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TETRAHEDRON: *ASYMMETRY*

# Asymmetric synthesis of tetracyclic substructures of *Strychnos* indole alkaloids

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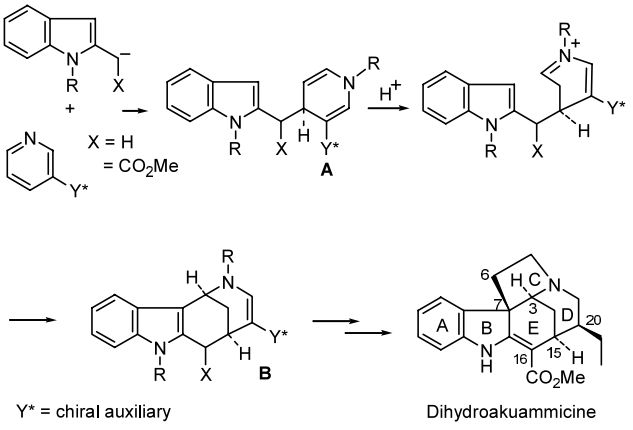
**Abstract**—The addition of the enolate of methyl 1-methyl-2-indoleacetate **1** and lithium 2-(lithiomethyl)indole-1-carboxylate **5** to pyridines and *N*-alkylpyridinium salts bearing a chiral auxiliary at the 3-position (tolylsulfinyl, acyl iron complexes, bornane-10,2-sultam), with subsequent acid cyclization of the resulting dihydropyridines, is investigated. 

## 1. Introduction

An inspection of the polycyclic structure of *Strychnos* alkaloids,[1] for instance dihydroakuammicine, reveals that the stereogenic carbons common to two or more rings are configurationally correlated and that their relative and absolute configurations could be unambiguously attained starting from a suitably functionalized enantiopure 2-(1,4-dihydro-4-pyridylmethyl)indole **A** (Scheme 1). In fact, as a consequence of the bridgehead character of carbons 3 and 15, the configuration at the dihydropyridine 4-carbon (C-15) would determine that of C-3 in the cyclization to the tetracyclic 1,5-methanoazocino[4,3-*b*]indole system **B** via a dihydropyridinium cation (bond formed $C_3$–$C_7$) and, afterwards, that of the quaternary C-7 center in the closure of the five-membered C-ring (bond formed $C_6$–$C_7$).[2,3]




**Scheme 1.**

The development of the above synthetic strategy would require the generation of a chiral non-racemic 1,4-dihydropyridine[4] by diastereofacial-selective addition of an appropriate indole-containing nucleophile to an activated pyridine or pyridinium salt carrying a chiral auxiliary at the 3-position.[5,6] Although the addition of indole-containing enolates to *N*-alkylpyridinium salts bearing an electron-withdrawing group at the 3-position has extensively been used in our laboratory as the initial step of a general and versatile method for the synthesis of indole alkaloids in the racemic series,[7] there are few examples of the use of this methodology for the enantioselective synthesis of alkaloids.[8]

In this paper we report the results of applying the strategy depicted in Scheme 1 for the preparation of enantiopure tetracyclic ABDE substructures of *Strychnos* alkaloids using several chiral auxiliaries Y*.

## 2. Results and discussion

Initially, we planned to use a sulfinyl group as the chiral auxiliary. The electron-withdrawing nature of

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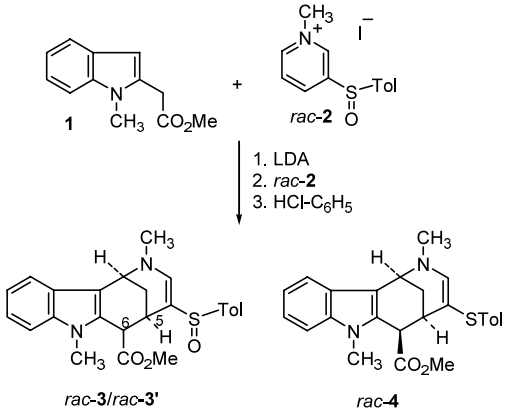
this group should allow an efficient nucleophilic attack of a 2-indoleacetic ester enolate on the 4-position of the pyridine ring. Although the preparation of enantiopure (*S*)-3-(*p*-tolylsulfinyl)pyridine has been reported in the literature,[9] to test the feasibility of the methodology we undertook a model study using the racemic tolylsulfinylpyridinium salt *rac*-**2**, which was easily accessible by methylation of the corresponding pyridine with methyl iodide (Scheme 2).



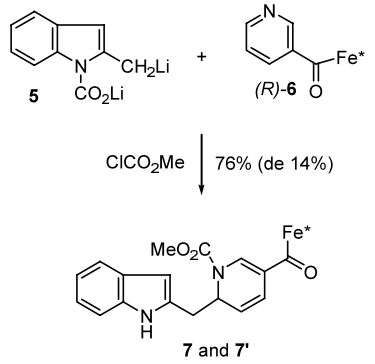

**Scheme 2.**

Interaction of the enolate of ester **1**[10] with pyridinium salt *rac*-**2** at −30°C, followed by acid cyclization of the resulting 1,4-dihydropyridine gave the expected tetracyclic derivatives as a mixture of four diastereomers, *cis*- and *trans*-*rac*-**3** and *cis*- and *trans*-*rac*-**3′** (*cis*/*trans* refers to the relative $H_5$–$H_6$ stereochemistry; **3** and **3′** refers to the relative configuration of the bridgehead carbons with respect to the sulfur), which were separated by flash chromatography (32% overall yield). Tetracyclic *cis* sulfide *rac*-**4** was also isolated in 12% yield.

Although the configuration of tetracycles *rac*-**3** and *rac*-**3′** is not known, the $H_5$–$H_6$ *cis*/*trans* relationship for the pairs of isomers *rac*-**3** (12% yield; 2:3 ratio) and *rac*-**3′** (20% yield; 3:2 ratio)[11] was deduced from the coupling constant of the doublet corresponding to $H_6$ (5 Hz in the *cis* isomers but 1.5 Hz in the *trans* isomers) in the $^1$H NMR spectra and from the existence of *gauche* effects on $C_4$ (in the *cis* isomers) or $C_{12}$ (in the *trans* isomers) in the $^{13}$C NMR spectra.[12] The same criteria allowed the assignment of the relative *cis* $H_5$–$H_6$ configuration in *rac*-**4**. The above results indicated that the addition of the enolate to the pyridinium salt had taken place with a low facial stereoselectivity. For this reason, no further experiments were performed using enantiopure **2**.

We then turned our attention to chiral α,β-unsaturated acyl iron complexes, which have been developed by Davies and used in a variety of stereoselective conjugate additions,[13] including the regio- and stereoselective addition of organolithium derivatives to nicotinoyl iron complexes to give the corresponding 4-alkyl-1,4-dihydropyridines.[14]

However, when chiral non-racemic nicotinoyl iron complex (*R*)-**6**[15] was treated with 2-(lithiomethyl)indole **5** and the crude mixture was trapped with methyl chloroformate, only a nearly equimolecular mixture of C-2 diastereomeric 1,2-dihydropyridines **7** and **7′** (57:43 ratio; absolute configuration at C-2 not determined) were obtained (Scheme 3). The chemical shift of H-2 ($\delta$ ~5.0) and C-2 ($\delta$ ~53.3) of the dihydropyridine ring were of diagnostic value.



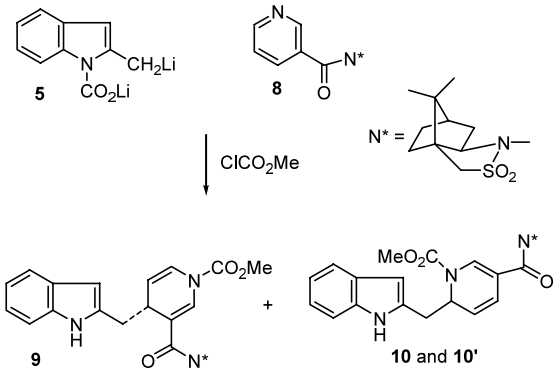

**Scheme 3.**

Although the chemical yield of the above addition–acylation sequence was excellent (76%) the regioselectivity of the process was not favorable to our synthetic interest, probably due to steric factors and the particular nature of the organolithium derivative **5**, which also bears a lithium carboxylate moiety.

As a further chiral auxiliary we selected (2*R*)-bornane-10,2-sultam,[16] which has been extensively used by Oppolzer in a number of enantioselective transformations, including conjugate nucleophilic additions to *N*-enoyl derivatives.

Acylation of this sultam with sodium hydride and nicotinoyl chloride hydrochloride gave the required nicotinoylsultam **8** in 92% yield. The addition of 2-(lithio-methyl)indole **5** to **8** followed by treatment of the resulting mixture with methyl chloroformate led to a mixture of the desired 1,4-dihydropyridine **9** (20%; a single stereoisomer) and 1,2-dihydropyridines **10** and **10′** (20%; two stereoisomers in a 2:3 ratio, whose configuration at C-2 was not determined), which could be separated after repeated purification by column chromatography (Scheme 4).

