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Asymmetric syntheses of *N*-acetyl-(*R*)-coniine and *N*-Boc-(2*R*,6*R*)-solenopsin A via ring-closing metathesis†

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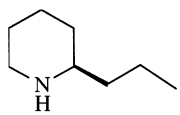
Abstract—Asymmetric syntheses of piperidine alkaloids *N*-acetyl-(*R*)-coniine and (2*R*,6*R*)-*trans*-solenopsin were achieved utilizing stereoselective additions of allylphenylsulfone to chiral alkyl-*N*-sulfinylimines and ring-closing olefin metathesis.

1. Introduction

Optically active piperidine alkaloids bearing a stereogenic carbon in the 2-position are an important group of natural products due to their potent biological activities and hence they have been the target of numerous synthetic strategies.[1] In our previous reports[2] we have described efficient protocols for the synthesis of homochiral 2-aryl substituted piperidines such as (*S*)-anatabine[2b] via stereoselective additions of functionalized allylsulfone carbanions to chiral aryl-*N*-sulfinylimines followed by substitution-induced ring closure. To further demonstrate the utility of our method, we undertook the synthesis of (*R*)-coniine **1**, the poisonous hemlock alkaloid and (2*R*,6*R*)-*trans*-solenopsin A **2**, a constituent of fire-ant venom. Except for some catalyst based asymmetric syntheses[3] of these alkaloids, most known strategies start from amino acids or substrates bearing chiral auxiliaries derived from the natural chiral pool.[4]



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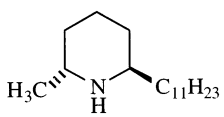

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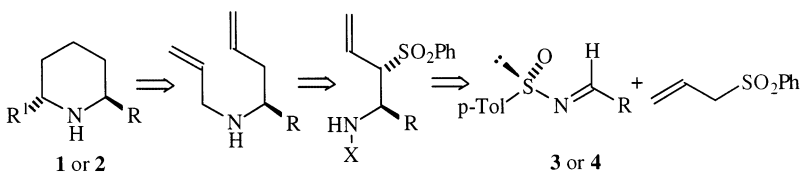
2. Results and discussion

An efficient retrosynthetic analysis (Fig. 1) leading to **1** and **2** suggested the use of non-racemic **3** or **4** and a ring-closing metathesis reaction (RCM). While Davis et al. have shown[5] that formation of chiral sulfinylimines, when R = aromatic, can be readily achieved, preparation of the alkyl analogs (R = alkyl) is more problematic. In fact, in our hands their previously reported procedure[5] for the condensation of (*S*)-*p*-toluenesulfonamide and laurinaldehyde yielded only a trace of **4**. The



1 or **2**

3 or **4**

1, R = C_3H_7; R^1 = H
2, R = $C_{11}H_{23}$; R = CH_3

3, R = C_3H_7
4, R = $C_{11}H_{23}$

Figure 1.

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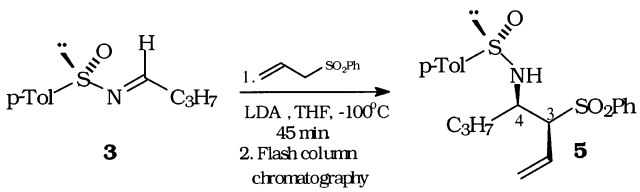
presence of Ti Lewis acids improved the yield of **4** to about 20% and the best yield of 45% was achieved when the condensation was carried out in the presence of 1 equivalent of $BF_3{\cdot}OEt_2$ and 4 Å molecular sieves. In our hands, following the Davis procedure using (*S*)-*p*-toluenesulfonamide, butanal and molecular sieves gave only 14% of **3**.[6] On the other hand, the one-pot procedure[5] improved the yield to 70%.

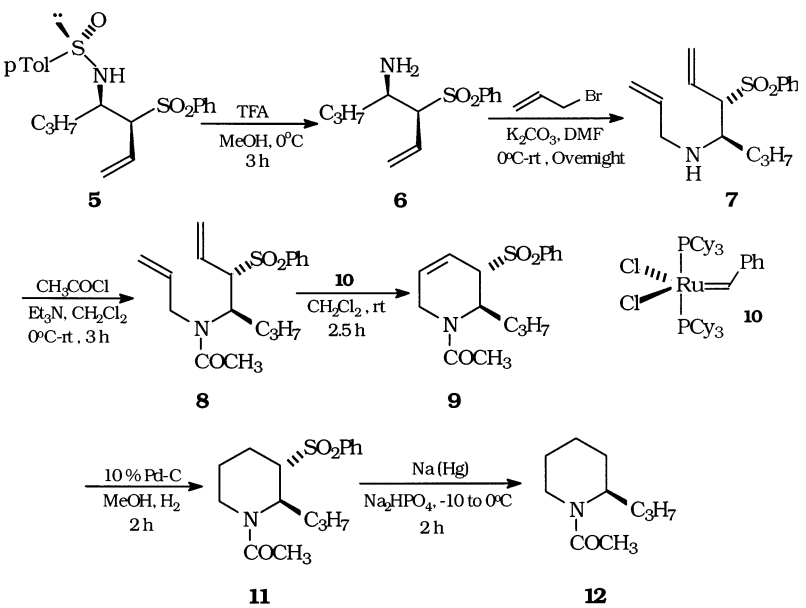
Our synthesis of coniine commences with the stereoselective addition of allylphenylsulfone, not bearing any additional functions, to sulfinylimine **3**. Allylphenylsulfone was deprotonated by lithium diisopropylamide (LDA) in THF at −100°C, followed by the addition of sulfinylimine **3** in THF to afford the product as a 1:1:3 mixture of three diastereomers of which the major isomer **5** was separated by flash column chromatography (Eq. (1)). Variation of the reaction conditions did not alter the diastereoselectivity appreciably. The ^{1}H NMR spectrum of **5** showed that the α-phenylsulfonyl proton appeared as a dd (J=10, 2.4 Hz). This fact, coupled with the 2D NOESY spectrum which showed a strong NOE effect between the hydrogens at C(3) and C(4), indicated the major isomer of **5** to possess the *anti*-stereochemistry in accordance with our earlier reports.[2]



