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Total syntheses of enantiomerically enriched *R*-(+)- and *S*-(−)-deplancheine†

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Total syntheses of indoloquinolizidine alkaloid (±)-, *R*-(+)-, and *S*-(−)-deplancheine are described here. The synthesis features an enantioselective intramolecular formal aza-[3 + 3] cycloaddition for the construction of the quinolizidine CD-ring. This application serves to introduce a new synthetic strategy for the synthesis of indoloquinolizidine alkaloids.

Introduction

Indole alkaloids have attracted strong interest from both chemists and biologists for decades because of their diverse medicinal properties.[1–5] The core structure in many indole alkaloids such as deplancheine (**1**, see Fig. 1),[6] tangutorine (**2**),[7] geissoschizine (**3**),[8] yohimbine (**4**), and reserpine (**5**),[1–5,9–11] is an indolo[2,3-*a*]quinolizine or indoloquinolizidine (see **6** in the box), in which the *S*-(−)-enantiomer of **6** is also a natural product.[12] *R*-(+)-Deplancheine (**1**), isolated from the New Caledonian plant *Alstonia deplanchei* van Heurck and Mueller Arg. (stem and bark),[5a] is one of the simplest indoloquinolizidines. It has subsequently been identified in a related plant *Alstonia undulata* Guillaum[5b–d] and from the South American tree *Aspidosperma marcgravianum* Woodson.[5e]

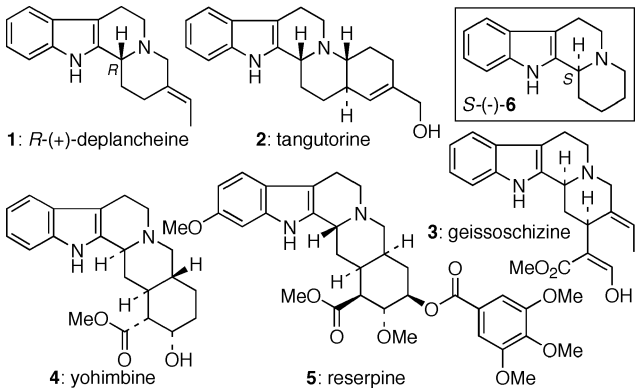
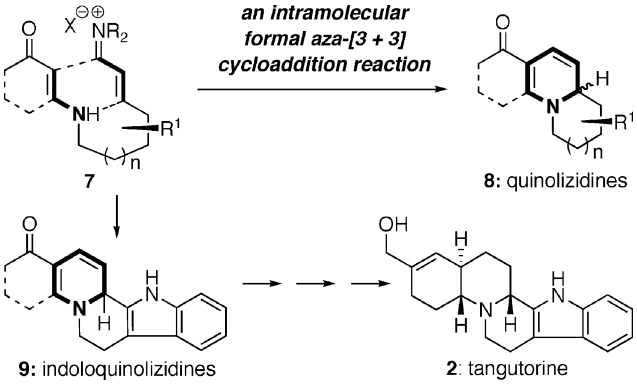


Fig. 1

Because of its simple structure, deplancheine (**1**) has become an often synthesized natural product to demonstrate new synthetic methodologies for the synthesis of indoloquinolizidine alkaloids.[13–15] Meyers' synthesis[15] of *S*-(−)-deplancheine (**1**) firmly established its actual absolute configuration. Most syntheses of the indoloquinolizidine natural products have been accomplished using the Pictet–Spengler cyclization.[10,11,16–18]

We became interested in deplancheine (**1**) because of our development in a formal aza-[3 + 3] cycloaddition method.[19–25] The intramolecular variant of this annulation strategy using vinylogous amides **7** tethered with an α,β-unsaturated iminium moiety represents a novel and stereoselective approach toward the synthesis of quinolizidines **8** or indoloquinolizidines **9** (Scheme 1).[23]

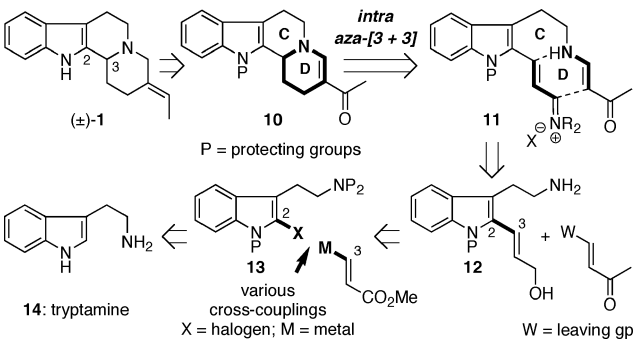


Scheme 1

We have communicated recently an application of this strategy in a total synthesis of (±)-tangutorine (**2**).[25,26] We wish to report here full details related to total syntheses of (±)-, *R*-(+)-, and *S*-(−)-deplancheine featuring an enantioselective intramolecular formal aza-[3 + 3] cycloaddition reaction.