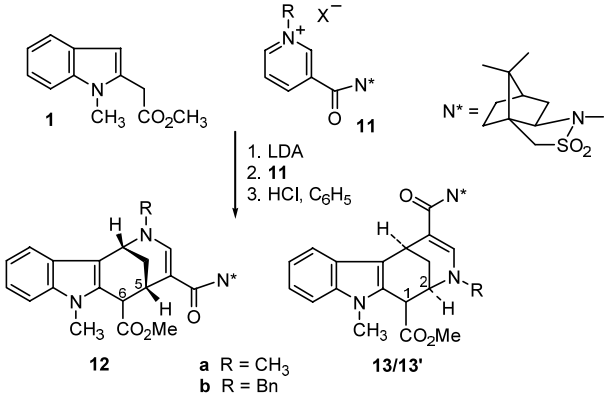
Diagnostic NMR signals for the structural assignment of these dihydropyridines were those of the $sp^3$ methine moiety (H-4, $\delta$ 3.5 and C-4, $\delta$ 33.8 for the 1,4-isomer and H-2, $\delta$ 5.1 and C-2, $\delta$ 53.0 for the 1,2-isomers). The absolute configuration of the new stereogenic center in **9** was assigned taking into account the configuration of the cyclized product *trans*-**12b**.



Scheme 4.

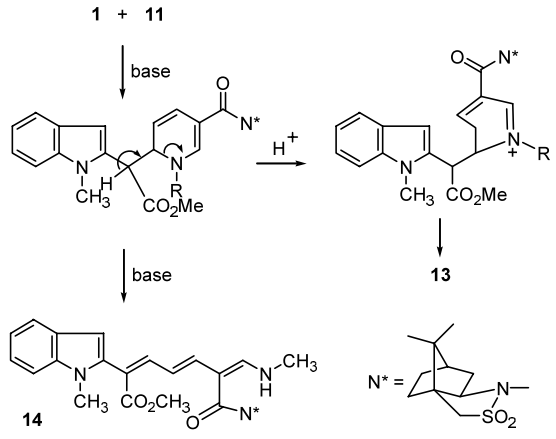
Unfortunately, all attempts to cyclize *N*-acyl-1,4-dihydropyridine **9** under acidic conditions (AcOH–dioxane–$H_2O$[3b] or HCl–benzene[10]) to a tetracyclic derivative resulted in failure, leading to complex unidentifiable mixtures.

These results prompted us to study a similar nucleophilic addition–cyclization sequence starting from indoleacetic ester **1** and *N*-alkylpyridinium salts **11a** and **11b**, which were prepared in 97 and 92% yield by alkylation of nicotinoyl sultam **8** with methyl iodide and benzyl chloride, respectively. Addition of the enolate derived from **1** to pyridinium salt **11a** followed by treatment of the resulting crude mixture of dihydropyridines with HCl in benzene gave a mixture of the expected tetracycles **12a** (10% yield) and the regioisomers **13a** (28% yield), which could be separated after repeated column chromatography (Scheme 5). In some runs, minor amounts of polyunsaturated amine **14**, formed by the opening of the 1,2-dihydropyridine ring promoted by the excess of base, were also isolated[17] (Scheme 6).



Scheme 5.

Tetracycles *cis*-**12a** and *trans*-**12a** epimers at C-6[18] possess the same absolute configuration at the bridgehead carbons, thus indicating that the nucleophilic addition to the 4-position of the pyridine ring had occurred with facial selectivity. The relative $H_5$–$H_6$ stereochemistry of **12** was deduced from the $H_5$–$H_6$ coupling constant



Scheme 6.

using the same criteria as in the above tetracycles *rac*-**3**. Formation of unnatural tetracycles **13a** (two epimers at C-1 of unknown absolute configuration at the bridgehead carbons[18]) can be accounted for by considering that, under acidic conditions, the 1,2-dihydropyridine initially formed by nucleophilic addition of the enolate to the 6-position of the pyridinium ring is protonated, and that the resulting 1,2-dihydropyridinium cation undergoes intramolecular conjugate addition by the indole ring. Probably, the bulkiness of the chiral auxiliary, which hinders the approach of the nucleophile to the adjacent 4-position of the pyridine ring, is responsible for this undesirable regioselectivity.

The use of benzylpyridinium salt **11b** in the above two-step sequence led to a similar result and allowed us to isolate (27% overall yield) the expected tetracycles **12b** (two epimers at C-6, *cis*-**12b** and *trans*-**12b**), again with the same absolute configuration at the bridgehead carbons, and two regioisomeric tetracycles **13b** and **13′b**, both of them with a $H_1$–$H_2$ *trans* relative stereochemistry ($J \sim 1.5$ Hz) and, consequently, with different absolute configuration (not determined) at the bridgehead carbons. The absolute configuration at the bridgehead carbons in tetracycles **12** was unambiguously established from the X-ray crystallographic analysis of *trans*-**12b**.[19] On the other hand, the structural assignment of tetracycles **13** was effected from the $^{13}C$ NMR chemical shift values of the bridgehead methine carbons ($\delta \sim 23$ and 56 for **13** versus $\delta \sim 29$ and 48 for tetracycles **12**).

In conclusion, the results presented here, in conjunction with those previously reported from a chiral oxazolinylpyridine,[6] show that the strategy for the synthesis of enantiopure tetracyclic precursors of *Strychnos* alkaloids based on the enantioselective generation of 1,4-dihydropyridines by nucleophilic addition of a 2-indolylmethyl moiety to pyridines or pyridinium salts bearing a chiral auxiliary at the 3-position, and their subsequent acid cyclization, suffers from two main drawbacks that seriously limit its application: the low

facial stereoselectivity, as a consequence of an inefficient coordination of the nucleophile with the chiral auxiliary, and/or the low regioselectivity due to the bulkiness of the chiral auxiliary.

## 3. Experimental

### 3.1. General

Melting points were determined in a capillary tube and are uncorrected. Unless otherwise indicated, NMR spectra were recorded at 200 or 300 MHz ($^1$H) and 50.3 or 75 MHz ($^{13}$C) and chemical shifts are reported in $\delta$ values downfield from TMS. Only noteworthy IR absorptions are listed. Thin-layer chromatography was done on $SiO_2$ (silica gel 60 $F_{254}$), and the spots were located with aqueous potassium permanganate solution or with iodoplatinate reagent. Column chromatography was carried out using the flash chromatography technique. All non-aqueous reactions were performed under an inert atmosphere. Solvents for chromatography were distilled at atmospheric pressure prior to use and dried following standard procedures. Drying of the organic extracts during the workup of reactions was performed over anhydrous $Na_2SO_4$ or $MgSO_4$. Evaporation of solvents was accomplished with a rotatory evaporator. Microanalyses and HRMS were performed by Centre D'Investigació i Desenvolupament (CSIC), Barcelona.

### 3.2. Preparation of 1-methyl-3-(*p*-tolylsulfinyl)-pyridinium iodide *rac*-2

A solution of methyl iodide (0.6 mL, 0.66 mmol) in benzene (1.2 mL) was slowly added to a cooled (0°C) solution of 3-(*p*-tolylsulfinyl)pyridine[9b] (700 mg, 3.22 mmol) in acetone (1 mL). The mixture was stirred for 12 h and the solid was filtered and dried to give *rac*-**2** (930 mg, 80%). *rac*-**2**: IR (NaCl) 1053 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 2.34 (s, 3H, $CH_3Ar$), 4.40 (s, 3H, N-$CH_3$), 7.42 and 7.76 (2d, $J$=8.1, 4H, ArH), 8.21 (dd, $J$=8.2, 6.0 Hz, 1H, H-5), 8.75 (dd, $J$=8.2, 1.2 Hz, 1H, H-4), 9.07 (d, $J$=6.0 Hz, 1H, H-6), 9.39 (s, 1H, H-2); $^{13}$C NMR (DMSO, 50.3 MHz) $\delta$ 21.2 ($CH_3Ar$), 48.9 (N-$CH_3$), 125.6 (C-*o*), 128.5 (C-5), 130.7 (C-*m*), 140.4 (C-*p*), 140.8 (C-4), 142.2 (C-6), 143.1 (C-*i*), 147.1 (C-3), 147.8 (C-2).

### 3.3. General procedure for the addition of methyl 1-methyl-2-indoleacetate 1 to the pyridinium salts *rac*-2 and 11

LDA (1.5 M in THF, 1.5 mmol) was added to a cooled (−78°C) solution of ester **1** (1 mmol) in THF (25 mL). The mixture was stirred for 1 h at this temperature, and the pyridium salt (1 mmol) was added portionwise. Then, the mixture was warmed to −30°C and stirred for 2 h. The suspension was acidified to pH 3–4 with a solution of HCl in benzene. The temperature of the mixture was raised to −10°C and stirring was continued for 90 min. The mixture was poured into saturated aqueous $Na_2CO_3$, and the aqueous phase was extracted with EtOAc. The combined organic phases were dried and evaporated to give a residue, which was column chromatographed.

