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Four-Step Total Synthesis of (+)-Euphococcinine and (±)-Adaline

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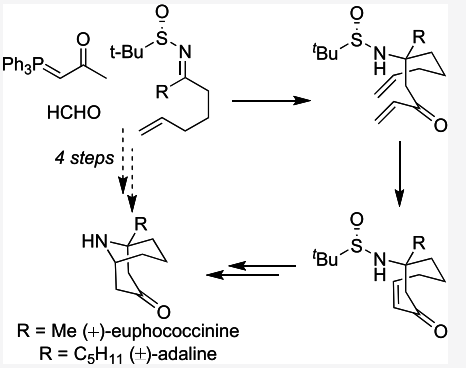
ABSTRACT: A four-step enantiospecific total synthesis of bicyclic homotropinone alkaloid euphococcinine and a racemic synthesis of adaline were reported. Key reactions in the synthesis are the diastereoselective addition of a Wittig phosphorene to the ketimines derived from Davis−Ellman sulfinamides, ring-closing metathesis, and intramolecular Michael reactions.



Piperidine, quinolizidine, indolizidine, and pyrrolidine alkaloids bearing the α-tertiary amine (attached to chiral quaternary carbon center) are structural units prevalent in bioactive natural products.[1] Some examples of these alkaloids include simple piperidinones such as adalinine **1**, bicyclic compounds ephococcinine **2**, adaline **3**, and complex natural products such as cyclindricine **C 4**, porantherine **5**, and lycopodine **6** (Figure 1).

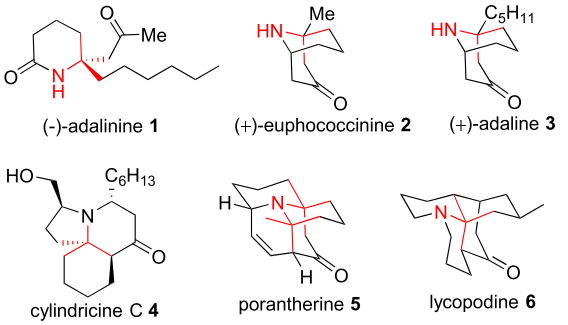


Figure 1. Alkaloids bearing α-tertiary amines attached to a chiral quaternary center.

Among the several methods described in the literature for the synthesis of chiral amines,[2a] the addition of nucleophiles to ketimines either in a Mannich fashion or by the addition of organometallic reagents is a frequently used reaction.[2b,e] Chiral sulfinimines pioneered by Davis and Ellman served as excellent substrates for the addition of various nucleophiles to aldimines and ketimines.[2] The addition of a variety of nucleophiles to the sulfinimines consistently provided the product amines with excellent diastereoselectivities. We recently found that the addition of lithium enolate of (acetylmethylene) triphenyl phosphorane **7** to nonracemic aldimines obtained from aldehydes and Ellman sulfinamide.[3] Herein, we report the addition of (acetylmethylene) triphenyl phosphorane to ketimine derived from acetophenone and its application to the synthesis of (+)-euphococcinine **2** and (±)-adaline **3**.

Our investigation began with the addition of lithium enolate of (acetyl methylene) triphenyl phosphorane **7** to the sulfinimine **8** derived from acetophenone (Scheme 1). The reaction of 2 equiv of the lithium enolate of **7** to sulfinimine **8** proceeded well. However, it was cumbersome to purify the product phosphorane **9** at this stage and also difficult to evaluate the diastereomeric ratio of **9**. Hence, **9** was subjected to Wittig olefination with various aldehydes to afford the β-sulfinamido enones **10**, which were purified by silica gel column chromatography. Thus, the reaction of crude **9** with different aldehydes such as acetaldehyde, benzaldehyde, *para*-bromo- and nitro-substituted benzaldehydes, and ethyl glyoxylate furnished the corresponding β-sulfinamido enones **10a−e** having a quaternary chiral center in moderate yields. It is important to note that the Wittig reaction of **9** with ketones did not proceed at all. Deprotection of the sulfinyl group in **10a−e** using saturated ethereal HCl followed by treatment with triethylamine afforded a separable mixture of *cis* and *trans*-2,2,6-trisubstituted piperidinones **11a−d** and **11a′−d′** in good,

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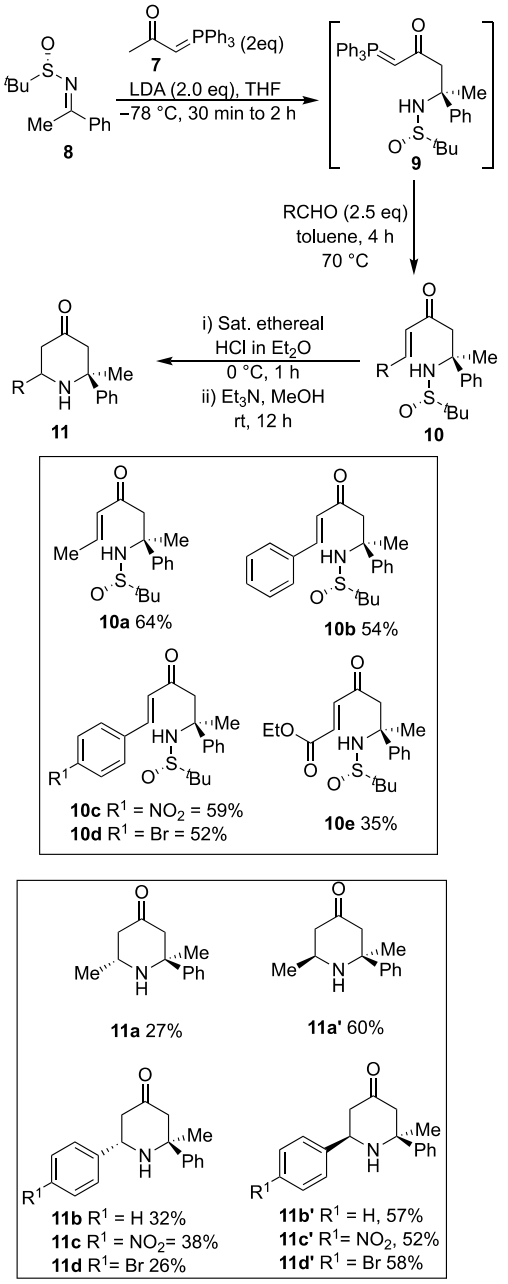
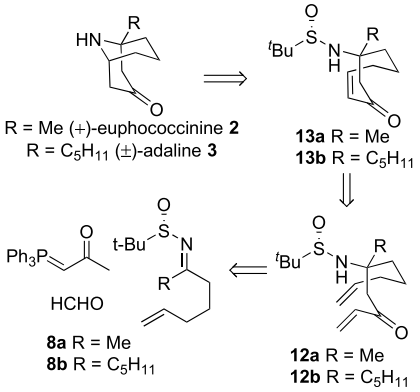
Scheme 1. Addition of the Lithium Enolate of 7 to Sulfinimine 8 and Elaboration of Piperidinones 11a−d



combined yields (Scheme 1). *cis*/*trans*-Stereochemistry of the formed piperidinones **11a−d** was established by comparison with that reported in the literature.[4] The origin of the diastereoselectivity in the addition reaction can be explained by a transition state similar to that proposed for the addition of phosphorene to aldimines.

