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Divergent enantioselective synthesis of hapalindole-type alkaloids using catalytic asymmetric hydrogenation of a ketone to construct the chiral core structure†

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A divergent enantioselective approach to hapalindole-type alkaloids is described. The route features a ruthenium-catalyzed asymmetric hydrogenation of a ketone *via* DKR to construct the chiral *trans*-1-indolyl-2-isopropenylcyclohexane skeleton and a switchable sequence of methylation and acetylation/aldol reaction to access a chiral quaternary stereocenter. (+)-Hapalindole Q (**1**, 13 steps, 5.9% overall yield), (–)-12-*epi*-hapalindole Q isonitrile (**2**, 15 steps, 5.5% overall yield), (–)-hapalindole D (**3**, 14 steps, 2.3% overall yield), and (+)-12-*epi*-fischerindole U isothiocyanate (**4**, 14 steps, 3.0% overall yield) were synthesized in 13–15 steps from a commercially available material to demonstrate the application of this approach.

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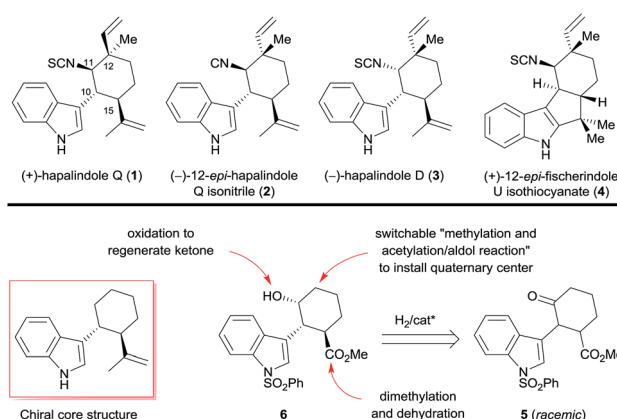
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Introduction

Owing to the unique and diverse molecular architectures of hapalindole-type alkaloids and their broad range of biological activities, they have recently attracted great interest as synthetic targets.¹ Since these hybrid isoprenoid–indole alkaloids derived from tryptophan and geraniol pyrophosphate were first isolated by Moore *et al.* in 1984 from the Stigonemataceae family of cyanobacteria,² more than 70 have been identified.³ Because they exhibit diverse chirality and have a quaternary stereocenter, they are challenging targets for enantioselective synthesis.⁴ Several hapalindole-type alkaloids have been synthesized in enantiomerically pure form by means of chiral pool⁵ and chiral resolution approaches.⁶ For example, Vaillancourt and Albizati synthesized (+)-hapalindole Q (**1**, Scheme 1) from (+)-camphor.^{5a} Fukuyama and Chen^{5b} and Natsume *et al.*^{5c} independently synthesized (–)-hapalindoles G and O from (–)-carvone. Baran *et al.* synthesized (+)-hapalindole Q (**1**), (–)-12-*epi*-fischerindole U isothiocyanate, (–)-fischerindole G, (+)-fischerindole I, and (+)-welwitindolinone A from (–)-carvone,^{5d–g} *ent*-12-*epi*-fischerindole G and 12-*epi*-fischerindole I from (+)-carvone,^{5g} and (–)-hapalindole U and (+)-ambiguine H from

(+)-*p*-menth-1-en-9-ol.^{3,5f} However, only one catalytic enantioselective synthesis of a hapalindole-type alkaloid has been reported: Kinsman and Kerr⁷ used an organocatalyzed asymmetric Diels–Alder reaction as a key step in the synthesis of (+)-hapalindole Q (**1**).

Recently, we developed a protocol for the catalytic asymmetric hydrogenation of racemic α -substituted ketones *via* dynamic kinetic resolution (DKR), allowing for the highly efficient enantioselective synthesis of natural products such as galantamine, lycorane, and Δ^9 -THC.⁸ During our ongoing work on the enantioselective construction of quaternary and/or contiguous stereocenters, we noted that a chiral *trans*-1-indolyl-2-isopropenylcyclohexane skeleton is a core structure present in various



Scheme 1 Selected hapalindole-type alkaloids and our divergent enantioselective synthetic strategy.

