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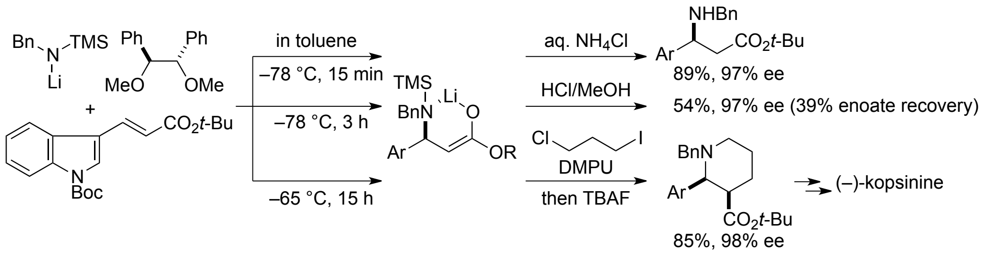

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# Critical Profiles of Chiral Diether-Mediated Asymmetric Conjugate Aminolithiation of Enoate with Lithium Amide as a Key to the Total Synthesis of (–)-Kopsinine

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ABSTRACT

Chiral diether-mediated asymmetric aminolithiation of indolylpropenoate with lithium amide in toluene at –78 °C for 15 min gave, after aqueous ammonium chloride quench, the corresponding conjugate addition product with 97% ee in 89% yield. If hydrogen chloride in methanol was selected as a quencher, however, aminolithiation at –78 °C for 3 h gave the corresponding adduct with 97% ee in 54% yield, along with recovery of the starting enoate in 39% yield. Based on this finding of an incomplete and slow reaction at −78 °C, the aminolithiation conditions were optimized to be at −60 °C for 15 h and subsequent enolate trap with alkyl halide upon an addition of DMPU afforded the desired aminoalkylation product with 98% ee in 89% yield. Further approach towards total synthesis of (–)-kopsinine was carried out by examining asymmetric aminoithiation with *N*-hydroxyethylamine equivalent, one-pot piperidine formation, and Claisen condensation.



## 1. Introduction

Chiral diether-mediated asymmetric conjugate addition reaction of a lithium amide with an enoate has been proven to be a powerful aminolithiation methodology, mainly because the intermediate lithium enolate is applicable as a carbon nucleophile to a further bond forming reaction with an electrophile, giving nearly enantiomerically pure ß-amino acid derivatives bearing two vicinal chiral centers in high yield. The conjugate addition step is usually very rapid and completes within hours, whereas the second alkylation step suffers from the low reactivity of an electrophilic alkyl halide, even in a toluene-THF solvent. It is also not so easy to determine whether the first conjugate addition reaction has completed, because highly reactive anionic species are involved in the reaction. TLC monitoring is a standard method of tracing the reaction progress in chemical laboratories; during spotting of the sample from a capillary, however, the reaction sometimes proceeds significantly because of an increase in the temperature, leading to the incorrect information that the reaction has completed. We describe herein that the speed of the chiral diether-mediated asymmetric conjugate addition is dependent on the structure of an enoate and is sometimes very slow at low temperature. Another approach toward the total synthesis of (–)-kopsinine[1,2] is also the subject of the present study.

## 2. Results and Discussion

### 2.1. Chiral Diether-Mediated Asymmetric Conjugate Aminolithiation with Lithium Amide and Subsequent Alkylation

Chiral diether **3**-mediated conjugate addition of lithium *N*-benzyl-*N*-trimethylsilylamide **1** with *t*-butyl 3-(*N*-Boc-indol-3-yl)propenoate **2a** was conducted in toluene at −78 °C for 15 min and then quenched with aqueous ammonium chloride to give the conjugate adduct **5a** with 97% ee in 89% isolated yield, indicating rapid and high yield generation of lithium enolate **4** with 97% ee (Table 1, entry 1). The sequence of conjugate addition followed by alkylation of lithium enolate **4** was carried out as previously reported for 1.5 h at −78 °C and then at −40 °C for 2 h in order to confirm the completion of the conjugate aminolithiation,[3] and then, after addition of 222 equiv of THF as a solvent, 6 equiv of HMPA as an activator by coordination to lithium, and iodide **6a** as an electrophile, at −40 °C for 3 h. The crude extracts were treated for protodesilylation with TBAF in THF at room temperature for 12 h. Silica gel column chromatography gave a 93:7 mixture of *anti*- and *syn*-**7a** with 86% ee in 70% yield (entry 2). Major byproducts were deBoc and its *N*-alkylated products **2b** and **2c** in 5% and 11% yield, respectively. DeBoc products derived from **5a** and **7a** were not observed. The chemical yield of 70% and 93:7 diastereomer ratio of **7a** were on the line of

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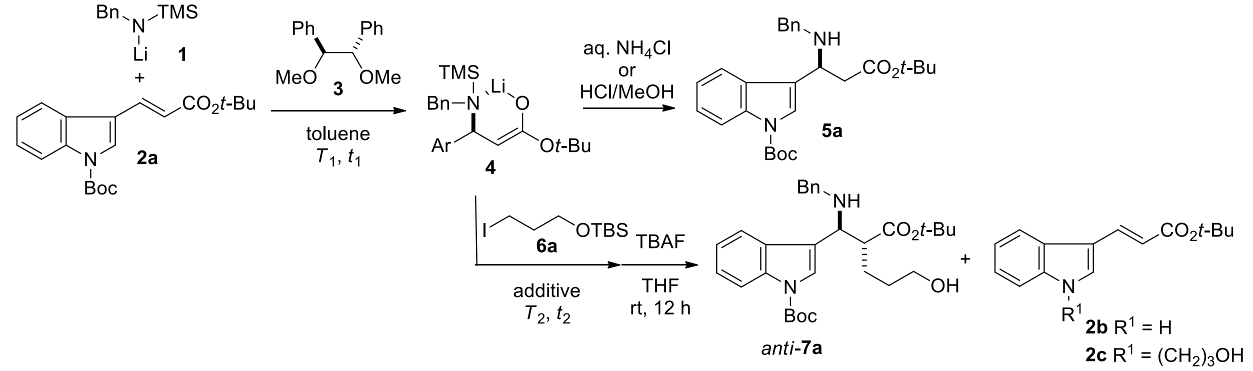
**Table 1.** Asymmetric Conjugate Aminolithiation in Toluene–Electrophile Trap of Lithium Enolate Upon Addition of Polar Additive.[a]




| entry | $T_1/t_1$ °C/h | quencher or additive (equiv) | $T_2/t_2$ °C/h | **5a** % yield | **5a** % ee | **7a** % yield | *anti*-**7a** % ee | *anti*:*syn* | **2a** % yield | **2b** % yield | **2c** % yield |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | −78/0.25 | aq $NH_4Cl$ | - | 89 | 97 | - | - | - | <2 | <1 | - |
| 2 | −78/1.5 then −40/2 | THF (222)/HMPA (6) | −40/3 | <1 | nd | 70 | 86 | 93:7 | <2 | 5 | 11 |
| 3 | −78/1.5 then −40/2 | DME (222)/HMPA (6) | −40/4 | <1 | nd | 70 | 82 | 93:7 | <5 | 7 | 11 |
| 4 | −78/1.5 then −40/2 | DMSO (254)/HMPA (6) | rt/1 | <5 | nd | 51 | 95 | 94:6 | <1 | 0 | 30 |
| 5 | −78/1.5 then −40/2 | DMF (233)/HMPA (6) | −40/3 | <8 | nd | 60 | 94 | 99:1 | <2 | 0 | 16 |
| 6[b] | −78/1.5 then −40/2 | DMF (233) | −40/4 | <8 | nd | 60 | 95 | 99:1 | <1 | 0 | 18 |
| 7 | −78/1.5 then −40/2 | DMF (30) | −40/18 | 15 | 88 | 57 | 88 | 86:14 | <1 | 3 | 10 |
| 8[b] | −78/1.5 then −40/2 | DMPU (222) | −40/2 | <1 | nd | 73 | 95 | 99:1 | <1 | 2 | 13 |
| 9 | −78/3 | HCl/MeOH | - | 54 | 97 | - | - | - | 39 | <1 | - |
| 10 | −78/15 | HCl/MeOH | - | 79 | 98 | - | - | - | 18 | <1 | - |
| 11 | −78/1.5 then −40/2 | HCl/MeOH | - | 75 | 95 | - | - | - | 5 | 12 | - |
| 12[b] | −65/15 | HCl/MeOH | - | 91 | 98 | - | - | - | <2 | 3 | - |
| 13[c] | −65/15 | HCl/MeOH | - | 96 | 96 | - | - | - | <1 | <1 | - |
| 14[b] | −65/15 | DMPU (222) | −40/2 | <1 | nd | 89 | 98 | 99:1 | <1 | 0 | 2 |

[a] With 3 equiv of **1**, 3.6 equiv of **3**, and 10 equiv of **6a**. Ar = 1-Boc-indol-3-yl. [b] Quoted from ref. 2. [c] With 1.5 equiv of **1** and 1.8 equiv of **3**.

acceptance or not; however, 86% ee was rather poorer than estimation because % ee of lithium enolate **4**, produced at least in 89% yield, should be 97% ee. In addition, it was not clear why significant amounts of **2b** and **2c** were produced.

Bidentate DME as an additive was similar to THF, giving **7a** with 82% ee in 70% yield (entry 3). DMSO was a better additive, giving *anti*-**7a** with 95% ee, albeit in a decreased 51% yield and **2c** in 30% yield at room temperature for 1 h (entry 4). DMF was also a good additive, giving *anti*-**7a** in 60% yield with high 94% and 95% ee and 99:1 dr in the absence and presence of HMPA, respectively (entries 5 and 6).[2] When the quantity of DMF was decreased to 30 equiv, alkylation became sluggish and after 18 h gave *anti*-**7a** with lower 88% ee and 86:14 dr in 57% yield, **2b** in 3% yield, and **2c** in 10% yield (entry 7). DMPU was the best additive among those examined, giving *anti*-**7a** with 95% ee and 99:1 dr in 73% yield, but along with **2b** in 2% and **2c** in 13% yield (entry 8).[2]

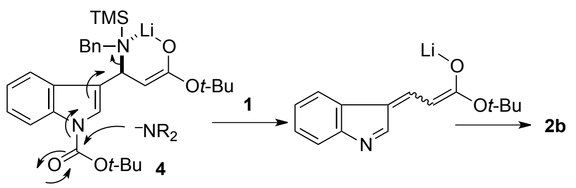
The lower yield and poorer % ee production of **7a** compared with **5a**, and the production of **2b** and **2c** in significant amounts implied a couple of possibilities: (1) incomplete conjugate addition reaction of lithium amide **1** with **2a** at the time of addition of the additive, resulting in **1** and **2a** remaining in the reaction mixture, led to the progression of further conjugate addition reactions without chirality control, and/or (2) addition of the additives to a completed reaction mixture, resulting in retro-Michael-type reaction of **4** to **1** and **2a**, and again conjugate addition but without chirality control. Since the 89% high yield production of **5a** with 97% ee was certainly confirmed by the isolation (Table 1, entry 1), it would be nonsense to doubt the incomplete conjugate addition of **1** to **2a**. Yet, this was shown not to be true by quenching the reaction with hydrogen chloride (HCl)/methanol, instead of aqueous ammonium chloride (Table 1, entry 1).

