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Stereospecific synthesis of 2,2,3-trisubstituted tetrahydroquinolines: application to the total syntheses of benzastatin E and natural virantmycin

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Abstract—An efficient methodology for the synthesis of 2,2,3-trisubstituted tetrahydroquinolines has been developed, which involves the triphenylphosphine–CCl_4-mediated stereospecific rearrangement of α,α-disubstituted indoline-2-methanols **15** to 2,2,3-trisubstituted tetrahydroquinolines **26**. The rearrangement precursors **15** are readily prepared by the diastereoselective Grignard addition to 2-acylindolines **13**. The total syntheses of (+)-benzastatin E (**1**) and natural virantmycin (**2a**) were accomplished utilizing this methodology. This rearrangement reaction might afford some chemical precedent for the biogenetic pathway of the benzastatin family.

1. Introduction

The stereoselective construction of chiral quaternary carbon centers is one of the most difficult transformations in organic synthesis. The difficulty is magnified when quaternary stereogenic centers is involved.[1] Substituted tetrahydroquinolines and tetrahydroisoquinolines are compounds of great interest, because many biologically and pharmacologically active alkaloids bear this skeleton.[2] Chiral quaternary carbons are often essential for these compounds, and thus, the asymmetric synthesis of these ring systems has been the subject of intense research[3] though this still remains to be a challenging task. Few publications have described the enantioselective synthesis of isoquinoline derivatives containing C-1 quaternary stereocenter[4] or C-3 quaternary stereocenter.[5] Among them, Shibasaki et al. has recently reported an elaborate enantioselective synthesis of 1,1-disubstituted isoquinolines using a Reissert-type reaction.[4a] On the other hand, methods for asymmetric synthesis of quinoline derivatives with quaternary stereocenter has been relatively undeveloped. Recently, Mikami et al. has described an efficient enantioselective synthesis of quinolines bearing a C-3 quaternary stereocenter or a spiro ring, by the catalytic ene-type reaction of 1,7-enynes.[6] To the best of our knowledge, however, there has been no reports of a general, stereoselective synthesis of 2,2-disubstituted tetrahydroquinolines.

The benzastatin family and virantmycin are a novel class of indoline and tetrahydroquinoline alkaloids isolated from *Streptomyces nitrosporeous*.[7–10] Benzastatins show inhibitory activity against glutamate toxicity and lipid peroxidation in rat liver microsomes that can be used to prevent brain ischemia injury, and consists of indoline alkaloids such as benzastatin E, and tetrahydroquinoline alkaloids such as benzastatin C which are structurally related to virantmycin.[7,8] (−)-Virantmycin, a potent inhibitor towards RNA and DNA viruses, is a unique 2,2-disubstituted tetrahydroquinoline alkaloid with contiguous quaternary and tertiary stereocenters.[9,10] To date, several research groups have reported the total syntheses of (±)-virantmycin,[11,12] and the total synthesis of unnatural (+)-virantmycin was reported by Shirahama et al. in 1996.[13] The synthesis of natural occurring form of virantmycin, however, has not been accomplished.

Several biosynthetic pathways have been suggested for the benzastatin family based on the cooccurence of indolines and tetrahydroquinolines. Yoo et al. speculated that the simple benzastatin A is oxygenated at the double bond to form an intermediate epoxide, which can then undergo cyclization to form the indoline or the tetrahydroquinoline skeleton.[8] On the other hand, Yoo et al. proposed that the indoline and the tetrahydroquinoline skeletons can interconvert through an aziridine intermediate, demonstrated by the treatment of simple aziridine compound with anhydrous

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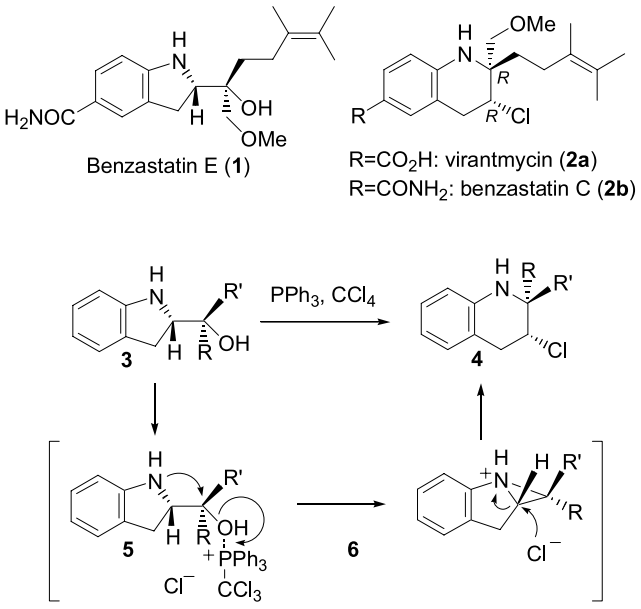
hydrogen chloride giving a mixture of indoline and tetrahydroquinoline.[14] This latter proposal indicates the biogenetic relationship between the indoline and the tetrahydroquinoline skeletons, and inspired us with the possibility of constructing the tetrahydroquinoline skeleton from indoline precursors via the intermediacy of aziridines, in a manner mimicking the biosynthetic process. Based on this proposed hypothesis, we designed the triphenylphosphine–CCl_4-mediated rearrangement from α,α-disubstituted indoline-2-methanol to 2,2,3-trisubstituted tetrahydroquinoline via the aziridine, followed by the ring opening attack of the chloride anion to the sterically less hindered carbon (Scheme 1). In this paper, we disclose the details of our development of stereoselective preparation of α,α-disubstituted indoline-2-methanols, and the stereospecific rearrangement of these precursors to furnish 2,2,3-trisubstituted tetrahydroquinolines, simultaneously constructing the contiguous quaternary and tertiary stereogenic centers. These methodologies were applied to efficient total syntheses of (+)-benzastatin E and natural virantmycin, which illustrates the utility of this methodology for the synthesis of various chiral indoline and tetrahydroquinoline alkaloids.[15,16]



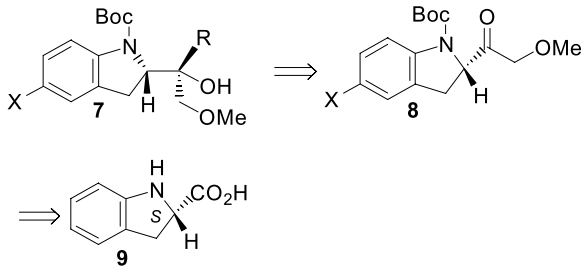
Scheme 1. Transformation of indolines to tetrahydroquinolines based on the proposed biosynthetic hypothesis.

2. Results and discussion

2.1. Diastereoselective synthesis of α,α-disubstituted indoline-2-methanols

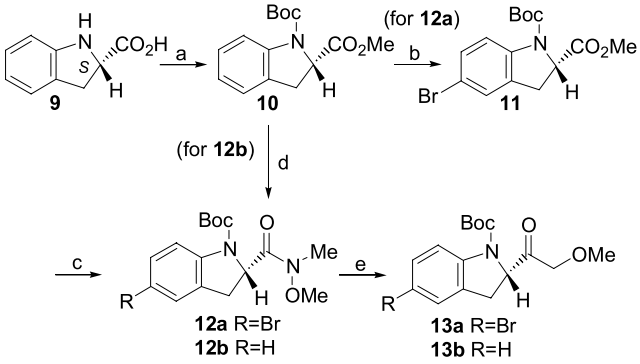
Our investigation of the stereospecific rearrangement of α,α-disubstituted indoline-2-methanols to 2,2,3-trisubstituted tetrahydroquinolines began with the development of a general route for the preparation of the rearrangement precursors. The synthetic scheme is outlined in Scheme 2. The key step, in terms of constructing the *tert*-alcohol moiety, is the diastereoselective Grignard addition to 2-acylindoline **8**.

The key intermediate 2-acylindoline **13** can be readily



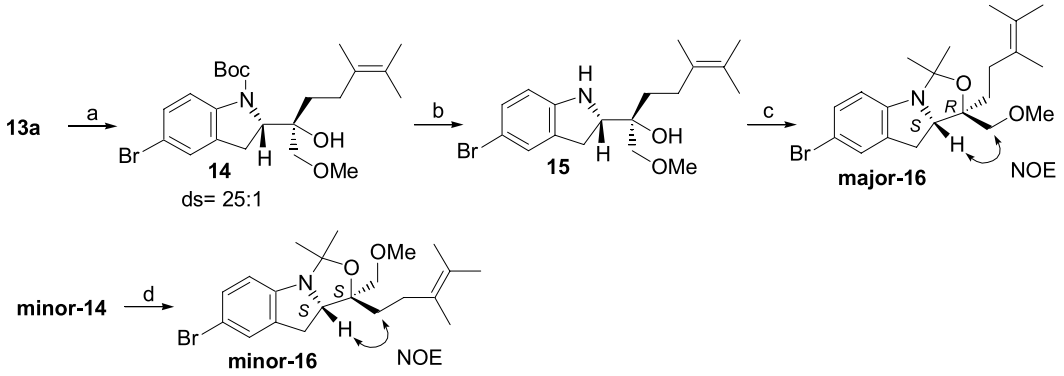
Scheme 2. Retrosynthetic analysis of α,α-disubstituted indoline-2-methanols **7**.

prepared from the commercially available (*S*)-(−)-indoline-2-carboxylic acid (**9**) as shown in Scheme 3. Carboxylic acid **9** was treated with sulfuric acid in methanol, followed by nitrogen protection with di-*tert*-butyl dicarbonate to provide methyl ester **10** in 92% yield. Bromination of **10** with NBS (1 equiv) in DMF afforded bromide **11** in 93% yield. The bromide was converted to Weinreb amide[17] **12a** by treatment with *N*,*O*-dimethylhydroxylamine hydrochloride and *i*-propylmagnesium chloride[18] in 83% yield. Coupling of methoxymethyl lithium,[19] derived from Sn–Li exchange of methyl tributylstannylmethyl ether, with **12a** afforded ketone **13a** in 61% yield. Simple 2-acylindoline **13b** with no substituent on the phenyl ring was obtained by directly converting **10** to Weinreb amide **12b** in 72% yield, followed by the coupling with methoxymethyl lithium to give **13b** in 56% yield.



Scheme 3. Reagents and conditions: (a) (i) MeOH, H_2SO_4, 80 °C; (ii) Boc_2O, CH_2Cl_2, rt, 92% (2 steps). (b) NBS, DMF, 0 °C, 93%. (c) *i*-PrMgCl, Me(MeONH)·HCl, THF, −20 to −10 °C, 83%. (d) *i*-PrMgCl, Me(MeONH)·HCl, THF, −20 to −10 °C, 72%. (e) $MeOCH_2Sn(n\text{-}Bu)_3$, *n*-BuLi, THF, −78 °C, 61% (**13a**), 56% (**13b**).

The Grignard addition to 2-acylindoline **13** proceeded with high diastereoselectivity and afforded the corresponding indoline-2-methanols in moderate to excellent yields.[20] In an initial experiment, reaction of 2-acylindoline **13a** with 3,4-dimethyl-3-pentenylmagnesium bromide[21] in THF at −78 °C furnished *tert*-alcohols in a 25:1 ratio of separable isomers (major-**14** and minor-**14**) (Scheme 4). The diastereoselectivity was determined by the HPLC analysis of the crude reaction mixture. The deprotection of the *N*-Boc group of major-**14** was achieved with HCO_2H/CH_2Cl_2 to give the rearrangement substrate, α,α-disubstituted indoline-2-methanol **15**. In order to determine the configuration of the newly created stereocenters, the *tert*-alcohols **14** were further converted to the corresponding



Scheme 4. Reagents and conditions: (a) 3,4-dimethyl-3-pentenylmagnesium bromide, THF, −78 °C, 91% (ds=25:1). (b) HCO_2H, CH_2Cl_2, 40 °C, 52%. (c) $Me_2C(OMe)_2$, PPTS, CH_2Cl_2, rt, 91%. (d) (i) HCO_2H, CH_2Cl_2, 40 °C, 76%; (ii) $Me_2C(OMe)_2$, PPTS, CH_2Cl_2, rt, 72%.

acetonides **16**. The absolute configuration of major-**14** was assigned as (9*S*,10*R*), and minor-**14** as (9*S*,10*S*), by the NOE experiment of the acetonides. The stereochemistry outcome of the diastereoselective Grignard addition can be rationalized by the Felkin–Anh model[22] depicted in Figure 1.

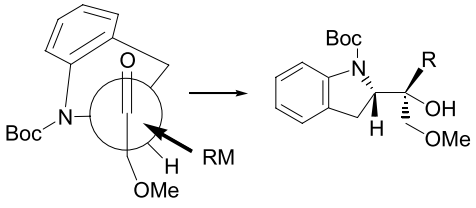


Figure 1. Diastereoselective Grignard addition.

To broaden the scope of this reaction, various 2-acylindolines were reacted with a series of Grignard reagents or alkyllithiums. The results are summarized in Table 1. In most cases, the reaction proceeded smoothly with high diastereoselectivities. It is noteworthy that either diastereomer can be easily obtained by exchanging the order of the metal reagent addition to Weinreb amide **12**, as shown in entries 1 and 2. The enantiomer of **14** can also be prepared by using (*R*)-(+)-indoline-2-carboxylic acid[23] as the starting material (entry 3). 2-Acylindolines with methoxymethyl group as the acyl group (**13a** and **13b**) reacted with variety of Grignard reagents and alkyllithiums, including vinyl Grignards (entries 8 and 9). However, the scope of the diastereoselective addition is somewhat limited when 2-acylindolines with alkyl groups (**13c**, **13e**–**h**) were applied as substrates. Alkyllithiums, such as methyllithium (entries 14 and 16), lithium phenylacetilide (entry 15) or phenyllithium (entry 17) reacts readily to furnish the corresponding *tert*-alcohols, whereas the Grignard reagents seemed to be less reactive. For example, **13h** does not react with methylmagnesium bromide under the standard conditions, resulting in the recovery of the starting material; the same applies to **13e** with 3-butenylmagnesium bromide, and **13f** with phenethylmagnesium chloride. All the obtained *tert*-alcohols **14** were converted to indoline-2-methanols **15** by the deprotection of the *N*-Boc group, thus efficiently providing the rearrangement precursors. The chiral HPLC analysis[24] of **15a** (the Boc-deprotected **14a**) shows that no racemization occurs during these manipulations (from **10** to **15**).

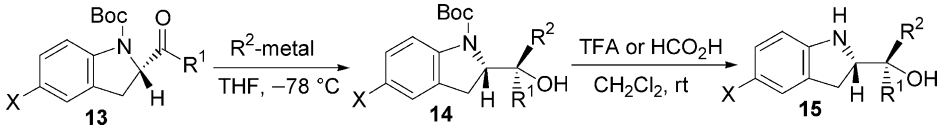
Furthermore, we satisfactorily accomplished the total synthesis of (+)-benzastatin E (**1**) in three steps from major-**16** as shown in Scheme 5. Benzastatin E (**1**) is the most potent inhibitor of glutamate toxicity using neuronal hybridoma N18-RE-105 among the benzastatin family.[8] The relative stereochemistry of **1** was elucidated by extensive NMR spectroscopic analysis, but the absolute stereochemistry was undetermined, leaving the question of which stereoisomer to aim at. Taking into account the proposed biosynthesis of benzastatins proceeding via the aziridine intermediate, the absolute configuration of indoline skeleton would be anticipated to reflect the configuration of tetrahydroquinolines such as (−)-virantmycin. Thus, one could speculate the absolute stereochemistry of benzastatin E to be 9*S*, and therefore the total synthesis of benzastatin E was carried out with major-**16**. Lithiation of major-**16** followed by the carboxylation with CO_2 provided **17**. Amidation of **17** with aqueous ammonia and 1,1′-carbonyldiimidazole (CDI) gave amide **18**. Removal of the acetonide protecting group from **18** with PPTS/MeOH furnished (+)-benzastatin E (**1**) $[\alpha]_D^{24}=+21.3$ (*c* 0.10, MeOH) (lit.[8] $[\alpha]_D^{18}=+17$ (*c* 0.1, MeOH))] in 64% yield. Spectral data (IR, ^{1}H NMR and ^{13}C NMR) for synthetic (+)-**1** are identical to that reported for the natural product. Therefore, the absolute stereochemistry of benzastatin E was confirmed as (9*S*,10*R*) as expected.

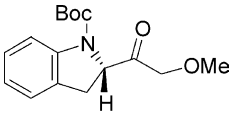
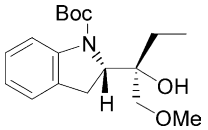
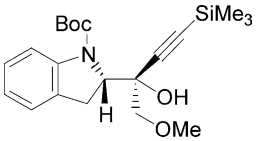
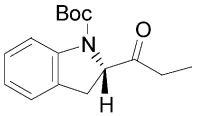
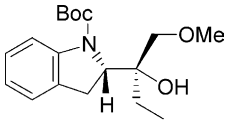
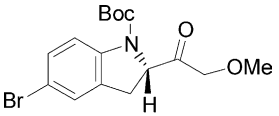
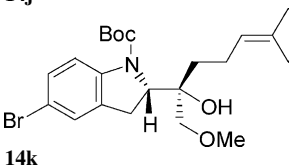
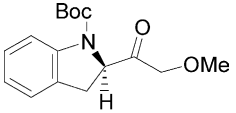
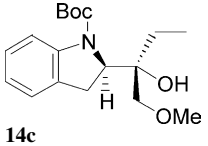
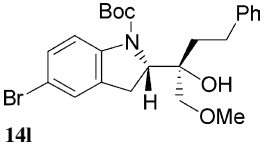
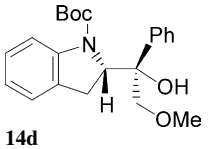
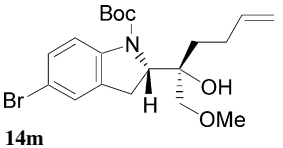
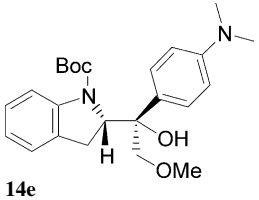
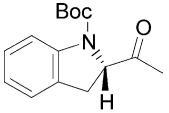
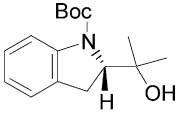
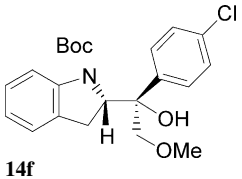
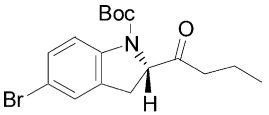
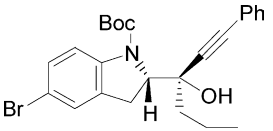
2.2. Stereospecific rearrangement from α,α-disubstituted indoline-2-ethanols to 2,2,3-trisubstituted tetrahydroquinolines

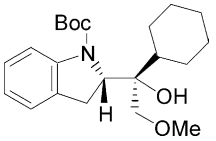
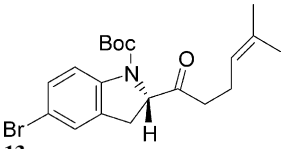
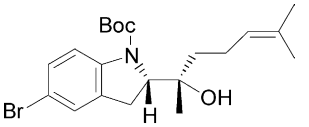
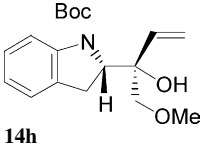
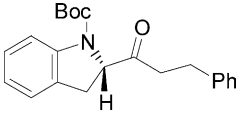
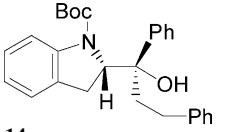
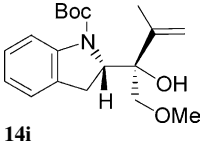
Having established the efficient method for the preparation of α,α-disubstituted indoline-2-methanols, the stereospecific rearrangement to 2,2,3-trisubstituted tetrahydroquinolines was investigated. Cossy et al. previously reported the ring-expansion reaction of *N*-benzylpyrrolidine-2-methanols to *N*-3-chloropiperidines using methanesulfonyl chloride, though they stated that no rearrangement occurs with α,α-disubstituted *N*-benzylpyrrolidine-2-methanols.[25] As speculated, this rearrangement did not proceed with our substrate **15a** resulting in crude mixture, probably due to the steric hindrance (Scheme 6).

Prior to the investigation of the rearrangement reaction of tertiary alcohols **15**, we decided to conduct a preliminary experiment with racemic α-monosubstituted

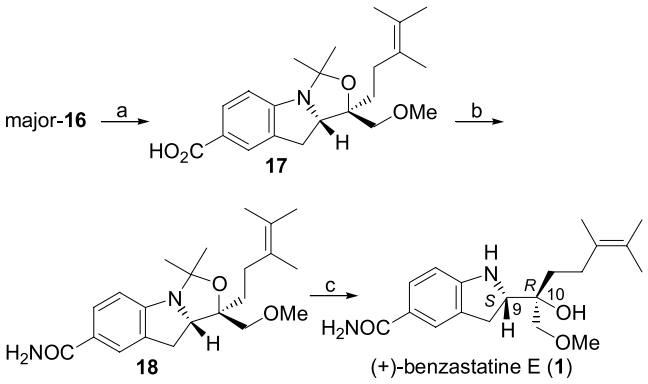
Table 1. Diastereoselective Grignard addition to 2-acylindolines **13**



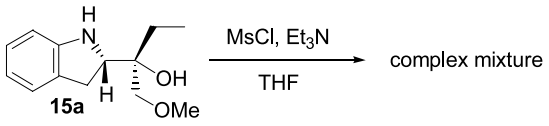
Entry	Substrate **13**[a]	Product **14**[b]	Yield[c]	Entry	Substrate **13**[a]	Product **14**[b]	Yield[c]
1	 **13b**	 **14a**	57% (16:1)[d]	10	**13b**	 **14j**	63 (38:1)
2[e]	 **13c**	 **14b**	86% (13:1)	11	 **13a**	 **14k**	67% (9:1)
3	 **13d**	 **14c**	62% (17:1)	12	**13b**	 **14l**	68% (8:1)
4	**13b**	 **14d**	94% (15:1)	13	**13b**	 **14m**	82% (11:1)
5	**13b**	 **14e**	84% (7:1)	14[e]	 **13e**	 **14n**	62%
6	**13b**	 **14f**	61% (9:1)	15[e]	 **13f**	 **14o**	85% (8:1)

7[f]	**13b**	 **14g**	85% (18:1)	16[e]	 **13g**	 **14p**	47% (10:1)
8	**13b**	 **14h**	97% (12:1)	17[e,g]	 **13h**	 **14q**	68% (38:1)
9	**13b**	 **14i**	100% (13:1)				

[a] Readily prepared from the corresponding Weinreb amide and either Grignard reagent or alkyllithium by the same method for preparation of **13** except for **13d**. Substrate **13d** was prepared from (*R*)-(+)-indoline-2-carboxylic acid.
[b] Absolute configuration of the major isomer was determined by NOE experiments of the corresponding acetonide derivative.
[c] Isolated yield of a mixture of diastereomers.
[d] Diastereomeric ratios determined by HPLC analysis of crude product mixtures.
[e] Alkyl lithium was used.
[f] 10 equiv of cyclohexylmagnesium bromide was used.
[g] 6 equiv of phenyllithium was used.

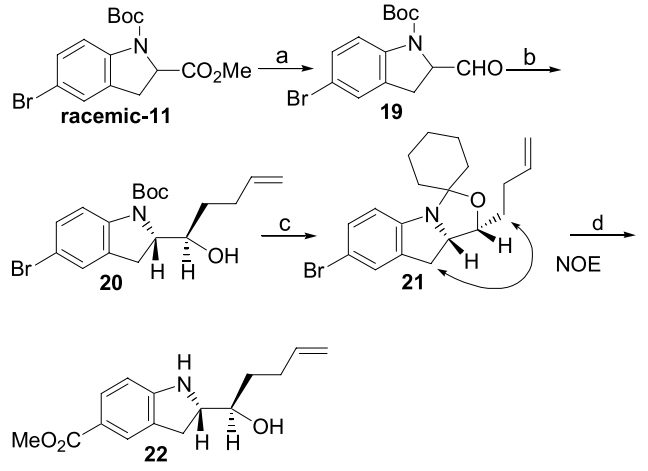


Scheme 5. Reagents and conditions: (a) *t*-BuLi, CO_2, Et_2O, −78 to 0 °C, 53%. (b) (i) CDI, 28%; (ii) aq NH_3, THF, rt, 74%; (c) PPTS, MeOH, rt, 64%.



Scheme 6. Attempt for the ring expansion using methanesulfonyl chloride.

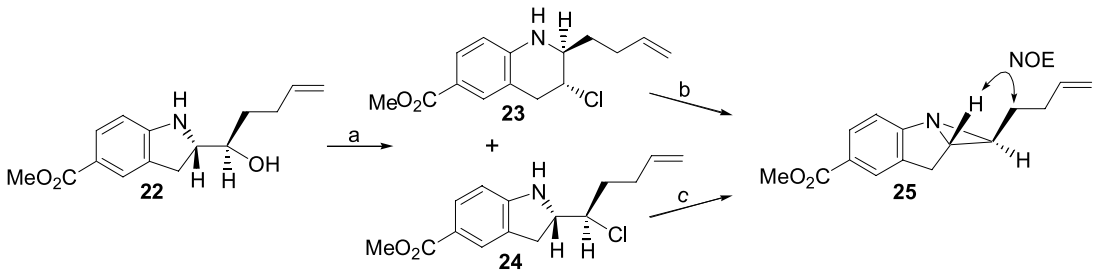
indoline-2-methanols. Synthesis of a representative substrate **22** is outlined in Scheme 7. Racemic ethyl ester **11** was converted to corresponding aldehyde **19** by reduction of **11** with LAH followed by Swern oxidization. In contrast to the Grignard reaction with 2-acylindolines **13** being highly diastereoselective, the Grignard reaction of the aldehyde **19** with 3-butenylmagnesium bromide proceeded in low diastereoselectivity. Lowering the reaction temperature to −87 °C was ineffective. The relative configuration of the Grignard adduct **20** was determined by the NOE experiment of the acetonide **21**, which was derived from **20** by deprotection of the *N*-Boc group, followed by the reaction with 1,1-dimethoxycyclohexane. The bromide on the phenyl ring of **21** was converted to a methyl ester group through a three step sequence, thus giving rise to the rearrangement precursor, α-monosubstituted indoline-2-methanol **22**.



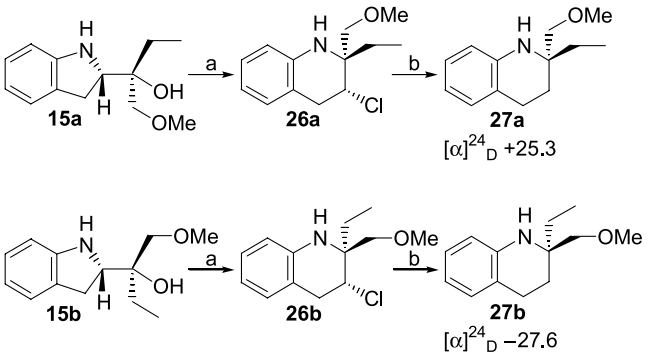
Scheme 7. Reagents and conditions: (a) (i) $LiAlH_4$, THF, −78 to 0 °C; (ii) SO_3·py, Et_3N, DMSO, CH_2Cl_2, 0 °C, 51% (2 steps). (b) 3-Butenylmagnesium bromide, THF, −78 °C, 75% (ds=3:1). (c) (i) TFA, CH_2Cl_2, 0 °C to rt, 59%; (ii) 1,1-dimethoxycyclohexane, *p*-TsOH, CH_2Cl_2, rt, 72%. (d) (i) *t*-BuLi, CO_2, Et_2O, −78 to 0 °C; (ii) $TMSCH_2N_2$, MeOH, 0 °C to rt; (iii) Amberlyst-15® ion exchange resin, MeOH, rt, 62% (3 steps).

Reaction of α-monosubstituted indoline-2-methanol **22** with PPh_3 (3 equiv) and CCl_4 (10 equiv) in CH_2Cl_2 at room temperature for 3 h delivered a 3:1 mixture of the desired rearrangement product **23** and Cl-substituted indoline **24** which was relatively unstable (the structure of **24** was characterized by ^1H NMR, ^{13}C NMR and EIMS) (Scheme 8).[26] The 5- and 6-membered ring of the products were confirmed by the HMBC experiments, and the relative stereochemistry was determined by the NOE experiment of the aziridine **25**, derived from **23** and **24** by: (1) formation of the aziridine ring by *t*-BuOK and (2) esterification of the resulting carboxylic acid. The indoline product **24** could be formed either by direct chlorination of the OH group of the substrate **22**, or via an aziridine intermediate as depicted in Scheme 1, in this case the chloride anion attacking the bridgehead carbon of the aziridine.

With the above result in mind, the triphenylphosphine–CCl_4-mediated rearrangement using α,α-disubstituted indoline-2-methanols **15a** and **15b** as substrates were initially examined. To our delight, treatment of **15a** with PPh_3 (3 equiv) and CCl_4 (10 equiv) in CH_2Cl_2 under reflux for 30 min afforded solely the desired rearrangement product tetrahydroquinoline **26a** as a single isomer in 63% yield (Scheme 9). Treatment of the diastereomer **15b** also gave **26b** as a sole isomer in 74% yield. Relative configurations of **26a** and **26b** were determined by comparison with the corresponding authentic racemic samples, reported by Shirahama et al.[12] Exposure of **26b** to $(n\text{-}Bu)_3SnH$ and azobisisobutyronitrile afforded the dechlorinated derivative **27b**, which was identical with the dechlorinated compound **27a** derived from **26a** except for the optical rotation. These results indicate that **26a** and **26b** have the opposite substituent orientation at C-2 position. The absolute configuration of **26a** was verified by the X-ray analysis as 2*R*,3*R* by the X-ray analysis of

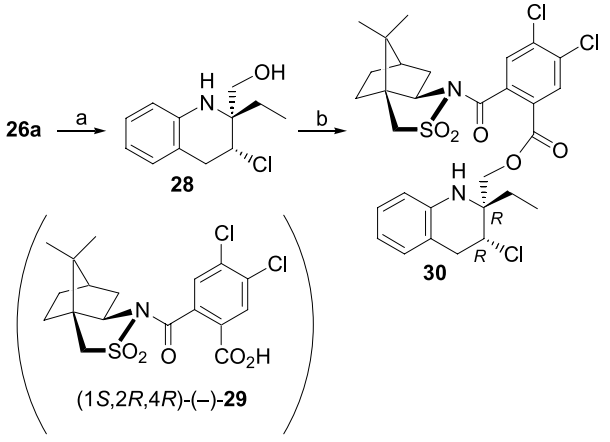


Scheme 8. Reagents and conditions: (a) PPh_3, CCl_4, CH_2Cl_2, rt, 91% (yield of a 3:1 mixture of **23** and **24**). (b) (i) *t*-BuOK, *t*-BuOH, 60 °C; (ii) $TMSCH_2N_2$, AcOH, MeOH, 0 °C to rt, 26% (2 steps). (c) (i) *t*-BuOK, *t*-BuOH, 60 °C; (ii) $TMSCH_2N_2$, AcOH, MeOH, 0 °C to rt, 47% (2 steps).