(1)

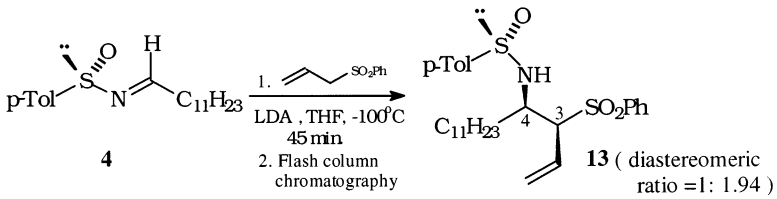
Desulfinylation of **5** by treatment with trifluoroacetic acid in methanol at 0°C afforded the amine **6**, as shown in Scheme 1. Monoallylation followed by protection of the secondary amine **7** to afford the acetamide **8** set the stage for metathesis ring closure. While neither amine **7** nor its hydrochloride salt underwent clean metathesis, treatment of a 0.1 M CH_2Cl_2 solution of the acetamide derivative **8** with 5 mol% of Grubbs catalyst **10** at room temperature for 2.5 h afforded **9** in excellent yield. In order to determine the absolute configurations of **9**, it was first necessary to establish the relative stereochemistry of the alkyl and phenylsulfonyl groups. ^{1}H NMR and NOESY experiments on **9** indicated a *trans* relationship, with the alkyl and $PhSO_2$ groups occupying pseudo diaxial positions since the C(5)H and C(6)H protons are in a *gauche* relationship ($J_{5,6}$ <1 Hz) in accordance with our previously reported arylpiperidines.[2] Reduction of the double bond to afford **11** and further reductive desulfonation afforded *N*-acetyl-(*R*)-coniine **12** whose absolute configuration as well as its enantiopurity were determined by comparing the optical rotation (vide experimental) value with that of the authentic sample prepared from (*S*)-coniine·HCl. Since we obtained compound **12** in enantiopure form, it is reasonable to assume that precursors **5**–**11** were also enantiopure. We did not attempt to hydrolyze the amide function due to the high volatility of **1**.[3a]

Next we decided to extrapolate the above reaction sequence to *trans*-solenopsin A, a 2,6-dialkylsubstituted piperidine by taking advantage of the known stereoselective C(6) methylation of the 2-substituted piperidine **22**[3] following Beak's α-lithiation procedure.[7] Addition of allylphenylsulfone to sulfinylimine **4** under the conditions described for **3** yielded the adduct as a mixture of three isomers whose ratio could not be ascertained because of the overlapping of the proton signals in the ^{1}H NMR spectrum. However, flash column chromatography afforded 1**3** as an inseparable 1:1.94 mixture of



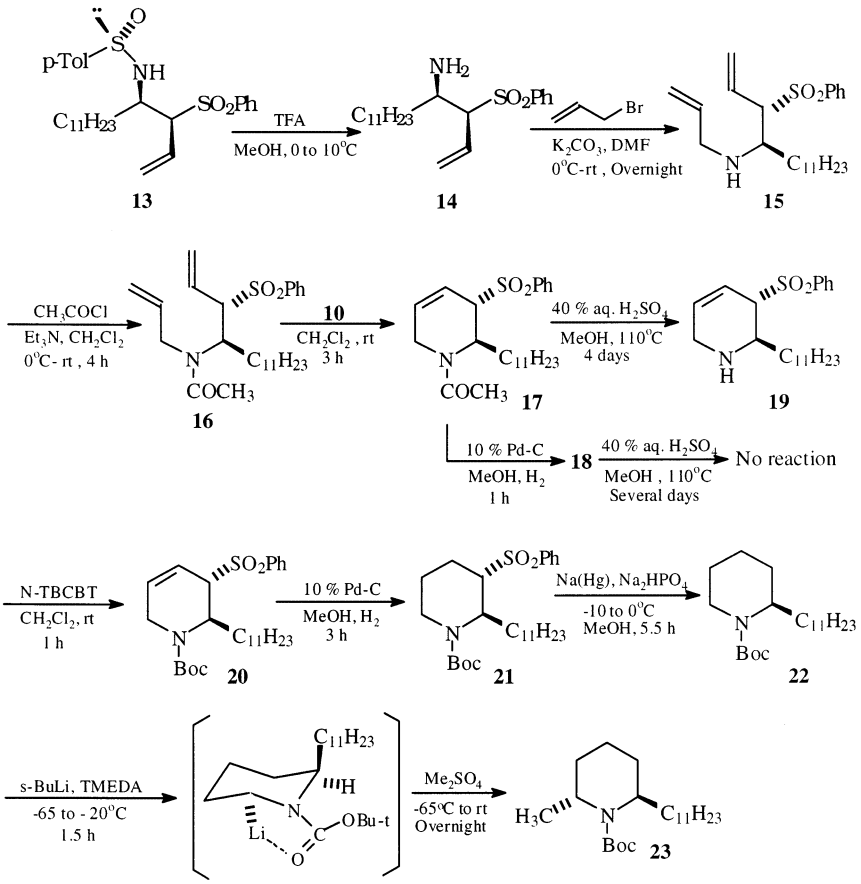
Scheme 1.

the major diastereomers in 52% isolated yield (Eq. (2)). Based on the coupling constants of C(3)H and C(4)H and also since both the isomers in mixture **13** showed similar 2D NOE patterns, we concluded that they are both *anti*-C(3)/C(4) diastereoisomers. The third isomer was isolated in 18% yield. The ratio of the major diastereomeric mixture was further confirmed from HPLC analysis of the carbamate derivative of the amine **14** by comparison with that of the racemic sample prepared via a different route. The diastereoselectivity during the allylphenylsulfone addition could not be improved further by varying the reaction conditions.



