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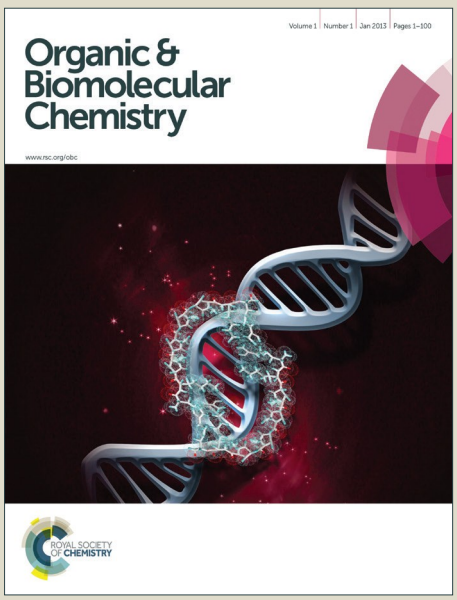

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Stereoselective total synthesis of (-)-Nupharamine utilizing an α-chlorosulfide and a sulfinimine for C-C bond formation.

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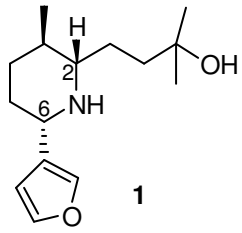
Abstract. An efficient stereoselective synthesis of the nuphar alkaloid, (-)-nupharamine is reported. The key features include the Lewis acid catalyzed reaction of an α-chlorosulfide with a silyl ketene acetal for C-C bond formation, creation of the stereocenter at C2 by a diastereoselective reaction of allyl indium with a sulfinimine and reductive amination for the introduction of the C6 stereocenter of the piperidine ring.

Keywords.

Nupharamine, α-chloro sulfide, sulfinimine, reductive amination, cross-metathesis.

Introduction.

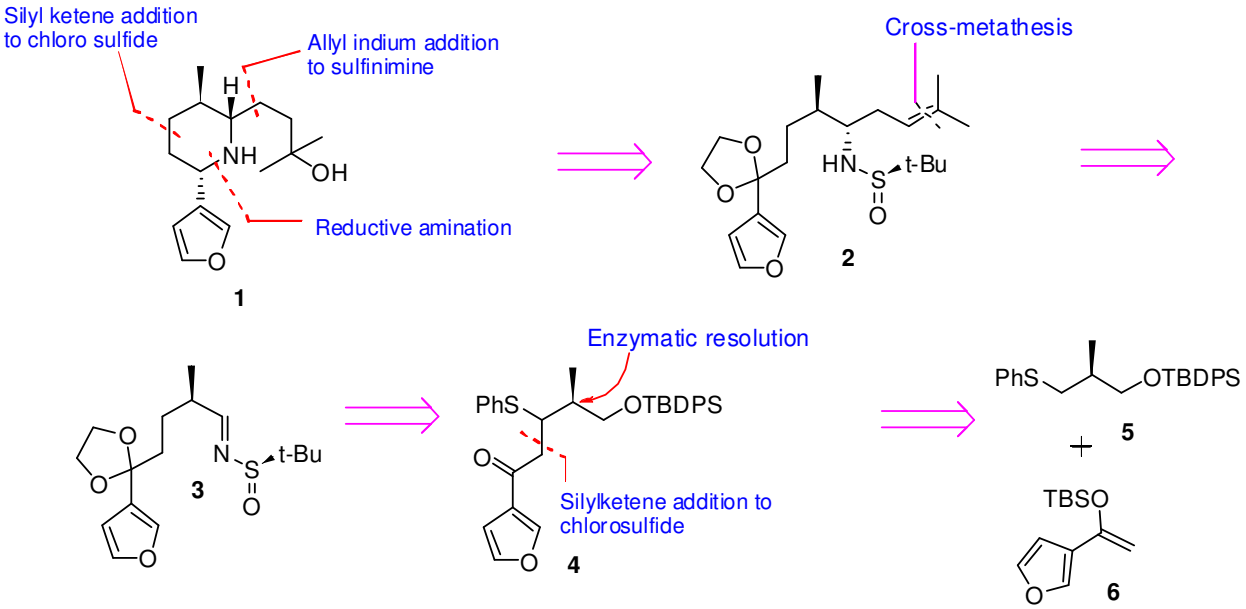
Nuphar alkaloids comprises the family of sesquiterpenoid and triterpenoid alkaloids possessing piperidine, indolizidine and quinolizidine ring systems that are isolated from aquatic plants of the genus Nuphar (*Nymphaeaceae*).[1] Nupharamine (**1**), was isolated from the Japanese water lily, *Nuphar japonica*[2] found in Japan and Korea. It has been used as a diuretic and for the treatment of stomach ache.[3] Other members of the family have been shown to possess antibiotic,[4a] antifungal,[4b] potent immunosuppressive,[4c] central paralytic effects,[5a,b,c] and antitumor activities.[5d,e] The structural motif common to nuphar alkaloids is the trisubstituted piperidine ring with a methyl group at C-3 and a 3-furyl substituent at C-6 position. Nuphar alkaloids have been targets for asymmetric synthesis due to their significant biological



(-)-Nupharamine

Figure 1. Nuphar alkaloid, nupharamine.

properties. The total synthesis of nupharamine **1** has been reported by several groups, utilizing a Diels-Alder strategy,[6] an intramolecular aza-Wittig reaction,[7] a cross-metathesis/reductive amination reaction,[8] intramolecular Mannich reaction[9] and allenic hydroxylamine cyclisation[10] as key steps.