Results and discussion

As outlined in Scheme 2, (±)-deplancheine (**1**) can be derived from the known pentacycle **10**,[14c] in which the quinolizidine CD-ring should be attainable *via* the intramolecular aza-[3 + 3] cycloaddition of vinylogous amide **11** that is tethered to an α,β-unsaturated iminium ion. Vinylogous amide **11** could be envisioned from condensing amino alcohol **12** with a β-diketone equivalent followed by oxidation of the allyl alcohol moiety. Amino alcohol **12** would be prepared from 2-bromo-tryptamine **13** *via* a cross-coupling process such as Heck-coupling with a



Scheme 2

† Electronic supplementary information (ESI) available: experimental procedures, ^{1}H NMR spectra, and characterizations for all new compounds. See http://www.rsc.org/suppdata/ob/b5/b503862f/

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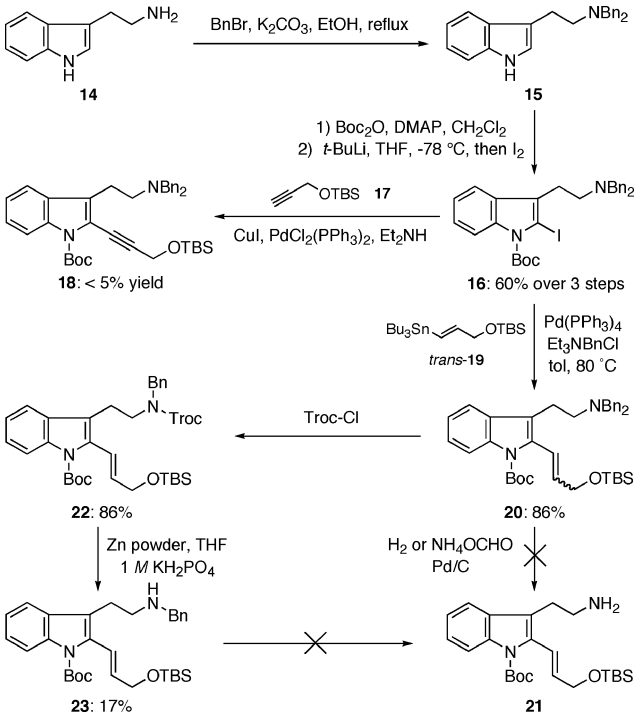
suitable 3-carbon synthon, and the preparation of **13** would commence with tryptamine **14**. It is noteworthy that a Heck-coupling[27] could be employed for constructing the C2–C3 bond[16–18] in place of the frequently used classic Pictet–Spengler cyclization.

Our immediate problems were associated with finding a suitable amino-protecting group for tryptamine **14** that would survive the functionalization at C2 and the subsequent cross-coupling reaction. As shown in Scheme 3, the first intermediate targeted for this purpose was the 2-iodo-*N*,*N*-dibenzyl-*N*-Boc-tryptamine **16**. Reaction of tryptamine **14** with BnBr in refluxing EtOH in the presence of K_2CO_3 afforded the known dibenzylamine **15**.[28] After capping the indole nitrogen with a Boc group, treatment of the doubly protected tryptamine intermediate with *t*-BuLi followed by quenching with iodine afforded the desired halogenated product **16** in 60% yield over 3 steps.

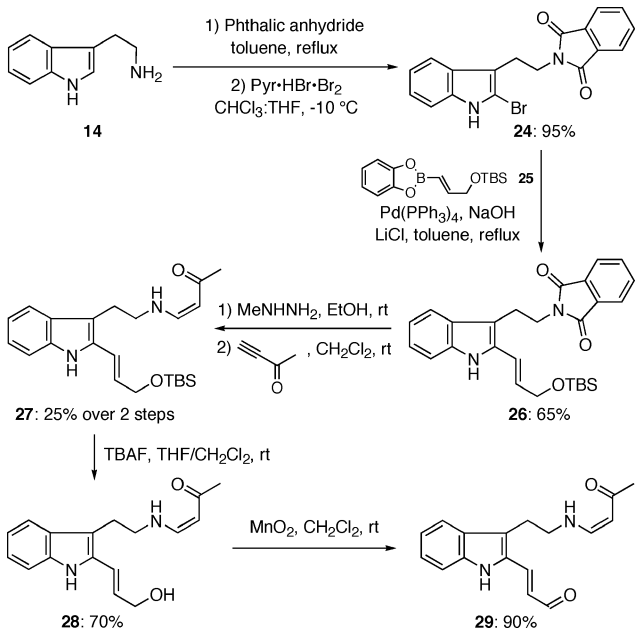


Scheme 3

With iodide **16** in hand, several coupling methods[29] were investigated. Initially, a Sonogashira coupling[30] with propargyl silyl ether **17**[31] was pursued (Scheme 3). Despite screening a large number of conditions, the desired coupling product **18** was only isolated in <5% yield at best, and the major by-product was consistently the homo-coupled alkyne.