Scheme 9. Reagents and conditions: (a) PPh_3, CCl_4, CH_2Cl_2, 40 °C, 63%. (b) $(n\text{-}Bu)_3SnH$, AIBN, benzene, 80 °C, 95%. (c) PPh_3, CCl_4, CH_2Cl_2, 40 °C, 64%; (b) $(n\text{-}Bu)_3SnH$, AIBN, benzene, 80 °C, 75%.

(1*S*,2*R*,3*R*)-(−)-camphorsultam[27] derivative **30**, derived from **26a** in a two-step sequence (Scheme 10).[16] Moreover, no racemization occurred during the rearrangement, confirmed by the chiral HPLC analysis of **26a**.[28] In the light of these results, the rearrangement is considered to be stereospecific.[29]



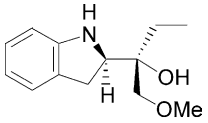
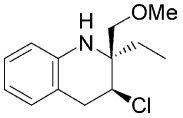
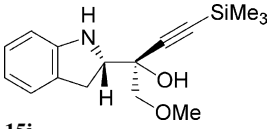
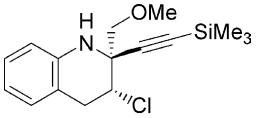
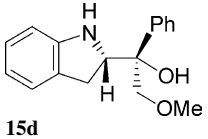
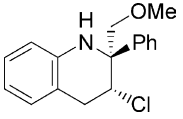
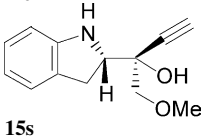
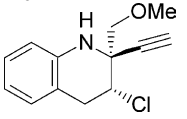
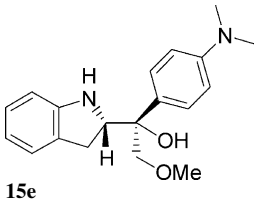
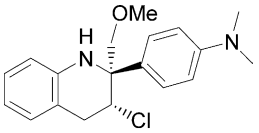
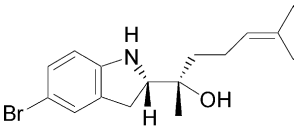
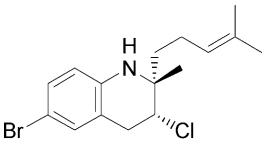
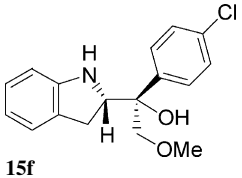
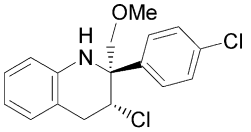
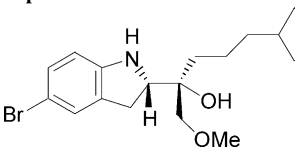
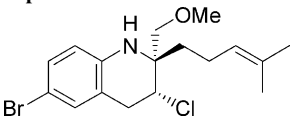
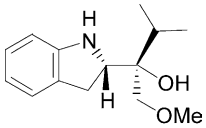
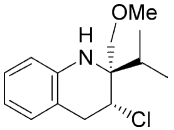
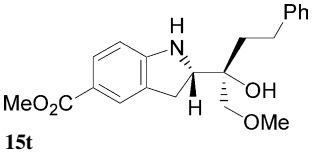
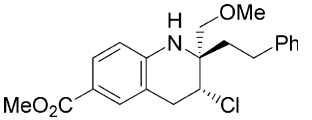
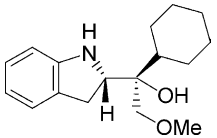
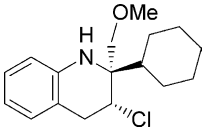
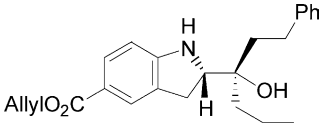
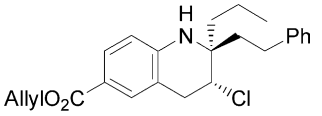
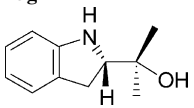
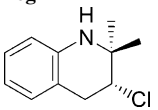
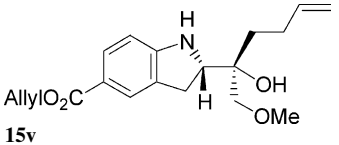
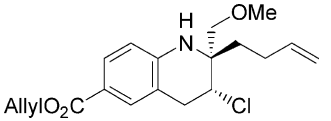
Scheme 10. Reagents and conditions: (a) $AlCl_3$, Me_2S, CH_2Cl_2, rt, 86%. (b) (1*S*,2*R*,4*R*)-(−)-**29**, DCC, DMAP, CH_2Cl_2, reflux, 64%.

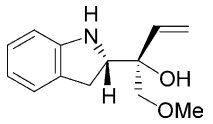
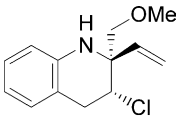
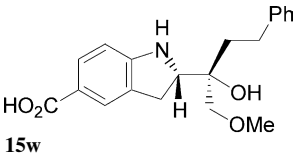
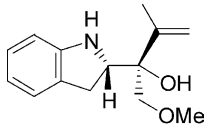
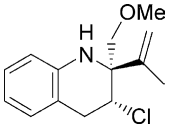
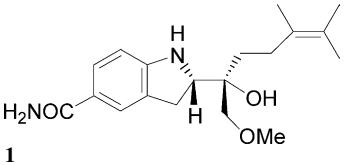
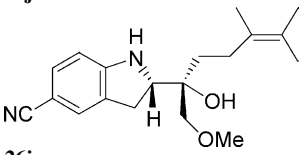
The utility of this rearrangement was investigated using various chiral indoline-2-methanol derivatives, as shown in Table 2. In most cases, the reactions provided single isomers in moderate to good yield.[30] The reaction of **15c** (enantiomer of **15a**) provided the antipode of **26a** (entry 1). Notably, the use of polymer-supported triphenylphosphine was also effective (entry 9). Unfortunately, the rearrangement was unsuccessful with some substrates. In the case of **15e**, a trace of rearrangement product **26e** was observed, but could not be isolated because of decomposition (entry 3). As shown in entries 17 and 18, the rearrangement proved to be quite sensitive to the substituent on the indoline aryl ring. Although the rearrangement proceeded smoothly with substrates with Br (entries 12 and 13) or ester groups (entries 14–16) substituted on the aryl ring, no reaction occurred with **15w** containing a carboxyl group (entry 17), and treatment of **1** resulted in the reduction of the amide group (entry 18).

Gratifyingly, the total synthesis of natural virantmycin was achieved utilizing our developed methodology for the construction of 2,2,3-trisubstituted tetrahydroquinolines (Scheme 11). Acylindoline **13b** was treated with iodine monochloride to afford **31** in 91% yield. Iodide **31** was subjected to diastereoselective Grignard addition with 2,3-dimethyl-3-pentenylmagnesium bromide[21] to give *tert*-alcohols **32** as a 19:1 mixture of separable isomers, as determined by HPLC analysis of the product mixture. The Boc protecting group of the major isomer was removed by treatment with HCO_2H to afford the rearrangement precursor **33**. The configurations of the newly created asymmetric centers in the Grignard adduct were determined by the NOE experiments of the acetonide derivative of **33**. Unfortunately, the rearrangement reaction was sluggish when **33** was subjected to the standard condition, giving a mixture of products including an undesired deiodinated product and an indole derivative (formed by dehydration followed by isomerization), along with the decomposition of the polysubstituted olefin (deduced from the disappearance of the olefinic carbon peak in the ^{13}C NMR spectrum). To overcome these problems we screened a number of aromatic and aliphatic phosphines, and found that the observed side reactions, such as reduction and isomerization to an indole, are suppressed to a certain extent with the usage of tri-*n*-butylphosphine as an alternative. As a result, tetrahydroquinoline **34** was provided as a single isomer in 45% yield by treating **33** with tri-*n*-butylphosphine and CCl_4. The tetrahydroquinoline **34** was carbonylated by reaction with 1 atm of CO in H_2O/DMF in the presence of catalytic $Pd(OAc)_2$ and K_2CO_3 to give (−)-virantmycin (**2a**) in 53% yield (80% based on recovered starting material). Synthetic **2a** was identical in all respects to natural virantmycin[10,13] [IR, ^1H NMR, ^{13}C NMR spectra, and $[\alpha]_D^{24} = -16.5$ (*c* 0.11, $CHCl_3$) (lit.[13] $[\alpha]_D^{18} = -11.1$ (*c* 0.175, $CHCl_3$))]. Our synthesis required only nine steps from the commercially available (*S*)-(−)-indoline-2-carboxylic acid (**9**).

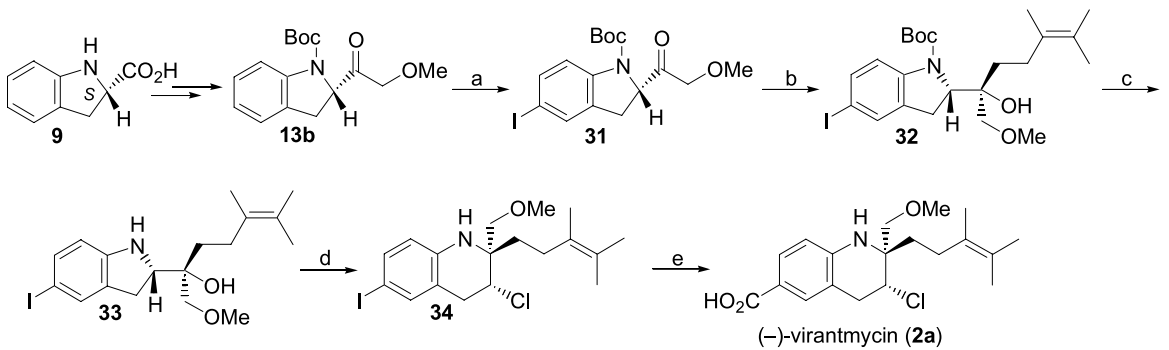
In summary, we have developed a new method for the synthesis of chiral 2,2,3-trisubstituted tetrahydroquinolines, involving the stereoselective preparation of α,α-disubstituted indoline-2-methanols, and its biomimetically inspired stereospecific rearrangement to tetrahydroquinolines in which contiguous quaternary and tertiary stereogenic centers are constructed in complete stereocontrol. The utility of this methodology for accessing various chiral indoline and tetrahydroquinoline alkaloids was clearly demonstrated by the total syntheses of benzastatin E and natural virantmycin.[31] The latter synthesis required only nine steps from the commercially available compound, which exhibits a sharp contrast to the previous syntheses of racemic and unnatural virantmycin. We believe that this stereospecific rearrangement reaction supports the biogenetic theory of benzastatin family involving the aziridine intermediate, though the alternative formation of these compounds via the epoxide intermediate cannot be ruled out without further biosynthetic experiments.

Table 2. Rearrangement from indolines **15** to tetrahydroquinolines **26**

Entry[a]	Substrate **15**	Product **26**[b]	Yield[c]	Entry[a]	Substrate **15**	Product **26**[b]	Yield[c]
1	 **15c**	 **26c**	63%	10	 **15j**	 **26j**	63%
2	 **15d**	 **26d**	63%	11	 **15s**	 **26s**	55%
3	 **15e**	 **26e**	Trace	12	 **15p**	 **26p**	62%
4	 **15f**	 **26f**	33%	13	 **15k**	 **26k**	41%
5	 **15r**	 **26r**	53%	14	 **15t**	 **26t**	50%
6	 **15g**	 **26g**	38%	15	 **15u**	 **26u**	52%
7	 **15n**	 **26n**	65%	16	 **15v**	 **26v**	46%

8	 **15h**	 **26h**	31%	17[d]	 **15w**	**26j**	No reaction
9	 **15i**	 **26i**	37% (44%)[e]	18	 **1**	 **26j**	61%

[a] All the reactions conducted were with Ph_3P (3 equiv) and CCl_4 (10 equiv), except for entry 9.
[b] The absolute stereochemistry was tentatively assigned by analogy with the reaction mechanism, except for **26c** (enantiomer of **26a**).
[c] Yield of isolated product after column chromatography.
[d] Racemic **15w** was used as a substrate.
[e] Polymer-supported triphenylphosphine was used.



Scheme 11. Reagents and conditions: (a) ICl, 2,6-di-*t*-butyl-4-methylpyridine, CH_2Cl_2, 0 °C to rt, 91%. (b) 3,4-Dimethyl-3-pentenylmagnesium bromide, THF, −78 °C, 73% (ds=19:1). (c) HCO_2H, CH_2Cl_2, 50 °C, 59%. (d) (n-Bu)$_3$P, CCl_4, CH_2Cl_2, reflux, 45%. (e) CO 1 atm, K_2CO_3, $Pd(OAc)_2$, H_2O/DMF, rt, 53% (80% based on recovered starting material).

3. Experimental

3.1. General procedure

Unless otherwise noted, all reactions were carried out in oven-dried glassware under a nitrogen atmosphere. Tetrahydrofuran (THF) was distilled from sodium metal/benzophenone ketyl. Dichloromethane (CH_2Cl_2) was distilled from calcium hydride. All other dry solvents were purchased from Aldrich in SureSeal™ containers. All other commercially obtained reagents were used as received. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian 400 or 500 spectrometer. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broadened. In the NMR spectral lists, chemical shifts which are assigned to the minor conformer are marked with an asterisk. Infrared spectra were recorded on a JASCO FT-IR-8900 spectrometer. Mass spectra were obtained on a JEOL HX-100, a SX-102A or a JMS-AX-505H mass spectrometer. Optical rotations were measured on a JASCO P-1030 polarimeter. Analytical TLC was performed on 0.25 mm pre-coated Merck silica gel 60 F_{254} plates. Flash column chromatography was performed on Merck silica gel 60 (230–400 mesh).

3.2. Preparation of 2-acylindolines 13a, b

3.2.1. 1-*tert*-Butyl 2-methyl (2*S*)-indoline-1,2-dicarboxylate (10). To a solution of carboxylic acid **9** (20.0 g, 123 mmol) in MeOH (200 ml) was added sulfuric acid (15 ml) dropwise at room temperature. The mixture was stirred for 6 h at 80 °C. The solvent was removed in vacuo. The residue was neutralized with 15% NaOH aq, then extracted with AcOEt (100 ml×2). The combined organic extracts were washed with 1 N NaOH aq (50 ml×2), brine (50 ml), dried over Na_2SO_4, filtered and evaporated to give the corresponding methyl ester (20.3 g, 94%).

To a solution of methyl ester (20.3 g, 114 mmol) in CH_2Cl_2 (100 ml) was added Boc_2O (40.3 g, 185 mmol) in CH_2Cl_2 (100 ml) at room temperature. After stirring at room temperature overnight, the solvent was evaporated. Purification by silica gel column chromatography (hexane to hexane–AcOEt 1:1) gave **10** (31.4 g, 92% from **9**) as a colorless solid (mp 43–45 °C). ^{1}H NMR (500 MHz, $CDCl_3$, two rotamers) 1.50 (9H, br), 3.11 (1H, dd, J=4.0, 16.0 Hz), 3.50 (1H, dd, J=14.0, 16.0 Hz), 3.75 (3H, s), 4.87 (1H, br), 6.95 (1H, t, J=7.0 Hz), 7.11 (1H, d, J=7.0 Hz), 7.14–7.22 (1H, m), 7.49* (0.3H, br), 7.89 (0.7H, br); ^{13}C NMR (125 MHz, $CDCl_3$, two rotamers) δ 28.2 (×3), 31.9*, 32.7, 52.3, 60.4, 81.3, 82.3*, 114.6, 122.5, 124.3, 124.4, 127.9, 141.6*, 142.5, 151.6, 152.6*, 172.4; IR ($CHCl_3$) cm^{-1}: 2981, 1741, 1709, 1485, 1390, 1169; HRMS calcd for $C_{15}H_{19}NO_4$ $(M)^+$ 277.1314, found 277.1305. Anal. Calcd for $C_{15}H_{19}NO_4$: C, 64.97; H, 6.91; N, 5.05. Found: C, 64.76; H, 6.70; N, 5.07; $[\alpha]_D^{24}=-70.6$ (c 0.84, $CHCl_3$).

3.2.2. 1-*tert*-Butyl 2-methyl (2*S*)-5-bromoindoline-1,2-dicarboxylate (11). NBS (8.79 g, 49.4 mmol) was added to a solution of **10** (13.7 g, 49.4 mmol) in DMF (50 ml) at 0 °C. The mixture was stirred for 2 h at 0 °C. After addition of water (50 ml), the aqueous solution was extracted with AcOEt (50 ml×2). The combined organic extracts were washed with water (50 ml), brine (50 ml), dried over Na_2SO_4, filtered and evaporated. Purification by silica gel column chromatography (hexane–AcOEt 5:1 to 2:1) provided **11** (16.4 g, 93%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.49 (9H, br), 3.09 (1H, d, J=16.5 Hz), 3.45–3.51 (1H, m), 3.75 (3H, s), 4.86 (1H, br), 7.22 (1H, s), 7.30 (1H, br d, J=7.0 Hz), 7.77 (1H, br s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.1 (×3), 32.2, 52.3, 60.4, 81.6, 114.7, 115.9, 127.3, 130.1, 130.6, 141.7, 151.3, 171.9; IR ($CHCl_3$) cm^{-1}: 2981, 1745, 1709, 1477, 1377, 1312, 1257, 1159, 1025; HRMS calcd for $C_{15}H_{18}NO_4Br$ $(M)^+$ 355.0419, found 355.0418; $[\alpha]_D^{24}=-31.9$ (c 0.83, $CHCl_3$).

3.2.3. *tert*-Butyl (2*S*)-5-bromo-2-{[methoxy(methyl)-amino]carbonyl}indoline-1-carboxylate (12a). To a slurry of Me(MeO)NH·HCl (2.36 g, 24.3 mmol) and **11** (5.76 g, 16.2 mmol) in THF (20 ml) was added *i*-PrMgCl in THF (16.1 ml, 2.0 M) dropwise at −20 °C. The mixture was stirred for 20 min at −10 °C. To the reaction mixture were added Me(MeO)NH·HCl (2.36 g, 24.3 mmol) and *i*-PrMgCl in THF (16.1 ml, 2.0 M) at −20 °C. After stirring for 10 min at −10 °C, the reaction was quenched with satd NH_4Cl aq (80 ml) and extracted with AcOEt (70 ml×2). The combined organic solution was washed with brine (80 ml), dried over Na_2SO_4, filtered and evaporated. Purification by silica gel column chromatography (hexane–AcOEt 5:1 to 1:1) gave **12a** (5.2 g, 83%) as a colorless solid (mp 105–106 °C). ^{1}H NMR (400 MHz, $CDCl_3$, two rotamers) δ 1.48 (6H, br s), 1.59 (3H, br s), 2.97 (1H, d, J=16.4 Hz), 3.22 (3H, s), 3.47 (1H, dd, J=11.6, 16.4 Hz), 3.75 (2H, br s), 3.81 (1H, br s), 5.20 (1H, br), 7.18 (1H, s), 7.28 (1H, br s), 7.35 (0.5H, br), 7.80 (0.5H, br d, J=8.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$, two rotamers) δ 28.2 (×3), 31.6*, 32.1, 32.6, 58.5*, 58.9, 61.3, 81.3, 82.3*, 114.5, 115.9, 127.2, 127.5, 130.5, 142.5, 151.5, 172.0; IR (KBr) cm^{-1}: 3000, 1702, 1679, 1478, 1378, 1320, 1256, 1161, 1029, 824; HRMS calcd for $C_{16}H_{21}N_2O_4BrNa$ $(M+Na)^+$ 407.0582, found 407.0583. Anal. Calcd for $C_{16}H_{21}N_2O_4Br$: C, 49.88; H, 5.49; N, 7.27; Br, 20.74. Found: C, 49.99; H, 5.50; N, 7.28; Br, 20.44; $[\alpha]_D^{24}=-89.4$ (c 0.90, $CHCl_3$).

3.2.4. *tert*-Butyl (2*S*)-2-{[methoxy(methyl)amino]carbonyl}indoline-1-carboxylate (12b). The procedure for the synthesis of **12a** was followed using **11** (7.03 g, 25.35 mmol), Me(MeO)NH·HCl (4.95 g, 50.7 mmol) and *i*-PrMgCl in THF (50.7 ml, 2.0 M) in THF (50 ml) to give **12b** (5.59 g, 72%) as a colorless solid (mp 109–111 °C). ^{1}H NMR (500 MHz, $CDCl_3$, two rotamers) δ 1.49 (6H, br s), 1.60 (3H, br s), 2.99 (1H, br), 3.22 (3H, s), 3.49 (1H, dd, J=11.8, 15.8 Hz), 3.75 (2H, br s), 3.82 (1H, br s), 5 18 (1H, br), 6.91 (1H, t, J=7.6 Hz), 7.07 (1H, d, J=7.6 Hz), 7.17 (1H, br), 7.50* (0.4H, br), 7.92 (0.6H, br), ^{13}C NMR (100 MHz, $CDCl_3$, two rotamers) δ 28.4 (×3), 32.0, 32.7, 58.3*, 58.8, 61.4, 80.9, 81.9*, 114.5, 122.1, 124.0, 124.5, 127.6, 128.0*, 129.0*, 142.1*, 143.0, 151.5, 152.5*, 171.6*, 172.3; IR (KBr) cm^{-1}: 2987, 1706, 1675, 1486, 1388, 1174, 757; HRMS calcd for $C_{16}H_{22}N_2O_4BrNa$ $(M+Na)^+$ 329.1477, found 329.1479. Anal. Calcd for $C_{16}H_{22}N_2O_4$: C, 62.73; H, 7.24; N, 9.14. Found: C, 62.66; H, 7.28; N, 9.12; $[\alpha]_D^{24}=-117.0$ (c 0.46, $CHCl_3$).

3.2.5. *tert*-Butyl (2*S*)-5-bromo-2-(methoxyacetyl)indoline-1-carboxylate (13a). To a solution of $MeOCH_2Sn(n\text{-}Bu)_3$ (1.30 g, 3.90 mmol) in THF (10 ml) was added *n*-BuLi in hexane (3.90 ml, 1.6 M) dropwise at −78 °C. After stirring for 10 min at −78 °C, a solution of Weinreb amide **12a** (500 mg, 1.30 mmol) in THF (5 ml) was added to the reaction mixture at −78 °C. The mixture was stirred for 15 min at −78 °C and quenched with satd NH_4Cl aq (20 ml). The product was extracted with AcOEt (30 ml×2) and the organic solution was washed with brine (30 ml), dried over Na_2SO_4, filtered and evaporated. Purification by silica gel column chromatography (hexane–AcOEt 10:1 to 2:1) gave **13a** (295 mg, 61%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.49 (9H, br), 2.98 (1H, dd, J=4.4, 16.8 Hz), 3.44 (3H, s), 3.48 (1H, br), 4.16 (2H, br), 5.07 (1H, br), 7.21 (1H, s), 7.31 (1H, br), 7.79 (1H, br); ^{13}C NMR (125 MHz, $CDCl_3$, two rotamers) δ 28.9 (×3), 31.1*, 32.0, 60.3, 63.9*, 64.7, 75.8, 82.7, 115.7, 116.8, (×2), 128.2, 131.5, 142.7, 151.9, 205.0; IR ($CHCl_3$) cm^{-1}: 2981, 1707, 1478, 1372, 1256, 1153, 1106, 1023, 909; HRMS calcd for $C_{16}H_{20}NO_4Br$ $(M)^+$ 369.0576, found 369.0567; $[\alpha]_D^{24}=-53.9$ (*c* 1.07, $CHCl_3$).

3.2.6. *tert*-Butyl (2*S*)-2-(methoxyacetyl)indoline-1-carboxylate (13b). The procedure for the synthesis of **13a** was followed using **12b** (2.12 g, 6.92 mmol), $MeOCH_2Sn(n\text{-}Bu)_3$ (6.96 g, 20.76 mmol), *n*-BuLi in hexane (13.1 ml, 1.6 M) in THF (50 ml) to give **13b** (1.13 g, 56%) as a colorless solid (mp 58–60 °C). ^{1}H NMR (500 MHz, $CDCl_3$, two rotamers) δ 1.50 (9H, br), 3.00 (1H, dd, J=4.5, 16.5 Hz), 3.43 (3H, s), 3.47 (1H, br), 4.18 (2H, br), 5.03 (1H, br), 6.94 (1H, t, J=7.5 Hz), 7.10 (1H, d, J=7.5 Hz), 7.19 (1H, br s), 7.48* (0.4H, br), 7.90 (0.6H, br); ^{13}C NMR (125 MHz, $CDCl_3$, two rotamers) δ 28.2 (×3), 30.9*, 31.7, 59.4, 63.3*, 64.0, 74.8, 75.4*, 81.6, 114.7 (×2), 122.6, 124.5, 127.9, 128.8*, 141.7*, 142.5, 151.4, 152.5*, 204.8; IR (KBr) cm^{-1}: 2976, 1732, 1704, 1488, 1395, 1154, 1111, 762; HRMS calcd for $C_{16}H_{21}NO_4Na$ $(M+Na)^+$ 314.1368, found 314.1373. Anal. Calcd for $C_{16}H_{21}NO_4$: C, 65.96; H, 7.27; N, 4.81. Found: C, 65.91; H, 7.11; N, 4.84; $[\alpha]_D^{24}=-92.4$ (*c* 0.65, $CHCl_3$).

3.3. Investigation of the diastereoselective Grignard addition

3.3.1. *tert*-Butyl (2*S*)-5-bromo-2-[(1*R*)-1-hydroxy-1-methoxymethyl-4,5-dimethylhex-4-enyl]indoline-1-carboxylate (major-14). To a solution of ketone **13a** (282 mg, 0.761 mmol) in THF (10 ml) was added 3,4-dimethyl-3-pentenylmagnesium bromide in THF (freshly prepared from the corresponding bromide (714 mg, 0.457 mmol) and Mg (146 mg, 0.686 mmol)) dropwise at −78 °C. The mixture was stirred for 15 min at −78 °C. The reaction was quenched with satd NH_4Cl aq (20 ml) and extracted with AcOEt (20 ml×2). The combined organic extracts were washed with brine (20 ml), dried over Na_2SO_4, filtered and evaporated. The diastereoselectivity (25:1) was determined by HPLC analysis. Purification by silica gel column chromatography (hexane–AcOEt 5:1) gave major-**14** (323 mg, 91%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.30 (1H, dt, J=5.0, 13.0 Hz), 1.40 (1H, dt, J=5.0, 13.0 Hz), 1.47 (3H, s), 1.55 (3H, s), 1.56 (3H, s), 1.56 (9H, s), 1.95–2.06 (2H, m), 3.07 (1H, dd, J=2.0, 17.5 Hz), 3.27 (1H, dd, J=11.0, 17.5 Hz), 3.35 (3H, s), 3.40 (2H, s), 4.74 (1H, d, J=9.5 Hz), 7.25–7.33 (3H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.0, 19.7, 20.4, 27.9, 28.1 (×3), 29.7, 31.2, 59.2, 64.8, 76.2, 76.7, 82.2, 115.3, 117.6, 123.9, 127.0, 127.2, 129.6 (×2), 134.3, 142.0; IR ($CHCl_3$) cm^{-1}: 3554, 3373, 2983, 2927, 1672, 1477, 1371, 1255, 1164, 1016, 909; HRMS calcd for $C_{23}H_{34}NO_4BrNa$ $(M+Na)^+$ 490.1569, found 490.1571; $[\alpha]_D^{24}=-45.4$ (*c* 0.86, $CHCl_3$).

3.3.2. *tert*-Butyl (2*S*)-5-bromo-2-[(1*S*)-1-hydroxy-1-methoxymethyl-4,5-dimethylhex-4-enyl]indoline-1-carboxylate (minor-14). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.55–1.68 (2H, m), 1.58 (9H, s), 1.63 (6H, s), 1.65 (3H, s), 2.08–2.19 (2H, m), 2.98 (3H, s), 3.07 (1H, d, J=9.8 Hz), 3.15 (1H, d, J=9.8 Hz), 3.19–3.27 (2H, m), 4.65 (1H, dd, J=2.4, 10.2 Hz), 7.25 (2H, d, J=9.8 Hz), 7.31 (1H, br s); ^{13}C NMR (500 MHz, $CDCl_3$) δ 18.3, 19.9, 20.5, 27.5, 28.3 (×3), 30.3, 33.2, 58.6, 66.0, 75.0, 76.2, 82.9, 115.6, 117.6, 124.0, 127.2, 127.6, 129.6, 135.0, 141.5, 155.2; IR (KBr) cm^{-1}: 3447, 2984, 2921, 2908, 2887, 2860, 1665, 1481, 1379, 1369; HRMS calcd for $C_{23}H_{34}NO_4BrNa$ $(M+Na)^+$ 490.1569, found 490.1567. Anal. Calcd for $C_{23}H_{34}BrNO_4$: C, 58.97; H, 7.32; N, 2.99; Br, 17.06. Found: C, 59.26; H, 7.20; N, 2.76; Br, 16.67; $[\alpha]_D^{24}=-77.5$ (*c* 0.98, $CHCl_3$); mp 103–106 °C.