(2)

Desulfinylation followed by monoallylation of the amine **14** as for **6**, afforded compound **15** (Scheme 2). Treatment of either amine **15** or its hydrochloride salt with Grubbs catalyst did not lead to a clean metathesis reaction. Also, all our attempts to protect the secondary nitrogen in **15** using several Boc transfer reagents were not successful, presumably due to the extensive hydrogen bonding of the amino proton with one of the sulfonyl oxygens, rendering the amine more basic than nucleophilic. Hence, we resorted to protection of the amine group as the acetamide **16**, which was then subjected to metathesis ring closure using 5 mol% of catalyst **10** at room temperature. Using these conditions, the ring-closing metathesis reaction afforded tetrahydropyridine derivative **17** in 92% yield. Hydrogenation of the olefin using 10% Pd/C produced amide **18**. Since the Boc group on nitrogen is vital for the stereoselective methylation of **22** at C(6), it was necessary to hydrolyze amide **18** and re-protect the product amine as the *tert*-butyl carbamate derivative. Unfortunately, however, our attempts to hydrolyze the amide function in **18** using 40% H_2SO_4 in MeOH at 110°C for 1 week led only to the recovery of starting material. On the other hand, we were pleased to find that the hydrolysis of **17** under the above reaction conditions afforded piperidine **19** in good yield. Treatment of **19** with *N*-*tert*-butoxycarbonyloxybenzotriazole (TBCBT)[8] in CH_2Cl_2 at room temperature yielded carbamate **20** in quantitative yield. All the above con-



Scheme 2. *N*-TBCBT = *N*-*tert*-butoxycarbonyloxybenzotriazole.

versions **13** through **20** were carried out on the inseparable ca. 1:1.9 mixture of isomers. Further, reductive removal of the sulfonyl group in **21** using Na/Hg provided the known **22** whose enantiomeric purity was found to be nearly 30% by comparing the specific rotation with that of the known compound.[3a] Lithiation of **22** with *sec*-BuLi/TMEDA, followed by treatment with dimethylsulfate following the procedure of Buchwald et al.,[3a] afforded *N*-Boc-(2*R*,6*R*)-solenopsin **23** with an e.e. of 30%. The optical purity and the absolute configuration were determined by comparing the specific rotation value with that of the known literature value.

3. Conclusions

A straightforward synthesis of both (*R*)-coniine and (2*R*,6*R*)-*trans*-solenopsin A derivatives **12** and **23** was achieved utilizing stereoselective additions of simple allylphenylsulfone to chiral non-racemic alkyl-*N*-sulfinylimines and ring-closing metathesis reactions as key steps. This methodology, which does not rely on amino acids as a chirality source, should also be applicable to procure the enantiomers of **12** and **23** by employing (*R*)-sulfinylimines.

4. Experimental

4.1. General

All air and moisture sensitive reactions were carried out in flame-dried, argon-flushed, two necked flasks sealed with rubber septa, and the dry solvents, reagents were introduced with a syringe. Tetrahydrofuran (THF) was freshly distilled from sodium/benzophenone. Reactions with cooling at −100°C were performed using a mixture of liquid nitrogen and MeOH. Flash column chromatography was carried out on Merck silica gel 60 (230–400 mesh), and pre-coated Merck silica gel plates (60F-25H) were used for TLC. Unless otherwise mentioned ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker AM-300 spectrometer. Coupling constants were determined directly from ^{1}H NMR spectra. Mass spectra (CI) were recorded at 60–70 eV. Optical rotations were measured on a Perkin Elmer 141 polarimeter with path length of 0.1 dm. Sulfinylimine **3** was prepared by following the Davis procedure.[5]

4.2. Preparation of (*S*)-(+)-*N*-dodecylidene-*p*-toluenesulfinamide 4

In a two-necked, round-bottomed flask equipped with a magnetic stirring bar, rubber septum and an argon inlet was placed powdered, freshly activated 4 Å molecular sieves (2 g) and (*S*)-(+)-*p*-toluenesulfinamide[6] (155 mg, 1 mmol). A solution of laurinaldehyde (184 mg, 1 mmol) in CH_2Cl_2 (6 mL) was introduced and the resultant mixture was cooled at −5°C. $BF_3{\cdot}OEt_2$ was introduced neat and the reaction mixture was stirred for 1 h, while maintaining the temperature between 0 and −5°C. The reaction mixture was quenched with water (1 mL) and filtered on a pad of $MgSO_4$ to remove the molecular sieves, and the filtrate was extracted with CH_2Cl_2 (3×15 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated to afford a crude product which was purified by flash column chromatography (8% EtOAc in *n*-hexane) to afford **4** (145 mg, 45%). $[\alpha]_D^{25}$ +176.3 (*c* 1.9, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 8.22 (t, $J=6$ Hz, 1H), 7.55 (d, $J=8.15$ Hz, 2H), 7.29 (d, $J=8.15$ Hz, 2H), 2.51–2.42 (m, 2H), 2.4 (s, 3H), 1.62–1.55 (m, 2H), 1.4–1.2 (m, 16H), 0.88 (t, $J=8$ Hz, 3H); ^{13}C NMR δ 167.4, 141.6, 141.5, 129.8, 124.6, 35.9, 31.9, 29.6, 29.5, 29.4, 29.3, 29.1, 28.9, 25.4, 22.7, 21.4, 14.1.