After a short survey of the reaction of sulfinamido phosphorane **9** with aldehydes, the strategy was applied for the synthesis of homotropinone alkaloids euphococcinine[5] and adaline[6] containing the bicyclic keto amine attached to a quaternary chiral center. Several syntheses of ephococcinine were reported in the literature.[7] Most of the syntheses were based on the nitro cycloaddition reaction reported by Holmes et al.,[8a] while the biomimetic synthesis involving the intramolecular Mannich reaction of a suitably substituted piperidine is a practical approach. The Davis group[8b] has elegantly applied this intramolecular Mannich reaction strategy for the synthesis of euphococcinine and adaline from *N*-sulfinyl amino ketone. We envisioned the synthesis of **2** and **3** by intramolecular Michael addition of the amine obtained by the deprotection of the sulfinyl group in **13a** and **13b**, respectively. The formation of **13a** and **13b** was planned by RCM of the diene in **12a** and **12b**, the synthesis of which was anticipated by the addition of the lithium enolate of **7** to sulfinimine **8a**,**b** derived from pent-1-en-5-one or undec-1-en-6-one and subsequent Wittig olefination (Scheme 2).

Scheme 2. Retrosynthesis for (+)-Euphococcinine and (±)-Adaline



Thus, the addition of lithium enolate of **7** to sulfinimine **8a** and further Wittig olefination with formalin afforded a separable mixture of diastereomers **12a′** and **12a** in 14% and 63% yields, respectively. Ring-closing metathesis of compound **12a** using Grubbs second generation catalyst (5 mol %) furnished the cyclooctenone **13a** in 71% yield along with the dimer **14** in 18% yield, respectively. Deprotection of the sulfinyl group in **13a** and further neutralization with Et_3N gave euphococcinine **2** in 83% yield. The spectral and physical properties were in complete agreement with that reported for the natural product in literature.[9] However, the addition of lithium enolate of **7** to sulfinimine **8b** was found to be nonselective. This can be attributed to the structure of the imine (which existed in a 1:1 mixture of E/Z isomers as evidenced from the ^{13}C NMR) in which both alkyl substitutions do not offer steric bias required for differentiation of the substituents in the addition of lithium enolate. The product **12b** was isolated in a 68% yield. We were not able to estimate the diastereomeric ratio of the product at this stage. Ring-closing metathesis of **12b** with Grubbs' second generation catalyst (5 mol %) formed the cyclooctenone **13b** in 69% yield (87% BRSM). The diastereomeric ratio of **13b** was found to be 1:1 from the ^1H NMR analysis. The removal of the sulfinyl group followed by intramolecular Michael addition reaction after neutralization with Et_3N afforded (±)-adaline **3** in 80% yield (Scheme 3).

In conclusion, the addition of lithium enolate of (acetylmethylene) triphenyl phosphorene to nonracemic sulfinylketimines was described. A Wittig reaction of the formed phosphorene with aldehydes afforded the *β*-sulfinamido enones with good diastereoselectivity in good to moderate yields. The *β*-sulfinamido enones were used in the synthesis of homotropinone alkaloids (+)-euphococcinine and (±)-adaline.

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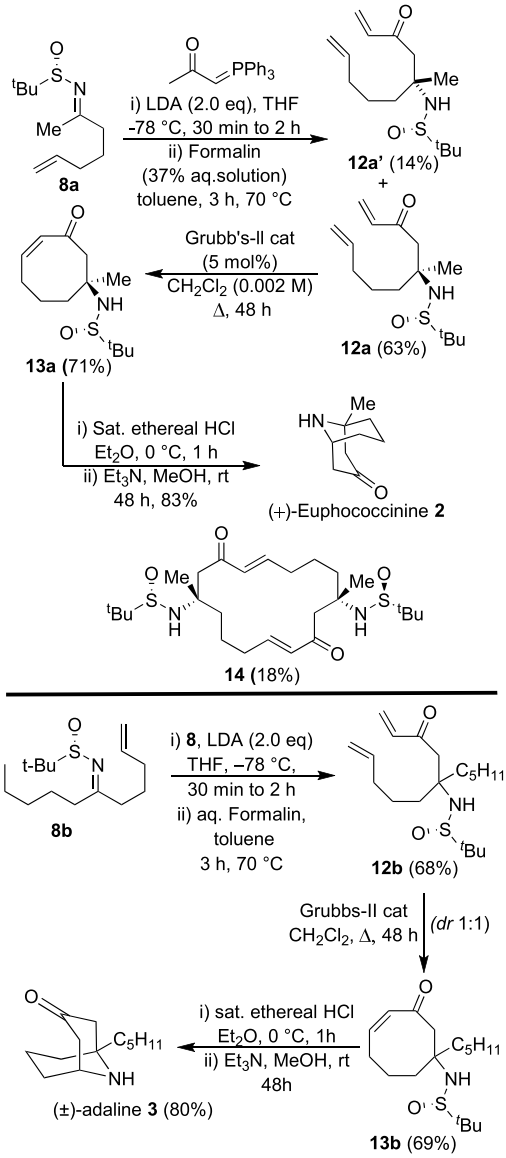
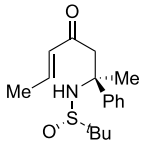
Scheme 3. Total Synthesis of Alkaloids (+)-Euphococcinine 2 and (±)-Adaline 3



EXPERIMENTAL SECTION

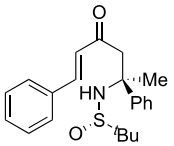
General Procedures. Column chromatography was performed on silica gel, Acme grade 100−200 mesh. TLC plates were visualized either with UV, in an iodine chamber, or with phosphomolybdic acid spray, unless noted otherwise. All reagents were purchased from commercial sources and used without additional purification. THF was freshly distilled over Na-benzophenone ketyl. Melting points were measured in open glass capillary tubes using a Büchi B-540 melting point apparatus, and values are uncorrected. Unless stated otherwise, ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on 400 MHz ultrashield Bruker spectrophotometers in $CDCl_3$ as a solvent with TMS or residual $CHCl_3$ as a reference. High-resolution mass spectra (HRMS) were recorded on a Waters XEVO G2-XS Q-TOF micromass spectrometer using electron spray ionization mode. Sulfinimine **8** was prepared according to the procedure described in the literature.[10]

*General Procedure for the Addition of (Acetylmethylene)-triphenylphosphorane **7** to Sulfinimines **8** and Successive Wittig Olefination Reaction of Resultant Sulfinamido Keto Phosphoranes **9** with Aldehydes.*



*(S_S)-(S,E)-6-((tert-Butyl(λ^1-oxidaneyl)-λ^3-sulfaneyl)amino)-6-phenylhept-2-en-4-one (**10a**).* To a stirred solution of (acetylmethylene)triphenylphosphorane **7** (0.86 g, 2.7 mmol) in dry THF (20 mL) at −78 °C was added dropwise LDA (2.7 mL of 1 M solution in THF, 2.7 mmol). The reaction mixture was stirred for 30 min at the same temperature. A solution of sulfinimine **8** (0.30 g, 1.34 mmol) in THF (5 mL) was added dropwise to the reaction mixture at −78 °C. It was stirred for 2 h at the same temperature. After completion of the reaction (TLC), it was quenched by the addition of sat. NH_4Cl solution (20 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine (20 mL) and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave the crude residue, which was purified by short silica gel column chromatography to remove excess of unreacted (acetylmethylene)-triphenylphosphorane **7**.