3.3.3. (2*R*)-2-[(2*S*)-5-Bromo-2,3-dihydro-1*H*-indol-2-yl]-1-methoxy-5,6-dimethylhept-5-en-2-ol (15). To a solution of major-**14** (2.29 g, 4.89 mmol) in CH_2Cl_2 (10 ml) was added formic acid (20 ml) at room temperature. After stirring for 18 h at room temperature, the reaction mixture was neutralized with 15% NaOH aq and extracted with AcOEt (50 ml×2). The combined organic extracts were washed with brine (50 ml), dried over Na_2SO_4, filtered and evaporated. Purification by silica gel column chromatography (hexane–AcOEt 5:1) yielded **15** (938 mg, 52%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.44–1.59 (2H, m), 1.64 (3H, s), 1.64 (3H, s), 1.66 (3H, s), 2.01 (1H, dt, J=5.5, 12.0 Hz), 2.15 (1H, dt, J=5.5, 12.0 Hz), 2.79 (1H, s), 2.90 (1H, dd, J=9.0, 15.5 Hz), 3.05 (1H, dd, J=10.5, 15.5 Hz), 3.39 (1H, d, J=9.5 Hz), 3.40 (3H, s), 3.49 (1H, d, J=9.5 Hz), 4.08 (1H, dd, J=9.0, 10.5 Hz), 4.26 (1H, br s), 6.49 (1H, d, J=8.5 Hz), 7.09 (1H, d, J=8.5 Hz), 7.15 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.2, 19.9, 20.5, 28.1, 30.3, 32.8, 59.4, 65.9, 72.7, 78.1, 110.3, 110.5, 124.2, 127.1, 127.3, 129.7, 131.0, 149.7; IR ($CHCl_3$) cm^{-1}: 3405, 2924, 1604, 1481, 1247, 1166, 1111; HRMS calcd for $C_{18}H_{26}NO_2Br$ $(M)^+$ 367.1147, found 367.1150; $[\alpha]_D^{24}=-33.5$ (*c* 0.75, $CHCl_3$).

3.3.4. (1*R*,9a*S*)-7-Bromo-1-methoxymethyl-3,3-dimethyl-1-(3,4-dimethylpent-3-enyl)-9,9a-dihydro-1*H*-[1,3]oxazolo[3,4-*a*]indole (major-16). To a solution of **15** (932 mg, 2.53 mmol) in CH_2Cl_2 (20 ml) was added 2,2-dimethoxypropane (3.11 ml, 25.3 mmol) and pyridinium *p*-toluenesulfonate (100 mg) at room temperature. The mixture was stirred for 4 h at room temperature. The solvent was concentrated in vacuo and satd $NaHCO_3$ aq (20 ml) was added to the residue. The product was extracted with AcOEt (20 ml×2) and the organic extracts were washed with brine (20 ml), dried over Na_2SO_4, filtered and evaporated. Purification by silica gel column chromatography (hexane–AcOEt 10:1 to 5:1) gave major-**16**

(945 mg, 91%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.08 (1H, dt, J=4.4, 13.2 Hz), 1.50 (3H, s), 1.51 (3H, s), 1.55 (3H, s), 1.57 (3H, s), 1.57–1.62 (1H, m), 1.65 (3H, s), 1.95 (1H, dt, J=4.4, 13.2 Hz), 2.05 (1H, dt, J=4.4, 13.2 Hz), 3.03 (1H, dd, J=9.8, 17.6 Hz), 3.09 (1H, dd, J=4.4, 17.6 Hz), 3.28 (1H, d, J=9.6 Hz), 3.38 (3H, s), 3.52 (1H, d, J=9.6 Hz), 4.34 (1H, dd, J=4.4, 9.8 Hz), 6.49 (1H, d, J=8.0 Hz), 7.09 (1H, dd, J=2.4, 8.0 Hz), 7.12 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.2, 19.8, 20.5, 25.8, 28.1, 29.0, 29.2, 31.3, 59.5, 70.3, 76.3, 82.1, 94.8, 110.7, 113.0, 124.0, 127.3, 127.5, 129.4, 134.4, 147.8; IR ($CHCl_3$) cm^{-1}: 2928, 1596, 1474, 1371, 1259, 1118, 969, 862; HRMS calcd for $C_{21}H_{30}NO_2Br$ $(M)^+$ 407.1460, found 407.1470; $[\alpha]_D^{24}=+101.5$ (c 1.59, $CHCl_3$).

3.3.5. (1*S*,9a*S*)-7-Bromo-1-methoxymethyl-3,3-dimethyl-1-(3,4-dimethylpent-3-enyl)-9,9a-dihydro-1*H*-[1,3]oxazolo[3,4-*a*]indole (minor-16). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.50 (3H, s), 1.59–1.64 (1H, m), 1.63 (3H, s), 1.64 (3H, s), 1.66 (6H, s), 1.74–1.81 (1H, m), 2.04–2.17 (2H, m), 2.96 (1H, dd, J=10.3, 17.1 Hz), 3.08 (1H, d, J=9.8 Hz), 3.12 (1H, d, J=9.8 Hz), 3.19 (3H, s), 3.39 (1H, dd, J=2.9, 17.1 Hz), 4.17 (1H, dd, J=2.9, 10.3 Hz), 6.55 (1H, d, J=7.8 Hz), 7.12 (1H, d, J=7.8 Hz), 7.16 (1H, s); ^{13}C NMR (500 MHz, $CDCl_3$) δ 18.4, 19.9, 20.5, 25.8, 28.2, 28.6, 31.3, 34.9, 59.0, 70.1, 73.7, 82.4, 95.1, 111.1, 113.4, 124.1, 127.4, 127.5, 129.4, 134.4, 148.2; IR (KBr) cm^{-1}: 3429, 2983, 2928, 2913, 2896, 2863, 1596, 1472, 1337, 1250, 1105. Anal. Calcd for $C_{21}H_{30}BrNO_2\cdot 1/6H_2O$: C, 61.31; H, 7.43; N, 3.40; Br, 19.42. Found: C, 61.35; H, 7.29; N, 3.41; Br, 19.42; $[\alpha]_D^{24}=+98.9$ (c 0.66, $CHCl_3$); mp 68–70 °C.

3.4. Diastereoselective Grignard addition to 2-acylindolines 13

3.4.1. Preparation of 2-acylindolines 13c–h.

3.4.1.1. *tert*-Butyl (2*S*)-2-propionylindoline-1-carboxylate (13c). To a solution of **12b** (1.22 g, 3.98 mmol) in THF (5 ml) was added EtMgBr in Et_2O (4.0 ml, 3 M) dropwise at 0 °C. After stirring at 0 °C for 1.5 h, the reaction was quenched with satd NH_4Cl aq (10 ml) and extracted with AcOEt (10 ml×2). The combined organic extracts were washed with brine (10 ml), dried over Na_2SO_4, filtered and evaporated. Purification by silica gel column chromatography (hexane–AcOEt 10:1 to 5:1) gave **13c** (611 mg, 56%) as a colorless solid (mp 74–76 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.07 (3H, t, J=6.5 Hz), 1.48 (9H, br), 2.53 (2H, br), 2.94 (1H, dd, J=5.0, 16.5 Hz), 3.48 (1H, br), 4.83 (1H, br), 6.95 (1H, t, J=7.5 Hz), 7.10 (1H, d, J=7.5 Hz), 7.20 (1H, br s), 7.91 (1H, br); ^{13}C NMR (125 MHz, $CDCl_3$) δ 7.35, 28.2 (×3), 30.5, 31.9, 66.3, 81.5, 114.7, 122.6, 124.4, 127.9, 142.6, 151.6, 160.9, 208.7; IR (KBr) cm^{-1}: 2978, 1720, 1700, 1485, 1397, 1322, 1151, 748; HRMS calcd for $C_{16}H_{21}NO_3$ $(M)^+$ 275.1521, found 275.1524. Anal. Calcd for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69; N, 5.09. Found: C, 69.57; H, 7.61; N, 5.13; $[\alpha]_D^{24}=-80.2$ (c 0.32, $CHCl_3$).SO

3.4.1.2. *tert*-Butyl (2*R*)-2-(methoxyacetyl)indoline-1-carboxylate (13d). The procedure for the synthesis of **13a** was followed using enantiomer of **12b** (124 mg, 0.405 mmol), $MeOCH_2Sn(n\text{-}Bu)_3$ (407 mg, 1.215 mmol), n-BuLi in hexane (0.8 ml, 1.6 M) and THF (5 ml) to give **13d** (52 mg, 44%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$, two rotamers) δ 1.50 (9H, br), 3.00 (1H, dd, J=4.5, 16.5 Hz), 3.43 (3H, s), 3.47 (1H, br), 4.18 (2H, br), 5.03 (1H, br), 6.94 (1H, t, J=7.5 Hz), 7.10 (1H, d, J=7.5 Hz), 7.19 (1H, br s), 7.48* (0.4H, br), 7.90 (0.6H, br); ^{13}C NMR (125 MHz, $CDCl_3$, two rotamers) δ 28.2 (×3), 30.9*, 31.7, 59.4, 63.3*, 64.0, 74.8, 75.4*, 81.6, 114.7 (×2), 122.6, 124.5, 127.9, 128.8*, 141.7*, 142.5, 151.4, 152.5*, 204.8; IR (KBr) cm^{-1}: 2976, 1732, 1704, 1488, 1395, 1154, 1111, 762; HRMS calcd for $C_{16}H_{21}NO_4Na$ $(M+Na)^+$ 314.1368, found 314.1373; $[\alpha]_D^{24}=+69.3$ (c 0.32, $CHCl_3$).

3.4.1.3. *tert*-Butyl (2*S*)-2-acetylindoline-1-carboxylate (13e). The procedure for the synthesis of **13c** was followed using **12b** (1.3 g, 4.24 mmol), MeLi in diethyl ether (5.6 ml, 1.14 M) and THF (10 ml) to give **13e** (800 mg, 72%) as a colorless solid (mp 100–102 °C). ^{1}H NMR (500 MHz, $CDCl_3$, two rotamers) δ 1.50 (9H, br), 2.15 (3H, br s), 2.97 (1H, dd, J=5.0, 16.5 Hz), 3.47 (1H, br), 4.78 (1H, br), 6.95 (1H, t, J=7.5 Hz), 7.12 (1H, d, J=7.5 Hz), 7.20 (1H, br s), 7.49* (0.4H, br), 7.90 (0.6H, br); ^{13}C NMR (125 MHz, $CDCl_3$, two rotamers) δ 24.7, 25.6*, 28.2 (×3), 30.9*, 31.6, 66.8, 81.7, 114.8 (×2), 122.7, 124.5, 128.0, 142.5, 151.6, 206.2; IR (KBr) cm^{-1}: 2984, 1699, 1485, 1395, 1321, 1262, 1157, 752; HRMS calcd for $C_{15}H_{19}NO_3$ $(M)^+$ 261.1364, found 261.1360. Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.90; H, 7.01; N, 5.40; $[\alpha]_D^{24}=-82.8$ (c 0.28, $CHCl_3$).

3.4.1.4. *tert*-Butyl (2*S*)-5-bromo-2-butyrylindoline-1-carboxylate (13f). The procedure for the synthesis of **13c** was followed using **12a** (1.0 g, 2.60 mmol), n-PrMgCl in diethyl ether (3.9 ml, 2.0 M) and THF (15 ml) to give **13f** (238 mg, 25%) as a colorless solid (mp 70–71 °C) along with the recovered **12a** (s27%). ^{1}H NMR (400 MHz, $CDCl_3$, two rotamers) δ 0.92 (3H, t, J=7.4 Hz), 1.48 (6H, br s), 1.56–1.66 (5H, m), 2.38–2.46 (2H, br m), 2.92 (1H, dd, J=4.9, 17.1 Hz), 3.46 (1H, br), 4.85 (1H, br), 7.22 (1H, br s), 7.32 (1.4H, br), 7.79* (0.6H, br); ^{13}C NMR (125 MHz, $CDCl_3$, two rotamers) δ 14.0, 16.8, 28.4 (×3), 30.7*, 31.6, 39.7, 40.5*, 66.1*, 66.6, 82.1, 115.2, 116.4 (×2), 127.8, 130.4*, 131.1, 142.3, 152.0, 207.5; IR (KBr) cm^{-1}: 2976, 2962, 2934, 2874, 1712, 1701, 1480, 1374, 1155, 1143; HRMS calcd for $C_{17}H_{22}NO_3BrNa$ $(M+Na)^+$ 390.0681, found 390.0673. Anal. Calcd for $C_{17}H_{22}NO_3Br$: C, 55.44; H, 6.02; N, 3.80; Br, 21.70. Found: C, 55.63; H, 5.65; N, 3.75; Br, 21.67; $[\alpha]_D^{24}=-34.8$ (c 0.58, $CHCl_3$).

3.4.1.5. *tert*-Butyl (2*S*)-5-bromo-2-(5-methylhex-4-enoyl)indoline-1-carboxylate (13g). The procedure for the synthesis of **13c** was followed using **12a** (2.1 g, 5.45 mmol), 4-methyl-3-pentenylmagnesium bromide in THF (freshly prepared from the corresponding bromide (5.96 g, 36.6 mmol) and Mg (1.33 g, 54.8 mmol)) and THF (15 ml) to give **13g** (991 mg, 45%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.48 (9H, br), 1.65 (3H, s), 1.68 (3H, s), 2.26 (2H, q, J=7.2 Hz), 2.39–2.56 (2H, m), 2.91 (1H, dd, J=5.2, 16.8 Hz), 3.43 (1H, br t, J=14.0 Hz), 4.81 (1H, br), 5.11 (1H, dt, J=1.2, 7.6 Hz), 7.20 (1H, s), 7.30 (1H, d, J=7.2 Hz), 7.74 (1H, br); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.7, 21.9, 25.7, 28.2 (×3), 31.3, 37.7, 66.4, 81.9, 114.9, 116.0, 122.3, 124.6, 127.3, 130.7, 132.9, 141.8, 151.3, 206.7; IR ($CHCl_3$) cm^{-1}: 2977, 2930, 1708, 1477,

1373, 1257, 1151; HRMS calcd for $C_{20}H_{26}NO_3BrNa$ $(M+Na)^+$ 430.0994, found 430.0969; $[\alpha]_D^{24}=-25.3$ (c 0.65, $CHCl_3$).

3.4.1.6. *tert*-Butyl (2*S*)-5-bromo-2-(3-phenylpropionyl)-indoline-1-carboxylate (13h). The procedure for the synthesis of **13c** was followed using **12a** (212 mg, 0.691 mmol), phenethylmagnesium chloride in THF (2.1 ml, 1.0 M) and THF (2 ml) to give **13h** (200 mg, 83%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$, two rotamers) δ 1.52 (9H, br), 2.76 (1H, dd, $J=5.4$, 16.6 Hz), 2.80–2.93 (4H, m), 3.39 (1H, br), 4.85 (1H, br), 6.94 (1H, t, $J=7.3$ Hz), 7.06 (1H, d, $J=7.3$ Hz), 7.13–7.26 (6.5H, m), 7.89* (0.5H, br s); ^{13}C NMR (125 MHz, $CDCl_3$, two rotamers) δ 28.2 (×3), 29.2, 31.5, 39.1, 39.9*, 66.5, 81.6, 114.8 (×2), 122.7, 124.5, 126.1, 128.0, 128.4 (×2), 128.5 (×2), 140.9, 142.5, 152.0, 207.0; IR ($CHCl_3$) cm^{-1}: 2980, 1725, 1700, 1487, 1394, 1158, 753; HRMS calcd for $C_{22}H_{25}NO_3$ $(M)^+$ 351.1835, found 351.1842; $[\alpha]_D^{24}=-68.5$ (c 1.05, $CHCl_3$).

3.4.2. Diastereoselective Grignard addition to 2-acylindolines 13.

3.4.2.1. *tert*-Butyl (2*S*)-2-[(1*R*)-1-hydroxy-1-(methoxymethyl)propyl]indoline-1-carboxylate (14a). To a solution of **13b** (1.06 g, 3.64 mmol) in THF (10 ml) was added EtMgBr in THF (7.3 ml, 1.0 M) dropwise at −78 °C. The mixture was stirred for 15 min at −78 °C. The reaction was quenched with satd NH_4Cl aq (10 ml) and extracted with AcOEt (10 ml×2). The combined organic extracts were washed with brine (10 ml), dried over Na_2SO_4, filtered and evaporated. The diastereoselectivity (16:1) was determined by HPLC analysis. Purification by silica gel column chromatography (hexane–AcOEt 5:1) gave **14a** (2.1 mg, 57%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.83 (3H, t, $J=7.0$ Hz), 1.24–1.31 (1H, m), 1.35–1.38 (1H, m), 1.57 (9H, s), 3.03 (1H, dd, $J=2.0$, 16.5 Hz), 3.28 (1H, dd, $J=10.5$, 16.5 Hz), 3.64 (3H, s), 3.39 (1H, d, $J=10.0$ Hz), 3.41 (1H, d, $J=10.0$ Hz), 4.80 (1H, d, $J=9.5$ Hz), 6.95 (1H, t, $J=7.5$ Hz), 7.11–7.15 (2H, m), 7.45 (1H, br); ^{13}C NMR (125 MHz, $CDCl_3$) δ 7.26, 24.9, 28.3 (×3), 30.1, 59.3, 64.6, 76.0, 77.2, 82.1, 116.3 (×2), 122.8, 124.1, 126.9, 131.9, 142.8; IR ($CHCl_3$) cm^{-1}: 3373, 2981, 1667, 1484, 1382, 1331, 1287, 1165, 1115, 1015; HRMS calcd for $C_{18}H_{27}NO_4Na$ $(M+Na)^+$ 344.1838, found 344.1845; $[\alpha]_D^{24}=-62.1$ (c 0.80, $CHCl_3$).

Synthesis of compounds **14b–q** were carried out by the method similar to that used for **14a**.

3.4.2.2. *tert*-Butyl (2*S*)-2-[(1*S*)-1-hydroxy-1-(methoxymethyl)propyl]indoline-1-carboxylate (14b). The general procedure was followed using **13c** (584 mg, 2.12 mmol), $MeOCH_2Sn(n\text{-}Bu)_3$ (1.42 g, 4.24 mmol), n-BuLi in hexane (2.4 ml, 1.6 M) and THF (5 ml) to give **14b** (586 mg, 86%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 (3H, t, $J=7.8$ Hz), 1.58 (9H, s), 1.61–1.70 (2H, m), 2.83 (3H, s), 3.06 (1H, d, $J=9.0$ Hz), 3.13 (1H, dd, $J=2.0$, 16.0 Hz), 3.16 (1H, d, $J=9.0$ Hz), 3.25 (1H, dd, $J=10.4$, 16.0 Hz), 4.66 (1H, dd, $J=2.0$, 10.4 Hz), 6.96 (1H, t, $J=7.2$ Hz), 7.12–7.21 (2H, m), 7.45 (1H, br d, $J=6.4$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.05, 27.2, 28.3 (×3), 30.4, 58.5, 65.3, 74.6, 76.2, 82.2, 114.5, 116.1, 122.8, 123.9, 126.4, 132.3, 142.0; IR ($CHCl_3$) cm^{-1}: 3385, 2981, 1659, 1484, 1387, 1165; HRMS calcd for $C_{18}H_{27}NO_4Na$ $(M+Na)^+$ 344.1837, found 344.1860; $[\alpha]_D^{24}=-78.5$ (c 0.43, $CHCl_3$).

3.4.2.3. *tert*-Butyl (2*R*)-2-[(1*S*)-1-hydroxy-1-(methoxymethyl)propyl]indoline-1-carboxylate (14c). The general procedure was followed using **13d** (51 mg, 0.175 mmol), EtMgBr in THF (0.35 ml, 1.0 M) and THF (1 ml) to give **14c** (35 mg, 62%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.83 (3H, t, $J=7.0$ Hz), 1.24–1.31 (1H, m), 1.35–1.38 (1H, m), 1.57 (9H, s), 3.03 (1H, dd, $J=2.0$, 16.5 Hz), 3.28 (1H, dd, $J=10.5$, 16.5 Hz), 3.64 (3H, s), 3.39 (1H, d, $J=10.0$ Hz), 3.41 (1H, d, $J=10.0$ Hz), 4.80 (1H, d, $J=9.5$ Hz), 6.95 (1H, t, $J=7.5$ Hz), 7.11–7.15 (2H, m), 7.45 (1H, br); ^{13}C NMR (125 MHz, $CDCl_3$) δ 7.26, 24.9, 28.3 (×3), 30.1, 59.3, 64.6, 76.0, 77.2, 82.1, 116.3 (×2), 122.8, 124.1, 126.9, 131.9, 142.8; IR ($CHCl_3$) cm^{-1}: 3373, 2981, 1667, 1484, 1382, 1331, 1287, 1165, 1115, 1015; HRMS calcd for $C_{18}H_{27}NO_4Na$ $(M+Na)^+$ 344.1838, found 344.1845; $[\alpha]_D^{24}=+52.7$ (c 0.32, $CHCl_3$).

3.4.2.4. *tert*-Butyl (2*S*)-2-[(1*R*)-1-hydroxy-2-methoxy-1-phenethyl]indoline-1-carboxylate (14d). The general procedure was followed using **13b** (353 mg, 1.21 mmol), PhMgBr in THF (2.4 ml, 1.0 M) and THF (3 ml) to give **14d** (418 mg, 94%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.60 (9H, s), 2.85 (1H, d, $J=16.5$ Hz), 2.99 (1H, dd, $J=10.0$, 16.5 Hz), 3.28 (3H, s), 3.73 (1H, d, $J=10.0$ Hz), 3.87 (1H, d, $J=10.0$ Hz), 4.91 (1H, br), 6.90 (1H, t, $J=7.5$ Hz), 7.03 (1H, d, $J=7.5$ Hz), 7.11 (1H, t, $J=7.5$ Hz), 7.24 (1H, t, $J=7.5$ Hz), 7.33 (2H, t, $J=7.5$ Hz), 7.48 (3H, d, $J=7.5$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.3 (×3), 30.0, 59.4, 64.8, 77.9, 79.5, 81.4, 115.9 (×2), 122.7, 123.7, 125.6 (×2), 126.6, 127.1, 128.1, 128.2 (×2), 132.4, 142.3; IR ($CHCl_3$) cm^{-1}: 3549, 2981, 2932, 1685, 1602, 1484, 1381, 1282, 1258, 1166, 1135; HRMS calcd for $C_{22}H_{27}NO_4Na$ $(M+Na)^+$ 392.1838, found 392.1837; $[\alpha]_D^{24}=-41.7$ (c 0.53, $CHCl_3$).

3.4.2.5. *tert*-Butyl (2*S*)-2-[(1*R*)-1-(4-dimethylaminophenyl)-1-hydroxy-2-methoxyethyl]indoline-1-carboxylate (14e). The general procedure was followed using **13b** (253 mg, 0.87 mmol), 4-(*N*,*N*-dimethyl)aniline magnesium bromide in THF (3.5 ml, 0.5 M) and THF (2 ml) to give **14e** (300 mg, 84%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.61 (9H, s), 2.89 (1H, d, $J=15.0$ Hz), 2.94 (6H, s), 2.98 (1H, dd, $J=10.0$, 15.0 Hz), 3.12 (1H, br s), 3.28 (3H, s), 3.71 (1H, d, $J=9.3$ Hz), 3.81 (1H, d, $J=9.3$ Hz), 4.85 (1H, br s), 6.72 (2H, d, $J=8.8$ Hz), 6.91 (1H, t, $J=7.3$ Hz), 7.05 (1H, d, $J=7.3$ Hz), 7.12 (1H, t, $J=7.3$ Hz), 7.34 (2H, d, $J=8.8$ Hz), 7.49 (1H, br); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.7 (×3), 30.4, 40.8 (×2), 59.8, 65.2, 78.6, 79.5, 81.5, 112.6 (×2), 116.3 (×2), 123.0, 124.0, 126.6 (×2), 126.8, 130.2, 133.0, 143.5, 149.9; IR (thin film) cm^{-1}: 3554, 2977, 1695, 1615, 1522, 1484, 1382, 1369, 1167, 1135, 751; HRMS calcd for $C_{24}H_{33}N_2O_4$ $(M+H)^+$ 413.2440, found 413.2430; $[\alpha]_D^{24}=-52.9$ (c 0.29, $CHCl_3$).

3.4.2.6. *tert*-Butyl (2*S*)-2-[(1*R*)-1-(4-chlorophenyl)-1-hydroxy-2-methoxyethyl]indoline-1-carboxylate (14f). The general procedure was followed using **13b** (320 mg, 1.10 mmol), 4-chlorophenylmagnesium bromide in diethyl ether (2.2 ml, 1.0 M) and THF (3 ml) to give **14f** (265 mg,

61%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.60 (9H, s), 2.83 (1H, d, J=16.3 Hz), 3.02 (1H, dd, J=10.0, 16.3 Hz), 3.30 (3H, s), 3.44 (1H, br), 3.70 (1H, d, J=9.6 Hz), 3.82 (1H, d, J=9.6 Hz), 4.87 (1H, br), 6.92 (1H, t, J=7.3 Hz), 7.04 (1H, d, J=7.3 Hz), 7.12 (1H, t, J=7.3 Hz), 7.29 (2H, d, J=8.6 Hz), 7.42 (2H, d, J=8.6 Hz), 7.45 (1H, br); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.7 (×3), 30.4, 59.8, 65.0, 78.0, 79.6, 81.9, 116.3 (×2), 123.2, 124.1, 127.0, 127.5 (×2), 128.6 (×2), 132.4, 133.4, 141.1, 143.2; IR (KBr) cm^{-1}: 3457, 2978, 1689, 1485, 1381, 1369, 1168, 751; HRMS calcd for $C_{22}H_{27}ClNO_4$ $(M+H)^+$ 404.1629, found 404.1622; $[\alpha]_D^{24}=-62.8$ (c 0.44, $CHCl_3$).

3.4.2.7. *tert*-Butyl (2*S*)-2-[(1*R*)-1-cyclohexyl-1-hydroxy-2-methoxyethyl]indoline-1-carboxylate (14g). The general procedure was followed using **13b** (200 mg, 0.69 mmol), cyclohexylmagnesium bromide in THF (6.7 ml, 1.0 M) and THF (2 ml) to give **14g** (154 mg, 85%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.01–1.17 (4H, m), 1.52–1.57 (2H, m), 1.57 (9H, s), 1.65 (1H, br), 1.76 (3H, br), 1.88 (1H, br), 3.16–3.26 (2H, m), 3.30 (3H, s), 3.47 (1H, d, J=9.3 Hz), 3.53 (1H, d, J=9.3 Hz), 4.77 (1H, br), 6.94 (1H, t, J=8.0 Hz), 7.12 (2H, t, J=8.0 Hz), 7.47 (1H, br); ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.8, 27.2, 27.4, 27.4, 28.1 (×3), 28.7, 30.7, 44.2, 59.5, 64.0, 74.8, 78.1, 81.6, 116.5 (×2), 123.0, 124.1, 126.9, 133.2, 143.3; IR (thin film) cm^{-1}: 3551, 3393, 2977, 2928, 2854, 1697, 1485, 1387, 1169, 751; HRMS calcd for $C_{22}H_{34}NO_4$ $(M+H)^+$ 376.2488, found 376.2486; $[\alpha]_D^{24}=-47.9$ (c 0.71, $CHCl_3$).

3.4.2.8. *tert*-Butyl (2*S*)-2-[(1*R*)-1-hydroxy-1-(methoxymethyl)prop-2-enyl]indoline-1-carboxylate (14h). The general procedure was followed using **13b** (200 mg, 0.69 mmol), vinylmagnesium bromide in THF (2.1 ml, 1.0 M) and THF (2 ml) to give **14h** (213 mg, 97%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.58 (9H, s), 3.03 (1H, dd, J=2.0, 16.8 Hz), 3.27 (1H, dd, J=10.0, 16.8 Hz), 3.40 (3H, s), 3.43 (1H, d, J=9.6 Hz), 3.54 (1H, d, J=9.6 Hz), 4.74 (1H, d, J=10.0 Hz), 5.14 (1H, dd, J=1.2, 11.0 Hz), 5.42 (1H, dd, J=1.2, 17.2 Hz), 5.66 (1H, dd, J=11.0, 17.2 Hz), 6.94 (1H, t, J=7.2 Hz), 7.10–7.15 (2H, m), 7.44 (1H, br); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.3 (×3), 29.8, 30.0, 59.5, 63.6, 78.7, 82.0, 116.1 (×2), 116.4, 122.8, 123.9, 126.9, 131.7, 136.8, 142.7; IR ($CHCl_3$) cm^{-1}: 3357, 2982, 2931, 1686, 1484, 1383, 1287, 1258, 1352, 1166, 1133, 1017, 936; HRMS calcd for $C_{18}H_{25}NO_4Na$ $(M+Na)^+$ 342.1681, found 342.1682; $[\alpha]_D^{24}=-56.6$ (c 0.69, $CHCl_3$).

3.4.2.9. *tert*-Butyl (2*S*)-2-[(1*R*)-1-hydroxy-1-(methoxymethyl)-2-methylallyl]indoline-1-carboxylate (14i). The general procedure was followed using **13b** (320 mg, 1.10 mmol), 2-methylallylmagnesium bromide in THF (6.6 ml, 0.5 M) and THF (5 ml) to give **14i** (380 mg, 100%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.61 (9H, s), 1.84 (3H, s), 3.08–3.16 (2H, m), 3.37 (3H, s), 3.52 (1H, d, J=10.0 Hz), 3.75 (1H, d, J=10.0 Hz), 4.73 (1H, br), 5.09 (1H, s), 5.22 (1H, s), 6.96 (1H, t, J=7.5 Hz), 7.13–7.17 (2H, m), 7.52 (1H, br); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.6, 28.2 (×3), 29.3, 59.3, 61.5, 75.7, 80.6, 81.2, 113.6, 116.0, 122.7, 123.6, 126.4, 132.6, 142.9, 145.2, 153.7; IR ($CHCl_3$) cm^{-1}: 3559, 2980, 2930, 1685, 1484, 1373, 1285, 1166, 1135, 1014, 911; HRMS calcd for $C_{19}H_{27}NO_4Na$ $(M+Na)^+$ 356.1838, found 356.1838; $[\alpha]_D^{24}=-53.1$ (c 0.23, $CHCl_3$).