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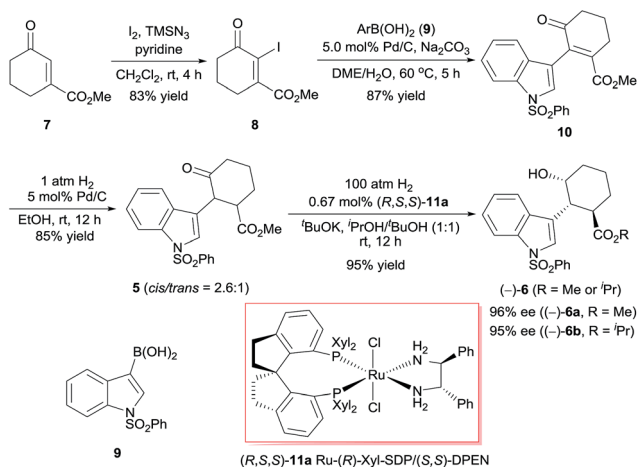


hapalindole-type alkaloids (Scheme 1). Interestingly, both enantiomers of the skeleton are found among the naturally occurring hapalindole-type alkaloids, and alkaloids with inverted stereochemistry at the chiral quaternary center at C12 of the cyclohexane ring are also common in nature. These unique stereochemical characteristics present great challenges for the divergent enantioselective synthesis of hapalindole-type alkaloids. We envisioned that the asymmetric hydrogenation of 2-(1*H*-indol-3-yl)-3-(methoxycarbonyl)cyclohexanone (**5**) could be used to access both enantiomers of the core skeleton by changing the configuration of the chiral catalyst; switching the order of the two carbon-carbon bond-forming reactions at C12 would install the chiral quaternary stereocenter (Scheme 1). Dimethylation of the ester group of the hydrogenation product **6** followed by a dehydration would be a practical way to generate the isopropenyl group. Construction of the quaternary stereocenter and subsequent introduction of an isonitrile or isothiocyanate group could be accomplished *via* a carbonyl group, which could be generated by oxidation of the hydroxyl group of **6**.

We herein report that we successfully employed the above-described strategy for the divergent enantioselective syntheses of (+)-hapalindole Q (**1**), (–)-12-*epi*-hapalindole Q isonitrile (**2**), (–)-hapalindole D (**3**), and (+)-12-*epi*-fischerindole U isothiocyanate (**4**) by using catalytic asymmetric hydrogenation of a ketone *via* DKR to construct the chiral core skeleton.

Results and discussion

We began by investigating the enantioselective synthesis of chiral alcohol **6**, which has three contiguous stereocenters, *via* catalytic asymmetric hydrogenation of ketone **5** (Scheme 2). Commercially available methyl 3-oxocyclohex-1-enecarboxylate (**7**) was treated with iodine in the presence of trimethylsilyl azide (TMSN₃) and pyridine using Sha and Huang's procedure⁹ to yield iodide **8** in 83% yield. Coupling of **8** with indolylboronic acid **9**¹⁰ and subsequent hydrogenation, both steps with Pd/C as the catalyst, afforded racemic ketone **5** in 74% yield over two steps. We investigated the asymmetric hydrogenation of **5** by



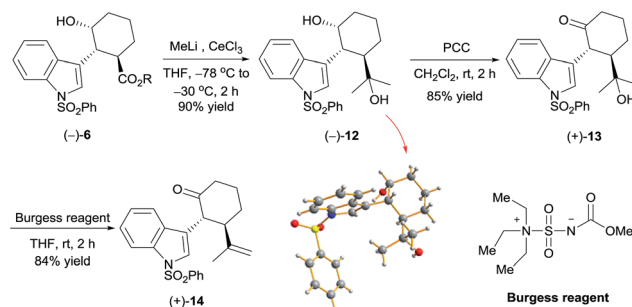
Scheme 2 Asymmetric synthesis of chiral alcohol (–)-**6**.