Consequently, both *cis* and *trans* isomers of vinyl stannane **19** were obtained *via* hydrostannylation[32] of **17**, and the *trans* isomer could be readily separated from *cis*-**19** using silica gel column chromatography. The ensuing Stille coupling[33] proved to be effective using *trans*-**19**. The desired coupling product **20** was isolated in good yield but with partial isomerization of the olefin. Unfortunately, the subsequent reductive debenzylation could not be accomplished without severe decompositions, including reduction of the allylic ether. Dealkylation of one benzyl group in **20** in exchange for a trichloroethoxycarbonyl (Troc) protecting group did give **22**.[34] Further reductive removal of the Troc group using Zn powder led to **23** in low yields, but attempts to remove the remaining benzyl group also failed.

An alternative protection of the tryptamine amino group was needed. Toward this goal, preparation of 2-bromo-*N*-phthalimidotryptamine **24** was accomplished in 95% yield over two steps from tryptamine **14**[35] (Scheme 4). The ensuing Suzuki–Miyaura coupling[36] of bromide **24** with vinyl catecholborane



Scheme 4

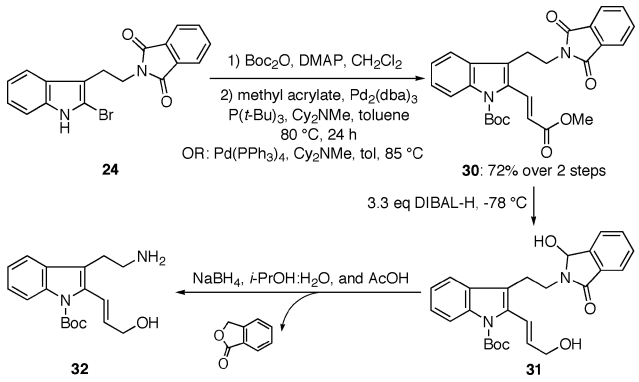
25, obtained from hydroboration of propargyl silyl ether **17**,[37] afforded the desired vinyl indole **26** in good yield, albeit only on very small scales (≤1 mmol).

Treatment of vinyl indole **26** with methyl hydrazine gave the corresponding free amine, and the addition of the free amine to 3-butyn-2-one in anhydrous CH_2Cl_2 afforded vinylogous amide **27** but only in 25% overall yield from **26**. Desilylation using TBAF followed by oxidation with MnO_2 furnished the key precursor **29** for the formal aza-[3 + 3] cycloaddition in 90%. However, attempts at the key formal cycloaddition failed using **29** because of both the small reaction scale and problems stemming from the unprotected indole nitrogen.

The short supply in materials was caused by the poor isolated yield (10–25%) obtained on larger reaction scales (≥2.5 mmol) used for the Suzuki–Miyaura coupling of **24**. This failure was likely linked to the stability of vinyl catecholborane **25**, which slowly decomposed upon standing or during attempts to re-purify it by chromatography or vacuum distillation.

The use of another coupling protocol became necessary and Fukuyama's[27] Heck coupling protocol[38] using acrylic acid esters proved to be useful. In addition, we elected to reinstall a Boc protecting group for the indole nitrogen to minimize potential side reactions throughout the synthetic sequence.

As shown in Scheme 5, treatment of bromide **24** with Boc_2O in the presence of DMAP gave the Boc protected indole intermediate, which was subjected to Fu and Littke's[39] improved conditions: excess methyl acrylate and a 1 : 1 ratio of Pd catalyst and the bulky P*t*-Bu_3 ligand. Phthalimido ester **30** was obtained

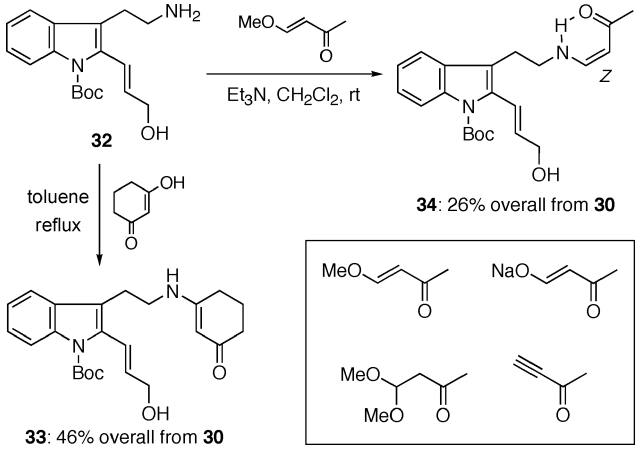


Scheme 5

in near quantitative yield. It was later found that the use of $Pd(PPh_3)_4$ was also effective.