3.4.2.10. *tert*-Butyl (2*S*)-2-[(1*R*)-1-hydroxy-1-(methoxymethyl)-3-trimethylsilanylprop-2-ynyl]indoline-1-carboxylate (14j). The general procedure was followed using **13a** (330 mg, 1.13 mmol), (trimethylsilylmethyl) magnesium bromide in THF (freshly prepared from trimethylsilylacetylene (0.96 ml, 6.79 mmol), MeMgBr in diethyl ether (1.13 ml, 3.40 mmol) and THF (1 ml)) and THF (5 ml) to give **14j** (280 mg, 63%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ −0.13 (9H, s), 1.58 (9H, s), 3.05 (1H, d, J=16.5 Hz), 3.38 (1H, dd, J=10.5, 16.5 Hz), 3.47 (3H, s), 3.54 (1H, d, J=10.5 Hz), 3.66 (1H, d, J=10.5 Hz), 4.90 (1H, d, J=10.5 Hz), 6.95 (1H, t, J=7.5 Hz), 7.11 (1H, d, J=7.5 Hz), 7.13 (1H, t, J=7.5 Hz), 7.42 (1H, br); ^{13}C NMR (125 MHz, $CDCl_3$) δ −0.55 (×3), 28.2 (×3), 31.1, 59.8, 63.5, 75.0, 77.0, 82.5, 89.8, 102.7, 116.2 (×2), 122.8, 124.0, 126.7, 131.6, 142.5; IR ($CHCl_3$) cm^{-1}: 3317, 2981, 1664, 1484, 1383, 1251, 1165, 1135, 861, 845; HRMS calcd for $C_{21}H_{31}NO_4SiNa$ $(M+Na)^+$ 412.1920, found 412.1941; $[\alpha]_D^{24}=-68.8$ (c 0.35, $CHCl_3$).

3.4.2.11. *tert*-Butyl (2*S*)-5-bromo-2-[(1*R*)-1-hydroxy-1-(methoxymethyl)-5-methylhex-4-enyl]indoline-1-carboxylate (14k). The general procedure was followed using **13a** (1.20 g, 3.24 mmol), 4-methyl-3-pentenylmagnesium bromide in THF (freshly prepared from the corresponding bromide (2.5 g, 15.3 mmol) and Mg (550 mg, 23 mmol)) and THF (15 ml) to give **14k** (992 mg, 67%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.26 (1H, dt, J=5.0, 14.0 Hz), 1.34–1.40 (1H, m), 1.53 (3H, s), 1.56 (9H, s), 1.62 (3H, s), 1.91–1.97 (1H, m), 2.01–2.07 (1H, m), 3.04 (1H, d, J=16.5 Hz), 3.26 (1H, dd, J=10.5, 16.5 Hz), 3.33 (3H, s), 3.38 (2H, s), 4.76 (1H, d, J=10.5 Hz), 4.96 (1H, t, J=7.0 Hz), 7.21–7.24 (2H, m), 7.32 (1H, br); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.4, 21.5, 25.5, 28.1 (×3), 29.7, 32.5, 59.2, 64.8, 76.8, 76.9, 82.3, 115.3, 117.5, 124.3, 127.0, 129.6, 131.3, 134.2, 142.0, 154.4; IR ($CHCl_3$) cm^{-1}: 3381, 2981, 2930, 1672, 1477, 1371, 1254, 1164; HRMS calcd for $C_{22}H_{32}NO_4BrNa$ $(M+Na)^+$ 476.1412, found 476.1412; $[\alpha]_D^{24}=-43.5$ (c 0.93, $CHCl_3$).

3.4.2.12. *tert*-Butyl (2*S*)-5-bromo-2-[(1*R*)-1-hydroxy-1-(methoxymethyl)-3-phenylpropyl]indoline-1-carboxylate (14l). The general procedure was followed using **13a** (1.0 g, 2.70 mmol), phenethylmagnesium chloride in THF (3.2 ml, 1.0 M) and THF (15 ml) to give **14l** (871 mg, 68%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.53 (9H, s), 1.61–1.70 (2H, m), 2.54 (1H, dt, J=5.2, 11.8 Hz), 2.67 (1H, dt, J=5.2, 11.8 Hz), 3.04 (1H, d, J=16.9 Hz), 3.25 (1H, dd, J=10.3, 16.9 Hz), 3.32 (3H, s), 3.38 (2H, s), 4.77 (1H, d, J=10.3 Hz), 7.01 (2H, d, J=6.6 Hz), 7.07–7.27 (6H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.2 (×3), 29.3, 29.8, 34.6, 59.3, 65.0, 76.3, 76.7, 82.6, 115.5, 117.7, 125.6, 127.2, 128.2 (×2), 128.3 (×2), 129.8, 134.1, 141.9, 142.4, 154.6; IR (film) cm^{-1}: 3394, 2978, 2930, 1702, 1668, 1476, 1369, 1329, 1166, 1137, 757; HRMS calcd for $C_{24}H_{30}NO_4BrNa$ $(M+Na)^+$ 498.1256, found 498.1265; $[\alpha]_D^{24}=-37.8$ (c 1.03, $CHCl_3$).

3.4.2.13. *tert*-Butyl (2*S*)-5-bromo-2-[(1*R*)-1-hydroxy-1-(methoxymethyl)-pent-4-enyl]indoline-1-carboxylate

(14m). The general procedure was followed using **13a** (715 mg, 1.93 mmol), 3-butenylmagnesium chloride in THF (4.6 ml, 0.5 M) and THF (10 ml) to give **14m** (671 mg, 82%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28–1.36 (1H, m), 1.38–1.46 (1H, m), 1.57 (9H, s), 1.95–2.04 (1H, m), 2.13–2.24 (1H, m), 3.04 (1H, d, J=16.9 Hz), 3.26 (1H, dd, J=9.5, 16.9 Hz), 3.35 (3H, s), 3.38 (2H, s), 4.77 (1H, d, J=10.9 Hz), 4.87 (1H, d, J=10.9 Hz), 4.92 (1H, d, J=19.1 Hz), 5.66–5.76 (1H, m), 7.24–7.26 (2H, m), 7.32 (1H, br); ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.2, 28.2 (×3), 29.8, 31.6, 59.3, 64.9, 76.0, 76.7, 82.5, 114.2, 115.4, 117.6, 127.1, 129.8, 134.2, 138.8, 142.0, 154.2; IR (film) cm^{-1}: 3401, 2977, 2928, 1703, 1670, 1477, 1369, 1167, 1015, 815; HRMS calcd for $C_{20}H_{28}NO_4BrNa$ $(M+Na)^+$ 448.1100, found 448.1122; $[\alpha]_D^{24}=-50.8$ (c 1.06, $CHCl_3$).

3.4.2.14. *tert*-Butyl (2*S*)-2-(1-hydroxy-1-methylethyl)-indoline-1-carboxylate (14n). The general procedure was followed using **13e** (760 mg, 2.91 mmol), methyllithium in diethyl ether (7.7 ml, 1.1 M) and THF (10 ml) to give **14n** (500 mg, 62%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.00 (3H, s), 1.22 (3H, s), 1.58 (9H, s), 2.84 (1H, d, J=16.5 Hz), 3.32 (1H, dd, J=10.5, 16.5 Hz), 4.51 (1H, d, J=10.5 Hz), 6.95 (1H, t, J=7.5 Hz), 7.12 (1H, d, J=7.5 Hz), 7.15 (1H, t, J=7.5 Hz), 7.47 (1H, br); ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.3, 26.8, 28.2 (×3), 30.9, 67.5, 74.3, 82.1, 116.2 (×2), 122.9, 124.1, 127.0, 131.4, 142.5; IR ($CHCl_3$) cm^{-1}: 3405, 2981, 1665, 1484, 1384, 1288, 1256, 1165, 1045, 1019; HRMS calcd for $C_{16}H_{23}NO_3Na$ $(M+Na)^+$ 300.1576, found 300.1568; $[\alpha]_D^{24}=-69.7$ (c 0.69, $CHCl_3$).

3.4.2.15. *tert*-Butyl (2*S*)-5-bromo-2-[(1*R*)-1-hydroxy-1-phenylethynylbutyl]indoline-1-carboxylate (14o). The general procedure was followed using **13f** (220 mg, 0.60 mmol), phenylacetyllithium in THF (1.8 ml, 1.0 M) and THF (5 ml) to give **14o** (240 mg, 85%) as a colorless solid (mp 122–124 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.01 (3H, t, J=7.1 Hz), 1.58 (9H, s), 1.66–1.76 (3H, m), 1.80–1.86 (1H, m), 3.12 (1H, dd, J=1.7, 16.8 Hz), 3.42 (1H, dd, J=9.9, 16.8 Hz), 4.70 (1H, dd, J=1.7, 9.9 Hz), 6.88 (2H, d, J=7.3 Hz), 7.16–7.34 (6H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.6, 17.2, 28.5 (×3), 31.7, 42.2, 67.5, 75.7, 83.5, 84.7, 89.0, 115.9, 118.1, 122.6, 124.5, 127.4, 128.3 (×2), 128.4, 130.2, 131.8 (×2), 134.6, 142.2; IR (KBr) cm^{-1}: 3489, 2960, 2931, 2872, 1688, 1668, 1479, 1369, 1335, 1165, 757; HRMS calcd for $C_{25}H_{28}NO_3BrNa$ $(M+Na)^+$ 492.1150, found 492.1158. Anal. Calcd for $C_{25}H_{28}NO_3Br$: C, 63.83; H, 6.00; N, 2.98; Br, 16.99. Found: C, 63.98; H, 5.70; N, 2.99; Br, 16.90; $[\alpha]_D^{24}=-48.8$ (c 0.94, $CHCl_3$).

3.4.2.16. *tert*-Butyl (2*S*)-5-bromo-2-[(1*S*)-1-hydroxy-1,5-dimethylhex-4-enyl]indoline-1-carboxylate (14p). The general procedure was followed using **13g** (20 mg, 0.049 mmol), methyllithium in diethyl ether (0.13 ml, 1.1 M) and THF (2 ml) to give **14p** (10 mg, 47%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (3H, s), 1.47–1.54 (2H, m), 1.57 (9H, s), 1.63 (3H, s), 1.69 (3H, s), 2.12–2.21 (2H, m), 2.77 (1H, d, J=16.8 Hz), 3.30 (1H, dd, J=10.4, 16.8 Hz), 4.60 (1H, dd, J=2.4, 10.4 Hz), 5.12 (1H, t, J=6.4 Hz), 7.23–7.33 (3H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.5, 20.9, 21.5, 25.5, 28.1 (×3), 30.5, 39.2, 66.5, 75.9, 82.7, 115.4, 117.5, 124.2, 127.1, 129.9, 131.5, 133.6, 141.8, 155.0; IR ($CHCl_3$) cm^{-1}: 3437, 2979, 1668, 1477, 1372, 1163, 1015; HRMS calcd for $C_{21}H_{30}NO_3Br$ $(M)^+$ 423.1409, found 423.1400; $[\alpha]_D^{24}=-72.1$ (c 0.38, $CHCl_3$).

3.4.2.17. *tert*-Butyl (2*S*)-2-[(1*R*)-1-hydroxy-1,3-diphenylpropyl]indoline-1-carboxylate (14q). The general procedure was followed using **13h** (17 mg, 0.048 mmol), phenyllithium in diethyl ether (0.3 ml, 0.94 M) and THF (1 ml) to give **14q** (14 mg, 68%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.55 (9H, s), 2.19 (1H, dt, J=4.9, 12.7 Hz), 2.32 (1H, br), 2.45 (1H, dt, J=3.9, 12.7 Hz), 2.65 (1H, br), 2.87 (1H, d, J=16.1 Hz), 3.11 (1H, br), 4.90 (1H, d, J=9.3 Hz), 6.86 (1H, t, J=7.0 Hz), 6.97 (1H, d, J=7.0 Hz), 7.03 (1H, br), 7.11–7.26 (9H, m), 7.43 (2H, d, J=7.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.5 (×3), 29.9, 30.9, 42.0, 67.9, 80.9, 82.3, 116.5 (×2), 123.3, 124.1, 125.9, 126.3, 127.0, 127.1, 127.6, 128.2, 128.3, 128.6 (×2), 128.6 (×2), 128.7, 132.2, 142.1, 142.9; IR (KBr) cm^{-1}: 2976, 2929, 1702, 1682, 1483, 1369, 1167, 751, 701; HRMS calcd for $C_{28}H_{32}NO_3$ $(M+H)^+$ 430.3282, found 430.2387; $[\alpha]_D^{24}=-59.6$ (c 1.40, $CHCl_3$).

3.5. Synthesis of (+)-benzastatin E (1)

3.5.1. (1*R*,9a*S*)-1-(Methoxymethyl)-3,3-dimethyl-1-(3,4-dimethylpent-3-enyl)-9,9a-dihydro-1*H*-[1,3]oxazolo[3,4-*a*]indole-7-carboxylic acid (17). To a solution of major-**16** (919 mg, 2.25 mmol) in ether (15 ml) was added *t*-BuLi in pentane (6.0 ml, 1.5 M) dropwise at −78 °C. After stirring for 15 min at −78 °C, a portion of CO_2 (2.0 g) was added to the reaction mixture at −78 °C. After warming up to room temperature, the reaction was quenched with satd NH_4Cl aq (30 ml) and extracted with AcOEt (30 ml×2). The combined organic extracts were washed with brine (30 ml), dried over Na_2SO_4, filtered and evaporated. Purification by silica gel column chromatography (hexane–AcOEt 10:1 to 1:2) provided **17** (446 mg, 53%) as a colorless solid (mp 210–213 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.08 (1H, dt, J=4.4, 13.2 Hz), 1.49 (3H, s), 1.54 (6H, s), 1.55 (3H, s), 1.56–1.65 (1H, m), 1.73 (3H, s), 1.95 (1H, dt, J=4.4, 13.2 Hz), 2.07 (1H, dt, J=4.4, 13.2 Hz), 3.06–3.10 (2H, m), 3.32 (1H, d, J=9.6 Hz), 3.40 (3H, s), 3.53 (1H, d, J=9.6 Hz), 4.45 (1H, dd, J=6.0, 9.6 Hz), 6.60 (1H, d, J=8.8 Hz), 7.74 (1H, s), 7.82 (1H, dd, J=1.6, 8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.4, 20.6, 26.0, 28.0, 28.5, 28.9, 30.7, 59.6, 70.2, 75.9, 82.1, 93.9, 109.3, 118.7, 124.0, 126.5, 127.0, 130.8, 131.9, 132.5, 152.9, 171.8; IR (KBr) cm^{-1}: 2913, 1666, 1607, 1450, 1369, 1296, 1272, 1217, 1120, 827, 768; HRMS calcd for $C_{22}H_{31}NO_4$ $(M)^+$ 373.2253, found 373.2265; $[\alpha]_D^{24}=+223.5$ (c 0.42, $CHCl_3$).

3.5.2. (1*R*,9a*S*)-1-Methoxymethyl-3,3-dimethyl-1-(3,4-dimethylpent-3-enyl)-9,9a-dihydro-1*H*-[1,3]oxazolo[3,4-*a*]indole-7-carboxamide (18). To a solution of **17** (103 mg, 0.276 mmol) in THF (5 ml) was added 1,1′-carbonyldiimidazole (134 mg, 0.827 mmol) at room temperature. The mixture was stirred for 30 min at room temperature. 1,1′-Carbonyldiimidazole (134 mg, 0.827 mmol) was added and stirred for another 30 min at room temperature. 28% NH_3 aq (5.0 ml) was added to the reaction mixture at room

temperature and stirred for 12 h at this temperature. After addition of water (20 ml), the aqueous solution was extracted with AcOEt (20 ml×2). The combined organic extracts were washed with brine (20 ml), dried over Na_2SO_4, filtered and evaporated. Purification by silica gel column chromatography (hexane–AcOEt 1:1 to AcOEt) gave **18** (76 mg, 74%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.06 (1H, dt, J=5.5, 13.2 Hz), 1.48 (3H, s), 1.53 (6H, s), 1.55 (3H, s), 1.55–1.62 (1H, m), 1.71 (3H, s), 1.95 (1H, dt, J=5.5, 13.2 Hz), 2.06 (1H, dt, J=5.5, 13.2 Hz), 3.01–3.17 (2H, m), 3.31 (1H, d, J=9.6 Hz), 3.39 (3H, s), 3.53 (1H, d, J=9.6 Hz), 4.42 (1H, dd, J=5.2, 8.8 Hz), 5.90 (2H, br), 6.59 (1H, d, J=8.8 Hz), 7.49 (1H, dd, J=2.4, 8.8 Hz), 7.52 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.4, 19.9 (×2), 20.6, 26.0, 28.0, 28.8, 28.9, 31.0, 59.6, 70.2, 76.0, 82.1, 94.2, 109.8, 123.0, 123.9, 124.1, 127.1, 132.1, 151.7, 169.4; IR ($CHCl_3$) cm^{-1}: 3534, 3417, 2928, 1663, 1609, 1492, 1444, 1370, 1272, 1118, 909; HRMS calcd for $C_{22}H_{32}N_2O_3Na$ $(M+Na)^+$ 395.2311, found 395.2313; $[\alpha]_D^{24}=+154.2$ (c 0.20, $CHCl_3$).

3.5.3. (+)-Benzastatin E (1). To a solution of **18** (70 mg, 0.188 mmol) in MeOH (5 ml) was added pyridinium *p*-toluenesulfonate (10 mg) at room temperature. The mixture was stirred for 3 h at room temperature. The solvent was concentrated in vacuo. The residue was purified by silica gel column chromatography (AcOEt to AcOEt–MeOH 10:1) to give **1** (40 mg, 64%) as a colorless solid (mp 171–174 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.48 (1H, dd, J=5.5, 14.0 Hz), 1.57 (1H, dd, J=4.5, 14.0 Hz), 1.64 (6H, s), 1.66 (3H, s), 2.01 (1H, dd, J=5.5, 13.0 Hz), 2.15 (1H, dd, J=4.5, 13.0 Hz), 2.70 (1H, br s), 2.97 (1H, dd, J=8.5, 16.0 Hz), 3.07 (1H, dd, J=11.0, 16.0 Hz), 3.42 (3H, s), 3.42 (1H, d, J=9.5 Hz), 3.52 (1H, d, J=9.5 Hz), 4.15 (1H, t, J=9.5 Hz), 4.65 (1H, br), 5.60 (2H, br), 6.58 (1H, d, J=7.5 Hz), 7.50 (1H, d, J=7.5 Hz), 7.55 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.3, 20.0, 20.6, 28.2, 30.0, 32.7, 59.6, 66.2, 73.0, 78.4, 107.8, 123.1, 124.1, 124.5, 127.2, 128.0, 128.6, 154.5, 169.3; IR (KBr) cm^{-1}: 3416, 3312, 2918, 1645, 1606, 1441, 1380, 1262, 1112, 773; HRMS calcd for $C_{19}H_{29}N_2O_3$ $(M+H)^+$ 333.2178, found 333.2187. Anal. Calcd for $C_{19}H_{28}N_2O_3\cdot 0.3H_2O$: C, 67.55; H, 8.53; N, 8.29. Found: C, 67.48; H, 8.59; N, 8.24; $[\alpha]_D^{24}=+21.3$ (c 0.10, MeOH).

3.6. Stereoselective rearrangement from α,α-disubstituted indoline-2-methanols to 2,2,3-trisubstituted tetrahydroquinolines

3.6.1. Investigation of the rearrangement reaction with α-monosubstituted indoline-2-methanol 22.

3.6.1.1. *tert*-Butyl 5-bromo-2-formylindoline-1-carboxylate (19). To a solution of lithium aluminum hydride (1.67 g, 44.1 mmol) in THF (40 ml) was added racemic-**11** (7.85 g, 22.0 mmol) in THF (20 ml) dropwise at −78 °C. After stirring for 3 h at −40 °C, the reaction mixture was quenched with H_2O (1.7 ml), 5 N NaOH aq (1.7 ml), then H_2O (5.1 ml), and stirred at room temperature for 30 min. To the mixture was added magnesium sulfate (10 g) and AcOEt (30 ml), and the mixture was filtered and evaporated. Purification by silica gel column chromatography (hexane–AcOEt 6:1 to 1:1) gave the corresponding alcohol (6.00 g, 83%).

To a solution of alcohol (5.78 g, 15.5 mmol) in CH_2Cl_2 (150 ml) was added Et_3N (8.7 ml, 62.1 mmol), DMSO (7.3 ml, 102.5 mmol), and pyridine sulfur trioxide complex(7.41 g, 46.6 mmol) at 0 °C. After stirring at room temperature for 3 h, H_2O (150 ml) was added, and the product was extracted with CH_2Cl_2 (50 ml×3). The combined organic extracts were washed with brine (150 ml), dried over Na_2SO_4, filtered and evaporated. Purification by silica gel column chromatography (hexane–AcOEt 4:1 to 3:2) yielded aldehyde **19** (3.09 g, 61%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.52 (9H, br), 3.14 (1H, dd, J=4.9, 16.6 Hz), 3.38 (1H, br), 4.75 (1H, br), 7.26 (1H, s), 7.32 (1H, s), 7.78 (1H, br s), 9.63 (1H, br s); ^{13}C NMR (125 MHz, $CDCl_3$, two rotamers) δ 28.2 (×3), 29.3, 60.0, 82.4, 115.2, 116.2 (×2), 127.6, 130.2*, 130.8, 141.6, 151.4, 198.3; IR (KBr) cm^{-1}: 3282, 3063, 2929, 1672, 1645, 1223, 751; HRMS calcd for $C_{14}H_{16}NO_3BrK$ $(M+K)^+$ 363.9951, found 363.9952.

3.6.1.2. *tert*-Butyl (2*S)-5-bromo-2-[(1*R**)-1-hydroxypent-4-enyl]indoline-1-carboxylate (20).** This diastereoselective Grignard addition was carried out by a method similar to that used for synthesis of **14a** with **19** (300 mg, 0.92 mmol), 3-butenylmagnesium bromide in THF (2.2 ml, 0.5 M) and THF (10 ml) to give **20** (264 mg, 75%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.43–1.44 (1H, m), 1.52–1.57 (1H, m), 1.57 (9H, s), 2.10–2.18 (1H, m), 2.27–2.31 (1H, m), 2.99 (1H, br), 3.20–3.25 (1H, m), 3.98 (1H, br), 4.49 (1H, br), 4.98 (1H, d, J=10.3 Hz), 5.05 (1H, dd, J=1.5, 15.6 Hz), 5.78–6.86 (1H, m), 7.24 (1H, s), 7.26 (1H, s), 7.47 (1H, br); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.6 (×4), 30.3, 31.6, 64.5, 73.3, 82.4, 115.4, 115.4, 116.8, 127.7, 130.3 (×2), 133.4, 138.4, 142.1; IR (liquid film) cm^{-1}: 3464, 2977, 2933, 1702, 1479, 1385, 1370, 1168, 1142; HRMS calcd for $C_{18}H_{24}NO_3BrNa$ $(M+Na)^+$ 404.08373, found 404.08407.

3.6.1.3. (1*R,9a*S**)-7-Bromo-1-but-3-enyl-3,3-dimethyl-9,9a-dihydro-1*H*-[1,3]oxazolo-[3,4-*a*]indole-3-spiro-1′-cyclohexane (21).** To a solution of **20** (144 mg, 0.38 mmol) in CH_2Cl_2 was added TFA (1 ml) at 0 °C. After stirring at room temperature for 20 min, the reaction mixture was neutralized with satd $NaHCO_3$ aq and extracted with AcOEt (5 ml×2). The combined organic extracts were washed with brine (10 ml), dried over Na_2SO_4, filtered and evaporated. Purification by silica gel column chromatography (hexane–AcOEt 9:1) gave the corresponding indoline-2-methanol (62 mg, 59%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.43–1.60 (2H, m), 2.08–2.18 (1H, m), 2.21 (1H, s), 2.24–2.31 (1H, m), 2.88 (1H, dd, J=9.5, 16.0 Hz), 3.00 (1H, dd, J=9.9, 16.0 Hz), 3.71–3.73 (1H, m), 3.82 (1H, br), 3.95 (1H, dt, J=3.7, 9.5 Hz), 4.96 (1H, d, J=9.6 Hz), 5.03 (1H, dd, J=1.8, 17.3 Hz), 5.76–5.86 (1H, m), 6.46 (1H, d, J=8.1 Hz), 7.06 (1H, br d, J=8.1 Hz), 7.13 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 29.3, 30.2, 31.9, 64.5, 71.3, 110.7 (×2), 115.0, 127.5, 129.7, 131.3, 137.9, 149.4; IR (KBr) cm^{-1}: 3304, 3327, 2929, 2889, 1483, 1248, 920, 814; HRMS calcd for $C_{13}H_{16}NOBr$ $(M)^+$ 281.0415, found 281.0418.

To a solution of indoline-2-methanol (110 mg, 0.39 mmol) in CH_2Cl_2 was added 1,1-dimethoxycyclohexane (0.6 ml, 3.9 mmol) and *p*-TsOH (7 mg, 0.04 mmol) at room

temperature. The mixture was stirred at 30 min at room temperature. After concentration of the reaction mixture, purification by silica gel column chromatography (hexane–AcOEt 19:1 to 9:1) afforded **21** (102 mg, 72%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.13–1.21 (1H, m), 1.29–1.33 (1H, m), 1.42–1.63 (8H, m), 1.78 (1H, dt, J=4.2, 12.3 Hz), 2.00–2.03 (1H, m), 2.06–2.15 (1H, m), 2.19–2.26 (1H, m), 2.72 (1H, dd, J=9.5, 16.0 Hz), 3.07 (1H, dd, J=7.7, 16.0 Hz), 4.11 (1H, dd, J=5.9, 14.5 Hz), 4.32 (1H, dd, J=8.4, 14.5 Hz), 4.95 (1H, d, J=10.3 Hz), 5.01 (1H, dd, J=1.8, 17.3 Hz), 5.75–5.85 (1H, m), 6.64 (1H, d, J=8.5 Hz), 7.09 (1H, d, J=8.5 Hz), 7.14 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.4, 23.9, 25.4, 30.2, 30.5, 30.8, 35.4, 37.2, 67.3, 74.4, 96.2, 113.6, 115.0, 117.9, 127.3, 129.3, 136.4, 138.0, 148.5; IR (liquid film) cm^{-1}: 2936, 2857, 1473; HRMS calcd for $C_{19}H_{24}NOBr$ (M)$^+$ 361.1041, found 361.1032.

3.6.1.4. Methyl (2*S)-2-[(1*R**)-1-hydroxypent-4-enyl]-indoline-5-carboxylate (22).** A method for the preparation of **17** was followed using **21** (115 mg, 0.32 mmol), *t*-BuLi in pentane (0.58 ml, 1.5 M) and THF (3 ml) to give the corresponding carboxylic acid (96 mg, crude yield 90%). The obtained carboxylic acid was used without further purification.

To a solution of crude carboxylic acid in MeOH (6 ml) was added $TMSCH_2N_2$ in hexane (2.5 ml, 2 M) at 0 °C. After stirring at room temperature overnight, the solvent was evaporated. The residue was purified by silica gel column chromatography (hexane–AcOEt 10:1) to give the corresponding methyl ester (92 mg, crude yield 92%). The obtained methyl ester was used without further purification.

To a solution of methyl ester in MeOH (1 ml) was added Amberlyst-15® ion exchange resin (10 mg) at room temperature. After stirring at room temperature for 4 h, the mixture was filtered and evaporated. Purification by silica gel column chromatography (hexane–AcOEt 7:3) gave **22** (51 mg, 62% from **21**) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.51–1.66 (2H, m), 2.13 (1H, s), 2.15–2.23 (1H, m), 2.29–2.36 (1H, m), 3.01 (1H, dd, J=10.3, 16.1 Hz), 3.07 (1H, dd, J=9.8, 16.1 Hz), 3.78–3.80 (1H, m), 3.86 (3H, s), 4.07 (1H, dt, J=2.9, 9.3 Hz), 4.22 (1H, br s), 5.02 (1H, d, J=10.7 Hz), 5.09 (1H, d, J=16.6 Hz), 5.82–5.90 (1H, m), 6.59 (1H, d, J=8.8 Hz), 7.75 (1H, s), 7.78 (1H, d, J=8.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.9, 30.1, 31.7, 51.6, 64.4, 71.8, 107.8, 115.2, 120.4, 126.7, 128.5, 130.6, 138.1, 155.0, 167.3; IR (KBr) cm^{-1}: 3404, 2932, 1676, 1616, 1307, 1276, 1121, 1090, 767; HRMS calcd for $C_{15}H_{19}NO_3$ (M)$^+$ 261.1365, found 261.1367.

3.6.1.5. Methyl (2*S,3*R**)-2-but-3-enyl-3-chloro-1,2,3,4-tetrahydroquinoline-6-carboxylate (23).** To a solution of **22** (10 mg, 0.038 mmol) in CH_2Cl_2 was added CCl_4 (0.04 ml, 0.42 mmol) and triphenylphosphine (30 mg, 0.11 mmol) at room temperature. The mixture was stirred at room temperature for 3 h, and concentrated. The ratio of **23** and **24** (**23**:**24**=3:1) was determined by the ^{1}H NMR analysis of the crude residue. Purification by silica gel column chromatography (hexane–AcOEt 19:1 to 4:1) gave a mixture of **23** and **24** (**23**/**24**=3:1, total 9.7 mg, total yield 91%). Analytical sample was obtained by further purification by Lobar column chromatography (hexane–AcOEt 19:1). ^{1}H NMR (400 MHz, CD_3OD) δ 1.53–1.61 (1H, m), 1.63–1.72 (1H, m), 2.10–2.19 (1H, m), 2.21–2.28 (1H, m), 2.93 (1H, dd, J=5.9, 16.9 Hz), 3.22 (1H, dd, J=4.4, 16.9 Hz), 3.37–3.41 (1H, m), 3.76 (3H, s), 4.25 (1H, dd, J=5.5, 9.9 Hz), 4.95 (1H, d, J=10.3 Hz), 5.05 (1H, dd, J=1.5, 16.8 Hz), 5.76–5.86 (1H, m), 6.51 (1H, d, J=8.8 Hz), 7.54–7.58 (2H, m); ^{13}C NMR (125 MHz, CD_3OD) δ 30.3, 35.3, 35.3, 51.9, 56.5, 58.0, 113.6, 115.6, 116.9, 117.8, 130.6, 132.5, 139.1, 149.3, 169.3; IR (KBr) cm^{-1}: 3367, 1696, 1684, 1609, 1293, 1282, 1238. Anal. Calcd for $C_{15}H_{18}NO_2Cl$: C, 64.40; H, 6.49; N, 5.01; Cl, 12.67. Found: C, 64.10; H, 6.29; N, 4.97; Cl, 12.59.