### 3.4. Reaction of methyl 1-methyl-2-indoleacetate 1 with 1-methyl-3-(*p*-tolylsufinyl)pyridinium iodide *rac*-2

Following the above general procedure, from ester **1** (285 mg, 1.4 mmol) and pyridinium iodide *rac*-**2** (500 mg, 1.4 mmol) a residue was obtained. Purification by column chromatography (EtOAc 100%, increasing polarity with EtOH) gave four fractions. Further purification of the first fraction by column chromatography (3:7 EtOAc/hexane) gave *rac*-**4** (73 mg, 12%) and traces of **1**. The second fraction was a mixture of *cis*-*rac*-**3** and *trans*-*rac*-**3**, which were separated after an additional flash chromatography (95:5 $Et_2O$/EtOH) to give (12% overall yield) pure *cis*-*rac*-**3** (27 mg) and *trans*-*rac*-**3** (45 mg). The third and fourth fractions gave *cis*-*rac*-**3′** (71 mg) and *trans*-*rac*-**3′** (48 mg), respectively (20% overall yield). *rac*-**4**: mp 154–156°C (EtOAc); IR (NaCl) 1719, 1610, 1201, 1166, 745 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 2.03 (dt, $J$=12.1, 2.7 Hz, 1H, H-12), 2.21 (dt, $J$=12.1, 3.5 Hz, 1H, H-12), 2.31 (s, 3H, $CH_3Ar$), 3.03 (s, 3H, $N_2$-$CH_3$), 3.11 (br s, 1H, H-5), 3.55 (s, 3H, $N_7$-$CH_3$), 3.88 (s, 3H, $OCH_3$), 4.10 (d, $J$=5.1 Hz, 1H, H-6), 4.48 (br s, 1H, H-1), 6.53 (s, 1H, H-3), 7.10–7.30 (m, 7H, ArH), 7.60 (d, $J$=7.0 Hz, 1H, H-11); $^{13}$C NMR ($CDCl_3$, 50.3 MHz) $\delta$ 20.9 ($CH_3Ar$), 31.0 ($N_7$-$CH_3$), 31.6 (C-12), 34.4 (C-5), 41.2 ($N_2$-$CH_3$), 47.6 (C-6), 48.8 (C-1), 52.4 ($OCH_3$), 91.9 (C-4), 109.1 (C-8), 111.1 (C-11b), 118.1 (C-11), 119.6 (C-10), 121.5 (C-9), 126.2 (C-11a), 126.3 (C-*o*), 129.5 (C-*m*), 133.4 (C-*p*), 136.9 (C-*i*), 137.4 (C-7a), 146.0 (C-3), 172.8 (CO); $m/z$ 447 (M$^+$+29, 7), 419 (M$^+$+1, 62), 418 (M$^+$, 100), 241 (14), 240 (79), 216 (16). Anal. calcd for $C_{25}H_{26}N_2O_2S{\cdot}1/2\ C_4H_8O_2$: C, 70.10; H, 6.54; N, 6.06; S, 6.93. Found: C, 69.95; H, 6.43; N, 6.35; S, 6.67. *cis*-*rac*-**3**: mp 156°C (acetone); IR (NaCl) 1741, 1618, 1470, 1167, 1029, 747 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 1.79 (dt, $J$=12.1, 3.3 Hz, 1H, H-12), 1.89 (dt, $J$=12.1, 2.7 Hz, 1H, H-12), 2.41 (s, 3H, $CH_3Ar$), 2.74 (m, 1H, H-5), 3.11 (s, 3H, $N_2$-$CH_3$), 3.56 (s, 3H, $N_7$-$CH_3$), 3.92 (s, 3H, $OCH_3$), 4.10 (d, $J$=5.2 Hz, 1H, H-6), 4.48 (br s, 1H, H-1), 6.87 (s, 1H, H-3), 7.10–7.30 (m, 5H, ArH), 7.57 (d, $J$=8.1 Hz, 2H, *o*-), 7.63 (d, $J$=7.0 Hz, 1H, H-11); $^{13}$C NMR ($CDCl_3$, 50.3 MHz) $\delta$ 21.4 ($CH_3Ar$), 29.9 (C-12), 30.0 (C-5), 30.9 ($N_7$-$CH_3$), 41.5 ($N_2$-$CH_3$), 48.5 (C-6), 48.9 (C-1), 52.7 ($OCH_3$), 103.4 (C-4), 109.1 (C-8), 111.4 (C-11b), 118.1 (C-11), 119.7 (C-10), 121.7 (C-9), 125.9 (C-11a, masked), 125.9 (C-*o*), 129.8 (C-*m*), 132.5 (C-6a), 136.3 (C-3), 137.3 (C-7a), 141.6 (C-3), 142.5 (C-*i*), 172.4 (CO); $m/z$ 475 (M$^+$+41, 2), 463 (M$^+$+29, 11), 435 (M$^+$+1, 73), 419 (30), 418 (57), 387 (22), 386 (61), 297 (25), 296 (100), 240 (52), 239 (10). Anal. calcd for $C_{25}H_{26}N_2O_3S{\cdot}1/2\ H_2O$: C, 67.69; H, 6.13; N, 6.31; S, 7.22. Found: C, 67.49; H, 6.10; N, 6.17; S, 6.81. *trans*-*rac*-**3**: mp 154°C (EtOH); IR (NaCl) 1731, 1613, 1470, 1200, 1030, 752 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 1.67 (dt, $J$=12.7, 3.1 Hz, 1H, H-12), 2.14 (dt, $J$=12.7, 2.5 Hz, 1H, H-12), 2.43 (s, 3H, $CH_3Ar$), 3.01 (br s, 1H, H-5), 3.12 (s, 3H, $N_2$-$CH_3$), 3.61 (s, 3H, $N_7$-$CH_3$), 3.64 (s, 3H, $OCH_3$), 4.48 (br s, 1H, H-1), 4.58 (d, $J$=1.8 Hz, 1H, H-6), 6.77 (s, 1H,

H-3), 7.10–7.25 (m, 3H, ArH), 7.33 (d, $J=8$ Hz, 2H, *m*-), 7.54 (d, $J=8.1$ Hz, 2H, *o*-), 7.60 (d, $J=7.5$ Hz, 1H, H-11); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 21.3 ($CH_3Ar$), 26.4 (C-12), 29.2 (C-5), 30.1 ($N_7$-$CH_3$), 41.8 ($N_2$-$CH_3$), 47.5 (C-6), 49.0 (C-1), 52.1 ($OCH_3$), 107.2 (C-4), 109.2 (C-8), 109.2 (C-11b), 118.1 (C-11), 119.5 (C-10), 121.5 (C-9), 124.9 (C-*o*), 125.4 (C-11a), 129.5 (C-*m*), 133.5 (C-6a), 137.0 (C-7a), 138.7 (C-*p*), 141.5 (C-*i* ), 144.3 (C-3), 171.4 (CO); *m*/*z* 475 ($M^+$+41, 1), 463 ($M^+$+29, 5), 435 ($M^+$+1, 53), 434 ($M^+$, 24), 419 (55), 418 (100), 296 (25), 240 (72), 216 (33). Anal. calcd for $C_{25}H_{26}N_2O_3S$: C, 69.10; H, 6.03; N, 6.44; S, 7.38. Found: C, 68.91; H, 5.90; N, 6.32; S, 7.11. *cis-rac*-**3′**: mp 202–204°C (acetone); IR (NaCl) 1733, 1607, 1471, 1036, 748 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 1.70 (dt, $J=12.3$, 3.5 Hz, 1H, H-12), 1.92 (dt, $J=12.3$, 2.5 Hz, 1H, H-12), 2.38 (s, 3H, $CH_3Ar$), 3.10 (s, 3H, $N_2$-$CH_3$), 3.24 (m, 1H, H-5), 3.55 (s, 3H, $N_7$-$CH_3$), 3.93 (s, 3H, $OCH_3$), 4.14 (d, $J=5.5$ Hz, 1H, H-6), 4.45 (br s, 1H, H-1), 6.69 (s, 1H, H-3), 7.10–7.48 (m, 7H, ArH), 7.60 (d, $J=7.1$ Hz, 1H, H-11); $^{13}$C NMR ($CDCl_3$, 50.3 MHz) $\delta$ 21.1 ($CH_3Ar$), 29.1 (C-5), 29.6 (C-12), 30.8 ($N_7$-$CH_3$), 41.4 ($N_2$-$CH_3$), 48.1 (C-6), 49.3 (C-1), 52.5 ($OCH_3$), 106.4 (C-4), 109.0 (C-8), 111.3 (C-11b), 117.5 (C-11), 119.5 (C-10), 121.5 (C-9), 124.8 (C-*o*), 125.4 (C-11a), 129.1 (C-*m*), 133.2 (C-6a), 137.1 (C-7a), 139.3 (C-*p*), 140.8 (C-*i* ), 143.4 (C-3), 171.8 (CO); *m*/*z* 475 ($M^+$+41, 2), 463 ($M^+$+29, 9), 435 ($M^+$+1, 59), 418 (27), 387 (22), 386 (60), 297 (21), 296 (21), 296 (100), 240 (15). Anal. calcd for $C_{25}H_{26}N_2O_3S{\cdot}1/2C_3H_6O$: C, 68.65; H, 6.30; N, 6.04; S, 6.91. Found: C, 68.40; H, 5.96; N, 6.31; S, 7.14. *trans-rac*-**3′**: mp 206°C (acetone); IR (NaCl) 1731, 1609, 1470, 1035 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 1.88 (dt, $J=12.5$, 3.3 Hz, 1H, H-12), 2.21 (dt, $J=12.5$, 2.2 Hz, 1H, H-12), 2.43 (s, 3H, $CH_3Ar$), 2.51 (d, $J=1.9$ Hz, 1H, H-6), 3.13 (s, 3H, $N_2$-$CH_3$), 3.15 (s, 3H, $N_7$-$CH_3$), 3.60 (s, 3H, $OCH_3$), 3.68 (br s, 1H, H-5), 4.53 (br s, 1H, H-1), 6.78 (s, 1H, H-3), 7.10–7.30 (m, 5H, ArH), 7.50 (d, $J=8.1$ Hz, 2H, *o*-), 7.61 (d, $J=7.0$ Hz, 1H, H-11); $^{13}$C NMR ($CDCl_3$, 50.3 MHz) $\delta$ 21.3 ($CH_3Ar$), 25.2 (C-5), 26.7 (C-12), 29.1 ($N_7$-$CH_3$), 41.8 ($N_2$-$CH_3$), 44.1 (C-6), 49.0 (C-1), 52.1 ($OCH_3$), 107.0 (C-4), 109.0 (C-8), 109.4 (C-11b), 118.2 (C-11), 119.5 (C-10), 121.5 (C-9), 124.9 (C-*o*), 125.5 (C-11a), 129.3 (C-*m*), 133.0 (C-6a), 137.2 (C-7a), 139.9 (C-*p*), 140.8 (C-*i* ), 143.5 (C-3), 171.1 (CO); *m*/*z* 475 ($M^+$+41, 2), 463 ($M^+$+29, 10), 435 ($M^+$+1, 100), 434 (M, 36), 418 (24), 359 (15), 296 (24). Anal. calcd for $C_{25}H_{26}N_2O_3S$: C, 69.10; H, 6.03; N, 6.44; S, 7.38. Found: C, 68.99; H, 6.01; N, 6.35; S, 7.29.