4.3. (3*S*)-Phenylsulfonyl-(4*R*)-[*N*-(*p*-tolylsulfinyl)-amino]hept-1-ene 5

In a two-necked, round-bottomed flask equipped with an argon inlet, rubber septum and a stirring bar was placed diisopropylamine (0.27 mL, 1.9 mmol) in THF (3 mL). At −50°C, *n*-BuLi (1.6 M in hexane, 1.08 mL, 1.73 mmol) was added and stirred for 15 min at the same temperature. The flask was further cooled to −100°C and a solution of allylphenylsulfone (315 mg, 1.73 mmol) in THF (9 mL) was added dropwise. After 15 min a solution of sulfinylimine **3** (300 mg, 1.44 mmol) in THF (5 mL) was introduced dropwise along the sides of the flask. After stirring the mixture for 45 min, the reaction was quenched with aq. NH_4Cl (1 mL) and extracted thoroughly with CH_2Cl_2 (3×20 mL). The combined organic part was washed with brine, dried ($MgSO_4$) and concentrated. Purification of the crude product by flash column chromatography (22% EtOAc in hexane) yielded the major isomer **5** as a viscous oil (293 mg, 52%). $[\alpha]_D^{25}$ +141.4 (*c* 1.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.92–7.85 (m, 2H), 7.65 (d, $J=8.4$ Hz, 1H), 7.64 (tt, $J=8.2$, 1.5 Hz, 2H), 7.53 (d, $J=8.4$ Hz, 2H), 7.3 (d, $J=8.4$ Hz, 2H), 5.85 (dt, $J=16.8$, 10.2 Hz, 1H), 5.26 (dd, $J=10.2$, 1.2 Hz, 1H), 5.04 (d, $J=10.2$ Hz, 1H, exchangeable with D_2O), 4.95 (d, $J=16.8$ Hz, 1H), 4.27 (dd, $J=9.9$, 2.4 Hz, 1H), 3.73 (tdd, $J=9.6$, 4.8, 2.7 Hz, 1H), 2.41 (s, 3H), 1.87–1.77 (m, 1H), 1.65–1.57 (m, 1H), 1.48–1.35 (m, 1H), 1.05–0.9 (m, 1H), 0.74 (t, 3H); ^{13}C NMR ($CDCl_3$) δ 141.4, 140.9, 138.7, 133.7, 129.7, 128.9, 128.8, 127.8, 126.1, 124.6, 73.4, 55.7, 34.9, 21.4, 19.5, 13.5. HRMS observed mass = 392.133469 (for MH^+, calculated value = 392.135413). Two minor diastereomers were obtained only in impure form and were not further characterized.

4.4. (4*R*)-Amino-(3*S*)-phenylsulfonylhept-1-ene 6

In a single-necked, round-bottomed flask equipped with a magnetic stirring bar and a rubber septum was placed a solution of the sulfinylimine **4** (250 mg, 0.64 mmol) in MeOH (6 mL) at 0°C under an Ar atmosphere. Trifluoroacetic acid (0.2 mL, 2.56 mmol) was added dropwise and the resultant solution was stirred at the same temperature for 3 h until a total disappearance of the starting material. The reaction mixture was then concentrated and the residual oil was dissolved in CH_2Cl_2 and transferred into a beaker. The beaker was immersed in an ice bath and a saturated aqueous $NaHCO_3$ was added until the pH rose to 8. The con-

tents of the beaker was transferred into a separatory funnel and extracted thoroughly with CH_2Cl_2 (3×20 mL). The combined organic extract was then washed with brine, dried ($MgSO_4$) and concentrated. Purification of the crude product by flash column chromatography (80% EtOAc in hexane) afforded the title compound as a colorless oil (140 mg, 87%). $[\alpha]_D^{25}$ −73.1 (*c* 1.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.87–7.83 (m, 2H), 7.64 (tt, J=7.8, 2.1 Hz, 1H), 7.54 (tt, J=7.8, 2.1 Hz, 2H), 6.04 (dt, J=17.1, 10.2 Hz, 1H), 5.36 (dd, J=10.2, 0.6 Hz, 1H), 4.96 (dt, J=17.1, 0.6 Hz, 1H), 3.76 (td, J=5.7, 2.1 Hz, 1H), 3.42 (dd, 10.2, 1.8 Hz, 1H), 1.76 (br, exchangeable with D_2O, 2H), 1.39–1.32 (m, 4H), 0.87 (t, J=7 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 141.1, 138.3, 134.1, 129.3, 126.6, 125.7, 74.2, 49.4, 38.1, 19.5, 14.2. HRMS observed mass=254.121693 (for MH^+, calculated value=254.121476).

4.5. (4*R*)-*N*-(2-Propenyl)amino-(3*S*)-phenylsulfonylhept-1-ene 7

Into a single-necked round-bottomed flask equipped with a magnetic stirring bar and a rubber septum was placed K_2CO_3 (135 mg, 0.98 mmol) in DMF (2 mL) at 0°C under an Ar atmosphere. Solutions of amine **6** (124 mg, 0.49 mmol), allyl bromide (71 mg, 0.59 mmol) in DMF (2, 0.5 mL) were added successively and the reaction mixture was brought to room temperature and stirred overnight. The mixture was quenched by adding water (0.5 mL) and then extracted with ether (3×15 mL). The combined ethereal part was washed with brine, dried ($MgSO_4$) and concentrated. Purification of the crude product by flash column chromatography (20% EtOAc in hexane) gave **7** as a colorless oil (104 mg, 73%). $[\alpha]_D^{25}$ −48.2 (*c* 0.85, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.87–7.83 (m, 2H), 7.64 (tt, J=7.2, 1.8 Hz, 1H), 7.53 (tt, J=8.4, 1.2 Hz, 2H), 6 (dt, J=17.1, 10.2 Hz, 1H), 5.9 (ddt, J=17.1, 10.2, 6 Hz, 1H), 5.35 (dd, J=10.2, 1.2 Hz, 1H), 5.2 (dq, J=17.1, 1.2 Hz, 1H), 5.12 (dt, J=10.2, 1.5 Hz, 1H), 4.96 (dt, J=17.1, 1.5 Hz, 1H), 3.57 (dd, J=10, 2.4 Hz, 1H), 3.46–3.25 (m, 3H), 1.7–1.5 (m, 2H), 1.31–1.24 (m, 2H), 0.89 (t, J=7 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 139.5, 136.5, 133.6, 129, 128.4, 127.3, 125, 116.3, 72.5, 55.6, 50.4, 34.6, 19.3, 13.9. HRMS observed mass=293.144964 (for MH^+, calculated value=293.144951).