3.6.1.6. Methyl (2*S)-2-[(1*R**)-1-chloropent-4-enyl]-indoline-5-carboxylate (24).** ^{1}H NMR (400 MHz, CD_3OD) δ 1.63–1.73 (1H, m), 1.90–1.98 (1H, m), 2.13–2.22 (1H, m), 2.29–2.38 (1H, m), 2.95 (1H, dd, J=7.3, 16.3 Hz), 3.19 (1H, dd, J=9.9, 16.3 Hz), 3.76 (3H, s), 3.87–3.91 (1H, m), 4.06–4.12 (1H, m), 4.96 (1H, d, J=10.2 Hz), 5.03 (1H, d, J=15.4 Hz), 5.74–5.84 (1H, m), 6.44 (1H, d, J=8.1 Hz), 7.59 (1H, d, J=1.5 Hz), 7.62 (1H, d, J=8.1 Hz); ^{13}C NMR (125 MHz, CD_3OD) δ 31.6, 33.9, 34.5, 52.0, 65.4, 67.4, 107.7, 116.0, 119.6, 126.8, 128.8, 132.0, 138.5, 157.4, 169.4; EI-MS *m*/*z* 279 (M)$^+$, 248, 224, 202, 188, 176, 144, 132, 117, 90, 77, 59, 41.

3.6.1.7. Methyl (1*S,7a*S**)-1-but-3-enyl-7,7a-dihydro-1*H*-azireno[1,2-*a*]indole-5-carboxylate (25).** To a solution of **23** (10 mg, 0.036 mmol) in *t*-BuOH (0.3 ml) was added *t*-BuOK in *t*-BuOH (0.05 ml, 1 M) at room temperature. After stirring at 60 °C for 3 h, the solvent was evaporated. To this residue was added MeOH (0.3 ml), followed by the addition of acetic acid in MeOH (0.36 ml, 0.1 N), then $TMSCH_2N_2$ in hexane (0.2 ml, 2 M) at 0 °C. The mixture was stirred at room temperature for 40 min. After addition of water (5 ml), the aqueous solution was extracted with AcOEt (5 ml×2). The combined organic extracts were washed with brine (10 ml), dried over Na_2SO_4, filtered and evaporated. Purification by silica gel column chromatography (hexane–AcOEt 4:1) afforded **25** (1.6 mg, 26% from **23**) as a colorless oil.

Compound **25** was obtained from **24** (3.5 mg, 0.0125 mmol) by the similar procedure (1.4 mg, 47% from **24**). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.53–1.56 (1H, m), 1.66–1.71 (2H, m), 2.23–2.33 (2H, m), 2.89 (1H, td, J=3.2, 6.7 Hz), 3.29 (1H, dd, J=6.7, 16.9 Hz), 3.34 (1H, d, J=16.9 Hz), 3.89 (3H, s), 4.99 (1H, d, J=9.8 Hz), 5.06 (1H, d, J=18.6 Hz), 5.81–5.89 (1H, m), 7.28 (1H, s), 7.85–7.87 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 31.4, 32.0, 32.8, 47.0, 52.2, 52.5, 115.5, 119.3, 126.8, 127.4, 129.8, 137.2, 137.9, 146.7, 162.6; IR (liquid film) cm^{-1}: 3386, 2922, 1718, 1611, 1438, 1275; HRMS calcd for $C_{15}H_{17}NO_2$ (M)$^+$ 243.1260, found 243.1267.

3.6.2. Investigation of the rearrangement reaction of indoline-2-methanols 15a, b to tetrahydroquinolines 26a, b.

3.6.2.1. (2*R*,3*R*)-3-Chloro-2-ethyl-2-(methoxymethyl)-1,2,3,4-tetrahydroquinoline (26a). Triphenylphosphine (135 mg, 0.420 mmol) was added to a solution of **15a** (31 mg, 0.14 mmol) and CCl_4 (135 µl, 1.40 mmol) in

CH_2Cl_2 (3 ml) at 40 °C. The mixture was stirred under reflux conditions for 30 min, and then concentrated. Purification by silica gel column chromatography (hexane–AcOEt 10:1 to 2:1) gave tetrahydroquinoline **26a** (21 mg, 63%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (3H, t, J=7.3 Hz), 1.66 (1H, dq, J=7.3, 14.8 Hz), 1.76 (1H, dq, J=7.3, 14.8 Hz), 3.05 (1H, dd, J=6.6, 16.8 Hz), 3.30 (1H, dd, J=5.2, 16.8 Hz), 3.35 (3H, s), 3.48 (1H, d, J=9.2 Hz), 3.53 (1H, d, J=9.2 Hz), 3.99 (1H, br s), 4.33 (1H, dd, J=5.2, 6.6 Hz), 6.53 (1H, d, J=8.1 Hz), 6.63 (1H, t, J=8.1 Hz), 6.96 (1H, d, J=8.1 Hz), 7.01 (1H, t, J=8.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.1, 27.2, 33.9, 57.0, 57.6, 59.4, 73.5, 114.7, 117.2, 117.6, 127.4, 129.4, 142.3; IR ($CHCl_3$) cm^{-1}: 3422, 2972, 2935, 2896, 1607, 1588, 1482, 1312, 1260, 1112, 980, 960, 834; HRMS calcd for $C_{13}H_{18}NOCl$ $(M)^+$ 239.1077, found 239.1075; $[\alpha]_D^{24}=+7.2$ (c 0.45, $CHCl_3$).

3.6.2.2. (2*S*,3*R*)-3-Chloro-2-ethyl-2-(methoxymethyl)-1,2,3,4-tetrahydroquinoline (26b). The method for the synthesis of **26a** was followed with **15b** (100 mg, 0.45 mmol), PPh_3 (355 mg, 1.35 mmol) and CCl_4 (434 μl, 4.50 mmol) and CH_2Cl_2 (5 ml) to give **26b** (80 mg, 74%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.94 (3H, t, J=7.6 Hz), 1.72 (1H, dq, J=7.6, 14.5 Hz), 1.82 (1H, dq, J=7.6, 14.5 Hz), 3.09 (1H, dd, J=6.8, 16.5 Hz), 3.24 (1H, dd, J=4.8, 16.5 Hz), 3.35 (3H, s), 3.40 (1H, d, J=9.5 Hz), 3.42 (1H, d, J=9.5 Hz), 3.99 (1H, br s), 4.44 (1H, dd, J=4.8, 6.8 Hz), 6.57 (1H, d, J=8.0 Hz), 6.67 (1H, t, J=8.0 Hz), 6.97 (1H, d, J=8.0 Hz), 7.01 (1H, t, J=8.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 7.5, 25.4, 34.0, 57.5, 57.9, 59.3, 75.1, 115.0, 117.7, 117.8, 127.3, 129.3, 142.1; IR ($CHCl_3$) cm^{-1}: 3424, 2972, 2935, 2883, 1607, 1588, 1498. 1481, 1307, 1156, 1111, 962; HRMS calcd for $C_{13}H_{18}NOCl$ $(M)^+$ 239.1077, found 239.1081; $[\alpha]_D^{24}=-30.2$ (c 0.67, $CHCl_3$).

3.6.2.3. (2*S*)-2-Ethyl-2-(methoxymethyl)-1,2,3,4-tetrahydroquinoline (27a). To a solution of **26a** (21 mg, 0.088 mmol) in benzene (5 ml) was added (n-Bu)$_3$SnH (0.047 ml, 0.175 mmol) and AIBN (catalytic) at room temperature. The mixture was stirred at 80 °C for 3 h. After concentration, satd KF aq was added, and the mixture was filtered. The product was extracted with AcOEt (5 ml×2), and the combined organic extracts were washed with brine (10 ml), dried over Na_2SO_4, filtered and evaporated. Purification by silica gel chromatography (hexane–AcOEt 5:1) afforded **27a** (17 mg, 95%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (3H, t, J=9.0 Hz), 1.57–1.72 (4H, m), 2.70 (2H, t, J=8.0 Hz), 3.17 (1H, d, J=11.0 Hz), 3.35 (3H, s), 3.36 (1H, d, J=11.0 Hz), 3.99 (1H, br s), 6.49 (1H, dd, J=2.0, 9.0 Hz), 6.58 (1H, dt, J=2.0, 9.0 Hz), 6.95 (1H, d, J=9.0 Hz), 6.97 (1H, t, J=9.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 7.97. 23.4, 27.0, 29.1, 53.9, 59.3, 59.4, 114.2, 116.4, 120.3, 126.6, 128.9, 143.5; IR ($CHCl_3$) cm^{-1}: 3421, 2968, 2930, 1605, 1482, 1313, 1110; HRMS calcd for $C_{13}H_{19}NO$ $(M)^+$ 205.1467, found 205.1461; $[\alpha]_D^{24}=+25.3$ (c 0.31, $CHCl_3$).

3.6.2.4. (2*R*)-2-Ethyl-2-(methoxymethyl)-1,2,3,4-tetrahydroquinoline (27b). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (3H, t, J=9.0 Hz), 1.57–1.72 (4H, m), 2.70 (2H, t, J=8.0 Hz), 3.17 (1H, d, J=11.0 Hz), 3.35 (3H, s), 3.36 (1H, d, J=11.0 Hz), 3.99 (1H, br s), 6.49 (1H, dd, J=2.0, 9.0 Hz), 6.58 (1H, dt, J=2.0, 9.0 Hz), 6.95 (1H, d, J=9.0 Hz), 6.97 (1H, t, J=9.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 7.97. 23.4, 27.0, 29.1, 53.9, 59.3, 59.4, 114.2, 116.4, 120.3, 126.6, 128.9, 143.5; IR ($CHCl_3$) cm^{-1}: 3421, 2968, 2930, 1605, 1482, 1313, 1110; HRMS calcd for $C_{13}H_{19}NO$ $(M)^+$ 205.1467, found 205.1461; $[\alpha]_D^{24}=-27.6$ (c 0.31, $CHCl_3$).

3.6.2.5. (2*R*,3*R*)-3-Chloro-2-ethyl-2-(hydroxymethyl)-1,2,3,4-tetrahydroquinoline (28). To a solution of **26a** (131mg, 0.55 mmol) in CH_2Cl_2 (5 ml) was added $AlCl_3$ (364 mg, 2.73 mmol) and Me_2S (401 μl, 5.46 mmol) at room temperature. After stirring at room temperature for 31 h, satd $NaHCO_3$ aq (10 ml) was added and extracted with AcOEt (10 ml×2). The combined organic extracts were washed with brine (20 ml), dried over Na_2SO_4, filtered and evaporated. Purification by silica gel chromatography (hexane–AcOEt 5:1 to 2:1) gave **28** (106 mg, 86%) as a colorless solid (mp 118–120 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 (3H, t, J=7.6 Hz), 1.72 (2H, q, J=7.6 Hz), 3.13 (1H, dd, J=8.0, 16.4 Hz), 3.28 (1H, dd, J=6.0, 16.4 Hz), 3.75 (2H, br d, J=3.6 Hz), 3.89 (1H, br s), 4.34 (1H, dd, J=6.0, 8.0 Hz), 6.57 (1H, d, J=8.0 Hz), 6.67 (1H, t, J=8.0 Hz), 6.96 (1H, d, J=8.0 Hz), 7.03 (1H, t, J=8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.0, 27.5, 34.0, 57.5, 58.0, 64.0, 114.5, 118.0 (×2), 127.5, 129.2, 142.0; IR (KBr) cm^{-1}: 3393, 2267, 1493, 1315, 1046, 752; HRMS calcd for $C_{12}H_{16}NOCl$ $(M)^+$ 225.0920, found 225.0922. Anal. Calcd for $C_{12}H_{16}NOCl$: C, 63.85; H, 7.15; N, 6.21. Found: C, 63.82; H, 7.06; N, 6.24; $[\alpha]_D^{24}=+8.3$ (c 0.18, $CHCl_3$).

*(1S,2R,3R)-(−)-**30***. To a solution of **28** (5 mg, 0.0222 mmol) and **29** (14.4 mg, 0.0333 mmol) in CH_2Cl_2 (5 ml) was added DCC (6.9 mg, 0.0333 mmol) and DMAP (3 mg) at 50 °C. The mixture was stirred at 50 °C for 1 h, and then concentrated. Purification by silica gel column chromatography (hexane–AcOEt 5:1 to 2:1) gave **30** as a colorless solid (9 mg, 64%). Recrystallization from ethanol gave an analytical sample (mp 212–215 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.98 (3H, s), 0.99 (3H, t, J=6.5 Hz), 1.20 (3H, s), 1.35–1.44 (2H, m), 1.55–1.69 (1H, m), 1.82–1.90 (1H, m), 1.92 (3H, br s), 2.12–2.20 (1H, m), 2.40–2.48 (1H, m), 3.17 (1H, dd, J=9.5, 17.0 Hz), 3.31 (1H, dd, J=5.5, 17.0 Hz), 3.39 (1H, d, J=14.0 Hz), 3.45 (1H, d, J=14.0 Hz), 4.04 (2H, br t, J=7.0 Hz), 4.36 (1H, dd, J=5.5, 9.5 Hz), 4.44 (1H, d, J=11.5 Hz), 4.51 (1H, d, J=11.5 Hz), 6.56 (1H, d, J=8.0 Hz), 6.67 (1H, t, J=8.0 Hz), 6.98 (1H, d, J=8.0 Hz), 6.99 (1H, t, J=8.0 Hz), 7.26 (1H, s), 7.50 (1H, s), 7.73 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 6.73, 19.9, 20.7, 26.4, 27.8, 33.1, 34.3, 37.7, 44.7, 47.7, 48.5, 53.1, 56.8, 57.3, 65.7, 67.1, 114.5, 117.5, 118.0, 127.6, 128.2, 129.0, 131.1, 131.5, 134.4, 135.0, 136.8, 142.4, 163.5, 165.2; IR (KBr) cm^{-1}: 3398, 2959, 1730, 1670, 1489, 1299, 1140, 1098, 750, 540; HRMS calcd for $C_{30}H_{33}N_2O_5Cl_3SNa$ $(M+Na)^+$ 661.1073, found 661.1071. Anal. Calcd for $C_{30}H_{33}N_2O_5Cl_3S\cdot 0.5H_2O$: C, 55.52; H, 5.28; N, 4.32. Found: C, 55.69; H, 5.02; N, 4.24; $[\alpha]_D^{24}=-40.9$ (c 0.29, $CHCl_3$).

3.6.3. Preparation of indoline-2-methanols 15 and the determination of the stereochemistry.

3.6.3.1. (2*R*)-2-[(2*S*)-2,3-Dihydro-1*H*-indol-2-yl]-1-methoxybutan-2-ol (15a). To a solution of **14a** (650 mg,

2.02 mmol) in CH_2Cl_2 (3 ml) was added TFA (3 ml) at 0 °C. After stirring at room temperature for 3 h, the reaction mixture was neutralized with satd $NaHCO_3$ aq and extracted with AcOEt (10 ml×2). The combined organic extracts were washed with brine (20 ml), dried over Na_2SO_4, filtered and evaporated. Purification by silica gel chromatography (hexane–AcOEt 2:1) afforded **15a** (440 mg, 99%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.97 (3H, t, J=7.7 Hz), 1.50–1.56 (1H, m), 1.62–1.69 (1H, m), 2.90 (1H, s), 2.92 (1H, dd, J=8.9, 17.5 Hz), 3.05 (1H, dd, J=10.9, 17.5 Hz), 3.38 (1H, d, J=9.8 Hz), 3.41 (3H, s), 3.49 (1H, d, J=9.8 Hz), 4.08 (1H, dd, J=8.9, 10.9 Hz), 4.24 (1H, br s), 6.65 (1H, d, J=7.5 Hz), 6.72 (1H, t, J=7.5 Hz), 7.02 (1H, t, J=7.5 Hz), 7.08 (1H, d, J=7.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.94, 27.4, 30.5, 59.5, 65.6, 72.9, 78.1, 109.4, 118.8, 124.4, 127.1, 128.6, 150.5; IR ($CHCl_3$) cm^{-1}: 3485, 3405, 2975, 2932, 2893, 1609, 1486, 1467, 1247, 1110; HRMS calcd for $C_{13}H_{20}NO_2$ $(M+H)^+$ 222.1494, found 222.1490; $[\alpha]_D^{24}=-44.2$ (c 0.62, $CHCl_3$).

Compounds **15b–j**, **15n**, **15q** were prepared by the method similar to that used for the preparation of **15a**.

Compounds **15k** and **15p** were prepared by the method similar to that used for the preparation of **15**.

3.6.3.2. (2*S*)-2-[(2*S*)-2,3-Dihydro-1*H*-indol-2-yl]-1-methoxybutan-2-ol (15b). The general method was followed using **14b** (580 mg, 1.80 mmol) to give **15b** (350 mg, 88%) as a colorless solid (mp 49–51 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.97 (3H, t, J=7.8 Hz), 1.55–1.70 (2H, m), 2.37 (1H, s), 2.97 (1H, dd, J=10.1, 16.2 Hz), 3.02 (1H, dd, J=10.1, 16.2 Hz), 3.30 (1H, d, J=8.8 Hz), 3.36 (3H, s), 3.49 (1H, d, J=8.8 Hz), 3.95 (1H, br s), 4.05 (1H, t, J=10.1 Hz), 6.64 (1H, d, J=7.3 Hz), 6.71 (1H, t, J=7.3 Hz), 7.01 (1H, t, J=7.3 Hz), 7.08 (1H, d, J=7.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 7.66, 28.6, 30.3, 59.4, 64.3, 74.0, 74.3, 109.6, 119.0, 124.6, 127.2, 129.0, 150.6; IR (KBr) cm^{-1}: 3468, 3320, 2919, 2883, 1489, 1463, 1111, 753; HRMS calcd for $C_{13}H_{20}NO_2$ $(M+H)^+$ 222.1494, found 222.1500. Anal. Calcd for $C_{13}H_{19}NO_2$: C, 70.56; H, 8.65; N, 6.33. Found: C, 70.51; H, 8.40; N, 6.53; $[\alpha]_D^{24}=-21.7$ (c 0.43, $CHCl_3$).

3.6.3.3. (2*S*)-2-[(2*R*)-2,3-Dihydro-1*H*-indol-2-yl]-1-methoxybutan-2-ol (15c). The general method was followed using **14c** (210 mg, 0.65 mmol) to give **15c** (137 mg, 95%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.97 (3H, t, J=7.7 Hz), 1.50–1.56 (1H, m), 1.62–1.69 (1H, m), 2.90 (1H, s), 2.92 (1H, dd, J=8.9, 17.5 Hz), 3.05 (1H, dd, J=10.9, 17.5 Hz), 3.38 (1H, d, J=9.8 Hz), 3.41 (3H, s), 3.49 (1H, d, J=9.8 Hz), 4.08 (1H, dd, J=8.9, 10.9 Hz), 4.24 (1H, br s), 6.65 (1H, d, J=7.5 Hz), 6.72 (1H, t, J=7.5 Hz), 7.02 (1H, t, J=7.5 Hz), 7.08 (1H, d, J=7.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.94, 27.4, 30.5, 59.5, 65.6, 72.9, 78.1, 109.4, 118.8, 124.4, 127.1, 128.6, 150.5; IR ($CHCl_3$) cm^{-1}: 3485, 3405, 2975, 2932, 2893, 1609, 1486, 1467, 1247, 1110; HRMS calcd for $C_{13}H_{20}NO_2$ $(M+H)^+$ 222.1494, found 222.1490; $[\alpha]_D^{24}=+34.5$ (c 0.64, $CHCl_3$).

3.6.3.4. (1*R*)-1-[(2*S*)-2,3-Dihydro-1*H*-indol-2-yl]-2-methoxy-1-phenylethanol (15d). The general method was followed using **14d** (410 mg, 1.11 mmol) to give **15d** (264 mg, 89%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.49 (1H, dd, J=8.8, 15.8 Hz), 2.68 (1H, dd, J=11.1, 15.8 Hz), 3.43 (3H, s), 3.49 (1H, d, J=9.9 Hz), 3.75 (1H, d, J=9.9 Hz), 3.77 (1H, s), 4.53 (1H, dd, J=8.8, 11.1 Hz), 4.51 (1H, br s), 6.66 (1H, d, J=7.3 Hz), 6.68 (1H, d, J=7.3 Hz), 6.92 (1H, d, J=7.3 Hz), 7.00 (1H, t, J=7.3 Hz), 7.29–7.31 (1H, m), 7.35–7.39 (2H, m), 7.50 (1H, s), 7.51–7.52 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.2, 59.7, 67.0, 74.6, 82.2, 109.3, 119.0, 124.3, 125.1 (×2), 127.0, 127.0, 128.0 (×2), 128.2, 141.7, 150.4; IR ($CHCl_3$) cm^{-1}: 3405, 2930, 2894, 1732, 1610, 1486, 1089; HRMS calcd for $C_{17}H_{20}NO_2$ $(M+H)^+$ 270.1494, found 270.1491; $[\alpha]_D^{24}=-97.0$ (c 0.41, $CHCl_3$).

3.6.3.5. (1*R*)-1-[(2*S*)-2,3-Dihydro-1*H*-indol-2-yl]-1-[4-(dimethylamino)phenyl]-2-methoxy-ethanol (15e). The general method was followed using **14e** (126 mg, 0.31 mmol) to give **15e** (86 mg, 90%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.55 (1H, dd, J=8.9, 16.1 Hz), 2.71 (1H, dd, J=13.9, 16.1 Hz), 2.96 (6H, s), 3.42 (3H, s), 3.47 (1H, d, J=9.8 Hz), 3.68 (1H, s), 3.72 (1H, d, J=9.8 Hz), 4.50 (1H, dd, J=8.9, 13.9 Hz), 4.52 (1H, br), 6.65 (2H, t, J=6.8 Hz), 6.73 (2H, d, J=8.8 Hz), 6.92 (1H, d, J=6.8 Hz), 6.99 (1H, t, J=6.8 Hz), 7.35 (2H, d, J=8.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 32.5, 40.8 (×2), 59.8, 67.6, 74.6, 82.8, 109.6, 112.4 (×2), 119.1, 124.6, 126.3 (×2), 127.4, 128.7, 129.9, 149.9, 151.0; IR (liquid film) cm^{-1}: 3403, 2888, 1614, 1523, 1486, 1083, 750; HRMS calcd for $C_{19}H_{25}N_2O_2$ $(M+H)^+$ 313.1916, found 313.1909; $[\alpha]_D^{24}=-97.4$ (c 0.45, $CHCl_3$).

3.6.3.6. (1*R*)-1-(4-Chlorophenyl)-1-[(2*S*)-2,3-dihydro-1*H*-indol-2-yl]-2-methoxyethanol (15f). The general method was followed using **14f** (150 mg, 0.37 mmol) to give **15f** (74 mg, 66%) as an orange oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.50 (1H, dd, J=8.8, 15.9 Hz), 2.66 (1H, dd, J=10.7, 15.9 Hz), 3.42 (3H, s), 3.48 (1H, d, J=9.8 Hz), 3.68 (1H, d, J=9.8 Hz), 3.72 (1H, s), 4.45 (1H, br s), 4.50 (1H, t, J=9.8 Hz), 6.68 (2H, m), 6.94 (1H, d, J=7.6 Hz), 7.01 (1H, t, J=7.6 Hz), 7.34 (2H, d, J=8.6 Hz), 7.46 (2H, d, J=8.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 32.2, 59.9, 66.7, 74.7, 81.9, 109.9, 119.6, 124.7, 127.1 (×2), 127.5, 128.5, 128.6 (×2), 133.3, 140.8, 150.7; IR (thin film) cm^{-1}: 3400, 2892, 1611, 1488, 1092, 753; HRMS calcd for $C_{17}H_{19}NO_2Cl$ $(M+H)^+$ 304.11043, found 304.11038; $[\alpha]_D^{24}=-92.6$ (c 0.25, $CHCl_3$).

3.6.3.7. (1*R*)-1-Cyclohexyl-1-[(2*S*)-2,3-dihydro-1*H*-indol-2-yl]-2-methoxyethanol (15g). The general method was followed using **14g** (150 mg, 0.40 mmol) to give **15g** (80 mg, 73%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.03–1.32 (5H, m), 1.56 (1H, tt, J=2.9, 12.2 Hz), 1.65 (1H, d, J=12.7 Hz), 1.71 (1H, d, J=12.2 Hz), 1.76–1.82 (2H, m), 2.07 (1H, d, J=12.7 Hz), 2.87 (1H, dd, J=8.4, 15.3 Hz), 3.05 (1H, dd, J=12.1, 15.3 Hz), 3.28 (1H, br s), 3.39 (3H, s), 3.45 (1H, d, J=9.3 Hz), 3.56 (1H, d, J=9.3 Hz), 4.18 (1H, dd, J=8.4, 12.1 Hz), 4.41 (1H, br s), 6.65 (1H, d, J=7.3 Hz), 6.7 (1H, t, J=7.3 Hz), 7.01 (1H, t, J=7.3 Hz), 7.08 (1H, d, J=7.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.0, 27.2, 27.3, 27.6, 28.2, 30.5, 45.1, 59.7, 66.4, 73.8, 78.2, 109.7, 119.1, 124.7, 127.4, 128.8, 150.9; IR (KBr) cm^{-1}: 3390, 2931, 2853, 1610, 1488, 1098, 760;

HRMS calcd for $C_{17}H_{25}NO_2$ $(M)^+$ 255.1885, found 275.1881; $[\alpha]_D^{24}=-36.6$ (*c* 0.58, $CHCl_3$).

3.6.3.8. (2*R*)-2-[(2*S*)-2,3-Dihydro-1*H*-indol-2-yl]-1-methoxybut-3-en-2-ol (15h). The general method was followed using **14h** (213 mg, 0.67 mmol) to give **15h** (107 mg, 73%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.89 (1H, dd, $J=9.3$, 16.1 Hz), 2.97 (1H, dd, $J=10.3$, 16.1 Hz), 3.22 (1H, br s), 3.42 (1H, d, $J=9.3$ Hz), 3.43 (3H, s), 3.49 (1H, d, $J=9.3$ Hz), 4.15 (1H, t, $J=9.8$ Hz), 4.33 (1H, br s), 5.26 (1H, d, $J=10.2$ Hz), 5.52 (1H, d, $J=16.7$ Hz), 5.84 (1H, dd, $J=10.2$, 16.7 Hz), 6.65 (1H, d, $J=7.8$ Hz), 6.72 (1H, t, $J=7.8$ Hz), 7.03 (1H, t, $J=7.8$ Hz), 7.07 (1H, d, $J=7.8$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 31.3, 59.5, 64.8, 74.4, 79.7, 109.4, 115.5, 118.9, 124.4, 127.1, 128.5, 137.1, 150.6; IR ($CHCl_3$) cm^{-1}: 3406, 2930, 2894, 1609, 1486, 1465, 1094; HRMS calcd for $C_{13}H_{18}NO_2$ $(M+H)^+$ 220.1338, found 220.1331; $[\alpha]_D^{24}=-34.6$ (*c* 0.28, $CHCl_3$).

3.6.3.9. (2*R*)-2-[(2*S*)-2,3-Dihydro-1*H*-indol-2-yl]-1-methoxy-3-methylbut-3-en-2-ol (15i). The general method was followed using **14i** (380 mg, 1.14 mmol) to give **15i** (232 mg, 87%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.83 (3H, s), 2.87 (1H, dd, $J=9.3$ Hz, 15.9), 2.97 (1H, dd, $J=10.7$, 15.9 Hz), 3.44 (1H, d, $J=9.2$ Hz), 3.44 (4H, s), 3.62 (1H, d, $J=9.2$ Hz), 4.27 (1H, t, $J=9.8$ Hz), 4.35 (1H, br s), 5.03 (1H, s), 5.25 (1H, s), 6.67 (1H, d, $J=7.0$ Hz), 6.73 (1H, t, $J=7.0$ Hz), 7.02–7.08 (1H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.6, 31.2, 59.5, 64.7, 75.7, 80.1, 109.3, 112.3, 118.9, 124.3, 127.0, 128.3, 144.3, 150.5; IR ($CHCl_3$) cm^{-1}: 3406, 2926, 2895, 1610, 1486, 1125, 1090; HRMS calcd for $C_{14}H_{20}NO_2$ $(M+H)^+$ 234.1494, found 234.1471; $[\alpha]_D^{24}=-46.5$ (*c* 0.22, $CHCl_3$).

3.6.3.10. (2*R*)-2-[(2*S*)-2,3-Dihydro-1*H*-indol-2-yl]-1-methoxy-4-trimethylsilanylbut-3-yn-2-ol (15j). The general method was followed using **14j** (280 mg, 0.72 mmol) to give **15j** (166 mg, 80%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.13 (9H, s), 3.15 (1H, dd, $J=9.2$, 15.8 Hz), 3.21 (1H, dd, $J=8.4$, 15.8 Hz), 3.46 (4H, s), 3.58 (2H, s), 4.17 (1H, t, $J=9.2$ Hz), 4.34 (1H, br s), 6.63 (1H, d, $J=7.3$ Hz), 6.72 (1H, t, $J=7.3$ Hz), 7.01 (1H, t, $J=7.3$ Hz), 7.08 (1H, d, $J=7.3$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ −0.12 (×3), 32.5, 59.7, 64.6, 71.4, 78.6, 90.5, 103.7, 109.3, 118.9, 124.2, 127.0, 128.3, 150.3; IR ($CHCl_3$) cm^{-1}: 3403, 2962, 2933, 2899, 1609, 1486, 1252, 1123, 1083; HRMS calcd for $C_{16}H_{24}NO_2Si$ $(M+H)^+$ 290.1576, found 290.1585; $[\alpha]_D^{24}=-52.7$ (*c* 0.30, $CHCl_3$).

3.6.3.11. (2*R*)-2-[(2*S*)-5-Bromo-2,3-dihydro-1*H*-indol-2-yl]-1-methoxy-6-methylhept-5-en-2-ol (15k). The general method was followed using **14k** (990 mg, 2.18 mmol) to give **15k** (411 mg, 53%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.43–1.50 (1H, m), 1.54–1.60 (1H, m), 1.63 (3H, s), 1.70 (3H, s), 1.97–2.05 (1H, m), 2.10–2.18 (1H, m), 2.80 (1H, s), 2.90 (1H, dd, $J=8.8$, 15.9 Hz), 3.04 (1H, dd, $J=11.2$ Hz, 15.9), 3.37 (1H, d, $J=9.8$ Hz), 3.40 (3H, s), 3.48 (1H, d, $J=9.8$ Hz), 4.07 (1H, t, $J=9.8$ Hz), 4.26 (1H, br s), 5.11 (1H, br t, $J=7.3$ Hz), 6.49 (1H, d, $J=8.8$ Hz), 7.09 (1H, d, $J=8.8$ Hz), 7.15 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.6, 21.9, 25.7, 30.4, 34.5, 59.4, 66.1, 72.8, 78.2, 110.3, 110.6, 124.1, 127.4, 129.8, 131.1, 131.9, 149.8; IR ($CHCl_3$) cm^{-1}: 3512, 3406, 2929, 1481, 1249, 1108; HRMS calcd for $C_{17}H_{24}NO_2BrNa$ $(M+Na)^+$ 376.0889, found 370.0890; $[\alpha]_D^{24}=-31.6$ (*c* 0.24, $CHCl_3$).