### 3.5. Reaction of lithium 2-(lithiomethyl)indole-1-carboxylate 5 with (*R*)-[Fe($\eta^5$-$C_5H_5$)(CO){$PPh_2$(*O*-(−)menthyl)}(nicotinoyl)] (*R*)-6

Butyllithium (1.6 M in hexanes, 3.2 mL, 5.1 mmol) was added to a cooled (−78°C) solution of 2-methylindole (0.65 g, 5.0 mmol) in THF (9 mL). After stirring for 5 min, a stream of dry $CO_2$ was bubbled into the solution for 5 min to give a yellowish solution, which was stirred for 20 min at −78°C. Then, excess of $CO_2$ was removed at reduced pressure at 0°C to give a residue, which was dissolved in THF (10 mL). The solution was cooled at −78°C and *tert*-butyllithium (1.7 M in pentane, 3 mL, 5.1 mmol) was added. The temperature was raised to −20°C and stirring was continued for 45 min. The mixture containing 2-(lithiomethyl)indole **5** was cooled at −78°C and was transferred via canula to a cooled (−78°C) solution of pyridine (*R*)-**6**[15] (0.59 g, 1.0 mmol) in THF (85 mL). After 3 h, methyl chloroformate (0.5 mL, 6.4 mmol) was added, and the mixture was stirred at −78°C for 30 min and at room temperature for additional 30 min. The organic solvent was removed at reduced pressure to give a residue, which was dissolved in $CH_2Cl_2$, washed with brine, and dried. Removal of the solvent followed by column chromatography (1:1 $Et_2O$/hexane) afforded starting 2-methylindole (0.3 g), methyl 2-indoleacetate (0.13 g) and a 43:57 mixture of the epimers, **7** and **7′**, respectively (0.60 g, 76%). **7**: $[\alpha]_D^{22}$ +213 (*c* 0.2, EtOH); IR (NaCl) 2955, 1914, 1721, 1438 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 0.07 (s, 3H, $CH_3$), 0.68 (d, $J=6.9$ Hz, 3H, $CH_3$), 0.86 (d, $J=6.6$ Hz, 3H, $CH_3$), 0.70–2.00 (m, 9H, menthyl), 2.85 (m, 1H, Ind-$CH_2$), 3.05 (m, 1H, Ind-$CH_2$), 3.70–3.90 (m, 4H, $CH_3O$, POCH), 4.26 (br s, 5H, $C_5H_5$), 5.00 (br s, 1H, H-2), 5.41 (br s, 1H, H-3), 6.18 (br s, 1H, H-4), 6.27 (s, 1H, H-3 ind), 6.99–7.52 (m, 13H, H-6, 12H, ArH), 8.11 (m, 2H, ArH), 8.30 (br s, 1H, NH); $^1$H NMR (DMSO-$d_6$, 300 MHz, 60°C) $\delta$ 0.22 (d, $J=6.7$ Hz, 3H, $CH_3$), 0.67 (d, $J=6.9$ Hz, 3H, $CH_3$), 0.78 (d, $J=6.3$ Hz, 3H, $CH_3$), 0.66–2.00 (m, 9H, menthyl), 2.83 (dd, $J=14.0$, 5.2 Hz, 1H, Ind-$CH_2$), 2.99 (dd, $J=14.0$, 7.2 Hz, 1H, Ind-$CH_2$), 3.69 (br s, 4H, $CH_3O$, POCH), 4.27 (m, 5H, $C_5H_5$), 5.03 (m, 1H, H-2), 5.42 (dd, $J=9.7$, 5.5 Hz, 1H, H-3), 6.10 (s, 1H, H-3 ind), 6.13 (br s, 1H, H-4), 6.85–7.56 (m, 13H, H-6, 12H, ArH), 7.93 (m, 2H, ArH), 10.75 (br s, 1H, NH); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 15.3 (C-10′), 21.5 (C-9′), 22.3 (C-7′), 22.9 (C-5′), 25.0 (C-8′), 31.6 (C-1′), 33.4 (Ind-$CH_2$), 34.1 (C-6′), 43.7 (C-2′), 49.7 (d, $J_{PC}=4.6$ Hz, C-4′), 53.4 (C-2), 53.8 ($CH_3O$), 77.0 (C-3′), 85.6 ($C_5H_5$), 101.9 (C-3 ind), 110.6 (C-7 ind), 119.6 (C-4 ind), 119.8 (C-5 ind, C-3), 121.2 (C-6 ind), 123.1 (C-4), 127.5 (d, $J_{PC}=11.0$ Hz, C-*m*), 127.6 (d, $J_{PC}=9.8$ Hz, C-*m*), 128.5 (C-3a ind), 129.9 (C-*p*), 131.5 (C-6), 131.9 (d, $J_{PC}=10.0$ Hz, C-*o*), 134.4 (C-2 ind), 136.1 (C-7a ind), 165.4 (CO), 221.8 (d, $J_{PC}=36.5$ Hz, CO). **7′**: $[\alpha]_D^{22}$ −16 (*c* 0.2, EtOH); IR (NaCl) 2955, 1914, 1725, 1437 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 0.20 (d, $J=6.9$ Hz, 3H, $CH_3$), 0.72 (d, $J=6.9$ Hz, 3H, $CH_3$), 0.87 (d, $J=6.6$ Hz, 3H, $CH_3$), 0.78–2.08 (m, 9H, menthyl), 2.99 (br s, 1H, Ind-$CH_2$), 3.30 (br s, 1H, Ind-$CH_2$), 3.80 and 3.87 (2s, 3H, $CH_3O$), 3.83 (s, 1H, POCH), 4.51 (m, 5H, $C_5H_5$), 5.00 (br s, 1H, H-2), 5.41 (dd, $J=9.8$, 5.6 Hz, 1H, H-3), 6.20 (br s, 1H, H-4), 6.33 (s, 1H, H-3 ind), 7.01–7.60 (m, 12H, ArH), 7.90 (br s, 1H, H-6), 8.10 (m, 2H, ArH), 8.33 (br s, 1H, NH); $^1$H NMR (DMSO-$d_6$, 300 MHz, 70°C) $\delta$ 0.29 (d, $J=6.9$ Hz, 3H, $CH_3$), 0.70 (d, $J=7.1$ Hz, 3H, $CH_3$), 0.80 (d, $J=6.3$ Hz, 3H, $CH_3$), 0.70–2.00 (m, 9H, menthyl), 2.90 (m, 1H, Ind-$CH_2$), 3.47 (br s, 1H, Ind-$CH_2$), 3.74 and 3.81 (2s, 3H, $CH_3O$), 3.70–3.90 (s masked, 1H, POCH), 4.45 (s, 5H, $C_5H_5$), 5.04 (m, 1H, H-2), 5.49 (dd, $J=9.5$, 5.2 Hz, 1H, H-3), 6.15 (br s, 1H, H-4), 6.19 (s, 1H, H-3 ind), 6.80–8.00 (m, 15H, H-6, ArH), 10.75 (br s, 1H, NH); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 15.3 (C-10′), 21.5 (C-9′), 22.2 (C-7′), 23.0 (C-5′), 25.0 (C-8′), 31.6 (C-1′), 34.0 (Ind-

$CH_2$), 34.1 (C-6′), 43.7 (C-2′), 49.7 (d, $J_{PC}=4.8$ Hz, C-4′), 53.3 (C-2), 53.4 and 53.9 ($CH_3O$), 77.0 (C-3′), 85.8 ($C_5H_5$), 101.8 (C-3 ind), 110.5 (C-7 ind), 119.5 (C-4 ind), 119.8 (C-5 ind), 121.2 (C-6 ind), 121.8 (C-3), 123.5 (C-4), 127.5 (d, $J_{PC}=10.2$ Hz, C-*m*), 127.6 (d, $J_{PC}=$ 10.2 Hz, C-*m*), 128.6 (C-3a ind), 129.8 (C-*p*), 130.0 (C-*p*), 131.8 (d, $J_{PC}=9.1$ Hz, C-*o*), 131.9 (d, $J_{PC}=9.6$ Hz, C-*o*), 132.0 (C-6), 134.3 (C-2 ind), 136.2 (C-7a ind).