4.6. (4*R*)-*N*-(2-Propenyl)-*N*-acetylamino-(3*S*)-phenylsulfonylhept-1-ene 8

To a stirred solution of **7** (0.75 mmol, 220 mg) in CH_2Cl_2 (5 mL) at 0°C under an Ar atmosphere was added dropwise Et_3N (0.16 mL, 1.13 mmol) followed by freshly distilled CH_3COCl (60 μl, 0.9 mmol). The resultant mixture was allowed to warm to room temperature, stirred for 3 h, when complete disappearance of **7** with appearance of a polar spot on TLC was observed. Cold water (1 mL) was added to quench the reaction and the mixture was extracted with EtOAc (3×20 mL). The combined organic part was washed with brine, dried ($MgSO_4$) and concentrated. Purification of the crude product by flash column chromatography (50% EtOAc in hexane) afforded pure **8** as a 1:1 mixture of two rotamers (200 mg, 80%, sticky solid). $[\alpha]_D^{25}$ −30 (*c* 2, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.81 (d, J=7.8 Hz, 2H), 7.64 and 7.62 (2t, 7.5 Hz, 1H), 7.54 and 7.52 (2t, J=7.8 Hz, 2H), 5.88 and 5.54 (m, dt, J=18, 10.2 Hz, 1H), 5.76 (m, 1H), 5.23 (br d, J=13 Hz, 1H), 5.15 (d, J=10.2 Hz, 1H), 5.13 and 4.82 (2d, J=18, 17 Hz), 5.06 (d, J=10.2 Hz, 1H), 4.08 and 4.49 (dd and dt, J=15.2, 4.8 Hz and 8.46, 2.76 Hz, 1H), 3.77 (br, 2H), 3.09 and 3.63 (2dd, J=15.2, 7.5 and 10.4, 8.4 Hz, 1H), 2.18 (m, 1H), 2.2 and 2 (2s, 3H), 1.78 (m, 1H), 1.33 (m, 2H), 0.93 (t, J=7.4 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 171.1, 139.8, 135.6, 134 and 133.4, 123, 129.7 and 128.6, 127.7 and 127.3, 125.8, 126.5, 73.7 and 73.6, 57, 46, 37.1, 34.2, 22.9 and 22.6, 14.6. HRMS observed mass=336.162590 (for MH^+ calculated value=336.163341).

4.7. *N*-Acetyl (5*S*)-phenylsulfonyl-(6*R*)-*n*-propyl-1,2,5,6-tetrahydropyridine 9

In a two-necked flask equipped with an argon inlet, a magnetic stirring bar and a rubber septum was placed Grubbs catalyst **10** (24 mg, 0.029 mmol, 5 mol%). A solution of **8** (191 mg, 0.57 mmol) in CH_2Cl_2 (6 mL) was introduced at room temperature and the resultant pink solution was stirred for 2.5 h when TLC analysis indicated complete consumption of **8**. The reaction mixture was exposed to air and concentrated. Purification by flash column chromatography (50% EtOAc in hexane) afforded **9** (160 mg, 92%). $[\alpha]_D^{25}$ +196 (*c* 1.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.88, 7.77 (2t, J=7 Hz, 2H), 7.64–7.6 (m, 1H), 7.56–7.5 (m, 2H), 6.08–6.02 (m, 1H), 5.45–5.41 (m, 1H), 5.28 and 4.75 (2t, J=6 Hz, 1H), 4.25 and 3.26 (2m, 1H), 3.6–3.75 (m, 2H), 2.25 and 1.76 (2s, 3H), 1.5–1.1 (m, 4H), 0.94 and 0.83 (2t, J=7 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 169.6 and 169.4, 137.1 and 136.7, 134 and 133.7, 132.1, 130 and 129.7, 128.9 and 128.6, 116.8 and 115.4, 73.5 and 73, 50.6 and 44.9, 42 and 38.5, 35 and 34.1, 30 and 21.6, 19.3 and 19.1, 13.8 and 13.6. HRMS observed mass=307.124416 (for MH^+, calculated mass=307.124216).

4.8. *N*-Acetyl (2*R*)-*n*-propyl-(3*S*)-phenylsulfonylpiperidine 11

In a two-necked flask equipped with a one way stopcock attached to a H_2 balloon, and a rubber septum was placed 10% Pd-C (50 mg). A solution of **10** (126 mg, 0.41 mmol) in MeOH (5 mL) was introduced and the resultant black suspension was stirred under a H_2 atmosphere for 2 h, when total disappearance of the starting material with formation of a non-polar spot was seen by TLC analysis. The reaction mixture was exposed to air and filtered through a pad of $MgSO_4$ and concentrated. Purification by flash column chromatography (50% EtOAc in hexane) afforded **11** as a mixture of two rotamers (110 mg, 87%). $[\alpha]_D^{25}$ −16 (*c* 2.25, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 8.02–7.99 (m, 2H), 7.88 (t, J=1.5 Hz, 1H), 7.66–7.58 (m, 2H), 5.17, 4.74 and 4.59 (t, J=7.8 Hz, dd, J=8.7, 6 Hz, and dt, J=13.2, 4.8 Hz, 1H), 3.69 and 3.13 (br d, J=13.2 Hz, and td, J=12.3, 3.3 Hz, 1H), 2.98–2.5 (m, 2H), 2.28 and 2.12 (2s, 3H), 2.05–1.89 (m, 4H), 1.6–1.3 (m, 3H),

1.2–0.98 (m, 1H), 0.92 and 0.73 (2t, $J=7.2$ Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 170.4 and 170, 138.3 and 138.2, 134.4 and 134.1, 129.8 and 129.7, 129.5 and 128.8, 62.1 and 61, 50.8 and 45.8, 41.3 and 33.1, 35.5 and 34.7, 22.1 and 21.4, 20.1 and 19.8, 19.6, 19.2 and 18.9, 14.1 and 13.7. HRMS observed mass = 310.150597 (for MH^+, calculated mass = 310.147691).