The treatment of ester **30** with methyl hydrazine succeeded in cleavage of the phthalimido group, but addition to the acrylate moiety was also observed, which had been a concern. An alternative deprotection of the phthalimide group followed Ganem's reductive sequence.[40] Therefore, reduction of **30** with slightly more than 3 equiv of DIBAL-H cleanly afforded hydroxyaminal **31**. After aqueous workup to remove aluminium salts, further reduction with $NaBH_4$ afforded an amide intermediate, which led to the free amine alcohol **32** upon treatment of the reduction mixture with HOAc.

Attempts to purify amino alcohol **32** were not successful, owing to the polarity of the product as well as the large amount of undesirable salts within the reaction mixture. As such, the intermediate amino alcohol **32** was only characterized after the formation of a vinylogous amide such as **33** (see Scheme 6), which was employed for the formal aza-[3 + 3] cycloaddition reaction en route to (±)-tangutorine (**2**).[25]

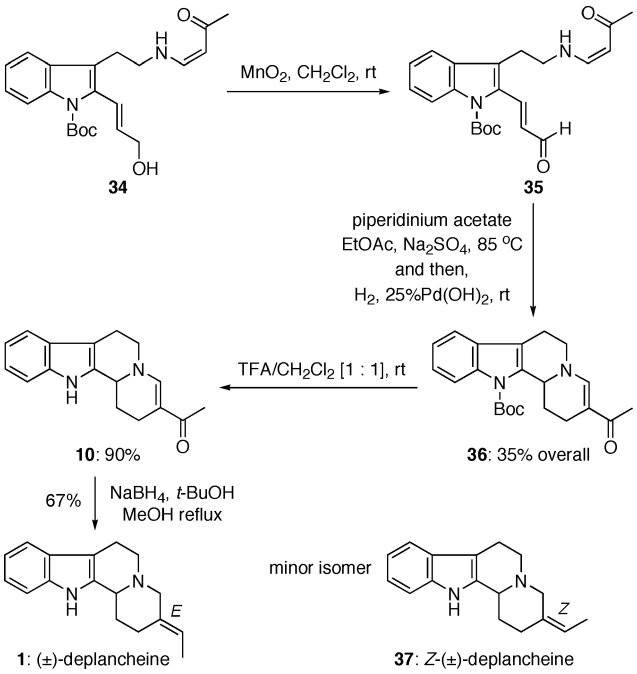


Scheme 6

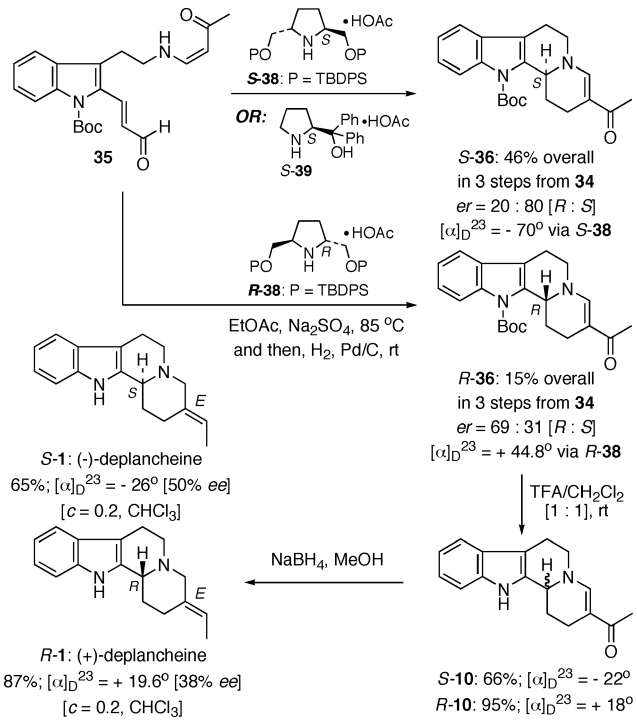
For the synthesis of (±)-deplancheine (**1**), several reagents for the formation of vinylogous amide were analyzed (Scheme 6). The utility of four different amide precursors was screened: 3-butyn-2-one,[41] acetylacetaldehyde dimethyl acetal,[42] 4-methoxy-3-buten-2-one,[43] and acetylacetaldehyde sodium salt.[44] The formation of the vinylogous amide was equally effective, and the use of 4-methoxy-3-buten-2-one was chosen based on its greatly reduced cost and vinylogous amide **34** was isolated in 26% overall yield starting from **30**. It is noteworthy that vinylogous amide **34** was distinctly in the *Z*-configuration, based on ^{1}H NMR coupling constants. In this configuration, a hydrogen bond between the NH and the carbonyl can occur, which results in a well-defined peak for the NH within the ^{1}H NMR spectrum.

