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.

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.5c Fukuyama and Chen6a and Natsume et al.5e 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–f ent-12-epi-fischerindole G and 12-epi-fischerindole I from (+)-carvone,5e and (−)-hapalindole U and (+)-ambiguine H from (+)-p-menth-1-en-9-ol.5g 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, lycorene, and Δ9-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

† Electronic supplementary information (ESI) available. CCDC 1453314. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c6sc00686h
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Scheme 1 Selected hapalindole-type alkaloids and our divergent enantioselective synthetic strategy.
hapalindole-type alkaloids (Scheme 1). Interestingly, both enan
tomers of the skeleton are found among the naturally occurring
hapalindole-type alkaloids, and alkaloids with inverted stereo-
chemistry at the chiral quaternary center at C12 of the cyclo-
hexane ring are also common in nature. These unique stereochemical characteristics present great challenges for the
divergent enantioselective synthesis of hapalindole-type alka-
loids. We envisioned that the asymmetric hydrogenation of 2-
(1H-indol-3-yl)-3-(methoxycarbonyl)cyclohexanone (5) could
be used to access both enantiomers of the core skeleton by chang-
ing 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 iso-
propenyl 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 iso-
thiocyanate (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). Commer-
cially 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 procedurea to yield iodide 8 in 83% yield. Coupling of 8 with indolylboronic
acid 9b 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
using our chiral spiro ruthenium catalysts.11 Careful opti-
mization of the reaction conditions (see ESIT) revealed that Ru-
(R)-Xyl-SDP/(S,S)-DPEN (R,S,S)-11a efficiently catalyzed the
hydrogenation of 5 in 1 : 1 (v/v) mixture of tPrOH and tBuOH,
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
chloride15 yielded alcohol (−)-12 in 90% yield (Scheme 3). X-ray
diffraction analysis of a crystal of (−)-12 showed its absolute
configuration to be 1R,2R,3R. Oxidation of (−)-12 with pyr-
ridinium 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 1S,2S,3S 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)b from optically active (+)-14 is
outlined in Scheme 4. Selective α-methylation of (+)-14 with methyl
iodide in the presence of lithium hexamethyldisilazide (LiHMDS)c
yielded ketone (+)-15 in 75% yield with 6 : 1 diaste-
reoselectivity. An aldol reaction of (+)-15 with acetaldehyde in
the presence of LiHMDS and zinc bromidee afforded alcohol
(+)-16 in 71% yield with 10 : 1 diastereoselectivity. Subse-
quently, intersecting with the syntheses described by Vaillan-
court and Albizati and Baran and Richter,fd (+)-16 was
dehydrated with Martin’s sulfamate 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 reac-
tions 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 2 Asymmetric synthesis of chiral alcohol (−)-6.

Scheme 3 Asymmetric synthesis of cycloketone (+)-14.
with NH$_4$OAc in the presence of NaBH$_3$CN; 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 CS$_2$ provided (+)-hapalindole Q (1) in 70% yield over two steps. The NMR spectroscopic data and the optical rotation ([α]$_D^{25}$ +27.8 (c 1.1 CH$_2$Cl$_2$), lit. [α]$_D^{25}$ +24.1 (c 1.1, CH$_2$Cl$_2$)).$^4$ 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),$^7$ which had previously been synthesized only in racemic form.$^9$ 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-acetylimidazole$^8$ yielded diketone (+)-20 in 70% yield. α-Methylation of (+)-20 with MeI in the presence of K$_2$CO$_3$ 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-butoxyaluminium hydride (LiAlH(O’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$^{20}$ afforded (−)-12-epi-hapalindole Q isonitrile (2) in 59% yield over three steps. The NMR spectroscopic data were identical to those reported by Braekman$^{17}$ and Li.$^9$ The absolute configuration of synthetic (−)-12-epi-hapalindole Q isonitrile (2) was assigned as 10R,11R,12S,15R 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 group by using the procedure described for the synthesis of (+)-hapalindole Q (1). By comparing the optical rotation of our synthetic (−)-hapalindole D (3, [α]$_D^{25}$ −224 (c 3.1 CH$_2$Cl$_2$)) with the optical rotation of natural hapalindole D ([α]$_D^{25}$ +239 (c 3.1 CH$_2$Cl$_2$)),$^{14}$ we assigned the absolute configuration of natural (+)-hapalindole D to be 10S,11R,12R,15S, 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...
trifluoromethanesulphonate (TMSOTf) to yield ketone (+)-26 in 50% yield over two steps. Finally, intersecting with the synthesis of Baran et al.,4d 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 ([α]D25 +217 (c 0.035, CH2Cl2), lit. [α]D25 +231 (c 0.035, CH2Cl2)°) 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

This project was supported by the National Natural Science Foundation of China, the National Basic Research Program of China (973 Program) (No. 2012CB821600), and the “111” project (No. B06005) of the Ministry of Education of China.

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