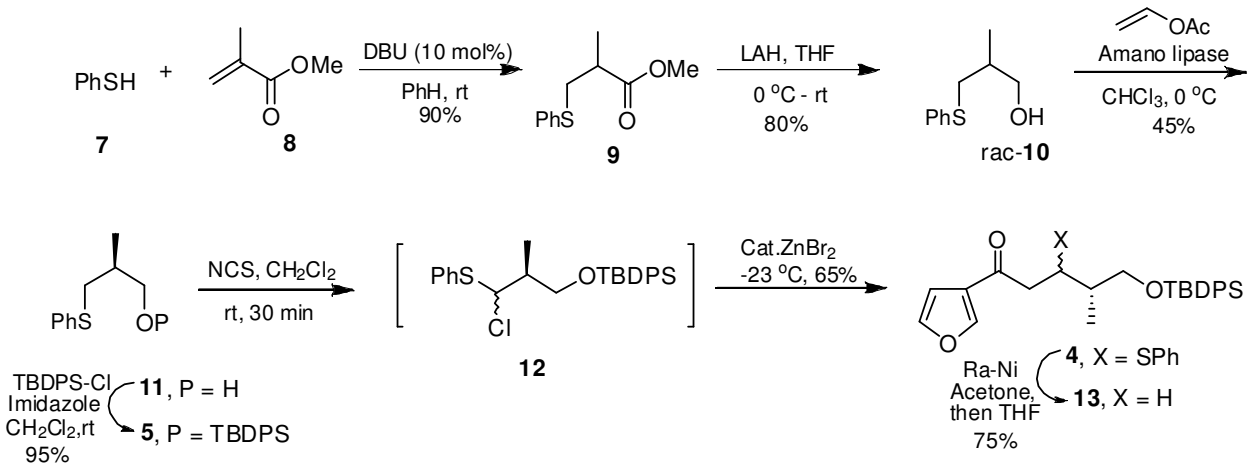
Scheme 1. Retrosynthetic analysis of nupharamine.

Results and discussion

Herein, we describe the stereoselective synthesis of (-)-nupharamine **1** by employing a Lewis acid catalyzed reaction of an α-chlorosulfide with a silyl ketene acetal, diastereoselective allylation of a *t*-butyl sulfinimine for C-N bond construction and reductive amination as key steps. The retrosynthetic analysis is depicted in Scheme **1**. Nupharamine was visualized to be

obtained by reductive amination of an amino ketone obtained from sulfinamide **2** which can be obtained by an allylation followed by cross-metathesis from sulfinimine **3.** Compound **3** was envisaged to be obtained from β-keto sufide **4** which in turn can be traced to sulfide **5** and silyl enol ether **6**.

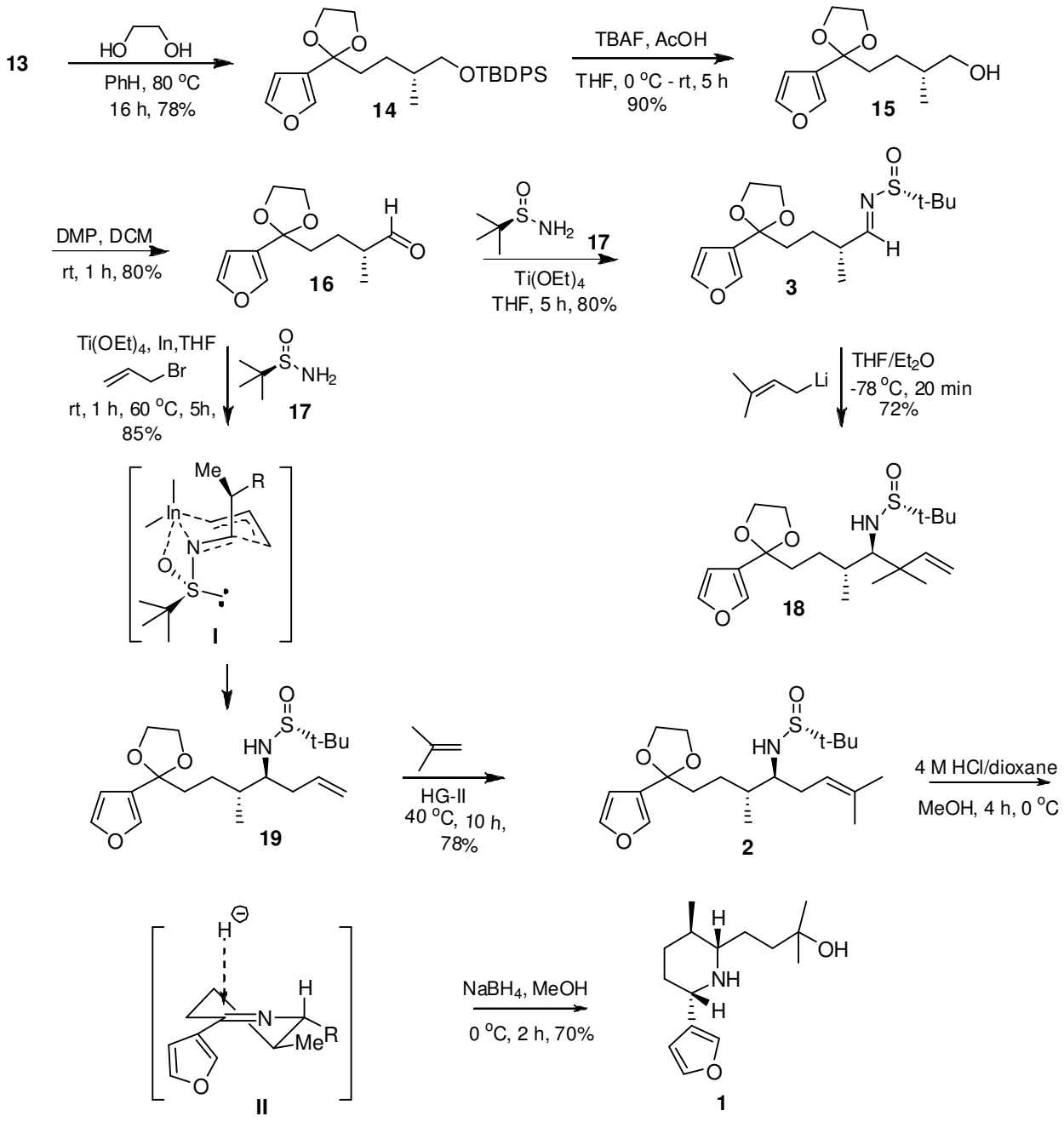
The synthesis began with the Michael addition of thiophenol **7** to methyl methacrylate **8** to furnish racemic ester **9**. LAH reduction furnished alcohol **10**, enzymatic resolution of which using vinyl acetate and Amano lipase furnished optically pure sulfide **11** (45% yield, 99.% ee).[11] The protection of **11** under standard conditions using TBDPS-Cl afforded the silyl ether **5**. Treatment of sulfide **5** with *N*-chlorosuccinimide furnished α-chlorosulfide **12** [12,13] which without isolation was reacted with silylketene acetal **6,** prepared from the corresponding ketone,[14] in the presence of catalytic amount of $ZnBr_2$ to yield keto sulfide **4,**[15] as a inseparable mixture of diastereomers in a 2:1 ratio. The thiophenyl residue in **4** was chemoselectively hydrogenolyzed using Ra-Ni pre-treated with acetone[16] to furnish compound **13,** Scheme **2**.