The key formal aza-[3 + 3] cycloaddition of vinylogous amide **35**, obtained from the Mn_2O oxidation of **34**, was then examined (Scheme 7). The use of piperidinium acetate salt proved to be effective, leading to indoloquinolizidine tetracycle **36** after hydrogenation in 35% yield over 3 steps. Simple treatment of **36** with a 1 : 1 mixture of TFA and CH_2Cl_2 gave the known tetracycle **10**, which matched that reported by Lounasmaa,[14c] thereby completing a formal synthesis of (±)-deplancheine. To complete the total synthesis, **10** was reduced using $NaBH_4$ in refluxing *t*-BuOH and MeOH[13h] to give (±)-deplancheine **1** in 67% yield. A minor isomer **37** was also found and was believed to be the *Z*-isomer of (±)-deplancheine **1**.

To complete the total syntheses of *R*-(+)-**1** and *S*-(−)-**1**, vinylogous amide **35** was subjected to an enantioselective aza-[3 + 3] formal cycloaddition protocol[45] using chiral amine salts *S*-**38** and *S*-**39** (Scheme 8). Indoloquinolizidine *S*-**36** was found in 69% overall yield after hydrogenation with an er of 80 : 20[46] in favor of the *S*-enantiomer. When using the chiral amine salt



Scheme 7



Scheme 8

S-**39**, the ratio was only 68 : 32 also in favor of the *S*-enantiomer. Removal of the Boc group followed by $NaBH_4$ reduction gave *S*-(−)-**1** in 42% yield over two steps with the *R* : *S* ratio = 25 : 75[46] and $[\alpha]_D^{23} = -26°$ [*c* = 0.2, $CHCl_3$] (an equivalent of 50% ee; lit.[13a,15] $[\alpha]_D^{23} = -52°$ [*c* = 1.0, $CHCl_3$]).

When using the chiral amine salt *R*-**38**, the HPLC ratio was 69 : 31 in favor of *R*-**36**. Deprotection of the Boc group followed by $NaBH_4$ reduction gave *R*-(+)-**1** in 83% overall yield with $[\alpha]_D^{23} = -19.6°$ [*c* = 0.2, $CHCl_3$] (an equivalent of 38% ee; lit.[13a,15] $[\alpha]_D^{23} = +52°$ [*c* = 1.0, $CHCl_3$]).

Conclusion

We have described here the total syntheses of the indoloquinolizidine natural products (±)-, *R*-(+)-, and *S*-(−)-deplancheine

in 10 steps with an overall yield in the range of 1.4–2.7%. The synthesis features an enatioselective intramolecular formal aza-[3 + 3] cycloaddition reaction of a vinylogous amide to furnish the quinolizidine CD-ring. This application serves to introduce a new synthetic strategy for the synthesis of indole alkaloids.