### *2.2. Quenching of the Conjugate Addition Reaction with Hydrogen Chloride/Methanol or Aqueous Ammonium Chloride*

The conjugate addition reaction of **1** with **2a** was quenched with HCl/methanol instead of aqueous ammonium chloride after 3 h at −78 °C to give, *to our surprise*, a mixture of **5a** with 97% ee in 54% yield and **2a** in 39% recovery yield (Table 1, entry 9). A prolonged 15 h reaction was not sufficient to complete the reaction, giving **5a** with 98% ee in 79% yield and recovering **2a** in 18% yield (entry 10). The previously established reaction conditions, that is, at −78 °C for 1.5 h and additional 2 h at −40 °C, gave **5a** with 95% ee in 75% yield, **2a** in 5% recovery, and **2b** in 12% yield (entry 11). These incomplete conjugate addition reactions rationalize the poorer % ee of **7a** because chiral diether **3** is kicked out from chelation and chiral ligand-free conjugate addition proceeded upon the addition of lithium coordinating additives like THF, DME, DMSO, DMF, HMPA, and DMPU at the alkylation step.

Fortunately, the reaction at −65 °C for 15 h gave **5a** with 98% ee in 91% yield along with very small amounts of **2a** and **2b** (entry 12). Use of smaller amounts of **1** (1.5 equiv) and **3** (1.8 equiv) led to the successful production of **5a** with 96% ee in 96% yield and trace amounts of **2a** and **2b** (entry 13). Under these specified conjugate addition conditions **7a** of 98% ee was satisfactorily obtained in 89% yield by adding DMPU as the best activator of lithium enolate **4**, as described previously (entry 14).[2]

Production of deBoc products **2b** and **2c** from **4** rather than directly from **2a** would be possible at a higher temperature–40 °C by nucleophilic attack of lithium amide **1** to an activated vinylogous type urethane carbonyl group of **4,** as shown in Scheme 1. This could explain the absence of the formation of a deBoc product of **5a**.




**Scheme 1.** Production of deBoc product **2b** from **4**.

These reaction profiles above indicate the incomplete conjugate addition reaction of **2a** with **1** at −78 °C. When DMPU was used as an activator, a retro-Michael type reaction would not be possible. By adding HCl/methanol as a quencher, the progress of the conjugate addition could be determined (Table 1, entry 9).

The remaining problem was to clarify what was happening in the reaction mixture after the addition of aqueous ammonium chloride, resulting in the high yield production of **5a**. Although the reason for the increased yield by the aqueous ammonium chloride quench (Table 1, entry 1 vs entry 9) is not fully clear, it could be that the reaction mixture becomes a heterogeneous ice–liquid suspension upon the addition of aqueous ammonium chloride at –78 °C, as shown in Figure 1. Upon removal of the cooling bath, the green color of the ice-liquid suspension changed gradually to brown, violet, yellow, and pale yellow (two-phase solution) during 20 min, suggesting that the quenching process required that period of time. Because of the slow hydrolysis of lithium amide **1** under heterogeneous suspension conditions, the remaining complex of **1-3** could undergo conjugate addition under a gradually elevating temperature to give **5a** with relatively high % ee in high yield. In contrast, a methanolic hydrogen chloride quench immediately gave a pale yellow solution, indicating almost spontaneous protonation of the reactive anionic species to stop the reaction.

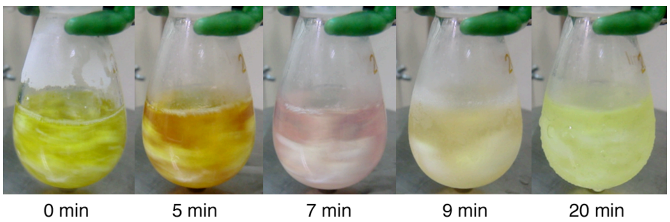


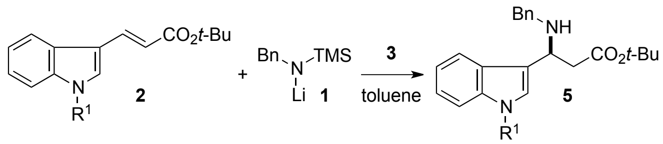

**Figure 1.** Heterogeneous Suspension to Two-Phase Solution (Table 1, entry 1) at 0, 5, 7, 9, and 20 min after Aqueous $NH_4Cl$ Quench at –78 °C and Cooling Bath Removal.

*2.3. Enantioselectivity and Reactivity Dependency on N-Substituent of 3-Indolylpropenoate*

*N*-Substituted indolylpropenoates **2** other than *N*-Boc **2a** were examined as a substrate in asymmetric conjugate amination. The conjugate addition of **1** to *N*-Ts enoate **2e** ($R^1$=Ts) at −78 °C for 3.5 h gave **5e** with 90% ee in 83% yield (Table 2, entry 2), lower than that of *N*-Boc-enoate **2a** giving **5a** with 97% ee in 89% yield after 15 min (Table 1, entry 1). The reaction progress of **2e** could be followed by TLC monitoring, and indicated that the reaction was not so fast during TLC sampling and spotting. The reaction of electron-donating *N*-*p*-methoxybenzyl ($R^1$=PMB) enoate **2f** was much slower and did not proceed at –78 °C, but did proceed at –40 °C for 4 h to give **5f** with 45% ee in 85% yield (entry 3).

The observed order of reactivity of **2a**~**2e**>**2f** seems to be consistent with the electron-withdrawing and -donating nature of the *N*-substituents. The electron-withdrawing nature of *N*-Boc and *N*-Ts groups, which block the lone pair electrons of the indole nitrogen from mesomerism with the dienoate system, would be the origin of the higher reactivity than **2f**. On the other hand, poorer electrophilicity of **2f** than that of **2a** and **2e** could be explained by the mesomeric effect of the indole nitrogen lone pair electrons. These results indicated that electron-withdrawing *N*-protecting groups, which allow for the reaction to proceed at a lower temperature, are desirable for obtaining higher % ee of products.

**Table 2.** Enantioselectivity and Reactivity Dependency on *N*-Substituent of 3-Indolylpropenoate **2**.[a]



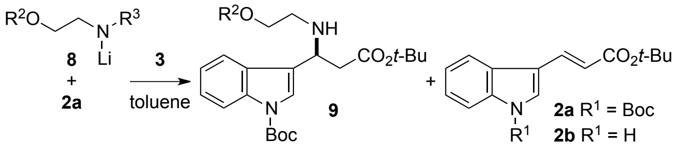

| entry | 2 | $R^1$ | *T*, *t* | 5 | yield | ee |
|---|---|---|---|---|---|---|
| 1[b] | **2a** | Boc | –78°C, 0.25 h | **5a** | 89% | 97% |
| 2 | **2e** | Ts | –78°C, 3.5 h | **5e** | 83% | 90% |
| 3 | **2f** | PMB | –40 °C, 4 h | **5f** | 85% | 45% |

[a] With 3 equiv of **1** and 3.6 equiv of **3**. Quenched with saturated aq $NH_4Cl$. Less than 3% recovery of **2**. [b] Quoted from ref. 2

*2.4. Asymmetric Conjugate Addition of Lithium Alkoxyethylamides.*

Because an *N*-hydroxyethyl intermediate is required for the total synthesis of (–)-kopsinine, we examined the performance of hydroxyethylamide equivalents **8a**–**c** in asymmetric conjugate addition. The reaction of TMS-amide **8a** bearing a *p*-methoxybenzyl (PMB) protection group with **2a** did not proceed at –78 °C, but at –40 °C for 5 h gave product **9a** with only 13% ee in 79% yield (Table 3, entry 1). Bulkier TBS-amide **8b** bearing a bulky trityl protection group was designed to prevent intramolecular five-membered chelate formation of the oxygen atom to lithium by bulkiness around the oxygen atom,[4] because the five-membered chelation kicks out chiral diether **3** from the lithium amide-**3** complex;[5] however, the reaction did not proceed at –78 °C, but at –40 °C for 10 h, giving **9b** with only 9% ee in 9% yield (entry 2). When sterically less hindered **8c**, having no TBS group, was utilized, the reaction proceeded at –78 °C to give *ent*-**9b** with only 17% ee in low yield (entry 3).

**Table 3.** Asymmetric Conjugate Addition of Lithium *N*-(Alkoxyethyl)amide **8**.[a]



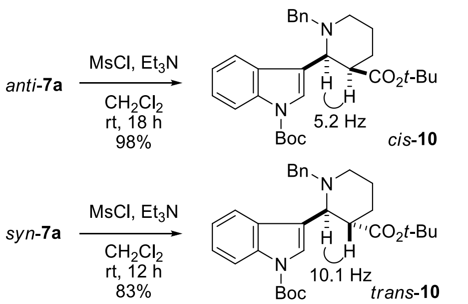

| entry | **8**/R²/R³ | *T*/*t* °C/h | **9** yield/ee | **2a** yield | **2b** yield |
|---|---|---|---|---|---|
| 1 | **8a**/PMB/TMS | –78/12 then –40/5 | **9a** 79%/13% ee | 2% | 14% |
| 2 | **8b**/$Ph_3C$/TBS | –78/17 then –40/10 | **9b** 9%/9% ee | 52% | 18% |
| 3 | **8c**/$Ph_3C$/H | –78/0.7 | *ent*-**9b** 18%/17% ee | 63% | 5% |

[a] With 3 equiv of **8** and 3.6 equiv of **3**. Quenched with saturated aq $NH_4Cl$. The absolute configuration of **9** was tentatively assigned by analogy.

In these reactions, the deBoc product **2b** was again observed whereas the deBoc product of **9** was not. It is likely that **2b** came from a lithium enolate intermediate like **4,** as shown in Scheme 1.

*2.5. Cyclization to Piperidines.*

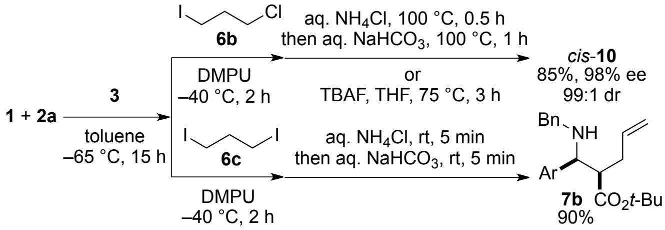
Cyclization of *anti*-**7a** with mesyl chloride and triethylamine in methylene chloride at room temperature for 18 h gave piperidine *cis*-**10** in 98% yield (Scheme 2).[2] In the same way, *syn*-**7a** was cyclized into piperidine *trans*-**10** in 83% yield. The coupling constants 5.2 and 10.1 Hz of the adjacent methine protons, respectively, indicated the relative configuration of *cis*- and *trans*-**10**.[6] The absolute configuration was confirmed by converting *cis*-**10** into (–)-kopsinine.[2]




**Scheme 2.** Cyclization to *cis*- and *trans*-Piperidines **10**.

*2.6. Attempted One-Pot [N+2+3] Cyclization.*

As shown in Scheme 2, an enolate trap with **6a** and MsCl treatment of *anti*-**7a** gave *cis*-**10** in three steps starting from **2a**. Successful one-pot [N+2+3] cyclization of **2a** to piperidine *cis*-**10** used chloroiodopropane **6b** as a C3 component (Scheme 3).[2] 1,3-Diiodopropane **6c** as a much more reactive C3 component, however, did not yield *cis*-**10** and gave HI elimination product **7b** in 90% yield.