Scheme 2. Synthesis of compound **13**.

The keto group in **13** was protected as its ketal using ethylene glycol[17] in the presence of catalytic amounts of *p*-toluenesulfonic acid to afford **14**. Deprotection of the silyl ether in **14**

using TBAF furnished the alcohol **15,** which on oxidation using DMP[18] yielded the aldehyde **16**. Treatment of **16** with (*R*)-*N*-*tert*-butanesulfinamide[19] in the presence of $Ti(OEt)_4$ furnished sulfinimine **3.** Attempted reactions of **3** with prenyl lithium[20] expecting to obtain homoallylic amine derivative **2** did not bear fruit and the terminal alkene **18** was obtained exclusively.[21]



Scheme 3. Synthesis of nupharamine.

Exploring an alternative route, the three component allylation was attempted using aldehyde **16**, sulfinamide **17** and allyl indium, generated in situ, as reacting partners.[22] The reaction proceeded cleanly to yield homoallyl amine derivative **19** selectively. The reaction outcome can be rationalized by invoking transition state **I**, wherein the allyl indium attacks the sulfinimine from the less hindered face by chelating to the oxygen atom. The trisubstituted alkene **2** was prepared via intermolecular olefin cross-metathesis[23] between olefin **19** and 2-methyl-2-butene using the second generation Hoveyda-Grubbs' catalyst (HG-II, 1.5 mol%) under solvent-free reaction conditions at 40 ^{o}C. The compound **2** on treatment with 4 N HCl[24] in dioxane resulted in the concurrent hydration of trisubstituted olefin, deprotection of the sulfinamide and 1,3-dioxolane groups to yield the amine.HCl, which on neutralization, followed by reduction using $NaBH_4$ in MeOH produced nupharamine **1** as the sole product[7] in 70% yield. The hydride delivery to the imine from the face opposite to the bulky C-2 substitutent as depicted in transition state **II** would explain the formation of **1**, Scheme **3**. The spectroscopic data and optical rotation of nupharamine **1** were in good agreement with those reported in the literature,[8] {$\mathbf{[\alpha]_D^{25}}$ = -37.5 (*c* 0.7, $CHCl_3$), lit.[8] $\mathbf{[\alpha]_D^{22}}$ = –38.7 (*c* 0.75, $CHCl_3$)}.

Conclusions

The α-chlorosulfide prepared from sulfide **5** has been employed in the reaction with silyl ketene acetal for C-C bond formation. The *t*-butyl sulfinamide auxiliary has been employed for the stereoselective creation of the C-2 stereogenic center by reaction with allyl indium. Reductive amination reaction has been utilized to create the C-6 stereocenter. The synthetic route disclosed can be readily adapted to prepare other members of nuphar alkaloids.

Experimental

General Information

All materials were used as received from a commercial supplier without further purification. All anhydrous reactions were performed using oven-dried or flame dried glassware. Tetrahydrofuran (THF) was distilled over Na/Ph_2CO under nitrogen atmosphere. Dichloromethane (CH_2Cl_2), and triethylamine (TEA) were dried over CaH_2 and distilled prior to use. All reactions were monitored by E. Merck analytical thin layer chromatography (TLC) plates and analyzed with 254 nm UV light and/or anisaldehyde–sulfuric acid or potassium permanganate or PMA treatment. Silica gel for column chromatography was purchased from Acme (Silica Gel 60-120, 100-200 mesh). All ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ using Gemini 200, Avance 300, Inova 400, Inova 500 spectrometers. Chemical shifts (δ) are reported in parts per million (ppm) relative to residual $CHCl_3$ as an internal reference (1H: δ 7.26 ppm, 13C: δ 77.00 ppm). Coupling constants (*J*) are reported in Hertz (Hz). Peak multiplicity is indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet) and m (multiplet). Mass spectra were recorded using Waters mass spectrometer. HPLC spectra were recorded using Waters 2998 spectrometer. High resolution mass (HRMS) were recorded using Applied Bio-Sciences HRMS spectrometer and Thermo LTQ-Orbitrap mass spectrometer. All IR-spectra were recorded using Nexus 870-FT-IR Thermo Nicolet spectrometer.