4.9. *N*-Acetyl (*R*)-coniine 12

In a two-necked flask equipped with a rubber septum, an Ar inlet and a magnetic stirring bar was placed **11** (87 mg, 0.28 mmol) and anhydrous Na_2HPO_4 (159 mg, 1.12 mmol) in MeOH (4 mL) at −10°C under an Ar atmosphere. Freshly prepared Na(Hg) (6%, 150 mg) was added in one portion and the resultant mixture was stirred at 0°C for 2 h, when total disappearance of the starting material was seen by TLC analysis. Ice-cold water (1 mL) was added to quench the reaction mixture, which was then filtered through a pad of $MgSO_4$ and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (30 mL), washed with brine and dried ($MgSO_4$). Evaporation of the solvent afforded the crude product, which was purified by flash column chromatography (25% EtOAc in hexane) to afford a colorless oil of **12** as a mixture of two rotamers (29 mg, 62%). $[\alpha]_D^{25}$ −48.6 (*c* 0.72, $CHCl_3$); [an authentic *N*-acetyl *S*-coniine sample prepared from *S*-coniine·HCl had $[\alpha]_D^{25}$ +46.9 (*c* 0.4, $CHCl_3$)]. ^{1}H NMR ($CDCl_3$) δ 4.78 and 4.54–4.46 (br and m, 1H), 3.85 and 3.59–3.55 (br and m, 1H), 3.11 and 2.58 (2br t, $J=12$ Hz, 1H), 2.23 and 2.09 (2s, 3H), 1.62–1.26 (m, 10H), 0.94 and 0.92 (2t, $J=7$ Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 169.8 and 169, 52.9 and 46.8, 40.9 and 35.4, 31.4 and 30.6, 28.1 and 27, 25.3 and 24.4, 20.8 and 20.5, 18.6 and 18.4, 18, 13.1. HRMS observed mass = 169.146002 (for M^+, calculated mass = 169.146664).

4.10. (3*S*)-Phenylsulfonyl-(4*R*)-[*N*-(*p*-tolylsulfinyl)-amino]pentadec-1-ene 13

A similar procedure was followed as in the case of **5** starting from **4** (401 mg, 1.25 mmol), allylphenylsulfone (273 mg, 1.5 mmol), *n*-BuLi (1.6 M, 0.94 mL, 1.5 mmol) and diisopropylamine (0.23 mL, 1.65 mmol) to obtain **13** (327 mg, 52%, inseparable mixture of two diastereomers in a 1:1.94 ratio) as the major product after flash column chromatographic purification (14% EtOAc in hexane). $[\alpha]_D^{25}$ +108 (*c* 1.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.88 (tt, $J=7$, 1.2 Hz, 2H×2), 7.67–7.62 (m, 3H×2), 7.57–7.5 (m, 2H×2), 7.32 and 7.29 (2d, $J=8$ Hz, 2H×2), 5.92 and 5.87 (2dt, $J=16.2$, 10.2 Hz, 1H×2), 5.41 and 5.12 (d, $J=9$ Hz, 1H×2, exchangeable with D_2O), 5.31 and 5.25 (dd, $J=10.2$ Hz, 1.2 Hz, 1H×2), 4.95 and 4.93 (d, $J=16.5$ Hz, 1H×2), 4.29 and 4.2 (2dd, $J=9.9$, 2.1 Hz, 1H×2, ratio 1:1.94), 3.73–3.68 (m, 1H×2), 2.3–2 (m, 1H×2), 1.85–1.8 (m, 1H×2), 1.7–1.55 (m, 1H×2), 1.4–1.1 (m, 19H×2), 1.1–0.95 (m, 1H×2), 0.89 (br t, $J=7$ Hz, 3H×2); ^{13}C NMR ($CDCl_3$) δ 139.9, 138, 137, 131.9, 128.1, 127.4, 127.2, 125.3, 124.9, 124.6, 72.7, 49.9, 30.4, 29.7, 28.1, 28, 27.8, 27.3, 24.2, 21.1, 19.8, 12.5. HRMS observed mass = 503.252688 (for M^+, calculated mass = 503.252688).

4.11. (4*R*)-Amino-(3*S*)-phenylsulfonylpentadec-1-ene 14

The experimental procedure used for **6** led to **14** (125 mg, 96%) from reaction of **13** (181 mg, 0.36 mmol) in MeOH (4 mL) and TFA (0.12 mL) at 0–10°C after 3 h. $[\alpha]_D^{25}$ −15.3 (*c* 1.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.85 (dt, $J=7.2$, 1.2 Hz, 2H), 7.64 (tt, $J=7.5$ Hz, 1.2 Hz, 1H), 7.54 (tt, $J=7.2$, 1.2 Hz, 2H), 6.04 (dt, $J=17.1$, 10.2 Hz, 1H), 5.37 (dd, $J=10.2$, 1.5 Hz, 1H), 4.96 (dd, $J=17.1$, 1.5 Hz, 1H), 3.7 (br, 1H), 3.44 (dd, $J=10.2$, 1.5 Hz, 1H), 1.96 (d, $J=5$ Hz, 2H, exchangeable with D_2O), 1.36–1.24 (m, 20H), 0.88 (t, $J=7$ Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 138.3, 134.1, 129.3, 129.2, 126.6, 125.7, 74.1, 49.7, 35.9, 32.3, 30, 29.9, 29.8, 29.7, 29.5, 29.2, 26.3, 23.1, 14.5. HRMS observed mass = 366.246036 (for MH^+, calculated mass = 366.246677).