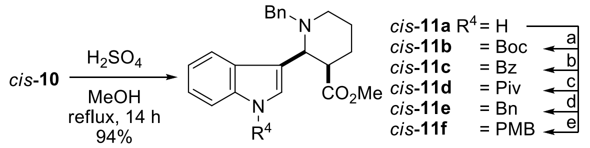



**Scheme 3.** One-Pot Alkylation with **6**.

*2.7. Claisen Condensation for C2 Elongation of* **10**

The remaining synthetic tasks for the total synthesis of (–)-kopsinine were (1) attachment of C2 to the ester moiety of *cis*-**10** by Claisen condensation, (2) replacement of the *N*-Bn group with a hydroxyethyl equivalent, and (3) cyclization to the established intermediate **20**. In our previous total synthesis,[2] replacement of the Bn group with a hydroxyethyl equivalent was the first manipulation. In this work, however, Claisen condensation of *cis*-**10** was examined to evaluate the effect of the *N*-substituent of the indole nitrogen.

The transesterification of *t*-butyl ester *cis*-**10** under Fischer methyl esterification conditions proceeded smoothly with concomitant removal of the *N*-Boc group to give methyl ester *cis*-**11a** in 94% yield (Scheme 4). The indole nitrogen of *cis*-**11a** was separately protected by Boc, benzoyl (Bz), pivaloyl (Piv), benzyl (Bn), and PMB groups to give *cis*-**11b**–**f** as substrates for the Claisen condensation.[7]

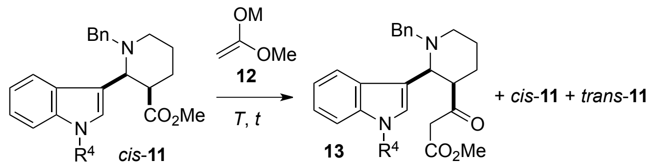



(a) $Boc_2O$, DMAP, $CH_3CN$; (b) BzCl, NaH, DMF; (c) PivCl, DMAP, $Et_3N$, $CH_2Cl_2$; (d) BnBr, NaH, DMF; (e) PMBCl, NaH, DMF.

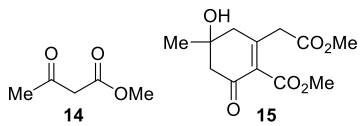
**Scheme 4.** *N*-Substituted Methyl Esters *cis*-**11a**–**f**.

A THF solution of *N*-Boc protected *cis*-**11b** was added at –78 °C to a THF solution of 4 equiv of sodium enolate **12a** (M=Na), generated *in situ* by treating methyl acetate with NaHMDS[8], and the mixture was stirred at –40 °C for 2 h. After removal of the cooling bath, the mixture was further stirred for 1 h at room temperature (Table 4, entry 1). Disappointingly, Claisen product *cis*-**13a** ($R^4$ = H) was obtained in only 7% yield, and the major product was a 4:1 mixture of *cis*- and *trans*-**11a** in 80% yield without the recovery of **11b**. At room temperature, sodium enolate **12a** or methoxide should isomerize *cis*-**11b** to *trans*-**11b** through a deprotonation-protonation sequence, and also attack the Boc group to give **11a** and **13a**. The reactions of *N*-Bz **11c** at –40 °C for 2 h and at room temperature for another 2 h, and *N*-Piv **11d** at room temperature for 15 h also resulted in *N*-deprotection to give *cis*-**11a** in 86% and 95% yield, respectively (entries 2 and 3). *N*-Bn *cis*-**11e** at room temperature for 15 h and *N*-PMB *cis*-**11f** at 0 °C for 4 h and at room temperature for 2 h were converted to the desired **13e** in 12% and **13f** in 26% yield with recovery of a significant amount of starting and isomerized methyl esters (entries 4 and 5). Fortunately, lithium enolate **12b** (M=Li) afforded the desired Claisen product **13f** in 90% yield starting from *cis*-**11f** (entry 6).

**Table 4.** Claisen Condensation of **11**.




| entry | *cis*-**11**/R[4] | **12**/M | *T* (°C)/*t* (h) | **13**/R[4] yield | **11** yield (*cis*: *trans*) |
|---|---|---|---|---|---|
| 1 | **11b**/Boc | **12a**/Na | –40/2 then rt/1 | **13a**/H 7% | **11a** 80% (4:1) |
| 2 | **11c**/Bz | **12a**/Na | –40/2 then rt/2 | 0% | **11a** 86% (1:0) |
| 3 | **11d**/Piv | **12a**/Na | rt/15 | 0% | **11a** 95% (1:0) |
| 4 | **11e**/Bn | **12a**/Na | rt/15 | **13e**/Bn 12% | **11e** 68% (0:1) |
| 5 | **11f**/PMB | **12a**/Na | 0/4 then rt/2 | **13f**/PMB 26% | **11f** 74% (3:7) |
| 6 | **11f**/PMB | **12b**/Li | –40/1.5 then 0/14 | **13f**/PMB 90% | 0% |
| 7 | **11a**/H | **12b**/Li | 0/15 | 0% | **11a** 88% (1:0)[a] |
| 8 | **11g**/Li | **12b**/Li | rt/17 | **13a**/H 66% | **11a** 8% (1:0) |

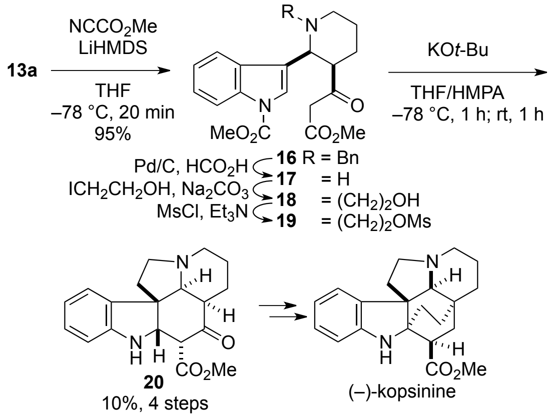



[a] Other byproducts were **14** and **15** in 24% and 27% yield, respectively.

Unfortunately, the reaction of *N*-protection free *cis*-**11a** with 16 equiv of **12b** at 0 °C for 15 h resulted in the recovery of *cis*-**11a** in 88% yield, along with self-Claisen condensation products **14** and **15** in 24% and 27% yield, respectively (entry 7). The production of **14** and **15** was rationalized by the reaction of **12b** with methyl acetate, generated by protonation of **12b** with the indole N–H of **11a**. Thus, this self-condensation could be avoidable by using lithiated **11a**. To our delight, the reaction of *N*-lithiated *cis*-**11g**, generated *in situ* by the lithiation of *cis*-**11a** with LiHMDS, with 16 equiv of **12b** at room temperature for 17 h successfully produced **13a** in 66% yield and *cis*-**11a** in 8% recovery (entry 8).

### *2.8. Construction of the Common Intermediate **20** of Kopsia Alkaloids*

Towards Natsume's intermediates **18** and **20**,[1d] **13a** was *N*-methoxycarbonylated to give indole **16** in 95% yield (Scheme 5). Hydrogenolysis of **16** removed the Bn group from the nitrogen to give secondary amine **17**, which was, without purification, hydroxyethylated to unstable **18**. Mesylation of **18,** followed by the tandem cyclization reported by Natsume[1d] afforded (–)-**20**,[9] a pentacyclic common intermediate for *kopsia* alkaloids in 10% yield over 4 steps. The hydrogenolysis step, however, lacked reproducibility, and the rest of the three-step transformation was low-yielding, probably due to the concomitant presence of the secondary amine and ketoester moiety. The problem observed in this approach was overcome by postponing the Claisen condensation reaction after the completion of *N*-hydroxyethylation.[2]




**Scheme 5.** Construction of the Common Intermediate **20**.

## 3. Conclusion

The reaction speed of chiral diether-mediated asymmetric aminolithiation of indolylpropenoate with lithium amide in toluene at a low temperature was substrate dependent. Completion of the reaction could be verified by a hydrogen chloride-methanol quench, but not by an aqueous ammonium chloride quench. The Claisen condensation was successfully conducted under proton source-free conditions. These findings led to the total synthesis of (–)-kopsinine.

## 4. Experimental section

### *4.1. General.*

All melting points are uncorrected. Silica gel was used for column chromatography. NMR (500 MHz for $^1$H and 125 MHz for $^{13}$C) was measured in $CDCl_3$ unless otherwise mentioned. Chemical shifts and coupling constants are presented in ppm relative to tetramethylsilane and Hz, respectively. Abbreviations are as follows: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad. $^{13}$C peak multiplicity assignments were made based on DEPT data. IR spectroscopy of oil and solid samples were measured as neat liquid films and KBr pellets, respectively. The wave numbers of maximum absorption peaks of IR spectroscopy are presented in $cm^{-1}$. DMSO, DMF, and DMPU were distillated prior to use. TMSCl was freshly distilled from $CaH_2$ prior to use. Dehydrated solvents were purchased and used without further desiccation. Other reagents were purchased and used as received.

### *4.2. Starting Materials*

*N*-Benzyltrimethylsilylamine,[10] 2-trityloxyethylamine,[11] **2a**,[2] **3**,[12] **5f**,[13] and **6a**[14] were prepared according to reported procedures.

#### *4.2.1. (E)-tert-Butyl 1-p-Toluenesulfonylindole-3-propenoate (**2e**)*

The reported procedure[13] using 1-*p*-toluenesulfonylindole-3-carbaldehyde[15] (13.5 g, 45 mmol), instead of 1-*p*-methoxybenzylindole-3-carbaldehyde, gave the title compound (15.4 g, 86%) as colorless prisms of mp 139.5–140.5 °C: $R_f$ = 0.6 (hexane/AcOEt 4/1). $^1$H NMR: 1.54 (9H, s), 2.35 (3H, s), 6.45 (1H, d, *J* = 16.2), 7.23–7.39 (4H, m), 7.68 (1H, d, *J* = 16.2), 7.71–7.81 (4H, m), 8.00 (1H, m). $^{13}$C NMR: 21.5 ($CH_3$), 28.2 ($CH_3$), 80.5 (C), 113.8 (CH), 118.4 (C), 120.4 (CH), 120.7 (CH), 124.0 (CH), 125.4 (CH), 127.0 (CH), 128.0 (CH), 128.3 (C), 130.1 (CH), 134.5 (CH), 134.9 (C), 135.7 (C), 145.5 (C) 166.5 (C). IR: 2978, 1705, 1636, 1366, 1150, 980. EIMS *m/z*: 397 ($M^+$), 324 (M – O*t*-Bu). Anal. Calcd for $C_{22}H_{23}NO_4S$: C, 66.48; H, 5.83; N, 3.52. Found: C, 66.34; H, 5.87; N, 3.36.