Methyl 2-Methyl-3-(phenylthio)propanoate (9)

To a stirred solution of freshly distilled methyl methacrylate **8** (20 g, 200 mmol, 1 eq) in benzene (400 mL) at rt was added DBU (3 mL, 20 mmol, 0.1 eq) followed by dropwise addition of thiophenol **7** (22.4 mL, 220 mmol, 1.1 eq) over a period of 15 min. The resulting solution was

then stirred at rt for 5 h. The reaction was quenched by the addition of 0.5 N HCl (40 mL) and the mixture extracted with EtOAc (2 x 100 mL). The combined organic layers were washed with 1N NaOH (50 mL), brine (100 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The resulting compound was purified by silica gel column chromatography using hexanes-EtOAc (98:2, v/v) as the eluent to afford compound **9** (37.8 g, 180 mmol) in 90% yield as an oil. **TLC R_f** = 0.4 (5% EtOAc-hexanes). **IR** (neat)**:** 2948, 1736, 1581, 1437, 1210, 1165, 742, 692 cm^{-1}. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.32-7.30 (d, *J* = 6.8 Hz, 2H), 7.25 (t, *J* = 6.8 Hz, 2H), 7.16 (t, *J* = 6.8 Hz, 1H), 3.64 (s, 3H), 3.23 (dd, *J* = 12.8, 6.7 Hz, 1H), 2.87 (dd, *J* = 12.8, 7.5 Hz, 1H), 2.70-2.59 (m, 1H), 1.26 (d, *J* = 6.7 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 174.8, 135.6, 129.8, 128.7, 126.2, 51.5, 39.4, 37.2, 16.5. **MS (ESI)**: 233 $[M+Na]^+$. **HRMS (ESI)**: *m/z* calcd for $C_{11}H_{14}O_2NaS$ 233.0612, found 233.0602.

2-Methyl-3-(phenylthio)propan-1-ol (**10**)

To a suspension of LAH (6.0 g, 158 mmol, 1 eq) in anhydrous THF (150 mL) cooled at 0 ^oC was added a solution of compound **9** (33.1 g, 158 mmol, 1 eq) in anhydrous THF (60 mL) dropwise over a period of 30 min. The reaction mixture was stirred for an additional 30 min at 0 ^oC and allowed to warm to rt and stirred for 2 h. The reaction mixture was diluted with ether (200 mL) and quenched with ice pieces. The reaction mixture was stirred at the room temperature for 1 h, the resulting reaction mixture was filtered through pad of Celite, the filter cake was washed with EtOAc (3x200 mL) and MeOH (100 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford the crude product. Purification of the crude residue by silica gel column chromatography using hexanes-EtOAc (8:2, v/v) as the eluent afforded racemic alcohol **10** (22.9 g, 126 mmol) in 80% yield as a colorless liquid. **TLC R_f** = 0.12 (20% EtOAc-hexanes). **IR** (neat): 3390, 2959, 2876,

1583, 1478, 1030, 739, 691 cm^{-1}. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.35 (t *J* = 6.7 Hz,, 2H), 7.28 (t, *J* = 6.7 Hz, 2H), 7.17 (t, *J* = 6.7 Hz, 1H), 3.64 (dd, *J* = 10.5, 5.2 Hz, 1H), 3.59 (dd, *J* = 10.5, 6.0 Hz, 1H), 3.07 (dd, *J* = 12.8, 6.7 Hz, 1H), 2.84 (dd, *J* = 12.8, 6.7 Hz, 1H), 2.00-1.91 (m, 1H), 1.63 (bs, 1H), 1.04 (d, *J* = 6.7 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 136.6, 128.7, 125.6, 66.4, 37.1, 35.3, 16.3. **MS (ESI)** 205 $[M + Na]^+$. **HRMS (ESI)**: *m/z* calcd for $C_{10}H_{14}ONaS$ 205.0663, found 205.0669.

(*S*)-2-Methyl-3-(phenylthio)propan-1-ol (11)

To a stirred solution of (±) alcohol **10** (18.2 g, 100 mmol, 1 eq) in anhydrous chloroform cooled at 0 °C was added vinyl acetate (34.4 g, 400 mmol, 4 eq) and Pseudomonas fluorescence Amano Lipase (PFL) (1.1 g). The resulting solution was then stirred at 0 °C for 5 h when HPLC using a chiral column revealed the absence of (*R*)-**11**. (HPLC: ee = 99.0%, Chiralpak IC column, mobile phase: hexane/isopropanol 98/02, flow rate: 1 mL/min, temperature = 25 °C, detection: UV 220 nm, retention time (*S*)-isomer = 21.67 min, (*R*)-isomer 19.88 min). The resulting reaction mixture was filtered through pad of Celite, dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield the crude product. Purification of the crude residue by column chromatography using hexanes-EtOAc (8:2, v/v) as the eluent afforded alcohol **11** (8.19 g, 45 mmol) in 45% yield as a colorless liquid. **$[\alpha]_D^{25}$** = + 11.5 (*c* 1.0, CH_2Cl_2).

(*S*)-*tert*-Butyl(2-methyl-3-(phenylthio)propoxy)diphenylsilane (5)

To a stirred solution of alcohol **11** (7.64 g, 42 mmol, 1 eq) in anhydrous dichloromethane (100 mL) cooled at 0 °C was added imidazole (6.28 g, 92.4 mmol, 2.2 eq) and TBDPS-Cl (12.70 g, 46.2 mmol, 1.1 eq). The reaction mixture was stirred for 1 h before being diluted with dichloromethane (50 mL), washed with water (100 mL), brine (50 mL) and dried over Na_2SO_4. The organic layer was evaporated under reduced pressure to afford the crude compound, which

was purified by column chromatography on silica gel using hexanes-EtOAc (9.5:0.5, v/v) as the eluent to afford compound **5** (16.7 g, 40 mmol) in 95% yield as a yellow oil. **TLC** $\mathbf{R}_f$ = 0.42 (5% EtOAc-hexanes). $[\alpha]_D^{25}$ = + 18.5 (*c* 1.0, $CHCl_3$). **IR** (neat): 2957, 2930, 2858, 1472, 1109 1084 738 700 503 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.65-7.59 (m, 4H), 7.38-7.24 (m, 8H), 7.20 (t, *J* = 7.5 Hz, 2H), 7.09 (t, *J* = 7.5 Hz, 1H), 3.63 (dd, *J* = 9.8, 4.5 Hz, 1H), 3.52 (dd, *J* = 9.8, 6.7 Hz, 1H), 3.21 (dd, *J* = 12.8, 6.0 Hz, 1H), 2.66 (dd, *J* = 12.8, 7.5 Hz, 1H), 2.01-1.86 (m, 1H), 1.06 (s, 9H), 1.09 (d, *J* = 6.7 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 137.2, 135.5, 133.5, 129.5, 128.7, 128.5, 127.6, 125.3, 67.4, 36.9, 35.7, 26.8, 19.2, 16.2. **MS (ESI)**: 443 $[M+Na]^+$. **HRMS (ESI)**: *m/z* calcd for $C_{26}H_{32}ONaSSi$ 443.1835, found 443.1846.