using our chiral spiro ruthenium catalysts **11**.¹¹ Careful optimization of the reaction conditions (see ESI†) revealed that Ru-(*R*)-Xyl-SDP/(*S,S*)-DPEN (*R,S,S*)-**11a** efficiently catalyzed the hydrogenation of **5** in a 1 : 1 (v/v) mixture of *i*-PrOH and *t*-BuOH, providing chiral alcohol (–)-**6** (*cis*, *trans* > 99%) in 95% isolated yield as a 3 : 1 mixture of the methyl ester (96% ee) and the isopropyl ester (95% ee). Similarly, chiral alcohol (+)-**6**, which has the opposite configuration, was obtained by using Ru-(*S*)-Xyl-SDP/(*R,R*)-DPEN (*S,R,R*)-**11a** as the catalyst (95% yield, (+)-**6a**, 96% ee, (+)-**6b**, 95% ee, (+)-**6a**/(+)-**6b** = 3 : 1).

Reaction of chiral alcohol (–)-**6** (as a mixture of methyl and isopropyl esters) with MeLi (6 equiv.) in the presence of cerium chloride¹² yielded alcohol (–)-**12** in 90% yield (Scheme 3). X-ray diffraction analysis of a crystal of (–)-**12** showed its absolute configuration to be 1*R*,2*R*,3*R*. Oxidation of (–)-**12** with pyridinium chlorochromate (PCC), followed by dehydration with Burgess's reagent,¹³ produced ketone (+)-**14** in 71% yield over two steps. By means of the same process, ketone (–)-**14** was synthesized from alcohol (+)-**6** with the 1*S*,2*S*,3*S* configuration. Thus, we obtained ketones (+)-**14** and (–)-**14**, which are key intermediates for the synthesis of hapalindole-type alkaloids, in 37.5% overall yield.