4.12. (4*R*)-*N*-(2-Propenyl)amino-(3*S*)-phenylsulfonylpentadec-1-ene 15

Experimental procedure was the same as in the case of **7** to afford **15** (95 mg, 70%) from reaction of **14** (122 mg, 0.334 mmol), allyl bromide (48 mg, 0.4 mmol), K_2CO_3 (92 mg, 0.668 mol) in DMF (4 mL) after overnight stirring. The product was isolated by flash column chromatography (22% EtOAc in hexane). $[\alpha]_D^{25}$ −15.8 (*c* 1.9, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.84 (dt, $J=7$, 1.5 Hz, 2H), 7.63 (tt, $J=7.5$, 1.2 Hz, 1H), 7.53 (tt, 6.3, 1.5 Hz, 2H), 6 (dt, $J=17.1$, 10.2 Hz, 1H), 5.89 (ddt, $J=17.1$, 10.2, 6 Hz, 1H), 5.41 (dd, $J=10.2$, 1.2 Hz, 1H), 5.19 (dq, $J=17.1$, 1.5 Hz, 1H), 5.1 (dq, $J=10.2$, 1.5 Hz, 1H), 4.97 (dd, $J=17.1$, 0.6 Hz, 1H), 3.57 (dd, $J=9.9$, 2.4 Hz, 1H), 3.42–3.99 (m, 1H), 3.33 (qdt, $J=16.2$, 6.3, 1.5 Hz, 2H), 1.9–1.6 (2m, 2H), 1.36–1.24 (m, 18H), 0.88 (t, $J=6.9$ Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 138.7, 137, 133.9, 129.4, 129.1, 127.7, 125.3, 116.5, 72.9, 56.2, 50.7, 32.8, 32.3, 30, 29.9, 29.8, 29.7, 29.4, 29, 26.3, 23.1, 14.5. HRMS observed mass = 405.270253 (for M^+, calculated mass = 405.270152).

4.13. (4*R*)-*N*-(2-Propenyl)acetamido-(3*S*)-phenylsulfonylpentadec-1-ene 16

A similar experimental procedure was followed as in the case of **8** to afford **16** (160 mg, 81%) as a mixture of two rotamers from **15** (178 mg, 0.44 mmol), CH_3COCl (52 mg, 0.66 mmol) and Et_3N (89 mg, 0.88 mmol) in CH_2Cl_2 (4 mL) at 0°C to room temperature. The product was purified by flash column chromatography (30% EtOAc in hexane). $[\alpha]_D^{25}$ −3.6 (*c* 3.9, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.84 (dt, $J=7$, 1.5 Hz, 2H), 7.62 (tt, $J=7.5$, 1.2 Hz, 1H), 7.51 (tt, 6.3, 1.5 Hz, 2H), 5.93–5.71 (m, 1H), 5.53 (dt, $J=17.1$, 10.2 Hz, 1H), 5.22 (br d, $J=16$ Hz, 1H), 5.13 (d, $J=10.2$ Hz, 1H), 5.08 (d, $J=10.2$ Hz, 1H), 4.82 (d, $J=17.1$ Hz, 1H), 4.48 (td, $J=10$, 2.7 Hz, 1H), 4.06 and 3.1 (2dd, $J=15.3$ and 4.8 Hz, $J=15.3$ and 7.5 Hz, 1H), 3.76 (br, 1H), 3.64 (dd, $J=10.2$, 8.4 Hz, 1H), 2.2 and 2 (2s, 3H), 1.8–1.6 (m, 2H), 1.4–1.15 (m, 18H), 0.88 (t, $J=7$ Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 172, 138.2, 134.6 and 134, 133.7, 129.9, 129.1 and 128.9, 128.7 and 128.6, 124.8 and 123.5, 116, 73.7 and 73.5, 57.5, 46.2, 33.9, 31.9, 29.6, 29.5, 29.4, 29.3, 29, 28.7, 28.6, 26.1, 22.7 and 22.4, 14.1.

HRMS observed mass = 447.280626 (for M^+, calculated value = 447.280716).

4.14. *N*-Acetyl-(5*S*)-phenylsulfonyl-(6*R*)-*n*-undecyl-1,2,5,6-tetrahydropyridine 17

The experimental procedure as used for **9** led, after stirring a solution of **16** (99 mg, 0.22 mmol) with Grubbs catalyst (9 mg, 0.011 mmol) in CH_2Cl_2 (2.5 mL) at room temperature for 2 h under an Ar atmosphere, to **17** (85 mg, 92%) as a mixture of two rotamers (ratio = 1:1.1 at room temperature) after flash column chromatography (56% EtOAc in hexane). $[\alpha]_D^{25}$ +52.5 (*c* 1.6, $CHCl_3$); δ 7.84 (dt, J = 7, 1.5 Hz, 2H), 7.62 (tt, J = 7.5, 1.2 Hz, 1H), 7.51 (tt, J = 6.3, 1.5 Hz, 2H), 6.08–6.01 and 5.7–5.6 (2m, 2H), 5.23 and 4.7 (2t, J = 6 Hz, 1H), 4.2 and 3.2 (2br d, J = 3 Hz, 1H), 3.7–3.64 (m, 2H), 2.25 and 1.76 (2s, 3H), 1.65–1.5 (m, 2H), 1.4–1.05 (m, 18H), 0.88 (t, J = 7 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 170.2 and 169.8, 137.4 and 137, 134.3 and 133.9, 132.4 and 130.4, 130 and 128.9, 129.3 and 129.2, 117 and 115.7, 65.5 and 64.5, 51 and 45.4, 42.3, 38.8, 33.2, 32.2, 32.1, 29.8, 29.7, 29.6, 29.5, 29.3, 26.2 and 26.1, 22.9, 22.2 and 21.8. HRMS observed mass = 419.249317 (for M^+, calculated mass = 419.249416).