(*S*)-5-(*tert*-Butyldiphenylsilyloxy)-1-(furan-3-yl)-4-methyl-3-(*R,S*)(phenylthio)pentan-1-one (4)

To a solution of compound **5** (4.20 g, 10 mmol, 1 eq) in anhydrous dichloromethane (50 mL) was added the solution of *N*-chlorosuccinimide (1.5 g, 11 mmol, 1.1 eq) in dichloromethane (50 mL) at ambient temperature and the mixture stirred for 15 min. Another flame-dry rb flask was charged with the solution of freshly prepared silyl ketene acetal **6** (4.28 g, 20 mmol, 2 eq) in dichloromethane (10 mL) followed by the addition of above generated chloro sulfide through canula and $ZnBr_2$ (1.5 mL, 1.5 mmol, 1.5 M in THF, 0.15 eq). The mixture was stirred at rt for 30 min. The reaction was quenched by the addition of H_2O (15 mL). The layers were separated and the aq layer extracted with EtOAc (2 X 50 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to furnish the crude product, which was purified by column chromatography on silica gel using hexanes-EtOAc (9.5:0.5, v/v) as the eluent to afford sulfide **4** (3.43 g, 6.5 mmol) as an inseparable mixture of diastereomers in 65% yield as a gummy liquid. **TLC** $\mathbf{R}_f$ = 0.3 (5% EtOAc-hexanes). **IR** (neat): 3448, 2959, 2930, 2857, 1725, 1467, 1375, 1259, 1111, 1038, 803,

703, 506 cm^{-1}. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.9 (s, 1H), 7.8 (s, 1H), 7.75 (s, 1H), 7.65 (s, 1H), 7.63-7.44 (m, 8H), 7.39-7.19 (m, 12H), 7.19-7.0 (m, 10H), 6.66 (s, 1H), 6.59 (s, 1H), 3.72-3.65 (m, 4H), 3.55-3.47 (m, 2H), 3.04 (dd, *J* = 15.8, 6.9 Hz, 1H), 2.91 (dd, *J* = 15.8, 7.9 Hz, 1H), 2.88 (dd, *J* = 12.8, 6.9 Hz, 1H), 2.82 (dd, *J* = 12.8, 5.8 Hz, 1H) 2.10-2.04 (m, 1H), 2.03-1.95 (m, 1H), 0.97 (d, *J* = 8.8 Hz, 3H), 0.93 (s, 9H), 0.86 (d, *J* = 6.9 Hz, 3H), 0.83 (s, 9H).**^{13}C NMR** (75 MHz, $CDCl_3$): δ 192.6, 192.2, 147.4, 147.3, 143.8, 143.7, 135.5, 135.3, 134.7, 133.5, 130.0, 129.7, 129.5, 129.4, 129.3, 129.1, 128.7, 128.5, 127.5, 127.4, 125.7, 125.3, 108.5, 108.3, 67.3, 66.5, 46.0, 44.4, 37.2, 37.0, 35.7, 35.4, 26.8, 26.6, 19.2, 19.0, 16.3, 16.2. **MS (ESI):** 551 $[M+Na]^+$. **HRMS (ESI)**: *m/z* calcd for $C_{32}H_{36}O_3NaSSi$ 551.2047, found 551.2048.

(*R*)-5-(*tert*-Butyldiphenylsilyloxy)-1-(furan-3-yl)-4-methylpentan-1-one (13)

A suspension of Raney-nickel (10 g) in acetone (20 mL) was stirred for 30 min at rt. Acetone was removed and the residue washed with THF (2 x 20 mL).The solution of compound **4** (10.4 g, 20 mmol, 1 eq) in anhydrous THF (30 mL) was added to the suspension of Raney-nickel in THF (20 mL) and the reaction mixture stirred at rt for 3 h. The Raney-nickel was removed by filtration through Celite plug and filter cake was washed with EtOAc (2 x 60 mL). The combined filtrates were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford the crude product which was purified by silica gel column chromatography by using hexanes-EtOAc (9.5:0.5, v/v) as the eluent to afford the compound **13** (6.3 g, 15 mmol) in 75% yield as a yellow liquid. **TLC R_f** = 0.2 (5% EtOAc-hexanes. **$[\alpha]_D^{25}$** = -3.5 (*c* 1.0, $CHCl_3$). **IR** (neat): 2932, 2860, 1677, 1468, 1389, 1154, 1107, 749, 701, 503 cm^{-1}. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.93 (s, 1H), 7.68-7.63 (m, 4H), 7.46-7.33 (m, 7H), 6.74 (d, *J* = 1.5 Hz, 1H), 3.53 (dd, *J* = 10.5, 6.1 Hz, 1H), 3.49 (dd, *J* = 10.5, 5.2 Hz, 1H), 2.70 (t, *J* = 6.7 Hz, 2H), 1.92-1.79 (m, 1H), 1.78-1.66 (m, 1H), 1.65-1.51 (m, 1H), 1.05 (s, 9H), 0.95 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 194.7, 146.8, 143.9, 135.6, 133.8, 129.6, 127.6, 108.8, 68.4, 38.1, 35.3, 27.7, 27.0, 19.4, 17.0. **MS (ESI)**: 443 $[M+Na]^+$. **HRMS (ESI)**: *m/z* calcd for $C_{26}H_{32}O_3NaSi$ 443.2013, found 443.2018.

