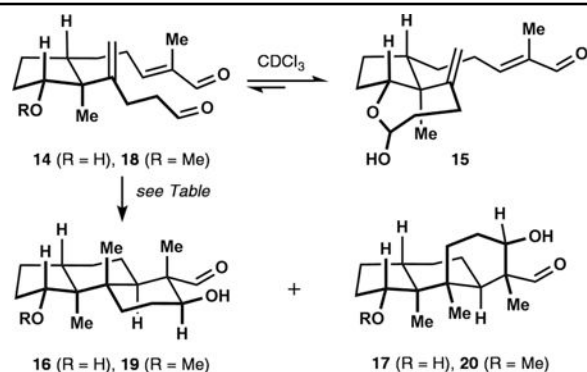Synthesis of the Polycyclization Precursor

Scheme 2.
Polycyclization En Route to the Tricyclic Core

Scheme 3.
Synthesis of (±)-Emindole SB (**3**)

Table 1.

Tether-Controlled Polycyclization

14 (R = H), **18** (R = Me)   **15**

16 (R = H), **19** (R = Me)   **17** (R = H), **20** (R = Me)

entry	conditions	ratio[a]
1	**14**, Fe(acac)$_3$, PhSiH$_2$(Oi-Pr), (CH$_2$CI)$_2$/ (CH$_2$OH)$_2$, 0 °C	5.0 (**16**) : 1.0 (**17**)
2	**14**, Fe(acac)$_3$, PhSiH$_2$(Oi-Pr), (CH$_2$CI)$_2$/ (CH$_2$OH)$_2$, −20 °C	7.1 (**16**) : 1.0 (**17**)
3	**14**, Fe(acac)$_3$, PhSiH$_2$(Oi-Pr), (CH$_2$CI)$_2$/ (CH$_2$OH)$_2$, 23 °C	3.1 (**16**) : 1.0 (**17**)
4	**14**, Fe(acac)$_3$, PhSiH$_2$(Oi-Pr), EtOH, 0 °C	1.5 (**16**): 1.0 (**17**)
5	**18**, Fe(acac)$_3$, PhSiH$_2$(Oi-Pr), (CH$_2$CI)$_2$ / (CH$_2$OH)$_2$, 0 °C	1.6 (**19**): 1.0 (**20**)
6	**18**, Fe(acac)$_3$, PhSiH$_2$(Oi-Pr), (CH$_2$CI)$_2$ / (CH$_2$OH)$_2$, 23 °C	1.9 (**19**) : 1.0 (**20**)
7	**18**, Fe(acac)$_3$, PhSiH$_2$(Oi-Pr), EtOH, 0 °C	1.0 (**19**) : 1.4 (**20**)

[a]According to integration of aldehyde peaks in ^{1}H NMR spectra of crude reaction mixtures.