4.15. (5*S*)-Phenylsulfonyl-(6*R*)-*n*-undecyl-1,2,5,6-tetrahydropyridine 19

In a single-necked round-bottomed flask equipped with a reflux condenser and a magnetic stirring bar was placed a methanolic solution of **17** (72 mg, 0.17 mmol in 1.5 mL of MeOH) and aq. 40% H_2SO_4 (3 mL) and the mixture was heated at 110°C for 4 days under an Ar atmosphere. TLC analysis indicated formation of a non-polar spot characteristic of an amine in addition to a small amount of the starting material, which did not reduce further with time. The reaction mixture was cooled to 0°C, and a saturated solution of aq. $NaHCO_3$ was added dropwise until the pH rose to 8. Extraction with CH_2Cl_2 (3×15 mL), washing of the organic layer with brine and drying over $MgSO_4$ afforded a crude mass, which was purified by flash column chromatography (22% EtOAc in hexane) to afford **19** (36 mg) and starting material (20 mg). Yield = 77%, based on recovered starting material. $[\alpha]_D^{25}$ +38 (*c* 1.05, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.9 (dq, J = 7.8, 0.6 Hz, 2H), 7.68 (tt, J = 7.2, 0.6 Hz, 1H), 7.58 (td, J = 6.9, 0.6 Hz, 2H), 6.22 (br d, J = 9.6 Hz, 1H), 5.65 (m, 1H), 3.46 (t, J = 7 Hz, 1H), 3.35 (br, 1H), 3.23 (br, 2H), 2.28 (br, 1H, exchangeable with D_2O), 1.59–1.54 (m, 1H), 1.42–1.2 (m, 19H), 0.88 (t, J = 7 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 137.4, 134.9, 134.1, 129.3, 128.9, 116.1, 61.5, 53.4, 49.7, 39.6, 31.9, 30.9, 29.7, 29.6, 29.5, 29.3, 29.1, 26, 22.7, 14.1.

4.16. *N*-Boc-(5*S*)-phenylsulfonyl-(6*R*)-*n*-undecyl-1,2,5,6-tetrahydropyridine 20

To a stirred solution of **19** (45 mg, 0.12 mmol) in CH_2Cl_2 (2 mL) was added *tert*-butoxycarbonyloxybenzotriazole (35 mg, 0.15 mmol), and the resulting mixture was stirred at rt under an Ar atmosphere for 1 h when total disappearance of the starting material with formation of a non-polar TLC spot was observed. Concentration of the reaction mixture under reduced pressure followed by flash column chromatographic purification (17% EtOAc in hexane) afforded pure **20** as a mixture of two rotamers as a colorless oil (57 mg, quantitative). $[\alpha]_D^{25}$ +29.6 (*c* 2.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.85 (dt, J = 7.2, 0.6 Hz, 2H), 7.61–7.45 (2m, 3H), 6–5.7 (2m, 2H), 4.9–4.75 (m, 1H), 3.85–3.6 (m, 2H), 3.3 (td, J = 6.9, 0.6 Hz, 1H), 1.62 and 1.52 (2s, 9H), 1.35–1.05 (m, 20H), 0.88 (t, J = 7 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 156, 137.8 and 137.2, 134.1 and 133.8, 132.1 and 131.7, 130 and 129.8, 129 and 128.9, 116, 80.9 and 80.4, 65.8 and 65.2, 48.8 and 47.5, 40.6 and 39.7, 33.2 and 32.7, 32.3, 30 and 29.9, 29.7, 29.6, 28.9, 28.8, 27.9, 26.3, 26.1, 23.1, 14.5.

4.17. *N*-Boc-(2*R*)-*n*-undecyl-(3*S*)-phenylsulfonylpiperidine 21

An experimental procedure as used in the case of **11** to afford **21** (56 mg, 93%) from **20** (60 mg, 0.126 mmol) and 10% Pd-C (30 mg). After stirring the reaction mixture under a H_2 atmosphere for 3 h, filtration and evaporation, purification by flash column chromatography (20% EtOAc in hexane) afforded **21** as a mixture of two rotamers. $[\alpha]_D^{25}$ −6.7 (*c* 0.75, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 8–7.92 (m, 2H), 7.68–7.54 (2m, 3H), 4.75–4.65 (2m, 1H), 4.15–3.9 (2m, 1H), 2.87–2.5 (3m, 2H), 2.3–1.85 (2m, 2H), 1.8–1.55 (m, 2H), 1.65 and 1.5 (2s, 9H), 1.3–1 (m, 20H), 0.88 (t, J = 6 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 156.1, 138, 133.9, 129.5, 129, 80.2 and 80.1, 61.9 and 61.3, 48.5, 38, 32.2, 31.9, 29.9, 29.8, 29.7, 29.3, 28.8, 27.2, 26, 23, 20.4, 18.3, 18, 14.5.

4.18. *N*-Boc-(2*R*)-*n*-undecylpiperidine 22

A similar experimental procedure was followed as in the case of **12** to afford **22** (20 mg, 56%) from **21** (29 mg, 0.06 mmol), Na(Hg) (30 mg) and Na_2HPO_4 (34 mg, 0.12 mmol) in MeOH (3 mL). The product was isolated by flash column chromatography (15% EtOAc in hexane). The ^{1}H and ^{13}C NMR spectra of this compound matched the reported literature values. $[\alpha]_D^{25}$ −6.4 (*c* 1.5, CH_2Cl_2), 30% e.e.; lit.[3a] for **22** with 99% e.e., $[\alpha]_D^{25}$ −21.2 (*c* 4.4, CH_2Cl_2).

4.19. (2*R*,6*R*)-(−)-*trans*-*N*-(*tert*-Butoxycarbonyl)-2-undecyl-6-methylpiperidine [(2*R*,6*R*)-(−)-*trans*-*N*-Boc-solenopsin A] 23

This compound was prepared by methylation of **22** according to the procedure of Buchwald et al.[3a] The product was isolated by flash column chromatography (10% EtOAc in hexane). Yield = 81%. $[\alpha]_D^{25}$ −7.9 (*c* 2, CH_2Cl_2) 30% e.e.; lit.[3a] for **23** with 99% e.e., $[\alpha]_D^{25}$ −26.3 (*c* 4.7, CH_2Cl_2).

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