#### 4.2.2. N-Trimethylsilyl(2-p-methoxybenzyloxyethyl)amine

To a solution of 2-*p*-methoxybenzyloxyethylamine[16] (14 g, 77 mmol) in THF (155 mL) was added a 1.64 M hexane solution of BuLi (49 mL, 80 mmol) at –78 °C over 10 min, and the mixture was stirred for 1 h at –78 °C. Then TMSCl (10 mL, 80 mmol) was added over 5 min, and the mixture was warmed up to rt and stirred for 3 h. Concentration and distillation (200–205 °C/0.2 mmHg) gave the title compound (7.0 g, 36%) as a colorless oil: $^1$H NMR ($C_6D_6$): −0.06 (9H, s), 0.69 (1H, br s), 2.89 (2H, dt, *J* = 8.1, 5.7), 3.27 (3H, s), 3.30 (2H, t, *J* = 5.7), 4.35 (2H, s), 6.80 (2H, d, *J* = 8.6), 7.23 (2H, d, *J* = 8.6). $^{13}$C NMR ($C_6D_6$): 0.14 ($CH_3$), 42.0 ($CH_2$), 54.7 ($CH_3$), 72.9 ($CH_2$), 73.5 ($CH_2$), 114.0 (CH), 129.4 (CH), 131.3 (C), 160.0 (C). IR: 3395, 2955, 1612, 1512, 1250, 841. EIMS *m/z*: 253 ($M^+$), 222 (M – OMe), 121 (PMB). HRMS–FAB *m/z*: $[M + H]^+$ calcd for $C_{13}H_{24}NO_2Si$, 254.1576; found, 254.1579.

#### 4.2.3. N-tert-Butyldimethylsilyl(2-trityloxyethyl)-amine

To a solution of 2-trityloxyethylamine (2.5 g, 8.3 mmol), $Et_3N$ (1.5 mL, 11 mmol), and DMAP (20 mg, 0.17 mmol) in $Et_2O$ (25 mL) was added TBSCl (1.5 g, 10 mmol) at 0 °C, and the mixture was stirred for 19 h at rt. The resulting precipitate was removed by filtration. Volatile materials were removed by evaporation, and the residue was dried *in vacuo* (70 °C/0.01 mmHg) to give the title compound as a colorless oil (2.2 g, 65%): $^1$H NMR ($C_6D_6$): −0.02 (6H, s), 0.51 (1H, t, *J* = 8.0), 0.90 (9H, s), 2.94 (2H, dt, *J* = 8.0, 6.0), 3.11 (1H, t, *J* = 6.0), 7.02–7.15 (9H, m), 7.55–7.60 (6H, m). $^{13}$C NMR: −4.9 ($CH_3$), 18.5 (C), 26.6 ($CH_3$), 42.9 ($CH_2$), 67.3 ($CH_2$), 86.7 (C), 127.5 (CH), 128.3 (CH), 129.2 (CH), 144.9 (C). IR: 3410, 2931, 1450, 1072. EIMS *m/z*: 387 (M – 2Me), 243 ($Ph_3C$). The oil was used without further purification.

### 4.3. Table 1

#### 4.3.1. Typical Procedure A (Entry 1). (−)-tert-Butyl (S)-3-Benzylamino-3-(1-tert-butoxycarbonylindol-3-yl)propanoate (5a)

To a solution of *N*-benzyltrimethylsilylamine (0.29 mL, 1.5 mmol) in toluene (4 mL), was added a 1.62 M hexane solution of BuLi (0.93 mL, 1.5 mmol) at –78 °C over 4 min, and the mixture was stirred for 30 min. Then a solution of chiral diether **3** (436 mg, 1.8 mmol) in toluene (2 mL) was added over 5 min, and after 30 min, a solution of enoate **2a** (172 mg, 0.5 mmol) in toluene (2 mL) was added over 6 min. The mixture was stirred for 15 min, and saturated aq $NH_4Cl$ (1.5 mL) was added. After 5 min, the cooling bath was removed, and the whole was allowed to warm up to rt. Then, saturated aq $NaHCO_3$ (10 mL) was added, and the organic layer was separated. The aqueous layer was extracted with AcOEt, and the combined organic layers were washed with brine and dried over $Na_2SO_4$. Concentration and column chromatography (hexane/AcOEt 16/1 to 3/2) gave the title compound[2] (200 mg, 89%) with 97% ee as a yellow oil, chiral ligand **3** (436 mg, quant) as colorless plates, **2a** (1.6 mg, 1%) as a yellow oil, and **2b**[17] (1.5 mg, 1%) as a yellow oil. The enantiomeric excess of **5a** was determined according to the previous report.[2]

#### 4.3.2. Typical Procedure B (Entry 2). (−)-tert-Butyl (2S,3S)-3-Benzylamino-3-(1-tert-butoxycarbonylindol-3-yl)-2-(3-hydroxypropyl)propanoate (syn-7a)

To a solution of *N*-benzyltrimethylsilylamine (0.59 mL, 3.0 mmol) in toluene (8 mL), was added a 1.54 M hexane solution of BuLi (1.95 mL, 3.0 mmol) at –78 °C over 3 min, and the mixture was stirred for 30 min. A solution of chiral diether **3** (872 mg, 3.6 mmol) in toluene (4 mL) was added over 7 min, and after 30 min, a solution of enoate **2a** (344 mg, 1.0 mmol) in toluene (4 mL) was added over 6 min. The mixture was stirred for 1.5 h at –78 °C and further 2 h at –40 °C, and a solution of 3-(*t*-butyldimethylsiloxy)-1-iodopropane (**6a**) (2.4 mL, 10 mmol) and HMPA (1.04 mL, 6 mmol) in THF (18 mL) was added over 30 min at –78 °C. The mixture was stirred for 2.5 h at –40 °C, and saturated aq $NH_4Cl$ (2 mL) was added. The cooling bath was removed, and after the whole was warmed up to rt, saturated aq $NaHCO_3$ (12 mL) was added. The organic layer was separated, and the aqueous layer was extracted with AcOEt. The combined organic layers were washed with brine, dried over $Na_2SO_4$, and then concentrated to give a colorless oil (4.7 g). The oil was dissolved in THF (15 mL), and TBAF·$3H_2O$ (4.7 g, 15 mmol) was added to the solution at rt. The mixture was stirred for 12 h, and saturated aq $NH_4Cl$ (6 mL) and saturated aq $NaHCO_3$ (10 mL) were added. The whole was extracted with benzene (30 mL × 3). The combined organic layers were washed with water (10 mL × 3) and brine, and dried over $Na_2SO_4$. Concentration and column chromatography (hexane/AcOEt 9/1 to 1/1) gave chiral ligand **3** (872 mg, quant) as colorless plates, **2b**[17] (13 mg, 5%) as a pale yellow oil, *anti*-**7a**[2] (333 mg, 65%) as white powder of mp 160–162 °C, **2c**[2] (33 mg, 11%) as a pale yellow oil, and the title compound (28 mg, 5%) as a pale yellow oil: $R_f$ = 0.2 (hexane/AcOEt 3/2). $[\alpha]^{25}_D$ −14.1 (*c* 1.11, $CHCl_3$). $^1$H NMR: 1.17 (9H, s), 1.48–1.57 (4H, m), 1.67 (9H, s), 1.78–1.90 (2H, m), 2.84 (1H, ddd, *J* = 10.3, 7.7, 2.9), 3.59–3.62 (3H, m), 3.78 (1H, d, *J* = 13.2), 4.14 (1H, d, *J* = 7.7), 7.21–7.33 (7H, m), 7.54 (1H, s), 7.67 (1H, m), 8.17 (1H, m). $^{13}$C NMR: 24.7 ($CH_2$), 27.6 ($CH_3$), 28.2 ($CH_3$), 30.6 ($CH_2$), 51.5 ($CH_2$), 51.6 (CH), 56.4 (CH), 62.2 ($CH_2$), 80.6 (C), 83.7 (C), 115.3 (CH), 119.8 (CH), 120.2 (C), 122.5 (CH), 124.2 (CH), 124.4 (CH), 127.0 (CH), 128.3 (CH), 128.4 (CH), 129.4 (C), 135.7 (C) 139.7 (C), 149.6 (C), 173.6 (C). IR: 3402, 2977, 1728. EIMS *m/z*: 508 ($M^+$), 417 (M – Bn). HRMS–FAB *m/z*: $[M + H]^+$ calcd for $C_{30}H_{41}N_2O_5$, 509.3015; found, 509.3029. The enantiomeric excess was not determined.

### 4.4. Table 2

#### 4.4.1. Entry 2. (−)-tert-Butyl (S)-3-Benzylamino-3-(1-p-toluenesulfonylindol-3-yl)propanoate (5e)

The typical procedure A of Table 1 using **2e** (397 mg, 1.0 mmol), instead of **2a**, gave the title compound (418 mg, 83%) with 90% ee as a pale yellow oil: $R_f$ = 0.2 (hexane/AcOEt 20/1). $[\alpha]^{25}_D$ −22.9 (*c* 1.30, $CHCl_3$) for 96% ee. $^1$H NMR: 1.35 (9H, s), 1.90 (1H, br s), 2.31 (3H, s), 2.66 (1H, dd, *J* = 5.5, 15.6), 2.78 (1H, dd, *J* = 8.6, 15.6), 3.56 (1H, d, *J* = 13.2), 3.65 (1H, d, *J* = 13.2), 4.37 (1H, dd, *J* = 5.5, 8.6), 7.18-7.33 (9H, m), 7.52 (1H, s), 7.69 (1H, d, *J* = 8.0), 7.74 (2H, d, *J* = 8.6), 7.99 (1H, d, *J* = 8.2). $^{13}$C NMR: 21.5 ($CH_3$), 27.9 ($CH_3$), 42.2 ($CH_2$), 51.3 ($CH_2$), 51.5 (CH), 80.8 (C), 113.9 (CH), 120.5 (CH), 123.1 (CH), 123.9 (CH), 124.8 (CH), 126.8 (CH), 127.0 (CH), 128.2 (CH), 128.4 (CH), 129.5 (C), 129.78 (C), 129.84 (CH), 135.3 (C) 135.7 (C), 140.2 (C), 144.9 (C), 171.0 (C). IR: 3332, 2978, 1728, 1597, 1450, 1381, 1119. EIMS *m/z*: 504 ($M^+$), 447 (M – *t*-Bu) , 413 (M – Bn) , 389 (M – $CH_2CO_2$*t*-Bu). Anal. Calcd for $C_{29}H_{32}N_2O_4S$: C, 69.02; H, 6.39; N, 5.55. Found: C, 68.72; H, 6.37; N, 5.39. The enantiomeric excess was determined by HPLC (Daicel Chiralcel OD-H, 254 nm, hexane/*i*-PrOH 50/1, 1.0 mL/min, minor 17.3 min and major 23.4 min).