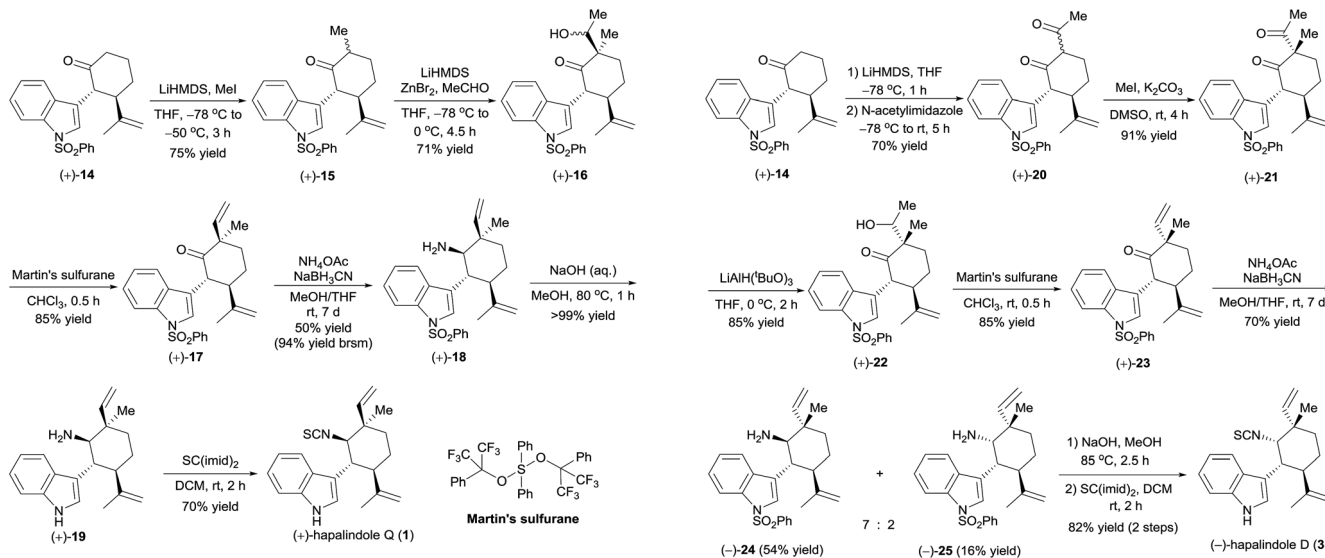
Having in hand the optically active ketones (+)-**14** and (–)-**14**, which contain the chiral core structure of the hapalindole family of alkaloids, we turned our efforts to the total synthesis of specific hapalindole alkaloids. The enantioselective total synthesis of (+)-hapalindole Q (**1**)¹⁴ from optically active (+)-**14** is outlined in Scheme 4. Selective α -methylation of (+)-**14** with methyl iodide in the presence of lithium hexamethyldisilazide (LiHMDS)¹⁵ yielded ketone (+)-**15** in 75% yield with 6 : 1 diastereoselectivity. An aldol reaction of (+)-**15** with acetaldehyde in the presence of LiHMDS and zinc bromide¹⁶ afforded alcohol (+)-**16** in 71% yield with 10 : 1 diastereoselectivity. Subsequently, intersecting with the syntheses described by Vaillancourt and Albizzati^{5a} and Baran and Richter,^{5d} (+)-**16** was dehydrated with Martin's sulfurane to afford ketone (+)-**17** (85% yield). Thus, we constructed the chiral quaternary stereocenter at the C12-position by a sequence involving the introduction of a methyl group and then a vinyl group. Note that all the reactions used for the synthesis of (+)-**17** could be performed on a gram scale.

Ketone (+)-**17** was transformed to amine (+)-**18** as a 6 : 1 mixture of diastereomers in 50% yield by a reductive amination



Scheme 3 Asymmetric synthesis of cycloketone (+)-**14**.

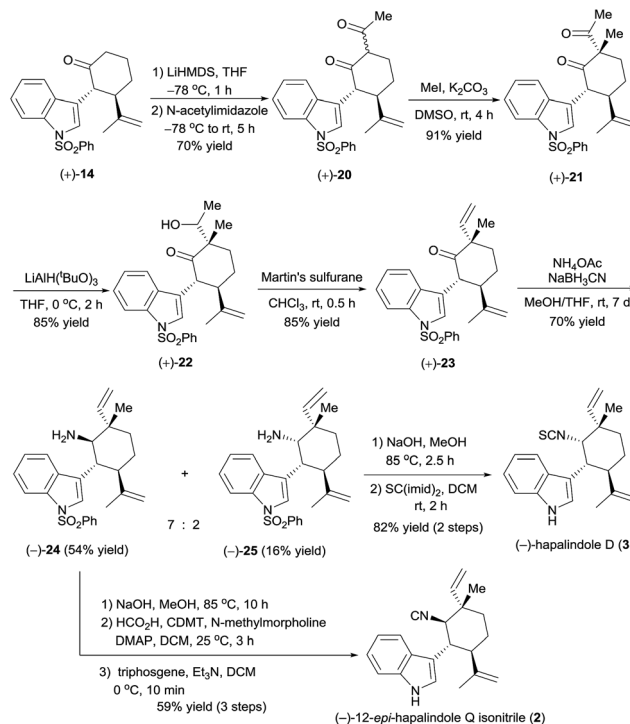




Scheme 4 Total synthesis of (+)-hapalindole Q (1).