Acknowledgements

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References

1 *Dictionary of Alkaloids*, ed. I. W. Southon and J. Buckingham, Chapman and Hall, London, 1989.
2 (*a*) R. B. Herbert, in The Monoterpenoid Indole Alkaloids, supplement to volume 25, part 4 of *The Chemistry of Heterocyclic Compounds*, J. E. Saxon, Wiley-Interscience, New York, 1994, ch. 1; (*b*) J. E. Saxon, in The Monoterpenoid Indole Alkaloids, supplement to volume 25, part 4 of *The Chemistry of Heterocyclic Compounds*, ed. J. E. Saxon, Wiley-Interscience, New York, 1994, ch. 8.
3 (*a*) J. E. Saxon, in *The Alkaloids*, ed. G. A. Cordell, Academic Press, New York, 1998, vol. 50 and 51; (*b*) M. Toyota and M. Ihara, *Nat. Prod. Rep.*, 1998, **15**, 327; (*c*) U. Scholz and E. Winterfeldt, *Nat. Prod. Rep.*, 2000, **17**, 349.
4 J. Bonjoch and D. Sole, *Chem. Rev.*, 2000, **100**, 3455.
5 A. I. Scott, *Acc. Chem. Res.*, 1970, **3**, 151.
6 (+)-Deplancheine (**1**) was initially isolated from the New Caledonian plant *Alstonia deplanchei* van Heurck et Mueller Arg. (Apocynaceae). See: (*a*) R. Besselièvre, H. P. Cosson, B. C. Das and H. P. Husson, *Tetrahedron Lett.*, 1980, **21**, 63. For subsequent isolations, see: (*b*) N. Petitfrere-Auvray, J. Vercauteren, G. Massiot, G. Lukacs, T. Sevenet, L. Le Men-Olivier, B. Richard and M. J. Jacquier, *Phytochemistry*, 1981, **20**, 1987; (*c*) D. Guillaume, A. M. Morfaux, B. Richard, G. Massiot, L. Le Men-Olivier, J. Pusset and T. Sevenet, *Phytochemistry*, 1984, **23**, 2407; (*d*) A. Cherif, G. Massiot, L. Le Men-Olivier, J. Pusset and S. Labarre, *Phytochemistry*, 1989, **28**, 667; (*e*) G. M. T. Robert, A. Ahond, C. Poupat, P. Potier, C. Jolles, A. Jousselin and H. Jacquemin, *J. Nat. Prod.*, 1983, **46**, 694.
7 J.-A. Duan, I. D. Williams, C.-T. Che, R.-H. Zhou and S.-X. Zhao, *Tetrahedron Lett.*, 1999, **40**, 2593.
8 (*a*) H. Rapoport, R. J. Windgassen, N. A. Hughes and T. P. Onak, *J. Am. Chem. Soc.*, 1960, **82**, 4404; (*b*) E. Wenkert and B. Wickberg, *J. Am. Chem. Soc.*, 1965, **87**, 1580.
9 (*a*) P. A. Shore and A. Giachetti, Reserpine: Basic and Clinical Pharmacology in *Handbook of Psychopharmacology*, ed. L. L. Iversen, S. D. Eversen, S. H. Snyder, Plenum, New York, 1978, vol. 10, p. 197; (*b*) J. M. Muller, E. Schlittler and H. J. Bein, *Experientia*, 1952, **8**, 338; (*c*) H. Pardell, *Am. J. Cardiol.*, 1990, **65**, 2H–5H; (*d*) R. Betarbet, T. B. Sherer and J. T. Greenamyre, *BioEssays*, 2002, **24**, 308.
10 C. Szántay, G. Blaskò, K. Honty and G. Dörnyei, Corynantheine, Yohimbine, and Related Alkaloids in *The Alkaloids: Chemistry and Pharmacology*, ed. A. Brossi, Academic, Orlando, 1986, vol. 27, p. 131.
11 J. Leonard, *Nat. Prod. Rep.*, 1999, **16**, 319.
12 For isolation, see: (*a*) S. R. Johns, J. A. Lamberton and J. L. Occolowitz, *J. Chem. Soc., Chem. Commun.*, 1966, 421; (*b*) S. R. Johns, J. A. Lamberton and J. L. Occolowitz, *Aust. J. Chem.*, 1966, **19**, 1951. For our recent total synthesis, see: (*c*) Y. Zhang, R. P. Hsung, X. Zhang, J. Huang, B. W. Slafer and A. Davis, *Org. Lett.*, 2005, **7**, 1047.
13 For the most recent total syntheses, see: (*a*) S. M. Allin, C. I. Thomas, K. Doyle and M. R. J. Elsegood, *J. Org. Chem.*, 2005, **70**, 357; (*b*) T. Itoh, Y. Matsuya, Y. Enomoto and A. Ohsawa, *Heterocycles*, 2001, **55**, 1165; (*c*) R. Lavilla, O. Coll, M. Nicolàs, B. A. Sufi, J. Torrents and J. Bosch, *Eur. J. Org. Chem.*, 1999, 2997; (*d*) M. Lounasmaa, K. Karinen and A. Tolvanen, *Heterocycles*, 1997, **45**, 1397; (*e*) M. Lounasmaa, P. Hanhinen and R. Jokela, *Heterocycles*, 1996, **43**, 443; (*f*) B. Tirkkonen, J. Miettinen, J. Salo, R. Jokela and M. Lounasmaa, *Tetrahedron*, 1994, **50**, 3537; (*g*) P. Rosenmund and M. Hosseini-Merescht, *Liebigs Ann. Chem.*, 1992, 1321; (*h*) P. J. Sankar, S. K. Das and V. S. Giri, *Heterocycles*, 1991, **32**, 1109; (*i*) T. Fujii, M. Ohba and N. Sasaki, *Chem. Pharm. Bull.*, 1989, **37**, 2822; (*j*) S. B. Mandal, V. S. Giri, M. S. Sabeena and S. C. Pakrashi, *J. Org. Chem.*, 1988, **53**, 4236; (*k*) K. Takasu, N. Nishida, A. Tomimura and M. Ihara, *J. Org. Chem.*, 2005, **70**, ASAP.
14 For some earlier syntheses, see: (*a*) L. Calabi, B. Danieli, G. Lesma and G. Palmisano, *Tetrahedron Lett.*, 1982, **23**, 2139; (*b*) L. E. Overman and T. C. Malone, *J. Org. Chem.*, 1982, **47**, 5297; (*c*) M. Hämeilä and M. Lounasmaa, *Acta Chem. Scand. Ser. B*, 1981, **35**, 217; (*d*) W. R. Ashcroft and J. A. Joule, *Tetrahedron Lett.*, 1980, **21**, 2341; (*e*) D. Thielke, J. Wegener and E. Winterfeldt, *Angew. Chem., Int. Ed. Engl.*, 1974, **13**, 602; (*f*) M. L. Rueppel and H. Rapoport, *J. Am. Chem. Soc.*, 1972, **94**, 3877; (*g*) K. E. Pfitzner and J. G. Moffatt, *J. Am. Chem. Soc.*, 1963, **85**, 3027.