#### 4.4.2. Entry 3. (−)-tert-Butyl (S)-3-Benzylamino-3-(1-p-methoxybenzylindol-3-yl)propanoate (5f)

The typical procedure A of Table 1 using **2f** (363 mg, 1.0 mmol), instead of **2a**, gave the title compound (402 mg, 85%) with 45% ee as a pale yellow oil. $^1$H and $^{13}$C NMR, IR, and MS were identical to those reported.[13]

### 4.5. Table 3

#### 4.5.1. Entry 1. (−)-tert-Butyl (S)-3-(2-p-Methoxybenzyloxyethylamino)-3-(1-tert-butoxycarbonylindol-3-yl)propanoate (**9a**)

The typical procedure A of Table 1 in 0.54 mmol scale using *N*-(2-*p*-methoxybenzyloxyethyl)trimethylsilylamine (407 mg, 1.6 mmol), instead of *N*-benzyltrimethylsilylamine, gave the title compound (233 mg, 79%) with 13% ee as a colorless oil: $R_f$ = 0.4 (hexane/AcOEt 4/1). $[\alpha]^{25}_{D}$ −1.81. (*c* 1.00, $CHCl_3$). $^1H$ NMR: 1.37 (9H, s), 1.65 (9H, s), 2.08 (1H, br s), 2.68–2.81 (4H, m), 3.50–3.56 (2H, m), 3.80 (3H, s), 4.38 (1H, dd, *J* = 6.3, 7.7), 4.42 (2H, s), 6.86 (2H, dd, *J* = 1.9, 8.3), 7.19–7.32 (4H, m), 7.52 (1H, s), 7.72 (1H, m), 8.15 (1H, m). $^{13}C$ NMR: 28.0 ($CH_3$), 28.2 ($CH_3$), 42.6 ($CH_2$), 47.1 ($CH_2$), 52.1 ($CH_3$), 55.2 (CH), 69.3 ($CH_2$), 72.6 ($CH_2$), 80.7 (C), 83.5 (C), 113.7 (CH), 115.2 (CH), 119.8 (CH), 121.9 (C), 122.4 (CH), 123.2 (CH), 124.3 (CH), 129.2 (C), 129.3 (CH), 130.4 (C), 135.8 (C), 149.7 (C), 159.1 (C), 171.1 (C). IR: 3325, 2978, 1736, 1365, 1157. FABMS *m/z*: 525 $[M + H]^+$. Anal. Calcd for $C_{30}H_{40}N_2O_6$: C, 68.68; H, 7.68; N, 5.34. Found: C, 68.48; H, 7.68; N, 5.32. The enantiomeric excess was determined by HPLC (Daicel Chiralcel AD-3, 254 nm, hexane/*i*-PrOH 25/1, 1.0 mL/min, minor 15.1 min and major 16.6 min).

#### 4.5.2. Entry 2. (−)-tert-Butyl (S)-3-(2-(trityloxy)-ethylamino-3-(1-(tert-butoxycarbonyl)indol-3-yl)-propanoate (**9b**)

The typical procedure A of Table 1 in 0.45 mmol scale using *N*-(2-trityloxyethyl)-*tert*-butyldimethylsilylamine (559 mg, 1.3 mmol), instead of *N*-benzyltrimethylsilylamine, gave the title compound (25 mg, 9%) with 9% ee as a yellow oil: $R_f$ = 0.5 (hexane/AcOEt 4/1). $[\alpha]^{25}_{D}$ −2.88. (*c* 1.10, $CHCl_3$). $^1H$ NMR: 1.39 (9H, s), 1.64 (9H, s), 2.07 (1H, br s), 2.69–2.83 (2H, m), 2.74 (2H, t, *J* = 5.4), 3.17–3.20 (2H, m), 4.38 (1H, dd, *J* = 5.6, 7.9), 7.18–7.42 (17H, m), 7.49 (1H, m), 7.72 (1H, m), 8.15 (1H, m). $^{13}C$ NMR: 28.0 ($CH_3$), 28.2 ($CH_3$), 42.3 ($CH_2$), 47.3 ($CH_2$), 52.1 (CH), 63.1 ($CH_2$), 80.7 (C), 83.5 (C), 86.5 (C), 115.2 (CH), 119.9 (CH), 121.8 (C), 122.4 (CH), 123.3 (CH), 124.4 (CH), 126.8 (CH), 127.7 (CH), 128.7 (CH), 129.0 (C), 135.8 (C), 144.1 (C), 149.6 (C), 171.2 (C). IR: 3425, 2978, 1738, 1373, 1157. EIMS *m/z*: 646 ($M^+$), 531 (M – $CH_2CO_2t$-Bu), 403 (M – $CPh_3$). HRMS–FAB *m/z*: $[M + H]^+$ calcd for $C_{41}H_{47}N_2O_5$, 647.3485; found, 647.3499. The enantiomeric excess was determined after removal of the trityl group (*vide infra*).

#### 4.5.3. Entry 3. (−)-tert-Butyl (R)-3-(2-(trityloxy)-ethylamino-3-(1-(tert-butoxycarbonyl)indol-3-yl)-propanoate (ent-**9b**)

The typical procedure A of Table 1 using 2-trityloxyethylamine (455 mg, 1.5 mmol), instead of *N*-benzyltrimethylsilylamine, gave the title compound (57 mg, 18%) with 17% ee as a yellow oil: $[\alpha]^{25}_{D}$ +5.63 (*c* 1.10, $CHCl_3$). $^1H$ and $^{13}C$ NMR, IR, MS, and $R_f$ were identical to those of **9b**. The enantiomeric excess was determined after removal of the trityl group (*vide infra*).

#### 4.5.4. Determination of the ee of **9b** and ent-**9b**. (−)-tert-Butyl (S)-3-(2-hydroxyethyl)amino-3-(1-tert-butoxycarbonylindol-3-yl)propanoate

To a solution of **9b** (10 mg, 0.015 mmol) in $CH_2Cl_2$ (1.6 mL) was added TFA (7 μL, 0.09 mmol) at –10 °C. The mixture was stirred for 12 h at –10 °C, and saturated aq $NaHCO_3$ (1 mL) was added. The whole was extracted with AcOEt, and the organic layer was washed with brine and dried over $Na_2SO_4$. Concentration and column chromatography (hexane/AcOEt 1/4 to 0/1) gave the title compound (5.3 mg, 85%) with 9% ee as a colorless oil: $R_f$ = 0.1 (hexane/AcOEt 3/2). $[\alpha]^{25}_{D}$ −1.96. (*c* 0.53, $CHCl_3$). $^1H$ NMR: 1.42 (9H, s), 1.67 (9H, s), 1.81–1.97 (2H, br s), 2.73–2.79 (3H, m), 2.85 (1H, dd, *J* = 8.9, 15.8), 3.57 (1H, td, *J* = 4.8, 11.1), 3.67 (1H, td, *J* = 5.4, 11.1), 4.41 (1H, dd, *J* = 4.6, 8.9), 7.24 (1H, m), 7.32 (1H, dd, *J* = 7.0, 7.2), 7.54 (1H, s), 7.69 (1H, m), 8.16 (1H, m). $^{13}C$ NMR: 28.0 ($CH_3$), 28.2 ($CH_3$), 42.1 ($CH_2$), 48.4 ($CH_2$), 51.4 (CH), 61.2 ($CH_2$), 81.0 (C), 83.7 (C), 115.4 (CH), 119.5 (CH), 121.7 (C), 122.5 (CH), 123.1 (CH), 124.5 (CH), 128.9 (C), 135.8 (C), 149.6 (C), 171.3 (C). IR: 3363, 2978, 1728, 1373, 1157. EIMS *m/z*: 404 ($M^+$), 359 (M – $CH_2OH$), 344 (M – $NHCH_2CH_2OH$), 289 (M – $CH_2CO_2t$-Bu). HRMS–FAB *m/z*: $[M + H]^+$ calcd for $C_{22}H_{33}N_2O_5$, 405.2389; found, 405.2386. The enantiomeric excess was determined by HPLC (Daicel Chiralcel AD-3, 254 nm, hexane/*i*-PrOH 9/1, 1.0 mL/min, minor 8.9 min and major 9.8 min).

### 4.6. Scheme 2

#### 4.6.1. tert-Butyl (2S,3S)-1-Benzyl-2-(1-tert-butoxycarbonylindol-3-yl)piperidine-3-carboxylate (trans-**10**)

The procedure reported for *cis*-**10**[2] using *syn*-**7** (67 mg, 0.13 mmol), instead of *anti*-**7**, gave the title compound (54 mg, 83%) as a colorless oil: $R_f$ = 0.8 (hexane/AcOEt 2/1). $^1H$ NMR: 1.09 (9H, s), 1.61–1.69 (3H, m), 1.64 (9H, s), 1.92–2.02 (2H, m), 2.87 (1H, d, *J* = 13.2), 2.91–2.98 (2H, m), 3.55 (1H, d, *J* = 10.1), 3.89 (1H, d, *J* = 13.2) 7.15–7.30 (7H, m), 7.50 (1H, s), 8.13 (2H, m). $^{13}C$ NMR: 24.6 ($CH_2$), 27.5 ($CH_3$), 28.1 ($CH_3$), 28.3 ($CH_2$), 50.2 (CH), 52.6 ($CH_2$), 59.5 ($CH_2$), 63.4 (CH), 79.8 (C), 83.3 (C), 115.0 (CH), 120.6 (C), 121.3 (CH), 122.3 (CH), 124.4 (CH), 124.6 (CH), 126.5 (CH), 128.0 (CH), 128.8 (CH), 129.1 (C), 136.0 (C), 139.3 (C), 149.5 (C), 173.4 (C). IR: 2977, 1728, 1366. EIMS *m/z*: 490 ($M^+$), 399 (M – Bn). HRMS–FAB *m/z*: $[M + H]^+$ calcd for $C_{30}H_{39}N_2O_4$, 491.2910; found, 491.2900. The relative configuration was determined on the basis of the coupling constants between the adjacent methine protons at 2.91–2.98 ppm and 3.55 ppm (*J* = 10.1 Hz).

### 4.7. Scheme 3

#### 4.7.1. Typical Procedure. (−)-tert-Butyl (2R,3S)-2-Allyl-3-benzylamino-3-(1-tert-butoxycarbonylindol-3-yl)propanoate (7**b**)

To a stirred solution of *N*-benzyltrimethylsilylamine (0.29 mL, 1.5 mmol) in toluene (4 mL), was added a 1.62 M hexane solution of BuLi (0.93 mL, 1.5 mmol) at –78 °C over 4 min. After 30 min, a solution of chiral diether **3** (436 mg, 1.8 mmol) in toluene (2 mL) was added over 5 min. After 30 min, a solution of enoate **2a** (172 mg, 0.5 mmol) in toluene (2 mL) was added over 6 min, and the mixture was stirred for 15 h at –65 °C. Then, a solution of 1,3-diiodopropane (**6b**) (0.54 mL, 5 mmol) in DMPU (8 mL) was added over 22 min at –78 °C, and the mixture was stirring at –40 °C. After 2 h, the reaction was quenched with saturated aq $NH_4Cl$ (2 mL), and the whole was stirred at rt for 5 min. Then, saturated $NaHCO_3$ (12 mL) was added, and the whole was stirred for 5 min. The organic layer was separated, and the aqueous layer was extracted with benzene (10 mL × 3). The combined organic layers were washed with water (10 mL × 4) and brine, and dried over $Na_2SO_4$. Concentration and column chromatography (hexane/AcOEt 100/1 to 4/1) gave chiral diether **3** (436 mg, quant) as colorless plates and the title compound (221 mg, 90%) as colorless needles of mp 136–138 °C: $R_f$ = 0.4 (hexane/AcOEt 4/1). $[\alpha]^{25}_{D}$ −16.8 (*c* 1.07, $CHCl_3$).$^1H$ NMR: 1.46 (9H, s), 1.69 (9H, s), 1.74 (1H, br s), 2.05 (1H, m), 2.21 (1H, m), 2.88 (1H, m), 3.55 (1H, d, *J* = 12.8), 3.69 (1H, d, *J* = 12.8), 4.05 (1H, d, *J* = 9.8), 4.91–4.95 (2H, m), 5.65 (1H, m), 7.16–7.35 (7H, m), 7.49 (1H, s), 7.77 (1H, m), 8.16 (1H, m). $^{13}C$ NMR: 28.06 ($CH_3$), 28.08 ($CH_3$), 34.8 ($CH_2$), 51.3 ($CH_2$), 52.0 (CH), 56.6 (CH), 80.6 (C), 83.6 (C), 115.3 (CH), 116.6 ($CH_2$), 119.9 (CH), 120.2 (C), 122.5 (CH), 124.4 (CH), 124.5 (CH), 126.7 (CH), 128.11 (CH), 128.15 (CH), 129.2 (C), 135.1 (CH), 136.0 (C), 140.4 (C), 149.6 (C), 173.6 (C). IR: 3120, 2985, 1732, 1712, 1450. EIMS *m/z*: 490 ($M^+$), 399 (M – Bn). Anal. Calcd for $C_{30}H_{38}N_2O_4$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.54; H, 7.81; N, 5.59.