with NH_4OAc in the presence of NaBH_3CN ; unreacted ketone (+)-17 was recovered in 47% yield, so the yield of (+)-18 was 94% based on recovered starting material. Removal of the phenylsulfonyl protecting group of (+)-18 by hydrolysis with aqueous methanolic sodium hydroxide, followed by formation of an isothiocyanate by reaction with $\text{CS}(\text{imid})_2$ provided (+)-hapalindole Q (1) in 70% yield over two steps. The NMR spectroscopic data and the optical rotation ($[\alpha]_{\text{D}}^{25} +27.8$ (c 1.1 CH_2Cl_2), lit. $[\alpha]_{\text{D}}^{25} +24.1$ (c 1.1, CH_2Cl_2)¹⁴) of our synthetic sample were comparable to those reported for the natural product.

Encouraged by the successful synthesis of (+)-hapalindole Q (1), we moved on to the synthesis of (–)-12-*epi*-hapalindole Q isonitrile (2),¹⁷ which had previously been synthesized only in racemic form.^{4f} The C12-*epi*-quaternary stereocenter was constructed by controlling the stereochemistry of the acylation-methylation sequence (Scheme 5). Specifically, treatment of optically active cycloketone (+)-14 with LiHMDS and trapping with *N*-acetylimidazole¹⁸ yielded diketone (+)-20 in 70% yield. α -Methylation of (+)-20 with MeI in the presence of K_2CO_3 afforded 91% yield of diketone (+)-21, which has a quaternary carbon center. Selective reduction of the acetyl group, which is less hindered than the ketone in (+)-21, was achieved by reaction with lithium tri-*tert*-butoxyaluminum hydride ($\text{LiAlH}(\text{O}^t\text{Bu})_3$),¹⁹ and the resulting alcohol, (+)-22, was dehydrated with Martin's sulfurane to afford ketone (+)-23 in 85% yield (note that the above mentioned reactions could be performed on a gram scale). This sequence resulted in the construction of the C12-*epi*-quaternary stereocenter with a vinyl group and methyl group arranged in a configuration opposite to that of ketone (+)-17. Next, in analogy to the synthesis of (+)-hapalindole Q (1), reductive amination of ketone (+)-23 gave amines (–)-24 and (–)-25 in 54% and 16% yields, respectively. After dephenylsulfonylation, the amino group of (–)-24 was converted to an isonitrile group by formylation with formic acid and 2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT), and dehydration of the resulting formamide with triphosgene^{5b} afforded (–)-12-*epi*-

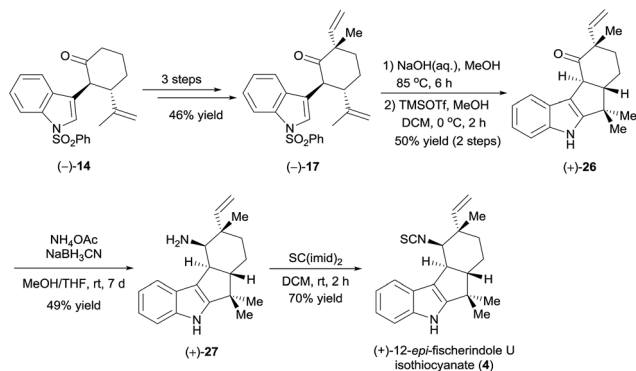
Scheme 5 Total synthesis of (–)-12-*epi*-hapalindole Q isonitrile (2) and (–)-hapalindole D (3).

hapalindole Q isonitrile (2) in 59% yield over three steps. The NMR spectroscopic data were identical to those reported by Braekman¹⁷ and Li.^{4f} The absolute configuration of synthetic (–)-12-*epi*-hapalindole Q isonitrile (2) was assigned as 10*R*,11*R*,12*S*,15*R* by inference from the X-ray crystal structure of alcohol (–)-12.