The addition product (obtained above) was dissolved in toluene (15 mL), and acetaldehyde (0.6 mL, 10 mmol) was added at room temperature. The resulting solution was stirred at 80 °C (oil bath) for 6 h. After completion of the reaction (TLC), most of the solvent was removed under reduced pressure. The crude residue thus obtained was purified by silica gel column chromatography using EtOAc/petroleum ether (2:3) as an eluent to furnish **10a** in 64% yield (0.26 g for 2 steps) (recovered sulfinimine **8**, 0.11 g) (94% yield of **10a** BRSM) as a colorless oil: R_f 0.5 (petroleum ether/EtOAc, 3:2); $[\alpha]_D^{24}$ +17.4 (*c* 0.7, $CHCl_3$); IR (neat) ν_{max} 3432, 3270, 2973, 2922, 1659, 1626, 1444, 1380, 1061 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, *J* = 8.0 Hz, 2H), 7.31 (t, *J* = 8.0 Hz, 2H), 7.22 (t, *J* = 8.4 Hz, 1H), 6.84 (ddd, *J* = 16.0 Hz, 12.4 Hz, 8.0 Hz, 1H), 6.10 (dd, *J* = 16.0 Hz, 4.0 Hz, 1H), 5.64 (s, 1H), 3.41 (AB_q, *J* = 17.6 Hz, 1H), 3.32 (AB_q, *J* = 17.6 Hz, 1H), 1.88 (dd, *J* = 6.8 Hz, 1.6 Hz, 3H), 1.71 (s, 3H), 1.29 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 199.2, 146.5, 143.7, 132.4, 128.3 (2C), 126.9, 125.2 (2C), 59.4, 56.0, 50.8, 29.0, 22.9 (3C), 18.3; HRMS (ESI-TOF) *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{25}NO_2SNa$ 330.1504, found 330.1506.



*(S_S)-(S,E)-5-((tert-Butyl(λ^1-oxidaneyl)-λ^3-sulfaneyl)amino)-1,5-diphenylhex-1-en-3-one (**10b**).* Compound **10b** was prepared from (acetylmethylene)triphenylphosphorane **7** (1.14 g, 3.60 mmol), LDA (1 M solution in THF, 3.60 mL, 3.60 mmol), sulfinimine **8** (0.40 g, 1.80 mmol), and benzaldehyde (0.95 mL, 9 mmol) using the general procedure described above **10b** in 54% yield (0.36 g for 2 steps) (recovered sulfinimine **8**, 0.157 g, 86% yield of **10b** BRSM) as a colorless oil: R_f 0.4 (petroleum ether/EtOAc, 7:3); $[\alpha]_D^{24}$ +18.0 (*c* 0.65, $CHCl_3$); IR (neat) ν_{max} 3271, 2962, 2923, 1649, 1606, 1449, 1380, 1062 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56−7.47 (m, 3H), 7.42 (d, *J* = 8.0 Hz, 2H), 7.39−7.36 (m, 3H), 7.33 (t, *J* = 8.0 Hz, 2H), (7.26−7.21 (m, 1H), 6.66 (d, *J* = 16.0 Hz, 1H), 5.72 (s, 1H), 3.57 (d, *J* = 17.6 Hz, 1H), 3.49 (d, *J* = 17.6 Hz, 1H), 1.76 (s, 3H), 1.32 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 199.1, 146.3, 143.3, 134.1, 130.6, 128.8 (2C), 128.3 (4C), 126.9, 126.4, 125.2 (2C), 59.6, 56.0, 51.8, 28.9, 22.9 (3C); HRMS (ESI-TOF) *m*/*z* [M + Na]$^+$ calcd for $C_{22}H_{27}NO_2SNa$ 392.1660, found 392.1652.

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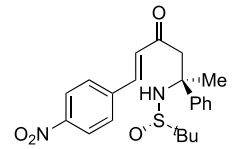
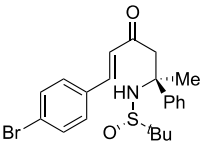
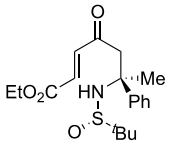


*(S_S)-(S,E)-5-((tert-Butyl(λ^1-oxidaneyl)-λ^3-sulfaneyl)amino)-1-(4-nitrophenyl)-5-phenylhex-1-en-3one (**10c**).* Compound **10c** was prepared from (acetylmethylene)triphenylphosphorane **7** (430 g, 1.34 mmol), LDA (1 M solution in THF, 1.4 mL, 1.35 mmol), sulfinimine **8** (0.15 g, 0.67 mmol), and 4-nitrobenzaldehyde (0.51 g, 3.35 mmol) using the general procedure described above **10c** in 59% yield (recovered sulfinimine **8** 0.044 g) (83% yield of **10c** BRSM) (0.165 g for 2 steps) as a colorless oil: R_f 0.4 (petroleum ether/EtOAc, 7:3); $[\alpha]_D^{24}$ +31.6 (*c* 0.50, $CHCl_3$); IR (neat) ν_{max} 3279, 2976, 2363, 1688, 1596, 1520, 1344, 1058 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, *J* = 7.6 Hz, 2H), 7.63 (d, *J* = 8.8 Hz, 2H), 7.51 (d, *J* = 16.0 Hz, 1H), 7.39 (d, *J* = 7.6 Hz, 2H), 7.32 (t, *J* = 8.0 Hz, 2H), 7.23 (t, *J* = 8.4 Hz, 1H), 6.75 (d, *J* = 16.4 Hz, 1H), 5.44 (s, 1H), 3.63 (AB_q *J* = 18.0 Hz, 1H), 3.56 (AB_q *J* = 18.0 Hz, 1H); ^{13}C NMR 1.73 (s, 3H), 1.30 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 198.3, 148.5, 146.2, 140.4, 139.8, 129.6, 128.8 (2C), 128.4 (2C), 127.0, 124.9 (2C), 124.0 (2C), 59.2, 56.0, 52.2, 29.3, 22.8 (3C); HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{22}H_{26}N_2O_4SNa$ 437.1511, found 437.1512.