*4.8. Scheme 4.*

*4.8.1. Methyl (2RS,3SR)-1-Benzyl-2-(indol-3-yl)piperidine-3-carboxylate (cis-**11a**)*

To a solution of (±)-*cis*-**10** (1.15 g, 2.3 mmol) in MeOH (20 ml) was added a solution of $H_2SO_4$ (0.66 mL, 12 mmol) in MeOH (19 mL) over 15 min at rt, and the whole was stirred under reflux for 14 h. To the mixture, was added saturated aq $NaHCO_3$ (40 mL) dropwise and then AcOEt (100 mL) at rt. The organic layer was separated and the aqueous layer was extracted with AcOEt. The combined organic layers were washed with brine and dried over $Na_2SO_4$. Concentration and column chromatography (hexane/AcOEt 4/1 to 3/1) gave the title compound (768 mg, 94%) as colorless needles of mp 153–155 °C: $R_f$ = 0.3 (hexane/AcOEt 3/2). $^1$H NMR: 1.70 (1H, m), 1.85–2.05 (3H, m), 2.52 (1H, ddd, *J* = 12.2, 4.0, 3.2), 2.62 (1H, *J* = ddd, 12.2, 11.3, 3.1), 3.15 (1H, ddd, *J* = 11.0, 5.0, 4.8), 3.21 (3H, s), 3.30 (1H, d, *J* = 14.0), 3.55 (1H, d, *J* = 14.0), 4.84 (1H, d, *J* = 4.8), 7.05 (1H, ddd, *J* = 8.3, 7.0, 1,3), 7.16 (1H, ddd, *J* = 8.3, 7.0, 1.3), 7.19–7.31 (6H, m), 7.35 (1H, d, *J* = 8.3), 7.47 (1H, d, *J* = 8.3), 8.14 (1H, br s). $^{13}$C NMR: 22.1 ($CH_2$), 23.7 ($CH_2$), 45.8 (CH), 46.7 ($CH_2$), 51.1 ($CH_3$), 55.4 (CH), 59.3 ($CH_2$), 110.8 (CH), 119.2 (CH), 119.3 (CH), 121.8 (CH), 122.7 (CH), 126.7 (CH), 128.0 (C), 128.1 (CH), 128.7 (C), 128.8 (CH), 135.1 (C), 140.0 (C), 174.1 (C). IR: 3410, 3122, 2935, 2842, 1737, 1456. EIMS *m/z*: 348 ($M^+$), 257 (M – Bn). Anal. Calcd for $C_{22}H_{24}N_2O_2$: C, 75.83; H, 6.94; N, 8.04. Found: C, 75.58; H, 7.00; N, 8.03.

*4.8.2. Methyl (2RS,3SR)-1-Benzyl-2-(1-tert-butoxycarbonylindol-3-yl)piperidine-3-carboxylate (cis-**11b**)*

To a stirred solution of *cis*-**11a** (48 mg, 0.14 mmol) and DMAP (6.4 mg, 0.052 mmol) in $CH_3CN$ (1.4 mL), was added $Boc_2O$ (0.063 mL, 0.28 mmol) dropwise at rt. After 30 min, to the mixture were added saturated aq $NH_4Cl$ (2 mL) and saturated aq $NaHCO_3$ (4 mL). The aqueous layer was extracted with AcOEt. The combined organic layers were washed with water and brine, and dried over $Na_2SO_4$. Concentration and column chromatography (hexane/AcOEt 9/1) gave the title compound (56 mg, 90%) as yellow amorphous solid: $R_f$ = 0.6 (hexane/AcOEt 4/1). $^1$H NMR: 1.67 (1H, m), 1.71 (9H, s), 1.85–1.97 (3H, m), 2.56 (1H, ddd, *J* = 12.2, 4.0, 3.1), 2.69 (1H, ddd, *J* = 12.2, 11.6, 2.5), 3.13 (1H, ddd, *J* = 9.8, 6.0, 4.6), 3.23 (3H, s), 3.38 (1H, d, *J* = 13.8), 3.46 (1H, d, *J* = 13.8), 4.75 (1H, d, *J* = 4.6), 7.14–7.41 (8H, m), 7.70 (1H, m), 8.07 (1H, m). $^{13}$C NMR: 21.8 ($CH_2$), 23.5 ($CH_2$), 28.1 ($CH_3$), 45.4 (CH), 46.9 ($CH_2$), 51.0 ($CH_3$), 54.8 (CH), 59.3 ($CH_2$), 83.8 (C), 114.8 (CH), 116.2 (C), 119.7 (CH), 122.1 (CH), 123.6 (CH), 124.2 (CH), 126.8 (CH), 128.1 (CH), 128.8 (CH), 131.6 (C), 134.3 (C), 139.1 (C), 149.8 (C), 173.3 (C). IR (neat): 2947, 1736, 1450. EIMS *m/z*: 448 ($M^+$), 347 (M – $CO_2$*t*-Bu), 232 (M – *N*-Boc indole). HRMS–FAB *m/z*: $[M + H]^+$ calcd for $C_{27}H_{33}N_2O_4$, 449.2423; found, 449.2440.

*4.8.3. Methyl (2RS,3SR)-1-Benzyl-2-(1-benzoylindol-3-yl)piperidine-3-carboxylate (cis-**11c**)*

To a stirred solution of *cis*-**11a** (70 mg, 0.20 mmol) in DMF (2 mL), was added NaH (60% w/w dispersion in mineral oil; 8 mg, 0.20 mmol) at rt. After 30 min, BzCl (0.023 mL, 0.20 mmol) was added dropwise. After 15 h, another portion of BzCl (0.012 mL, 0.10 mmol) was added. After 2 h, the reaction was quenched with water, and the aqueous layer was extracted with benzene. The combined organic layers were washed with water and brine, and dried over $Na_2SO_4$. Concentration and column chromatography (hexane/AcOEt 97/3 to 90/10) gave the title compound (61 mg, 67%) as pale yellow amorphous solid: $R_f$ = 0.6 (hexane/AcOEt 7/3). $^1$H NMR: 1.66 (1H, m), 1.77–1.92 (3H, m), 2.51 (1H, ddd, *J* = 12.5, 4.3, 4.0), 2.56 (1H, ddd, *J* = 12.5, 10.4, 3.0), 3.14 (1H, ddd, *J* = 10.2, 4.9, 4.6), 3.27 (3H, s), 3.48 (1H, d, *J* = 14.0), 3.52 (1H, d, *J* = 14.0), 4.71 (1H, d, *J* = 4.9), 7.22–7.79 (14H, m), 8.36 (1H, m). $^{13}$C NMR: 22.4 ($CH_2$), 23.1 ($CH_2$), 45.0 (CH), 47.2 ($CH_2$), 51.1 ($CH_3$), 55.1 (CH), 59.3 ($CH_2$), 116.0 (CH), 117.8 (C), 119.6 (CH), 123.5 (CH), 125.0 (CH), 125.4 (CH), 126.9 (CH), 128.2 (CH), 128.6 (CH), 128.7 (CH), 129.4 (CH), 131.6 (C), 132.1 (CH), 134.6 (C), 135.4 (C), 139.5 (C), 168.5 (C), 173.3 (C). IR (neat): 2947, 1735, 1690. EIMS *m/z*: 452 ($M^+$), 361 (M – Bn), 347 (M – Bz). HRMS–FAB *m/z*: $[M + H]^+$ calcd for $C_{29}H_{29}N_2O_3$, 453.2178; found, 453.2160.

*4.8.4. Methyl (2RS,3SR)-1-Benzyl-2-(1-pivaloylindol-3-yl)piperidine-3-carboxylate (cis-**11d**)*

To a stirred solution of *cis*-**11a** (70 mg, 0.20 mmol) and DMAP (30 mg, 0.24 mmol) in $CH_2Cl_2$ (4 mL), were added $Et_3N$ (0.049 mL, 0.34 mmol) and PivCl (0.051 mL, 0.40 mmol) dropwise at 0 °C. After the mixture was stirred for 15 h at rt, another portion of DMAP (49 mg, 0.40 mmol) and PivCl (0.051, 0.40 mmol) were added, and the whole was stirred for further 3 h. The reaction was quenched by addition of saturated aq $NH_4Cl$ (2 mL) and saturated aq $NaHCO_3$ (4 mL). The aqueous layer was extracted with AcOEt. The combined organic layers were washed with 10% $Na_2CO_3$ and brine, and dried over $Na_2SO_4$. Concentration and column chromatography (hexane/AcOEt 97/3 to 95/5) gave the title compound (74 mg, 81%) as colorless oil: $R_f$ = 0.6 (hexane/AcOEt 4/1). $^1$H NMR: 1.51 (9H, s), 1.70 (1H, m), 1.86 (1H, m), 1.95–1.99 (2H, m), 2.51 (1H, ddd, *J* = 12.5, 4.3, 4.0), 2.68 (1H, ddd, *J* = 12.5, 10.1, 3.1), 3.16 (1H, ddd, *J* = 7.3, 7.3, 4.9), 3.28 (3H, s), 3.55 (2H, s), 4.63 (1H, d, *J* = 4.9), 7.18–7.43 (8H, m), 7.83 (1H, s), 8.48 (1H, m). $^{13}$C NMR: 22.5 ($CH_2$), 23.1 ($CH_2$), 28.6 ($CH_3$), 41.2 (C), 44.2 (CH), 47.4 ($CH_2$), 51.2 ($CH_3$), 55.4 (CH), 59.0 ($CH_2$), 117.0 (CH), 117.6 (C), 119.2 (CH), 123.2 (CH), 123.9 (CH), 125.2 (CH), 126.9 (CH), 128.2 (CH), 128.7 (CH), 130.1 (C), 136.2 (C), 138.9 (C), 175.0 (C), 177.0 (C). IR: 2947, 1736, 1690. EIMS *m/z*: 432 ($M^+$), 375 (M – *t*-Bu), 341 (M – Bn). HRMS–FAB *m/z*: $[M + H]^+$ calcd for $C_{27}H_{33}N_2O_3$, 433.2491; found, 433.2501.