In addition, using the minor product of the reductive amination, (–)-25, we synthesized (–)-hapalindole D (3)¹⁴ in 82% yield over two steps by dephenylsulfonylation and transformation of the amino group to an isothiocyanate by using the procedure described for the synthesis of (+)-hapalindole Q (1). By comparing the optical rotation of our synthetic (–)-hapalindole D (3, $[\alpha]_{\text{D}}^{25} -224$ (c 3.1 CH_2Cl_2)) with the optical rotation of natural hapalindole D ($[\alpha]_{\text{D}}^{25} +239$ (c 3.1 CH_2Cl_2)),¹⁴ we assigned the absolute configuration of natural (+)-hapalindole D to be 10*S*,11*R*,12*R*,15*S*, which is opposite to that depicted in Scheme 5.

To further demonstrate the utility and generality of this strategy, we selected tetracyclic (+)-12-*epi*-fischerindole U isothiocyanate (4),²⁰ which was first isolated in 1994 by Moore *et al.*,²¹ as another synthetic target. As suggested by the absolute configuration of this molecule, we started the synthesis from ketone (–)-14 (Scheme 6). Ketone (–)-14 was methylated with MeI, and a subsequent aldol reaction with acetaldehyde in the presence of LiHMDS and dehydration using Martin's sulfurane according to the procedure described for the synthesis of (+)-17 (see Scheme 4) afforded ketone (–)-17 in 46% yield over three steps. Ketone (–)-17 was then hydrolyzed in aqueous sodium hydroxide and cyclized in the presence of trimethylsilyl





Scheme 6 Total synthesis of (+)-12-epi-fischerindole U isothiocyanate (4).

trifluoromethanesulfonate (TMSOTf) to yield ketone (+)-26 in 50% yield over two steps. Finally, intersecting with the synthesis of Baran *et al.*,^{5d} ketone (+)-26 was converted to (+)-12-epi-fischerindole U isothiocyanate (4) by reductive amination and isothiocyanate formation (34% yield over two steps).

The synthetic (+)-12-epi-fischerindole U isothiocyanate (4) displayed identical spectra and a similar optical rotation ($[\alpha]_D^{25} +217$ (c 0.035, CH_2Cl_2), lit. $[\alpha]_D^{25} +231$ (c 0.035, CH_2Cl_2)²¹) to those reported for the natural product.

Conclusions

In conclusion, we achieved divergent enantioselective total syntheses of four hapalindole-type alkaloids, namely, (+)-hapalindole Q (1, 13 steps, 5.9% (11.0% brsm) overall yield), (–)-12-epi-hapalindole Q isonitrile (2, 15 steps, 5.5% overall yield), (–)-hapalindole D (3, 14 steps, 2.3% overall yield), and (+)-12-epi-fischerindole U isothiocyanate (4, 14 steps, 3.0% overall yield), from commercially available methyl 3-oxocyclohex-1-enecarboxylate. Our synthetic strategy features a ruthenium-catalyzed asymmetric hydrogenation of a ketone *via* DKR to construct the chiral core structure and a switchable sequence of methylation and acetylation/aldol reaction to install a chiral quaternary stereocenter. We anticipate that this strategy will find applications in the synthesis of other hybrid isoprenoid-indole alkaloids.

Acknowledgements

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Notes and references

- V. Bhat, A. Dave, J. A. MacKay and V. H. Rawal, in *The Alkaloids: Chemistry and Biology*, ed. K. Hans-Joachim, Academic Press, New York, 2014, vol. 73, pp. 65–160.
- R. E. Moore, C. Cheuk and G. M. Patterson, *J. Am. Chem. Soc.*, 1984, **106**, 6456.