(*R*)-t*ert*-Butyl(4-(2-(furan-3-yl)-1,3-dioxolan-2-yl)-2-methylbutoxy)diphenylsilane (14)

To a stirred solution of compound **13** (6.3 g, 15 mmol, 1 eq) in benzene (60 mL) cooled at 0 ^oC, ethylene glycol (3.1 mL) and *p*-toluenesulfonic acid (0.28 g, 1.5 mmol, 0.1 eq) were added. The resulting mixture was stirred at reflux (Dean-Stark system containing benzene in the trap) for 10 h. An aq saturated solution of $NaHCO_3$ (5 mL) was added. The layers were separated and the aqueous layer was extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over on Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography using hexanes-EtOAc (9:1, v/v) as the eluent to afford the compound **14** (5.42 g, 11.7 mmol) in 78% yield as an oil. **TLC R_f** = 0.32 (5% EtOAc-hexanes). **$[\alpha]_D^{25}$** = + 4.1 (*c* 1.0, $CHCl_3$). **IR** (neat): 2930, 1459, 1395, 1215, 1163, 1104, 767, 702, 606 cm^{-1}. **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.68-7.61 (m, 5H), 7.44-7.33 (m, 7H), 6.30 (s, 1H), 4.02-3.94 (m, 2H), 3.90-3.83 (m, 2H), 3.48 (dd, *J* = 10.1, 5.8 Hz, 1H), 3.41 (dd, *J* = 10.1, 6.7 Hz, 1H), 1.98-1.78 (m, 2H), 1.70-1.48 (m, 2H), 1.26-1.13 (m, 1H), 1.02 (s, 9H), 0.91 (d, *J* = 6.7 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 143.1, 139.9, 135.5, 134.0, 129.6, 129.4, 127.5, 108.7, 107.8, 68.7, 64.6, 37.0, 35.7, 26.9, 26.8, 19.2, 16.7. **MS (ESI)**: 465 $[M+H]^+$. **HRMS (ESI)**: *m/z* calcd for $C_{28}H_{37}O_4Si$ 465.2456, found 465.2465.

(*R*)-4-(2-(Furan-3-yl)-1,3-dioxolan-2yl)-2-methylbutan-1-ol (15)

To a solution of compound **14** (5.42 g, 11.7 mmol, 1 eq) in anhydrous THF (45 mL) cooled at 0 °C was added TBAF (11.7 mL, 1.0 M in THF, 1 eq). The reaction mixture was stirred at ambient temperature for 5 h and then concentrated in vacuo. The residue was purified by silica gel

column chromatography using hexanes-EtOAc (8:2, v/v) as the eluent to afford the alcohol **15** (2.37 g, 10.5 mmol) in 90% yield as an oil. **TLC** $\mathbf{R}_f$ = 0.1 (20% EtOAc-hexanes). $[\alpha]_D^{25}$ = - 11.7 (*c* 2.0, $CHCl_3$). **IR** (neat): 3421, 2954, 2883, 1663, 1465, 1187, 1044, 874, 800, 602 cm^{-1}. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.38 (s, 1H), 7.36 (s, 1H), 6.32 (s, 1H), 4.01-3.96 (m, 2H), 3.92-3.87 (m, 2H), 3.48 (dd, *J* = 10.5, 5.6 Hz, 1H), 3.42 (dd, *J* = 10.5, 6.1 Hz, 1H), 2.01-1.95 (m, 1H), 1.91-1.85 (m, 1H), 1.66-1.59 (m, 1H), 1.54-1.47 (m, 1H), 1.26-1.19 (m, 1H), 0.90 (d, *J* = 6.7 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 143.1, 139.8, 127.6, 108.6, 107.7, 67.6, 64.5 36.8, 35.5, 26.6, 16.5. **MS (ESI)**: 249 $[M+Na]^+$. **HRMS (ESI)**: *m/z* calcd for $C_{12}H_{18}NaO_4$ 249.1097, found 249.1113.

(*R*)-4-(2-(Furan-3-yl)-1,3-dioxolan-2yl)-2-methylbutanal (16)

To a stirred solution of alcohol **15** (1.13 g, 5 mmol, 1 eq) in anhydrous dichloromethane (20 mL) was added solid $NaHCO_3$ (2.0 g, 25 mmol, 5 eq) followed by the Dess-Martin periodinane (2.5 g, 6.0 mmol, 1.2 eq). After stirring for 30 min, the reaction mixture was filtered through a pad of Celite. The filtrate was washed with the aq saturated $Na_2S_2O_3$ (20 mL) and saturated aqueous $NaHCO_3$ (20 mL), brine (20 mL) and dried over Na_2SO_4. The solution was filtered and concentrated under reduced pressure to provide the aldehyde **16** (0.9 g, 4 mmol) in 80% yield as a clear colorless oil which was used without further purification. **TLC** $\mathbf{R}_f$ = 0.21 (20% EtOAc-hexanes). $[\alpha]_D^{25}$ = - 13.5 (*c* 1.0, $CHCl_3$). **IR** (neat): 2930, 1720, 1664, 1459, 1389, 1156, 1108, 756, 602 cm^{-1}. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 9.59 (d, *J* = 1.5 Hz, 1H). 7.39 (s, 1H), 7.37 (s, 1H), 6.32 (s, 1H), 4.01-3.97 (m, 2H), 3.92-3.87 (m, 2H), 2.37-2.32 (m, 1H), 1.97-1.88 (m, 2H), 1.85-1.78 (m, 1H), 1.50-1.43 (m, 1H), 1.08 (d, *J* = 6.7 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 203.9, 143.1, 139.6, 127.2, 108.3, 107.1, 64.4, 45.6, 36.4, 24.1, 13.1. **MS (ESI)**: 279 $[M+Na]^+$.