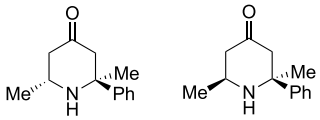


*(S_S)-(S,E)-1-(4-Bromophenyl)-5-((tert-butyl(λ^1-oxidaneyl)-λ^3-sulfaneyl)amino)-5-phenylhex-1-en-3-one (**10d**).* Compound **10d** was prepared from (acetylmethylene)triphenylphosphorane **7** (0.86 g, 2.69 mmol), LDA (1 M solution in THF, 2.7 mL, 2.69 mmol), sulfinimine **8** (0.30 g, 1.34 mmol), and 4-bromobenzaldehyde (1.22 g, 6.73 mmol) using the general procedure described above **10d** in 52% yield (0.27 g for 2 steps) (recovered sulfinimine **8**, 0.093 g) (84% yield of **10d** BRSM) as a colorless oil: R_f 0.4 (petroleum ether/EtOAc, 7:3); $[\alpha]_D^{24}$ +24.0 (*c* 1.0, $CHCl_3$); IR (neat) ν_{max} 3160, 2958, 2923, 1649, 1608, 1449, 1380, 1060 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 8.0 Hz, 2H), 7.47−7.38 (m, 3H), 7.35 (d, *J* = 8.8 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.23 (t, *J* = 8.0 Hz, 1H), 6.63 (d, *J* = 16.0 Hz, 1H), 5.59 (s, 1H), 3.56 (ABq, *J* = 18.0 Hz, 1H), 3.48 (ABq, *J* = 18.0 Hz, 1H), 1.75 (s, 3H), 1.30 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 198.8, 146.3 (2C), 141.8, 133.1 (2C), 132.2, 129.9 (2C), 128.4 (2C), 126.9 (2C), 125.1, 124.9, 59.4, 56.0, 51.9, 29.1, 22.8 (3C); HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{22}H_{26}BrNO_2SH$ 448.0946, found 448.0946.



*(S_S)-Ethyl (S,E)-6-((tert-Butyl(λ^1-oxidaneyl)-λ^3-sulfaneyl)amino)-4-oxo-6-phenylhept-2-enoate (**10e**).* Compound **10e** was prepared from (acetylmethylene)triphenylphosphorane **7** (0.85 g, 2.69 mmol), LDA (1 M solution in THF, 2.7 mL, 2.69 mmol), sulfinimine **8** (0.30 g, 1.34 mmol), and ethyl glyoxalate (50% solution in toluene) (1.37 mL, 6.73 mmol) using the general procedure described above **10e** in 35% yield (0.173 g for 2 steps) (recovered sulfinimine **8**, 0.157 g, 73% yield of **10e** BRSM) as a colorless oil: R_f 0.4 (petroleum ether/EtOAc, 3:2); $[\alpha]_D^{24}$ +7.1 (*c* 2.0, $CHCl_3$); IR (neat) ν_{max} 3405, 2986, 2947, 1678, 1494, 1107 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36−7.28 (m, 4H), 7.25−7.20 (m, 1H), 6.96 (d, *J* = 16.0 Hz, 1H), 6.62 (d, 16.0 Hz, 1H), 5.28 (s, 1H), 4.23 (q, *J* = 8.0 Hz, 2H), 3.57 (ABq, *J* = 16.0 Hz, 1H), 3.51 (ABq, *J* = 16.0 Hz, 1H), 1.69 (s, 3H), 1.31−1.26 (m, 12H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 198.6, 165.2, 146.0, 139.3, 131.3, 128.5 (2C), 127.1, 124.8 (2C), 61.4, 59.2, 56.0, 52.2, 29.3, 22.8 (3C), 14.0; HRMS (ESI-TOF) *m*/*z* $[M + Na]^+$ calcd for $C_{19}H_{27}NO_4SNa$ 388.1558, found 388.1554.

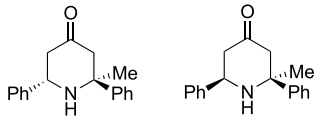
*General Procedure for Intramolecular aza-Michael Cyclization Reaction: The Following Synthesis of **11a** and **11a′** Is Representative.*



11a **11a′**

*(2S,6R)-2,6-Dimethyl-2-phenylpiperidin-4-one (**11a**).* To stirred solution of **10a** (0.075 g, 0.24 mmol) in Et_2O (2 mL) at 0 °C was added a saturated solution of ethereal HCl (w/v) (0.8 mL). The reaction mixture was stirred for 0.45 h at the same temperature. After completion of the reaction (TLC), the solvent was evaporated off and the resultant amine hydrochloride salt was dissolved in MeOH (5 mL) and Et_3N (0.16 mL, 1.2 mmol) was added. The reaction mixture was stirred for 12 h at room temperature. The solvent was evaporated off and water (5 mL) was added to the residue and was extracted with EtOAc (2 × 5 mL). The organic layers were washed with brine (1 × 5 mL) and dried over anhydrous Na_2SO_4. Evaporation of solvent followed by silica gel column chromatography of the resulting crude residue with petroleum ether/EtOAc as an eluent afforded the separable diastereomers **11a** in 27% (0.013 g) and **11a′** in 60% (0.029 g) yields, respectively, as a colorless oil: **11a** R_f 0.5 (petroleum ether/EtOAc, 8:2); $[\alpha]_D^{24}$ +10.0 (*c* 0.5, $CHCl_3$); IR (neat) ν_{max} 2965, 2924, 2363, 2329, 1710, 1494, 1446, 1285 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 84 Hz, 2H), 7.37 (t, *J* = 8.0 Hz, 2H), 7.27 (t, *J* = 8.0 Hz, 1H), 3.46−3.37 (m, 1H), 2.64 (dd, *J* = 16.0 Hz, 4.0 Hz, 1H), 2.57 (d, *J* = 16.0 Hz, 1H), 2.44 (dq, *J* = 8.0 Hz, 4.0 Hz, 1H), 2.09 (dd, *J* = 12.0 Hz, 1.6 Hz, 1H), 1.63 (brs, 1H), 1.43 (s, 3H), 1.28 (d, *J* = 8.0 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 209.7, 148.1, 128.5 (2C), 127.1, 124.7 (2C), 59.0, 54.1, 50.2, 47.3, 25.7, 23.1; HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{17}NOH$ 204.1388, found 204.1387.

*(2S,6S)-2,6-Dimethyl-2-phenylpiperidin-4-one (**11a′**):* R_f 0.4 (petroleum ether/EtOAc, 7:3); $[\alpha]_D^{24}$ −13.4 (*c* 1.2, $CHCl_3$); IR (neat) ν_{max} 3293, 2967, 2925, 2365, 2330, 1708, 1447, 1376, 1023 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, *J* = 8.0 Hz, 2H), 7.31 (t, *J* = 8.4 Hz, 2H), 7.20 (t, *J* = 7.8 Hz, 1H), 3.17 (dd, *J* = 16.0 Hz, 4.0 Hz, 1H), 2.78−2.67 (m, 1H), 2.44 (d, *J* = 12.0 Hz, 1H), 2.22 (dq, *J* = 16.0 Hz, 4.0 Hz, 1H), 2.01 (dd, *J* = 12.0 Hz, 1.6 Hz, 1H), 1.88 (brs, 1H), 1.48 (s, 3H), 1.13 (d, *J* = 8.0 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 209.2, 145.0, 128.6 (2C), 126.8, 125.9 (2C), 59.6, 51.6, 49.6, 47.1, 34.0, 22.5; HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{17}NOH$ 204.1388, found 204.1385.