- T. J. Maimome, Y. Ishihara and P. S. Baran, *Tetrahedron*, 2015, **71**, 3652.
- For selected total syntheses of hapalindole-type alkaloids in racemic form, see: (a) H. Muratake and M. Natsume, *Tetrahedron*, 1990, **46**, 6331; (b) H. Muratake, H. Kumagami and M. Natsume, *Tetrahedron*, 1990, **46**, 6351; (c) A. C. Kinsman and M. A. Kerr, *Org. Lett.*, 2001, **3**, 3189; (d) A. Chandra and J. N. Johnston, *Angew. Chem., Int. Ed.*, 2011, **50**, 7641; (e) R. J. Rafferty and R. M. Williams, *J. Org. Chem.*, 2012, **77**, 519; (f) Z. Lu, M. Yang, P. Chen, X. Xiong and A. Li, *Angew. Chem., Int. Ed.*, 2014, **53**, 13840; for selected synthetic studies on hapalindole-type alkaloids, see: (g) H. Muratake and M. Natsume, *Tetrahedron*, 1990, **46**, 6343; (h) P. Harrington and M. A. Kerr, *Synlett*, 1996, 1047; (i) P. Harrington and M. A. Kerr, *Can. J. Chem.*, 1998, **76**, 1256; (j) A. C. Kinsman and M. A. Kerr, *Org. Lett.*, 2000, **2**, 3517; (k) M. A. Brown and M. A. Kerr, *Tetrahedron Lett.*, 2001, **42**, 983; (l) J. N. Johnston, M. A. Plotkin, R. Viswanathan and E. N. Prabhakaran, *Org. Lett.*, 2001, **3**, 1009; (m) R. Viswanathan, E. N. Prabhakaran, M. A. Plotkin and J. N. Johnston, *J. Am. Chem. Soc.*, 2003, **125**, 163; (n) R. Viswanathan, D. Mutnick and J. N. Johnston, *J. Am. Chem. Soc.*, 2003, **125**, 7266; (o) A. Chandra, R. Viswanathan and J. N. Johnston, *Org. Lett.*, 2007, **9**, 5027; (p) R. J. Rafferty and R. M. Williams, *Tetrahedron Lett.*, 2011, **52**, 2037; (q) R. J. Rafferty and R. M. Williams, *Heterocycles*, 2012, **86**, 219.
- (a) V. Vaillancourt and K. F. Albizati, *J. Am. Chem. Soc.*, 1993, **115**, 3499; (b) T. Fukuyama and X. Chen, *J. Am. Chem. Soc.*, 1994, **116**, 3125; (c) M. Sakagami, H. Muratake and M. Natsume, *Chem. Pharm. Bull.*, 1994, **42**, 1393; (d) P. S. Baran and J. M. Richter, *J. Am. Chem. Soc.*, 2004, **126**, 7450; (e) P. S. Baran and J. M. Richter, *J. Am. Chem. Soc.*, 2005, **127**, 15394; (f) P. S. Baran, T. J. Maimome and J. M. Richter, *Nature*, 2007, **446**, 404; (g) J. M. Richter, Y. Ishihara, T. Masuda, B. W. Whitefield, T. Lamas, A. Pohjakallio and P. S. Baran, *J. Am. Chem. Soc.*, 2008, **130**, 17938; (h) A. D. Hutters, K. W. Quasdorf, E. D. Styduhar and N. K. Garg, *J. Am. Chem. Soc.*, 2011, **133**, 15797; (i) K. W. Quasdorf, A. D. Hutters, M. W. Lodewyk, D. J. Tantillo and N. K. Garg, *J. Am. Chem. Soc.*, 2012, **134**, 1396; (j) K. M. Allan, K. Kobayashi and V. H. Rawal, *J. Am. Chem. Soc.*, 2012, **134**, 1392; (k) N. A. Weires, E. D. Styduhar, E. L. Baker and N. K. Garg, *J. Am. Chem. Soc.*, 2014, **136**, 14710.
- K. Komine, Y. Nomura, J. Ishihara and S. Hatakeyama, *Org. Lett.*, 2015, **17**, 3918.
- A. C. Kinsman and M. A. Kerr, *J. Am. Chem. Soc.*, 2003, **125**, 14120.
- (a) S.-F. Zhu and Q.-L. Zhou, in *Privileged Chiral Ligands and Catalysts*, ed. Q.-L. Zhou, Wiley-VCH Verlag GmbH, Weinheim, 2011, pp. 137–170; (b) J.-H. Xie and Q.-L. Zhou, *Aldrichimica Acta*, 2015, **48**, 33; for papers, see: (c) J.-Q. Chen, J.-H. Xie, D.-H. Bao, S. Liu and Q.-L. Zhou, *Org. Lett.*, 2012, **14**, 2714; (d) C. Liu, J.-H. Xie, Y.-L. Li, J.-Q. Chen and Q.-L. Zhou, *Angew. Chem., Int. Ed.*, 2013, **52**, 593; (e) G. Li, J.-H. Xie, J. Hou, S.-F. Zhu and Q.-L. Zhou,