### 3.6. Preparation of (2*R*)-*N*-nicotinoylbornane-10,2-sultam 8

A solution of nicotinic acid (3.43 g, 27.9 mmol) and thionyl chloride (18 mL) was heated at reflux for 90 min. Removal of the excess of thionyl chloride provided the nicotinoyl chloride hydrochloride as a white solid, which was used without further purification. A solution of (2*R*)-bornane-10,2-sultam (4.0 g, 18.6 mmol) in toluene (80 mL) was slowly added to a suspension of sodium hydride (55%, 2.4 g, 55.8 mmol) in toluene (40 mL) and the mixture was stirred at rt for 30 min. Then, a suspension of nicotinoyl chloride hydrochloride (3.8 g, 33.48 mmol) in toluene (80 mL) was slowly added and the mixture was stirred for 2 h 30 min. The reaction was quenched with saturated aqueous $NH_4Cl$ and the phases were separated. The aqueous phase was extracted with EtOAc and the combined organic extracts were dried and concentrated to furnish **8** (5.48 g, 92%). **8**: $[\alpha]_D^{22}$ −212 (*c* 1, EtOH); mp 136°C (acetone); IR (NaCl) 1673, 1336, 1302 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 1.02 (s, 3H, $CH_3$), 1.32 (s, 3H, $CH_3$), 1.40–2.15 (m, 7H, bornane), 3.43 and 3.55 (2d, $J=13.7$ Hz, 2H, $CH_2SO_2$), 4.16 (m, 1H, CHNCO), 7.37 (dd, $J=7.9$, 4.9 Hz, 1H, H-5), 8.06 (dt, $J=7.9$, 1.8 Hz, 1H, H-4), 8.76 (dd, $J=4.9$, 1.8 Hz, 1H, H-6), 8.92 (s, 1H, H-2); $^{13}C$ NMR ($CDCl_3$, 75 MHz) $\delta$ 19.9 (C-7), 21.0 (C-8), 26.3 (C-5), 32.7 (C-6), 38.0 (C-3), 44.7 (C-4), 47.6 (C-7), 48.1 (C-1), 53.1 (C-10), 65.5 (C-2), 122.6 (C-5 pyr), 129.6 (C-3 pyr), 136.5 (C-4 pyr), 149.9 (C-6 pyr), 152.8 (C-2 pyr), 167.7 (CO). Anal. calcd for $C_{16}H_{20}N_2O_3S$: C, 59.98; H, 6.29; N, 8.74; S, 10.00. Found: C, 59.99; H, 6.38; N, 8.77; S, 10.11.

### 3.7. Reaction of lithium 2-(lithiomethyl)indole-1-carboxylate 5 with (2*R*)-*N*-nicotinoylbornane-10,2-sultam 8

A suspension of 2-(lithiomethyl)indole **5**, prepared as described above from 2-methylindole (615 mg, 4.7 mmol), was transferred via canula at −78°C to a cooled (−78°C) solution of sultam **8** (500 mg, 1.6 mmol) in THF (28 mL). After 3 h of stirring, methyl chloroformate (0.6 mL, 7.8 mmol) was added, and the mixture was stirred at −30°C for 30 min and at room temperature for additional 30 min. The mixture was poured into saturated aqueous $Na_2CO_3$, and the aqueous phase was extracted with EtOAc. The combined organic extracts were dried and concentrated to give a residue, which was chromatographed (gradient from 7:3 hexane/EtOAc to EtOAc). The first fraction provided unreacted **5**. The second fraction gave 254 mg of a mixture of **9** and **10**, which were separated after an additional column chromatography (7:3 $Et_2O$/hexane) furnishing pure **10** (65 mg, 8%) and **9** (99 mg). The third fraction gave 350 mf of **9** and **10′**, which were separated by column chromatography (4:6 EtOAc/hexane) furnishing pure **9** (63 mg, 20% overall yield) and **10′** (95 mg, 12%). **9**: IR (NaCl) 2960, 1738, 1675, 1442, 1331, 1268, 1239, 749 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 0.98 (s, 3H, $CH_3$), 1.23 (s, 3H, $CH_3$), 1.30–2.10 (m, 7H, sultam), 3.00 (dd, $J=15.0$, 8.2 Hz, 1H, Ind-$CH_2$), 3.23 (d, $J=15.0$ Hz, 1H, Ind-$CH_2$), 3.40 and 3.49 (2d, $J=13.7$ Hz, 2H, $CH_2SO_2$), 3.42–3.50 (m, 1H, H-4), 3.77 (s, 3H, $CH_3O$), 4.14 (dd, $J=7.2$, 4.1 Hz, 1H, $CHNSO_2$), 5.10 (br s, 1H, H-5), 6.23 (s, 1H, H-3 ind), 6.80 (br s, 1H, H-6), 7.03–7.28 (m, 3H, ArH), 7.52 (d, $J=7.4$ Hz, 1H, H-4 ind), 7.75 (br s, 1H, H-2), 8.45 (br s, 1H, NH); $^{13}C$ NMR ($CDCl_3$, 75 MHz) $\delta$ 19.8 (C-10), 21.0 (C-8), 26.6 (C-5), 32.9 (C-6), 33.8 (C-4 pyr), 36.5 (Ind-$CH_2$), 37.9 (C-3), 45.0 (C-4), 47.7 (C-7), 47.9 (C-1), 53.2 (C-10), 54.1 ($CH_3O$), 65.3 (C-2), 101.3 (C-3 ind), 110.4 (C-7 ind), 111.8 (C-5 pyr), 113.0 (C-3 pyr), 119.3 (C-4 ind), 119.7 (C-5 ind), 120.8 (C-6 ind), 122.0 (C-6 pyr), 128.6 (C-3a ind), 136.0 (C-2 ind), 136.2 (C-7a ind), 136.7 (C-2 pyr), 151.2 ($CO_2CH_3$), 169.4 ($CONSO_2$), *m*/*z* 509 ($M^+$), 380 (22), 379 (100), 106 (21), 93 (19); HRMS calcd for $C_{27}H_{30}N_3O_5S$ 508.1906, found 508.1872. **10**: $^1H$ NMR ($CDCl_3$, 200 MHz, most relevant signals) $\delta$ 1.04 (s, 3H, $CH_3$), 1.30 (s, 3H, $CH_3$), 3.10 (m, 2H, Ind-$CH_2$), 3.79 (s, 3H, $CH_3O$), 5.10 (m, 1H, H-2), 5.75 (m, 1H, H-3), 6.30 (s, 1H, H-3 ind), 6.50 (d, $J=9.3$ Hz, H-4), 7.74 (s, 1H, H-6), 8.50 (br s, 1H, NH). **10′**: IR (NaCl) 2958, 1728, 1667, 1442, 1329, 1266, 750 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 1.00 (s, 3H, $CH_3$), 1.21 (s, 3H, $CH_3$), 0.90–2.04 (m, 7H, sultam), 2.96 (dd, $J=13.4$, 4.6 Hz, 1H, Ind-$CH_2$), 3.12 (dd, $J=13.4$, 9.4 Hz, 1H, Ind-$CH_2$), 3.43 and 3.52 (2d, $J=13.7$ Hz, 2H, $CH_2SO_2$), 3.86 (s, 3H, $CH_3O$), 4.09 (dd, $J=7.5$, 4.4 Hz, 1H, $CHNSO_2$), 5.01 (m, 1H, H-2), 5.43 (dd, $J=9.6$, 5.8 Hz, 1H, H-3), 6.29 (s, 1H, H-3 ind), 6.32 (d, $J=9.6$ Hz, 1H, H-4), 7.10 (m, 2H, H-5, H-6 ind), 7.32 (d, $J=7.3$ Hz, 1H, H-7 ind), 7.52 (d, $J=7.5$ Hz, 1H, H-4 ind), 7.76 (br s, 1H, H-6), 8.30 (br s, 1H, NH); $^{13}C$ NMR ($CDCl_3$, 75 MHz) $\delta$ 19.9 (C-9), 21.0 (C-8), 26.6 (C-5), 32.6 (C-6), 32.9 (Ind-$CH_2$), 37.8 (C-3), 44.9 (C-4), 47.8 (C-7), 48.0 (C-1), 53.0 (C-2 pyr), 53.4 (C-10), 54.2 ($CH_3O$), 65.4 (C-2), 101.6 (C-3 ind), 110.7 (C-7 ind), 113.0 (C-5 pyr), 119.4 (C-4 ind), 119.8 (C-5 ind), 120.0 (C-3 pyr), 121.2 (C-6 ind), 121.8 (C-6 pyr), 128.4 (C-3a ind), 133.6 (C-2 pyr), 135.7 (C-6 pyr), 136.1 (C-7a ind), 153.5 ($CO_2CH_3$), 166.8 ($CONSO_2$); *m*/*z* 509 ($M^+$), 380 (22), 379 (100), 106 (21), 93 (18); HRMS calcd for $C_{27}H_{30}N_3O_5S$ 508.1906, found 508.1882.