11b **11b′**

*(2S,6S)-2-Methyl-2,6-diphenylpiperidin-4-one (**11b**).* Compounds **11b** and **11b′** were prepared from the keto enone **10b** (0.090 g, 0.24 mmol) using the general procedure described above in 32% (0.021 g) and 57% (0.037 g) yields, respectively, as a colorless oil: **11b** R_f 0.5 (petroleum ether/EtOAc, 8:2); $[\alpha]_D^{24}$ +5.7 (*c* 0.4, $CHCl_3$); IR (neat) ν_{max} 2968, 2932, 1712, 1498, 1447, 1289, 1027 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.67 (dd, *J* = 8.8 Hz, 1.2 Hz, 2H), 7.53 (d, *J* = 7.6 Hz, 2H), 7.40 (t, *J* = 8.0 Hz, 4H), 7.35−7.27 (m, 2H), 4.43 (dd, *J* = 11.2 Hz, 3.6 Hz, 1H), 2.75 (d, *J* = 13.2 Hz, 1H), 2.66−2.58 (m, 2H), 2.57−2.50 (m, 1H), 1.72 (brs, 1H), 1.59 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 208.8, 148.1, 143.1, 128.7 (2C), 128.5 (2C), 127.9, 126.7 (2C), 124.9 (2C), 58.7, 55.9, 54.8, 50.2, 24.8; HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{19}NOH$ 266.1545, found 266.1545.

*(2S,6R)-2-Methyl-2,6-diphenylpiperidin-4-one (**11b′**):* R_f 0.5 (petroleum ether/EtOAc, 7:3); $[\alpha]_D^{24}$ −11.2 (*c* 0.6, $CHCl_3$); IR (neat) ν_{max} 3027, 2968, 2924, 1714, 1495, 1446, 1289, 1028 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.43−7.33 (m, 8H), 7.32−7.23 (m, 2H), 3.72 (dd, *J* = 11.2 Hz, 4.0 Hz, 1H), 3.27 (dd, *J* = 13.2 Hz, 1.6 Hz,

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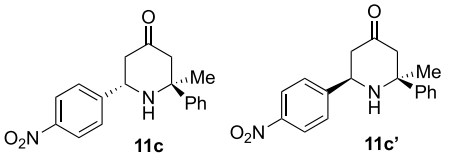
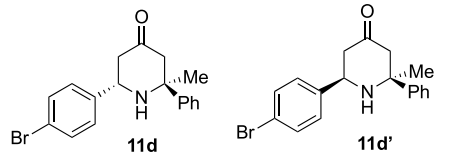
1H), 2.64 (d, J = 14.4 Hz, 1H), 2.51 (dd, J = 12.4 Hz, 8.0 Hz, 1H), 2.43 (dq, J = 12.0 Hz, 4.0 Hz, 1H), 2.21 (brs, 1H), 1.60 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 208.7, 144.9, 142.5, 128.8 (2C), 128.7 (2C), 127.8, 126.9, 126.5 (2C), 125.9 (2C), 59.7, 55.6, 51.6, 49.1, 34.0; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{18}H_{19}NOH$ 266.1545, found 266.1549.



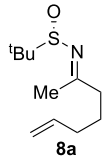
*(2S,6S)-2-Methyl-6-(4-nitrophenyl)-2-phenylpiperidin-4-one (**11c**).* Compounds **11c** and **11c′** were prepared from the keto enone **10c** (0.14 g, 0.33 mmol), saturated ethereal HCl (w/v) (1.4 mL), and Et_3N (0.23 mL, 1.65 mmol) using the general procedure described above **11c** in 38% yield (0.040 g) as a white solid and **11c′** 52% (0.056 g) yields as colorless oils: **11c** R_f 0.5 (petroleum ether/EtOAc, 7:3); $[\alpha]_D^{24}$ +8.7 (c 0.4, $CHCl_3$); mp 95−97 °C; IR (neat) ν_{max} 3306, 2969, 2924, 1713, 1601, 1520, 1347, 768 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, J = 8.8 Hz, 2H), 7.72 (d, J = 8.8 Hz, 2H), 7.67 (d, J = 8.8 Hz, 2H), 7.41 (t, J = 8.0 Hz, 2H), 7.31 (t, J = 8.0 Hz, 1H), 4.55 (dd, J = 11.2 Hz, 3.2 Hz, 1H), 2.78 (d, J = 13.6 Hz, 1H), 2.67−2.59 (m, 2H), 2.49 (dd, J = 12.0 Hz, 4.0 Hz, 1H), 1.78 (brs, 1H), 1.61 (3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 207.3, 150.3, 147.5, 147.4, 128.6 (2C), 127.6 (2C), 127.4, 124.8 (2C), 124.0 (2C), 58.8, 55.4, 54.7, 49.6, 24.6; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{18}H_{18}N_2O_3H$ 311.1396, found 311.1396.

*(2S,6R)-2-Methyl-6-(4-nitrophenyl)-2-phenylpiperidin-4-one (**11c′**):* R_f 0.5 (petroleum ether/EtOAc, 6:4); $[\alpha]_D^{24}$ −73 (c 0.76, $CHCl_3$); IR (neat) ν_{max} 3323, 2970, 2924, 1716, 1601, 1520, 1347, 771 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.18 (dd, J = 8.8 Hz, 4.0 Hz, 2H), 7.54 (d, J = 8.8 Hz, 2H), 7.45−7.32 (m, 4H), 7.29−7.23 (m, 1H), 3.81 (dd, J = 10.4 Hz, 4.4 Hz, 1H), 3.28 (d, J = 16.0 Hz, 1H), 2.65 (d, J = 16.4 Hz, 1H), 2.47−2.36 (m, 2H), 2.17 (brs, 1H), 1.57 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 207.3, 149.7, 147.3, 144.3, 128.9 (2C), 127.4 (2C), 127.2, 125.7 (2C), 123.9 (2C), 59.7, 55.1, 51.4, 48.6, 33.9; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{18}H_{18}N_2O_3H$ 311.1396, found 311.1395.