3.6.3.12. 2-[(2*S*)-2,3-Dihydro-1*H*-indol-2-yl]propan-2-ol (15n). The general method was followed using **14n** (500 mg, 1.80 mmol) to give **15n** (270 mg, 85%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.21 (3H, s), 1.28 (3H, s), 3.01 (1H, dd, $J=9.8$, 15.7 Hz), 3.05 (1H, dd, $J=9.8$, 15.7 Hz), 3.85 (1H, t, $J=9.8$ Hz), 6.67 (1H, d, $J=7.2$ Hz), 6.74 (1H, t, $J=7.2$ Hz), 7.04 (1H, t, $J=7.2$ Hz), 7.10 (1H, d, $J=7.2$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.4, 28.2, 30.9, 68.5, 70.7, 109.6, 119.2, 124.6, 127.2, 129.3, 150.7; IR ($CHCl_3$) cm^{-1}: 3393, 2978, 1608, 1487, 1467, 1247; HRMS calcd for $C_{11}H_{15}NO$ $(M)^+$ 177.1154, found 177.1157; $[\alpha]_D^{24}=-53.5$ (*c* 0.60, $CHCl_3$).

3.6.3.13. (2*S*)-2-[(2*S*)-5-Bromo-2,3-dihydro-1*H*-indol-2-yl]-6-methylhept-5-en-2-ol (15p). The general method was followed using **14p** (210 mg, 0.49 mmol) to give **15p** (98 mg, 61%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.14 (3H, s), 1.44–1.57 (2H, m), 1.64 (3H, s), 1.71 (3H, s), 2.03–2.10 (1H, m), 2.12–2.18 (1H, m), 2.95 (1H, dd, $J=9.2$ Hz, 16.0), 3.02 (1H, dd, $J=10.7$, 16.0 Hz), 3.88 (1H, t, $J=9.8$ Hz), 3.98 (1H, br), 5.14 (1H, br t, $J=6.8$ Hz), 6.48 (1H, d, $J=7.8$ Hz), 7.09 (1H, d, $J=7.8$ Hz), 7.15 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.6, 21.1, 22.3, 25.6, 30.7, 40.6, 67.5, 72.7, 110.5, 110.7, 124.1, 127.5, 129.8, 131.5, 131.9, 149.8; IR ($CHCl_3$) cm^{-1}: 2978, 2918, 1481; HRMS calcd for $C_{16}H_{23}NOBr$ $(M+H)^+$ 324.0963, found 324.0956; $[\alpha]_D^{24}=-16.0$ (*c* 0.72, $CHCl_3$).

3.6.3.14. (1*R*)-1-[(2*S*)-2,3-Dihydro-1*H*-indol-2-yl]-1,3-diphenylpropan-1-ol (15q). The general method was followed using **14q** (90 mg, 0.21 mmol) to give **15q** (69 mg, 100%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.09 (1H, dt, $J=4.3$, 13.2 Hz), 2.15–2.22 (2H, m), 2.47 (1H, dd, $J=9.0$, 16.3 Hz), 2.76 (1H, dt, $J=4.3$, 12.7 Hz), 2.83 (1H, dd, $J=10.3$, 16.3 Hz), 2.96 (1H, s), 4.03 (1H, br s), 4.29 (1H, t, $J=10.0$ Hz), 6.67 (1H, d, $J=7.3$ Hz), 6.71 (1H, t, $J=7.3$ Hz), 6.93 (1H, d, $J=7.3$ Hz), 7.01 (1H, t, $J=7.6$ Hz), 7.10 (2H, d, $J=7.3$ Hz), 7.15 (1H, t, $J=6.8$ Hz), 7.24 (2H, t, $J=7.6$ Hz), 7.29 (1H, t, $J=6.8$ Hz), 7.4 (2H, t, $J=7.6$ Hz), 7.51 (2H, d, $J=6.8$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 30.2, 31.7, 44.5, 69.1, 76.1, 110.4, 120.2, 124.9, 125.7 (×2), 125.9, 127.0, 127.4, 128.6 (×2), 128.6 (×2), 128.6 (×2), 129.6, 142.9, 143.0, 150.5; IR (KBr) cm^{-1}: 3466, 3362, 3027, 1486, 1245, 770, 700; HRMS calcd for $C_{23}H_{24}NO$ $(M+H)^+$ 330.18579, found 330.18813; $[\alpha]_D^{24}=-80.7$ (*c* 0.42, $CHCl_3$).

The configurations of the newly created asymmetric centers in **15** were determined by the NOE experiments of the corresponding acetonides. The acetonides **16a–b**, **16d–k**, **16p–q** were prepared by the method similar to that used for the preparation of major-**16**.

3.6.3.15. (1*R*,9a*S*)-1-Ethyl-1-(methoxymethyl)-3,3-dimethyl-9,9a-dihydro-1*H*-[1,3]oxazolo[3,4-*a*]indole (16a). The general method was followed using **15a** (30 mg, 0.14 mmol) to give **16a** (32 mg, 87%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.81 (3H, t, $J=7.3$ Hz), 1.14–1.21 (1H, m), 1.49–1.62 (1H, m), 1.54 (3H, s), 1.67 (3H, s),

3.03 (1H, dd, J=9.7, 16.8 Hz), 3.09 (1H, dd, J=4.2, 16.8 Hz), 3.27 (1H, d, J=9.3 Hz), 3.39 (3H, s), 3.51 (1H, d, J=9.3 Hz), 4.34 (1H, dd, J=4.2, 9.7 Hz), 6.66 (1H, d, J=7.3 Hz), 6.72 (1H, t, J=7.3 Hz), 7.01 (1H, t, J=7.3 Hz), 7.04 (1H, d, J=7.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 7.10, 23.0, 25.5, 29.3, 31.3, 59.4, 69.6, 75.6, 82.0, 94.8, 111.9, 118.7, 124.2, 126.4, 131.8, 148.6; IR ($CHCl_3$) cm^{-1}: 2986, 2932, 2894, 1603, 1478, 1462, 1266, 1113; HRMS calcd for $C_{16}H_{23}NO_2$ $(M)^+$ 261.1729, found 261.1724; $[\alpha]_D^{24}=+135.6$ (c 0.78, $CHCl_3$).

3.6.3.16. (1*S*,9a*S*)-1-Ethyl-1-(methoxymethyl)-3,3-dimethyl-9,9a-dihydro-1*H*-[1,3]oxazolo[3,4-*a*]indole (16b). The general method was followed using **15b** (66 mg, 0.30 mmol) to give **16b** (56 mg, 72%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.98 (3H, t, J=7.3 Hz), 1.51 (3H, s), 1.66 (3H, s), 1.70–1.79 (2H, m), 2.97 (1H, dd, J=10.6, 16.8 Hz), 3.07 (1H, d, J=9.8 Hz), 3.17 (1H, d, J=9.8 Hz), 3.18 (3H, s), 3.34 (1H, dd, J=2.9, 16.8 Hz), 4.17 (1H, dd, J=2.9, 10.6 Hz), 6.69 (1H, d, J=7.5 Hz), 6.73 (1H, t, J=7.5 Hz), 7.02 (1H, t, J=7.5 Hz), 7.06 (1H, d, J=7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 8.08, 26.0, 28.4, 28.7, 31.5, 59.0, 69.2, 73.5, 82.6, 95.1, 112.3, 119.1, 124.5, 126.7, 131.8, 148.9; IR ($CHCl_3$) cm^{-1}: 2987, 2931, 1603, 1478, 1461, 1264, 1106; HRMS calcd for $C_{16}H_{23}NO_2$ $(M)^+$ 261.1728, found 261.1725; $[\alpha]_D^{24}=+144.3$ (c 1.06, $CHCl_3$).

3.6.3.17. (1*R*,9a*S*)-1-(Methoxymethyl)-3,3-dimethyl-1-phenyl-9,9a-dihydro-1*H*-[1,3]oxazolo[3,4-*a*]indole (16d). The general method was followed using **15d** (33 mg, 0.12 mmol) to give **16d** (30 mg, 80%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.70 (3H, s), 1.74 (3H, s), 2.67 (1H, dd, J=7.1, 16.1 Hz), 2.84 (1H, dd, J=9.3, 16.1 Hz), 3.43 (3H, s), 3.82 (2H, s), 4.61 (1H, dd, J=7.1, 9.3 Hz), 6.69 (1H, t, J=7.3 Hz), 6.73 (1H, d, J=7.3 Hz), 6.83 (1H, d, J=7.3 Hz), 7.00 (1H, t, J=7.3 Hz), 7.16–7.21 (3H, m), 7.31 (2H, d, J=7.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.1, 31.7, 32.9, 59.7, 70.5, 79.7, 85.6, 97.5, 114.4, 121.1, 124.2, 126.4 (×2), 126.7, 126.8, 127.4 (×2), 132.6, 141.6, 148.9; IR ($CHCl_3$) cm^{-1}: 2930, 2894, 1477, 1258, 1102; HRMS calcd for $C_{20}H_{24}NO_2$ $(M+H)^+$ 310.1807, found 310.1812; $[\alpha]_D^{24}=-39.1$ (c 1.15, $CHCl_3$).

3.6.3.18. (1*R*,9a*S*)-1-(Methoxymethyl)-1-[4-(dimethylamino)phenyl]-3,3-dimethyl-9,9a-dihydro-1*H*-[1,3]oxazolo[3,4-*a*]indole (16e). The general method was followed using **15e** (50 mg, 0.16 mmol) to give **16e** (14 mg, 25%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.60 (3H, s), 1.71 (3H, s), 2.70 (1H, dd, J=6.6, 16.1 Hz), 2.80 (1H, dd, J=9.1, 16.1 Hz), 2.89 (6H, s), 3.42 (3H, s), 3.74 (1H, d, J=9.8 Hz), 3.77 (1H, d, J=9.8 Hz), 4.59 (1H, dd, J=6.6, 9.1 Hz), 6.58 (2H, d, J=8.8 Hz), 6.69 (1H, t, J=7.8 Hz), 6.80 (2H, t, J=7.8 Hz), 6.99 (1H, t, J=7.8 Hz), 7.15 (2H, d, J=8.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.5, 31.9, 33.6, 40.8 (×2), 59.9, 71.0, 80.2, 85.8, 97.4, 112.0 (×2), 114.8, 121.3, 124.6, 126.3, 126.8, 127.3 (×2), 133.5, 149.3, 149.6; IR (thin film) cm^{-1}: 2984, 2990, 1615, 1522, 1478; HRMS calcd for $C_{22}H_{29}N_2O_2$ $(M+H)^+$ 353.2229, found 353.2239; $[\alpha]_D^{24}=-58.2$ (c 0.47, $CHCl_3$).

3.6.3.19. (1*R*,9a*S*)-1-(4-Chlorophenyl)-1-(methoxymethyl)-3,3-dimethyl-9,9a-dihydro-1*H*-[1,3]oxazolo[3,4-*a*]indole (16f). The general method was followed using **15f** (43 mg, 0.14 mmol) to give **16f** (28 mg, 57%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.71 (3H, s), 1,72 (3H, s), 2.63 (1H, dd, J=5.3, 16.2 Hz), 2.86 (1H, dd, J=9.0, 16.2 Hz), 3.41 (3H, s), 3.75 (1H, d, J=9.8 Hz), 3.79 (1H, d, J=9.8 Hz), 4.55 (1H, dd, J=5.3, 9.0 Hz), 6.67–6.73 (2H, m), 6.81 (1H, d, J=7.7 Hz), 6.69 (1H, t, J=7.7 Hz), 7.13 (2H, d, J=8.8 Hz), 7.22 (2H, d, J=8.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.1, 31.8, 32.8, 59.9, 70.6, 79.8, 85.3, 97.9, 114.5, 121.4, 124.6, 127.0, 127.8 (×2), 128.1 (×2), 132.3, 132.9, 140.5, 149.0; IR (thin film) cm^{-1}: 2987, 2929, 1478, 1092, 753; HRMS calcd for $C_{20}H_{23}NO_2Cl$ $(M+H)^+$ 344.14173, found 344.14187; $[\alpha]_D^{24}=-61.5$ (c 1.34, $CHCl_3$).

3.6.3.20. (1*R*,9a*S*)-1-Cyclohexyl-1-(methoxymethyl)-3,3-dimethyl-9,9a-dihydro-1*H*-[1,3]oxazolo[3,4-*a*]indole (16g). The general method was followed using **15g** (53 mg, 0.19 mmol) to give **16g** (45 mg, 74%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.13–1.21 (5H, m), 1.40 (3H, s), 1.55 (3H, s), 1.59–1.73 (5H, m), 1.81 (1H, d, J=11.7 Hz), 2.95 (1H, dd, J=9.6, 16.2 Hz), 3.25 (1H, dd, J=8.1, 16.2 Hz), 3.38 (3H, s), 3.46 (1H, d, J=9.8 Hz), 3.53 (1H, d, J=9.8 Hz), 4.40 (1H, dd, J=8.1, 9.6 Hz), 6.70 (1H, d, J=7.6 Hz), 6.78 (1H, t, J=7.6 Hz), 7.04 (1H, t, J=7.6 Hz), 7.10 (1H, d, J=7.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.8, 26.9, 27.2, 27.2, 28.2, 29.6, 31.5, 31.6, 43.6, 59.6, 70.9, 77.0, 84.2, 95.4, 113.5, 120.4, 124.7, 127.2, 133.9, 148.5; IR (liquid film) cm^{-1}: 2924, 2853, 1481, 1104, 745; HRMS calcd for $C_{20}H_{29}NO_2$ $(M)^+$ 315.2198, found 312.2205; $[\alpha]_D^{24}=+73.6$ (c 0.62, $CHCl_3$).

3.6.3.21. (1*R*,9a*S*)-1-(Methoxymethyl)-3,3-dimethyl-1-vinyl-9,9a-dihydro-1*H*-[1,3]oxazolo[3,4-*a*]indole (16h). The general method was followed using **15h** (47 mg, 0.21 mmol) to give **16h** (56 mg, 100%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.60 (3H, s), 1.79 (3H, s), 3.06–3.08 (2H, m), 3.43 (3H, s), 3.47 (1H, d, J=9.3 Hz), 3.51 (1H, d, J=9.3 Hz), 4.40 (1H, dd, J=4.9, 6.8 Hz), 4.98 (1H, d, J=18.5 Hz), 5.24 (1H, d, J=13.4 Hz), 5.75 (1H, dd, J=13.4, 18.5 Hz), 6.75 (2H, t, J=7.8 Hz), 7.01 (2H, t, J=7.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.7, 30.2, 31.4, 59.7, 68.3, 77.6, 83.1, 96.5, 113.0, 115.7, 119.7, 124.5, 126.6, 131.2, 136.6, 148.5; IR ($CHCl_3$) cm^{-1}: 2931, 2894, 1712, 1604, 1478, 1461, 1105; HRMS calcd for $C_{16}H_{21}NO_2$ $(M)^+$ 259.1572, found 259.1575; $[\alpha]_D^{24}=+82.2$ (c 0.16, $CHCl_3$).

3.6.3.22. (1*R*,9a*S*)-1-Isopropenyl-1-(methoxymethyl)-3,3-dimethyl-9,9a-dihydro-1*H*-[1,3]oxazolo[3,4-*a*]indole (16i). The general method was followed using **15i** (36 mg, 0.15 mmol) to give **16i** (19 mg, 45%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 (3H, s), 1.53 (3H, s), 1.54 (3H, s), 2.80 (1H, dd, J=9.5, 16.1 Hz), 3.04 (1H, dd, J=7.7, 16.1 Hz), 3.33 (3H, s), 3.52 (1H, d, J=9.9 Hz), 3.56 (1H, d, J=9.9 Hz), 4.21 (1H, dd, J=7.7, 9.5 Hz), 4.89 (1H, s), 5.01 (1H, s), 6.70 (1H, d, J=7.6 Hz), 6.73 (1H, t, J=7.6 Hz), 6.93–6.97 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.8, 26.3, 32.0, 32.8, 59.6, 69.9, 78.3, 86.8, 97.4, 113.2, 115.1, 121.4, 124.5, 126.9, 133.7, 144.7, 148.8; IR ($CHCl_3$) cm^{-1}: 2928, 2895, 1477, 1560, 1095; HRMS calcd for $C_{17}H_{24}NO_2$ $(M+H)^+$ 274.1807, found 274.1811; $[\alpha]_D^{24}=+26.4$ (c 0.69, $CHCl_3$).

3.6.3.23. (1*R*,9a*S*)-1-(Methoxymethyl)-3,3-dimethyl-1-trimethylsilylethynyl-9,9a-dihydro-1*H*-[1,3]oxazolo-[3,4-*a*]indole (16j). The general method was followed using **15j** (25 mg, 0.086 mmol) to give **16j** (22 mg, 77%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ −0.15 (9H, s), 1.50 (3H, s), 1.73 (3H, s), 3.06 (1H, dd, J=9.9, 16.5 Hz), 3.26 (1H, dd, J=2.6, 16.5 Hz), 3.43 (3H, s), 3.51 (2H, s), 4.28 (1H, dd, J=2.6, 9.9 Hz), 6.62 (1H, d, J=7.7 Hz), 6.70 (1H, t, J=7.7 Hz), 6.94–7.00 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ −0.39 (×3), 25.0, 30.8, 31.6, 60.2, 67.8, 75.4, 79.2, 91.3, 97.6, 103.8, 112.8, 119.4, 124.4, 126.3, 131.8, 148.4; IR ($CHCl_3$) cm^{-1}: 2961, 2931, 1479, 1461, 1266, 1251, 1106; HRMS calcd for $C_{19}H_{28}NO_2Si$ $(M+H)^+$ 330.1881, found 330.1887; $[\alpha]_D^{24}$ = +194.0 (c 0.44, $CHCl_3$).

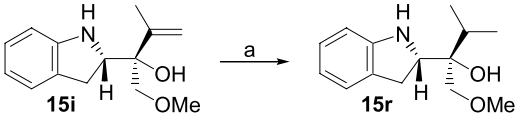
3.6.3.24. (1*R*,9a*S*)-1-(Methoxymethyl)-3,3-dimethyl-1-(4-methylpent-3-enyl)-9,9a-dihydro-1*H*-[1,3]oxazolo-[3,4-*a*]indole (16k). The general method was followed using **15k** (436 mg, 1.23 mmol) to give **16k** (370 mg, 76%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.11 (1H, dt, J=6.8, 12.7 Hz), 1.52 (3H, s), 1.54 (3H, s), 1.55–1.60 (1H, m), 1.63 (3H, s), 1.64 (3H, s), 1.91–1.97 (1H, m), 2.01–2.07 (1H, m), 3.02 (1H, dd, J=10.3, 17.3 Hz), 3.07 (1H, dd, J=4.7, 17.3 Hz), 3.29 (1H, d, J=8.8 Hz), 3.38 (3H, s), 3.53 (1H, d, J=8.8 Hz), 4.35 (1H, dd, J=4.7, 10.3 Hz), 4.99 (1H, br t, J=6.8 Hz), 6.50 (1H, d, J=7.8 Hz), 7.11 (1H, d, J=7.8 Hz), 7.13 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.5, 21.8, 25.6, 25.7, 29.2, 30.8, 31.4, 59.6, 70.2, 76.2, 82.0, 94.9, 110.8, 113.0, 124.4, 127.5, 129.4, 131.4, 134.4, 147.9; IR ($CHCl_3$) cm^{-1}: 2629, 1474, 1259, 1112; HRMS calcd for $C_{20}H_{28}NO_2Br$ $(M)^+$ 393.1303, found 393.1303; $[\alpha]_D^{24}$ = +131.0 (c 0.36, $CHCl_3$).

3.6.3.25. (1*S*,9a*S*)-7-Bromo-1,3,3-trimethyl-1-(4-methylpent-3-enyl)-9,9a-dihydro-1*H*-[1,3]oxazolo[3,4-*a*]indole (16p). The general method was followed using **15p** (95 mg, 0.293 mmol) to give **16p** (86 mg, 80%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.99 (3H, s), 1.49 (3H, s), 1.58–1.62 (2H, m), 1.64 (3H, s), 1.65 (3H, s), 1.70 (3H, s), 2.04–2.10 (2H, m), 2.93 (1H, dd, J=3.4, 17.1 Hz), 3.05 (1H, dd, J=10.3, 17.1 Hz), 4.15 (1H, dd, J=3.4, 10.3 Hz), 5.12 (1H, br t, J=6.8 Hz), 6.54 (1H, d, J=8.2 Hz), 7.12 (1H, d, J=8.2 Hz), 7.15 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.7, 21.0, 22.8, 25.6, 25.8, 29.6, 31.6, 41.0, 70.0, 81.8, 94.3, 110.7, 113.1, 124.1, 127.5, 129.5, 131.8, 133.8, 148.2; IR ($CHCl_3$) cm^{-1}: 2985, 2931, 1474, 1381, 1370, 1256; HRMS calcd for $C_{19}H_{27}NOBr$ $(M+H)^+$ 364.1276, found 364.1259; $[\alpha]_D^{24}$ = +97.5 (c 0.47, $CHCl_3$).

3.6.3.26. (1*R*,9a*S*)-3,3-Dimethyl-1-phenethyl-1-phenyl-9,9a-dihydro-1*H*-[1,3]oxazolo[3,4-*a*]indole (16q). The general method was followed using **15q** (23 mg, 0.070 mmol) to give **16q** (mg, 54%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.58 (3H, s), 1.76 (3H, s), 2.28–2.49 (3H, m), 2.61 (1H, dd, J=7.4, 16.1 Hz), 2.71 (1H, dd, J=8.6, 16.1 Hz), 2.79–2.86 (1H, m), 4.51 (1H, t, J=8.0 Hz), 6.73 (1H, t, J=7.4 Hz), 6.78 (1H, d, J=7.4 Hz), 6.84 (1H, d, J=7.4 Hz), 7.02 (1H, d, J=7.4 Hz), 7.13–7.34 (10H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.0, 30.5, 32.4, 34.0, 45.4, 75.9, 86.3, 97.6, 115.5, 121.9, 124.5, 125.9, 126.4 (×2), 126.8, 127.0, 128.0 (×2), 128.5 (×2), 128.6 (×2), 133.7, 142.9, 143.1, 149.5; IR (thin film) cm^{-1}: 3026, 2986, 2934, 1477, 1237, 1207, 747, 701; HRMS calcd for $C_{26}H_{28}NO$ $(M+H)^+$ 370.21709, found 370.21417; $[\alpha]_D^{24}$ = −32.0 (c 0.21, $CHCl_3$).

3.6.4. Preparation of 15r.

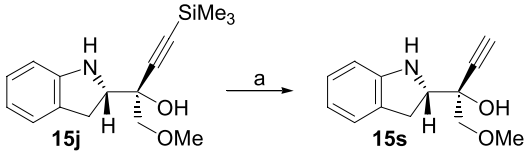
3.6.4.1. (2*R*)-2-[(2*S*)-2,3-Dihydro-1*H*-indol-2-yl]-1-methoxy-3-methylbutan-2-ol (15r). A solution of **15i** (50 mg, 0.214 mmol), 20 wt% $Pd(OH)_2$/C (50 mg) in methanol (5 ml) was stirred under H_2 atmosphere at room temperature for 2.5 h. $Pd(OH)_2$ was removed by filtration and the filtrate was evaporated. The resulting residue was purified by silica gel column chromatography (hexane–AcOEt 5:1) to give **15r** (32 mg, 63%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.96 (3H, d, J=6.8 Hz), 1.08 (3H, d, J=6.8 Hz), 1.90–1.96 (1H, m), 2.90 (1H, dd, J=8.0, 15.2 Hz), 3.03–3.09 (1H, m), 3.25 (1H, s), 3.41 (3H, s), 3.44 (1H, d, J=9.8 Hz), 3.58 (1H, d, J=9.8 Hz), 4.23 (1H, dd, J=8.0, 11.7 Hz), 4.42 (1H, s), 6.66 (1H, d, J=7.2 Hz), 6.72 (1H, t, J=7.2 Hz), 7.03 (1H, t, J=7.2 Hz), 7.10 (1H, d, J=7.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.3, 17.3, 30.1, 33.7, 59.5, 66.0, 73.8, 77.2, 109.4, 118.9, 124.4, 127.1, 128.5, 150.7; IR (KBr) cm^{-1}: 3417, 3385, 2963, 2933, 1611, 1469, 1250, 1107; HRMS calcd for $C_{14}H_{22}NO_2$ $(M+H)^+$ 236.1651, found 236.1638; $[\alpha]_D^{24}$ = −51.2 (c 0.16, $CHCl_3$) (Scheme 12).



Scheme 12. Reagents and conditions: (a) H_2, $Pd(OH)_2$/C, MeOH, rt, 63%.

3.6.5. Preparation of 15s.

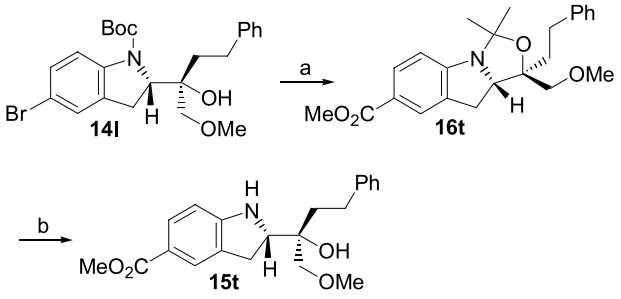
3.6.5.1. (2*R*)-2-[(2*S*)-2,3-Dihydro-1*H*-indol-2-yl]-1-methoxy-but-3-yn-2-ol (15s). To a solution of **15j** (91 mg, 0.314 mmol) in THF (1 ml) was added TBAF in THF (0.35 ml, 1 M) at room temperature. The mixture was stirred under the same temperature for 1 h. After addition of water, the aqueous solution was extracted with AcOEt. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and evaporated. Purification by silica gel chromatography (hexane–AcOEt 5:1 to 2:1) gave **15s** (59 mg, 86%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.45 (1H, s), 3.15 (1H, dd, J=10.0 Hz, 16.9), 3.21 (1H, dd, J=10.3, 16.9 Hz), 3.37 (1H, br s), 3.46 (3H, s), 3.55 (1H, d, J=9.8 Hz), 3.58 (1H, d, J=9.8 Hz), 4.19 (1H, t, J=9.5 Hz), 4.50 (1H, br), 6.65 (1H, d, J=7.5 Hz), 6.72 (1H, t, J=7.5 Hz), 7.01 (1H, t, J=7.5 Hz), 7.07 (1H, d, J=7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 32.3, 59.7, 64.6, 71.4, 74.1, 78.4, 82.5, 109.6, 119.2, 124.4, 127.3, 128.3, 150.3; IR ($CHCl_3$) cm^{-1}: 3556, 3402, 3306, 2933, 2898, 1609, 1486, 1466, 1124, 1085; HRMS calcd for $C_{13}H_{15}NO_2Na$ $(M+Na)^+$ 240.1000, found 240.0986; $[\alpha]_D^{24}$ = −65.4 (c 0.15, $CHCl_3$) (Scheme 13).



Scheme 13. Reagents and conditions: (a) 1 M TBAF, THF, rt, 86%.

3.6.6. Preparation of 15t.

3.6.6.1. (1*R*,9a*S*)-1-(Methoxymethyl)-3,3-dimethyl-1-phenethyl-9,9a-dihydro-1*H*-[1,3]oxazolo[3,4-*a*]indole-7-carboxylic acid methyl ester (16t). The procedure for the preparation of **15a** was followed using **14l** (868 mg, 1.82 mmol) to give the corresponding indoline-2-methanol (660 mg, 96%) (Scheme 14).



Scheme 14. Reagents and conditions: (a) (i) TFA, CH_2Cl_2, rt, 96%; (ii) 2,2-dimethoxypropane, *p*-TsOH, CH_2Cl_2, rt, 78%; (iii) *t*-BuLi, CO_2, Et_2O, −78 °C, 82%; (iv) $TMSCH_2N_2$, MeOH, ice bath, 95%. (b) PPTS, MeOH, rt, 95%.

The obtained indoline-2-methanol (64 mg, 1.70 mmol) was converted to the corresponding acetonide (554 mg, 78%) by the method similar to that used for the synthesis of major-**16**.

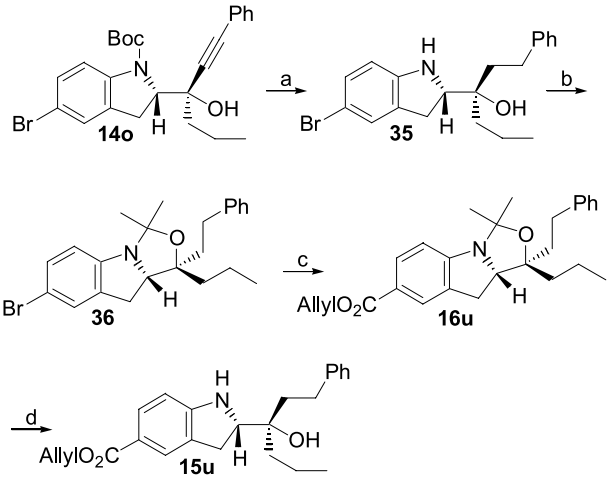
The conversion of the obtained acetonide (543 mg, 1.3 mmol) to the corresponding carboxylic acid (405 mg, 82%) was carried out by the method similar to that used for the synthesis of **17**.

The method for the synthesis of **22** was followed using the obtained carboxylic acid (300 mg, 0.79 mmol) to give **16t** (294 mg, 95%) as a colorless solid (mp 124–126 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.39 (1H, dt, J=4.4, 13.0 Hz), 1.57 (3H, s), 1.75 (3H, s), 1.92 (1H, dt, J=5.4, 12.7 Hz), 2.59 (1H, dt, J=5.4, 13.0 Hz), 2.68 (1H, dt, J=4.4, 12.7 Hz), 3.07–3.08 (2H, m), 3.34 (1H, d, J=9.3 Hz), 3.39 (3H, s), 3.58 (1H, d, J=9.3 Hz), 3.83 (3H, s), 4.45 (1H, dd, J=6.3, 8.3 Hz), 6.58 (1H, d, J=8.3 Hz), 7.05 (2H, d, J=7.3 Hz), 7.12 (1H, t, J=7.3 Hz), 7.20 (2H, t, J=7.3 Hz), 7.65 (1H, s), 7.74 (1H, d, J=8.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.1, 28.8, 29.7, 31.1, 32.7, 51.8, 59.9, 70.7, 76.4, 82.2, 94.7, 110.0, 120.4, 126.0, 126.4, 128.5 (×2), 128.6 (×2), 130.3, 132.1, 142.6, 152.7, 167.5; IR (KBr) cm^{-1}: 2938, 1699, 1607, 1273; HRMS calcd for $C_{24}H_{30}NO_4$ $(M+H)^+$ 396.21748, found 396.21800; $[\alpha]_D^{24}=+201.5$ (*c* 1.06, $CHCl_3$).