- Adv. Synth. Catal.*, 2013, **355**, 1597; (f) L.-J. Cheng, J.-H. Xie, Y. Chen, L.-X. Wang and Q.-L. Zhou, *Org. Lett.*, 2013, **15**, 764.
- 9 C.-K. Sha and S.-J. Huang, *Tetrahedron Lett.*, 1995, **36**, 6927.
- 10 F.-X. Felpin, *J. Org. Chem.*, 2005, **70**, 8575.
- 11 (a) J.-H. Xie, L.-X. Wang, S.-F. Zhu, Y. Fu, B.-M. Fan, H.-F. Duan and Q.-L. Zhou, *J. Am. Chem. Soc.*, 2003, **125**, 4404; (b) J.-H. Xie and Q.-L. Zhou, *Acta Chim. Sin.*, 2014, **72**, 778.
- 12 T. Imamoto, N. Takiyama, K. Nakamura, T. Hatajima and Y. Kamiya, *J. Am. Chem. Soc.*, 1989, **111**, 4392.
- 13 Y. Ueda, K. Iwahashi, K. Iguchi and H. Ito, *Synthesis*, 2011, 1532.
- 14 R. E. Moore, C. Cheuk, X.-Q. G. Yang, G. M. L. Patterson, R. Bonjouklian, T. A. Smitka, J. S. Mynderse, R. S. Foster, N. D. Jones, J. K. Swartzendruber and J. B. Deeter, *J. Org. Chem.*, 1987, **52**, 1036.
- 15 O. L. Epstein and J. K. Cha, *Angew. Chem., Int. Ed.*, 2005, **44**, 121.
- 16 K. Tanino, K. Onuki, K. Asano, M. Miyashita, T. Nakamura, Y. Takahashi and I. Kuwajima, *J. Am. Chem. Soc.*, 2003, **125**, 1498.
- 17 D. Klein, D. Daloz, J. C. Braekman, L. Hoffmann and V. Demoulin, *J. Nat. Prod.*, 1995, **58**, 1781.
- 18 T. Kaiho, K. Sannohe, S. Kajjiya, T. Suzuki, K. Otsuka, T. Ito, J. Kamiya and M. Maruyama, *J. Med. Chem.*, 1989, **32**, 351.
- 19 (a) E. W. Colvin, J. Martin, W. Parker, R. A. Raphael, B. Shroot and M. Doyle, *J. Chem. Soc., Perkin Trans. 1*, 1972, 860; (b) D. R. Bhowmik and R. V. Venkateswaran, *Tetrahedron Lett.*, 1999, **40**, 7431.
- 20 Baran *et al.* have recently reported the enantioselective total synthesis of (–)-*epi*-fischerindole U isothiocyanate from (*R*)-carvone, the enantiomer of the natural (+)-12-*epi*-fischerindole U isothiocyanate (4). See ref. 5*d* and *g*.
- 21 K. Stratmann, R. E. Moore, R. Bonjouklian, J. B. Deeter, G. M. L. Patterson, S. Shaffer, C. D. Smith and T. A. Smitka, *J. Am. Chem. Soc.*, 1994, **116**, 9935.