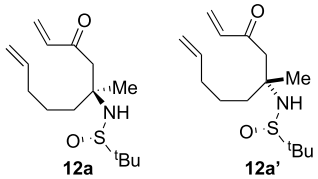


*(2S,6S)-6-(4-Bromophenyl)-2-methyl-2-phenylpiperidin-4-one (**11d**).* Compounds **11d** and **11d′** were prepared from the keto enone **10d** (0.085 g, 0.19 mmol) using the general procedure described above in 26% yield (0.017 g) as a colorless oil and 58% yield (0.035 g) as a white solid: **11d** R_f 0.5 (petroleum ether/EtOAc, 8:2); $[\alpha]_D^{24}$ +14 (c 0.71, $CHCl_3$); IR (neat) ν_{max} 2967, 2924, 1711, 1486, 1443, 1288, 1008 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.66 (dd, J = 8.0 Hz, 4.0 Hz, 2H), 7.52 (dd, J = 6.8 Hz, 1.6 Hz, 2H), 7.40 (t, J = 8.0 Hz, 4H), 7.30 (t, J = 7.2 Hz, 1H), 4.39 (dd, J = 11.2 Hz, 3.2 Hz, 1H), 2.74 (d, J = 13.2 Hz, 1H), 2.62−2.54 (m, 2H), 2.47 (dd, J = 12.8 Hz, 11.2 Hz, 1H), 1.68 (brs, 1H), 1.58 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 208.3, 147.8 (2C), 142.1 (2C), 131.9, 131.8, 128.5, 128.4, 127.3, 124.9, 124.7, 121.6, 58.6, 55.3, 54.8, 50.0, 24.7; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{18}H_{18}BrNOH$ 344.0650, found 344.0651.

*(2S,6R)-6-(4-Bromophenyl)-2-methyl-2-phenylpiperidin-4-one (**11d′**):* R_f 0.5 (petroleum ether/EtOAc, 7:3); $[\alpha]_D^{24}$ −19.0 (c 0.86, $CHCl_3$); mp 115−119 °C; IR (neat) ν_{max} 3461, 3316, 2923, 2363, 1713, 1486, 1442, 1289, 1238, 1078, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, J = 8.4 Hz, 2H), 7.39−7.32 (m, 4H), 7.28−7.24 (m, 1H), 7.22 (d, J = 8.4 Hz, 2H), 3.66 (dd, J = 9.6 Hz, 5.6 Hz, 1H), 3.24 (d, J = 14.4 Hz, 1H), 2.61 (d, J = 14.4 Hz, 1H), 2.45−2.32 (m, 2H), 2.04 (brs, 1H), 1.53 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 208.2, 144.6 (2C), 141.5 (2C), 131.8, 128.9, 128.3 (2C), 127.0 (2C), 125.8, 121.5, 59.6, 55.1, 51.5, 48.9, 34.0; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{18}H_{18}BrNOH$ 344.0650, found 344.0647.



*(S_S)-(E)-N-(tert-Butyl(λ^1-oxidaneyl)-λ^3-sulfaneyl)hept-6-en-2-imine (**8a**).* To a stirred solution of hept-6-en-2-one[11a] (0.70 g, 6.19 mmol) in THF at room temperature were added *tert*-butylsulfinamide(0.50 g, 4.13 mmol) and tetraethoxytitanium (1.37 mL, 6.19 mmol). The reaction mixture was refluxed for 12 h. After completion of the reaction (TLC), it was quenched by the addition of water (0.5 mL), and the solid residue thus formed was filtered through a short pad of Celite. The Celite pad was washed with CH_2Cl_2 (2 × 5 mL). Evaporation of the solvent under reduced pressure and silica gel column chromatography of the crude residue thus obtained using EtOAc/petroleum ether (1:9) as an eluent gave the imine **8a** in 73% yield (0.671 g) as a colorless oil: R_f 0.6 (petroleum ether/EtOAc, 9:1); $[\alpha]_D^{24}$ +56.4 (c 1.2, $CHCl_3$); IR (neat) ν_{max} 2924, 2853, 2364, 1630, 1582 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.78 (ddd, J = 16.4 Hz, 9.6 Hz, 6.4 Hz, 1H), 5.07−4.94 (m, 2H), 2.48−2.39 (m, 2H), 2.31 (s, 3H), 2.16−2.01 (m, 2H), 1.76−1.62 (m, 2H), 1.23 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 185.2, 138.0, 115.2, 56.2, 42.6, 33.0, 24.6, 23.1, 22.1 (3C); HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{11}H_{21}NOSH$ 216.1422, found 216.1425.



*Preparation of **12a′** and **12a**.* To a stirred solution of (acetylmethylene)triphenylphosphorane **7** (0.61 g, 1.92 mmol) in dry THF (20 mL) at −78 °C was added LDA (1 M solution in THF, 2.0 mL, 1.92 mmol) dropwise. The reaction mixture was stirred for 45 min at the same temperature. A solution of the sulfinimine **8a** (0.20 g, 0.96 mmol) in THF (5 mL) was added dropwise to the reaction mixture at −78 °C. It was stirred for 2 h at the same temperature. After completion of the reaction (TLC), it was quenched by the addition of sat. NH_4Cl solution (20 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine (20 mL) and dried over anhydrous $NaSO_4$. Evaporation of the solvent gave the crude residue, which was purified on short silica gel column chromatography to remove excess of unreacted (acetylmethylene)triphenylphosphorane **7**.

The addition product obtained above was dissolved in toluene (15 mL), and formalin (37% solution in H_2O) (0.75 mL, 9.6 mmol) was added at room temperature. The resulting solution was stirred at 80 °C for 4 h. After completion of the reaction (TLC), most of the solvent was removed under reduced pressure. The crude residue thus obtained was purified by silica gel column chromatography using EtOAc/petroleum ether (2:3) as an eluent to furnish **12a′** in 14% (0.039 g for 2 steps) and **12a** in 63% (0.173 g for 2 steps) yields, respectively, as a colorless oil: **12a′** R_f 0.5 (petroleum ether/EtOAc, 7:3); $[\alpha]_D^{24}$ +51.0 (c 1.0, $CHCl_3$); IR (neat) ν_{max} 2949, 2924, 1690, 1611, 1462, 1402, 1056 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.31 (dd, J = 17.6 Hz, 10.4 Hz, 1H), 6.18 (d, J = 17.6 Hz, 1H), 5.85−5.71 (m, 2H), 5.00 (d, J = 17.2 Hz, 1H), 4.94 (d, J = 10.0 Hz, 1H), 4.62 (s, 1H), 3.06 (AB_q, J = 17.6 Hz, 1H), 2.65 (AB_q, J = 17.6 Hz, 1H), 2.04 (quart., J = 6.8 Hz, 2H), 1.82 (ddd, J = 18.0 Hz, 14.0 Hz, 4.4 Hz, 1H), 1.67 (ddd, J = 17.2 Hz, 12.0 Hz, 5.2 Hz, 1H), 1.51−1.32 (m, 2H), 1.30 (s, 3H), 1.18 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 199.7, 138.4, 137.2, 128.2, 114.8, 56.7, 55.5, 49.7, 40.0, 33.8, 26.0, 22.9, 22.6 (3C); HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{15}H_{27}NO_2SH$ 286.1841, found 286.1841.