3.6.6.2. (2*S*)-2-[(1*R*)-1-Hydroxy-1-(methoxymethyl)-3-phenylpropyl]-2,3-dihydro-1*H*-indole-5-carboxylic acid methyl ester (15t). The method for the synthesis of **1** was followed using **16t** (257 mg, 0.65 mmol) to give **15t** (220 mg, 95%) as a colorless solid (mp 129–130 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.73 (1H, dt, J=5.1, 13.2 Hz), 1.83 (1H, dt, J=5.1, 13.2 Hz), 2.60 (1H, dt, J=5.1, 12.8 Hz), 2.69 (1H, s), 2.77 (1H, dt, J=5.1, 12.8 Hz), 2.91 (1H, dd, J=9.2, 15.8 Hz), 3.02 (1H, dd, J=10.6, 15.8 Hz), 3.39 (3H, s), 3.44 (1H, d, J=8.8 Hz), 3.51 (1H, d, J=8.8 Hz), 3.80 (3H, s), 4.14 (1H, t, J=9.5 Hz), 4.65 (1H, br s), 6.53 (1H, d, J=8.1 Hz), 7.17 (3H, m), 7.23–7.27 (2H, m), 7.67 (1H, s), 7.72 (1H, dd, J=1.5, 8.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 29.6, 29.9, 36.2, 51.5, 59.5, 66.1, 73.0, 78.0, 107.7, 120.0, 125.9, 126.0, 128.0, 128.2 (×2), 128.4 (×2), 130.6, 142.1, 155.1, 167.3; IR (KBr) cm^{-1}: 3431, 3370, 2949, 2905, 1699, 1611, 1437, 1285, 1269, 1092; HRMS calcd for $C_{21}H_{26}NO_4$ $(M+H)^+$ 356.1862, found 356.1846. Anal. Calcd for $C_{21}H_{25}NO_4$: C, 70.96; H, 7.09; N, 3.94. Found: C, 70.71; H, 7.04; N, 3.89; $[\alpha]_D^{24}=-6.1$ (*c* 1.05, $CHCl_3$).

3.6.7. Preparation of 15u.

3.6.7.1. (3*R*)-3-[(2*S*)-5-Bromo-2,3-dihydro-1*H*-indol-2-yl]-1-phenylhexan-3-ol (35). A solution of **14o** (66 mg, 0.139 mmol), 10 wt% Pd/C (7 mg) in AcOEt (1 ml) was stirred under H_2 atmosphere at room temperature for 24 h. Pd/C was removed by filtration and the filtrate was evaporated. The resulting residue was purified by silica gel column chromatography (hexane–AcOEt 19:1) to give the crude reduced product (24 mg, crude yield 36%). The obtained product was used without further purification (Scheme 15).



Scheme 15. Reagents and conditions: (a) (i) H_2, Pd/C, AcOEt, rt; (ii) TFA, CH_2Cl_2, rt, 32% (2 steps). (b) 2,2-Dimethoxypropane, PPTS, CH_2Cl_2, 72%. (c) (i) *t*-BuLi, CO_2, Et_2O, −78 °C, 87%; (ii) allylbromide, K_2CO_3, DMF, rt, 89%. (d) PPTS, MeOH–CH_2Cl_2, rt, 92%.

Deprotection of the *N*-Boc group was carried out by the method similar to that used for the preparation of **15a** to give **35** (11 mg, 32% from **14o**) as a colorless solid (mp 128–129 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (3H, t, J=7.3 Hz), 1.27–1.50 (3H, m), 1.54–1.65 (2H, m), 1.78 (1H, dt, J=4.9, 12.9 Hz), 2.07 (1H, s), 2.51 (1H, dt, J=4.9, 12.9 Hz), 2.65 (1H, dt, J=4.9, 12.9 Hz), 2.82 (1H, dd, J=9.2, 16.0 Hz), 3.04 (1H, dd, J=10.2, 16.0 Hz), 3.17 (1H, br s), 3.94 (1H, t, J=9.9 Hz), 6.45 (1H, d, J=8.8 Hz), 7.03 (1H, d, J=8.8 Hz), 7.08–7.13 (4H, m), 7.18–7.23 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.8, 17.1, 29.7, 30.0, 36.2, 39.9, 66.3, 73.7, 111.0, 111.1, 125.9, 127.6, 128.2 (×2), 128.4 (×2), 129.8, 131.7, 142.2, 149.5; IR (KBr) cm^{-1}: 3373, 3300, 2956, 2872, 1482, 1252; HRMS calcd for $C_{20}H_{25}NOBr$ $(M+H)^+$ 374.1119, found 374.1136. Anal. Calcd for $C_{20}H_{24}NOBr$: C, 64.17; H, 6.46; N, 3.74; Br,

21.35. Found: C, 64.26; H, 6.33; N, 3.72; Br, 21.29; $[\alpha]_D^{24} = -36.5$ (*c* 1.00, $CHCl_3$).

3.6.7.2. (1*R*,9a*R*)-7-Bromo-3,3-dimethyl-1-phenethyl-1-propyl-9,9a-dihydro-1*H*-[1,3]oxazolo[3,4-*a*]indole (36). The method for the preparation of major-**16** was followed using **35** (4.8 mg, 0.013 mmol) to give **36** (3.8 mg, 72%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94 (3H, t, J=7.3 Hz), 1.25–1.44 (4H, m), 1.49 (3H, s), 1.64 (3H, s), 1.68–1.72 (1H, m), 1.78–1.86 (1H, m), 2.53 (1H, dt, J=5.1, 12.9 Hz), 2.68 (1H, dt, J=4.4, 12.9 Hz), 2.95–2.97 (2H, m), 4.21 (1H, dd, J=5.9, 8.8 Hz), 6.41 (1H, d, J=8.8 Hz), 7.01–7.04 (4H, m), 7.08–7.12 (1H, m), 7.17–7.22 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.7, 17.6, 25.7, 29.3, 29.5, 31.6, 34.0, 39.7, 70.9, 83.3, 94.1, 110.4, 112.4, 125.7, 127.6, 128.3 (×2), 128.4 (×2), 129.6, 133.9, 142.5, 147.7; IR (liquid film) cm^{-1}: 2958, 2933, 1476, 1367, 1262; HRMS calcd for $C_{23}H_{29}NOBr$ $(M+H)^+$ 414.1433, found 414.1454; $[\alpha]_D^{24} = +114.1$ (*c* 0.65, $CHCl_3$).

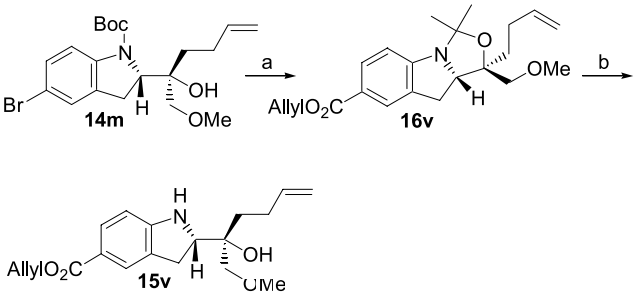
3.6.7.3. (1*R*,9a*R*)-3,3-Dimethyl-1-phenethyl-1-propyl-9,9a-dihydro-1*H*-[1,3]oxazolo[3,4-*a*]indole-7-carboxylic acid allyl ester (16u). Compound **36** (74 mg, 0.179 mmol) was converted to the corresponding carboxylic acid (59 mg, 87%) by the method similar to that used for the preparation of **17**.

To the solution of carboxylic acid (59 mg, 0.155 mmol) in DMF (1.2 ml) was added K_2CO_3 (32 mg, 0.23 mmol) and allyl bromide (0.02 ml, 0.236 mmol) at room temperature. After stirring at room temperature for 2 h, water (10 ml) was added. The product was extracted with diethyl ether (10 ml×2), and the combined organic extracts were washed with brine (20 ml), dried over Na_2SO_4, filtered and evaporated. Purification by silica gel column chromatography (hexane–AcOEt 9:1) gave **16u** (58 mg, 89%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (3H, t, J=7.0 Hz), 1.27–1.49 (4H, m), 1.51 (3H, s), 1.65–1.73 (1H, m), 1.69 (3H, s), 1.79–1.87 (1H, m), 2.54 (1H, dt, J=4.7, 12.0 Hz), 2.69 (1H, dt, J=4.7, 13.2 Hz), 2.93–3.05 (2H, m), 4.29 (1H, dd, J=5.5, 9.9 Hz), 4.69–4.71 (2H, m), 5.20 (1H, d, J=9.5 Hz), 5.33 (1H, d, J=19.0 Hz), 5.92–6.01 (1H, m), 6.59 (1H, d, J=8.3 Hz), 7.00 (2H, d, J=7.3 Hz), 7.08 (1H, t, J=7.3 Hz), 7.17 (2H, t, J=7.3 Hz), 7.61 (1H, d, J=1.7 Hz), 7.72 (1H, dd, J=1.7, 8.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.7, 17.6, 25.9, 28.6, 29.3, 30.9, 33.7, 39.3, 64.9, 70.9, 83.3, 93.3, 109.0, 117.6, 119.6, 125.7, 126.2, 128.2 (×2), 128.4 (×2), 130.4, 131.5, 132.7, 142.3, 152.3, 166.4; IR (liquid film) cm^{-1}: 2958, 2934, 2872, 1707, 1610, 1292, 1265, 1217, 1169; HRMS calcd for $C_{27}H_{34}NO_3$ $(M+H)^+$ 420.2539, found 420.2520; $[\alpha]_D^{24} = +209.8$ (*c* 0.57, $CHCl_3$).

3.6.7.4. (2*S*)-2-[(1*R*)-1-Hydroxy-1-(2-phenylethyl)butyl]indoline-5-carboxylic acid allyl ester (15u). Method for the synthesis of **1** was followed using **16u** (56 mg, 0.133 mmol) to give **15u** (47 mg, 92%) as a colorless solid (mp 125–126 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.02 (3H, t, J=7.3 Hz), 1.38–1.53 (2H, m), 1.55–1.61 (1H, m), 1.65–1.75 (2H, m), 1.90 (1H, dt, J=4.9, 13.2 Hz), 1.96 (1H, s), 2.62 (1H, dt, J=4.9, 13.2 Hz), 2.75 (1H, dt, J=4.9, 13.0 Hz), 2.98 (1H, dd, J=9.3, 15.9), 3.14 (1H, dd, J=10.7, 15.9 Hz), 4.10 (1H, t, J=9.8 Hz), 4.24 (1H, br s), 4.77–4.78 (2H, m), 5.26 (1H, d, J=11.7 Hz), 5.39 (1H, d, J=15.6 Hz), 5.99–6.07 (1H, m), 6.62 (1H, d, J=8.3 Hz), 7.19–7.22 (3H, m), 7.29–7.32 (2H, m), 7.77 (1H, s), 7.81 (1H, d, J=8.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.8, 17.1, 29.6, 29.7, 36.3, 39.8, 65.0, 66.3, 74.1, 108.2, 117.6, 120.6, 125.9, 126.3, 128.2 (×2), 128.5 (×2), 128.8, 130.6, 132.7, 142.1, 155.0, 166.4; IR (KBr) cm^{-1}: 3452, 3309, 2950, 1682, 1614, 1269; HRMS calcd for $C_{24}H_{30}NO_3$ $(M+H)^+$ 380.2226, found 380.2246. Anal. Calcd for $C_{24}H_{29}NO_3$: C, 75.96; H, 7.70; N, 3.69. Found: C, 75.83; H, 7.41; N, 3.70; $[\alpha]_D^{24} = -14.9$ (*c* 1.15, $CHCl_3$).

3.6.8. Preparation of 15v.

3.6.8.1. (1*R*,9a*S*)-1-But-3-enyl-1-(methoxymethyl)-3,3-dimethyl-9,9a-dihydro-1*H*-[1,3]oxazolo[3,4-*a*]-indole-7-carboxylic acid allyl ester (16v). Compound **14m** (459 mg, 1.08 mmol) was converted to the corresponding indoline-2-methanol (290 mg, 83%) by the method similar to that used for the preparation of **15a** (Scheme 16).



Scheme 16. Reagents and conditions: (a) (i) TFA, CH_2Cl_2, rt, 83%; (ii) 2,2-dimethoxypropane, PPTS, CH_2Cl_2, 72%; (iii) *t*-BuLi, CO_2, Et_2O, −78 °C, 83%; (iv) AllylBr, K_2CO_3, DMF, rt, 96%. (b) PPTS, MeOH, rt, 80%.

The obtained indoline-2-methanol (280 mg, 0.86 mmol) was converted to the corresponding acetonide (227 mg, 72%) by the method similar to that used for the synthesis of major-**16**.

Conversion of the obtained acetonide (206 mg, 0.56 mmol) to the corresponding carboxylic acid (154 mg, 83%) was carried out by the method similar to that used for the synthesis of **17**.

Method for the synthesis of **16u** was followed using the obtained carboxylic acid (128 mg, 0.39 mmol) to give **16v** (137 mg, 96%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.12–1.19 (1H, m), 1.53 (3H, s), 1.60–1.65 (1H, m), 1.68 (3H, s), 1.96–2.06 (1H, m), 2.08–2.17 (1H, m), 3.07–3.08 (2H, m), 3.29 (1H, d, J=8.8 Hz), 3.38 (3H, s), 3.51 (1H, d, J=8.8 Hz), 4.42 (1H, dd, J=6.2, 8.4 Hz), 4.77 (2H, dd, J=1.5, 5.9 Hz), 4.85 (1H, d, J=10.3 Hz), 4.91 (1H, dd, J=1.8, 19.0 Hz), 5.30 (1H, dd, J=1.5, 10.3 Hz), 5.39 (1H, dd, J=1.5, 19.0 Hz), 5.63–5.74 (1H, m), 5.98–6.08 (1H, m), 6.59 (1H, d, J=7.8 Hz), 7.2 (1H, d, J=1.5 Hz), 7.79 (1H, d, J=7.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.7, 27.2, 28.5, 29.7, 30.7, 59.5, 64.9, 70.2, 75.9, 81.8, 94.2, 109.7, 114.2, 117.7, 120.0, 126.0, 130.1, 131.9, 132.7, 138.6, 152.6, 166.3; IR (liquid film) cm^{-1}: 2985, 2929, 1709, 1610, 1292, 1265, 1212, 1169, 1122; HRMS calcd for $C_{22}H_{29}NO_4Na$ $(M+Na)^+$ 394.1994, found 394.2021; $[\alpha]_D^{24} = +229.8$ (*c* 0.52, $CHCl_3$).

3.6.8.2. (2*S*)-2-[(1*R*)-1-Hydroxy-1-(methoxymethyl)-pent-4-enyl]indoline-5-carboxylic acid allyl ester (15v). Method for the synthesis of **1** was followed using **16v** (135 mg, 0.363 mmol) to give **15v** (96 mg, 80%) as a colorless solid (mp 132–134 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.51–1.65 (1H, m), 1.68 (1H, dt, J=5.5, 13.0 Hz), 2.06–2.13 (1H, m), 2.22–2.28 (1H, m), 2.70 (1H, s), 2.98 (1H, dd, J=8.8, 15.9 Hz), 3.07 (1H, dd, J=10.3, 15.9 Hz), 3.42 (1H, d, J=9.3 Hz), 3.43 (3H, s), 3.51 (1H, d, J=9.3 Hz), 4.17 (1H, t, J=9.8 Hz), 4.71 (1H, br s), 4.78 (2H, d, J=5.9 Hz), 4.99 (1H, d, J=8.8 Hz), 5.07 (1H, d, J=18.6 Hz), 5.27 (1H, d, J=11.7 Hz), 5.40 (1H, d, J=15.6 Hz), 5.80–5.88 (1H, m), 6.00–6.08 (1H, m), 6.58 (1H, d, J=8.8 Hz), 7.76 (1H, s), 7.81 (1H, d, J=8.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.4, 29.8, 33.3, 59.4, 64.8, 66.0, 73.0, 78.0, 107.5, 114.6, 117.5, 119.8, 126.0, 128.0, 130.7, 132.7, 138.4, 155.2, 166.4; IR (KBr) cm^{-1}: 3434, 3284, 2907, 1681, 1613, 1271, 1234, 1117, HRMS calcd for $C_{19}H_{25}NO_4Na$ $(M+Na)^+$ 354.1691, found 354.1690. Anal. Calcd for $C_{19}H_{25}NO_4$: C, 68.86; H, 7.60; N, 4.23. Found: C, 68.60; H, 7.58; N, 4.28; $[\alpha]_D^{24}=+4.6$ (c 0.27, $CHCl_3$).

3.6.9. Preparation of 15w.

3.6.9.1. (1*R,9a*S**)-7-Bromo-1-(methoxymethyl)-3,3-dimethyl-1-phenethyl-9,9a-dihydro-1*H*-[1,3]oxazolo-[3,4-*a*]indole (37).** Compound **14l** (868 mg, 1.82 mmol) was converted to the corresponding indoline-2-methanol (660 mg, 96%) by the method similar to that used for the preparation of **15a** (Scheme 17).

Method for the synthesis of major-**16** was followed using the obtained indoline-2-methanol (641 mg, 1.70 mmol) to give **37** (554 mg, 78%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.43 (1H, dt, J=4.6, 13.0 Hz), 1.55 (3H, s), 1.70 (3H, s), 1.92 (1H, dt, J=5.2, 13.0 Hz), 2.60 (1H, dt, J=5.2, 13.0 Hz), 2.69 (1H, dt, J=4.6, 13.0 Hz), 3.04 (1H, dd, J=9.3, 17.1 Hz), 3.09 (1H, dd, J=4.4, 17.1 Hz), 3.33 (1H, d, J=8.8 Hz), 3.39 (3H, s), 3.59 (1H, d, J=8.8 Hz), 4.39 (1H, dd, J=4.9, 7.8 Hz), 6.51 (1H, d, J=8.8 Hz), 7.07–7.11 (4H, m), 7.15 (1H, t, J=7.3 Hz), 7.22–7.27 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.8, 29.3, 29.6, 31.4, 32.8, 59.6, 70.5, 76.4, 82.0, 95.2, 111.0, 113.1, 125.7, 127.6, 128.3 (×2), 128.3 (×2), 129.5, 134.3, 142.4, 147.8; IR ($CHCl_3$) cm^{-1}: 2931, 1475, 1259, 1109; HRMS calcd for $C_{22}H_{26}NO_4Br$ $(M)^+$ 415.1147, found 415.1128.

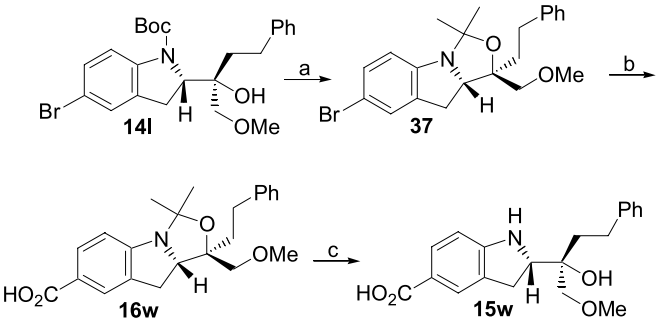
3.6.9.2. (1*R,9a*S**)-1-(Methoxymethyl)-3,3-dimethyl-1-phenethyl-9,9a-dihydro-1*H*-[1,3]oxazolo[3,4-*a*]indole-7-carboxylic acid (16w).** Method for the synthesis of **17** was followed using **37** (280 mg, 0.672 mmol) to give **16w** (159 mg, 63%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.43 (1H, dt, J=3.9, 12.7 Hz), 1.59 (3H, s), 1.78 (3H, s), 1.96 (1H, dt, J=5.1, 12.7 Hz), 2.62 (1H, dt, J=5.1, 12.7 Hz), 2.69 (1H, dt, J=3.9, 12.7 Hz), 3.10–3.11 (2H, m), 3.37 (1H, d, J=9.3 Hz), 3.41 (3H, s), 3.61 (1H, d, J=9.3 Hz), 4.49 (1H, dd, J=6.2, 8.3 Hz), 6.61 (1H, d, J=8.8 Hz), 7.08 (2H, d, J=7.2 Hz), 7.14 (1H, t, J=7.2 Hz), 7.23 (2H, t, J=7.2 Hz), 7.72 (1H, s), 7.83 (1H, d, J=8.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.9, 27.0, 28.5, 29.4, 30.7, 32.5, 59.7, 70.5, 76.0, 82.0, 94.3, 109.5, 119.0, 125.8, 126.8, 128.3 (×2), 128.4, 131.1, 132.0, 142.3, 153.0, 172.3; IR (KBr) cm^{-1}: 2984, 2929, 1672, 1607, 1270; HRMS calcd for $C_{23}H_{28}NO_4$ $(M+H)^+$ 382.2018, found 382.2009.

3.6.9.3. (2*S)-2-[(1*R**)-1-Hydroxy-1-(methoxymethyl)-3-phenylpropyl]-2,3-dihydro-1*H*-indole-5-carboxylic acid (15w).** Method for the synthesis of **22** was followed using **16w** (44 mg, 0.116 mmol) to give **15w** (20 mg, 51%) as a colorless oil. ^{1}H NMR (500 MHz, CD_3OD) δ 1.80 (2H, t, J=8.8 Hz), 2.62–2.68 (1H, m), 2.73–2.79 (1H, m), 3.00 (1H, dd, J=9.8, 16.4 Hz), 3.11 (1H, dd, J=9.2, 16.4 Hz), 3.41 (3H, s), 3.47 (1H, d, J=9.3 Hz), 3.51 (1H, d, J=9.3 Hz), 4.16 (1H, t, J=9.8 Hz), 6.54 (1H, d, J=8.8 Hz), 7.14 (1H, t, J=7.2 Hz), 7.20 (2H, d, J=7.2 Hz), 7.25 (2H, t, J=7.2 Hz), 7.64 (1H, s), 7.68 (1H, d, J=8.8 Hz); ^{13}C NMR (125 MHz, CD_3OD) δ 30.5, 30.6, 37.5, 59.6, 65.9, 75.3, 76.9, 108.0, 119.8, 126.7, 127.0, 129.3 (×2), 129.4 (×2), 129.6, 132.0, 144.1, 158.0, 170.9; IR (KBr) cm^{-1}: 3408, 2926, 1673, 1609, 1285, 1264; HRMS calcd for $C_{20}H_{24}NO_4$ $(M+H)^+$ 342.1705, found 342.1706.

3.6.10. Rearrangement from indoline-2-methanols 15 to tetrahydroquinolines 26.

Compounds **26c–d**, **26f–k**, **26n**, **26p**, **26r–v**, **15x** were obtained by the method similar to that used for the synthesis of **26a**.

3.6.10.1. (2*S*,3*S*)-3-Chloro-2-ethyl-2-(methoxymethyl)-1,2,3,4-tetrahydroquinoline (26c). The general method was followed using **15c** (6.1 mg, 0.028 mmol) to give **26c** (5.4 mg, 80%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.92 (3H, t, J=7.3 Hz), 1.66 (1H, dq, J=7.3, 14.8 Hz), 1.76 (1H, dq, J=7.3, 14.8 Hz), 3.05 (1H, dd, J=6.6, 16.8 Hz), 3.30 (1H, dd, J=5.2, 16.8 Hz), 3.35 (3H, s), 3.48 (1H, d, J=9.2 Hz), 3.53 (1H, d, J=



Scheme 17. Reagents and conditions: (a) (i) TFA, CH_2Cl_2, rt, 96%; (ii) 2,2-dimethoxypropane, PPTS, CH_2Cl_2, 78%. (b) (i) t-BuLi, CO_2, Et_2O, −78 °C, 63%; (ii) Amberlyst-15® ion exchange resin, MeOH, rt, 51%.

9.2 Hz), 3.99 (1H, br s), 4.33 (1H, dd, J=5.2, 6.6 Hz), 6.53 (1H, d, J=8.1 Hz), 6.63 (1H, t, J=8.1 Hz), 6.96 (1H, d, J=8.1 Hz), 7.01 (1H, t, J=8.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 7.1, 27.2, 33.9, 57.0, 57.6, 59.4, 73.5, 114.7, 117.2, 117.6, 127.4, 129.4, 142.3; IR ($CHCl_3$) cm^{-1}: 3422, 2972, 2935, 2896, 1607, 1588, 1482, 1312, 1260, 1112, 980, 960, 834; HRMS calcd for $C_{13}H_{18}NOCl$ $(M)^+$ 239.1077, found 239.1075; $[\alpha]_D^{24}=-6.9$ (c 0.32, $CHCl_3$).

3.6.10.2. (2*R*,3*R*)-3-Chloro-2-(methoxymethyl)-2-phenyl-1,2,3,4-tetrahydroquinoline (26d). The general method was followed using **15d** (14 mg, 0.052 mmol) to give **26d** (9.5 mg, 63%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.76 (2H, m), 3.29 (3H, s), 3.93 (1H, d, J=8.8 Hz), 3.99 (1H, d, J=8.8 Hz), 4.57 (1H, t, J=3.5 Hz), 4.84 (1H, br s), 6.65 (1H, d, J=8.0 Hz), 6.72 (1H, t, J=8.0 Hz), 6.86 (1H, d, J=8.0 Hz), 7.10 (1H, t, J=8.0 Hz), 7.22–7.39 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.5, 57.7, 59.6, 61.9, 78.7, 113.0, 116.2, 117.2, 125.8 (×2), 127.2, 127.5, 128.6 (×2), 129.6, 141.6, 142.9; IR ($CHCl_3$) cm^{-1}: 3437, 2926, 1606, 1484, 1316, 1271, 1109, 972; HRMS calcd for $C_{17}H_{18}NOCl$ $(M)^+$ 287.1073, found 287.1078; $[\alpha]_D^{24}=+142.0$ (c 0.20, $CHCl_3$).

3.6.10.3. (2*R*,3*R*)-3-Chloro-2-(4-chlorophenyl)-2-(methoxymethyl)-1,2,3,4-tetrahydroquinoline (26f). The general method was followed using **15f** (74 mg, 0.244 mmol) to give **26f** (26 mg, 33%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.75 (1H, dd, J=3.7, 16.9 Hz), 2.82 (1H, dd, J=3.7, 16.9 Hz), 3.31 (3H, s), 3.89 (1H, d, J=8.8 Hz), 3.94 (1H, d, J=8.8 Hz), 4.53 (1H, t, J=3.7 Hz), 4.77 (1H, s), 6.67 (1H, t, J=7.6 Hz), 6.73 (1H, d, J=7.6 Hz), 6.88 (1H, d, J=7.6 Hz), 7.71 (1H, t, J=7.6 Hz), 7.28 (2H, d, J=8.8 Hz), 7.34 (2H, d, J=8.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 33.6, 57.7, 59.9, 62.0, 78.6, 113.7, 116.6, 118.0, 127.9 (×2), 128.1, 129.1 (×2), 130.1, 133.6, 141.7, 142.0; IR (thin film) cm^{-1}: 3428, 3380, 2924, 2896, 1488, 1110, 752; HRMS calcd for $C_{17}H_{17}NOCl_2$ $(M)^+$ 321.0687, found 321.0668; $[\alpha]_D^{24}=+109.2$ (c 0.35, $CHCl_3$).

3.6.10.4. (2*R*,3*R*)-3-Chloro-2-isopropyl-2-(methoxymethyl)-1,2,3,4-tetrahydroquinoline (26r). The general method was followed using **15r** (35 mg, 0.198 mmol) to give **26r** (25 mg, 65%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.04 (6H, t, J=8.0 Hz), 2.00–2.07 (1H, m), 3.10 (1H, dd, J=7.0, 17.0 Hz), 3.26 (1H, dd, J=5.0, 17.0 Hz), 3.32 (3H, s), 3.53 (1H, d, J=9.0 Hz), 3.63 (1H, d, J=9.0 Hz), 4.03 (1H, br s), 4.48 (1H, dd, J=5.0, 7.0 Hz), 6.55 (1H, d, J=8.0 Hz), 6.65 (1H, t, J=8.0 Hz), 6.96 (1H, d, J=8.0 Hz), 7.01 (1H, t, J=8.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.6, 17.7, 33.6, 34.4, 57.2, 58.8, 59.2, 73.3, 114.5, 117.3 (×2), 127.4, 129.1, 142.3; IR ($CHCl_3$) cm^{-1}: 3429, 2966, 2930, 1607, 1482, 1311, 1261, 1116, 980; HRMS calcd for $C_{14}H_{20}NOCl$ $(M)^+$ 253.1233, found 253.1232; $[\alpha]_D^{24}=+25.0$ (c 0.15, $CHCl_3$).

3.6.10.5. (2*R*,3*R*)-3-Chloro-2-cyclohexyl-2-(methoxymethyl)-1,2,3,4-tetrahydroquinoline (26g). The general method was followed using **15g** (80 mg, 0.290 mmol) to give **26g** (32 mg, 38%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.16–1.40 (5H, m), 1.59–1.65 (2H, m), 1.77–1.83 (4H, m), 3.07 (1H, dd, J=6.4, 17.0 Hz), 3.28 (1H, dd, J=5.1, 17.0 Hz), 3.33 (3H, s), 3.51 (1H, d, J=9.3 Hz), 3.63 (1H, d, J=9.3 Hz), 4.06 (1H, br s), 4.50 (1H, t, J=5.1 Hz), 6.54 (1H, d, J=7.3 Hz), 6.65 (1H, dt, J=1.0, 7.3 Hz), 6.97 (1H, d, J=7.3 Hz), 7.01 (1H, t, J=7.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.8, 27.3, 27.4, 27.5, 27.9, 34.6, 44.7, 57.3, 59.2, 59.5, 73.6, 114.7, 117.5, 117.5, 127.7, 129.5, 142.5; IR (KBr) cm^{-1}: 3402, 3365, 2926, 2852, 1487, 1099, 746; HRMS calcd for $C_{17}H_{24}NOCl$ $(M)^+$ 293.1546, found 293.1568; $[\alpha]_D^{24}=+11.6$ (c 0.46, $CHCl_3$).