HRMS (ESI): *m/z* calcd for $C_{13}H_{20}O_5Na$ 279.1200, found 279.1203. Note: The mass is for the hemiacetal formed by dissolving the aldehyde in methanol.

***(R,E)-N-((R)*-4-(2-(Furan-3-yl)-1,3-dioxolan-2-yl)-2-methylbutylidene)-2-methylpropane-2-sulfinamide (3)**

To a stirred solution of aldehyde **16** (0.25 g, 1 mmol, 1 eq) in anhydrous THF (5 mL) was added $Ti(OEt)_4$ (0.41 mL, 2 mmol, 2 eq) under a N_2 atmosphere. Then, (*R*)-*tert* butanesulfinamide **17** (0.12 g, 1mmol, 1 eq) was added. The reaction solution was stirred at rt for 5 h. While rapidly stirring, the reaction was quenched by adding equal volumes of brine (5 mL) and EtOAc (5 mL). The mixture was diluted with EtOAc (10 mL) and stirred vigorously for 20 min. The resulting mixture was filtered through a pad of Celite, and the filter cake was washed with EtOAc (10 mL). The combined filtrates were washed with brine (10 mL), the combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The compound was purified by silica gel column chromatography using hexanes-EtOAc (8:2, v/v) as the eluent to furnish compound **3** (1.04 g, 3.2 mmol) in 80% yield as an oil. **TLC R_f =** 0.2 (20% EtOAc-hexanes). **$[\alpha]_D^{25}$** = -177.5 (*c* 1.0, $CHCl_3$). **IR** (neat): 3138, 2958, 2868, 1623, 1502, 1462, 1365, 1193, 1074, 1023, 868, 687 cm^{-1}. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.93 (d, *J* = 5.2 Hz, 1H), 7.38-7.34 (m, 2H), 6.30 (s, 1H), 4.02-3.94 (m, 2H), 3.93-2.84 (m, 2H), 2.69-2.52 (m, 1H), 1.98-1.85 (m, 2H), 1.83-1.66 (m, 1H), 1.60-1.47 (m, 1H), 1.18 (s, 9H), 1.13 (d, *J* = 6.8 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 172.8, 143.2, 139.9, 127.6, 108.6, 107.4, 64.7, 56.4, 37.1, 29.7, 27.6, 22.4, 17.1. **MS (ESI)**: 328 $[M+H]^+$. **HRMS (ESI):** *m/z* calcd for $C_{16}H_{26}O_4NS$ 328.1577, found 328.1576.

***(R)-N-((4R,5R)-7-(*2-(Furan-3-yl)-1,3-dioxolan-2-yl)-3,3,5-methylhept-1-en-4-yl)-2-methylpropane-2-sulfinamide (18)**

Lithium (0.2 g) was added in small pieces to a solution of 3-methylbut-2-enyl phenyl ether (0.34 g, 2 mmol, 4 eq) in dry diethyl ether/dry THF (1:1 v/v, 5 mL) under nitrogen, followed by three

drops of methanol. At the first appearance of a green coloration, the reaction mixture was cooled to 5 ^{o}C and stirred for a further 2 h. The now orange solution was transferred to a stirred solution of the compound **3** (0.16 g, 0.5 mmol) in dry diethyl ether (4 mL) at -78 ^{o}C. The resulting mixture was stirred at the same temperature for 20 min, and the reaction was then quenched by the slow addition of methanol (15 mL). Diethyl ether (10 mL) and water (10 mL) were added, the phases were separated, and the aqueous phase was extracted with diethyl ether (2 x 10 mL). The combined extracts were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford the crude product, which was purified by column chromatography on silica gel using hexanes-EtOAc (8:2, v/v) as the eluent to furnish compound **18** (0.12 g, 0.36 mmol) in 72% yield as an oil. **TLC** $\mathbf{R_f}$ = 0.1 (20% EtOAc-hexanes). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.40-7.34 (m, 2H), 6.36 (s, 1H), 5.80 (dd, *J* = 17.3, 11.3 Hz, 1H), 5.0 (dd, *J* = 11.3, 1.5 Hz, 1H), 4.96 (dd, *J* = 17.3, 1.5 Hz, 1H), 4.0-3.96 (m, 2H), 3.90-3.86 (m, 2H), 3.34 (d, *J* = 9.0 Hz, 1H), 2.89 (d, *J* = 8.3 Hz, 1H), 2.02-1.95 (m, 1H), 1.97-1.82 (m, 1H), 1.76-1.64 (m, 2H), 1.56-1.43 (m, 1H), 1.25 (s, 9H), 1.02 (s, 3H), 0.09 (s, 3H), 0.84 (d, *J* = 6.7 Hz, 3H).

***(R)-N-((4S,5R)-7-(*2-(Furan-3-yl)-1,3-dioxolan-2-yl)-5-methylhept-1-en-4-yl)-2-methylpropane-2-sulfinamide (19)**

To a stirred solution of aldehyde **16** (0.9 g, 4 mmol, 1 eq) in anhydrous THF (6 mL) was added (*R*)-*N*-*tert*-butanesulfinamide **17** (0.43 g, 3.6 mmol, 0.9 eq), indium powder (0.52 g, 4.4 mmol, 1.1 eq) and $Ti(OEt)_4$ (1.67 mL, 8 mmol, 2 eq) at rt. The resulting reaction mixture was stirred for 1 h, after which time allyl bromide (0.48 mL, 5.45 mmol, 1.36 eq) was added via syringe over 2 min at rt. The mixture was heated to 60 °C for 5 h. After cooling to rt, the reaction mixture is carefully added to a mixture of ethyl acetate:brine (50 mL, 4:1 v/v) with stirring. The resulting white suspension was filtered through a short plug of Celite, and washed with ethyl acetate (20 mL). The combined filtrates were washed with brine (10 mL), dried over Na_2SO_4, filtered and