### 3.8. Preparation of (2*R*)-*N*-(1-methylnicotinoyl)-bornane-10,2-sultam iodide 11a

A solution of methyl iodide (1.40 mL, 22.4 mmol) in benzene (2 mL) was slowly added to a cooled (0°C) solution of sultam **8** (2.08 g, 6.5 mmol) in acetone (4 mL) and benzene (2 mL). The mixture was stirred for 12 h and the solid was filtered and dried to give **11a** (2.92 g, 97%). **11a**: $[\alpha]_D^{22}$ −179 (*c* 1, EtOH); mp 203°C (acetone); IR (NaCl) 2953, 1680, 1333, 1315, 1201, 1135 $cm^{-1}$; $^1H$ NMR (DMSO, 300 MHz) $\delta$ 0.96 (s, 3H, $CH_3$), 1.21 (s, 3H, $CH_3$), 1.30–2.07 (m, 7H, bornane),

3.76 and 3.99 (2d, $J=14.0$ Hz, 2H, $CH_2SO_2$), 4.14 (dd, $J=7.9$, 4.7 Hz, 1H, CHNCO), 4.40 (s, 3H, N-$CH_3$), 8.27 (dd, $J=8.1$, 6.1 Hz, 1H, H-5), 8.75 (d, $J=8.1$ Hz, 1H, H-4), 9.15 (d, $J=6.1$ Hz, 1H, H-6), 9.34 (s, 1H, H-2); $^{13}$C NMR (DMSO, 75 MHz) $\delta$ 19.7 (C-9), 21.3 (C-8), 26.0 (C-5), 32.1 (C-6), 37.6 (C-3), 44.7 (C-4), 47.7 (C-7), 48.7 (C-1), 48.9 (N-$CH_3$), 52.5 (C-10), 64.9 (C-2), 128.4 (C-5 pyr), 132.9 (C-3 pyr), 144.8 (C-4 pyr), 145.5 (C-6 pyr), 148.5 (C-2 pyr), 163.2 (CO). Anal. calcd for $C_{17}H_{23}IN_2O_3S$: C, 44.16; H, 5.01; N, 6.06; S, 6.93; I, 27.45. Found: C, 44.07; H, 5.01; N, 6.08; S, 6.97; I, 27.33.

### 3.9. Preparation of (2*R*)-*N*-(1-benzylnicotinoyl)-bornane-10,2-sultam chloride 11b

Benzyl chloride (3.6 mL, 43.8 mmol) was added to a solution of sultam **8** (2.0 g, 6.2 mmol) in methanol (12 mL). The mixture was heated to 70°C in a sealed tube for 24 h. The solvent was concentrated and the excess of benzyl chloride was removed by vacuum distillation. The residue was washed with $Et_2O$ and dried to give **11b** (2.59 g, 92%). **11b**: $[\alpha]_D^{22}$ −121 (*c* 1, EtOH); mp 170°C (acetone); IR (NaCl) 1680, 1333, 1306, 1169, 1136 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 0.99 (s, 3H, $CH_3$), 1.21 (s, 3H, $CH_3$), 1.25–2.13 (m, 7H, bornane), 3.51 and 3.56 (2d, $J=14.3$ Hz, 2H, $CH_2SO_2$), 4.17 (br s, 1H, CHNCO), 6.33 (br s, 2H, $CH_2C_6H_5$), 7.36 (br s, 3H, H-*p*, -*m*), 7.68 (br s, 2H, H-*o*), 8.24 (br s, 1H, H-5), 8.58 (d, $J=7.3$ Hz, 1H, H-4), 9.43 (br s, 1H, H-6), 10.09 (br s, 1H, H-2); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 19.7 (C-9), 21.1 (C-8), 26.2 (C-5), 32.6 (C-6), 37.8 (C-3), 44.7 (C-4), 47.8 (C-7), 48.7 (C-1), 53.1 (C-10), 64.6 ($CH_2C_6H_5$), 65.5 (C-2), 128.2 (C-5 pyr), 129.3 (C-*m*), 129.8 (C-*p*), 129.9 (C-*o*), 132.3 (C-*i* ), 133.1 (C-3 pyr), 144.6 (C-4 pyr), 144.6 (C-6 pyr), 148.4 (C-2 pyr), 162.6 (CO). Anal. calcd for $C_{23}H_{27}ClN_2O_3S{\cdot}3/2H_2O$: C, 58.28; H, 6.38; N, 5.90; S, 6.76. Found: C, 58.10; H, 6.30; N, 5.90; S, 6.76.

### 3.10. Reaction of methyl 1-methyl-2-indoleacetate 1 with (2*R*)-*N*-(1-methylnicotinoyl)bornane-10,2-sultam iodide 11a