15 For a total synthesis of *S*-(−)-deplancheine, see: A. I. Meyers, T. Sohda and M. F. Loewe, *J. Org. Chem.*, 1986, **51**, 3108. Also see ref. 13*a*.
16 For an excellent review, see: E. D. Cox and J. M. Cook, *Chem. Rev.*, 1995, **95**, 1797.
17 For some elegant examples of Pictet–Spengler cyclizations, see: (*a*) J. Yu, T. Wang, X. Liu, J. Deschamps, J. Flippen-Anderson, X. Liao and J. M. Cook, *J. Org. Chem.*, 2003, **68**, 7565; (*b*) J. Yu, X. Wearing and J. M. Cook, *Tetrahedron Lett.*, 2003, **44**, 543; (*c*) J. Yu, T. Wang, X. Wearing, J. Ma and J. M. Cook, *J. Org. Chem.*, 2003, **68**, 5852; (*d*) S. Zhao, X. Liao and J. M. Cook, *Org. Lett.*, 2002, **4**, 687.
18 For a recent example on catalytic asymmetric Pictet–Spengler cyclization, see: M. S. Taylor and E. N. Jacobsen, *J. Am. Chem. Soc.*, 2004, **126**, 10558.
19 For reviews, see: (*a*) R. P. Hsung, A. V. Kurdyumov and N. Sydorenko, *Eur. J. Org. Chem.*, 2005, 23; (*b*) H. A. Coverdale and R. P. Hsung, *Chemtracts*, 2003, **16**, 238; (*c*) R. P. Hsung, L.-L. Wei, H. M. Sklenicka, H. C. Shen, M. J. McLaughlin and L. R. Zehnder, *Trends in Heterocyclic Chemistry*, Research Trends, Poojapura, Trivandrum, India, 2001, vol. 7, p. 1.
20 For recent studies in this area, see: (*a*) K. M. Goodenough, W. J. Moran, P. Raubo and J. P. A. Harrity, *J. Org. Chem.*, 2005, **70**, 207; (*b*) M. M. Abelman, J. K. Curtis and D. R. James, *Tetrahedron Lett.*, 2003, **44**, 6527; (*c*) S. J. Hedley, W. J. Moran, D. A. Price and J. P. A. Harrity, *J. Org. Chem.*, 2003, **68**, 4286; (*d*) M.-Y. Chang, J. Y.-C. Lin, S. T. Chen and N.-C. Chang, *J. Chin. Chem. Soc.*, 2002, **49**, 1079; (*e*) S. J. Hedley, W. J. Moran, A. H. G. P. Prenzel, D. A. Price and J. P. A. Harrity, *Synlett*, 2001, 1596; (*f*) I. W. Davies, J.-F. Marcoux and P. J. Reider, *Org. Lett.*, 2001, **3**, 209; (*g*) I. W. Davies, M. Taylor, J.-F. Marcoux, J. Wu, P. G. Dormer, D. Hughes and P. J. Reider, *J. Org. Chem.*, 2001, **66**, 251; (*h*) P. Nemes, B. Balázs, G. Tóth and P. Scheiber, *Synlett*, 1999, 222; (*i*) D. H. Hua, Y. Chen, H.-S. Sin, P. D. Robinson, C. Y. Meyers, E. M. Perchellet, J.-P. Perchellet, P. K. Chiang and J.-P. Biellmann, *Acta Crystallogr., Sect. C*, 1999, **55**, 1698; (*j*) P. Benovsky, G. A. Stephenson and J. R. Stille, *J. Am. Chem. Soc.*, 1998, **120**, 2493; (*k*) D. Heber and Th. Berghaus, *J. Heterocycl. Chem.*, 1994, **31**, 1353; (*l*) K. Paulvannan and J. R. Stille, *Tetrahedron Lett.*, 1993, **34**, 215; K. Paulvannan and J. R. Stille, *Tetrahedron Lett.*, 1993, **34**, 6677.
21 N. Sydorenko, R. P. Hsung, O. S. Darwish, J. M. Hahn and J. Liu, *J. Org. Chem.*, 2004, **69**, 6732.
22 (*a*) H. M. Sklenicka, R. P. Hsung, M. J. McLaughlin, L.-L. Wei, A. I. Gerasyuto and W. W. Brennessel, *J. Am. Chem. Soc.*, 2002, **124**, 10435; (*b*) H. M. Sklenicka, R. P. Hsung, L.-L. Wei, M. J. McLaughlin, A. I. Gerasyuto, S. J. Degen and J. A. Mulder, *Org. Lett.*, 2000, **2**, 1161; (*c*) R. P. Hsung, L.-L. Wei, H. M. Sklenicka, C. J. Douglas, M. J. McLaughlin, J. A. Mulder and L. J. Yao, *Org. Lett.*, 1999, **1**, 509.
23 For intramolecular formal aza-[3 + 3] cycloaddition, see: L.-L. Wei, H. M. Sklenicka, A. I. Gerasyuto and R. P. Hsung, *Angew. Chem., Int. Ed.*, 2001, **40**, 1516.
24 M. J. McLaughlin, R. P. Hsung, K. C. Cole, J. M. Hahn and J. Wang, *Org. Lett.*, 2002, **4**, 2017.
25 S. Luo, C. A. Zificsak and R. P. Hsung, *Org. Lett.*, 2003, **5**, 4709.
26 For two other total syntheses of tangutorine, see: (*a*) S. Luo, J. Zhao and H. Zhai, *J. Org. Chem.*, 2004, **69**, 4548; (*b*) T. Putkonen, A. Tolvanen, R. Jokela, S. Caccamese and N. Parrinelloc, *Tetrahedron*, 2003, **59**, 8589 and references cited therein.
27 S. Kobayashi, T. Ueda and T. Fukuyama, *Synlett*, 2000, 883.
28 (*a*) R. L. Parsons, J. D. Berk and M. E. Kuehne, *J. Org. Chem.*, 1993, **58**, 7482; (*b*) K. M. Czerwinski and C. A. Zificsak, unpublished results.
29 For a review of palladium coupling reactions of heterocycles, including indoles, see: J. J. Li and G. W. Gribble, Palladium in Heterocyclic Chemistry: A Guide for the Synthetic Chemist, *Tetrahedron Organic Chemistry Series Vol. 20*, Elsevier, Oxford UK, 2000.
30 K. Sonogashira, in *Metal-Catalyzed Cross-Coupling Reactions*, ed. F. Diederich and P. J. Stang, Wiley-VCH, Weinheim, Germany, 1998, p. 203.
31 P. A. Wender, S. M. Sieburth, J. J. Petraitis and S. K. Singh, *Tetrahedron*, 1981, **37**, 3967.
32 G. Oddon and D. Uguen, *Tetrahedron Lett.*, 1998, **39**, 1153.
33 V. Farina, V. Krishnamurthy and W. J. Scott, *Org. React.*, 1997, **50**, 1.
34 H. Kapnang and G. Charles, *Tetrahedron Lett.*, 1983, **24**, 3233.