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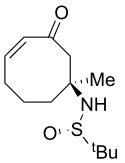
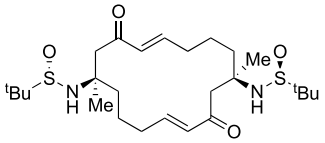
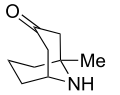
*(S_S)-(S)-5-((tert-Butyl(λ^1-oxidaneyl)-λ^3-sulfaneyl)amino)-5-methyldeca-1,9-dien-3-one (**12a**):* R_f 0.5 (petroleum ether/EtOAc, 6:4); $[\alpha]_D^{24}$ +28 (*c* 1.0, $CHCl_3$); IR (neat) ν_{max} 3422, 2927, 2363, 1671, 1610, 1460, 1402, 1053 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.31 (dd, *J* = 17.6 Hz, 10.4 Hz, 1H), 6.20 (dd, *J* = 17.6 Hz, 0.8 Hz, 1H), 5.83−5.69 (m, 2H), 5.02−4.89 (m, 2H), 4.77 (s, 1H), 3.02 (AB_q, *J* = 17.6 Hz, 1H), 2.78 (AB_q, *J* = 17.6 Hz, 1H), 2.02 (quart., *J* = 6.8 Hz, 2H), 1.69 (ddd, *J* = 18.4 Hz, 13.6 Hz, 4.8 Hz, 1H), 1.63 (ddd, *J* = 16.4 Hz, 11.6 Hz, 5.2 Hz, 1H), 1.48−1.38 (m, 1H), 1.36 (s, 3H), 1.33−1.27 (m, 1H), 1.20 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.2, 138.4, 137.2, 128.5, 114.8, 56.6, 55.6, 49.3, 40.4, 38.8, 25.7, 23.0, 22.7 (3C); HRMS (ESI-TOF) *m*/*z* $[M + Na]^+$ calcd for $C_{15}H_{27}NO_2SNa$ 308.1660, found 308.1661.



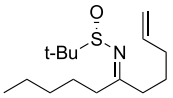
*(S_S)-(S,Z)-7-((tert-Butyl(λ^1-oxidaneyl)-λ^3-sulfaneyl)amino)-7-methylcyclooct-2-en-1-one (**13a**).* To a solution of **12a** (0.15 g, 0.52 mmol) in CH_2Cl_2 (0.002 M, 260 mL) was added Grubbs' second generation catalyst (0.022 g, 0.026 mmol), and the mixture was stirred under reflux for 48 h. After completion of the reaction (TLC), most of the solvent was evaporated off, and the crude residue thus obtained was purified by silica gel column chromatography using petroleum ether/EtOAc (2:3) as an eluent to furnish **13a** 71% (0.096 g) and **14** in 18% (0.024 g) yields, respectively, as a colorless oil: **13a** R_f 0.4 (petroleum ether/EtOAc, 1:1); $[\alpha]_D^{20}$ +39.0 (*c* 1.0, $CHCl_3$); IR (neat) ν_{max} 2953, 2926, 1685, 1657, 1467, 1051 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.48 (dt, *J* = 12.0, 8.4 Hz, 1H), 6.18 (d, *J* = 12.0 Hz, 1H), 3.39 (s, 1H), 3.12−2.86 (m, 2H), 2.78−2.56 (m, 2H), 1.83−1.61 (m, 4H), 1.40 (s, 3H), 1.17 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 198.8, 142.8, 136.0, 55.9, 55.7, 55.3, 34.5, 29.3, 25.6, 22.5 (3C), 19.8; HRMS (ESI-TOF) *m*/*z* $[M + Na]^+$ calcd for $C_{13}H_{23}NO_2SNa$ 280.1347, found 280.1346.



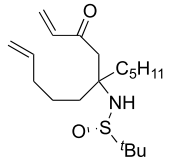
*(S_S)-(2E,7S,10E,15S)-7,15-Bis((tert-butyl(λ^1-oxidaneyl)-λ^3-sulfaneyl)amino)-7,15-dimethylcyclohexadeca-2,10-diene-1,9-dione (**14**):* R_f 0.3 (petroleum ether/EtOAc, 2:3); $[\alpha]_D^{24}$ + 45.4 (*c* 0.7, $CHCl_3$); IR (neat) ν_{max} 2981, 2953, 2926, 1685, 1651, 1618, 1467, 1051 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.76−6.62 (m, 1H), 6.09 (d, *J* = 15.6 Hz, 1H), 4.60 (s, 1H), 2.84 (d, *J* = 13.6 Hz, 1H), 2.73 (d, *J* = 13.6 Hz, 1H), 2.48−2.26 (m, 1H), 2.18−2.11 (m, 1H), 1.76−1.59 (m, 1H), 1.37 (s, 3H), 1.35−1.26 (m, 3H), 1.23 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 199.8, 148.2, 132.7, 57.4, 55.7, 51.6, 40.6, 32.2, 24.4, 22.8 (3C), 21.9; HRMS (ESI-TOF) *m*/*z* $[M + Na]^+$ calcd for $C_{26}H_{46}N_2O_4S_2Na$ 537.2797, found 537.2798.



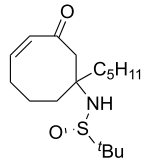
*(+)-Euphococcinine (**2**).* To a stirred solution of **13a** (0.070 g, 0.27 mmol) in Et_2O (2 mL) was added saturated ethereal HCl (0.7 mL) at 0 °C. The reaction mixture was stirred for 45 min at 0 °C. After completion of the reaction (TLC), most of the solvent was evaporated off, the crude amine hydrochloride salt was dissolved in MeOH (5 mL), and Et_3N (0.2 mL, 1.35 mmol) was added. The reaction mixture was stirred for 48 h at room temperature. After completion of the reaction (TLC), most of solvent was evaporated off, and the residue was diluted with water (5 mL) and extracted with EtOAc (2 × 10 mL). The organic layers were washed with brine (1 × 10 mL) and dried over anhydrous Na_2SO_4. Evaporation of the solvent followed by silica gel column chromatography of the resulting crude residue with methanol/ethyl acetate (MeOH/EtOAc 0.5:4.5) as an eluent furnished euphococcinine (**2**) in 83% yield (0.034 g) as a white solid: R_f 0.5 (MeOH/EtOAc, 0.5:4.5); $[\alpha]_D^{23}$+6.8 (*c* 0.7, MeOH) [lit.[9] $[\alpha]_D^{20}$ +5.4 (*c* 0.65, MeOH)]; mp 31−33 °C (lit.[9] 32−34 °C); IR (neat) ν_{max} 3430, 2978, 2930, 1717, 1471, 1201, 1147, 1025 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.68−3.57 (m, 1H), 2.52 (dd, *J* = 16.0 Hz, 6.8 Hz, 1H), 2.36 (t, *J* = 15.6 Hz, 2H), 2.18 (d, *J* = 16.0 Hz, 1H), 2.07 (brs, 1H), 1.72−1.37 (m, 6H), 1.16 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 210.9, 53.4, 52.4, 49.7, 46.1, 38.4, 31.5, 31.1, 18.0; HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_9H_{15}NOH$ 154.1232, found 154.1232.