Operating as described in the general procedure, from ester **1** (264 mg, 1.3 mmol) and pyridinium iodide **11a** (600 mg, 1.3 mmol) a residue was obtained. Purification by column chromatography (1:1 EtOAc/hexane) provided four fractions. The first one gave a mixture of the starting ester **1** and (2*R*)-bornane-10,2-sultam. The second fraction provided *trans*-**12a** (19 mg, 3%). The third fraction gave a mixture of *cis*-**13a** and *trans*-**13a**, which were separated by further chromatography ($Et_2O$; *cis*-**13a**: 40 mg; *trans*-**13a**: 158 mg; 28% overall yield). The last fraction gave *cis*-**12a** (50 mg, 7%). *cis*-**12a**: $[\alpha]_D^{22}$ −385 (*c* 0.4, $CHCl_3$); mp 220°C ($CH_2Cl_2$); IR (NaCl) 2954, 1728, 1592, 1333 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 0.92 (s, 3H, $CH_3$), 1.17 (s, 3H, $CH_3$), 1.17–1.91 (m, 7H, sultam), 1.96 (dt, $J=12.5$, 3.5 Hz, 1H, H-12), 2.03 (dt, $J=12.5$, 2.5 Hz, 1H, H-12), 3.27 (s, 2H, $CH_2SO_2$), 3.28 (s, 3H, $N_2$-$CH_3$), 3.52 (s, 3H, $N_7$-$CH_3$), 3.73 (s, 3H, $CH_3O$), 4.09 (m, 1H, H-5), 4.10 (m, 1H, $CHNSO_2$), 4.20 (d, $J=5.4$ Hz, 1H, H-6), 4.53 (br t, 1H, H-1), 7.10–7.30 (m, 3H, H-8, H-9, H-10), 7.58 (d, $J=7.7$ Hz, 1H, H-11), 7.62 (s, 1H, H-3); $^{13}$C NMR ($CDCl_3$, 50.3 MHz) $\delta$ 19.9 (C-9′), 20.6 (C-8′), 26.9 (C-5′), 28.4 (C-5), 29.5 (C-12), 30.6 ($N_7$-$CH_3$), 32.4 (C-6′), 36.8 (C-3′), 42.8 ($N_2CH_3$), 44.5 (C-4′), 47.8 (C-7′), 47.9 (C-1′), 48.7 (C-1), 49.1 (C-6), 52.5 (C-10′), 52.9 ($CH_3O$), 65.4 (C-2′), 101.9 (C-4), 109.3 (C-8), 110.7 (C-11b), 117.4 (C-11), 119.7 (C-10), 121.6 (C-9), 125.4 (C-11a), 134.0 (C-6a), 137.3 (C-7a), 151.9 (C-3), 166.2 (NCO), 171.8 ($CO_2$). Anal. calcd for $C_{29}H_{35}N_3O_5S{\cdot}1/2H_2O$: C, 63.70; H, 6.64; N, 7.68; S, 5.86. Found: C, 63.45; H, 6.41; N, 7.37; S, 6.05. *trans*-**12a**: $[\alpha]_D^{22}$ −153 (*c* 0.4, $CHCl_3$); mp 260°C ($CH_2Cl_2$); IR (NaCl) 3000, 1700, 1595, 1319 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 0.91 (s, 3H, $CH_3$), 1.16 (s, 3H, $CH_3$), 0.90–2.00 (m, 8H, sultam, H-12), 2.38 (dt, $J=12.3$, 2.6 Hz, 1H, H-12), 3.23 (s, 3H, $N_2$-$CH_3$), 3.20 and 3.25 (2d, $J=13.7$ Hz, 2H, $CH_2SO_2$), 3.56 (s, 3H, $N_7$-$CH_3$), 3.74 (s, 3H, $CH_3O$), 3.84 (m, 1H, H-5), 3.89 (d, $J=1.7$ Hz, 1H, H-6), 4.25 (dd, $J=7.1$, 4.4 Hz, 1H, $CHNSO_2$), 4.59 (br t, 1H, H-1), 7.10–7.25 (m, 3H, H-8, H-9, H-10), 7.28 (s, 1H, H-3), 7.60 (d, $J=7.7$ Hz, 1H, H-11); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 19.9 (C-9′), 21.8 (C-8′), 25.7 (C-12), 26.8 (C-5′), 29.5 (C-5), 29.6 ($N_7$-$CH_3$), 32.9 (C-6′), 37.4 (C-3′), 42.7 ($N_2CH_3$), 45.0 (C-4′), 45.5 (C-6), 47.6 (C-7′), 47.7 (C-1′), 49.4 (C-1), 52.2 ($CH_3O$), 52.9 (C-10′), 64.9 (C-2′), 104.2 (C-4), 109.3 (C-8), 109.8 (C-11b), 117.8 (C-11), 119.3 (C-10), 121.2 (C-9), 125.6 (C-11a), 133.9 (C-6a), 137.4 (C-7a), 150.6 (C-3), 165.9 (NCO), 171.8 ($CO_2$). Anal. calcd for $C_{29}H_{35}N_3O_5S{\cdot}3/2H_2O$: C, 62.50; H, 7.06; N, 7.16; S, 5.46. Found: C, 62.51; H, 6.89; N, 6.94; S, 5.68. *cis*-**13a**: $[\alpha]_D^{22}$ +8 (*c* 0.4, $CHCl_3$); mp 275°C (EtOH); IR (NaCl) 3000, 1738, 1601, 1324 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 0.93 (s, 3H, $CH_3$), 1.21 (s, 3H, $CH_3$), 1.21–1.95 (m, 8H, sultam, H-12), 2.00 (ddd, $J=12.3$, 3.0, 2.0 Hz, 1H, H-12), 3.07 (s, 3H, $N_3$-$CH_3$), 3.23 (s, 2H, $CH_2SO_2$), 3.48 (s, 3H, $N_{11}$-$CH_3$), 3.76 (s, 3H, $CH_3O$), 4.22 (dd, $J=7.4$, 4.3 Hz, 1H, $CHNSO_2$), 4.28 (m, 1H, H-6), 4.28 (br s, 1H, H-1), 4.49 (br t, 1H, H-2), 7.10–7.25 (m, 3H, H-8, H-9, H-10), 7.33 (s, 1H, H-4), 7.70 (d, $J=7.7$ Hz, 1H, H-7); $^{13}$C NMR ($CDCl_3$, 50.3 MHz) $\delta$ 19.9 (C-9′), 20.9 (C-8′), 22.8 (C-6), 26.8 (C-5′), 28.3 (C-12), 30.1 ($N_{11}$-$CH_3$), 32.6 (C-6′), 37.3 (C-3′), 44.3 ($N_3$-$CH_3$), 44.9 (C-4′), 47.7 (C-1), 47.8 (C-7′), 47.9 (C-1′), 52.6 (C-10′), 52.7 ($CH_3O$), 55.8 (C-2), 64.9 (C-2′), 108.4 (C-10), 108.4 (C-6a), 118.0 (C-5), 119.1 (C-7), 119.7 (C-8), 121.4 (C-9), 124.5 (C-6a), 128.0 (C-11a), 137.0 (C-10a), 149.9 (C-4), 166.5 (NCO), 172.1 ($CO_2$). Anal. calcd for $C_{29}H_{35}N_3O_5$: C, 64.78; H, 6.56; N, 7.81; S, 5.96. Found: C, 64.71; H, 6.58; N, 7.72; S, 6.01. *trans*-**13a**: $[\alpha]_D^{22}$ +6 (*c* 0.4, $CHCl_3$), $[\alpha]_D^{22}$ +7 (*c* 0.2, EtOH); mp 250°C (acetone); IR (NaCl) 3000, 1700, 1598, 1322 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 0.92 (s, 3H, $CH_3$), 1.20 (s, 3H, $CH_3$), 1.26–1.92 (m, 7H, sultam), 1.80 (m, 1H, H-12), 2.30 (ddd, $J=12.5$, 3.4, 1.6 Hz, 1H, H-12), 3.17 (s, 3H, $N_3$-$CH_3$), 3.22 (s, 2H, $CH_2SO_2$), 3.53 (s, 3H, $N_{11}$-$CH_3$), 3.74 (s, 3H, $CH_3O$), 3.93 (d, $J=1.4$ Hz, 1H, H-1), 4.00 (m, 1H, H-6), 4.25 (dd, $J=7.1$, 3.6 Hz, 1H, $CHNSO_2$), 4.53 (br t, 1H, H-2), 7.01–7.17 (m, 3H, H-8, H-9, H-10), 7.37 (s, 1H, H-4), 7.64 (d, $J=7.7$ Hz, 1H, H-7); $^{13}$C NMR ($CDCl_3$, 50.3 MHz) $\delta$ 19.8 (C-9′), 20.8 (C-8′), 22.8 (C-6), 25.7 (C-12), 26.7 (C-5′), 29.7 ($N_{11}$-$CH_3$), 32.5

(C-6′), 37.2 (C-3′), 42.0 ($N_3$-$CH_3$), 43.8 (C-1), 44.9 (C-4′), 47.5 (C-7′), 47.8 (C-1′), 52.6 (C-10′), 52.6 ($CH_3O$), 56.7 (C-2), 65.1 (C-2′), 107.5 (C-6a), 108.2 (C-10), 117.0 (C-5), 118.7 (C-7), 120.0 (C-8), 121.4 (C-9), 125.0 (C-6b), 126.8 (C-11a), 137.3 (C-10a), 149.9 (C-4), 165.9 (NCO), 170.8 ($CO_2$). Anal. calcd for $C_{29}H_{35}N_3O_5S$: C, 64.78; H, 6.56; N, 7.81; S, 5.96. Found: C, 64.64; H, 6.42; N, 7.68; S, 5.83. **14**: IR (NaCl) 3000, 1624, 1584, 1322, 1245 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz, most relevant signals) $\delta$ 0.99 (s, 3H, $CH_3$), 1.27 (s, 3H, $CH_3$), 0.90–1.90 (m, 7H, sultam), 2.95 and 3.05 (2d, $J=5.2$ Hz, 3H, NH-C$H_3$), 3.18 and 3.36 (2d, $J=13.7$ Hz) and 3.34 and 3.40 (2d, $J=13.7$ Hz, 2H, $CH_2SO_2$), 3.55 (s, 3H, $CH_3O$), 3.75 (s, 3H, N-$CH_3$ ind), 4.10 (m, 1H, $CHNSO_2$), 4.75 (br s, 1H, NH-$CH_3$), 6.05 (dd, $J=15.0$, 11.0 Hz, 1H, H-4), 6.45 (s, 1H, H-3 ind), 7.10–7.40 (m, 5H, Ar ind, H-5, H-7), 7.60 (d, 1H, H-4 ind), 7.75 (d, $J=11.0$ Hz, 1H, H-3), 9.40 (br s, 1H, NH); $^{13}C$ NMR ($CDCl_3$, 50.3 MHz) $\delta$ 19.8 (C-9′), 20.8 (C-8′), 26.7 (C-5′), 30.3 (N-$CH_3$), 32.6 (C-6′), 35.8 (NH-$CH_3$), 37.1 (C-3′), 44.7 (C-4′), 47.7 (C-7′), 48.0 (C-1′), 51.8 ($CH_3O$), 52.5 (C-10′), 64.8 (C-2′), 100.0 (C-6), 103.1 (C-3 ind), 109.2 (C-7 ind), 112.6 (C-4), 116.1 (C-2), 119.0 (C-4 ind), 120.4 (C-5 ind), 121.0 (C-6 ind), 127.7 (C-3a ind), 135.1 (C-2 ind), 137.3 (C-7a ind), 142.0 (C-5), 148.4 (C-3), 155.6 (C-7), 167.7 (NCO), 170.8 ($CO_2$).

### 3.11. Reaction of methyl 1-methyl-2-indoleacetate 1 with (2*R*)-*N*-(1-benzylnicotinoyl)bornane-10,2-sultam chloride 11b