*4.8.5. Methyl (2RS,3SR)-1-Benzyl-2-(1-benzylindol-3-yl)piperidine-3-carboxylate (cis-**11e**)*

To a suspension of NaH (60% w/w dispersion in mineral oil; 38 mg, 0.95 mmol), washed with pentane, in DMF (4 mL) was added *cis*-**11a** (250 mg, 0.72 mmol) in DMF (3 mL) over 5 min at 0 °C. After the mixture was stirred for 25 min at rt, BnBr (0.10 mL, 0.86 mmol) was added dropwise. After 1.2 h, to the mixture was added water. The aqueous layer was extracted with benzene. The combined organic layers were washed with water and brine, and dried over $Na_2SO_4$. Concentration and column chromatography (hexane/AcOEt 9/1 to 4/1) gave the title compound (273 mg, 87%) as colorless solids of mp 128.0–128.5 °C: $R_f$ = 0.6 (hexane/AcOEt 3/2). $^1$H NMR: 1.69 (1H, m), 1.85–2.00 (3H, m), 2.50 (1H, ddd, *J* = 12.0, 4.0, 3.3), 2.60 (1H, *J* = ddd, 12.0, 10.0, 3.1), 3.16 (1H, ddd, *J* = 11.0, 4.8, 4.6), 3.19 (3H, s), 3.32 (1H, d, *J* = 14.0), 3.53 (1H, d, *J* = 14.0), 4.84 (1H, d, *J* = 4.8), 5.33 (2H, s), 7.02–7.06 (3H, m), 7.12 (1H, m), 7.20–7.30 (10H, m), 7.49 (1H, m). $^{13}$C NMR: 22.2 ($CH_2$), 23.6 ($CH_2$), 45.9 (CH), 46.9 ($CH_2$), 49.9 ($CH_2$), 50.9 ($CH_3$), 55.5 (CH), 59.5 ($CH_2$), 109.4 (CH), 110.7 (C), 119.1 (CH), 119.5 (CH), 121.7 (CH), 126.4 (CH), 126.7 (CH), 127.0 (CH), 127.5 (CH), 128.1 (CH), 128.7 (CH), 128.8 (CH), 130.0 (C), 135.6 (C), 137.8 (C), 140.0 (C), 173.8 (C). IR (neat): 3028, 2947, 2804, 1734, 1454. EIMS *m/z*:

438 ($M^+$), 347 (M – Bn). Anal. Calcd for $C_{29}H_{30}N_2O_2$: C, 79.42; H, 6.89; N, 6.39. Found: C, 79.38; H, 6.83; N, 6.27.

*4.8.6. Methyl (2RS,3SR)-1-Benzyl-2-(1-p-methoxybenzylindol-3-yl)piperidine-3-carboxylate (cis-**11f**)*

To a stirred suspension of NaH (60% w/w dispersion in mineral oil; 32 mg, 0.80 mmol), washed with pentane, in DMF (3 mL) was added *cis*-**11a** (200 mg, 0.57 mmol) in DMF (3 mL) over 9 min at 0 °C. After 20 min, PMBCl (0.087 mL, 0.63 mmol) was added dropwise. After the mixture was stirred for 80 min at rt, the reaction was quenched with water. The aqueous layer was extracted with benzene. The combined organic layers were washed with water and brine, and dried over $Na_2SO_4$. Concentration and column chromatography (hexane/AcOEt 90/10 to 85/15) gave the title compound (233 mg, 86%) as colorless solids of mp 122.0–123.0 °C: $R_f$ = 0.6 (hexane/AcOEt 3/2). $^1$H NMR: 1.67 (1H, m), 1.81–2.00 (3H, m), 2.49 (1H, ddd, *J* = 11.4, 4.0, 3.6), 2.60 (1H, ddd, *J* = 12.0, 11.4, 2.5), 3.13 (1H, m), 3.15 (3H, s), 3.31 (1H, d, *J* = 13.8), 3.51 (1H, d, *J* = 13.8), 3.68 (3H, s), 4.83 (1H, d, *J* = 4.1), 5.21 (2H, s), 6.78 (2H, d, *J* = 8.9), 6.94 (2H, d, *J* = 8.9), 7.00–7.24 (9H, m), 7.47 (1H, m). $^{13}$C NMR: 22.1 ($CH_2$), 23.6 ($CH_2$), 45.8 (CH), 46.8 ($CH_2$), 49.3 ($CH_2$), 50.7 ($CH_3$), 55.0 ($CH_3$), 55.4 (CH), 59.3 ($CH_2$), 109.4 (CH), 110.4 (C), 114.0 (CH), 118.9 (CH), 119.4 (CH), 121.5 (CH), 126.5 (CH), 126.8 (CH), 127.6 (CH), 127.9 (CH), 128.7 (CH), 129.5 (C), 129.6 (C), 135.4 (C), 139.5 (C), 158.9 (C), 173.5 (C). IR (neat): 3024, 2939, 1736. EIMS *m/z*: 468 ($M^+$), 377 (M – Bn), 347 (M – PMB). Anal. Calcd for $C_{30}H_{32}N_2O_3$: C, 76.90; H, 6.88; N, 5.98. Found: C, 76.90; H, 6.94; N, 5.95.

*4.9. Table 4*

*4.9.1. Typical Procedure (Entry 4). Methyl 3-((2RS,3SR)-1-Benzyl-2-(1-benzylindol-3-yl)piperidin-3-yl)-3-oxopropanoate (**13e**)*

To a stirred 0.5 M THF solution of NaHMDS (12.4 mL, 6.2 mmol), was added AcOMe (0.49 mL, 6.2 mmol) in THF (6 mL) over 10 min at –78 °C. After 1 h, *cis*-**11e** (170 mg, 0.39 mmol) in THF (6 mL) was added over 10 min, and the mixture was stirred for 15 h at rt. The reaction was quenched with saturated aq $NaHCO_3$ (10 mL), and the aqueous layer was extracted with $Et_2O$. The combined organic layers were washed with brine and dried over $Na_2SO_4$. Concentration and column chromatography (DIOL silica gel MB100-40/75, hexane/AcOEt 15/1) gave **13e** (23 mg, 12%) as yellow solids of mp 138.5–140.0 °C: $R_f$ = 0.4 (hexane/AcOEt 3/2). $^1$H NMR: 1.67 (1H, m), 1.81–1.97 (3H, m), 2.45 (1H, ddd, *J* = 11.9, 4.3, 4.0), 2.56 (1H, ddd, *J* = 11.9, 11.3, 2.5), 2.99 (1H, d, *J* = 15.5), 3.35 (1H, d, *J* = 15.5), 3.36 (1H, d, *J* = 13.5), 3.37 (1H, m), 3.52 (3H, s), 3.58 (1H, d, *J* = 13.5), 4.85 (1H, d, *J* = 4.4), 5.32 (2H, s), 7.03 (1H, m), 7.06–7.30 (13H, m), 7.46 (1H, m). $^{13}$C NMR: 22.1 ($CH_2$), 23.2 ($CH_2$), 46.8 ($CH_2$), 47.6 ($CH_2$), 50.1 ($CH_2$), 52.0 ($CH_3$), 52.6 (CH), 55.1 (CH), 59.2 ($CH_2$), 109.8 (CH), 119.1 (CH), 119.6 (CH), 122.0 (CH), 126.5 (CH), 126.8 (CH), 127.6 (CH), 127.6 (CH), 128.2 (CH), 128.6 (C), 128.7 (CH), 128.8 (CH), 129.2 (C), 135.7 (C), 137.4 (C), 139.4 (C), 167.7 (C), 203.3 (C). IR (neat): 3031, 2947, 1744, 1705, 1620, 1450. EIMS *m/z*: 480 ($M^+$), 389 (M – Bn). HRMS–FAB *m/z*: $[M + H]^+$ calcd for $C_{31}H_{33}N_2O_3$, 481.2491; found, 481.2498: and *trans*-**11e** (115 mg, 68%) as yellow solids of mp 108.0–109.5 °C: $R_f$ = 0.6 (hexane/AcOEt 3/2). $^1$H NMR: 1.61–1.72 (3H, m), 1.97–2.04 (2H, m), 2.87 (1H, d, *J* = 13.4), 2.98–3.09 (2H, m), 3.27 (3H, s), 3.68 (1H, d, *J* = 10.4), 3.92 (1H, d, *J* = 13.4), 5.23 (1H, d, *J* = 16.2), 5.29 (1H, d, *J* = 16.2), 7.01–7.25 (14H, m), 8.06 (1H, br s). $^{13}$C NMR: 24.7 ($CH_2$), 28.8 ($CH_2$), 49.7 ($CH_2$), 50.6 (CH), 51.0 ($CH_3$), 52.6 ($CH_2$), 59.2 ($CH_2$), 62.6 (CH), 109.6 (CH), 115.6 (C), 119.1 (CH), 120.9 (CH), 121.8 (CH), 126.4 (CH), 126.5 (CH), 127.0 (C), 127.2 (CH), 127.4 (CH), 127.9 (CH), 128.6 (CH), 128.9 (CH), 136.9 (C), 137.7 (C), 139.7 (C), 175.0 (C). IR (neat): 3420, 3028, 2945, 2790, 1732, 1454. EIMS *m/z*: 438 ($M^+$), 347 (M – Bn). Anal. Calcd for $C_{29}H_{30}N_2O_2$: C, 79.42; H, 6.89; N, 6.39. Found: C, 79.51; H, 6.90; N, 6.42.

*4.9.2. Entry 1. Methyl 3-((2RS,3SR)-1-Benzyl-2-(indol-3-yl)piperidin-3-yl)-3-oxopropanoate (**13a**)*

To a stirred 0.5 M THF solution of NaHMDS (2.0 mL, 1.0 mmol), was added AcOMe (0.079 mL, 1.0 mmol) in THF (1 mL) over 3 min at –78 °C. After 1 h, *cis*-**11b** (112 mg, 0.25 mmol) in THF (1 mL) was added over 4 min, and the mixture was stirred for 2 h at –40 °C. Then the cooling bath was removed, and the mixture was stirred for further 1 h. The reaction was quenched with saturated aq $NaHCO_3$ (3 mL), and the aqueous layer was extracted with AcOEt. The combined organic layers were washed with brine and dried over $Na_2SO_4$. Concentration and column chromatography (hexane/AcOEt 4/1 to 3/2) gave **11a** (70 mg, 80% *cis*/*trans* 4/1) as yellow oil and the title compound (8 mg, 7%) as yellow gum: $R_f$ = 0.3 (hexane/AcOEt 3/2). $^1$H NMR: 1.69 (1H, m), 1.81–1.99 (3H, m), 2.46 (1H, ddd, *J* = 12.2, 4.0, 3.2), 2.56 (1H, ddd, *J* = 12.2, 11.0, 2.5), 2.99 (1H, d, *J* = 15.6), 3.34 (1H, d, *J* = 13.7), 3.36 (1H, d, *J* = 15.6), 3.37 (1H, m), 3.52 (3H, s), 3.57 (1H, d, *J* = 13.7), 4.85 (1H, d, *J* = 4.5), 7.05–7.46 (10H, m), 8.34 (1H, m). $^{13}$C NMR: 22.1 ($CH_2$), 23.1 ($CH_2$), 46.6 ($CH_2$), 47.9 ($CH_2$), 52.0 ($CH_3$), 52.6 (CH), 54.9 (CH), 59.0 ($CH_2$), 111.2 (CH), 118.7 (CH), 119.7 (CH), 122.1 (CH), 123.3 (CH), 126.8 (CH), 128.2 (CH), 128.3 (C), 128.6 (C), 128.7 (CH), 135.2 (C), 139.4 (C), 167.8 (C), 203.7 (C). IR: 3039, 2947, 1743, 1704. EIMS *m/z*: 390 ($M^+$), 358 (M – MeOH), 299 (M – Bn). HRMS–FAB *m/z*: $[M + H]^+$ calcd for $C_{24}H_{27}N_2O_3$, 391.2022; found, 391.2014.