35 L. Chu, M. H. Fisher, M. T. Goulet and M. J. Wyvratt, *Tetrahedron Lett.*, 1997, **38**, 3871.
36 N. Miyaura and A. Suzuki, *Chem. Rev.*, 1995, **95**, 2457.
37 W. R. Roush, personal communication. The boronic acid has been described but without experimental detail, see: (*a*) J. Uenishi, R. Kawahama, O. Yonemitsu, A. Wada and M. Ito, *Angew. Chem., Int. Ed.*, 1998, **37**, 320; (*b*) W. R. Roush, J. A. Champoux and B. C. Peterson, *Tetrahedron Lett.*, 1996, **37**, 8989.
38 R. F. Heck, *Org. React.*, 1982, **27**, 345.
39 A. F. Littke and G. C. Fu, *J. Am. Chem. Soc.*, 2001, **123**, 6989.
40 J. O. Osby, M. G. Martin and B. Ganem, *Tetrahedron Lett.*, 1984, **25**, 2093.
41 J. D. Winkler, J. Axten, A. H. Hammach, Y.-S. Kwak, U. Lengweiler, M. J. Lucero and K. N. Houk, *Tetrahedron*, 1998, **54**, 7045.
42 D. M. Burness, *J. Org. Chem.*, 1956, **21**, 97.
43 H.-J. Teuber and R. Quintanilla-Licea, *J. Prakt. Chem./Chem.-Ztg.*, 1994, **336**, 452.
44 (*a*) R. N. Schut, *Chem. Ind. (London)*, 1960, 1246–1247; (*b*) For the preparation of the sodium salt, see: W. S. Johnson, E. Woroch and F. J. Mathews, *J. Am. Chem. Soc.*, 1947, **69**, 566.
45 A. I. Gerasyuto, R. P. Hsung, N. Sydorenko and B. W. Slafer, *J. Org. Chem.*, 2005, **70**, ASAP.
46 Enantiomeric ratios were determined on an Agilent HPLC instrument equipped with a Chiralcel OD column.