Operating as described above, from ester **1** (273 mg, 1.34 mmol) and pyridinium chloride **11b** (600 mg, 1.34 mmol) a residue was obtained. Purification by column chromatography (8:2 $Et_2O$/hexane) gave as first fraction consisting of a mixture of ester **1** and (2*R*)-bornane-10,2-sultam. The second fraction gave a mixture of *trans*-**12b**, *trans*-**13b** and *trans*-**13′b** (160 mg). Further purifications by column chromatography (4:6 EtOAc/hexane; 9.7:0.3 $CH_2Cl_2$/EtOAc; 9:1 $CH_2Cl_2$/EtOAc) provided analytical samples. The third fraction gave *cis*-**12b** (60 mg). The overall yield for the four isomers was 27%. *cis*-**12b**: $[\alpha]_D^{22}$ −387 (*c* 0.4, $CHCl_3$); mp 260–262°C (EtOH); IR (NaCl) 1730, 1593, 1324, 1199, 747 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 200 MHz) $\delta$ 0.90 (s, 3H, $CH_3$), 1.05 (s, 3H, $CH_3$), 1.12–1.95 (m, 8H, 7H sultam, H-12), 1.99 (dm, $J=12.4$ Hz, 1H, H-12), 3.25 (s, 2H, $CH_2SO_2$), 3.52 (s, 3H, N-$CH_3$), 3.76 (s, 3H, $CH_3O$), 4.10 (m, 1H, $CHNSO_2$), 4.11 (m, 1H, H-5), 4.20 (d, $J=5.0$ Hz, 1H, H-6), 4.54 and 4.74 (2d, $J=15.2$ Hz, 2H, C$H_2C_6H_5$), 4.60 (br t, 1H, H-1), 7.10–7.49 (m, 9H, ArH), 7.79 (s, 1H, H-3); $^{13}C$ NMR ($CDCl_3$, 50.3 MHz) $\delta$ 19.9 (C-9′), 20.4 (C-8′), 26.8 (C-5′), 28.6 (C-5), 29.7 (C-12), 30.6 (N-$CH_3$), 32.3 (C-6′), 36.7 (C-3′), 44.4 (C-4′), 47.0 (C-6), 47.7 (C-7′), 47.9 (C-1′), 48.5 (C-1), 52.4 (C-10′), 52.9 ($CH_3O$), 59.0 ($CH_2SO_2$), 65.3 (C-2′), 102.2 (C-4), 109.2 (C-8), 110.7 (C-11b), 117.3 (C-11), 119.6 (C-10), 121.5 (C-9), 125.2 (C-11a), 127.7 (C-*m*), 128.0 (C-*p*), 129.0 (C-*o*), 134.1 (C-6a), 136.1 (C-*i*), 137.3 (C-7a), 151.7 (C-3), 166.6 (NCO), 171.7 ($CO_2$). Anal. calcd for $C_{35}H_{39}N_3O_5S$: C, 68.49; H, 6.40; N, 6.84; S, 5.22. Found: C, 68.09; H, 6.62; N, 6.74; S, 5.10. *trans*-**12b**: $[\alpha]_D^{22}$ −267 (*c* 0.4, $CHCl_3$); mp 249–250°C (EtOH); IR (NaCl) 1733, 1596, 1321, 1196, 751 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 0.90 (s, 3H, $CH_3$), 1.05 (s, 3H, $CH_3$), 1.00–1.95 (m, 8H, 7H, sultam, H-12), 2.38 (dt, $J=12.4$, 2.2 Hz, 1H, H-12), 3.20 and 3.25 (2d, $J=13.7$ Hz, 2H, $CH_2SO_2$), 3.57 (s, 3H, N-$CH_3$), 3.73 (s, 3H, $CH_3O$), 3.90 (m, 1H, H-5), 3.94 (d, $J=1.6$ Hz, 1H, H-6), 4.25 (m, 1H, $CHNSO_2$), 4.43 and 4.73 (2d, $J=15.1$ Hz, 2H, C$H_2C_6H_5$), 4.66 (br t, 1H, H-1), 7.08–7.48 (m, 8H, ArH), 7.36 (s, 1H, H-3), 7.52 (d, $J=7.5$ Hz, 1H, H-11); $^{13}C$ NMR ($CDCl_3$, 75 MHz) $\delta$ 19.7 (C-9′), 20.8 (C-8′), 25.9 (C-12), 26.7 (C-6′), 29.5 (C-5), 29.8 (N-$CH_3$), 32.7 (C-5′), 37.2 (C-3′), 44.9 (C-4′), 45.4 (C-6), 47.4 (C-1), 47.5 (C-7′), 47.6 (C-1′), 52.1 ($CH_3O$), 52.8 (C-10′), 58.9 ($CH_2C_6H_5$), 64.8 (C-2′), 104.6 (C-4), 109.3 (C-8), 109.8 (C-11b), 117.7 (C-11), 119.2 (C-10), 121.1 (C-9), 125.4 (C-11a), 127.8 (C-*m*), 128.1 (C-*p*), 128.8 (C-*o*), 134.0 (C-6a), 136.1 (C-*i*), 137.3 (C-7a), 150.2 (C-3), 167.2 (NCO), 171.6 ($CO_2$). Anal. calcd for $C_{35}H_{39}N_3O_5S$: C, 68.49; H, 6.40; N, 6.84; S, 5.22. Found: C, 68.30; H, 6.44; N, 6.81; S, 5.04. *trans*-**13b**: IR (NaCl) 1736, 1598, 1323, 1196, 749 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 0.92 (s, 3H, $CH_3$), 1.15 (s, 3H, $CH_3$), 1.24–1.96 (m, 7H, sultam), 1.77 (ddd, $J=12.5$, 4.2, 2.8 Hz, 1H, H-12), 2.28 (ddd, $J=12.5$, 3.2, 1.5 Hz, 1H, H-12), 3.23 (s, 2H, $CH_2SO_2$), 3.40 (s, 3H, N-$CH_3$), 3.68 (s, 3H, $CH_3O$), 3.73 (d, $J=1.6$ Hz, 1H, H-1), 4.16 (m, 1H, H-6), 4.25 (m, 1H, $CHNSO_2$), 4.48 and 4.57 (2d, $J=15.4$ Hz, 2H, C$H_2C_6H_5$), 4.56 (br s, 1H, H-2), 7.03–7.38 (m, 8H, ArH), 7.56 (s, 1H, H-4), 7.65 (d, $J=7.7$ Hz, 1H, H-7); $^{13}C$ NMR ($CDCl_3$, 50.3 MHz) $\delta$ 19.9 (C-9′), 20.9 (C-8′), 23.2 (C-6), 26.1 (C-12), 26.8 (C-5′), 29.6 (N-$CH_3$), 32.6 (C-6′), 37.3 (C-3′), 44.7 (C-1), 45.0 (C-4′), 47.7 (C-7′), 47.9 (C-1′), 52.6 ($CH_3O$), 52.7 (C-10′), 55.1 (C-2), 59.4 ($CH_2C_6H_5$), 65.1 (C-2′), 108.2 (C-6a), 108.3 (C-10), 116.9 (C-5), 118.9 (C-7), 120.3 (C-8), 121.5 (C-9), 125.1 (C-6b), 127.0 (C-11a), 127.5 (C-*m*), 128.2 (C-*p*), 129.0 (C-*o*), 136.7 (C-*i*), 137.4 (C-10a), 149.5 (C-4), 166.5 (NCO), 170.8 ($CO_2$). *trans*-**13′b**: IR (NaCl) 1700, 1595, 1325, 1196, 747 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 200 MHz) $\delta$ 0.89 (s, 3H, $CH_3$), 1.03 (s, 3H, $CH_3$), 1.10–1.92 (m, 8H, 7H sultam, H-12), 2.20 (dm, $J=12.4$ Hz, 1H, H-12), 3.37 (s, 2H, $CH_2SO_2$), 3.50 (s, 3H, N-$CH_3$), 3.68 (s, 3H, $CH_3O$), 3.92 (d, $J=1.4$ Hz, 1H, H-1), 4.04 (m, 1H, H-6), 4.26 (dd, $J=7.8$, 4.4 Hz, 1H, $CHNSO_2$), 4.30 (br t, 1H, H-2), 4.52 (s, 2H, C$H_2C_6H_5$), 7.09–7.39 (m, 8H, ArH), 7.51 (s, 1H, H-4), 8.28 (d, $J=6.6$ Hz, 1H, H-7); $^{13}C$ NMR ($CDCl_3$, 50.3 MHz) $\delta$ 19.8 (C-9′), 20.8 (C-8′), 23.8 (C-6), 26.2 (C-12), 26.7 (C-5′), 29.6 (N-$CH_3$), 32.7 (C-6′), 37.0 (C-3′), 44.5 (C-1), 44.8 (C-4′), 47.5 (C-7′), 47.8 (C-1′), 52.6 ($CH_3O$), 52.7 (C-10′), 53.3 (C-2), 58.5 ($CH_2C_6H_5$), 65.1 (C-2′), 107.6 (C-6a), 108.2 (C-10), 116.8 (C-5), 119.1 (C-7), 121.3 (C-8), 121.6 (C-9), 125.5 (C-6b), 127.7 (C-11a), 127.9 (C-*m*), 128.2 (C-*p*), 129.0 (C-*o*), 136.0 (C-*i*), 137.3 (C-10a), 150.8 (C-4), 165.3 (NCO), 170.4 ($CO_2$).

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19. The experiment was done on an Enraf–Nonius CAD4 diffractometer using graphite monochromated Mo Kα radiation. The structure was solved by direct methods using SHELXS97 [Sheldrick, G. M. 1997, SHELX97. Programs for Crystal Structure Analysis (Release 97-2), University of Göttingen, Germany] after applying Lorentz, polarization, and absorption (semiempirical PSI scan method) corrections. Full-matrix least squares refinement (SHELXL-97) with anisotropic thermal parameters for non-H atoms and riding thermal parameters for H-atoms (positioned at calculated positions) converged to a $R$ factor of 0.0449 (calculated for the reflections with $I>2\sigma(I)$). Crystal data: $C_{35}H_{39}N_3O_5S$, hexagonal, space group $P3_1$, $a=18.168(3)$, $b=18.168(3)$, $c=8.318(2)$ Å, $V=2377.7$ Å$^3$, $Z=3$, $\mu$(Mo Kα)$=0.149$ mm$^{-1}$, $D_{calcd}=1.286$ g/cm$^3$. Data collection was up to a resolution of $2\theta=50.0°$ producing 7683 reflections. Largest peak and hole at the final difference Fourier synthesis were 0.156 and −0.198 e Å$^{-3}$. Calculations were done using the WinGX package (Farrugia, L. J. *J. Appl. Cryst.* **1999**, *32*, 837–838).