concentrated under reduced pressure to afford the crude product which was purified by column chromatography on silica gel using hexanes-EtOAc (7:3, v/v) to give the amine **20** (1.25 g, 3.4 mmol) in 85 % yield as a yellow color oil. **TLC** $\mathbf{R}_f = 0.21$ (30% EtOAc-hexanes). $\mathbf{[\alpha]_D^{25}}$ = - 7.9 (*c* 1.2, $CHCl_3$). **IR** (neat): 3448, 2931, 1626, 1389, 1218, 1048, 760, 703, 613 cm^{-1}. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.38-7.34 (m, 2H), 6.30 (s, 1H), 5.81-5.71 (m, 1H), 5.17-5.11 (m, 2H), 4.0-3.96 (m, 2H), 3.90-3.86 (m, 2H), 3.22-3.17 (m, 2H), 2.41-2.30 (m, 1H), 2.23-2.15 (m, 1H), 2.02-1.95 (m, 1H), 1.84-1.77 (m, 1H), 1.76-1.59 (m, 2H), 1.58-1.49 (m, 1H), 1.18 (s, 9H), 0.87 (d, *J* = 6.7 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 143.2, 139.9, 134.7, 127.6, 119.0, 108.6, 107.6, 64.6, 58.3, 55.7, 37.4, 36.0, 26.3, 24.2, 22.7, 14.8. **MS (ESI)**: 370 $[M+H]^+$. **HRMS (ESI)**: *m/z* calcd for $C_{19}H_{32}O_4NS$ 370.2047, found 370.2052.

(*R*)-*N*-((3*R*,4*S*)-1-(2-(Furan-3-yl)-1,3-dioxolan-2-yl)-3,7-dimethyl-oct-6-en-4-yl)-2-methylpropane-2-sulfinamide (2)

2-Methyl-2-butene (1.5 mL) was collected in a sealed tube, cooled at -78 ^oC, containing compound **19** (0.55 g, 1.5 mmol, 1 eq) and Hoveyda-Grubbs-II catalyst (19.0 mg, 0.023 mmol, 0.015 eq). The resulting reaction mixture was slowly warmed to rt and refluxed at 40 °C for 10 h. Excess 2-methyl-2-butene was evaporated and the residue was purified by column chromatography on silica gel using hexanes-EtOAc (7:3, v/v) to give the cross-metathesis product **2** (0.46 g, 1.1 mmol) in 78% yield as an oil. **TLC** $\mathbf{R}_f = 0.3$ (30% EtOAc-hexanes). $\mathbf{[\alpha]_D^{25}}$ = - 21.5 (*c* 1.0, $CHCl_3$). **IR** (neat): 3448, 2922, 2852, 1713, 1461, 1214, 1122, 1028, 926, 748, 667 cm^{-1}. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.38-7.33 (m, 2H), 6.30 (s, 1H), 5.09 (t, *J* = 6.8 Hz, 1H), 4.02-3.98 (m, 2H), 3.92-3.88 (m, 2H), 3.16-3.08 (m, 2H), 2.26-2.12 (m, 2H), 2.03-1.92 (m, 1H), 1.84-1.41 (m, 4H), 1.72 (s, 3H), 1.63 (s, 3H), 1.18 (s, 9H), 0.87 (d, *J* = 6.4 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 143.2, 139.9, 135.4, 127.6, 120.1, 108.6, 107.7, 64.7, 59.3, 55.5, 37.5, 35.8, 30.1, 26.3, 25.9, 22.6, 18.0, 14.8. **MS (ESI):** 354 $[M+H]^+$. **HRMS (ESI):** *m/z* calcd

for $C_{19}H_{32}O_3NS$ 354.2111, found 354.2112. Note: The mass is for the ketone resulting from the hydrolysis of the dioxolane.

4-((*2S,3R,6S*)-6-(Furan-3-yl)-3-methylpiperidin-2-yl)-2-methylbutane-2-ol (1)

To a solution of compound **2** (0.15 g, 0.4 mmol, 1 eq) in anhydrous MeOH (4 mL) cooled at 0 °C was added HCl in 1,4-dioxane (4 M, 0.5 mL, 2 mmol, 5 eq). The reaction mixture was stirred for 4 h at 0 °C. The solvent and excess HCl were removed under reduced pressure. The residue was diluted with dichloromethane (5 mL) then washed with aq saturated solution of Na_2CO_3 (5 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was dissolved in anhydrous MeOH (4 mL) cooled at 0 °C and $NaBH_4$ (30 mg, 0.8 mmol, 2 eq), was added and the mixture stirred at the same temperature for 2 h. The solvent was removed under reduced pressure, the reaction mixture was diluted with dichloromethane (5 mL) and water (2 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 x 5 mL). The combined organic layers were dried over $NaSO_4$, filtered and concentrated under reduced pressure. Purification on silicagel doped with Et_3N using a dichloromethane-MeOH (95:5, v/v) afforded nupharamine (70 mg, 0.28 mmol) in 70 % yield as an oil. **TLC R_f** = 0.3 (5% MeOH-dichloromethane). **$[\alpha]_D^{25}$** = -37.5 (*c* 0.7, $CHCl_3$). {lit.[8] **$[\alpha]_D^{22}$** = –38.7 (c 0.75, $CHCl_3$)}. **IR** (neat): 3444, 3019, 2923, 2855, 1636, 1461, 1376, 1218, 1079, 769 cm^{-1}. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.36-7.33 (m, 2H), 6.42 (s, 1H), 3.62 (dd, *J* = 11.5, 2.2 Hz, 1H), 2.42-2.37 (m, 1H), 1.9-1.72 (m, 4H), 1.6-1.42 (m, 4H), 1.26-1.13 (m, 2H), 1.21 (s, 3H), 1.19 (s, 3H), 0.9 (d, *J* = 6.4 Hz, 3H). **MS (ESI)**: 252 $[M+H]^+$. **HRMS (ESI)**: *m/z* calcd for $C_{15}H_{26}O_2N$ 252.1958, found 252.1966.

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