*4.9.3. Entry 5. Methyl 3-((2RS,3SR)-1-Benzyl-2-(1-p-methoxybenzylindol-3-yl)piperidin-3-yl)-3-oxopropanoate (**13f**)*

The typical procedure using *cis*-**11f** (50 mg, 0.11 mmol), instead of *cis*-**11e**, gave the title compound (14 mg, 26%) as a yellow oil: $R_f$ = 0.4 (hexane/AcOEt 3/2). $^1$H NMR: 1.67 (1H, m), 1.81–1.98 (3H, m), 2.45 (1H, ddd, *J* = 11.9, 4.0, 3.1), 2.56 (1H, ddd, *J* = 11.9, 11.0, 2.4), 2.97 (1H, d, *J* = 15.6), 3.34 (1H, d, *J* = 15.6), 3.35 (1H, m), 3.37 (1H, d, *J* = 13.4), 3.52 (3H, s), 3.56 (1H, d, *J* = 13.4), 3.76 (3H, s), 4.85 (1H, d, *J* = 4.4), 5.23 (1H, d, *J* = 15.9), 5.27 (1H, d, *J* = 15.9), 6.82 (2H, d, *J* = 8.9), 6.99 (2H, d, *J* = 8.9), 7.05–7.31 (9H, m), 7.45 (1H, m). $^{13}$C NMR: 22.2 ($CH_2$), 23.2 ($CH_2$), 46.8 ($CH_2$), 47.6 ($CH_2$), 49.6 ($CH_2$), 52.0 ($CH_3$), 52.6 (CH), 55.1 ($CH_3$), 55.2 (CH), 59.2 ($CH_2$), 109.6 (C), 109.8 (CH), 114.2 (CH), 119.1 (CH), 119.5 (CH), 121.9 (CH), 126.8 (CH), 127.5 (CH), 127.8 (CH), 128.2 (CH), 128.7 (CH), 129.2 (C), 129.4 (C), 135.6 (C), 139.5 (C), 159.1 (C), 167.8 (C), 203.3 (C). IR: 3024, 2931, 1744, 1712, 1612. FABMS *m/z*: 511 (M + H). HRMS–FAB *m/z*: $[M + H]^+$ calcd for $C_{32}H_{35}N_2O_4$, 511.2597; found, 511.2604.

*4.9.4. Entry 7. Methyl 5-Hydroxy-2-methoxycarbonyl-5-methyl-3-oxocyclohexen-1-acetate (**15**)*

The typical procedure using a solution of LiHMDS (2.8 mL, 1.9 mmol), AcOMe (0.14 mL, 1.7 mmol) in THF (1.5 mL), and *cis*-**11a** (37 mg, 0.11 mmol) in THF (1.6 mL), instead of a solution of NaHMDS (6.2 mmol), AcOMe (6.2 mmol) in THF, and *cis*-**11e** (0.39 mmol) in THF, respectively, followed by column chromatography (hexane/AcOEt 17/3) gave *cis*-**11a** (33 mg, 88%) as a colorless solid, **14**[18] (23 mg, 24%) as a colorless oil, and the title compound (24 mg, 27%) as a colorless oil: $R_f$ = 0.1 (hexane/AcOEt 7/3). $^1$H NMR: 1.33 (3H, s), 2.64 (1H, d, *J* = 15.6), 2.65 (1H, d, *J* = 15.6), 2.82 (1H, d, *J* = 16.2), 2.94 (1H, d, *J* = 16.2), 3.54 (2H, s), 3.70 (3H, s), 3.74 (3H, s), 3.99 (1H, br s). $^{13}$C NMR: 27.3 ($CH_3$), 44.5 ($CH_2$), 50.4 ($CH_2$), 51.7 ($CH_3$), 52.1

($CH_2$), 52.3 ($CH_3$), 70.1 (C), 136.1 (C), 163.2 (C), 167.3 (C), 172.5 (C), 203.2 (C). IR: 3510, 2954, 1736. FABMS *m/z*: 257 (M + H). HRMS–FAB *m/z*: $[M + H]^+$ calcd for $C_{12}H_{17}O_6$, 257.1025; found, 257.1026.

*4.9.5. Entry 8. Methyl 3-((2RS,3SR)-1-Benzyl-2-(indol-3-yl)piperidin-3-yl)-3-oxopropanoate (**13a**)*

To a stirred solution of **11a** (1.0 g, 2.9 mmol) in THF (11 mL), was added a 1.0 M THF solution of LiHMDS (5.7 mL, 5.7 mmol) over 3 min at –78 °C. After 1 h, the solution was added over 5 min to a preformed solution of enolate, prepared from AcOMe (3.7 mL, 47 mmol) and LiHMDS (1.1 g, 66 mmol) in THF (180 mL) at –78 °C. The mixture was stirred for 17 h at rt, and saturated aq $NaHCO_3$ (100 mL) was added. The organic layer was separated, and the aqueous layer was extracted with $Et_2O$. The combined organic layers were washed with brine and dried over $Na_2SO_4$. Concentration and column chromatography (DIOL silica gel MB100-40/75, hexane/AcOEt 6/1 to 3/1) gave the title compound (727 mg, 66%) as a yellow gum and **11a** (82 mg, 8%) as a pale yellow oil.

*4.10. Scheme 5*

*4.10.1. Methyl 3-((2RS,3SR)-1-Benzyl-2-(1-methoxycarbonylindol-3-yl)piperidin-3-yl)-3-oxopropanoate (**16**)*

To a stirred solution of **13a** (640 mg, 1.6 mmol) in THF (32 mL) was added a 1.0 M THF solution of LiHMDS (4.9 mL, 4.9 mmol) over 3 min at –78 °C. After 40 min, $NCCO_2Me$ (0.50 mL, 6.2 mmol) was added over 2 min. After 20 min, the reaction was quenched with saturated aq $NH_4Cl$ (4 mL), and the whole was warmed up to rt. After addition of saturated aq $NaHCO_3$ (10 mL), the organic layer was separated, and the aqueous layer was extracted with AcOEt. The combined organic layers were washed with brine and dried over $Na_2SO_4$. Concentration and column chromatography (DIOL silica gel MB100-40/75, hexane/AcOEt 9/1) gave the title compound (701 mg, 95%) as yellow oil: $R_f$ = 0.4 (hexane/AcOEt 3/2). $^1H$ NMR: 1.70 (1H, m), 1.81–2.03 (3H, m), 2.50 (1H, ddd, $J$ = 12.5, 4.0, 4.0), 2.62 (1H, ddd, $J$ = 12.5, 11.0, 3.1), 3.05 (1H, d, $J$ = 15.5), 3.31 (1H, d, $J$ = 15.5), 3.36 (1H, ddd, $J$ = 10.2, 5.2, 4.6), 3.41 (1H, d, $J$ = 13.7), 3.54 (3H, s), 4.04 (3H, s), 4.05 (1H, d, $J$ = 13.7), 4.76 (1H, d, $J$ = 4.6), 7.11–7.41 (8H, m), 7.63 (1H, s), 8.17 (1H, m). $^{13}C$ NMR: 21.9 ($CH_2$), 22.9 ($CH_2$), 46.6 ($CH_2$), 47.6 ($CH_2$), 52.0 (CH), 52.1 ($CH_3$), 53.8 ($CH_3$), 54.2 (CH), 59.0 ($CH_2$), 115.1 (CH), 116.2 (C), 119.3 (CH), 123.0 (CH), 124.9 (CH), 127.0 (CH), 128.3 (CH), 128.4 (CH), 128.7 (CH), 131.1 (C), 134.7 (C), 138.9 (C), 151.3 (C), 167.5 (C), 202.8 (C). IR: 3024, 2954, 1743, 1628. EIMS *m/z*: 448 ($M^+$), 357 (M – Bn). HRMS–FAB *m/z*: $[M + H]^+$ calcd for $C_{26}H_{29}N_2O_5$, 449.2076; found, 449.2062.

*4.10.2. (±)-20-Deethyl-2β,16β-dihydro-17-oxo-vincadifformine (**20**)*

A suspension of **16** (43 mg, 0.096 mmol) and Pd/C (10 wt%, 34 mg, 0.032 mmol) in $HCO_2H$ (1.8 mL) was stirred for 5 h at rt and filtrated through a celite pad, which was successively washed with MeOH. The combined filtrate and washings were concentrated. To the residue, was added saturated aq $Na_2CO_3$ (3 mL), and the whole was extracted with AcOEt. The combined organic layers were washed with brine, dried over $Na_2SO_4$, and concentrated to give yellow oil (29 mg).

The residual yellow oil was dissolved in $CH_3CN$ (1.8 mL), and $Na_2CO_3$ (61 mg, 0.58 mmol) and 2-iodoethanol (45 μL, 0.58 mmol) were added. The mixture was stirred for 21 h at 60 °C, and water (3 mL) and benzene were added. The organic layer was separated, and the aqueous layer was extracted with benzene. The combined organic layers were washed with water and brine, dried over $Na_2SO_4$, and concentrated to give yellow oil (29 mg).

The residual yellow oil was dissolved in $CH_2Cl_2$ (2 mL), and $Et_3N$ (0.13 mL, 0.96 mmol) and MsCl (8.9 μL, 0.12 mmol) were added. After 20 h, the reaction was quenched with water (3 mL), and the organic layer was separated. The aqueous layer was extracted with AcOEt, and the combined organic layers were washed with brine, dried over $Na_2SO_4$, and concentrated to give yellow oil (16 mg).

The residual yellow oil was dissolved in THF (1.0 mL) and HMPA (0.20 mL), and a 1.0 M solution of KO*t*-Bu in THF (0.24 mL, 0.24 mmol) was added over 1 min at –78 C. The mixture was stirred for 1 h at –78 °C and then 1 h at rt, and the reaction was quenched with saturated aq $NH_4Cl$ (0.5 mL) and saturated aq $NaHCO_3$ (2 mL). The organic layer was separated, and the aqueous layer was extracted with AcOEt. The combined organic layers were washed with brine and dried over $Na_2SO_4$. Concentration and column chromatography (hexane/AcOEt 4/1) gave the title compound (3.0 mg, 10%) as colorless oil. $^1H$ and $^{13}C$ NMR, IR, and MS were identical to those reported.[9]

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