3.6.10.6. (2*R*,3*R*)-3-Chloro-2-dimethyl-2-(methoxymethyl)-1,2,3,4-tetrahydroquinoline (26n). The general method was followed using **15n** (35 mg, 0.198 mmol) to give **26n** (25 mg, 65%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (3H, s), 1.32 (3H, s), 3.07 (1H, dd, J=9.0, 17.5 Hz), 3.23 (1H, dd, J=6.0, 17.5 Hz), 3.73 (1H, br s), 4.10 (1H, dd, J=6.0, 9.0 Hz), 6.51 (1H, d, J=8.0 Hz), 6.67 (1H, t, J=8.0 Hz), 6.98 (1H, d, J=8.0 Hz), 7.02 (1H, t, J=8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.0, 28.4, 34.8, 53.2, 62.6, 114.6, 117.7, 118.0, 127.5, 129.2, 142.4; IR ($CHCl_3$) cm^{-1}: 3473, 3415, 2972, 2936, 1608, 1588, 1497, 1485, 1462; HRMS calcd for $C_{11}H_{14}NCl$ $(M)^+$ 195.0815, found 195.0820; $[\alpha]_D^{24}=-28.9$ (c 0.34, $CHCl_3$).

3.6.10.7. (2*R*,3*R*)-3-Chloro-2-(methoxymethyl)-2-vinyl-1,2,3,4-tetrahydroquinoline (26h). The general method was followed using **15h** (32 mg, 0.146 mmol) to give **26h** (10.8 mg, 31%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.93 (1H, dd, J=4.0 Hz, 17.5), 3.28 (1H, dd, J=4.0, 17.5 Hz), 3.41 (3H, s), 3.58 (1H, d, J=8.5 Hz), 3.63 (1H, d, J=8.5 Hz), 4.24 (1H, t, J=4.0 Hz), 4.32 (1H, br s), 5.26 (1H, d, J=9.5 Hz), 5.29 (1H, d, J=16.5 Hz), 5.89 (1H, dd, J=9.5, 16.5 Hz), 6.63 (1H, d, J=8.0 Hz), 6.66 (1H, t, J=8.0 Hz), 6.95 (1H, d, J=8.0 Hz), 7.05 (1H, t, J=8.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 10.0, 33.7, 56.3, 59.6, 60.4, 113.7, 116.6, 117.1, 117.6, 127.5, 129.6, 139.0, 141.6; IR ($CHCl_3$) cm^{-1}: 3433, 2927, 2897, 1608, 1590, 1482, 1313, 1271, 1115, 933; HRMS calcd for $C_{13}H_{16}NOCl$ $(M)^+$ 237.0920, found 237.0917; $[\alpha]_D^{24}=+72.4$ (c 0.22, $CHCl_3$).

3.6.10.8. (2*R*,3*R*)-3-Chloro-2-isopropenyl-2-(methoxymethyl)-1,2,3,4-tetrahydroquinoline (26i). The general method was followed using **15i** (48 mg, 0.206 mmol) to give **26i** (19 mg, 37%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.81 (3H, s), 2.86 (1H, dd, J=3.2, 16.8 Hz), 3.22 (1H, dd, J=3.6, 16.8 Hz), 3.41 (3H, s), 3.68 (1H, d, J=9.2 Hz), 3.76 (1H, d, J=9.2 Hz), 4.42 (1H, br t, J=2.8 Hz), 4.58 (1H, br s), 5.05 (1H, s), 5.07 (1H, s), 6.59 (1H, d, J=8.0 Hz), 6.63 (1H, t, J=8.0 Hz), 6.92 (1H, d, J=8.0 Hz), 7.04 (1H, t, J=8.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.7, 33.6, 55.6, 59.5, 62.8, 76.6, 112.9, 115.8, 115.9, 117.1, 127.5, 129.6, 141.8, 144.9; IR ($CHCl_3$) cm^{-1}: 3456, 2926, 1609, 1502, 1483, 1315, 1275, 1112, 971, 914; HRMS calcd for $C_{14}H_{19}NOCl$ $(M+H)^+$ 252.1156, found 252.1160; $[\alpha]_D^{24}=+63.5$ (c 0.17, $CHCl_3$).

3.6.10.9. (2*R*,3*R*)-3-Chloro-2-(methoxymethyl)-2-trimethylsilanylethynyl-1,2,3,4-tetrahydroquinoline (26j). The general method was followed using **15j** (30 mg, 0.104 mmol) to give **26j** (20 mg, 63%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.11 (9H, s), 3.24 (2H, d,

J=8.5 Hz), 3.41 (3H, s), 3.77 (2H, s), 4.35 (1H, br s), 4.36 (1H, t, J=8.5 Hz), 6.62 (1H, d, J=8.0 Hz), 6.68 (1H, t, J=8.0 Hz), 7.00 (1H, t, J=8.0 Hz), 7.05 (1H, d, J=8.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ −0.3 (×3), 33.0, 59.9, 64.8, 68.3, 77.9, 93.6, 108.8, 118.5, 124.1, 127.3, 127.8, 128.1, 150.3; IR ($CHCl_3$) cm^{-1}: 3410, 2962, 1610, 1485, 1468, 1403, 1251, 1096, 846; HRMS calcd for $C_{16}H_{22}$NOClSi $(M)^+$ 307.1159, found 307.1158; $[\alpha]_D^{24}$=+19.0 (c 0.14, $CHCl_3$).

3.6.10.10. (2*R*,3*R*)-3-Chloro-2-ethynyl-2-(methoxymethyl)-1,2,3,4-tetrahydroquinoline (26s). The general method was followed using **15s** (55 mg, 0.253 mmol) to give **26s** (33 mg, 55%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.70 (1H, s), 3.24 (2H, d, J=9.0 Hz), 3.48 (3H, s), 3.76 (1H, d, J=10.5 Hz), 3.79 (1H, d, J=10.5 Hz), 4.30 (1H, br s), 4.40 (1H, t, J=9.0 Hz), 6.64 (1H, d, J=8.0 Hz), 6.70 (1H, t, J=8.0 Hz), 7.02 (1H, t, J=8.0 Hz), 7.06 (1H, d, J=8.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 32.9, 59.8, 65.1, 67.3, 77.6, 109.1, 115.0, 118.9, 124.3, 127.4, 127.8, 129.6, 150.0; IR ($CHCl_3$) cm^{-1}: 3408, 3305, 2934, 1610, 1485, 1248, 1117, 1097, 968; HRMS calcd for $C_{13}H_{14}$NOCl $(M)^+$ 235.0764, found 235.0768; $[\alpha]_D^{24}$=−24.0 (c 0.30, $CHCl_3$).

3.6.10.11. (2*R*,3*R*)-6-Bromo-3-chloro-2-methyl-2-(4-methylpent-3-enyl)-1,2,3,4-tetrahydroquinoline (26p). The general method was followed using **15p** (45 mg, 0.139 mmol) to give **26p** (30 mg, 62%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (3H, s), 1.46–1.55 (1H, m), 1.57 (3H, s), 1.68 (3H, s), 1.72–1.80 (1H, m), 1.97–2.10 (2H, m), 3.05 (1H, dd, J=7.4, 16.8 Hz), 3.23 (1H, dd, J=5.6, 16.8 Hz), 3.83 (1H, br s), 4.11 (1H, dd, J=5.6, 7.4 Hz), 5.09 (1H, t, J=7.2 Hz), 6.38 (1H, d, J=9.6 Hz), 7.08 (1H, s), 7.09 (1H, d, J=9.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.7, 22.0, 24.8, 25.7, 34.0, 34.8, 55.2, 61.2, 109.0, 116.1, 119.8, 123.6, 130.0, 131.6, 132.0, 141.1; IR ($CHCl_3$) cm^{-1}: 3424, 2971, 2932, 1716, 1599, 1488, 1447, 1380, 1301, 1123; HRMS calcd for $C_{16}H_{21}$NClBr $(M)^+$ 341.0545, found 341.0544; $[\alpha]_D^{24}$=+37.4 (c 0.56, $CHCl_3$).

3.6.10.12. (2*R*,3*R*)-6-Bromo-3-chloro-2-(methoxymethyl)-2-(4-methylpent-3-enyl)-1,2,3,4-tetrahydroquinoline (26k). The general method was followed using **15k** (39 mg, 0.110 mmol) to give **26k** (17 mg, 41%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.55–1.63 (1H, m), 1.59 (3H, s), 1.67 (3H, s), 1.69–1.75 (1H, m), 1.98–2.08 (2H, m), 3.02 (1H, dd, J=6.0, 17.5 Hz), 3.29 (1H, dd, J=4.5, 17.5 Hz), 3.36 (3H, s), 3.47 (1H, d, J=9.5 Hz), 3.52 (1H, d, J=9.5 Hz), 4.05 (1H, br s), 4.31 (1H, t, J=6.0 Hz), 5.07 (1H, br t, J=7.0 Hz), 6.42 (1H, d, J=9.0 Hz), 7.08 (1H, s), 7.09 (1H, d, J=9.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.6, 21.6, 25.6, 33.6, 34.5, 56.6, 57.6, 59.3, 73.7, 109.0, 116.2, 119.2, 123.5, 130.2, 131.8, 132.1, 141.2; IR ($CHCl_3$) cm^{-1}: 3426, 2929, 1711, 1599, 1489, 1377, 1301, 1111, 977; HRMS calcd for $C_{17}H_{23}$NOClBr $(M)^+$ 371.0651, found 371.0655; $[\alpha]_D^{24}$=−11.6 (c 0.39, $CHCl_3$).

3.6.10.13. Methyl (2*R*,3*R*)-3-chloro-2-(methoxymethyl)-2-(2-phenylethyl)-1,2,3,4-tetrahydroquinoline-6-carboxylate (26t). The general method was followed using **15t** (102 mg, 0.304 mmol) to give **26t** (45 mg, 50%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.82–1.87 (1H, m), 1.95–2.01 (1H, m), 2.58 (2H, t, J=8.4 Hz), 3.01 (1H, dd, J=6.6, 16.9 Hz), 3.23–3.28 (1H, m), 3.28 (3H, s), 3.46 (1H, d, J=9.2 Hz), 3.50 (1H, d, J=9.2 Hz), 3.74 (3H, s), 4.31 (1H, t, J=5.9 Hz), 4.39 (1H, s), 6.39 (1H, d, J=9.5 Hz), 7.05–7.10 (3H, m), 7.15–7.18 (2H, m), 7.60–7.62 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.3, 33.6, 37.0, 51.5, 56.3, 58.0, 59.4, 73.8, 113.7, 116.0, 118.8, 126.0, 128.2 (×2), 128.5 (×2), 129.6, 131.6, 141.4, 146.3, 167.1; IR (KBr) cm^{-1}: 3361, 2948, 1707, 1610, 1436, 1288, 1253, 1128, 1104; HRMS calcd for $C_{21}H_{24}NO_3ClK$ $(M+K)^+$ 412.1082, found 412.1074; $[\alpha]_D^{24}$=−29.4 (c 0.10, $CHCl_3$).

3.6.10.14. (2*S*,3*R*)-3-Chloro-2-phenethyl-2-propyl-1,2,3,4-tetrahydroquinoline-6-carboxylic acid allyl ester (26u). The general method was followed using **15u** (300 mg, 0.791 mmol) to give **26u** (164 mg, 52%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (3H, t, J=7.3 Hz), 1.25–1.32 (1H, m), 1.37–1.45 (1H, m), 1.55 (1H, dt, J=4.4, 12.8 Hz), 1.71 (1H, dt, J=4.4, 13.0 Hz), 1.78 (1H, dt, J=4.4, 13.0 Hz), 1.91 (1H, dt, J=5.9 Hz, 12.8), 2.60 (1H, dt, J=5.1, 12.6 Hz), 2.69 (1H, dt, J=5.1, 12.6 Hz), 3.10 (1H, dd, J=6.6, 17.3 Hz), 3.29 (1H, dd, J=5.1, 17.3 Hz), 4.05–4.10 (1H, m), 4.29 (1H, dd, J=5.1, 6.6 Hz), 4.72–4.73 (2H, m), 5.21 (1H, d, J=9.5 Hz), 5.34 (1H, d, J=19.1 Hz), 5.94–6.03 (1H, m), 6.42 (1H, d, J=8.1 Hz), 7.09–7.25 (5H, m), 7.69–7.71 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.4, 16.0, 29.3, 33.5, 36.2, 37.9, 57.6, 58.3, 64.9, 113.5, 116.1, 117.6, 118.5, 126.0, 128.2, 128.5, 129.6 (×2), 131.7 (×2), 132.7, 141.5, 146.6, 166.3; IR (thin film) cm^{-1}: 3368, 2959, 2935, 2873, 1693, 1610, 1513, 1281, 1250, 1129; HRMS calcd for $C_{24}H_{29}NO_2Cl$ $(M+H)^+$ 398.1887, found 398.1914; $[\alpha]_D^{24}$=−2.2 (c 0.31, $CHCl_3$).

3.6.10.15. (2*R*,3*R*)-2-But-3-enyl-3-chloro-2-(methoxymethyl)-1,2,3,4-tetrahydroquinoline-6-carboxylic acid allyl ester (26v). The general method was followed using **15v** (83 mg, 0.250 mmol) to give **26v** (41 mg, 46%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.70–1.76 (1H, m), 1.84–1.90 (1H, m), 2.16 (2H, q, J=7.8 Hz), 3.11 (1H, dd, J=6.3, 17.1 Hz), 3.36 (1H, dd, J=4.4, 17.1 Hz), 3.39 (3H, s), 3.54 (1H, d, J=9.3 Hz), 3.58 (1H, d, J=9.3 Hz), 4.35 (1H, t, J=5.4 Hz), 4.52 (1H, s), 4.78 (2H, d, J=5.8 Hz), 4.99 (1H, d, J=8.8 Hz), 5.06 (1H, d, J=14.7 Hz), 5.27 (1H, d, J=8.8 Hz), 5.39 (1H, d, J=18.6 Hz), 5.76–5.85 (1H, m), 6.00–6.08 (1H, m), 6.54 (1H, d, J=8.8 Hz), 7.74 (1H, s), 7.76 (1H, d, J=8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 33.8, 34.5, 56.4, 58.0, 59.6, 65.0, 73.9, 113.5, 115.0, 116.0, 117.7, 118.7, 129.7, 131.7, 132.7, 137.8, 146.2, 166.2; IR (liquid film) cm^{-1}: 3364, 2928, 1704, 1611, 1515, 1281, 1252, 1128, 1105; HRMS calcd for $C_{19}H_{25}NO_3Cl$ $(M+H)^+$ 350.1522, found 350.1526; $[\alpha]_D^{24}$=+17.1 (c 1.01, $CHCl_3$).

3.6.10.16. (2*S*)-2-[(1*S*)-1-Hydroxy-1-(methoxymethyl)-4,5-dimethylhex-4-enyl]indoline-5-carbonitrile (15x). The general method was followed using **1** (26 mg, 0.0782 mmol) to give **15**× (15 mg, 61%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.47 (1H, dt, J=5.0, 12.5 Hz), 1.55 (1H, dt, J=5.0, 12.5 Hz), 1.63 (6H, s), 1.65 (3H, s), 1.99 (1H, dt, J=5.0, 12.5 Hz), 2.15 (1H, dt, J=5.0, 12.5 Hz), 2.61 (1H, s), 2.96 (1H, dd, J=9.0, 16.5 Hz), 3.06 (1H, dd, J=11.0, 16.5 Hz), 3.42 (3H, s), 3.43 (1H, d,

J=9.0 Hz), 3.52 (1H, d, J=9.0 Hz), 4.15 (1H, t, J=9.5 Hz), 4.84 (1H, br s), 6.54 (1H, d, J=8.0 Hz), 7.25 (1H, s), 7.29 (1H, d, J=8.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.2, 19.9, 20.5, 28.0, 29.9, 32.6, 59.5, 66.0, 72.9, 78.4, 99.9, 108.0, 120.6, 124.6, 126.9, 127.8, 128.9, 133.0, 154.6; IR ($CHCl_3$) cm^{-1}: 3543, 3423, 2923, 2215, 1614, 1495, 1412, 1264, 1109, 972; HRMS calcd for $C_{19}H_{27}N_2O_2$ $(M+H)^+$ 315.2072, found 315.2065; $[\alpha]_D^{24}=+14.5$ (c 0.29, $CHCl_3$).

3.6.11. Synthesis of (−)-virantmycin.

3.6.11.1. *tert*-Butyl (2*S*)-5-iodo-2-(methoxyacetyl)-indoline-1-carboxylate (31). Iodine monochloride in CH_2Cl_2 (1.4 ml, 1.0 M) was added to a solution of **13b** (100 mg, 0.34 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine (282 mg, 1.37 mmol) in CH_2Cl_2 (2 ml) at 0 °C, and the mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with AcOEt (10 ml), poured into $Na_2S_2O_3$ aq (10 ml) and the organic material was extracted with AcOEt(10 ml×2). The combined extracts were washed with 1 N HCl (20 ml), satd $NaHCO_3$ aq (20 ml) and brine (20 ml), dried over Na_2SO_4 and concentrated. Purification by silica gel flash chromatography (toluene–AcOEt 9:1) furnished **31** (130 mg, 91%) as a colorless solid (mp 72–74 °C). ^{1}H NMR (500 MHz, CD_3OD, two rotamers) δ 1.44–1.54 (9H, m), 2.96 (1H, br d, J=17.6 Hz), 3.41 (3H, s), 3.41–3.42 (1H, br m), 4.21 (2H, s), 5.09 (1H, dd, J=11.7, 4.9 Hz), 7.23* (0.3H, br s), 7.40 (1H, s), 7.44 (1H, d, J=8.8 Hz), 7.55 (0.7H, br s); ^{13}C NMR (125 MHz, CD_3OD) δ 28.5 (×3), 31.8, 59.8, 64.6, 76.1, 82.9, 117.3, 132.5, 134.7, 137.6 (×2), 144.2, 152.8, 206.2; IR ($CHCl_3$) cm^{-1}: 2981, 2935, 1708, 1693, 1476, 1371, 1152; HRMS calcd for $C_{16}H_{20}NO_4INa$ $(M+Na)^+$ 440.0335, found 440.0358; $[\alpha]_D^{24}=-46.0$ (c 0.82, $CHCl_3$).

3.6.11.2. *tert*-Butyl (2*S*)-2-[(1*R*)-1-hydroxy-1-methoxymethyl-4,5-dimethylhex-4-enyl]-5-iodoindoline-1-carboxylate (major-32). The prepared Grignard reagent (0.5 M THF solution, 7.8 ml) was added dropwise to a solution of **31** (813 mg, 1.95 mmol) in THF (3 ml) at −78 °C in N_2 atmosphere, and the reaction mixture was stirred at this temperature for 1 h. After the addition of satd NH_4Cl aq, the reaction mixture was allowed to warm to room temperature. The organic material was extracted with AcOEt (10 ml×2), and then the combined extracts were washed with brine (20 ml), dried over Na_2SO_4 and concentrated. Purification by silica gel flash chromatography (hexane–AcOEt 9:1) furnished the corresponding alcohol **32** (770 mg, 77%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.31 (1H, dt, J=5.2, 12.7 Hz), 1.41 (1H, dt, J=5.2 Hz, 12.7), 1.52 (3H, s), 1.55 (3H, s), 1.57 (9H, s), 1.58 (3H, s), 1.99 (1H, dt, J=5.2, 12.7 Hz), 2.04 (1H, dt, J=5.2, 12.7 Hz), 3.08 (1H, dd, J=2.0, 16.9 Hz), 3.26 (1H, dd, J=10.3, 16.9 Hz), 3.35 (3H, s), 3.40 (2H, s), 4.73 (1H, br d, J=9.8 Hz), 7.24 (1H, br s), 7.43–7.44 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.2, 19.8, 20.5, 28.1, 28.3 (×3), 29.6, 31.4, 59.3, 64.7, 76.3, 76.9, 82.4, 85.8, 118.3, 124.1, 127.4, 133.0, 134.8, 135.8 (×2), 142.8; IR ($CHCl_3$) cm^{-1}: 2983, 2928, 1687, 1672, 1475, 1370, 1164; HRMS calcd for $C_{23}H_{34}NO_4INa$ $(M+Na)^+$ 538.1431, found 538.1417; $[\alpha]_D^{24}=-36.3$ (c 0.46, $CHCl_3$).

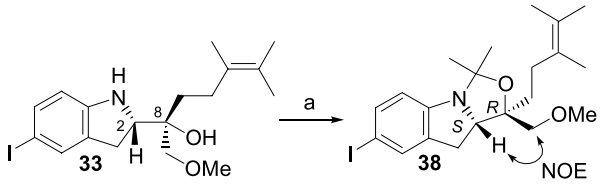
3.6.11.3. *tert*-Butyl (2*S*)-2-[(1*S*)-1-hydroxy-1-methoxymethyl-4,5-dimethylhex4-enyl]-5-iodoindoline-1-carboxylate (minor-32). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.57 (9H, s), 1.62 (6H, s), 1.65 (3H, s), 1.57–1.65 (2H, m), 2.11 (1H, dt, J=5.3, 12.5 Hz), 2.18 (1H, dt, J=5.3, 12.5 Hz), 2.88 (3H, s), 3.07 (1H, d, J=9.5 Hz), 3.15 (1H, d, J=9.5 Hz), 3.16–3.26 (2H, m), 4.64 (1H, dd, J=2.9, 10.2 Hz), 7.20–7.22 (1H, m), 7.43–7.45 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.3, 19.9, 20.5, 27.6, 28.2, 28.3, 28.9, 30.2, 33.3, 58.7, 65.9, 75.0, 76.3, 77.4, 82.9, 85.9, 118.2, 124.1, 127.6, 133.1, 135.4, 135.6, 142.3; IR ($CHCl_3$) cm^{-1}: 2983, 2926, 1665, 1476, 1371, 1163; HRMS calcd for $C_{23}H_{34}NO_4INa$ $(M+Na)^+$ 538.1431, found 538.1437; $[\alpha]_D^{24}=-53.9$ (c 0.49, $CHCl_3$).

3.6.11.4. (2*R*)-2-[(2*S*)-2,3-Dihydro-5-iodo-1*H*-indol-2-yl]-1-methoxy-5,6-dimethylhept-5-en-2-ol (33). Formic acid (1 ml) was added to a solution of **32** (115 mg, 0.22 mmol) in CH_2Cl_2 (1 ml) at room temperature, and the mixture was stirred under reflux conditions for 2 h. The reaction mixture was poured into water, basified to pH 8 with $NaHCO_3$, and the organic material was extracted with AcOEt (5 ml×2). The combined organic extracts were washed with brine (10 ml), dried over Na_2SO_4 and concentrated. The crude product was purified by silica gel flash chromatography (hexane–AcOEt 3:2) to give **33** (55 mg, 59%) as a colorless solid (mp 104–106 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.47 (1H, dt, J=5.1, 13.9 Hz), 1.55 (1H, dt, J=5.1, 13.9 Hz), 1.64 (3H, s), 1.66 (6H, s), 2.01 (1H, dt, J=5.1, 12.5 Hz), 2.15 (1H, dt, J=5.1, 12.5 Hz), 2.78 (1H, s), 2.89 (1H, dd, J=8.8, 16.1 Hz), 3.05 (1H, dd, J=11.0, 16.1 Hz), 3.39 (1H, d, J=9.5 Hz), 3.40 (3H, s), 3.49 (1H, d, J=9.5 Hz), 4.07 (1H, t, J=9.9 Hz), 4.28 (1H, br s), 6.41 (1H, d, J=8.1 Hz), 7.27 (1H, d, J=8.1 Hz), 7.33 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.5, 20.1, 20.7, 28.3, 30.3, 33.0, 59.5, 66.0, 72.7, 78.3, 79.5, 111.2, 124.3, 127.1, 131.5, 133.0, 135.7, 150.3; IR ($CHCl_3$) cm^{-1}: 3513, 3407, 2925, 1602, 1479, 1417, 1248, 1112; HRMS calcd for $C_{18}H_{27}NO_2I$ $(M+H)^+$ 416.1087, found 416.1073. Anal. Calcd for $C_{18}H_{26}NO_2I$: C, 52.06; H, 6.31; N, 3.37; I, 30.56. Found: C, 52.08; H, 6.40; N, 3.55; I, 30.69; $[\alpha]_D^{24}=-25.9$ (c 0.19, $CHCl_3$).

3.6.11.5. (2*R*,3*R*)-3-Chloro-2-(3,4-dimethyl-pent-3-enyl)-6-iodo-2-methoxymethyl-1,2,3,4-tetrahydroquinoline (34). Tri-*n*-butylphosphine (140 μl, 0.54 mmol) was added dropwise to a solution of **33** (15 mg, 0.036 mmol) and carbon tetrachloride (110 μl, 1.08 mmol) in CH_2Cl_2 (2 ml) at reflux (bath temp. 55 °C) in N_2 atmosphere. The reaction mixture was stirred under reflux conditions for 1 h, and then concentrated. The resulting residue was purified by silica gel flash chromatography (hexane–AcOEt 19:1) to give **34** (7.1 mg, 45%) as a colorless solid (mp 98–100 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.54 (3H, s), 1.57–1.62 (7H, m), 1.75 (1H, dt, J=5.2, 13.2 Hz), 2.00 (1H, dt, J=4.6, 12.2 Hz), 2.08 (1H, dt, J=4.6, 12.2 Hz), 3.02 (1H, dd, J=5.9, 17.1 Hz), 3.29 (1H, dd, J=5.9, 17.1 Hz), 3.36 (3H, s), 3.49 (1H, d, J=7.8 Hz), 3.53 (1H, d, J=7.8 Hz), 4.10 (1H, s), 4.31 (1H, t, J=5.9 Hz), 6.34 (1H, d, J=7.8 Hz), 7.26 (1H, s), 7.27 (1H, d, J=7.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.4, 19.9, 20.6, 27.7, 33.0, 33.5, 56.4, 57.6, 59.4, 73.7, 78.1, 116.8, 119.8, 124.6, 126.7, 136.1, 137.7, 142.0; IR ($CHCl_3$) cm^{-1}: 2926, 1597, 1488, 1299, 1109; HRMS calcd for $C_{18}H_{25}NOClI$ $(M)^+$ 433.0670, found 433.0652; $[\alpha]_D^{24}=-10.3$ (c 0.64, $CHCl_3$).

3.6.11.6. (−)-Virantmycin (2a). A mixture of **34** (21 mg, 0.048 mmol), $Pd(OAc)_2$ (6.1 mg, 0.027 mmol) and K_2CO_3 (27 mg, 0.194 mmol) in 0.5 ml of H_2O and 0.5 ml of methanol was stirred vigorously at room temperature in 1 atm CO atmosphere for 18 h. After the addition of water, the organic material was extracted with AcOEt (5 ml×2). The combined organic extracts were washed with brine (10 ml), dried over Na_2SO_4 and concentrated. The crude residue was purified by silica gel flash chromatography (hexane–AcOEt 9:1 to 1:1) to give (−)-virantmycin (**2a**) as a yellow oil (9.0 mg, 53%) along with the recovered **34** (7.1 mg, 34%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.61 (6H, s), 1.63 (3H, s), 1.61–1.67 (1H, m), 1.81 (1H, dt, J=4.9, 13.2 Hz), 2.01 (1H, dt, J=4.9, 12.2 Hz), 2.09 (1H, dt, J=4.9, 12.2 Hz), 3.12 (1H, dd, J=5.9, 17.6 Hz), 3.37 (1H, dd, J=4.9, 17.6 Hz), 3.39 (3H, s), 3.56 (1H, d, J=8.8 Hz), 3.58 (1H, d, J=8.8 Hz), 4.37 (1H, t, J=5.4 Hz), 4.65 (1H, br s), 6.54 (1H, d, J=7.8 Hz), 7.76–7.78 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.4, 19.9, 20.6, 27.8, 33.5, 33.6, 56.2, 58.0, 59.4, 74.0, 113.5, 116.0, 117.6, 124.8, 126.5, 130.4, 132.4, 147.2, 171.6; IR ($CHCl_3$) cm^{-1}: 2926, 1710, 1675, 1609, 1290, 1132, 1111; HRMS calcd for $C_{19}H_{27}NO_3Cl$ $(M+H)^+$ 352.1679, found 352.1668; $[\alpha]_D^{24}=-16.5$ (c 0.11, $CHCl_3$).

3.6.11.7. Determination of the stereochemistry of major-32. The configurations of the newly created asymmetric centers in major-**32** was determined after NOE experiments of the acetonide **38**, which was derived from **33** by acetonization with 2,2-dimethoxypropane. As a result, major-**32** has (2*S*,8*R*) configuration (Scheme 18).



Scheme 18. Reagents and conditions: (a) 2,2-dimethoxypropane, PPTS, CH_2Cl_2, rt, 64%.

3.6.11.8. (1*R*,9a*S*)-7-Iodo-1-methoxymethyl-3,3-dimethyl-1-(3,4-dimethylpent-3-enyl)-9,9a-dihydro-1*H*-[1,3]oxazolo[3,4-*a*]indole (38). Method for the synthesis of major-**16** was followed using **33** (17 mg, 0.041 mmol) to give **38** (12 mg, 64%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.09 (1H, dt, J=4.2, 13.2 Hz), 1.50 (6H, s), 1.55–1.60 (7H, m), 1.65 (3H, s), 1.94 (1H, dt, J=4.9, 12.6 Hz), 2.05 (1H, dt, J=4.2, 12.6 Hz), 3.01 (1H, dd, J=10.3, 17.4 Hz), 3.07 (1H, dd, J=4.4, 17.4 Hz), 3.28 (1H, d, J=9.8 Hz), 3.38 (3H, s), 3.52 (1H, d, J=9.8 Hz), 4.33 (1H, dd, J=4.4, 10.3 Hz), 6.41 (1H, d, J=7.8 Hz), 7.27 (1H, d, J=7.8 Hz), 7.30 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.3, 19.9, 20.5, 25.8, 28.1, 29.1, 29.1, 31.3, 59.6, 70.1, 76.3, 80.1, 82.2, 94.8, 113.7, 124.1, 127.4, 133.3, 135.0, 135.4, 148.5; IR ($CHCl_3$) cm^{-1}: 2928, 2862, 1474, 1258, 1117; HRMS calcd for $C_{21}H_{31}NO_2I$ $(M+H)^+$ 456.1399, found 456.1407; $[\alpha]_D^{24}=+68.4$ (c 1.20, $CHCl_3$).

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