*(S_S)-N-(tert-Butyl(λ^1-oxidaneyl)-λ^3-sulfaneyl)undec-1-en-6-imine (**8b**).* The compound **8b** prepared using a procedure described for **8a** from undec-1-en-6-one[11b] (0.83 g, 4.96 mmol), *tert*-butylsulfinamide (0.50 g, 4.13 mmol), and tetraethoxytitanium (0.90 mL, 4.96 mmol) gave **7b** in 67% yield (0.671 g) as a colorless oil: R_f 0.6 (petroleum ether/EtOAc, 9:1); $[\alpha]_D^{24}$ +5.8 (*c* 1.0, $CHCl_3$); IR (neat) ν_{max} 2957, 2927, 2862, 1620, 1456, 1360, 1076 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (*E*/*Z* 1:1) δ 5.74 (ddd, *J* = 16.0 Hz, 8.0 Hz, 4.0 Hz, 1H), 5.01−4.86 (m, 2H), 2.71−2.48 (m, 2H), 2.42−2.28 (m, 2H), 2.11−1.95 (m, 3H), 1.68−1.59 (m, 2H), 1.57−1.47 (m, 2H), 1.41−1.35 (m, 2H), 1.18 and 1.17 (s, 9H), 1.09 (brs, 1H), 0.83 (t, *J* = 8.0 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) (*E*/*Z* 1:1) δ 188.7 and 188.6 (1C), 138.7 and 138.1 (1C), 115.5 and 115.1 (1C), 56.23 and 56.19 (1C), 41.3, 40.9, and 40.1 (1C), 36.6 and 36.0 (1C), 34.2 and 33.7 (1C), 33.1, 31.9, and 31.3 (1C), 27.1 and 26.6 (1C), 25.3 and 24.6 (1C), 22.2, 22.1 (3C), 13.94 and 13.90 (1C); HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{29}NOSNa$ 294.1868, found 294.1869.



*(S_S)-5-((tert-Butyl(λ^1-oxidaneyl)-λ^3-sulfaneyl)amino)-5-pentyldeca-1,9-dien-3-one (**12b**).* The compound **12b** was prepared using a procedure similar to that described for the synthesis of **12a**. Thus, the reaction of **7** (0.70 g, 2.20 mmol), LDA (1 M solution in THF, 2.20 mL, 2.20 mmol), and sulfinimine **8b** (0.30 g, 1.1 mmol) afforded **12b** in 67% (0.196 g for 2 steps) yield as a colorless oil: R_f 0.5 (petroleum ether/EtOAc, 3:2); $[\alpha]_D^{24}$ +14.5 (*c* 1.5, $CHCl_3$); IR (neat) ν_{max} 3433, 2927, 2863, 1675, 1610, 1460, 1403, 1064 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.30 (dd, *J* = 16.0 Hz, 8.0 Hz, 1H), 6.19 (dd, *J* = 16.0 Hz, 4.0 Hz, 1H), 5.84−5.71 (m, 2H), 5.03−4.92 (m, 2H), 4.79 (s, 1H), 3.02 (dd, *J* = 16.0 Hz, 4.0 Hz, 1H), 2.76 (d, *J* = 16.0 Hz, 1H), 2.09−1.98 (m, 2H), 1.84−1.71 (m, 1H), 1.70−1.62 (m, 3H), 1.44−1.21 (m, 6H), 1.20 (s, 9H), 0.85 (t, *J* = 8.0 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) (diastereomeric mixture 1:1) δ 200.20 and 200.17 (1C), 138.3, 137.1, 128.2, 114.9, 59.07, and 59.04 (1C), 55.70 and 55.69 (1C), 47.4 and 47.3 (1C), 36.9 and 36.6 (1C), 36.4 and 36.2 (1C), 33.85 and 33.81 (1C), 32.03 and 31.98 (1C), 22.8 and 22.7 (1C), 22.5 (3C), 14.0; HRMS (ESI-TOF) *m*/*z* $[M + Na]^+$ calcd for $C_{19}H_{35}NO_2SNa$ 364.2286, found 364.2285.



*(S_S)-(Z)-7-((tert-Butyl(λ^1-oxidaneyl)λ^3-sulfaneyl)amino)-7-pentylcyclooct-2-en-1-one (**13b**).* Using a procedure similar to that described for the synthesis of **12a**, the compound **13b** was prepared from **12b** (0.10 g, 0.28 mmol), CH_2Cl_2 (0.002 M, 140 mL), and Grubbs' second generation catalyst (0.012 g, 0.014 mmol) in 69% (0.061 g) yield, with recovery of the starting material **12b** (0.013 g) (77% yield of **13b** BRSM) as a colorless oil: R_f 0.4 (petroleum ether/

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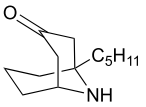
EtOAc, 1:1); $[\alpha]_D^{20}$+6.1 (1.0, $CHCl_3$); IR (neat) ν_{max} 3434, 3273, 2924, 2859, 2713, 2562, 1654, 1064 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (diastereomeric mixture 1:1) δ 6.58−6.47 (m, 1H), 6.23 (d, J = 12.0 Hz, 1H), 3.50 (d, J = 8.0 Hz, 1H), 3.04−2.93 (m, 1H), 2.92−2.79 (m, 1H), 2.72−2.61 (m, 1H), 2.11−1.98 (m, 1H), 1.88−1.62 (m, 7H), 1.41−1.26 (m, 6H), 1.24 and 1.21 (s, 9H), 0.89 (t, J = 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) (diastereomeric mixture 1:1) δ 200.4 and 199.4 (1C), 143.1 and 142.8 (1C), 136.3 and 136.2 (1C), 58.4 and 58.2 (1C), 56.4 and 56.3 (1C), 53.1, 52.0, 35.3, 33.4, 32.0, 25.83, and 25.77 (1C), 22.76 and 22.72 (1C), 22.58 and 22.55 (3C), 20.3 and 20.0 (1C), 14.0; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{17}H_{31}NO_2SH$ 314.2154, found 314.2154.



*(±)-Adaline (**3**).* Using a procedure described for the synthesis of **2**, compound **3** was prepared from **13b** (0.05 g, 0.15 mmol) in 80% yield (0.027 g) as a colorless oil: R_f 0.5 (MeOH/EtOAc, 0.5:4.5); IR (neat) ν_{max} 3435, 2927, 2853, 1703, 1464, 1356 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.67 (brs, 1H), 2.54 (dd, J = 16.0 Hz, 8.0 Hz, 1H), 2.37 (d, J = 16.0 Hz, 2H), 2.19 (d, J = 16.0 Hz, 1H), 1.97 (brs, 1H), 1.76−1.57 (m, 4H), 1.55−1.46 (m, 1H), 1.44−1.36 (m, 3H), 1.34−1.21 (m, 6H), 0.87 (t, J = 8.0 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 211.3, 54.7, 51.5, 49.6, 46.5, 44.6, 36.5, 32.3, 31.5, 22.5, 22.2, 17.8, 14.0; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{13}H_{23}NOH$ 210.1858, found 210.1861.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c00938.

^1H and ^{13}C NMR spectra of all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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